

NEW ANNULATION METHODS EMPLOYING BIFUNCTIONAL
CONJUNCTIVE REAGENTS.
TOTAL SYNTHESIS OF (-)-HOMALOMENOLS A AND B.

by

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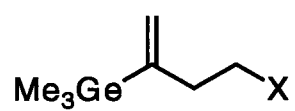
ABSTRACT

This thesis is divided into two parts. Part 1 describes the use of the bifunctional conjunctive reagent **13** in novel annulation sequences. As previously developed in our laboratories, compound **13** was converted into the key organocopper(I) reagent **15** which can be used as the synthetic equivalent of a 1-butene a^2,d^4 -synthon **14** or a 1-butene d^2,d^4 -synthon **21**.

The preparation of structurally complex tricyclic ring systems of general structures **32** and **32a** was accomplished via an annulation sequence involving: (a) the stereoselective conjugate addition of the organocopper(I) reagent **15** to bicyclic enones of general structure **19** to afford the vinylgermane intermediates **19a**, (b) conversion of the vinylgermane adducts **19a** into the corresponding keto vinyl iodides **19b**, and (c) intramolecular Pd(0)-catalyzed coupling reactions of the vinyl iodides **19b** to generate the unique tricyclic keto alkenes **32** and **32a**.

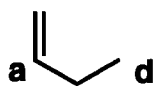
The use of the organocopper(I) reagent **15** as the synthetic equivalent of the d^2,d^4 -synthon **21** was employed in an annulation sequence designed to generate tricyclic compounds bearing an allylic, angular hydroxyl group (see general structure **33**). The key step in this sequence involved the cyclization of the keto vinyl iodides **19b** via a lithium-iodine exchange reaction and subsequent closure of the resultant vinyl lithium species onto the carbonyl carbon.

Part 2 of this thesis describes the first total syntheses of the sesquiterpenes (-)-homalomenol A (**168b**) and B (**169b**). The preparation of these products involved the conversion of the enantiomerically homogeneous allylic acetate **181b** to the bicyclic enone **177b** via a known five-membered ring annulation sequence. The key steps were the stereoselective conjugate additions of the organocopper(I) reagents **178** and **179** to the bicyclic enone **177b**. The resultant bicyclo[4.3.0]nonan-2-ones **175b** and **176b** were then readily converted to the products **168b** and **169b**, respectively, via two synthetic steps.

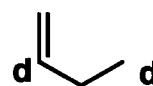


13 X = I

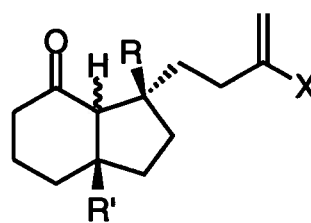
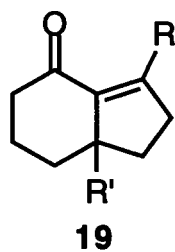
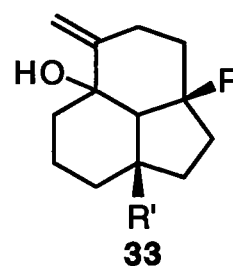
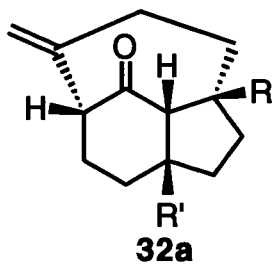
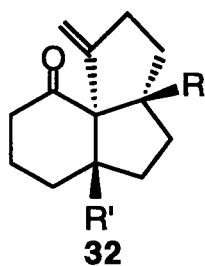
15 X = Cu(CN)Li



14

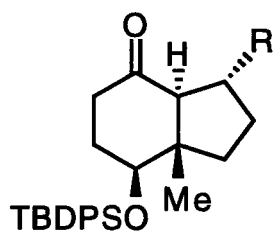
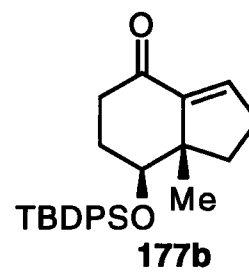
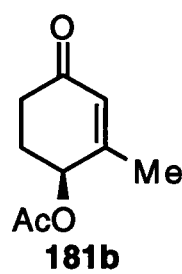
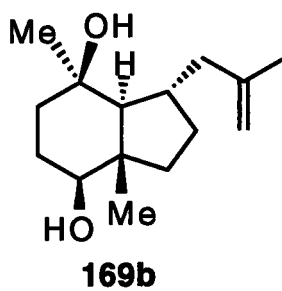
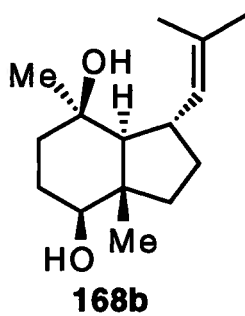


21



19a X = GeMe₃

19b X = I



175b R =

176b R =

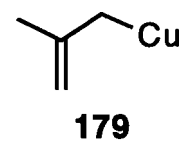
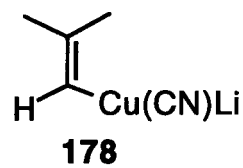


TABLE OF CONTENTS

	Page
ABSTRACT	ii
TABLE OF CONTENTS	iv
LIST OF TABLES	xvii
LIST OF FIGURES	xxii
LIST OF GENERAL PROCEDURES	xxiii
LIST OF ABBREVIATIONS	xxiv
ACKNOWLEDGMENTS	xxvii
<u>PART 1: ANNULATION SEQUENCES EMPLOYING THE BIFUNCTIONAL</u>	
<u>CONJUNCTIVE REAGENTS 4-iodo-2-trimethylgermyl-1-butene (13)</u>	
<u>AND 5-iodo-2-trimethylgermyl-1-pentene (31).</u>	
I. INTRODUCTION	1
1.1. GENERAL	1
1.2. BACKGROUND	3
1.3. PROPOSALS.....	8
II. DISCUSSION	11
2.1. FIVE-MEMBERED RING ANNULATIONS BASED ON	
PALLADIUM(0)-CATALYZED INTRAMOLECULAR	
COUPLING	11
2.1.1. INTRODUCTORY REMARKS	11
2.1.2. PREPARATION OF THE BIFUNCTIONAL REAGENT 4-	
iodo-2-trimethyl-germyl-1-butene (13)	16
2.1.3. PREPARATION OF THE CYCLIZATION SUBSTRATES	19
2.1.4. CYCLIZATION STUDIES	24

2.1.5. CONCLUSION	33
2.2. ATTEMPTS TO ACHIEVE SIX-MEMBERED RING ANNULATIONS BASED ON PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING	35
2.2.1. INTRODUCTORY REMARKS	35
2.2.2. PREPARATION OF THE BIFUNCTIONAL REAGENT 5- IODO-2-TRIMETHYL-GERMYL-1-PENTENE (31)	36
2.2.3. PREPARATION OF THE CYCLIZATION PRECURSORS	38
2.2.4. CYCLIZATION STUDIES	41
2.3. THE FORMATION OF TRICYCLIC RING SYSTEMS EMPLOYING THE ANNULATION METHOD BASED ON THE PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING	44
2.3.1. INTRODUCTORY REMARKS	44
2.3.2. PREPARATION OF THE BICYCLIC[4.3.0]NON-9-EN-2- ONES	44
2.3.3. PREPARATION OF THE BICYCLIC KETO VINYLGERMANES	49
2.3.3.1. Literature Precedent for Conjugate Addition Reactions to Bicyclo[4.4.0]dec-10-en-2-ones	49
2.3.3.2. Literature Precedent for Conjugate Addition Reactions to Bicyclo[3.3.0]oct-8-en-2-ones	52
2.3.3.3. Literature Precedent for Conjugate Addition Reactions to Bicyclo[4.3.0]non-9-en-2-ones	55
2.3.3.4. Conjugate Addition Reactions to the Bicyclo- [4.3.0]non-9-en-2-ones 74 , 75 , 95 , and 96	56
2.3.4. PREPARATION OF THE KETO VINYL IODIDES	74
2.3.5. CYCLIZATION STUDIES	79
2.3.6. CONCLUSION	101
2.4. THE FORMATION OF TRICYCLIC COMPOUNDS BEARING AN ALLYLIC, ANGULAR HYDROXYL GROUP VIA A METAL- HALOGEN EXCHANGE REACTION.....	103
2.4.1. INTRODUCTORY REMARKS	103

2.4.2. CYCLIZATION STUDIES	103
2.4.3. CONCLUSION	119
III. EXPERIMENTAL	121
3.1. GENERAL	121
3.1.1. DATA ACQUISITION AND PRESENTATION	121
3.1.2. SOLVENTS AND REAGENTS	124
3.2. SYNTHESIS OF BICYCLIC COMPOUNDS VIA THE FIVE-MEMBERED RING ANNULATION SEQUENCE	126
3.2.1. SYNTHESIS OF 2-(CARBOMETHOXY)-2-CYCLOHEXEN-1-ONE (47):	126
3.2.2. SYNTHESIS OF 4-iodo-2-trimethylgermyl-1-butene (13) VIA THE CORRESPONDING VINYLSTANNANE REAGENT	127
3.2.2.1. Synthesis of 3-Trimethylstannyl-3-buten-1-ol (48a):	127
3.2.2.2. Synthesis of 4-Chloro-2-trimethylstannyl-1-butene (45):	128
3.2.2.3. Synthesis of 4-Iodo-2-trimethylgermyl-1-butene (13):..	128
3.2.3. SYNTHESIS OF 4-iodo-2-trimethylgermyl-1-butene (13) VIA A PLATINUM CATALYZED HYDROGERMYLATION REACTION	130
3.2.3.1. Synthesis of 3-Trimethylgermyl-3-buten-1-ol (52):	130
3.2.3.2. Synthesis of 4-Iodo-2-trimethylgermyl-1-butene (13):..	131
3.2.4. PREPARATION OF THE CUPRATE REAGENT 15 :	132
3.2.5. GENERAL PROCEDURE 1: PREPARATION OF THE KETO VINYLGERMANES	132
3.2.5.1. Synthesis of 3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (59):	133
3.2.5.2. Synthesis of 3-Methyl-3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (60):	134
3.2.5.3. Synthesis of 3,5,5-Trimethyl-3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (61):	135

a. Via Conjugate Addition of the Cuprate Reagent 15 to Isophorone (55) in the Presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$:	135
b. Via Conjugate Addition of the Cuprate Reagent 15 to Isophorone (55) in the Presence of TMSBr :	136
c. Via Conjugate Addition of the Cuprate Reagent 15 to Isophorone (55) in the Presence of TMSCl and $\text{BF}_3 \cdot \text{Et}_2\text{O}$:	136
d. Via Conjugate Addition of the Cuprate Reagent 15 to Isophorone (55) in the Presence of TMSBr and $\text{BF}_3 \cdot \text{Et}_2\text{O}$:	137
3.2.5.4. Synthesis of (3 <i>R</i> , 5 <i>R</i>)-2-Methyl-5-(1-methylethenyl)-3-[3-(trimethylgermyl)-3-butenyl]-cyclohexanone (62): ..	137
3.2.5.5. Synthesis of 2-Carbomethoxy-3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (63):	138
3.2.5.6. Synthesis of (3 <i>R</i> , 5 <i>R</i>)-2,3-Dimethyl-5-(1-methylethenyl)-1-trimethylsiloxycyclo-hexene (70) and (2 <i>S</i> , 3 <i>R</i> , 5 <i>R</i>)-2-(2-Bromo-2-propenyl)-2,3-dimethyl-5-(1-methylethenyl)cyclo-hexanone (71):.....	139
3.2.6. GENERAL PROCEDURE 2A: PREPARATION OF THE KETO VINYL IODIDES FROM THE CORRESPONDING KETO VINYLGERMANES	141
3.2.6.1. Synthesis of 3-(3-Iodo-3-butenyl)cyclohexanone (64): .	142
3.2.6.2. Synthesis of 3-(3-Iodo-3-butenyl)-3,5,5-trimethyl-cyclohexanone (66):	143
3.2.6.3. Synthesis of (3 <i>R</i> , 5 <i>R</i>)-3-(3-Iodo-3-butenyl)-2-methyl-5-(1-methylethenyl)cyclo-hexanone (67):	144
3.2.6.4. Synthesis of 2-Carbomethoxy-3-(3-iodo-3-butenyl)-cyclohexanone (68):	145
3.2.7. GENERAL PROCEDURE 2B: PREPARATION OF THE KETO VINYL IODIDES FROM THE CORRESPONDING KETO VINYLGERMANES	141
3.2.7.1. Synthesis of 3-(3-Iodo-3-butenyl)-3-methylcyclo-hexanone (65):.....	142
3.2.8. GENERAL PROCEDURE 3: Pd(0)-CATALYZED CYCLIZATION REACTION OF THE KETO VINYL IODIDES	146
3.2.8.1. Synthesis of 9-Methylbicyclo[4.3.0]non-9-en-2-one (74):	146

a. Via the Pd(0)-Catalyzed Cyclization Reaction Described in General Procedure 3:	146
b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (high dilution (0.008 M)):	147
c. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (high dilution (0.008 M) and no <i>t</i> -BuOH present in the base mixture):	147
3.2.8.2. Synthesis of 6,9-Dimethylbicyclo[4.3.0]non-9-en-2- one (75):	148
3.2.8.3. Synthesis of 4,4,6,9-Tetramethylbicyclo[4.3.0]non-9- en-2-one (76):	149
3.2.8.4. Synthesis of (1 <i>S</i> , 4 <i>R</i> , 6 <i>R</i>)-1-Methyl-9-methylene-4-(1- methylethenyl)bicyclo[4.3.0]-nonan-2-one (77):	150
a. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 19 mol% Pd(PPh ₃) ₄ :	150
b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 15 mol% Pd(PPh ₃) ₄ :	150
c. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 10 mol% Pd(PPh ₃) ₄ :	151
d. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 5 mol% Pd(PPh ₃) ₄ :	151
e. Via the Pd(0)-Catalyzed Cyclization Reaction Employing CuCl as an Additive:	151
f. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd ₂ (dba) ₃ /PPh ₃ as the Catalyst:	152
g. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd ₂ (dba) ₃ /Ph ₃ As as the Catalyst:	152
h. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd ₂ (dba) ₃ /Tri(2-furyl)-phosphine (67a) as the Catalyst:	153
i. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd ₂ (dba) ₃ /Triisopropyl-phosphite (67b) as the Catalyst:	153
j. Via the Pd(0)-Catalyzed Cyclization Reaction Employing PdCl ₂ (dppf) as the Catalyst:	154

k. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd(OAc) ₂ /PPh ₃ as the Catalyst:	154
l. Via the Cyclization Reaction Employing a Stoichiometric Amount of Ni(COD) ₂ :	155
3.2.8.5. Synthesis of (1 <i>R</i> *, 6 <i>S</i> *)-1-Carbomethoxy-9- methylenebicyclo[4.3.0]nonan-2-one (78):	156
a. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd(PPh ₃) ₄ as the Catalyst and Cs ₂ CO ₃ as the Base:	156
b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd ₂ (dba) ₃ /PPh ₃ as the Catalyst and Cs ₂ CO ₃ as the Base:	157
3.2.8.6. Synthesis of (1 <i>S</i> , 2 <i>R</i> , 4 <i>R</i> , 5 <i>S</i>)-1,2-Dimethyl-6- methylene-4-(1-methylethenyl)bicyclo-[3.2.1]heptan- 8-one (81):	158
3.3. ATTEMPTS AT SYNTHESIS OF SIX-MEMBERED RINGS VIA A PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING REACTION	160
3.3.1. SYNTHESIS OF 5-iodo-2-trimethylgermyl-1- pentene (31) VIA THE CORRESPONDING VINYLSTANNANE COMPOUND	160
3.3.1.1. Synthesis of 5-Chloro-2-trimethylstannyl-1-pentene (83a):	160
3.3.1.2. Synthesis of 5-Iodo-2-trimethylgermyl-1-pentene (31):	161
3.3.2. SYNTHESIS OF THE CUPRATE REAGENT 87 AND THE KETO VINYLGERMANES	162
3.3.2.1. Synthesis of 3-[4-(Trimethylgermyl)-4-pentenyl]- cyclohexanone (85):	162
3.3.2.2. Synthesis of (3 <i>R</i> , 5 <i>R</i>)-2-Methyl-5-(1-methylethenyl)-3- [4-(trimethylgermyl)-4-pentenyl]-cyclohexanone (86):	164
3.3.3. SYNTHESIS OF THE KETO VINYL IODIDES	165
3.3.3.1. Synthesis of 3-(4-Iodo-4-pentenyl)cyclohexanone (91):	165
3.3.3.2. Synthesis of (3 <i>R</i> , 5 <i>R</i>)-3-(4-Iodo-4-pentenyl)-2-methyl- 5-(1-methylethenyl)cyclohexanone (92):	166

3.3.4. CYCLIZATION REACTIONS TO FORM SIX-MEMBERED RINGS	167
3.3.4.1. Synthesis of 10-Methylbicyclo[4.4.0]dec-10-en-2-one (93):	167
a. Via the Pd(0)-Catalyzed Cyclization Reaction Conditions Described in General Procedure 3:	167
b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (0.02 M dilution and no <i>t</i> -BuOH present in the base mixture):	167
c. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (0.004 M dilution and no <i>t</i> -BuOH present in the base mixture):	168
3.3.4.2. Synthesis of (4 <i>R</i> , 6 <i>R</i>)-1-Methyl-10-methylene-4-(1-methylethenyl)bicyclo[4.4.0]decan-2-one (94):	169
3.4. THE FORMATION OF TRICYCLIC RING SYSTEMS EMPLOYING THE ANNULATION METHOD BASED ON THE PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING	170
3.4.1. SYNTHESIS OF THE BICYCLIC ENONES:	170
3.4.1.1. Synthesis of 3-[2-(1,3-Dioxan-2-yl)ethyl]cyclohexanone (102):	170
3.4.1.2. Synthesis of Bicyclo[4.3.0]non-9-en-2-one (95):	171
3.4.1.3. Synthesis of 3-[2-(1,3-Dioxan-2-yl)ethyl]-3-methylcyclohexanone (103):	172
3.4.1.4. Synthesis of 6-Methylbicyclo[4.3.0]non-9-en-2-one (96):	174
3.4.2. SYNTHESIS AND EPIMERIZATION OF THE BICYCLIC KETO VINYLGERMANES	175
3.4.2.1. Synthesis of (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-Methyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (130a) and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-Methyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (130b):	175
3.4.2.2. Epimerization of compounds 130a and 130b :	180
3.2.2.3. Synthesis of (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-6,9-Dimethyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (131a) and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-6,9-Dimethyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-	

one (131b):	181
3.4.2.4. Epimerization of compounds 131a and 131b :	185
3.4.2.5. Synthesis of (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (132a) and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-[3-(trimethylgermyl)-3-butenyl]-bicyclo[4.3.0]-nonan-2-one (132b):	186
3.4.2.6. Epimerization of compounds 132a and 132b :	189
3.4.2.7. Synthesis of (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-6-Methyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo-[4.3.0]nonan-2-one (133a) and (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-6-Methyl-9-[3-(trimethylgermyl)-3-butenyl]-bicyclo[4.3.0]nonan-2-one (133b):	190
3.4.2.8. Epimerization of compounds 133a and 133b :	196
3.4.3. CONVERSION OF THE BICYCLIC KETO VINYL-GERMANES INTO THE CORRESPONDING KETO VINYL IODIDES	197
3.4.3.1. Synthesis of (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-(3-Iodo-3-butenyl)-9-methylbicyclo[4.3.0]nonan-2-one (135a) and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-(3-Iodo-3-butenyl)-9-methylbicyclo-[4.3.0]nonan-2-one (135b):	197
3.4.3.2. Synthesis of (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-6,9-Dimethyl-9-(3-iodo-3-butenyl)bicyclo[4.3.0]nonan-2-one (136):	199
3.4.3.3. Synthesis of (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-(3-Iodo-3-butenyl)-bicyclo[4.3.0]nonan-2-one (137a) and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-(3-Iodo-3-butenyl)bicyclo[4.3.0]nonan-2-one (137b):	200
3.4.3.4. Synthesis of (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-(3-Iodo-3-butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (138a) and (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>S</i> *)-9-(3-Iodo-3-butenyl)-6-methylbicyclo-[4.3.0]nonan-2-one (138b):	202
3.4.4. Pd(0)-CATALYZED CYCLIZATION REACTIONS OF THE BICYCLIC VINYL IODIDES TO PRODUCE TRICYCLIC RING SYSTEMS	204
3.4.4.1. Synthesis of (1 <i>S</i> *, 5 <i>S</i> *, 8 <i>S</i> *)-5-Methyl-2-methylenetricyclo[6.4.0.0 ^{1,5}]dodecan-12-one (139) and (1 <i>S</i> *, 4 <i>S</i> *, 7 <i>R</i> *, 11 <i>S</i> *)-1-Methyl-8-methylenetricyclo-[5.3.2.0 ^{4,11}]dodecan-12-one (140):	204
a. Via a Pd(0)-Catalyzed Cyclization of the Cis-Fused Vinyl Iodide 135a :	204

b. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide 135b :	210
c. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide 135b employing modified reaction conditions:	210
3.4.4.2. Synthesis of (1 <i>S</i> *, 5 <i>S</i> *, 8 <i>S</i> *, 12 <i>S</i> *)-5-Methyl-2-methylenetricyclo[6.4.0.0 ^{1,5}]dodecan-12-ol (142):	211
3.4.4.3. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 7 <i>R</i> *, 11 <i>S</i> *, 12 <i>S</i> *)-1-Methyl-8-methylenetricyclo[5.3.2.0 ^{4,11}]dodecan-12-ol (144):	212
3.4.4.4. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 7 <i>R</i> *, 11 <i>S</i> *, 12 <i>S</i> *)-1-Methyl-8-methylene-12- <i>p</i> -nitrobenzoyloxytricyclo[5.3.2.0 ^{4,11}]-dodecane (145):	215
3.4.4.5. Synthesis of (1 <i>R</i> *, 4 <i>S</i> *, 7 <i>R</i> *, 11 <i>S</i> *)-1,4-Dimethyl-8-methylenetricyclo[5.3.2.0 ^{4,11}]-dodecan-12-one (146):	217
3.4.4.6. Synthesis of (1 <i>R</i> *, 5 <i>S</i> *, 8 <i>S</i> *)-2-Methylenetricyclo[6.4.0.0 ^{1,5}]dodecan-12-one (147) and (1 <i>S</i> *, 4 <i>R</i> *, 7 <i>R</i> *, 11 <i>S</i> *)-8-Methylenetricyclo[5.3.2.0 ^{4,11}]dodecan-12-one (148):	220
a. Via a Pd(0)-Catalyzed Cyclization of the Cis-Fused Vinyl Iodide 137a :	220
b. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide 137b :	223
3.4.4.7. Synthesis of (1 <i>R</i> *, 4 <i>R</i> *, 7 <i>R</i> *, 11 <i>R</i> *)-4-Methyl-8-methylenetricyclo[5.3.2.0 ^{4,11}]-dodecan-12-one (149) and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>R</i> *)-9-(3-Butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (150):	224
a. Via a Pd(0)-Catalyzed Cyclization of the Cis-Fused Vinyl Iodide 138a :	224
b. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide 138b :	227
3.5. SYNTHESIS OF TRICYCLIC COMPOUNDS BEARING AN ALLYLIC, ANGULAR HYDROXYL GROUP	228
3.5.1. GENERAL PROCEDURE 4: CYCLIZATION REACTIONS OF THE KETO VINYL IODIDES VIA A METAL-HALOGEN EXCHANGE REACTION	228
3.5.1.1. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>R</i> *)-1-Methyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (154):	228

3.5.1.2. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>S</i> *)-1-Methyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (157), (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>S</i> *, 12 <i>S</i> *)-1-Methyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (158), and (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>R</i> *)-9-(3-Butenyl)-9-methylbicyclo[4.3.0]nonan-2-one (159):	233
3.5.1.3. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>S</i> *)-1,4-Dimethyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (160) and (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>R</i> *)-9-(3-Butenyl)-6,9-dimethylbicyclo[4.3.0]nonan-2-one (161):	239
3.5.1.4. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>R</i> *)-9-Methylene-tricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (155):	246
3.5.1.5. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>S</i> *)-9-Methylene-tricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (162), (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>S</i> *, 12 <i>S</i> *)-9-Methylene-tricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (163), and (1 <i>S</i> *, 6 <i>S</i> *, 9 <i>R</i> *)-9-(3-Butenyl)bicyclo[4.3.0]nonan-2-one (164):	250
3.5.1.6. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>S</i> *)-4-Methyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (156):	256
3.5.1.7. Synthesis of (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>R</i> *, 12 <i>R</i> *)-4-Methyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (165), (1 <i>S</i> *, 4 <i>S</i> *, 8 <i>S</i> *, 12 <i>R</i> *)-4-Methyl-9-methylenetricyclo[6.3.1.0 ^{4,12}]dodecan-8-ol (166), and (1 <i>R</i> *, 6 <i>S</i> *, 9 <i>R</i> *)-9-(3-Butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (167):	260

PART 2: TOTAL SYNTHESIS OF (-)-HOMALOMENOLS A AND B.

I. INTRODUCTION	266
1.1. GENERAL	266
1.2. PROPOSAL	266
II. DISCUSSION	270
2.1. RETROSYNTHETIC ANALYSIS	270
2.2. SYNTHESIS OF (-)-HOMALOMENOL B (169b)	272

2.2.1. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS ALLYLIC ACETATE 181b	272
2.2.2. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS BICYCLIC ENONE 177b	279
2.2.3. SYNTHESIS OF THE BICYCLIC KETONE 176b	285
2.2.4. SYNTHESIS OF (-)-HOMALOMENOL B (169b)	291
2.3. SYNTHESIS OF (-)-HOMALOMENOL A (168b)	295
2.3.1. PREPARATION OF THE BICYCLIC KETONE 175b	295
2.3.1.1. Model Studies for the Preparation of Reagent 178	295
2.3.1.2. Literature Precedent on the Effects of Various Additives on the Stereoselectivity of Conjugate Addition Reactions.	297
2.3.1.3. Conjugate Addition of the Cuprate Reagents 178 and 203 to the Bicyclic Enone 177b	300
2.3.2. SYNTHESIS OF (-)-HOMALOMENOL A (168b)	307
2.3.3. SYNTHESIS OF THE (-)-MONOACETATE 215	310
2.4. CONCLUSION	313

III. EXPERIMENTAL

3.1. SYNTHESIS OF (-)-HOMALOMENOL B (169b)	315
3.1.1. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS ALLYLIC ACETATE 181b	315
3.1.1.1. Synthesis of 3-Methyl-3-cyclohexen-1-one (182):	315
3.1.1.2. Synthesis of 1-Methyl-7-oxabicyclo[4.1.0]heptan-3- one (185):	317
3.1.1.3. Synthesis of 4-Acetoxy-3-methyl-2-cyclohexen-1-one (181):	318
3.1.1.4. Synthesis of (<i>R</i>)-(+)-4-Hydroxy-3-methyl-2- cyclohexen-1-one (186a) and (<i>S</i>)-(-)-4-Acetoxy-3- methyl-2-cyclohexen-1-one (181b):	319
3.1.1.5. Synthesis of the ester 188b :	321
3.1.2. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS BICYCLO[4.3.0] ENONE 177b	323

3.1.2.1. Synthesis of (<i>S</i>)-(+)-4-(tert-Butyldiphenylsiloxy)-3-methyl-2-cyclohexen-1-one (180b):	323
3.1.2.2. Synthesis of (3 <i>S</i> , 4 <i>S</i>)-(+)-4-(tert-Butyldiphenylsiloxy)-3-[2-(1,3-dioxan-2-yl)ethyl]-3-methylcyclohexanone (189):	325
3.1.2.3. Synthesis of (5 <i>S</i> , 6 <i>S</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-6-methylbicyclo[4.3.0]non-9-en-2-one (177b):	328
3.1.2.4. Synthesis of 2-methyl-3-(tri- <i>n</i> -butylstannyl)propene (194):	330
3.1.3. PREPARATION OF THE BICYCLIC KETONE 176b	331
3.1.3.1. Synthesis of (1 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-6-methyl-9-(methallyl)bicyclo[4.3.0]nonan-2-one (196) and (1 <i>S</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-6-methyl-9-(methallyl)-bicyclo[4.3.0]nonan-2-one (176b):	331
3.1.3.2. Epimerization of compound 176b :	336
3.1.4. SYNTHESIS OF (-)-HOMALOMENOL B (169b)	337
3.1.4.1. Synthesis of (1 <i>S</i> , 2 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-2,6-dimethyl-9-(methallyl)-bicyclo[4.3.0]nonan-2-ol (197):	337
3.1.4.2. Synthesis of (-)-Homalomenol B (169b):	340
3.2. ROUTE TO THE SYNTHESIS OF (-)-HOMALOMENOL A (168b) .	344
3.2.1. PREPARATION OF THE BICYCLIC KETONE 175b	344
3.2.1.1. Synthesis of 1-Iodo-2-methylpropene (202):	344
3.2.1.2 Synthesis of (1 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>R</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (213), (1 <i>S</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (175b), and (1 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-(tert-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (212):	346
a. Via Conjugate Addition of the Cuprate Reagent 178 to the Enone 177b in the Presence of TMSBr and BF ₃ •Et ₂ O; General Procedure 5:	346

b. Via Conjugate Addition of the Cuprate Reagent 178 to the Enone 177b in the Presence of TMSBr at -78 °C:	353
c. Via Conjugate Addition of the Cuprate Reagent 178 to the Enone 177b in the Presence of TMSBr at -78 °C to -10 °C:	353
3.2.2. SYNTHESIS OF (-)-HOMALOMENOL A (168b)	355
3.2.2.1. Synthesis of (1 <i>S</i> , 2 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-(tert-Butyl- diphenylsiloxy)-2,6-dimethyl-9-(2-methyl-1- propenyl)bicyclo[4.3.0]nonan-2-ol (214):	355
3.2.2.2. Synthesis of (-)-Homalomenol A (168b):	357
3.2.3. SYNTHESIS OF (1 <i>S</i> , 2 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> , 9 <i>S</i>)-(-)-5-ACETOXY-2,6- DIMETHYL-9-(2-METHYL-1-PROPENYL)-BICYCLO- [4.3.0]NONAN-2-OL (215):	361
IV. REFERENCES AND FOOTNOTES	363
V. APPENDIX	374
5.1. APPENDIX 1: X-RAY CRYSTALLOGRAPHIC DATA	374

LIST OF TABLES

Table	Page
1. Preparation of the Cyclization Substrates	20
2. Palladium(0)-Catalyzed Cyclization Reactions of the Keto Vinyl Iodides	25
3. The Effects of Different Catalysts on the Cyclization Reaction	29
4. Attempts at the Synthesis of Bridged Bicyclic Ketones using the Pd(0)-Catalyzed Cyclization Reaction	33
5. Preparation of the Cyclization Precursors for the Six-Membered Ring Annulation Sequence	41
6. Attempts at Six-Membered Ring Formation by Employing the Pd(0)-Catalyzed Cyclization Reaction	43
7. Preparation of the Bicyclic Enones 95 and 96 According to a Modified Version of Helquist's Annulation Sequence	48
8. Results of the Conjugate Addition Reactions of Reagent 15 to the Bicyclo-[4.3.0]non-9-en-2-ones	58
9. Consistent IR and ^1H nmr Differences Between the Cis-Fused and Trans-Fused Vinylgermane Epimers	69
10. The Thermodynamically Controlled Equilibration of the Cis- and Trans-fused Bicyclo[4.3.0]nonan-2-ones	71
11. Equilibration Studies of the Vinylgermane Bicyclo[4.3.0]nonan-2-ones	73
12. Conversion of the Keto Vinylgermanes into the Corresponding Keto Vinyl Iodides	75
13. Differences in the Position of the Carbonyl Absorbances in the Cis- and Trans-Fused Vinyl Iodides	78
14. Cyclization Studies in Forming Fused and Bridged Tricyclic Keto Alkenes	94
15. Cyclization Reactions of the Trans-Fused Vinyl Iodides to Yield Tricyclic Compounds Bearing an Allylic, Angular Hydroxyl Group	104
16. Δ ppm for those Protons in a 1,3-Diaxial Relationship with the Angular Hydroxyl Group	109
17. Cyclization Reactions of the Cis-Fused Vinyl Iodides to Yield Tricyclic Compounds Bearing an Allylic, Angular Hydroxyl Group	110
18. Δ ppm for those Protons in Close Proximity to the Angular Hydroxyl Group in the Beta-OH Products	112

19.	Differences in the Chemical Shift of the Vinyl Proton H-x' Between the Beta-OH and Alpha-OH Products	114
20.	¹ H nmr Data (400 MHz, CDCl ₃) for the Bridged Keto Alkene 81 : COSY and NOE Experiments	159
21.	¹ H nmr Data (400 MHz, C ₆ D ₆) for the Trans-Fused Compound 130b : COSY Experiment	177
22.	¹ H nmr Data (400 MHz, acetone-d ₆) for the Cis-Fused Compound 130a : COSY and NOE Experiments	179
23.	¹ H nmr Data (400 MHz, acetone-d ₆) for the Cis-Fused Vinylgermane Compound 131a : COSY and NOE Experiments	184
24.	¹ H nmr Data (400 MHz, CDCl ₃) for the Cis-Fused Vinylgermane Compound 132a : COSY and NOE Experiments	188
25.	¹ H nmr Data (400 MHz, C ₆ D ₆) for the Trans-Fused Vinylgermane Compound 133b : COSY and NOE Experiments	192
26.	¹ H nmr Data (400 MHz, C ₆ D ₆) for the Cis-Fused Vinylgermane Compound 133a : COSY and NOE Experiments	194
27.	¹ H nmr (500 MHz, C ₆ D ₆) and ¹³ C nmr (125.8 MHz, C ₆ D ₆) Data for the Cis-Fused Vinylgermane Compound 133a : HMQC and HMBC Experiments	195
28.	¹ H nmr Data (400 MHz, CDCl ₃) for the Fused Tricyclic Compound 139 : COSY and NOE Experiments	206
29.	¹ H nmr Data (400 MHz, CDCl ₃) for the Bridged Tricyclic Compound 140 : COSY and NOE Experiments	208
30.	¹ H nmr (500 MHz, CDCl ₃) and ¹³ C nmr (125.8 MHz, CDCl ₃) Data for the Bridged Compound 140 : HMQC and HMBC Experiments	209
31.	¹ H nmr Data (400 MHz, CDCl ₃) for the Bridged Alcohol 144 : COSY Experiment	214
32.	¹ H nmr Data (400 MHz, C ₆ D ₆) for the Bridged Compound 146 : COSY and NOE Experiments	219
33.	¹ H nmr Data (400 MHz, CDCl ₃) for the Fused Tricyclic Compound 147 : COSY and NOE Experiments	222
34.	¹ H nmr Data (400 MHz, C ₆ D ₆) for the Bridged Compound 149 : COSY and NOE Experiments	226

35.	^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound 154 : COSY Experiment	231
36.	^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound 154 : COSY Experiment	231
37.	Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound 154 in CDCl_3 vs. Pyridine- d_5	232
38.	^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound 158 : COSY and NOE Experiments	234
39.	^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound 157 : COSY Experiment	237
40.	^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound 157 : COSY Experiment	237
41.	Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound 157 in CDCl_3 vs. Pyridine- d_5	238
42.	^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound 160 : COSY Experiment	242
43.	^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound 160 : COSY and NOE Experiments	242
44.	Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound 160 in CDCl_3 vs. Pyridine- d_5	243
45.	^1H nmr (500 MHz, CDCl_3) and ^{13}C nmr (100.4 MHz, CDCl_3) Data for the Tricyclic Compound 160 : HMQC and HMBC Experiments.....	244
46.	^1H nmr (500 MHz, pyridine- d_5) and ^{13}C nmr (125.8 MHz, pyridine- d_5) Data for the Tricyclic Compound 160 : HMQC and HMBC Experiments	245
47.	^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound 155 : COSY Experiment	248
48.	^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound 155 : COSY Experiment	248
49.	Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound 155 in CDCl_3 vs. Pyridine- d_5	249
50.	^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound 163 : COSY Experiment	251

51.	¹ H nmr Data (400 MHz, CDCl ₃) for the Tricyclic Compound 162 : COSY Experiment	254
52.	¹ H nmr Data (400 MHz, pyridine-d ₅) for the Tricyclic Compound 162 : COSY Experiment	254
53.	Comparison of the ¹ H nmr (400 MHz) Chemical Shifts of Compound 162 in CDCl ₃ vs. Pyridine-d ₅	255
54.	¹ H nmr Data (400 MHz, CDCl ₃) for the Tricyclic Compound 156 : COSY Experiment	258
55.	¹ H nmr Data (400 MHz, pyridine-d ₅) for the Tricyclic Compound 156 : COSY Experiment	258
56.	Comparison of the ¹ H nmr (400 MHz) Chemical Shifts of Compound 156 in CDCl ₃ vs. Pyridine-d ₅	259
57.	¹ H nmr Data (400 MHz, CDCl ₃) for the Tricyclic Compound 166 : COSY Experiment	261
58.	¹ H nmr Data (400 MHz, CDCl ₃) for the Tricyclic Compound 165 : COSY Experiment	264
59.	¹ H nmr Data (400 MHz, pyridine-d ₅) for the Tricyclic Compound 165 : COSY Experiment	264
60.	Comparison of the ¹ H nmr (400 MHz) Chemical Shifts of Compound 165 in CDCl ₃ vs. Pyridine-d ₅	265
61.	Attempts to Cyclize Keto Acetal 189 to Form the Bicyclic Enone 177b	283
62.	The Effects of Additives on the Conjugate Addition of Reagents 178 or 203 to the Enone 177b	301
63.	¹ H nmr Data (400 MHz, CDCl ₃) for the Keto Acetal 189 : COSY Experiment	327
64.	¹ H nmr Data (400 MHz, CDCl ₃) for the Trans-Fused Compound 176b : COSY and NOE Experiments	333
65.	¹ H nmr Data (400 MHz, CDCl ₃) for the Cis-Fused Compound 196 : COSY and NOE Experiments	335
66.	¹ H nmr Data (400 MHz, CDCl ₃) for the Tertiary Alcohol 197 : COSY and NOE Experiments	339
67.	¹ H nmr Data (400 MHz, CDCl ₃) for (-)-Homalomenol B (169b): COSY and NOE Experiments	342

68.	Comparison of the Reported Spectral Data for (+)-Homalomenol B (169a) with that of the Synthetic (-)-Homalomenol B (169b)	343
69.	¹ H nmr Data (400 MHz, CDCl ₃) for Compound 175b : COSY and NOE Experiments	350
70.	¹ H nmr Data (400 MHz, CDCl ₃) for Compound 212 : COSY and NOE Experiments	352
71.	¹ H nmr Data (400 MHz, CDCl ₃) for (-)-Homalomenol A (168b): COSY and NOE Experiments	359
72.	Comparison of the Reported Spectral Data for (+)-Homalomenol A (168a) with that of the Synthetic (-)-Homalomenol A (168b)	360
73.	Comparison of the Reported Spectral Data for the (+)-Monoacetate 215 with that of the Synthetic Monoacetate 215	362

LIST OF FIGURES

Figure	Page
1. The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Cis-Fused Vinylgermane 133a	64
2. The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Trans-Fused Vinylgermane 133b	66
3. The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Cis-Fused Vinyl Iodide 138a	76
4. The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Trans-Fused Vinyl Iodide 138b	77
5. The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Fused Keto Alkene 139	83
6. The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Bridged Keto Alkene 140	86
7. The ^1H nmr Spectrum (400 MHz) of the Tricyclic Alcohol 154 in a) CDCl_3 and b) pyridine- d_5	106
8. The ^1H nmr Spectra (400 MHz, CDCl_3) of 188a and 188b in a) the absence and b) presence of $\text{Eu}(\text{fod})_3$	276
9. The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Cis-Fused Ketone 196	287
10. The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Trans-Fused Ketone 176b ...	289
11. The ^1H nmr Spectrum (400 MHz, CDCl_3) of (-)-Homalomenol B (169b)	294
12. The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Trans-Fused Ketone 175b ...	304
13. The ^1H nmr Spectrum (400 MHz, CDCl_3) of (-)-Homalomenol A (168b)	309
14. The ^1H nmr Spectrum (400 MHz, CDCl_3) of the (-)-Monoacetate 215	311
15. The ^1H nmr Spectrum (200 MHz, CDCl_3) of the (+)-Monoacetate 215 from Dr. T. V. Sung	312

LIST OF GENERAL PROCEDURES

General Procedure	Page
1. Preparation of the Keto Vinylgermanes	132
2a. Preparation of the Keto Vinyl Iodides from the Corresponding Keto Vinylgermanes	141
2b. Preparation of the Keto Vinyl Iodides from the Corresponding Keto Vinylgermanes	141
3. Pd(0)-Catalyzed Cyclization Reaction of the Keto Vinyl Iodides	146
4. Cyclization Reactions of the Keto Vinyl Iodides Via a Metal-Halogen Exchange Reaction	228
5. The Conjugate Addition of the Cuprate Reagent 178 to the Enone 177b	346

LIST OF ABBREVIATIONS

Å	-	angstrom(s)
α	-	1,2 relative position
$[\alpha]_D^t$	-	specific rotation at the sodium D line (589.3 nm) and at the temperature t
Ac	-	acetyl or acetate
anal.	-	analysis
APT	-	attached proton test
aq	-	aqueous
β	-	1,3 relative position
br	-	broad
BnBr	-	benzyl bromide
Bu	-	butyl
c	-	concentration in g/100 mL
calcd.	-	calculated
COSY	-	(^1H - ^1H homonuclear) correlation spectroscopy
C-x	-	carbon number x
d	-	doublet
δ	-	chemical shift in parts per million from TMS
Δ	-	reflux
$\Delta\delta$	-	chemical shift difference
dba	-	dibenzilideneacetone
DCC	-	<i>N,N</i> -dicyclohexylcarbodiimide
DEG	-	diethyleneglycol
DIBAL	-	diisobutylaluminum hydride
DMAP	-	4-dimethylaminopyridine
DMF	-	<i>N,N</i> -dimethylformamide

DMSO	-	dimethylsulfoxide
dppf	-	1,1'-bis(diphenylphosphino)ferrocene
Ed., Eds.	-	editor, editors
equiv.	-	equivalent
Et	-	ethyl
FT	-	Fourier transform
γ	-	1,4 relative position
glc	-	gas liquid chromatography
HMBC	-	heteronuclear multiple bond coherence
HMPA	-	hexamethylphosphoramide
HMQC	-	heteronuclear multiple quantum coherence
H.O.	-	higher order
HRMS	-	high resolution mass spectroscopy
H-x	-	hydrogen number x
<i>i</i>	-	iso
IR	-	infrared
<i>J</i>	-	coupling constant in Hz
LDA	-	lithium diisopropylamide
lit.	-	literature
L.O.	-	lower order
LRMS	-	low resolution mass spectroscopy
m	-	multiplet
<i>m</i>	-	meta
<i>m</i> -CPBA	-	<i>m</i> -chloroperbenzoic acid
Me	-	methyl
nmr	-	nuclear magnetic resonance
NOE	-	nuclear Overhauser effect

<i>p</i>	-	para
P	-	protecting group
PCC	-	pyridinium chlorochromate
Ph	-	phenyl
pH	-	$-\log_{10} [\text{H}^+]$
PLE	-	pig liver esterase
ppm	-	parts per million
PPTS	-	pyridinium <i>p</i> -toluenesulfonate
Pr	-	propyl
q	-	quartet
R_f	-	retardation factor (ratio of distance traveled by the center of a zone to the distance simultaneously traveled by the mobile phase)
rt	-	room temperature
s	-	singlet
t	-	triplet
<i>t</i>	-	tertiary
TBAF	-	tetrabutylammonium fluoride
TBDPS	-	<i>tert</i> -butyldiphenylsilyl
Th	-	thienyl
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
TMS	-	trimethylsilyl
Tris	-	tris(hydroxymethyl)aminomethane
<i>p</i> -Ts	-	<i>para</i> -toluenesulfonyl
-ve	-	negative
•	-	coordination or complex

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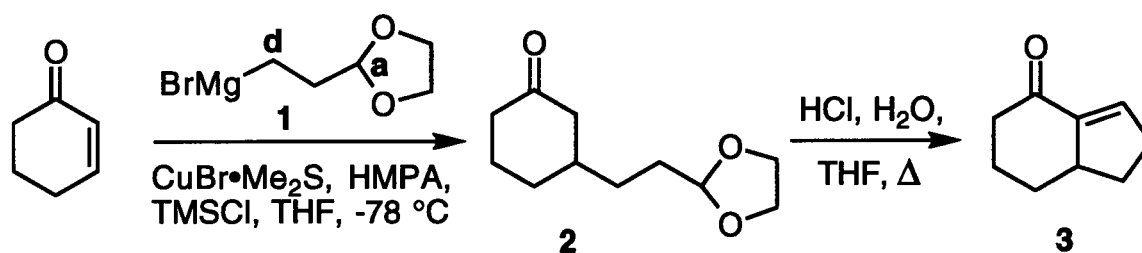
PART 1: ANNULATION SEQUENCES EMPLOYING THE BIFUNCTIONAL CONJUNCTIVE REAGENTS 4-iodo-2-trimethylgermyl-1-butene (13) AND 5-iodo-2-trimethylgermyl-1-pentene (31).

I. INTRODUCTION

1.1. GENERAL

Synthetic organic chemists have always striven to achieve more effective and selective ways to push forward the boundaries of organic synthesis. The construction of complex molecules, for example, has seen a dramatic and continuing growth which has paralleled our increase in knowledge of the chemical sciences. In the past decade there has been a tremendous amount of growth in the design of new synthetic methods for the stereoselective construction of carbon-carbon bonds. In addition to discovering new synthetically useful reactions, the organic chemist faces the challenge of learning to control reactivity so that selectivity of product formation can be accomplished.

The discovery of new and efficient methods for the construction of highly functionalized ring systems is of considerable interest to the synthetic chemist. This objective has, in part, led to the development of bifunctional conjunctive reagents which possess two potentially reactive sites. These bifunctional conjunctive reagents have been defined by Trost¹ as "simple building blocks which are incorporated in whole or in part into a more complex system". The two reactive sites can be either nucleophilic or electrophilic in nature and have been termed "donor" (**d**) and "acceptor" (**a**) sites, respectively.² The bifunctional conjunctive reagents must be constructed to allow the coexistence of the two reactive sites which can be deployed either simultaneously or sequentially. The number of such reagents that have been developed recently are too numerous to mention here.³ The following example⁴ (**Scheme 1**), however, illustrates how such a reagent can be effectively employed in an annulation sequence.

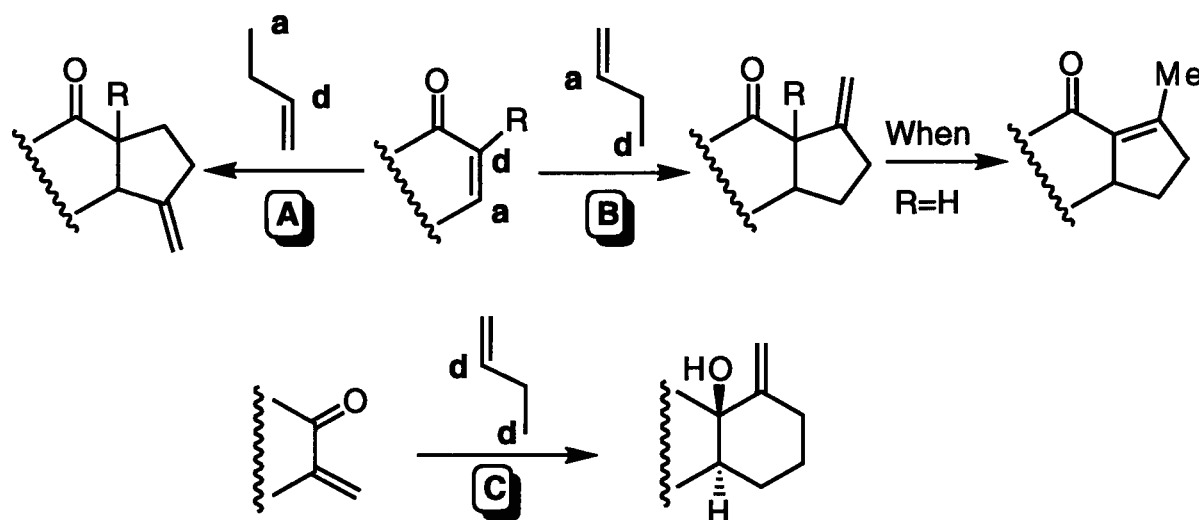


Scheme 1⁴

The bifunctional Grignard reagent **1** serves as the synthetic equivalent of an a¹,d³-synthon.⁵ The acceptor site in the reagent is masked as an acetal and is revealed in the second step of the sequence by conversion of the acetal to an aldehyde moiety. The first step of the sequence deploys the donor site in an intermolecular copper(I)-catalyzed conjugate addition of a Grignard reagent to form the keto acetal **2**. This is followed by an intramolecular aldol condensation to form the bicyclic enone **3**. The use of bifunctional conjunctive reagents to perform similar annulation processes will be the focus of much of the work described in Part 1 of this thesis.

1.2. BACKGROUND

The application of bifunctional reagents to annulation sequences has been studied extensively in our laboratories, and three such sequences are outlined in **Scheme 2**. In each annulation sequence the substrate is an α,β -unsaturated ketone and the bifunctional conjunctive reagent serves as the synthetic equivalent of a 1-butene synthon. The regioisomeric methylenecyclopentane annulation sequences **A**⁶ and **B**⁷ employ synthons which bear umpolung⁸ reactivity. The methylenecyclohexane annulation sequence **C**⁹ employs a 1-butene d^2,d^4 -synthon.

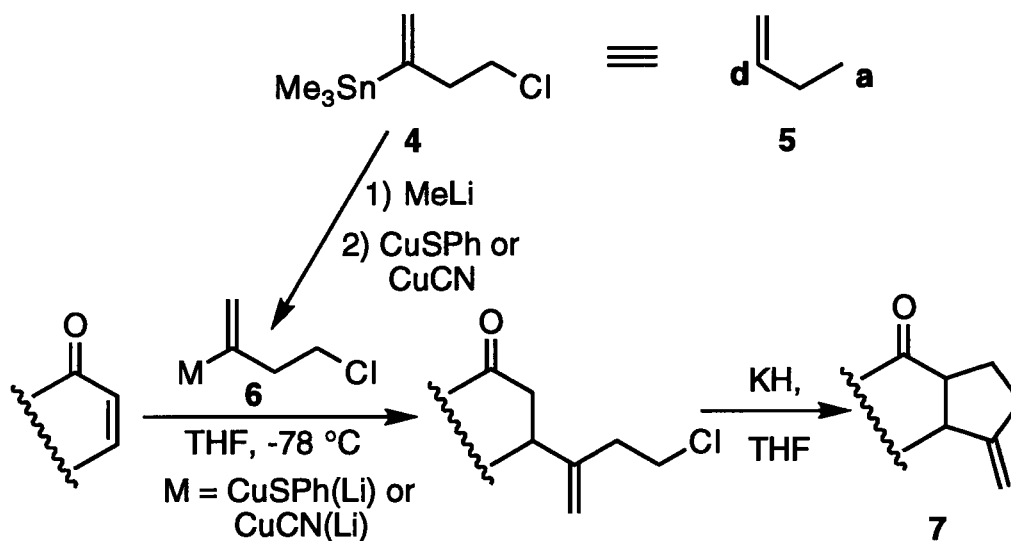


Scheme 2

A discussion of the bifunctional conjunctive reagents developed to carry out the annulation sequences **A**, **B**, and **C** (**Scheme 2**), along with their application to the synthesis of natural products follows.

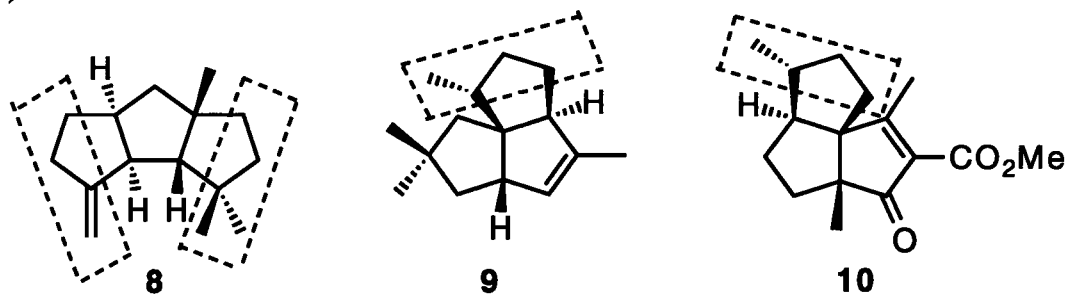
Previous work in our laboratories has led to the development of the methylenecyclopentane annulation sequence shown in **Scheme 3** (see also route **A**, **Scheme 2**).⁶ The bifunctional conjunctive reagent used in this route, 4-chloro-2-trimethylstannyl-1-butene (**4**),¹⁰ serves as the synthetic equivalent of the 1-butene d^2,a^4 -synthon **5**. The latent donor activity of **4** is first unmasked by transmetallation with MeLi. A copper(I) salt is then added, thereby forming the organocopper(I) reagent **6**, which adds in a conjugate fashion to

cyclic enone systems. The acceptor site is then deployed in the subsequent intramolecular alkylation step to generate the bicyclic keto alkene **7**.

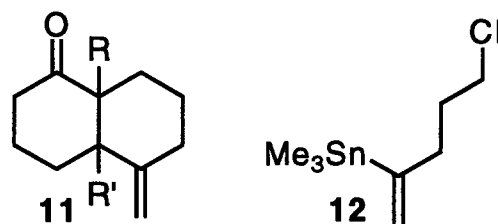


Scheme 3⁶

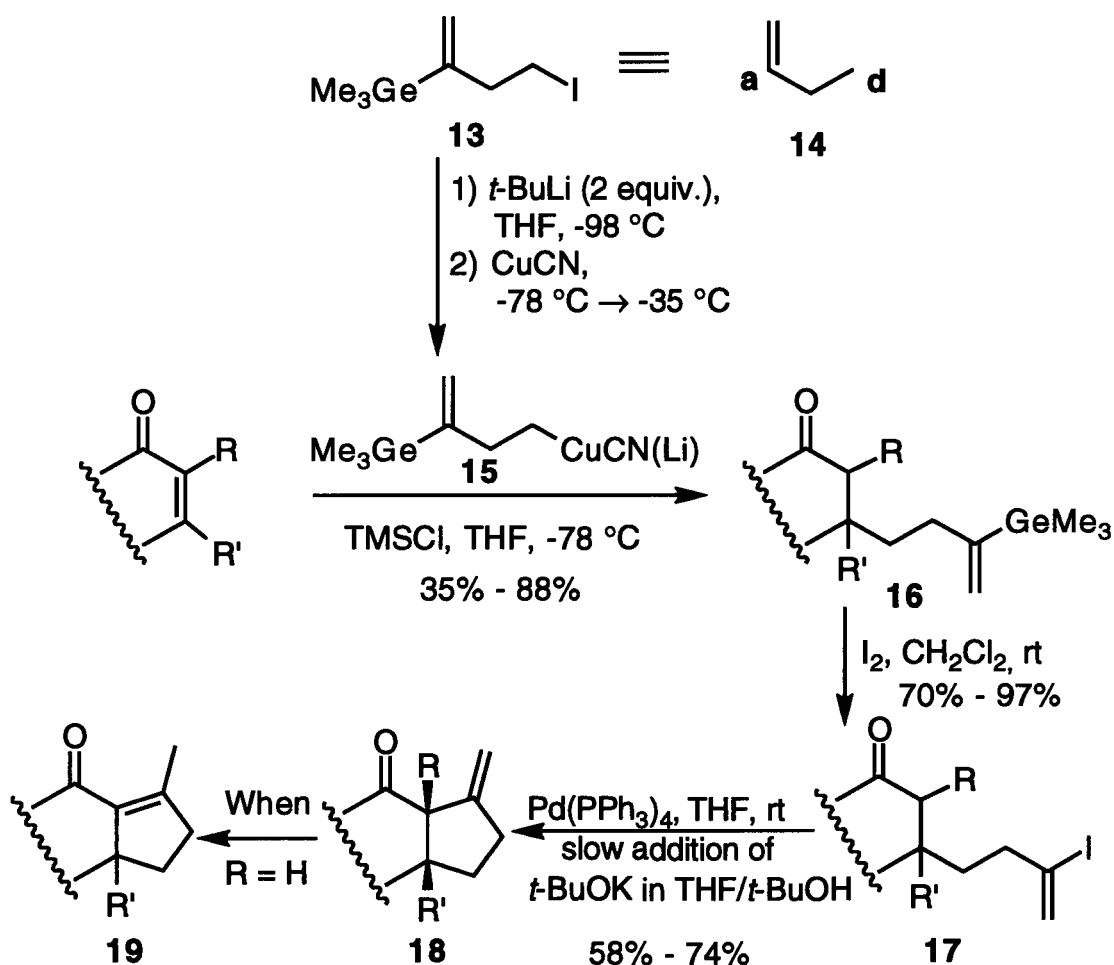
This annulation sequence has been successfully employed in the synthesis of natural products such as (±)- $\Delta^9(12)$ -capnellene (**8**),¹¹ (±)-pentalene (**9**),¹¹ and (±)-methylcantabrenonate (**10**)¹² (the incorporated bifunctional reagent is highlighted in each natural product shown below).



The annulation sequence illustrated in **Scheme 3** has been extended to the formation of six-membered rings (general structure **11**) by employing the bifunctional conjunctive reagent **12** (the one-carbon homologue of reagent **4**).¹³



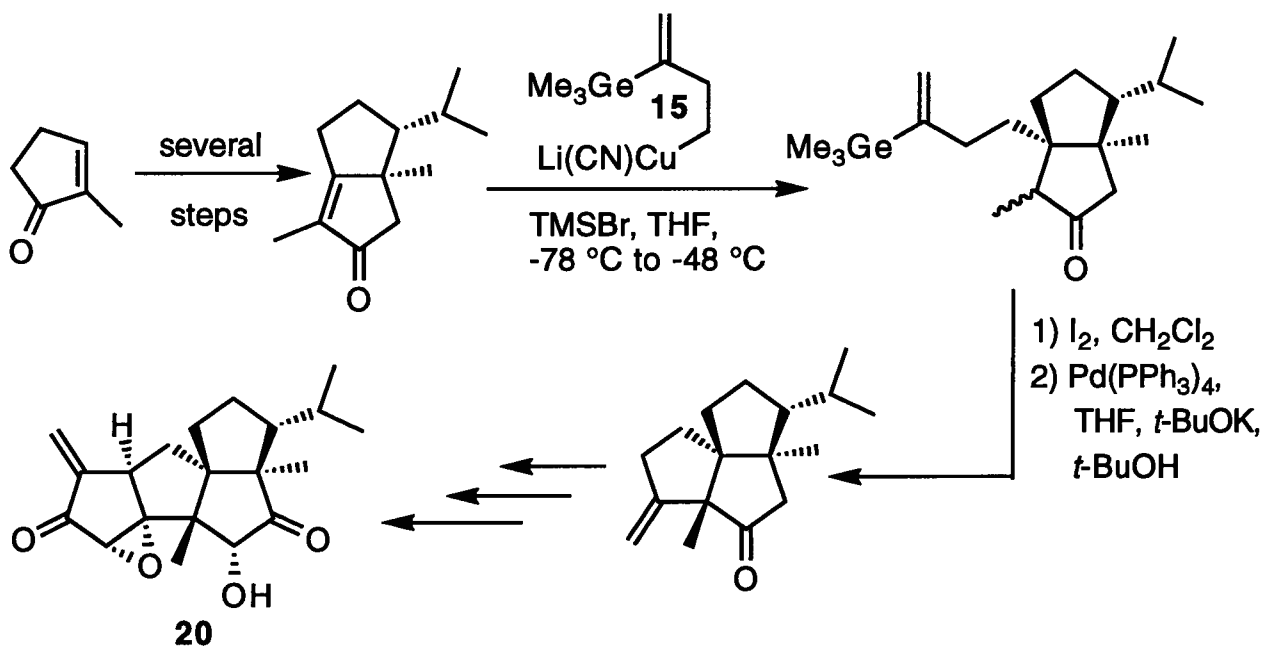
More recently, work in our laboratories⁷ has led to the development of a complementary, regioisomeric methylenecyclopentane annulation procedure (route **B**, **Scheme 2**) using the bifunctional conjunctive reagent **13** (**Scheme 4**). 4-Iodo-2-trimethylgermyl-1-butene (**13**) serves as the synthetic equivalent of the 1-butene a^{2,d^4} -synthon **14** and possesses umpolung reactivity compared with that of the previous synthon **5**. By converting reagent **13** to the organocopper(I) species **15**, the donor site of the bifunctional reagent can be utilized in a 1,4-conjugate addition reaction to an enone.



Scheme 4⁷

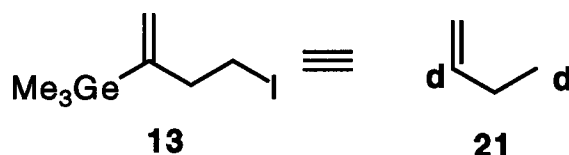
The vinylgermane function in **13** is stable to the lithium-iodine exchange conditions required to generate reagent **15**, in contrast to the more labile vinylstannane moiety.¹⁴ Unmasking of

the acceptor site of the bifunctional reagent **13** is achieved by converting the vinylgermane adduct **16** to the corresponding vinyl iodide **17**. The final step in the annulation sequence employs a Pd(0)-catalyzed coupling reaction between an enolate carbon (donor) and the iodo substituted alkene carbon (acceptor) to generate bicyclic keto alkenes of general structure **18**. In practice, this was accomplished by the slow addition of a solution of *t*-BuOK in THF-*t*-BuOH to a solution of Pd(PPh₃)₄ (~20 mol%) and the vinyl iodide **17** in THF. Under these basic reaction conditions, when R = H, isomerization of the alkene function from the exocyclic position to the conjugated endocyclic position occurs, generating bicyclic enones of general structure **19**. The general applicability of this annulation method (Scheme 4) has resulted in its use for the total synthesis of (±)-crinipellin B (**20**) (Scheme 5).¹⁵

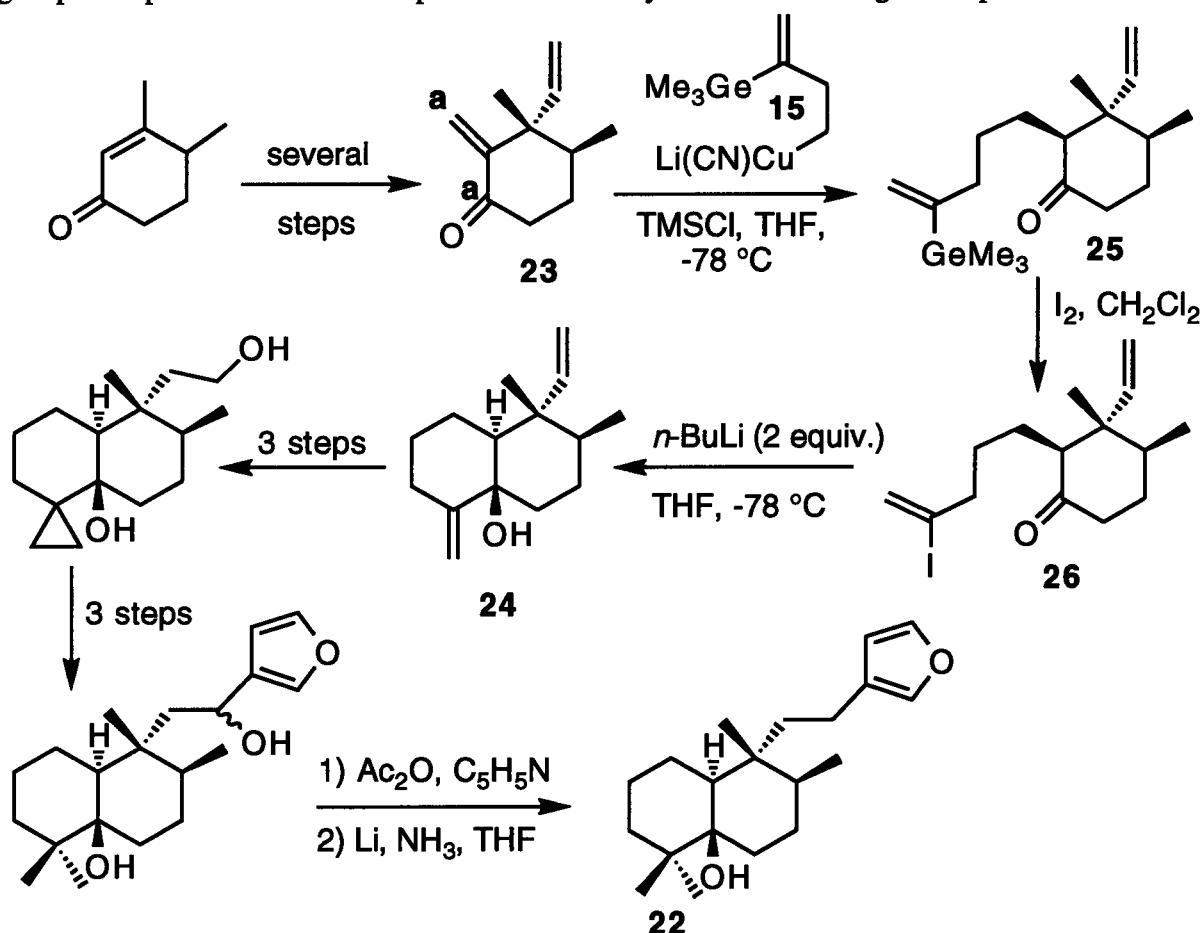


Scheme 5¹⁵

The vinylgermane bifunctional reagent **13** can also be employed in an annulation sequence designed to generate ring systems bearing a tertiary allylic alcohol function (route C, Scheme 2).^{9,16} In this route, the bifunctional conjunctive reagent **13** serves as the synthetic equivalent of the 1-butene d²,d⁴-synthon **21**.

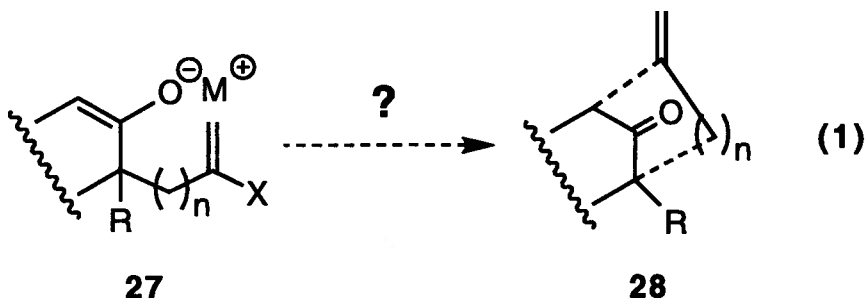


This sequence was employed in the total synthesis of (±)-ambliol B (**22**) (Scheme 6).⁹ The conversion of the exocyclic enone **23** to the bicyclic allylic alcohol **24** (Scheme 6) illustrates the use of reagent **13** in the annulation sequence described above. The 1,4-conjugate addition reaction to generate compound **25** deploys the d^4 center of reagent **15** and is similar to that described in the previous annulation sequence (Scheme 4). The ring closure step harnesses the donor capability of the vinyl iodide moiety of compound **26** via a lithium-iodine exchange reaction. The resulting vinyl lithium species attacks the carbonyl carbon in an intramolecular fashion, thereby generating the bicyclic compound **24**. Further functional group manipulations in this compound led to the synthesis of the target compound **22**.

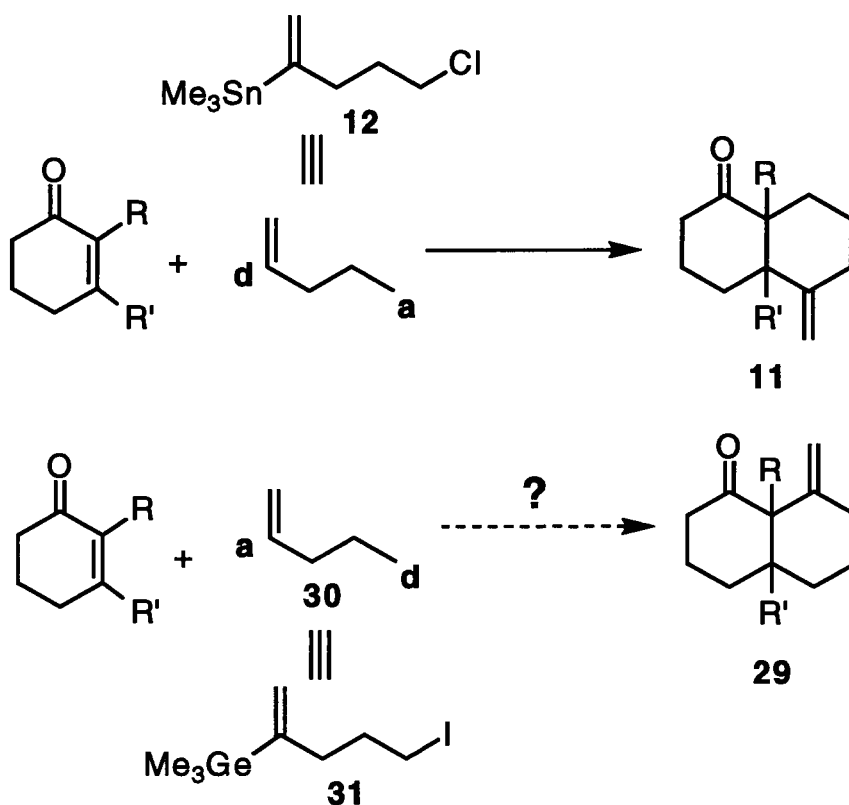


1.3. PROPOSALS

The bifunctional conjunctive reagent 4-iodo-2-trimethylgermyl-1-butene (**13**) has proven synthetically useful in promoting two novel annulation sequences (routes **B** and **C**, **Scheme 2**, page 3). One of the aims of the research described in Part 1 of this thesis deals with the optimization of the annulation sequence illustrated in **Scheme 4** (page 5). Could the conditions for the conjugate addition and cyclization reactions be modified to improve the yields of these steps? Could a catalyst other than $\text{Pd}(\text{PPh}_3)_4$ be used to effect the ring closure step? How general is this sequence? It follows that one might be able to extend the $\text{Pd}(0)$ -catalyzed cyclization reaction to generate different types of ring systems. For example, could such a cyclization reaction be utilized to convert the enolate **27** to the bridged bicyclic keto alkene **28** (equation 1)?

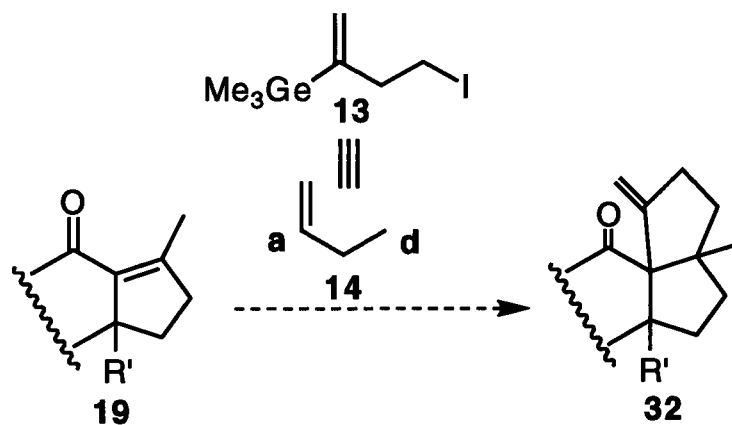


The use of a higher homologue reagent such as the vinylstannane compound **12** has proven successful in promoting a methylenecyclohexane annulation method.¹³ That is, by generating the one-carbon homologue of the vinylstannane reagent **4**, the methylenecyclopentane annulation sequence depicted in **Scheme 3** (page 4) was extended to generate functionalized bicyclo[4.4.0]dodecane compounds of general structure **11** (**Scheme 7**). Could the annulation sequence in **Scheme 4** be augmented to allow for the formation of six-membered rings of general structure **29** (**Scheme 7**)? To do so would require the use of a 1-pentene a^2, d^5 synthon **30**. The bifunctional reagent 5-iodo-2-trimethylgermyl-1-pentene (**31**) could be used as a viable synthetic equivalent of the 1-pentene synthon **30**.

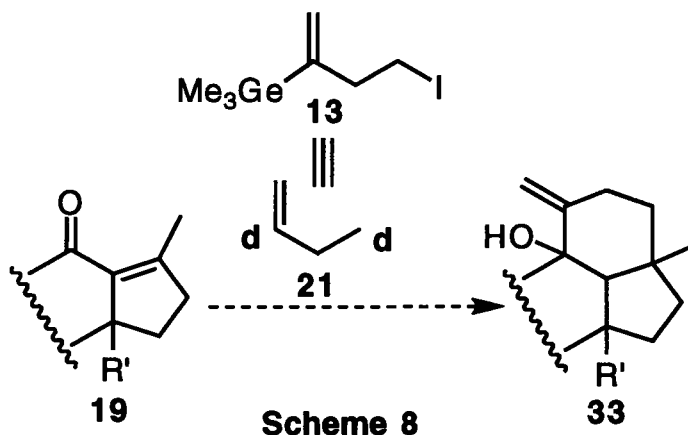


Scheme 7

The ease of synthesis of the bicyclic enones of general structure **19** (generated in Scheme 4) prompted us to envisage their use in a further annulation sequence to generate tricyclic ring systems. Could the bifunctional vinylgermane reagent **13**, used as the synthetic equivalent of the 1-butene a²,d⁴-synthon **14**, generate more complex ring systems of general structure **32**? What would be the stereochemical outcome of the conjugate addition reaction of the organocuprate **15** (Scheme 4) to the bicyclic enone **19**?



Finally, the annulation sequence depicted in **Scheme 6** (page 7), in which the vinylgermane reagent **13** serves as the synthetic equivalent of the 1-butene d^2,d^4 -synthon **21**, has only been utilized in this one example.¹⁷ How general is this annulation method? Could this method also be applied to generate more complex, tricyclic ring systems of general structure **33** (**Scheme 8**)?



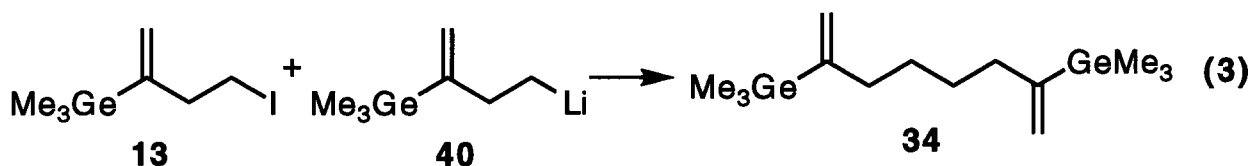
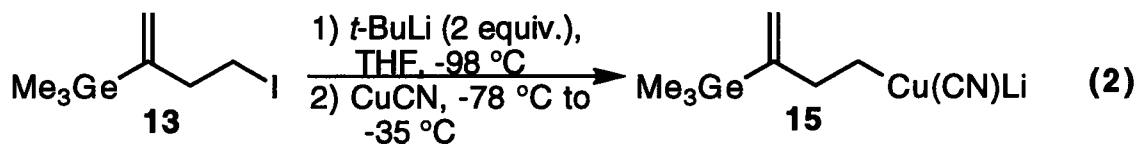
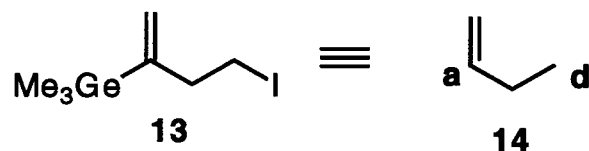
The exploration of these possibilities was an important motivation in the synthetic investigations which are to be detailed in Part 1 of this thesis. It was the purpose of this work to improve and extend the use of the bifunctional conjunctive reagent 4-iodo-2-trimethylgermyl-1-butene (**13**) (as the synthetic equivalent of either the 1-butene a^2,d^4 -synthon **14** or the 1-butene d^2,d^4 -synthon **21**) in the annulation sequences outlined above.

II. DISCUSSION

2.1. FIVE-MEMBERED RING ANNULATIONS BASED ON PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING

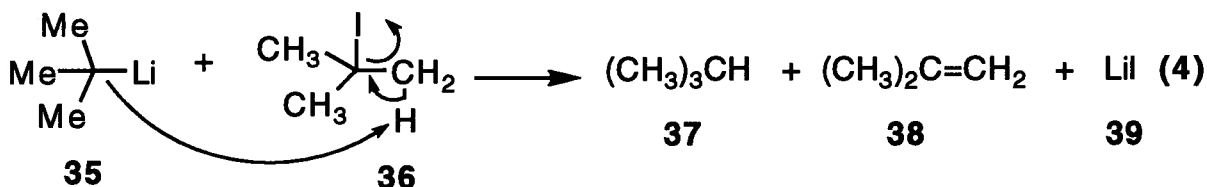
2.1.1. INTRODUCTORY REMARKS

Recent work⁷ in our laboratories has led to the development of a five-membered ring annulation sequence employing the bifunctional reagent **13** as the synthetic equivalent to the 1-butene a^2,d^4 -synthon **14** (Scheme 4, page 5). The vinylgermane **13** was converted to the key organocopper(I) reagent **15** by performing a metal-halogen exchange reaction followed by the addition of a copper(I) source (equation 2).⁷ Thus, treatment of a cold (-98 °C) THF solution of reagent **13** with two equivalents of *tert*-butyllithium followed by the addition of 1.1 to 1.2 equivalents of CuCN and brief warming to -35 °C, gave a homogeneous tan solution containing the organocopper(I) reagent **15**. The structure of the organocopper(I) reagent **15** is displayed below as a simple monomer, even though there is no evidence to support this. For simplistic purposes, all future organocopper(I) reagents will be displayed as monomers.

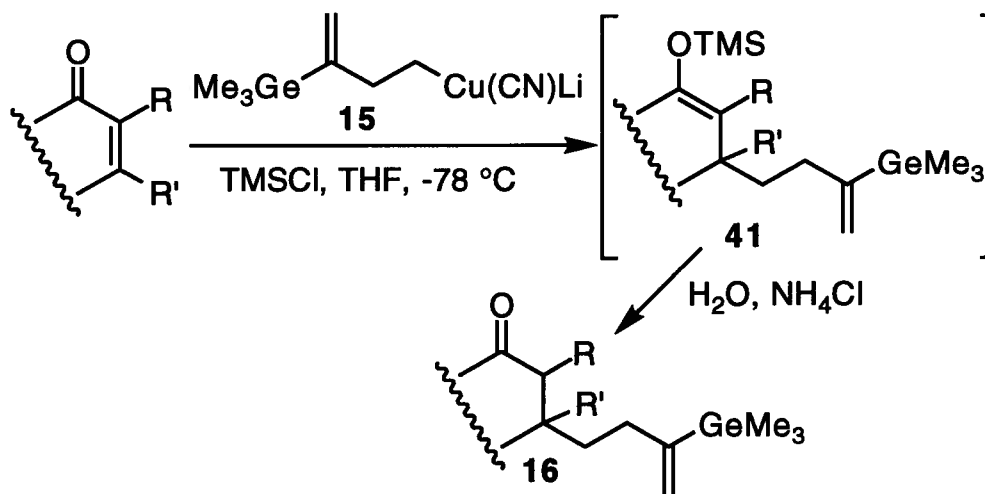


It was found necessary to employ two equivalents of *tert*-butyllithium to avoid formation of the coupled product **34** (equation 3). The reaction of *tert*-butyllithium (**35**) with

tert-butyl iodide (**36**, formed from the metal-halogen exchange with **13**) appears to be competitive with the lithium-iodine exchange process, probably giving 2-methylpropane (**37**), 2-methylpropene (**38**), and lithium iodide (**39**) (equation 4). This reaction consumes one equivalent of *tert*-butyllithium. Thus, if less than two equivalents of *tert*-butyllithium are used, the iodide **13** and the alkyllithium species **40** (produced by the metal-halogen exchange with reagent **13**) are present together in solution and will react to form the coupled product **34** (equation 3).



The annulation sequence commences with the 1,4-addition of the organocopper(I) reagent **15** to a suitable α,β -unsaturated ketone (**Scheme 9**). This reaction proceeded in the presence of trimethylsilyl chloride¹⁸ to afford the intermediate silyl enol ether **41** which, upon hydrolysis gave the keto vinylgermane **16**. The reported yields⁷ for this reaction ranged from 35% to 88%, depending on the structure of the starting α,β -unsaturated ketone (*vide infra*).

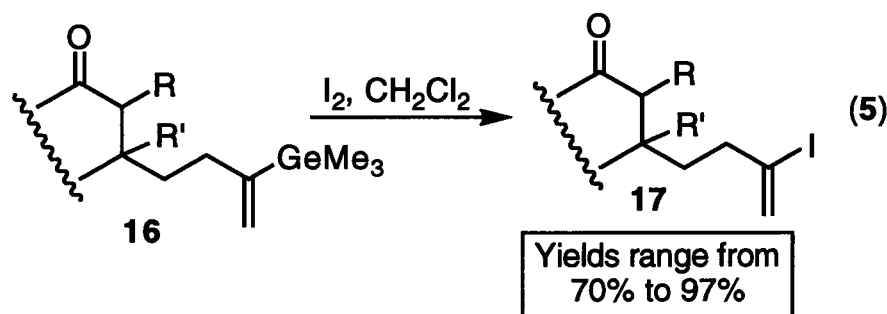


Scheme 9

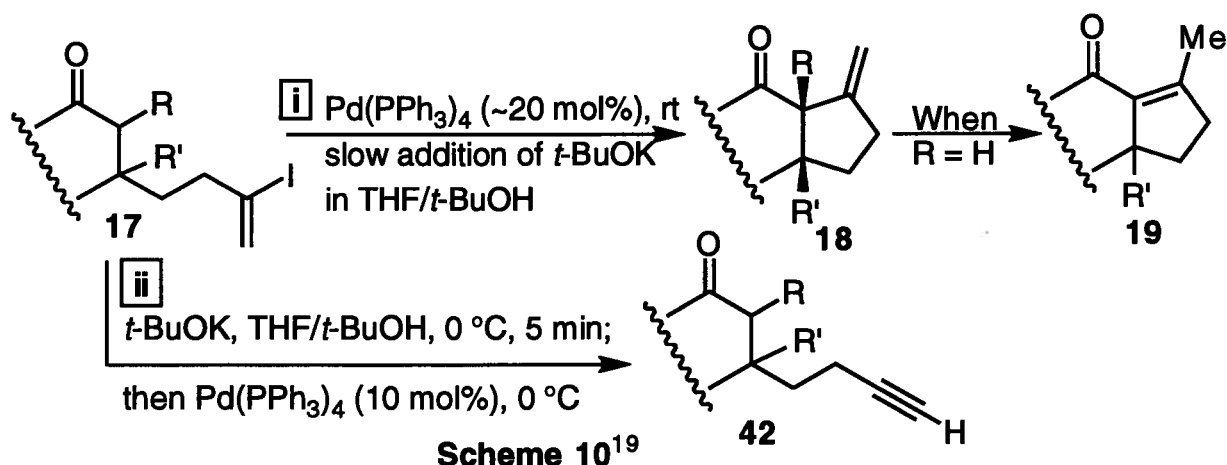
Could the conditions for the conjugate addition reaction be optimized to increase the yields

of the keto vinylgermane products? In particular, could the yield for the cuprate addition of reagent **15** to the hindered enone isophorone (reported yield⁷ for this reaction was 35%) be enhanced?

The second step of the annulation sequence (the conversion of the vinylgermanes **16** into the vinyl iodides **17**) was shown to proceed without incident and in high yield (equation 5).⁷ With the vinyl iodide substrates in hand, the cyclization reactions could be executed.

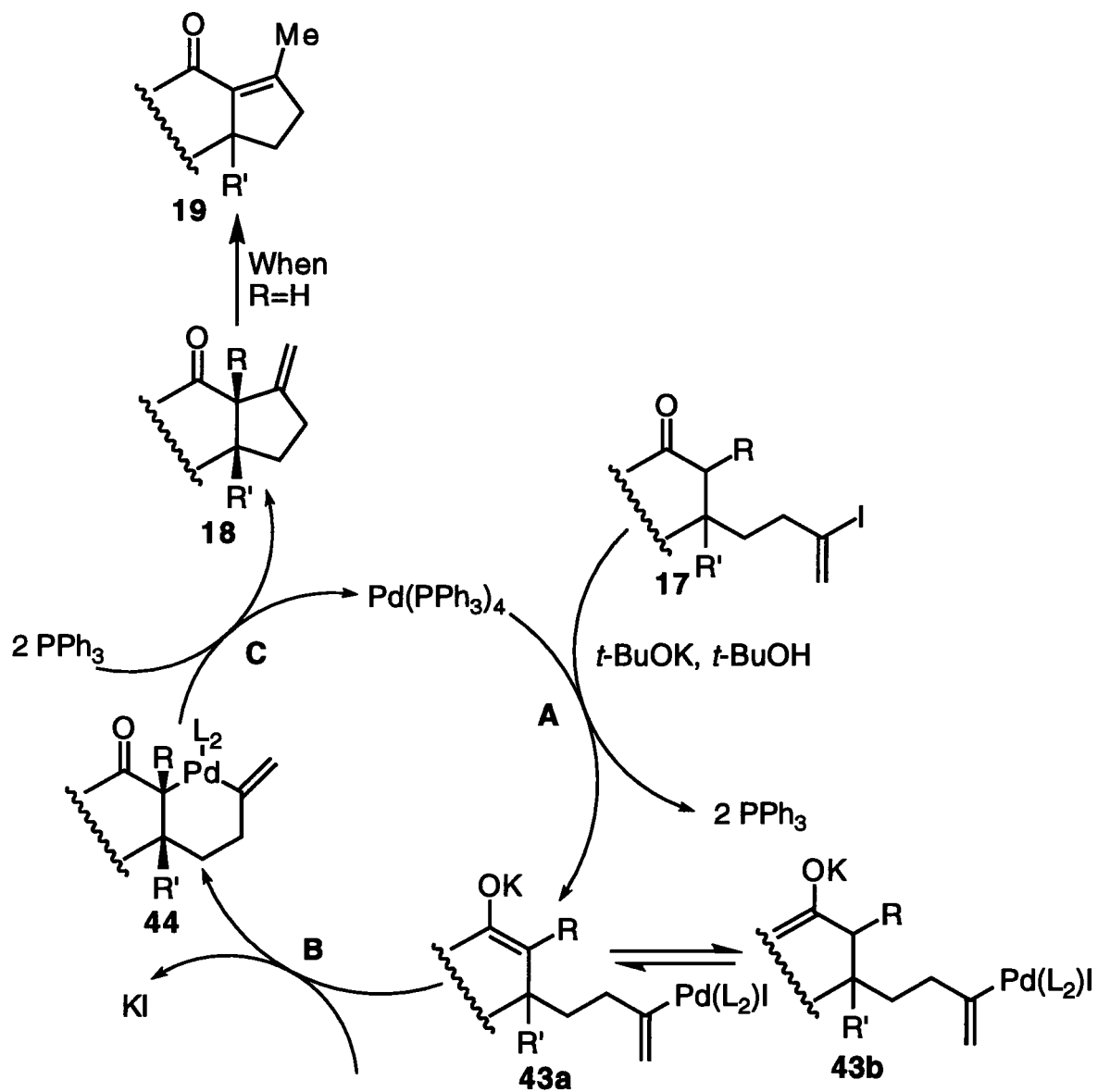


As reported,⁷ reaction conditions (route i, **Scheme 10**) were developed to convert the vinyl iodides **17** into the bicyclic keto alkenes **18** or the enones **19** (**Scheme 10**). The cyclization reaction occurred upon the addition of a solution of *t*-BuOK in THF/*t*-BuOH to a solution of Pd(PPh₃)₄ (~20 mol%) and the vinyl iodide **17** in THF. It was essential to maintain a low concentration of base in the reaction media (route i, **Scheme 10** employs a slow addition of base over 3 h via a syringe pump) since higher concentrations of base (route ii, **Scheme 10**) favored elimination of HI to form the undesired alkyne **42**.¹⁹



The mechanism of the cyclization reaction was not studied; however, a catalytic cycle based on literature precedent was proposed by Marais.²⁰ Three basic processes are postulated, labeled A through C in **Scheme 11**. In step A (oxidative addition and enolate anion formation), the palladium(0) catalyst inserts into the carbon-iodine bond of compound **17** and the potassium enolate **43a** is formed by reaction with the base *t*-BuOK. Two possible potassium enolates can be formed (**43a** and **43b**) under the equilibration conditions. Only species **43a** participates in the next step, thus the equilibrium between the two enolates is continually shifted to the left as **43a** is consumed in step B. In step B, the six-membered ring palladacycle **44** is formed from the enolate **43a**. This process is formally a transmetallation since the potassium enolate is replaced by a "palladium enolate" in which the palladium(II) is bonded to the α -carbon rather than the oxygen atom. Empirical evidence supports this step since as soon as the dropwise addition of the base commences, potassium iodide starts to precipitate from the reaction mixture. The final step in the catalytic cycle (step C) is the reductive elimination of palladium(0) from the palladacycle **44**. In this step, carbon-carbon bond formation takes place to give compound **18** and the palladium(0) catalyst is regenerated. Finally, due to the basic reaction conditions, when the product **18** has R=H, isomerization of the double bond into conjugation with the ketone occurs to give enones of general structure **19**.

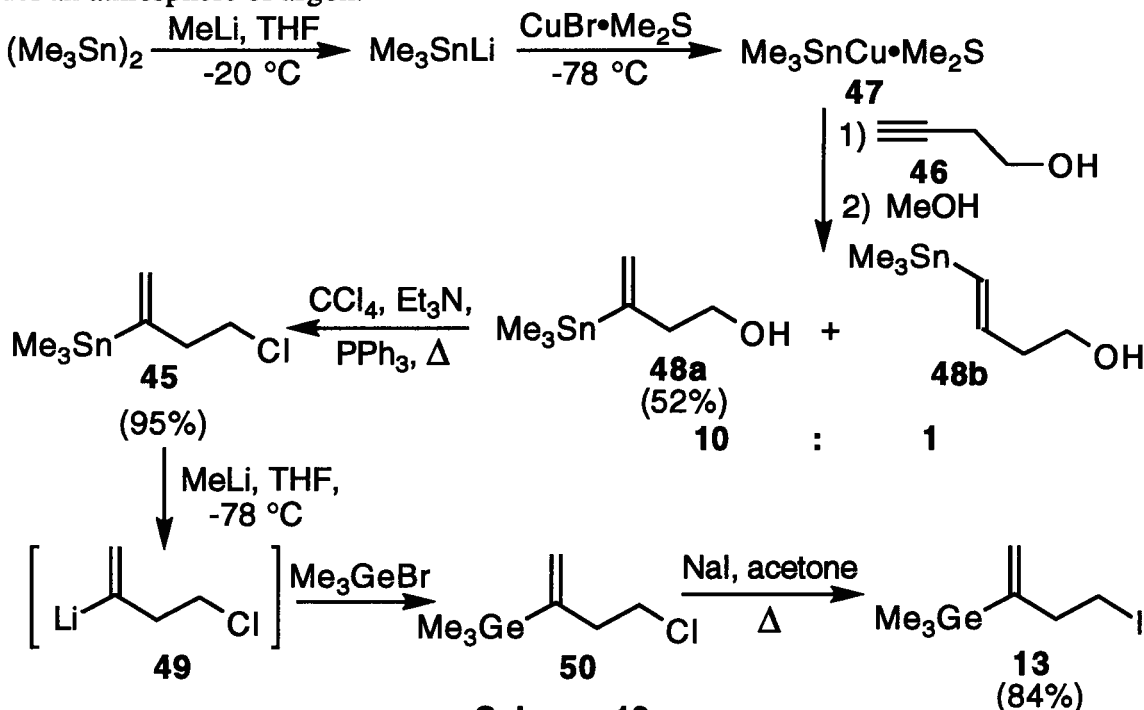
The reported yields⁷ for this novel Pd(0)-catalyzed cyclization reaction ranged from 58% to 74% (*vide infra*). Could the reaction conditions be modified to improve the yield of this reaction? Is it necessary to employ 20 mol% of Pd(PPh₃)₄? Could other Pd(0) or Ni(0) catalysts be employed to effect this cyclization reaction? These questions motivated us to further investigate the general applicability and use of this annulation sequence. Sections 2.1.3. (pages 19-23) and 2.1.4. (pages 24-33) detail the experiments that were carried out to improve both the conjugate addition reaction and the Pd(0)-catalyzed cyclization reaction.



Scheme 11

2.1.2. PREPARATION OF THE BIFUNCTIONAL REAGENT 4-iodo-2-trimethylgermyl-1-butene (13)

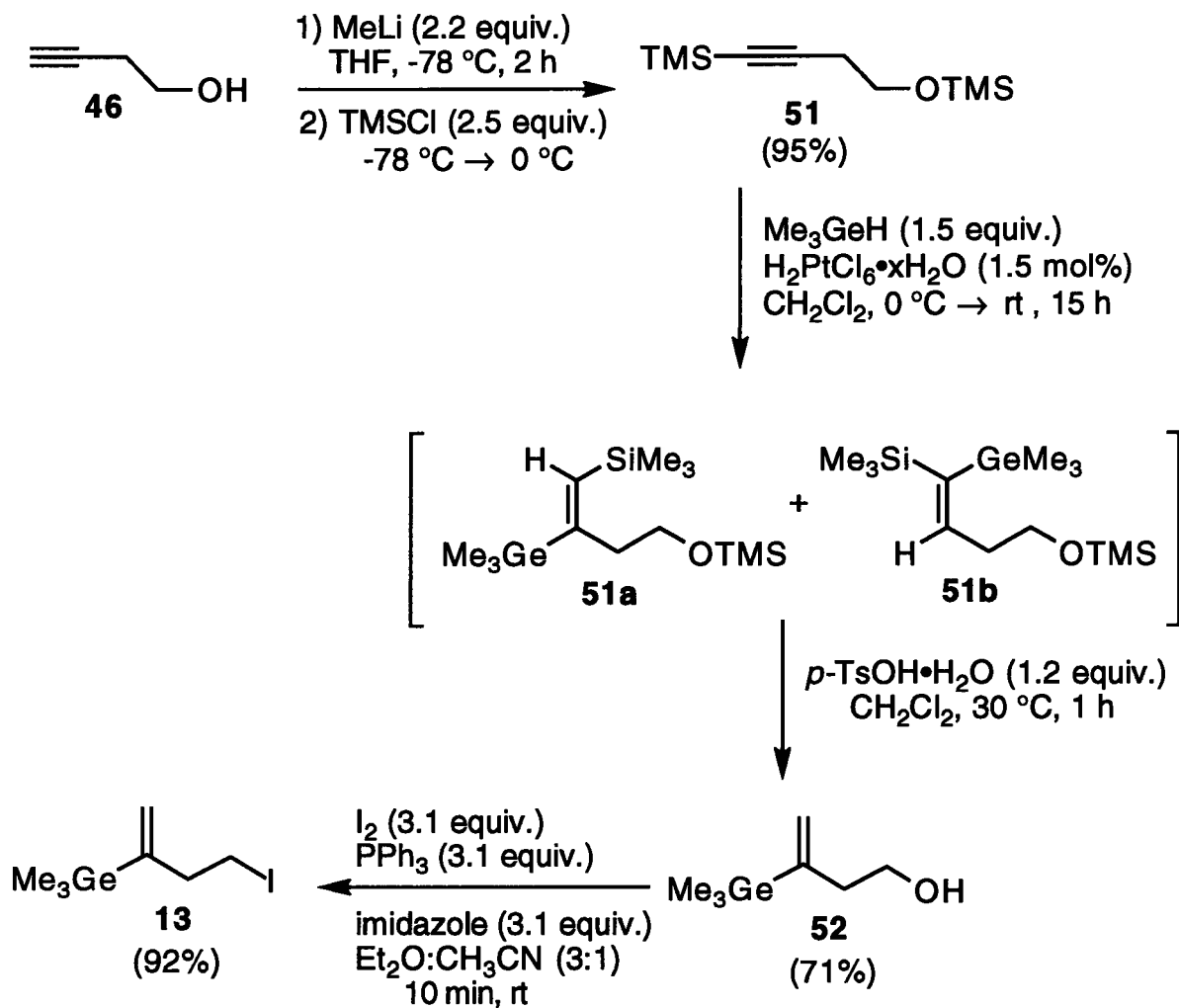
The bifunctional reagent **13** was originally synthesized⁷ via the corresponding 4-chloro-2-trimethylstannyl-1-butene (**45**) (Scheme 12). The vinylstannane compound **45**, in turn, was prepared from the commercially available 3-butyn-1-ol (**46**) via the stannylcopper(I) reagent **47**.²¹ The synthesis of the vinylstannane reagent **48a** could be accomplished on large scale (*vide infra*); however, the two regioisomers that are formed (**48a** and **48b**) can only be separated by drip column chromatography. This is a particularly time-consuming operation, especially when working on large scale. The vinylstannane alcohol **48a** was converted to the chloride **45** in 95% yield. Transmetalation of the vinylstannane chloride **45** with MeLi at -78 °C, followed by the addition of trimethylgermanium bromide to the resultant vinyl lithium species **49**, afforded 4-chloro-2-trimethylgermyl-1-butene (**50**) (Scheme 12). The volatile vinylgermane chloride **50** was immediately converted to the iodide **13** via a halide interconversion. The bifunctional reagent was thereby formed in an 84% yield (from the vinylstannane chloride **45**) and could be stored indefinitely in the freezer under an atmosphere of argon.



Scheme 12

This synthesis⁷ involves the use of two expensive reagents, namely hexamethylditin (~\$5 per gram) and trimethylgermanium bromide (~\$5 per gram). Moreover, the reaction to form the vinylstannane alcohol **48a** is low yielding (52%) and involves a very tedious separation from the corresponding regioisomer **48b**.

While we were conducting the annulation studies, a discovery was made in our laboratories which gave us access to a more expedient and economical route for the preparation of the vinylgermane reagent **13** (Scheme 13).²² With this route in hand, we could eliminate the expensive, time-consuming preparation of the vinylstannane chloride **45**. Starting with the commercially available 3-butyne-1-ol (**46**), the dianion was formed with MeLi at -78 °C and silylated with trimethylsilyl chloride to form 4-trimethylsiloxy-1-trimethylsilyl-1-butyne (**51**) in 95% yield.²² The key step involves a platinum catalyzed hydrogermylation reaction of the alkyne **51** with Me₃GeH. This was accomplished using a catalytic amount of H₂PtCl₂•xH₂O and 1.5 equivalents of Me₃GeH.²³ The resultant product mixture contained two major compounds, **51a** and **51b**, which were immediately subjected to a protodesilylation reaction employing *p*-TsOH•H₂O. Both isomers, **51a** and **51b**, were converted to the vinylgermane alcohol **52**, which was isolated in 71% overall yield. That the vinylgermane moiety was present in this compound was shown by the ¹H nmr spectrum (400 MHz, CDCl₃), which exhibited a nine proton singlet at δ 0.23 (-GeMe₃) and two one proton multiplets at δ 5.34 and 5.63 (vinyl protons). The alcohol **52** was converted to the iodide **13** by reaction with PPh₃•I₂.²⁴ With a high yielding, convenient synthesis of the bifunctional reagent **13** in hand, we turned our attention to the annulation sequence.



Scheme 13

2.1.3. PREPARATION OF THE CYCLIZATION SUBSTRATES

In order to prepare the keto vinyl iodide cyclization substrates, the enones **53-57** in **Table 1** were chosen as starting materials. All of the enones are commercially available, except for enone **57** which was synthesized from 2-(carbomethoxy)cyclohexanone (**58**)²⁵ by employing a selenoxide elimination reaction (equation 6).²⁶

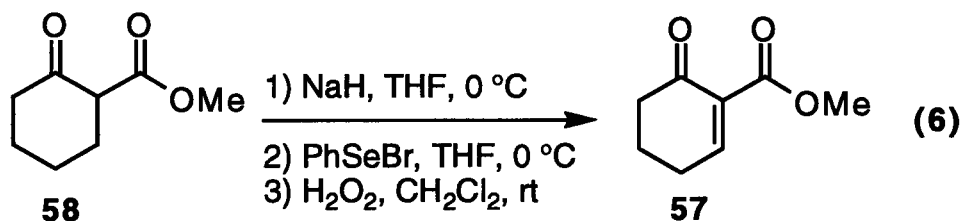


Table 1 contains a summary of the preparation of the keto vinyl iodide cyclization precursors along with results previously obtained by Piers and Marais.⁷ The synthesis of the keto vinyl iodide **64** (entry 1) was accomplished, for example, in the following manner. The organocopper(I) reagent **15** was prepared as described in the introductory remarks (equation 2) and was allowed to react, in the presence of an additive (TMSCl or TMSBr), with 2-cyclohexen-1-one (**53**). After hydrolysis of the intermediate silyl enol ether, workup of the reaction mixture and purification of the crude oil, the conjugate addition adduct **59** was isolated in pure form (89% yield using TMSBr as the additive or 73% yield⁷ using TMSCl as the additive). Confirmation of the assigned structure was obtained from the ¹H nmr spectrum (400 MHz, CDCl₃) of **59**, which exhibited a nine-proton singlet at δ 0.20 for the methyl substituents on germanium, and two one-proton multiplets in the vinylic region at δ 5.19 and 5.50. Treatment of the vinyl germane compound **59** with iodine in dichloromethane²⁷ afforded the corresponding vinyl iodide cyclization precursor **64** in 94% yield. The ¹H nmr (400 MHz, CDCl₃) resonances of the vinyl protons of **64** appeared at δ 5.69 (m, 1H) and 6.02 (m, 1H), significantly downfield from the values for the corresponding protons in the starting material **59** (*vide supra*). Also, the singlet at δ 0.20 (9H, -GeMe₃), evident in ¹H nmr spectrum of compound **59**, was no longer present in the spectrum of the vinyl iodide **64**. Thus, it was evident that the replacement of the trimethylgermane moiety

Table 1: Preparation of the Cyclization Substrates

$\text{Enone} \xrightarrow[2) \text{H}_2\text{O}]{1) \text{Me}_3\text{Ge}-\text{C}(\text{=CH}_2)-\text{CH}_2-\text{Cu}(\text{CN})\text{Li}, \text{Additive, THF, } -78^\circ\text{C}}$
 $\text{Keto Vinylgermane} \xrightarrow{\text{I}_2, \text{CH}_2\text{Cl}_2} \text{Keto Vinyl Iodide}$

Entry	Enone	Keto Vinylgermane	Yield using TMSBr ^a	Yield using TMSCl ^b	Keto Vinyl Iodide (Yield) ^c
1			89%	73%	64 (94%)
2			95%	--- ^d	65 (98%)
3			59%	35% ^e	66 (95%)
4			95%	88%	67 (97%)
5			90%	--- ^d	68 (94%)

a- Reaction conditions: reagent **15**, TMSBr (~3 equiv.), THF, -78 °C; H₂O.

b- Reaction conditions employed by Piers and Marais⁷: reagent **15**, TMSCl (~3 equiv.), THF, -78 °C; H₂O.

c- Reaction conditions: I₂, CH₂Cl₂, rt, overnight.

d- The conjugate addition of reagent **15** to this enone was not explored by Piers and Marais.

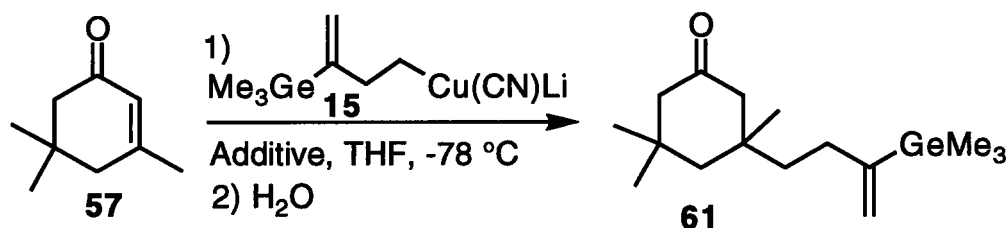
e- HMPA was added and the reaction mixture was allowed to warm slowly to rt overnight.

with the more electronegative iodine atom had taken place. The remaining keto vinyl iodides **65-68** were prepared in an analogous manner. The synthesis of the vinylgermane adducts **61-63** requires a few additional comments.

The addition of the organocopper(I) reagent **15** to (*R*)-(-)-carvone (**56**) proceeded in the precedented²⁸ stereoselective manner, trans to the substituent at carbon five. The ¹H nmr spectrum (400 MHz, CDCl₃) indicated that the product **62** was, in fact, a pair of diastereomers (epimers at C-2, in a ratio of ~4:1, *vide infra*). Starting with the α,β -unsaturated keto ester **57**, the conjugate addition product **63** was obtained in good yield (90%). The ¹H nmr spectrum (400 MHz, CDCl₃) confirmed that **63** was a mixture of tautomers (**63a** and **63b**, *vide infra*). The presence of the vinyl germane moiety was confirmed by signals at δ 0.20 and 0.21 (s, s, 9H, ratio undetermined). Two singlets at δ 3.69 and 3.73 (3H, ratio ~5:1) confirmed the presence of the carbomethoxy group.

Conjugate addition reactions of organocopper(I) reagents are known to occur much more readily in the presence of additives such as TMSCl¹⁸ and TMSBr.²⁹ In **Table 1**, entries 1, 3 and 4 compare the results of the conjugate addition reaction in the presence of TMSBr to that obtained by Piers and Marais⁷ using TMSCl as the additive. It was found that replacement of the additive TMSCl by TMSBr increased the yields of the reactions significantly. Particularly striking is the improvement in yield for entry 3 in which the yield of the conjugate addition of reagent **15** to isophorone (**55**) increased from 35% to 59%. Isophorone is a highly hindered enone and the reluctance of this enone to undergo 1,4-additions is well documented.³⁰ However, by replacing TMSCl with TMSBr, one can effect the reaction without using HMPA and obtain the adduct **61** in a much better yield. This result led us to investigate the effectiveness of other additives used in conjugate addition reactions. For example, the mixture of the Lewis acid BF₃ with cuprates has been proven to enhance carbon-carbon bond forming reactions.³¹ BF₃•Et₂O has also been used in conjunction with TMSCl in a variety of conjugate addition reactions.³² As seen in **Scheme 14**, BF₃•Et₂O alone did not effectively promote the conjugate addition of the reagent **15** to

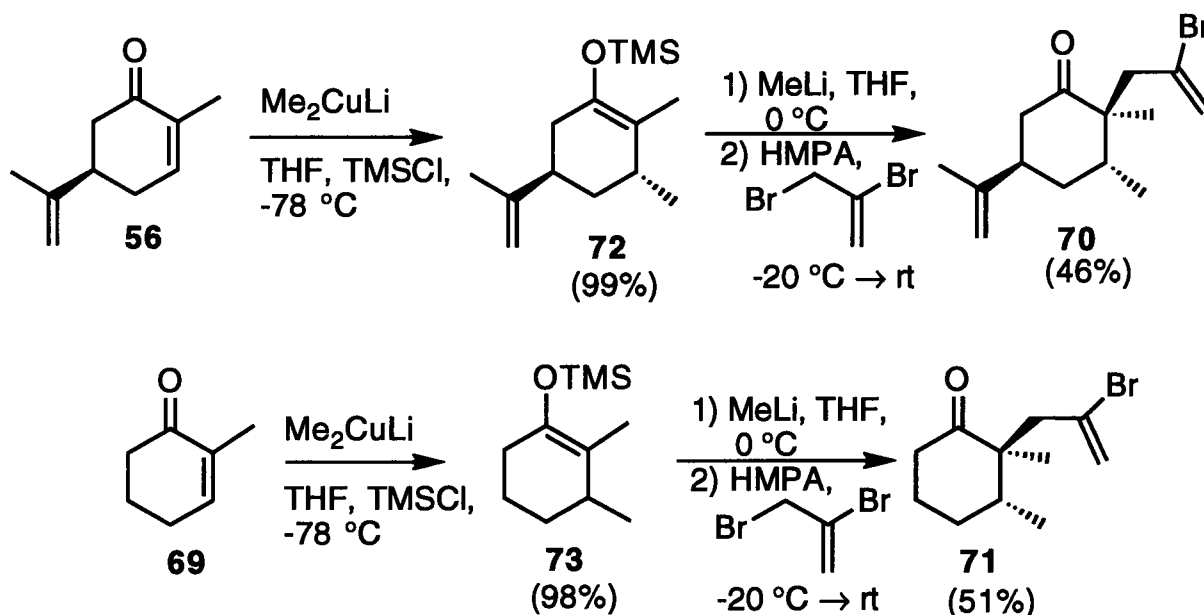
isophorone (**55**) (yield of **61** = 19%). However, when this Lewis acid was used with either TMSCl or TMSBr, the yield of the reaction improved dramatically. The optimum conditions (yield of **61** = 72%) for the conjugate addition reaction to isophorone (**55**) were found to employ both TMSBr (3.2 equiv.) and BF₃•Et₂O (1.1 equiv.) as additives.



Additive	Yield
TMSCl	35% ⁷
TMSBr	59%
BF ₃ •Et ₂ O	19%
TMSCl + BF ₃ •Et ₂ O	66%
TMSBr + BF ₃ •Et ₂ O	72%

Scheme 14

The synthesis of two additional cyclization precursors will now be described. Starting with the commercially available α,β -unsaturated ketones (*R*)-(-)-carvone (**56**) and 2-methyl-2-cyclohexen-1-one (**69**), the cyclization precursors **70** and **71** were formed (Scheme 15). This was accomplished by treating the enones **56** and **69** with Me₂CuLi and trapping the resultant enolates with TMSCl. The enolates were regenerated by reacting the silyl enol ethers **72** and **73** with MeLi. Alkylation of the resultant enolates with 2,3-dibromopropene provided the cyclization precursors **70** and **71**. While this synthesis could, in theory, be accomplished in one pot, the yields were much better when the silyl enol ethers **72** and **73** were isolated.



Scheme 15

The ^1H nmr spectrum (400 MHz, CDCl_3) confirmed that the vinyl bromide **70** was, in fact, a single diastereomer. The presence of the added methyl group in compound **70** was confirmed by the three proton doublet at δ 0.92 ($J = 8$ Hz, secondary Me). The signals at δ 4.72 (s, 1H), 4.79 (s, 1H), 5.52 (m, 1H), and 5.56 (m, 1H) confirmed the presence of four vinyl protons. The expected stereochemistry of the conjugate addition reaction and the subsequent alkylation was based on literature precedent.^{33,34}

The ^1H nmr spectrum (400 MHz, CDCl_3) of **71** indicated a 3:1 mixture of diastereomers; the expected stereochemistry³⁴ of the major product is indicated in **Scheme 15**. The two doublets at δ 0.95 and 1.10 (3H, ratio ~3:1, $J = 8$ Hz for each d) confirmed the presence of the secondary methyl group in compound **71**. The signals at δ 2.62, 2.71, 3.09, and 3.18 (d, d, d, d, 2H, ratio ~1:3:1:3, $J = 14$ Hz for each d) revealed the presence of the allylic protons and the signals at δ 5.50, 5.55, 5.58, and 5.63 (m, m, m, m, 2H, ratio ~1:3:1:3) confirmed the presence of the two vinyl protons.

2.1.4. CYCLIZATION STUDIES

As previously mentioned, Piers and Marais⁷ developed a palladium(0)-catalyzed cyclization reaction to convert the keto vinyl iodides **17** into the bicyclic ketones **18** or the enones **19** (Scheme 10, page 13). Table 2 contains a summary of the cyclization reactions that were performed using this method. Marais⁷ had performed the cyclization reactions on the substrates listed in entries 1, 3, and 4 of Table 2. These examples were repeated in the hopes of improving the yields. A solution of the keto vinyl iodide **65** and Pd(PPh₃)₄ (23 mol%) in THF was treated with *t*-BuOK in THF/*t*-BuOH (dropwise addition over 3-4 h) to provide, after workup and purification, the enone **75** in 65% yield. The IR spectrum of this compound revealed the presence of a conjugated enone (1679, 1627 cm⁻¹). The ¹H nmr spectrum (400 MHz, CDCl₃) of **75** showed signals due to a tertiary methyl group (δ 0.83 (s, 3H)) and a vinylic methyl group (δ 1.99 (br s, 3H)). In a similar fashion, substrates **64** and **66-68** were converted into the annulation products **74** and **76-78**, respectively. In the case of the vinyl iodide **68**, the relatively low pK_a of the proton at carbon two (proton alpha to the ketone and ester functions) allowed us to employ the weaker base Cs₂CO₃ for the cyclization reaction. The *cis*-fused stereochemistry of the keto diene **77** was confirmed by NOE difference experiments.³⁵ Compound **78** was thus assumed to also possess a *cis*-fused ring junction.

Decreasing the quantity of Pd(PPh₃)₄ (10 mol% vs. 20 mol%) used in the cyclization reactions was initially explored by Piers and Marais, as shown in equation 7.¹⁹ However, in this experiment employing 10 mol% of Pd(PPh₃)₄ (equation 7), the base was added in one portion, thereby increasing the probability of HI elimination. In fact, the alkyne **79** was obtained almost exclusively.

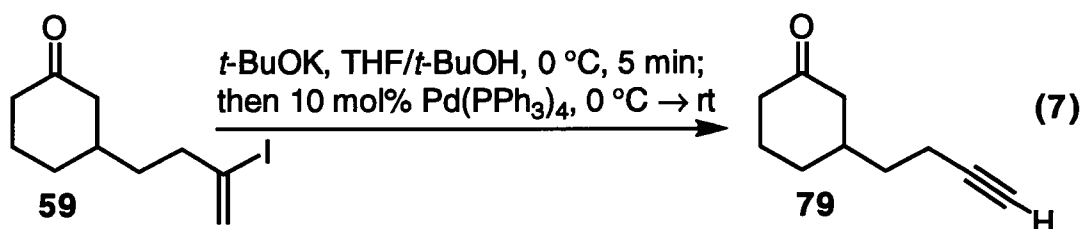


Table 2: Palladium(0)-Catalyzed Cyclization Reactions of the Keto Vinyl Iodides

Entry	Keto Vinyl Iodide	Product	Yield ^a
1			64% ^b
2			65%
3			83% ^c
4			80% ^d
5			43% ^e

a- Reaction conditions: ~20 mol% Pd(PPh₃)₄, THF, rt, 10 min; then dropwise addition of *t*-BuOK in THF/*t*-BuOH.

b- Piers and Marais⁷ reported a 59% yield for this reaction.

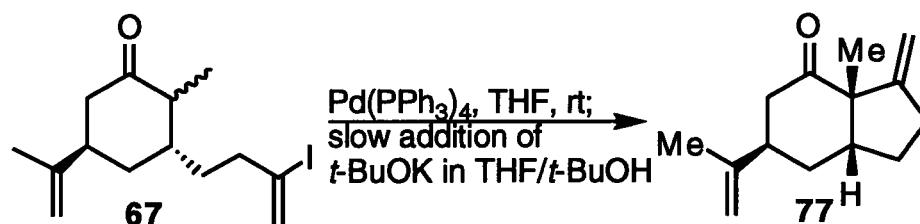
c- Piers and Marais⁷ reported a 74% yield for this reaction.

d- Piers and Marais⁷ reported a 65% yield for this reaction.

e- Reaction conditions: Cs₂CO₃ (5 equiv.), THF, rt; then Pd(PPh₃)₄ (28 mol%), 50-60 °C, 6 h.

It was important to investigate the effect of the amount of palladium catalyst on the yield, using the standard cyclization reaction conditions (slow addition of base). For this

study, the keto vinyl iodide **67** was chosen as the substrate for the Pd(0)-catalyzed cyclization reaction. **Scheme 16** summarizes the results from this study. The yield of the reaction decreased when the amount of palladium catalyst used was decreased. The yield of compound **77** dropped off significantly when the amount of palladium catalyst was scaled down from 10 mol% to 5 mol% (70% yield vs. 52% yield, respectively). This indicates that the catalytic cycle is not entirely efficient. For this reason, the amount of palladium catalyst used in all subsequent reactions was ~20-30 mol%.

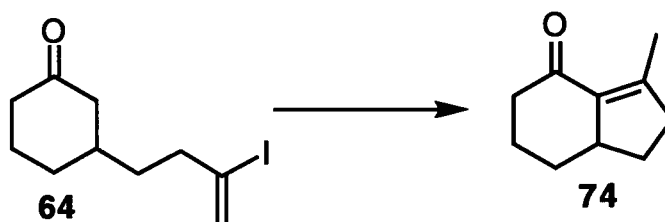


mol% of $\text{Pd(PPh}_3)_4$	Yield of 77
20 mol%	80%
15 mol%	73%
10 mol%	70%
5 mol%	52%

Scheme 16

How do the other reaction conditions affect this reaction? The equilibration of the two possible enolate anions of the starting material (see **43a** and **43b**, **Scheme 11**, page 15) occurs intermolecularly with the proton source, $t\text{-BuOH}$. The cyclization reaction, however, is an intramolecular process. The effect of the concentration of the catalyst, substrate and base in the reaction mixture on the yield of the reaction was investigated. By increasing the dilution of the catalyst, substrate and base in the reaction mixture (0.002 M vs. 0.02 M, 0.008 M vs. 0.1 M, and 0.009 M vs. 0.08 M, respectively; see entry 2, **Scheme 17**), the yield of the cyclized product **74** dropped slightly from 64% to 52%. When $t\text{-BuOH}$ was removed from the base mixture (entry 3, **Scheme 17**), the yield of **74** dropped further to 42%. By increasing

the dilution of the reactants in the reaction mixture and decreasing the availability of a proton source, we can assume that the equilibration of the two possible enolates is slowed somewhat. In theory, this should not affect the yield of the reaction since the desired enolate is being constantly consumed in the cyclization reaction (**Scheme 11**, page 15). In practice (**Scheme 17**), however, these changes to the reaction conditions did lower the yield of the product **74** slightly. It is difficult to speculate whether these changes in the yield of the reaction were statistically significant.



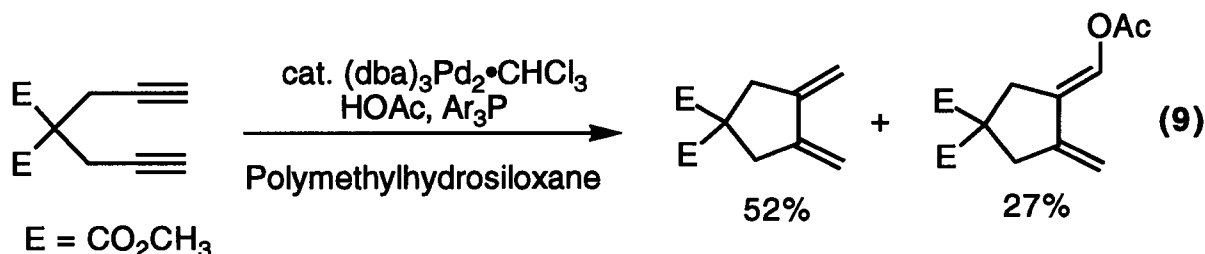
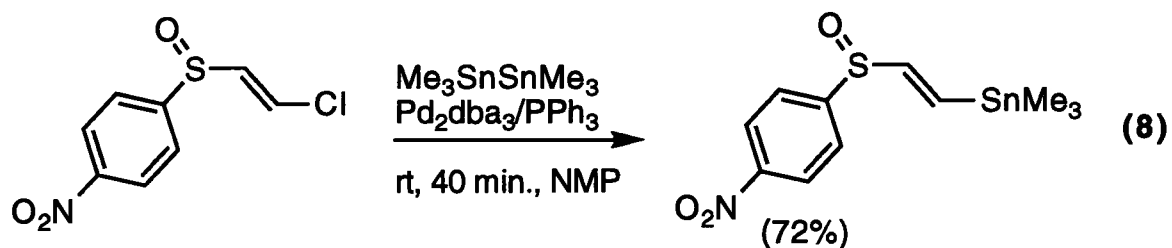
Entry	Reaction Conditions	Yield of 74
1	Pd(PPh ₃) ₄ (24 mol%), THF (0.1 M concentration ^a); <i>t</i> -BuOK in THF/ <i>t</i> -BuOH	64%
2	Pd(PPh ₃) ₄ (26 mol%), THF (0.008 M concentration ^b); <i>t</i> -BuOK in THF/ <i>t</i> -BuOH	52%
3	Pd(PPh ₃) ₄ (22 mol%), THF (0.008 M concentration ^c); <i>t</i> -BuOK in THF (no <i>t</i> -BuOH)	42%

a-0.1 M refers to the concentration of **64** in the reaction mixture;
the concentration of Pd(PPh₃)₄ in the reaction mixture was 0.02 M;
the concentration of the base in the reaction mixture was ~0.08 M.
b-0.008 M refers to the concentration of **64** in the reaction mixture;
the concentration of Pd(PPh₃)₄ in the reaction mixture was 0.002 M;
the concentration of the base in the reaction mixture was ~0.009 M.
c-0.008 M refers to the concentration of **64** in the reaction mixture;
the concentration of Pd(PPh₃)₄ in the reaction mixture was 0.002 M;
the concentration of the base in the reaction mixture was ~0.009 M

Scheme 17

As seen in **Table 2** (page 25), the cyclized products **74-78** were obtained in moderate to good yields. Could the moderate yields be improved by employing a different Pd(0)

catalyst or, perhaps, a Ni(0) catalyst? A number of Pd(0) catalysts were initially investigated using the vinyl iodide **67** as the cyclization precursor. **Table 3** summarizes the results of this study. It was obvious that Pd(PPh₃)₄ (entry 1, 80% yield of **77**) is the best catalyst to date for this particular cyclization reaction. The only other comparable Pd(0) catalyst was Pd₂(dba)₃/PPh₃ (entry 3, **Table 3**), which provided the target compound **77** in 67% yield. The use of Pd₂(dba)₃/PPh₃ and Pd₂(dba)₃/Ph₃As as catalysts in coupling reactions has been reported by Farina *et al.* (equation 8)³⁶ and Trost and Lee (equation 9).³⁷



When the Pd₂(dba)₃/PPh₃ catalyst was employed with the vinyl iodide substrate **68**, a slightly better yield of product **78** was obtained (47% (equation 10) vs. 43% with Pd(PPh₃)₄ (entry 5, **Table 2**)). On the other hand, the use of Pd₂(dba)₃/AsPh₃ as a catalyst for the cyclization of **67** (entries 4 and 5, **Table 3**) failed to generate **77** in an acceptable yield.

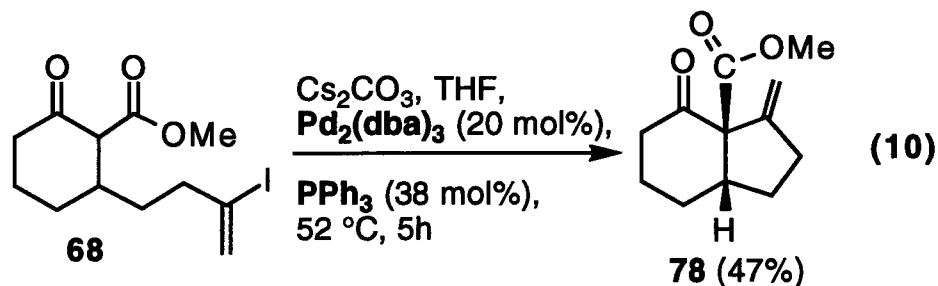
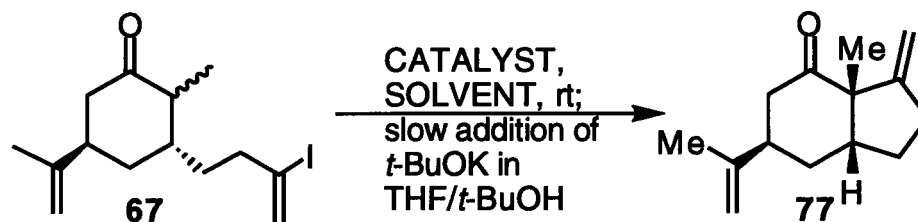
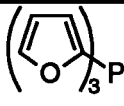
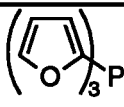
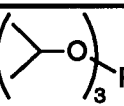
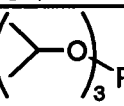
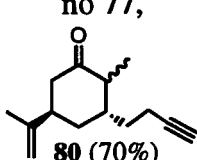
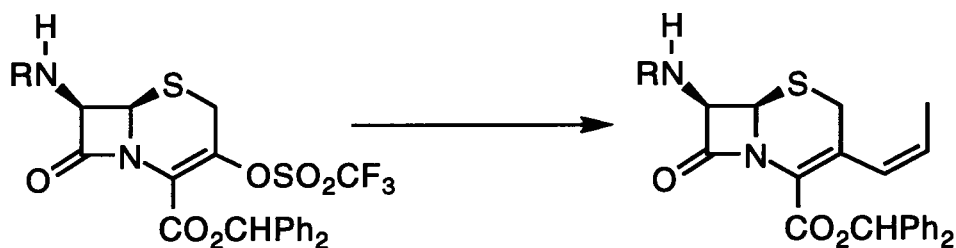


Table 3: The Effects of Different Catalysts on the Cyclization Reaction

ENTRY	CATALYST (mol%)	LIGAND (mol%)	SOLVENT	YIELD OF 77
1	Pd(PPh ₃) ₄ (20 mol%)	—	THF	80%
2	Pd(PPh ₃) ₄ (10 mol%), CuCl (50 mol%)	—	THF	32%
3	Pd ₂ (dba) ₃ (19 mol%)	PPh ₃ (38 mol%)	THF	67%
4	Pd ₂ (dba) ₃ (23 mol%)	Ph ₃ As (88 mol%)	THF	6%
5	Pd ₂ (dba) ₃ (20 mol%)	Ph ₃ As (40 mol%)	THF	8%
6	Pd ₂ (dba) ₃ (19 mol%)	 38 mol%	THF	34%
7	Pd ₂ (dba) ₃ (20 mol%)	 40 mol%	NMP	negligible
8	Pd ₂ (dba) ₃ (20 mol%)	 40 mol%	THF	16%
9	PdCl ₂ (dppf) (18 mol%)	dppf	THF	6%
10	Pd(OAc) ₂ (20 mol%)	PPh ₃ (40 mol%)	THF	negligible
11	Pd(OAc) ₂ (20 mol%)	 40 mol%	THF	negligible
12	PdCl ₂ (PPh ₃) ₂ (20 mol%), CuI (40 mol%)	PPh ₃ (40 mol%)	DMF	negligible
13	Ni(COD) ₂ (1.1 equiv.)	COD	THF	no 77,  80 (70%)

The use of copper(I)halides in Pd(0)-catalyzed coupling reactions has been known to improve the yields of such reactions.³⁸ However, when we attempted the cyclization of **67** with Pd(PPh₃)₄ in the presence of 50 mol% CuCl, the cyclized product **77** was obtained in poor yield (entry 2, **Table 3**). Similarly, the use of PdCl₂(PPh₃)₂ and CuI³⁹ provided only a negligible amount of the product **77** (entry 12, **Table 3**).

It has been proposed⁴⁰ that the rate-determining step in Pd(0)-catalyzed coupling reactions is the transmetallation step (step **B**, **Scheme 11**, page 15), consisting of a nucleophilic attack at Pd(II). Farina *et al.*³⁶ hypothesized that making the palladium species less electron-rich should enhance the transmetallation rate. The use of a more electron-withdrawing ligand, such as tri(2-furyl)phosphine, was shown to dramatically enhance the yield of the coupling reaction illustrated in **Scheme 18**.³⁶

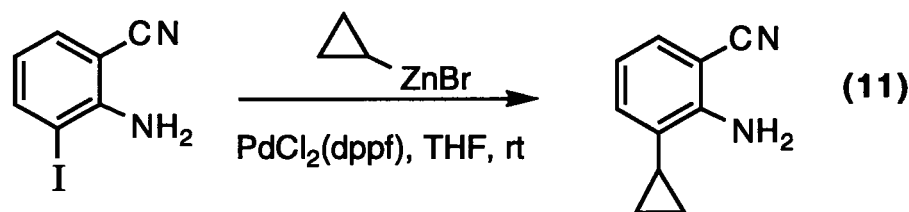


Conditions	% Yield
$\text{Pd(PPh}_3)_4$ LiBr, THF, 16 h, 50 °C	21%
$\text{Pd}_2(\text{dba})_3$ ZnCl ₂ , NMP, rt	91%

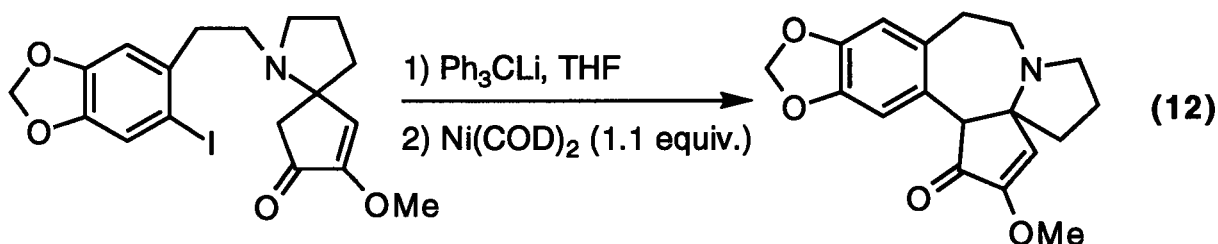
Scheme 18³⁶

However, as seen in **Table 3**, the use of more electron-withdrawing ligands such as tri(2-furyl)phosphine (entries 6 and 7, **Table 3**) and triisopropyl phosphite⁴¹ (entries 8 and 11, **Table 3**) did not effectively promote the cyclization reaction to produce the desired product **77**.

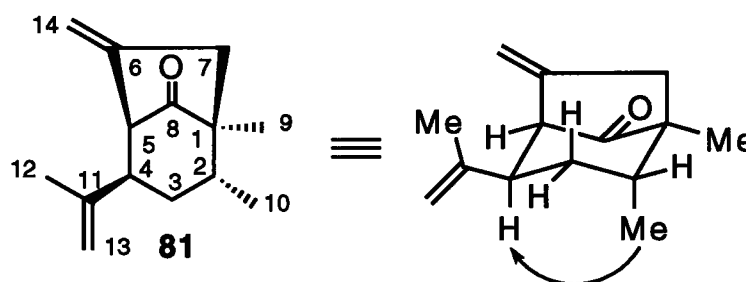
The use of $\text{PdCl}_2(\text{dppf})$ ⁴² has proven successful in catalyzing cross-coupling reactions; one such example^{42a} is illustrated in equation **11**. However, the use of this catalyst (entry 9, **Table 3**) failed in our attempts to synthesize compound **77**.



Semmelhack *et al.*⁴³ have reported the stoichiometric use of $\text{Ni}(\text{COD})_2$ in an intramolecular coupling reaction (see equation **12**). However, in our case, the use of $\text{Ni}(\text{COD})_2$ (entry 13, **Table 3**) seemed to promote the HI elimination reaction and 70% of the uncyclized acetylene **80** was obtained instead of the desired bicyclic compound **77**. The IR spectrum of **80** exhibited the absorbances characteristic of a terminal acetylene at 3296 and 2117 cm^{-1} , while a carbonyl stretch was in evidence at 1709 cm^{-1} . This disappointing result led us to abandon the study of other $\text{Ni}(0)$ reagents for the cyclization reaction.



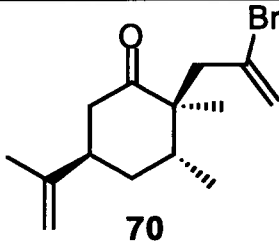
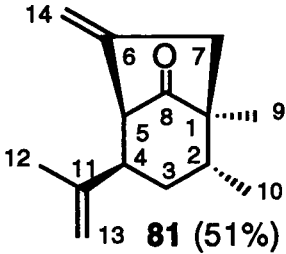
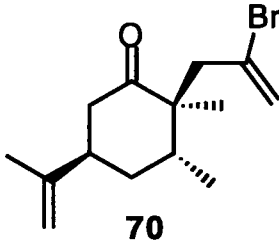
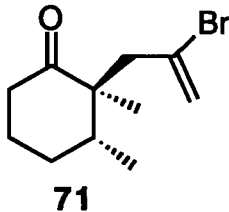
We wanted to extend the 5-membered ring Pd(0)-catalyzed annulation sequence to generate bridged bicyclic keto alkenes (equation 1, page 8). The cyclization precursors **70** and **71** shown in **Table 4** were thus subjected to the Pd(0)-catalyzed cyclization conditions described above. When the vinyl bromide **70** was treated under Pd(0)-catalyzed cyclization conditions (entry 1, **Table 4**), the bridged bicyclic compound **81** was obtained in 51% yield (70% based on consumed starting material). A combination of ^1H nmr, COSY and NOE experiments was used to determine the structure of compound **81** (see **Table 20**, experimental, page 159). The bridgehead proton (H-5) was evident as a broad singlet at δ 2.79; this proton showed COSY correlations to H-4 (δ 2.70, br d, $J = 12$ Hz), H-14 (δ 4.69, br s), and H-14' (δ 5.13, br s). Irradiation of the signal due to Me-10 (δ 0.90, d, $J = 8$ Hz) led to the nuclear Overhauser enhancement of the signal due to H-4; this result was consistent with the relative stereochemistry shown below.



This cyclization result was only obtained in one instance and could not be reproduced. Since it was no longer necessary to choose a base that would allow enolate equilibration, we repeated the cyclization reaction employing $\text{KN}(\text{SiMe}_3)_2$ (entry 2, **Table 4**). This resulted in no product formation, but rather a mixture of starting material and unidentifiable side products. Moreover, the attempt to cyclize the vinyl bromide **71** (~3:1 mixture of diastereomers; the expected stereochemistry of the major compound is indicated in entry 3, **Table 4**) employing the Pd(0)-catalyzed conditions failed to produce any of the desired cyclized product. These results could be due to the fact that the vinyl bromide function was present versus the usual vinyl iodide moiety. We eventually abandoned our

attempts at forming bridged bicyclic compounds using the Pd(0)-catalyzed cyclization conditions.

Table 4: Attempts at the Synthesis of Bridged Bicyclic Ketones using the Pd(0)-Catalyzed Cyclization Reaction

Entry	Cyclization Precursor	Conditions	Product
1	 70	1) Pd(PPh ₃) ₄ , THF, rt 2) slow addition of <i>t</i> -BuOK in THF/ <i>t</i> -BuOH	 81 (51%)
2	 70	1) KN(SiMe ₃) ₂ , THF, 0 °C 2) Pd(PPh ₃) ₄ , rt, 22 h	No Cyclized Product Obtained
3	 71	1) Pd(PPh ₃) ₄ , THF, rt 2) slow addition of <i>t</i> -BuOK in THF/ <i>t</i> -BuOH	No Cyclized Product Obtained

2.1.5. CONCLUSION

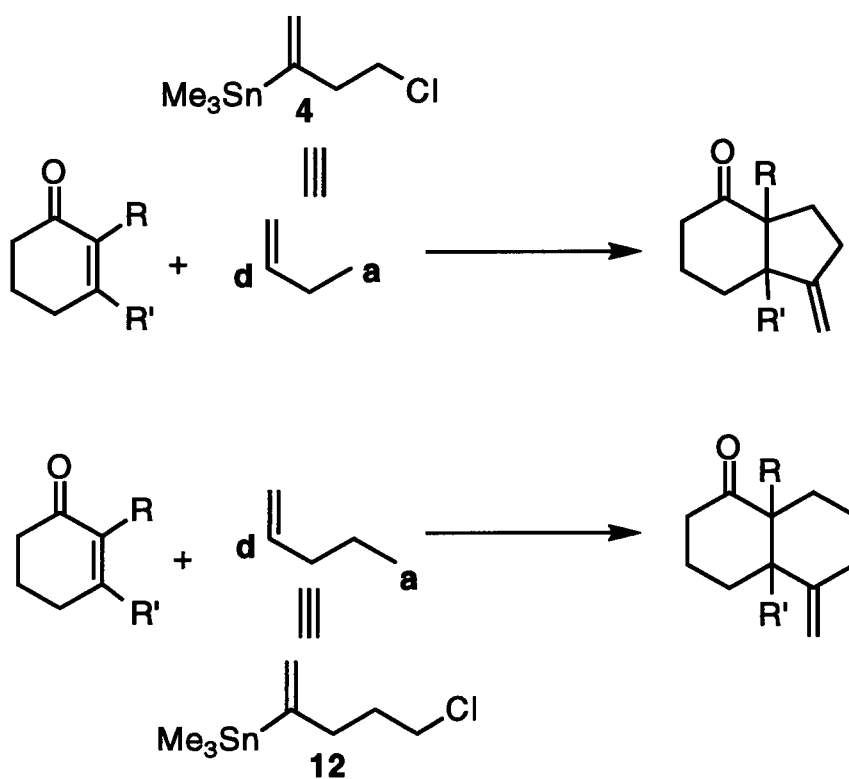
The five-membered ring annulation sequence developed by Piers and Marais⁷ was employed to generate the bicyclic enones **74–76** and the bicyclic keto alkenes **77** and **78**. The conditions for the conjugate addition of the organocopper(I) reagent **15** to α,β -unsaturated enones were optimized by replacing TMSCl with TMSBr. This modification improved the yields of the conjugate addition reactions, particularly in the case of the hindered enone isophorone (see page 22). The Pd(0)-catalyzed cyclization reaction was also studied. It was

found that 20 mol% of $\text{Pd}(\text{PPh}_3)_4$ was necessary to obtain the cyclized products in good yield. The yields for the cyclization of certain keto vinyl iodides (see entries 1, 3, and 4, **Table 2**, page 25) were improved from that reported by Piers and Marais.⁷ It was also found that the use of other $\text{Pd}(0)$ and $\text{Ni}(0)$ catalysts did not effectively promote the cyclization reaction. Finally, the $\text{Pd}(0)$ -catalyzed cyclization reaction was unsuccessful in forming bridged bicyclic keto alkenes (see **Table 4**).

2.2. ATTEMPTS TO ACHIEVE SIX-MEMBERED RING ANNULATIONS BASED ON PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING

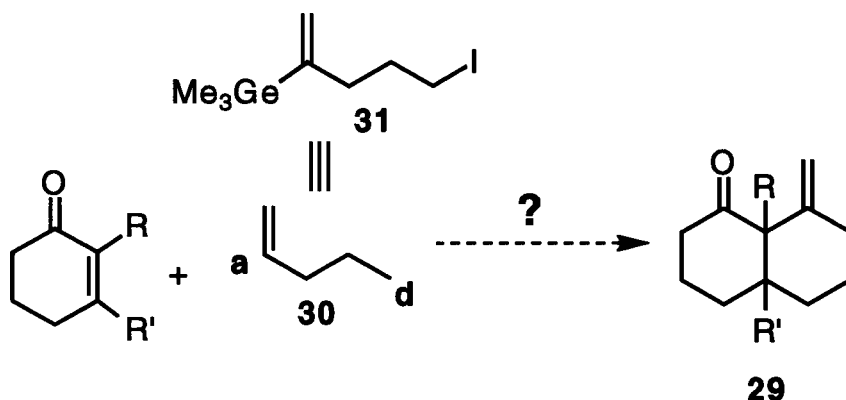
2.2.1. INTRODUCTORY REMARKS

The five-membered ring annulation method employing the bifunctional conjunctive reagent 4-chloro-2-trimethylstannyl-1-butene (**4**) was extended to allow for the formation of six-membered rings (**Scheme 7a**).⁴⁴ This was accomplished by utilizing the one-carbon homologue of reagent **4** (i.e. 5-chloro-2-trimethylstannyl-1-pentene (**12**)).



Scheme 7a

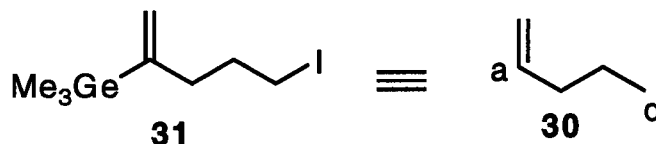
In a similar manner, we hoped to extend the Pd(0)-catalyzed cyclization reaction to the formation of six-membered rings with the specific aim of preparing substances of general structure **29** (**Scheme 7b**). The following sections outline the synthesis of the bifunctional vinylgermane reagent **31** (the one-carbon homolog of reagent **13**) and the attempts of utilizing this reagent in conjunction with the Pd(0)-catalyzed cyclization reaction to synthesize six-membered rings.



Scheme 7b

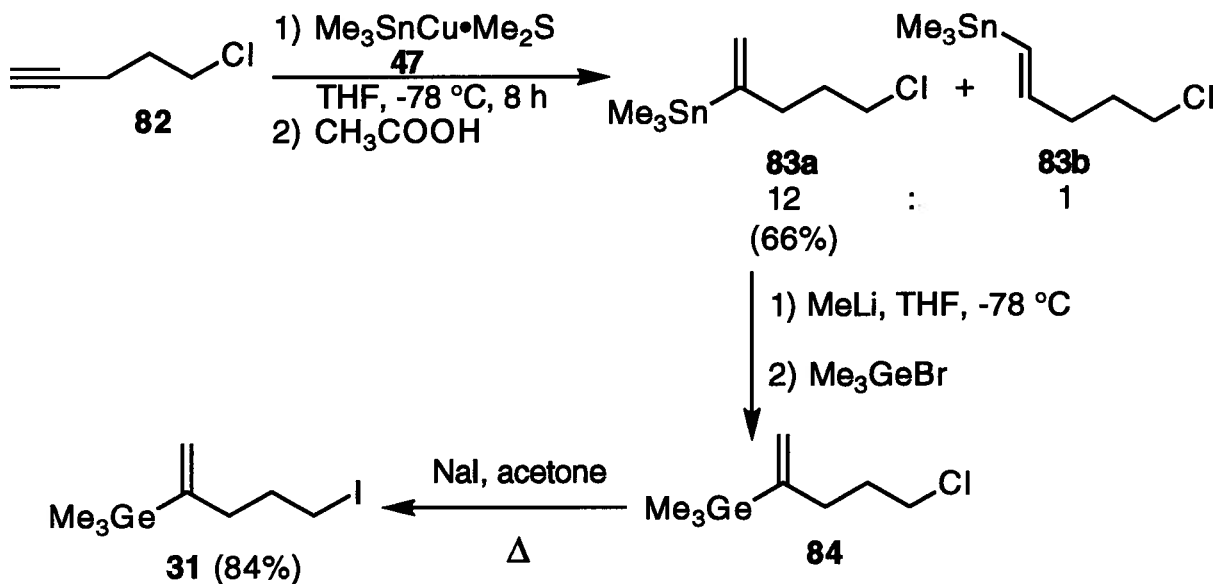
2.2.2. PREPARATION OF THE BIFUNCTIONAL REAGENT 5-iodo-2-TRIMETHYLGERMYL-1-PENTENE (31)

In order to attempt the formation of six-membered rings employing the Pd(0)-catalyzed cyclization reaction, we required a bifunctional reagent that would serve as the synthetic equivalent of the 1-pentene a^2,d^5 -synthon **30**, namely 5-iodo-2-trimethylgermyl-1-pentene (**31**).



Since the stereoselective platinum-catalyzed hydrogermylation method for constructing 2-trimethylgermyl-1-alkenes²² (Scheme 13, page 18) had not yet been developed at the time during which we carried out this brief study, compound **31** was synthesized from the corresponding vinylstannane **12** (Scheme 19). The commercially available 5-chloro-1-pentyne (**82**) was treated with the stannylcopper(I) reagent **47** to generate a 12:1 mixture of the vinylstannane regioisomers **83a** and **83b**. The desired isomer **83a** was separated by drip column chromatography and isolated in 66% yield. Transmetalation of **83a** with MeLi, followed by the addition of trimethylgermanium bromide, afforded the vinylgermane chloride **84**. The chloride **84** was immediately converted into the desired compound **31** (84% yield from the corresponding vinylstannane chloride **83a**) by means of a halide

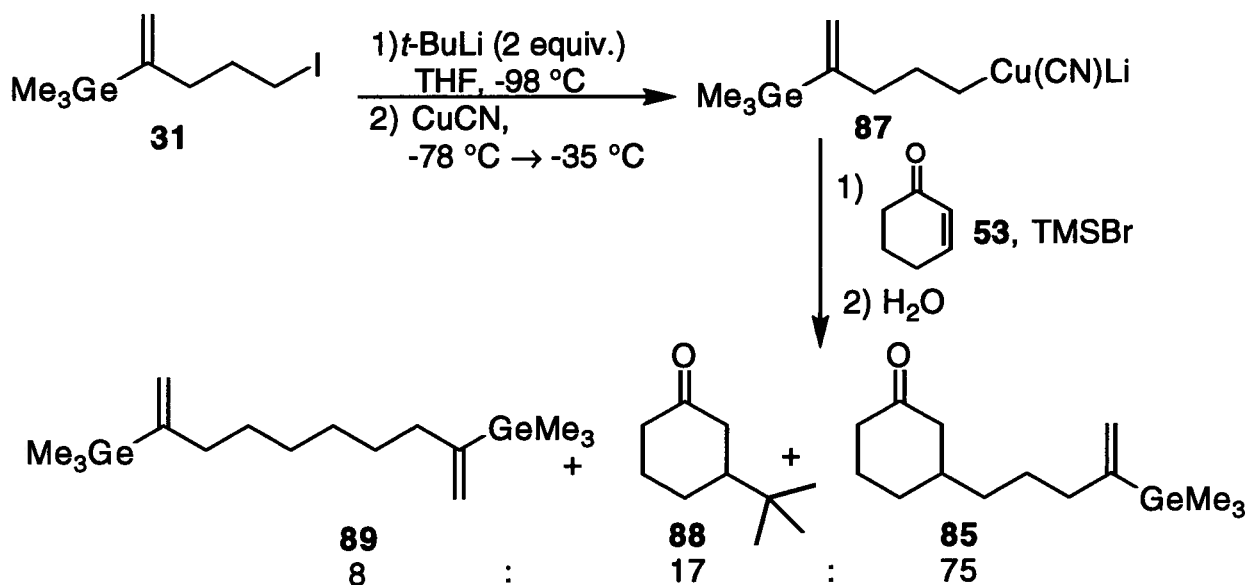
interconversion. The ^1H nmr spectrum (400 MHz, CDCl_3) of **31** confirmed the presence of the vinylgermane moiety by a 9-proton singlet at δ 0.20 ($-\text{GeMe}_3$) and two 1-proton multiplets at δ 5.26 and 5.57 (vinyl protons).



Scheme 19

2.2.3. PREPARATION OF THE CYCLIZATION PRECURSORS

In order to prepare the keto vinyl iodide cyclization precursors, the commercially available enones **53** and **56** in **Table 5** (page 41) were chosen as starting materials. The synthesis of the keto vinylgermanes **85** and **86** required the formation and use of the organocopper(I) reagent **87** (**Scheme 20**). Treatment of a cold (-98 °C) THF solution of compound **31** with two equivalents of *tert*-butyllithium followed by the addition of 1.1 equivalents of CuCN and brief warming to -35 °C, gave a homogeneous tan solution containing the organocopper(I) reagent **87** (**Scheme 20**). Trimethylsilyl bromide and 2-cyclohexen-1-one (**53**) were then added to the organocopper(I) species **87**. After hydrolysis of the intermediate silyl enol ether and workup of the reaction mixture, the glc analysis of the crude oil indicated a complex mixture of products. Three identifiable products were present in a 75:17:8 ratio and accounted for ~70% of the crude mixture. The major product was the desired keto vinylgermane **85** which, after purification, was obtained in 50% yield. The next major product was determined to be the *tert*-butyl adduct **88**. The ¹H nmr spectrum (400 MHz, CDCl₃) of **88** had a characteristic 9-proton singlet at δ 0.90, indicating the presence of the tertiary butyl group.

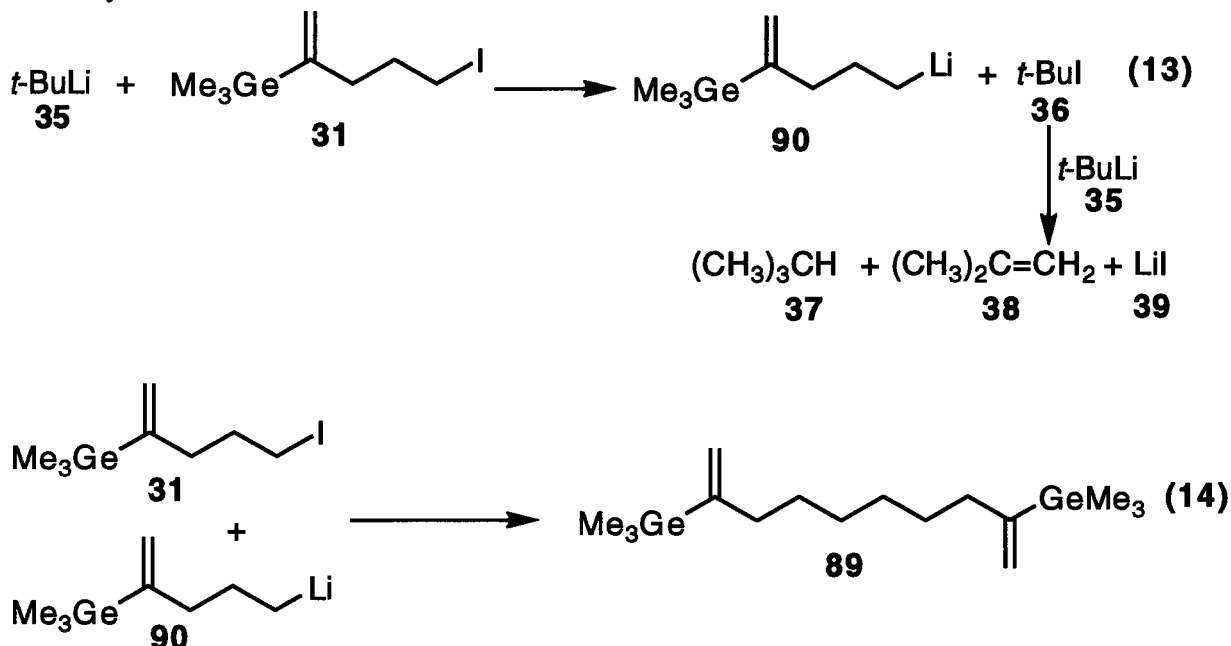


Scheme 20

Finally, the minor product was found to be the vinylgermane dimer **89**. The ¹H nmr

spectrum (400 MHz, CDCl₃) of **89** indicated an 18-proton singlet at δ 0.20 (-GeMe₃ groups), an 8-proton multiplet at δ 1.22-1.43, a 4-proton triplet at δ 2.17 (J = 10 Hz, allylic methylene protons) and two 2-proton multiplets at δ 5.12 and 5.50 (vinyl protons).

The presence of the two byproducts **88** and **89** indicated that the reaction of *t*-BuLi (**35**) with compound **31** (equation 13) was competitive with the reaction of the resultant lithium species **90** with unreacted **31** (equation 14). The reaction of *t*-BuLi (**35**) with the iodide **31** generates the desired lithium species **90** and *t*-BuI (**36**). A second equivalent of *t*-BuLi (**35**) is necessary to react with *t*-BuI (**36**) to generate compounds **37**, **38**, and **39** (equation 13). Thus, two equivalents of *t*-BuLi (**35**) are required for each equivalent of the vinylgermane iodide **31**. Since the formation of the byproduct **89** consumes some of the iodide **31** (equation 14), it follows that there must be some unreacted *t*-BuLi (**35**) present in the reaction media. The unreacted *tert*-butyllithium, in the presence of a copper(I) source, will add in a conjugate fashion to the enone **53**, hence accounting for the formation of the *tert*-butyl adduct **88**.



In order to avoid these side reactions (i.e. the formation of the dimer **89** and the *tert*-butyl adduct **88**), it was decided to alter the experimental procedure so as to minimize the

reaction shown in equation 14. This was accomplished by slow addition of a solution of compound **31** to a cold (-98 °C) solution of *tert*-butyllithium in dry THF (i.e. inverse order of addition of reagents as compared to **Scheme 20**; see equation 15). To the resultant lithium species **90** was added copper(I) cyanide followed by trimethylsilyl bromide and the enone **53**. The vinylgermane adduct **85** was thus obtained in 75% yield, and the byproducts **88** and **89** were no longer detected by glc analysis of the crude reaction mixture.

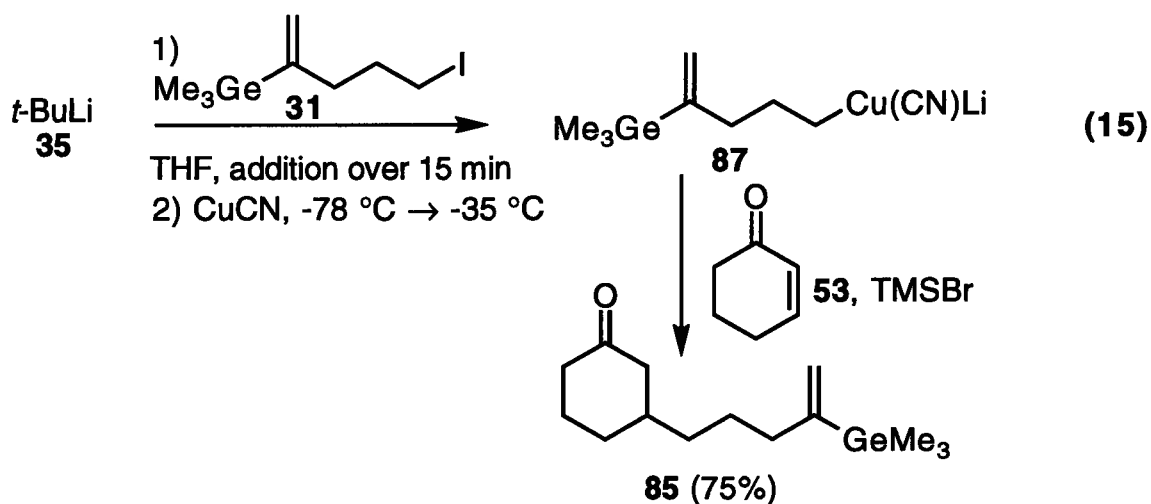
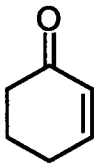
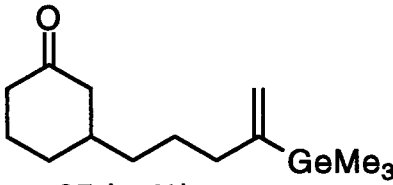
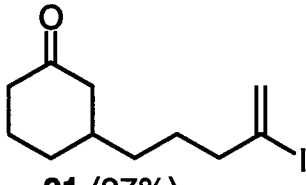
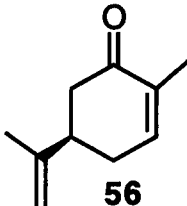
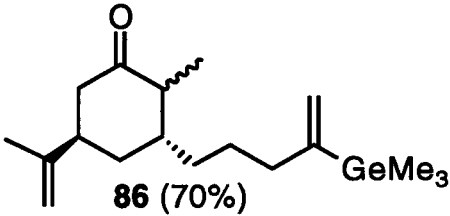
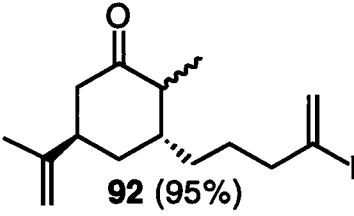


Table 5 summarizes the preparation of the keto vinyl iodide cyclization precursors. By employing the modified conditions for the preparation of the lithium species **90**, as described above, we were able to obtain the vinylgermane adducts **85** and **86** in good yields (75% and 70%, respectively). The keto vinyl iodides **91** and **92** were obtained in excellent yields (97% and 95%, respectively) by treating the vinylgermane adducts **85** and **86** with iodine in CH₂Cl₂. With the cyclization precursors in hand, we were now able to conduct the Pd(0)-catalyzed cyclization studies.

Table 5: Preparation of the Cyclization Precursors for the Six-Membered Ring Annulation Sequence

Entry	Enone	Keto Vinylgermane (Yield) ^a	Keto Vinyl Iodide (Yield) ^b
1	 53	 85 (75%)	 91 (97%)
2	 56	 86 (70%)	 92 (95%)

a- Reaction conditions: reagent **87** prepared via the slow addition of **31** to *tert*-butyllithium, TMSBr (~3 equiv.), THF, -78 °C; H₂O.

b- Reaction conditions: I₂, CH₂Cl₂, rt, overnight.

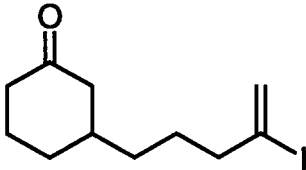
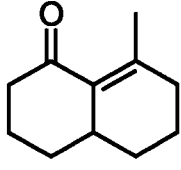
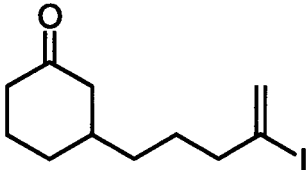
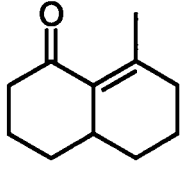
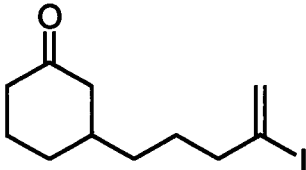
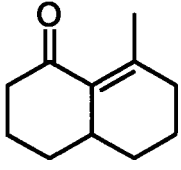
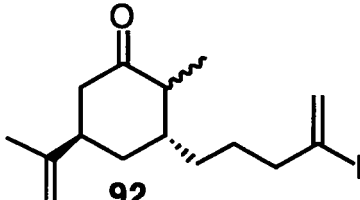
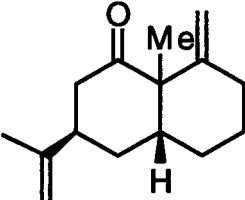
2.2.4. CYCLIZATION STUDIES

Previous studies (**Table 3**, page 29) had indicated that Pd(PPh₃)₄ was the best catalyst for effecting the intramolecular cyclization reaction to generate five-membered rings. **Table 6** (page 43) summarizes our attempts at forming six-membered rings with the Pd(PPh₃)₄ catalyst. The optimum conditions used for the five-membered ring annulation reaction (entry 1, **Table 6**) failed to work for this six-membered ring example. The bicyclic enone **93** was obtained in only 5% yield. The vinyl methyl group in compound **93** was

evident in the ^1H nmr spectrum (400 MHz, CDCl_3) as a three-proton doublet at δ 1.85 (J = 2 Hz). When the conditions were modified by increasing the dilution of the catalyst, substrate and base in the reaction mixture (i.e. the concentration of **91** was diluted from 0.1 M to 0.02 M) and eliminating the *t*-BuOH from the base mixture (entry 2, **Table 6**), the yield of product **93** increased from 5% to 27%. As shown in entry 3, the best yield for enone **93** (41%) was achieved by increasing the dilution of the reactants in the reaction mixture to 0.004 M. These results are difficult to explain since similar modifications in the five-membered ring studies led to a decrease in product yield (**Scheme 17**, page 27). The use of different palladium catalysts did not improve this result, as was the case in the five-membered ring annulation studies (**Table 3**, page 29). When the optimized conditions described in entry 3 (**Table 6**) were applied to the vinyl iodide **92**, the cyclized product **94** was obtained in a dismal 2% yield (entry 4, **Table 6**). The methyl groups in the keto diene **94** were evident in the ^1H nmr spectrum (400 MHz, CDCl_3) as two 3-proton singlets at δ 1.27 (tertiary methyl group) and 1.75 (vinyl methyl group). The vinyl protons were evident as four 1-proton singlets at δ 4.70, 4.75, 4.81, and 4.94. Unfortunately, we did not have a sufficient amount of compound **94** to determine the stereochemistry at the ring junction.

These poor results led us to abandon any further attempts at forming six-membered rings using the Pd(0)-catalyzed cyclization conditions. The synthesis of six-membered rings using this method requires the formation of a seven-membered ring palladacycle (see step **B**, **Scheme 11**, page 15). The formation of this palladacycle is probably the rate determining step (*vide supra*). Thus, if the seven-membered ring formation is slow, the cycle might break down and other side reactions could compete with the intended cyclization. It should be noted that the mass balance for the reactions reported in **Table 6** was poor and no starting material was recovered. Attempts to recover and identify any side products were unsuccessful.

Table 6: Attempts at Six-Membered Ring Formation by Employing the Pd(0)-Catalyzed Cyclization Reaction

Entry	Keto Vinyl Iodide	Conditions	Product (Yield)
1a	 91	1) Pd(PPh ₃) ₄ (34 mol%), <u>THF (0.1 M)</u> 2) slow addition of <i>t</i> -BuOK in THF/ <i>t</i> -BuOH	 93 (5%)
2	 91	1) Pd(PPh ₃) ₄ (34 mol%), <u>THF (0.02 M)</u> 2) slow addition of <i>t</i> -BuOK in THF ^b	 93 (27%)
3	 91	1) Pd(PPh ₃) ₄ (36 mol%), <u>THF (0.004 M)</u> 2) slow addition of <i>t</i> -BuOK in THF ^b	 93 (41%)
4	 92	1) Pd(PPh ₃) ₄ (36 mol%), <u>THF (0.005 M)</u> 2) slow addition of <i>t</i> -BuOK in THF ^b	 94 (2%)

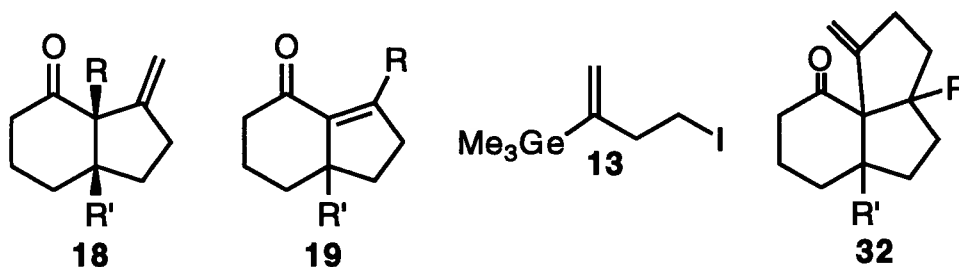
a- Conditions used for this entry were very similar to those reported for the five-membered ring annulation sequence.

b- No *t*-BuOH was used in the base mixture.

2.3. THE FORMATION OF TRICYCLIC RING SYSTEMS EMPLOYING THE ANNULATION METHOD BASED ON THE PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING

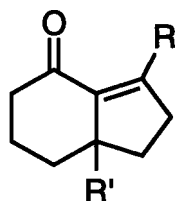
2.3.1. INTRODUCTORY REMARKS

As described in Section 2.1., the methylenecyclopentane annulation sequence was optimized and successfully employed in the synthesis of functionalized bicyclo[4.3.0]nonane systems **18** and **19**. The latter products (general structure **19**) could undergo yet another annulation sequence with the bifunctional vinylgermane reagent **13** to produce more complex tricyclic ring systems of general structure **32**. The exploration of this possibility is the main focus of the work to be described. There were several questions which needed to be addressed. How reactive are enones **19** to the 1,4-conjugate addition conditions employed in the methylenecyclopentane annulation sequence? What would be the stereochemical outcome of such reactions? And finally, will the Pd(0)-catalyzed cyclization reaction proceed smoothly and effectively to afford the tricyclo[6.4.0.0^{1,5}]dodecan-12-ones of general structure **32**?



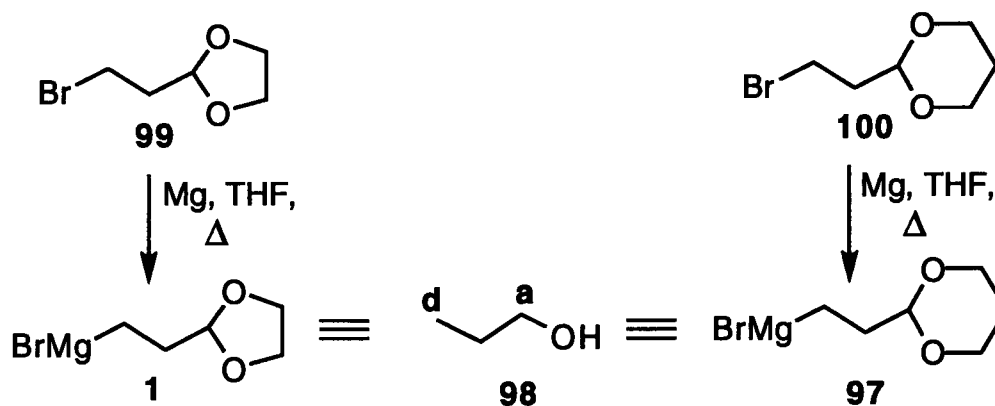
2.3.2. PREPARATION OF THE BICYCLIC[4.3.0]NON-9-EN-2-ONES

In order to begin our attempts at synthesizing the tricyclic keto alkenes of general structure **32**, it was first necessary to prepare the bicyclic enones **74**, **75**, **95**, and **96**. The enones **74** and **75** (in which R = Me) were prepared as previously described in Section 2.1. (page 25). However, when R = H (enones **95** and **96**), an annulation route employing a three carbon synthon was necessary for their construction (see below).



- 74** R=Me, R'=H
75 R=Me, R'=Me
95 R=H, R'=H
96 R=H, R'=Me

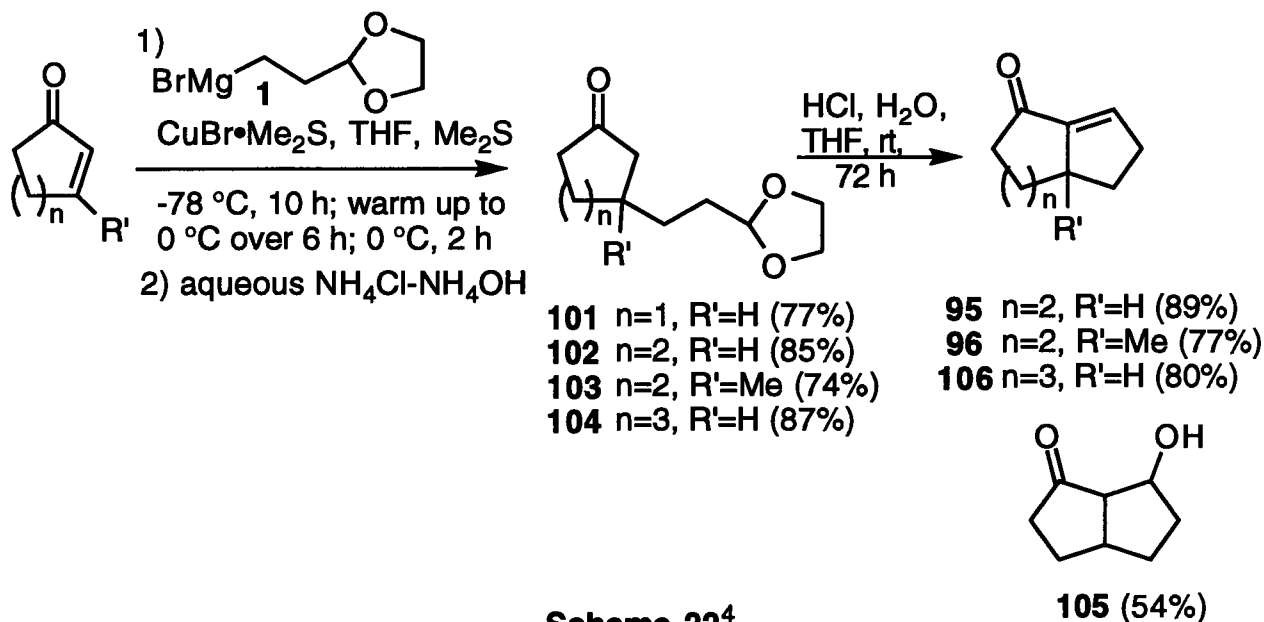
The Grignard reagents **1** and **97** are suitable synthetic equivalents to the α^1, δ^3 -synthon **98** and can be obtained by reacting concentrated solutions of the corresponding commercially available bromo acetals **99** and **100** with an excess of freshly ground magnesium turnings (**Scheme 21**).⁴⁵



Scheme 21

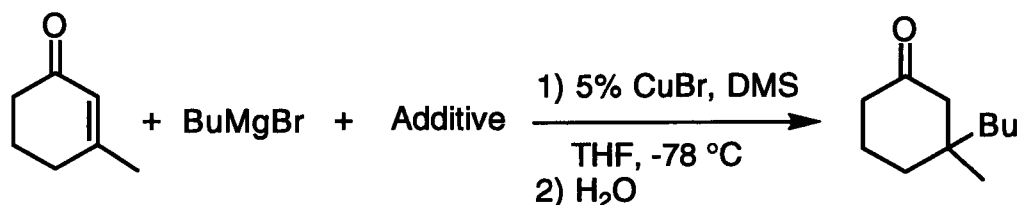
Helquist and coworkers^{4,46} developed an annulation sequence which involves the conjugate addition of the Grignard reagent **1** to an enone substrate, followed by hydrolysis of the acetal function and an intramolecular aldol cyclization reaction. Four such examples are presented in **Scheme 22**. 2-Cyclopenten-1-one, 2-cyclohexen-1-one, 3-methyl-2-cyclohexen-1-one and 2-cyclohepten-1-one underwent a copper(I)-catalyzed conjugate addition with the Grignard reagent **1** to provide the resultant keto acetals **101-104** in isolated yields ranging from 74% to 87%. The next step in the sequence involved acidic treatment of the acetals **101-104**. The bicyclic ketol **105** did not undergo spontaneous dehydration following the acid mediated

cyclization reaction. It seems that β -hydroxy ketones of this type do not undergo elimination of water under these reaction conditions. However, in the other three cases, dehydration occurred to yield, after workup and purification, enones **95**, **96**, and **106**.



Scheme 22⁴

Stowell⁴⁷ discovered that the formation of the Grignard reagent **97** from the six-membered ring bromo acetal **100** was higher yielding than the formation of reagent **1** from the corresponding five-membered ring bromo acetal **99** (**Scheme 20**). For this reason, we chose to employ the Grignard reagent **97** in Helquist's annulation method to generate enones **95** and **96**. This annulation procedure was further modified according to the method of Kuwajima and coworkers.⁴⁸ Kuwajima and coworkers reported that the use of TMSCl and HMPA greatly improves the yields of copper(I)-catalyzed conjugate addition reactions, particularly in cases of unreactive enones (see **Scheme 23**).



Additive	Yield of Ketone
None	1-2%
TMSCl (2 equiv.)	30-40%
TMSCl/HMPA (1-2 equiv. each)	99%

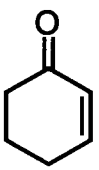
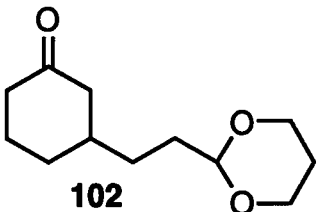
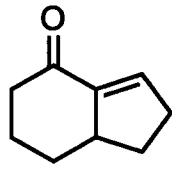
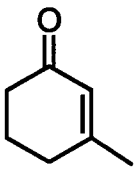
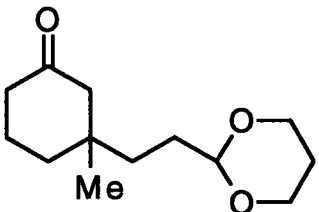
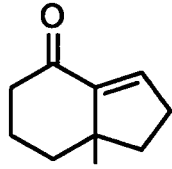
Scheme 23⁴⁸

Table 7 summarizes the preparation of the bicyclic enones **95** and **96**. By employing the modifications reported by Kuwajima and coworkers,⁴⁸ the preparation of the keto acetals **102** and **103** was accomplished cleanly and efficiently (see **Table 7**). Thus, treatment of 2-cyclohexen-1-one (**53**) with the Grignard reagent **97** in the presence of TMSCl, HMPA, and a catalytic amount of CuBr•Me₂S afforded, after workup and purification, the keto acetal **102** in 88% yield (entry 1, **Table 7**). The IR spectrum of **102** exhibited an absorbance at 1714 cm⁻¹ for a carbonyl function characteristic of cyclohexanones, and the ¹H nmr spectrum (400 MHz, C₆D₆) indicated the presence of the cyclic acetal moiety (two broad dd, 2H each, at δ 3.30-3.36 and 3.79-3.83; and a triplet, 1H, at δ 4.29-4.32).

A solution of each of the keto acetals **102** and **103** in THF was refluxed in the presence of 0.1 M hydrochloric acid to generate the bicyclic enones **95** and **96** in 73% and 61% yield, respectively (**Table 7**). The spectral data of enones **95** and **96** were identical with those reported by Helquist and coworkers.⁴ Helquist's cyclization conditions were carried out at room temperature (**Scheme 22**). We found that by refluxing a solution of each keto acetal in HCl/H₂O/THF, the reaction went to completion in a much shorter time (14-19 h (**Table 7**) vs. 72 h (**Scheme 22**)). However, the yields of the bicyclic enones **95** and **96** were slightly lower than those reported by Helquist and coworkers. With the bicyclic enones **74**,

75, **95**, and **96** in hand, we were ready to attempt the annulation sequence to generate the tricyclic keto alkenes of general structure **32**.

Table 7: Preparation of the Bicyclic Enones **95** and **96** According to a Modified Version of Helquist's Annulation Sequence

Entry	Enone	Keto Acetal (Yield) ^a	Bicyclic Enone (Yield) ^b
1	 53	 102 (88%)	 95 (73%)
2	 54	 Me 103 (95%)	 Me 96 (61%)

a- Reaction Conditions:

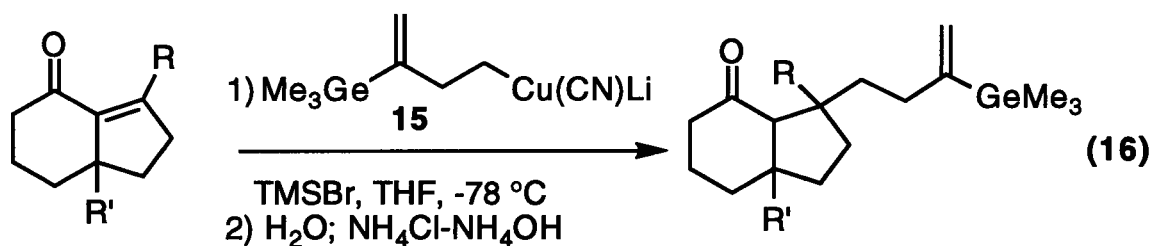
1) Grignard reagent **97** (1.3 equiv.), TMSCl (2.5 equiv.), HMPA (2.5 equiv.), CuBr•Me₂S (~15 mol%), THF, -78 °C 3-5 h; warmed to -48 °C for 1 h

2) H₂O; aqueous NH₄Cl-NH₄OH

b- Reaction Conditions: THF/0.1 M HCl (2:1), Δ, 14-19 h

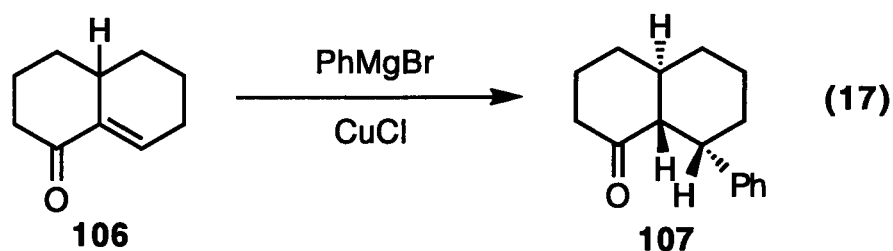
2.3.3. PREPARATION OF THE BICYCLIC KETO VINYLGERMANES

The first step in the preparation of the cyclization precursors involves the conjugate addition of the organocopper(I) reagent **15** to a bicyclo[4.3.0]non-9-en-2-one (equation **16**). Similar addition reactions have been reported for bicyclo[4.4.0]dec-10-en-2-ones and bicyclo[3.3.0]oct-8-en-2-ones, and these examples will be described below.

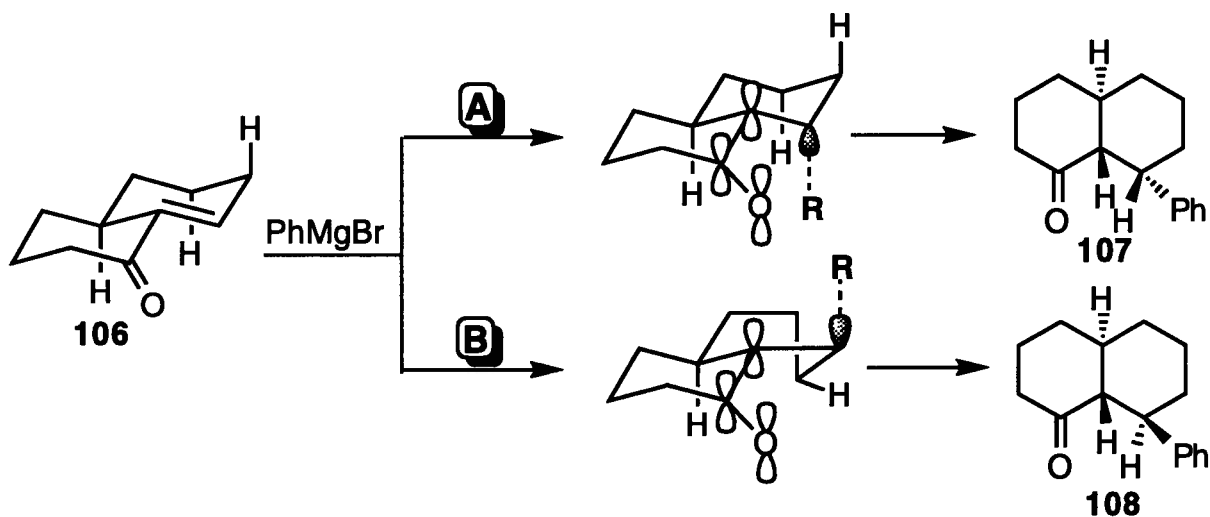


2.3.3.1. Literature Precedent for Conjugate Addition Reactions to Bicyclo[4.4.0]dec-10-en-2-ones

It has been suggested that the preferred mode of addition of organometallic reagents to α,β -unsaturated ketones is antiparallel entry during which continuous overlap of the developing sigma bond with the π system of the enone is possible through the transition state.⁴⁹ Conjugate addition reactions are typically under kinetic control and the stereochemical result has often been explained on the basis of attack of the nucleophile perpendicular to the olefinic bond, and from the least hindered side of the molecule.^{50,51} In cyclohexenones where there are no over-riding steric factors, the stereochemical outcome of this process is axial substitution. For example, House and Thompson⁵⁰ found that the reaction of phenyl magnesium bromide and copper(I) chloride with the bicyclo[4.4.0]dec-10-en-2-one (**106**) resulted in the stereoselective formation of the phenyl adduct **107** (equation **17**).

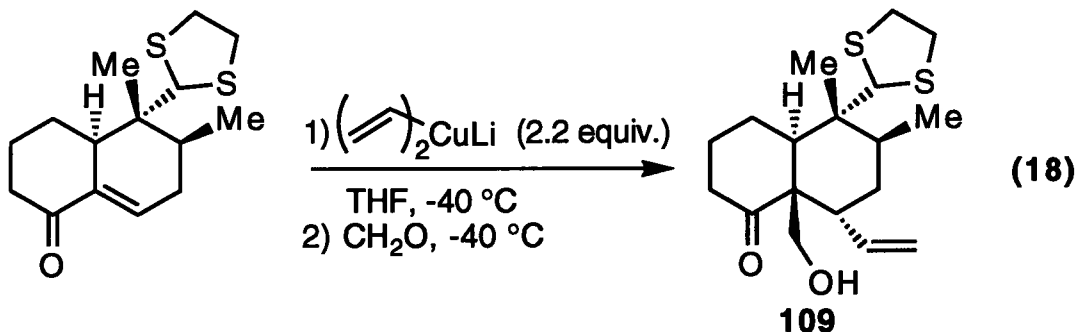


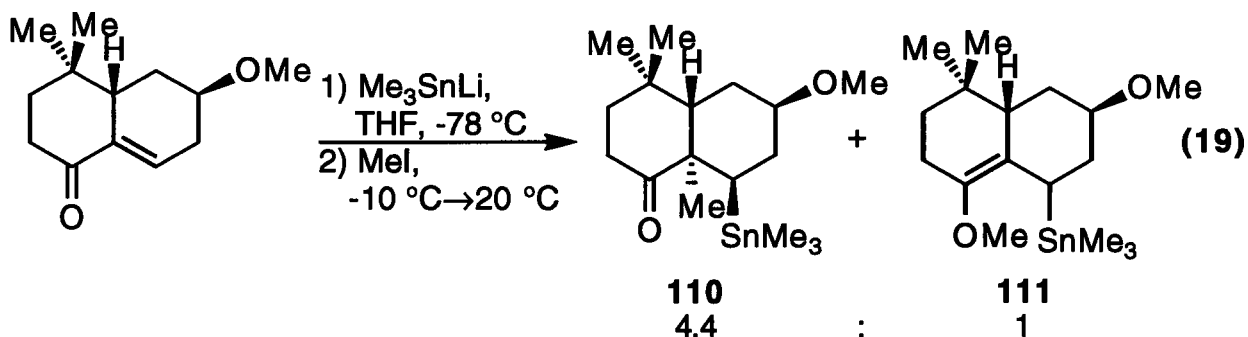
Scheme 24 illustrates the two possible pathways (**A** and **B**) for the conjugate addition reaction that allows the cuprate reagent to approach the enone **106** in a perpendicular fashion. Pathway **A** proceeds via a chair-chair transition state and generates the observed adduct **107**. Pathway **B**, on the other hand, must adopt a chair-boat conformation to preserve the stereoelectronic stabilization. The chair-boat conformation is clearly less favorable than the chair-chair conformation and this explains the sole formation of adduct **107** (House and Thompson report no evidence of adduct **108**).



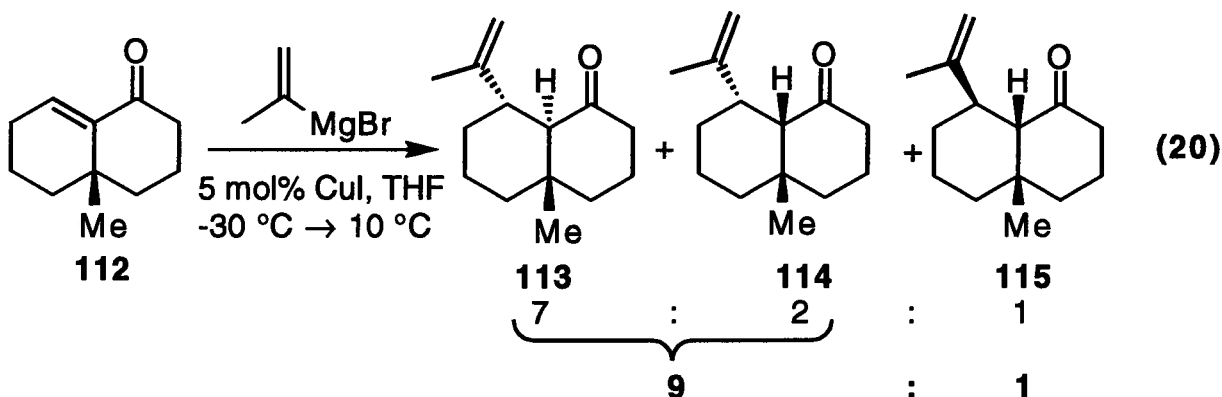
Scheme 24⁵⁰

Similar stereochemical results have been observed by Ley *et al.*⁵² (equation 18) and Welzel and coworkers⁵³ (equation 19). In both cases, the conjugate addition reaction proceeded stereoselectively to yield the axial adducts **109** and **110** (equations 18 and 19, respectively). The relative stereochemistry of the minor O-alkylation product **111** (equation 19) was not determined.



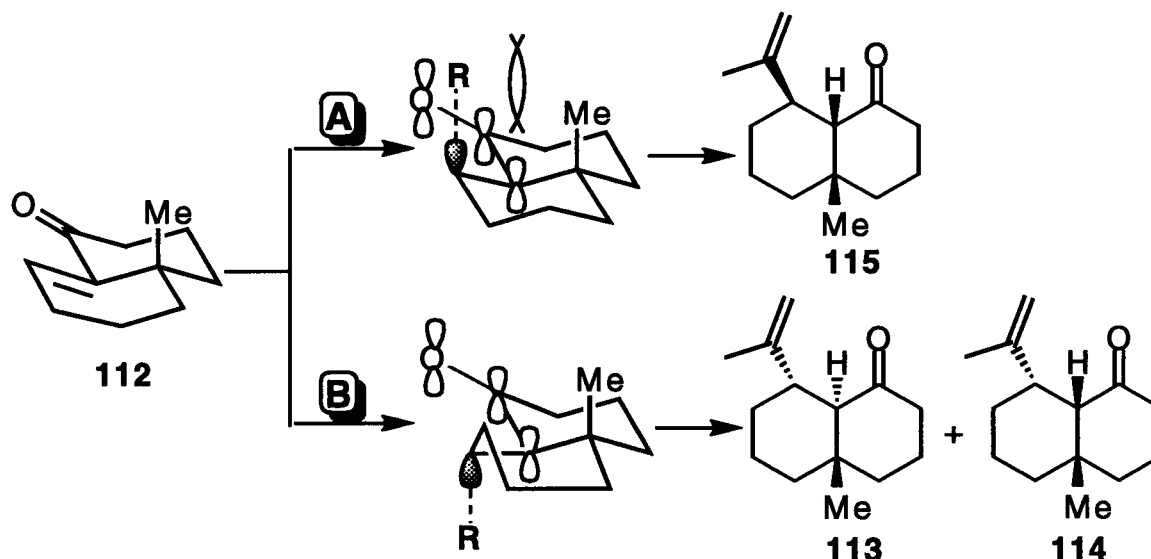


In the conjugate addition reactions depicted in equations 17, 18, and 19 there were no serious steric interactions. That is, these reactions were controlled exclusively by stereoelectronic factors. Obviously, steric factors can play an important role in determining the nature of the transition state.⁵⁴ What would be the stereochemical outcome of a case in which the reagent approaching the enone system from a perpendicular direction would encounter severe non-bonded interactions? One such case, reported by Boeckman and Silver,⁴⁹ is the copper(I)-catalyzed addition of an isopropenyl Grignard reagent to 6-methylbicyclo[4.4.0]dec-10-en-2-one (112) (equation 20). The equatorial adducts 113 and 114 were, in this case, favored over the axial adduct 115.



As illustrated in **Scheme 25**, two possible pathways **A** and **B** result in the formation of the adducts 113-115. Although pathway **A** leads to a chair-chair transition state, this route is disfavored due to a severe pseudo 1,3-diaxial steric interaction between the angular methyl group and the incoming organocopper(I) reagent. Pathway **B** is the major route since it

allows for the less hindered approach of the isopropenyl Grignard reagent while retaining the perpendicular approach of the reagent. In the absence of the angular methyl group, the stereochemical outcome of the conjugate addition reaction would be reversed, resulting in the sole formation of the axial adduct (see equation 17 and **Scheme 24**).



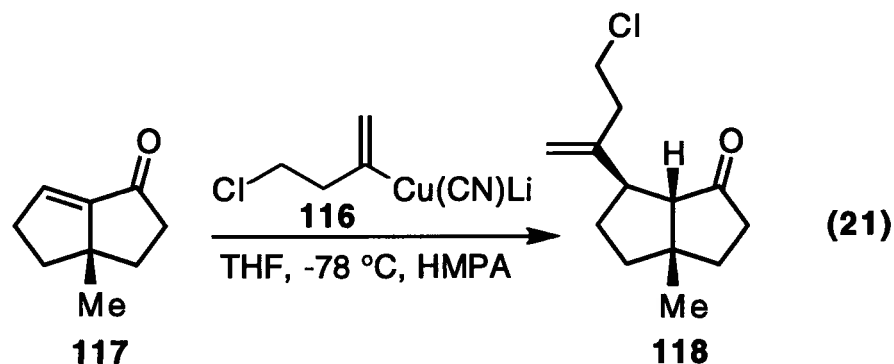
Scheme 25

From the above examples, one can see that there is a balance between steric and stereoelectronic factors. Both these factors must be taken into account when attempting to predict the stereochemical outcome of a conjugate addition reaction.

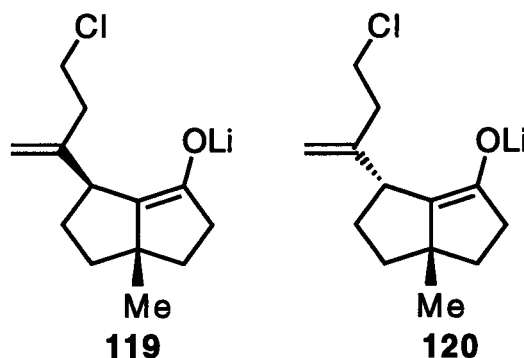
2.3.3.2. Literature Precedent for Conjugate Addition Reactions to Bicyclo[3.3.0]oct-8-en-2-ones

There is ample literature precedent for stereoselective conjugate addition reactions to bicyclo[3.3.0]oct-8-en-2-ones. If stereoelectronic factors play a key role in regulating the stereochemistry of such reactions, the transition states can be assumed to be product-like (i.e. enolate-like) in nature. Thus, the developing bond at the β -carbon of the enone system is created, as nearly as possible, in a direction perpendicular to the plane of the forming enolate anion. Piers and Renaud^{12,55} found that the addition of the organocopper(I) reagent 116 to 5-

methylbicyclo[3.3.0]oct-8-en-2-one (**117**) led to the stereoselective formation of the 1,4-addition adduct **118** (equation 21).



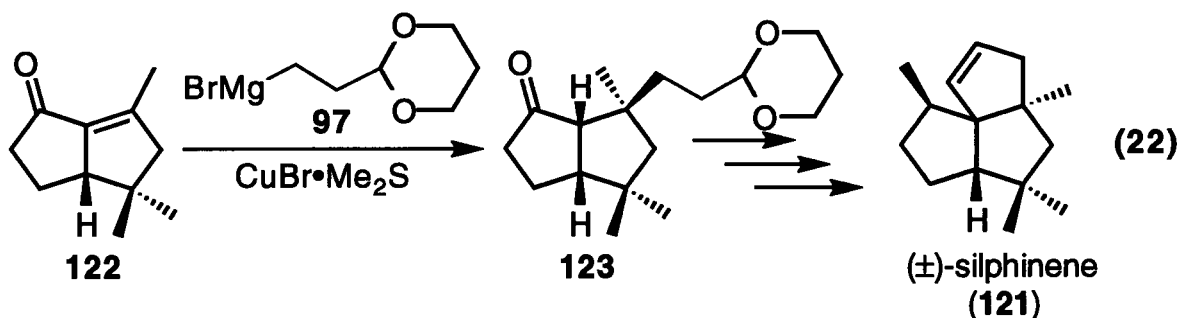
Upon examination of molecular models of the two possible enolate anions (**119** and **120**) that could result from the reaction of **116** with **117**, only **119** can comfortably adopt a conformation such that the newly introduced side chain is attached to the ring system in an orientation perpendicular to the plane of the adjacent enolate double bond.⁵⁶



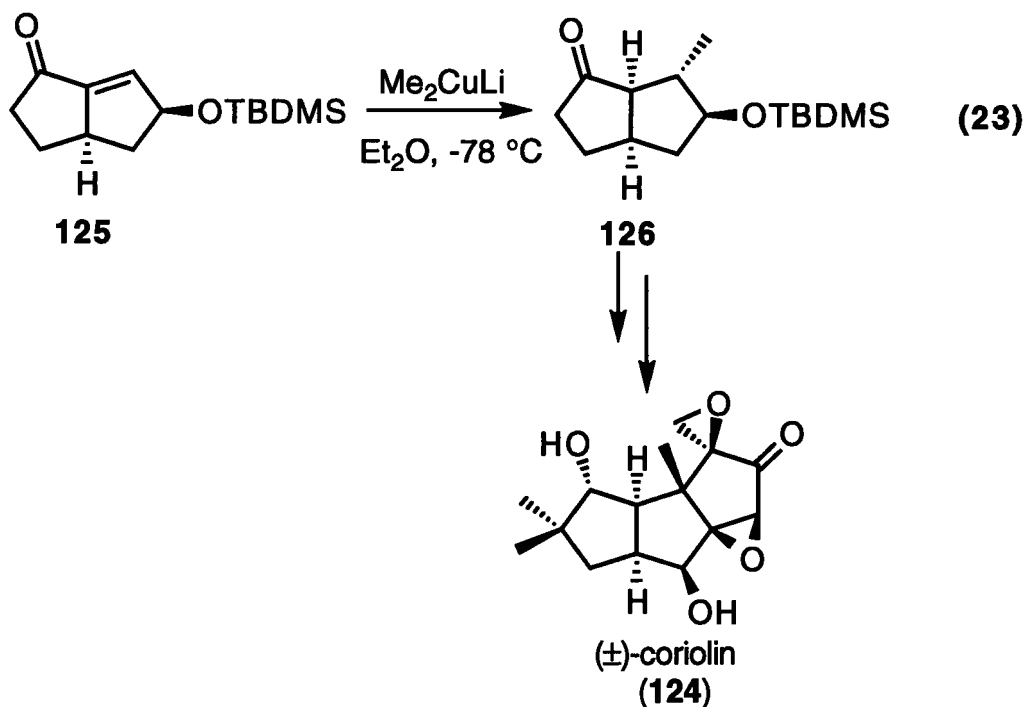
As a result, the conjugate addition of the organocopper(I) reagent **116** takes place *cis* to the angular methyl group, even though this is the more hindered face of the enone system. This result is in contrast to that obtained for the conjugate addition reactions to bicyclo-[4.4.0]dec-10-en-2-ones in which there is an angular methyl group (equation 20). Obviously, in the latter cases, steric factors play a bigger role than in the conjugate addition reactions to bicyclo[3.3.0]oct-8-en-2-ones.

Another example of a stereoselective conjugate addition reaction to a bicyclo[3.3.0]oct-8-en-2-one was reported by Paquette and Leone-Bay⁵⁷ in their work on the

synthesis of (±)-silphinene (**121**). The copper(I)-catalyzed conjugate addition of the Grignard reagent **97** to the enone **122** afforded exclusively the adduct **123**, in which the side chain had been introduced stereoselectively *cis* to the angular hydrogen (equation **22**).

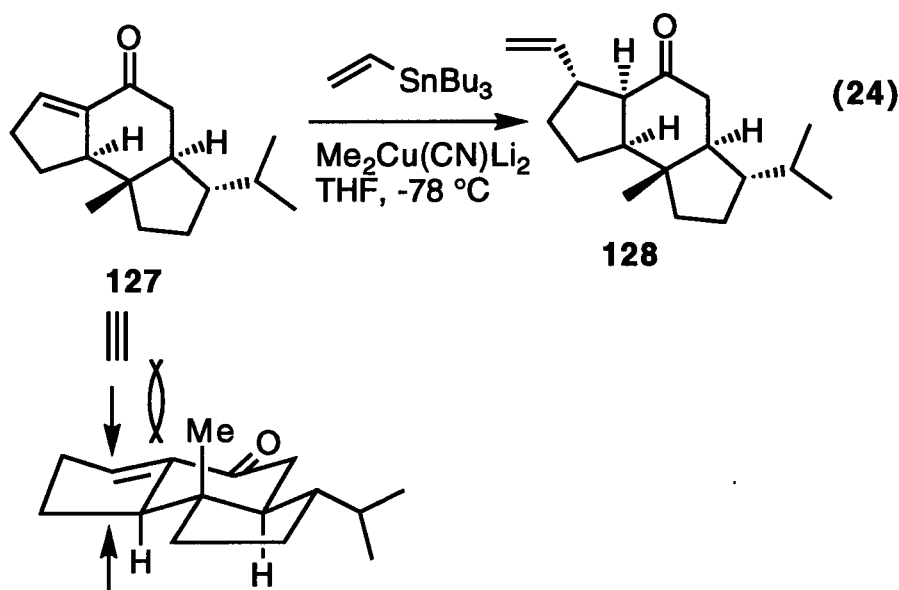


In a paper describing their synthesis of (±)-coriolin (**124**), Ikegami and coworkers⁵⁸ reported the stereoselective addition of lithium dimethylcuprate to the functionalized bicyclo-[3.3.0]oct-8-en-2-one **125** (equation **23**). The adduct **126**, in which the methyl group had been introduced *cis* to the angular hydrogen, was an intermediate in the synthesis of (±)-coriolin (**124**).

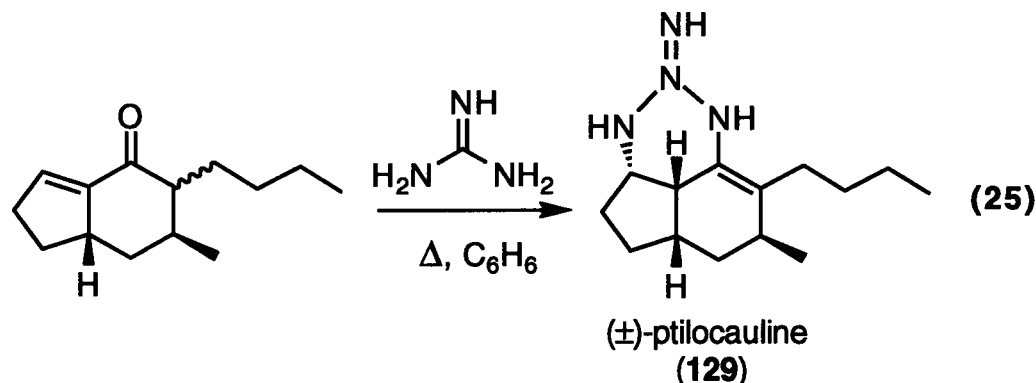


2.3.3.3. Literature Precedent for Conjugate Addition Reactions to Bicyclo[4.3.0]non-9-en-2-ones

As previously described, there has been extensive literature precedent for conjugate addition reactions to functionalized bicyclo[4.4.0]dec-10-en-2-ones and bicyclo[3.3.0]oct-8-en-2-ones. The stereochemistry of such additions has been governed by both steric and stereoelectronic factors. The annulation sequence to be detailed in this section involves conjugate addition of a cuprate reagent to bicyclo[4.3.0]non-9-en-2-ones. Surprisingly, there is very little literature precedent for predicting the stereochemical outcome of such a reaction. In the synthesis of 18-oxo-3-virgene, Paquette and Wang⁵⁹ exposed enone **127** to a mixed higher order cuprate prepared from tri-*n*-butyl(vinyl)stannane and $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ (equation **24**). The sole adduct **128** was obtained. Paquette and Wang rationalize that the 1,4-addition and subsequent protonation both occurred from the less hindered direction (i.e. that steric effects govern this reaction).



The only other known example of an addition to a bicyclo[4.3.0]non-9-en-2-one was reported by Snider and Faith⁶⁰ in their synthesis of (±)-ptilocaulin (**129**) (equation **25**). However, this reaction is known to be reversible and ptilocaulin is the thermodynamically more stable of the two possible isomers.⁶¹



2.3.3.4. Conjugate Addition Reactions to the Bicyclo[4.3.0]non-9-en-2-ones **74**, **75**, **95**, and **96**

There is no obvious literature precedent for a steric and/or stereoelectronic bias for conjugate addition reactions to bicyclo[4.3.0]non-9-en-2-ones. If, however, the stereochemical outcome of the conjugate addition to these enones behaves in a manner similar to that observed with bicyclo[4.4.0]dec-10-en-2-ones and bicyclo[3.3.0]oct-8-en-2-ones, one would expect the addition to proceed *cis* to the angular group, providing there are no serious steric interactions. **Table 8** summarizes the results of the conjugate addition of the organocopper(I) reagent **15** to the bicyclo[4.3.0]non-9-en-2-ones. The intermediate silyl enol ethers were hydrolyzed to give, in all cases, a mixture of *cis*- and *trans*-fused addition products, with the *cis*-fused epimer predominating. We were very pleased to observe that the conjugate addition reaction had proceeded stereoselectively in each case and that the yields for these reactions were excellent. Interestingly enough, in each of the cases studied, the vinylgermane side chain had been introduced *trans* to the angular group. This result is opposite to that observed with the bicyclo[4.4.0]dec-10-en-2-ones and the bicyclo[3.3.0]oct-8-en-2-ones.

Within the set of substrates examined, the size of the angular group clearly had no significant effect on the stereochemical outcome of the addition. When the angular group is a proton ($R' = H$, see entries 1 and 3, **Table 8**), there are no significant steric differences between the approach of cuprate reagent **15** to the alpha or beta face of the enone. Yet, in

these cases, the cuprate reagent was still introduced *trans* to the angular proton. Since steric factors do not seem to govern the stereochemistry of the conjugate addition reaction, we tried to rationalize the results based on stereoelectronic factors. As previously discussed (see pages 52-53), if the transition state is assumed to be product-like in nature, the developing bond at the β -carbon of the enone system is created, as nearly as possible, in a direction perpendicular to the plane of the forming enolate anion. Upon examination of molecular models of the two possible enolate anions (**129a** and **129b**) that could result from the reaction of reagent **15** with an enone of general structure **19**, it appears that **129b** can more comfortably adopt a conformation such that the newly introduced vinylgermane side chain is in an orientation perpendicular to the plane of the adjacent enolate double bond. However, our results indicate that the enolate **129a** must be the intermediate in the conjugate addition reaction. Clearly, we cannot rationalize our results based on either steric or conventional stereoelectronic effects. Each entry in **Table 8** will now be discussed in detail, including the verification of the stereochemistry for each product.

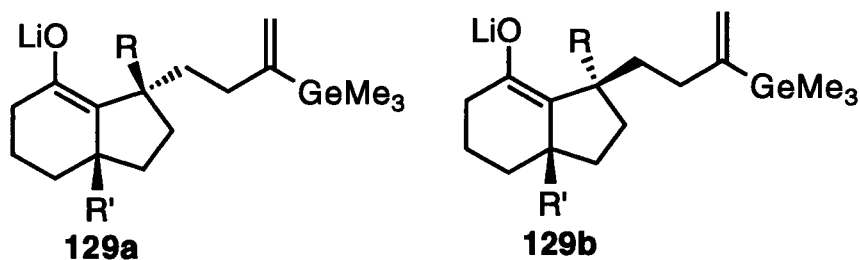
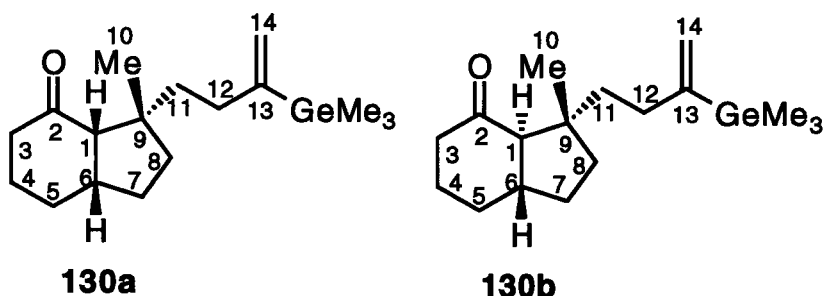


Table 8: Results of the Conjugate Addition Reactions of Reagent **15** to the Bicyclo-[4.3.0]non-9-en-2-ones

Entry	Bicyclic Enone	R	R'	Yield ^a	Cis-Fused Adduct	Trans-Fused Adduct
					RATIO ^b	
1	74	Me	H	89%	130a 9	130b 1
2	75	Me	Me	86%	131a 20	131b 1
3	95	H	H	88%	132a 5	132b 1
4	96	H	Me	98%	133a 6	133b 1

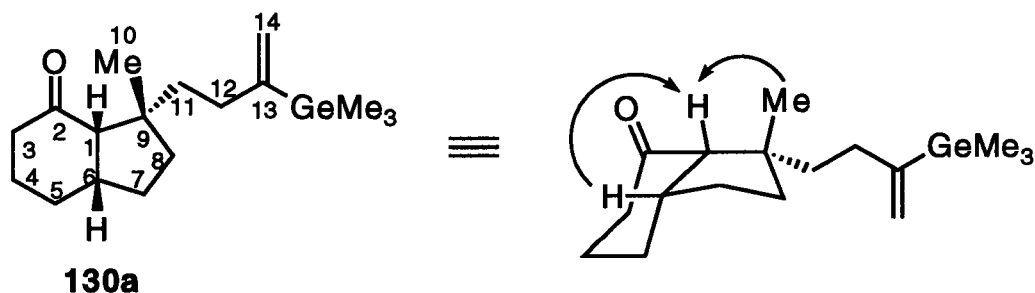
a- This yield refers to the isolated yield of the cis- and trans-fused adducts combined.

b- The ratio was determined by ¹H nmr spectroscopic analysis of the crude product mixture.

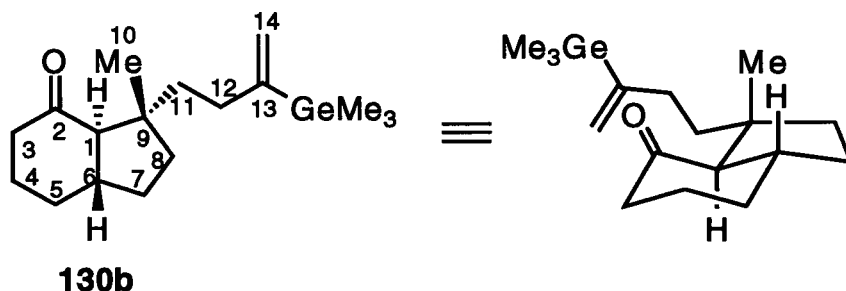


Enone **74** (entry 1, **Table 8**) was treated with two equivalents of the organocopper(I) reagent **15** in the presence of TMSBr to afford, after hydrolysis of the intermediate silyl enol ether, a 9:1 mixture of the cis- and trans-fused adducts **130a** and **130b** in 89% overall yield.

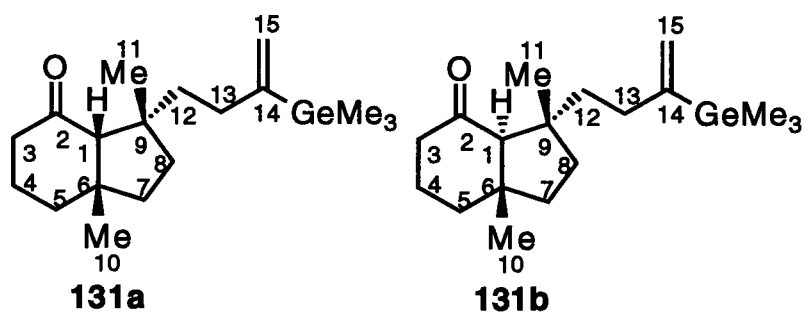
It was evident that these isomers were epimeric when, under epimerizing conditions (NaOMe/MeOH, *vide infra*), isomer **130a** equilibrated to a mixture of **130a** and **130b**. Similarly, isomer **130b** was also equilibrated to a mixture of **130a** and **130b** when treated with NaOMe/MeOH (*vide infra*). These two isomers were readily separated by flash chromatography. In fact, separation of the cis- and trans-fused epimers was easily accomplished for all the entries listed in **Table 8**.



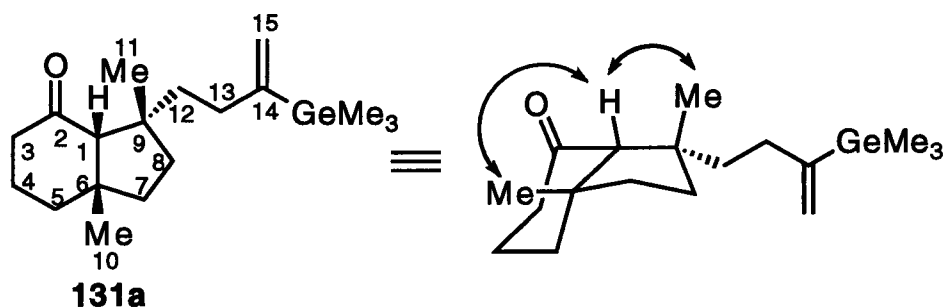
The ^1H nmr spectrum (400 MHz, acetone- d_6) of **130a** revealed a signal for the Me_3Ge group at δ 0.20 (s), a signal for the tertiary methyl group (Me-10) at δ 1.13 (s), and two signals for the vinylic protons at δ 4.61 (d, $J = 1$ Hz) and 4.96 (br s). The angular proton H-1 was evident as a doublet at δ 2.31 ($J = 9$ Hz). The COSY spectrum allowed the assignment of the other angular proton H-6 (δ 2.43-2.47, m) through the correlation of its signal to the H-1 resonance (see **Table 22**, experimental, page 179). NOE difference experiments were consistent with the assignment of the relative configuration at each of the carbons 1, 6 and 9. Irradiation of the signal at δ 1.13 (Me-10) caused an enhancement of the signal at δ 2.31 (H-1). Irradiation of the signal at δ 2.43-2.47 (H-6) also caused an enhancement of the signal at δ 2.31 (H-1). These experiments confirmed that the ring junction was cis-fused and they were consistent with the assigned stereochemical outcome of the conjugate addition reaction.



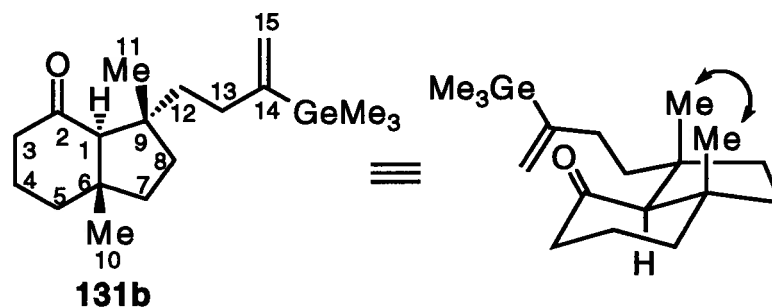
The ^1H nmr spectrum (400 MHz, CDCl_3) of the trans-fused isomer **130b** indicated a signal for the Me_3Ge group at δ 0.19 (s), a signal for the tertiary methyl group (Me-10) at δ 1.09 (s), and two signals for the vinyl protons at δ 5.12-5.13 (m) and 5.48-5.49 (m). The angular proton H-1 was evident as a doublet at δ 1.85 with a larger coupling constant (J = 12.5 Hz) than that observed for the corresponding proton in the cis-fused isomer **130a** (J = 9 Hz). Compound **130b** was epimerized to a mixture of **130a** and **130b**. Thus, the stereochemistry at C-9 was shown to be identical to that observed for the epimer **130a**.



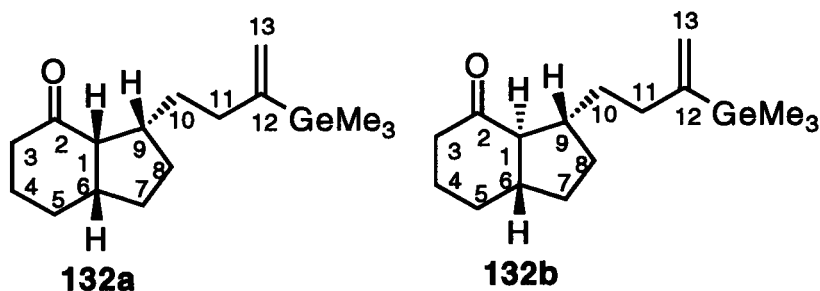
When enone **75** (entry 2, Table 8) was treated with two equivalents of the organocopper(I) reagent **15** in the presence of TMSBr, a 20:1 mixture of the cis- and trans-fused adducts **131a** and **131b** was obtained in 86% overall yield. The ^1H nmr spectrum (400 MHz, acetone- d_6) of the cis-fused epimer **131a** revealed the following diagnostic signals: δ 0.20 (s, $-\text{GeMe}_3$), 1.08 (br s, Me-10), 1.13 (br s, Me-11), 1.96 (br s, H-1), 4.61-4.62 (m, H-15), and 4.95-4.96 (m, H-15').



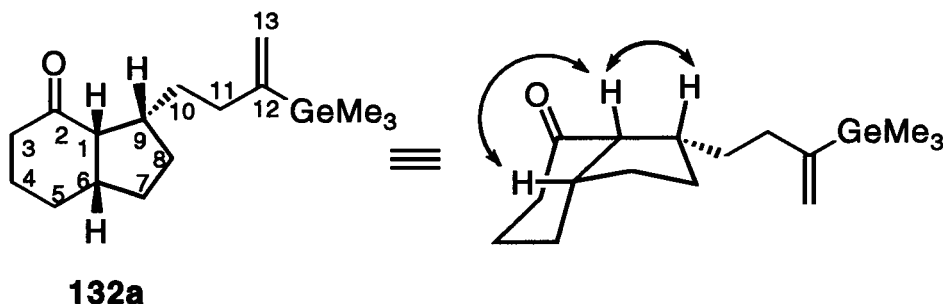
NOE difference experiments were consistent with the stereochemistry of the cis-fused adduct **131a**. Irradiation of the signal at δ 1.08 (Me-10) caused an enhancement of the signal at δ 1.96 (H-1), thereby confirming the nature of the ring junction (cis). Irradiation of the signal at δ 1.13 (Me-11) also caused an enhancement of the signal at δ 1.96 (H-1). Irradiation of the signal at δ 1.96 (H-1) caused enhancement of the signals of both methyl groups (Me-10 and Me-11). These results were consistent with the assigned stereochemistry at C-9.



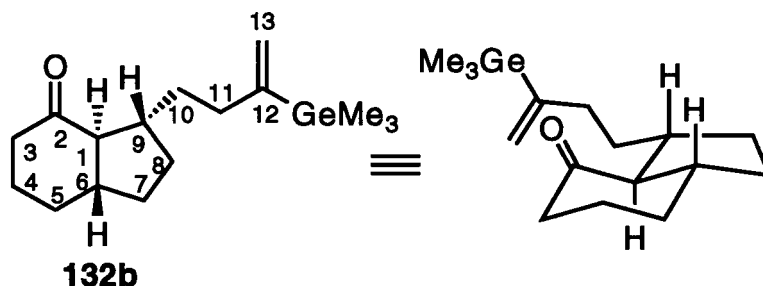
The ^1H nmr spectrum (400 MHz, acetone- d_6) of the trans-fused adduct **131b** revealed signals at δ 0.19 (s, -GeMe₃), 0.92 (s, Me), 1.30 (s, Me), 2.28 (s, H-1), 5.14 (br s, H-15), and 5.50 (br s, H-15'). In NOE difference experiments, irradiation of the signal at δ 0.92 (Me) caused an enhancement of the signal at δ 1.30 (Me) and vice versa. Upon examination of molecular models, it becomes clear that a nuclear Overhauser enhancement between the two methyl groups is possible only when the ring junction is trans-fused. When this epimer was subjected to equilibrating conditions (NaOMe/MeOH, *vide infra*), it was completely converted into the cis-fused isomer **131a**.



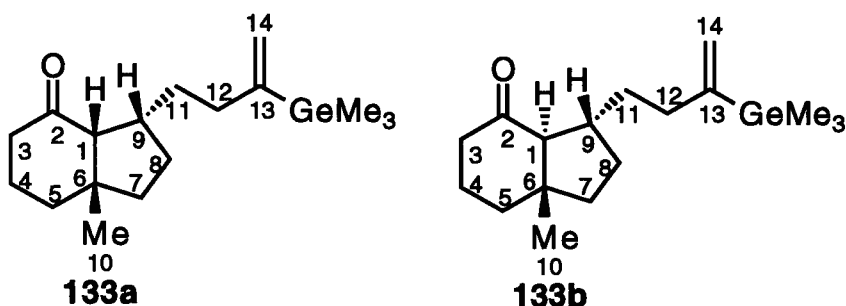
Enone **95** (entry 3, **Table 8**) was treated with 1.5 equivalents of the organocopper(I) reagent **15** in the presence of TMSBr to give a 5:1 mixture of **132a** and **132b** in 88% overall yield. The ^1H nmr spectrum (400 MHz, CDCl_3) of the major cis-fused epimer **132a** revealed a signal for the Me_3Ge group at δ 0.18 (s), a signal for H-1 at δ 2.68-2.72 (dd, $J = 8, 8$ Hz), and two multiplets at δ 5.13-5.14 and 5.46-5.47 for the vinyl protons (H-13 and H-13'). The COSY spectrum allowed the assignment of H-6 (δ 2.08-2.15, m) and H-9 (δ 2.37-2.43, m) through the correlation of their signals to that of the angular proton H-1 (see **Table 24**, experimental, page 188).



NOE difference experiments were consistent with the assignment of the relative configuration at each of the carbons 1, 6, and 9. Irradiation of the signal at δ 2.08-2.15 (H-6) led to the enhancement of the signal at δ 2.68-2.72 (H-1). Irradiation of the signal at δ 2.37-2.43 (H-9) also led to enhancement of the signal at δ 2.68-2.72 (H-1). Irradiation of the signal at δ 2.68-2.72 (H-1) produced enhancement of the signals at δ 2.08-2.15 (H-6) and 2.37-2.43 (H-9).



The ^1H nmr spectrum (400 MHz, CDCl_3) of the trans-fused adduct **132b** revealed resonances at δ 0.20 (s, $-\text{GeMe}_3$), 5.14 (br s, vinyl proton), and 5.50 (br s, vinyl proton). The signal due to the angular proton H-1 could not be assigned; however, **132b** equilibrated to a mixture of **132a** and **132b** when treated with base (*vide infra*).



Enone **96** (entry 4, **Table 8**) was treated with two equivalents of the organocopper(I) reagent **15** in the presence of TMSBr to afford a 6:1 mixture of the cis- and trans-fused adducts **133a** and **133b** in 98% overall yield. The ^1H nmr spectrum (400 MHz, C_6D_6) of the major cis-fused epimer **133a**, illustrated in **Figure 1**, revealed the following characteristic signals: the $-\text{GeMe}_3$ signal at δ 0.26 (s), the angular methyl group (Me-10) at δ 0.83 (s), the angular proton H-1 at δ 2.33 (d, $J = 10.5$ Hz), and the vinyl protons (H-14 and H-14') at δ 5.27 (br d, $J = 2.5$ Hz) and 5.61-5.62 (m). The COSY spectrum allowed the assignment of H-9 (δ ~2.10-2.15, m) through the correlation of its signal to that of the angular proton H-1 (see **Table 26**, experimental, page 194). The ^{13}C nmr spectrum (125.8 MHz, C_6D_6) indicated the presence of a carbonyl function at δ 211.7 and a disubstituted double bond at δ 122.1 and 153.8. An APT experiment allowed the differentiation of the signals due to

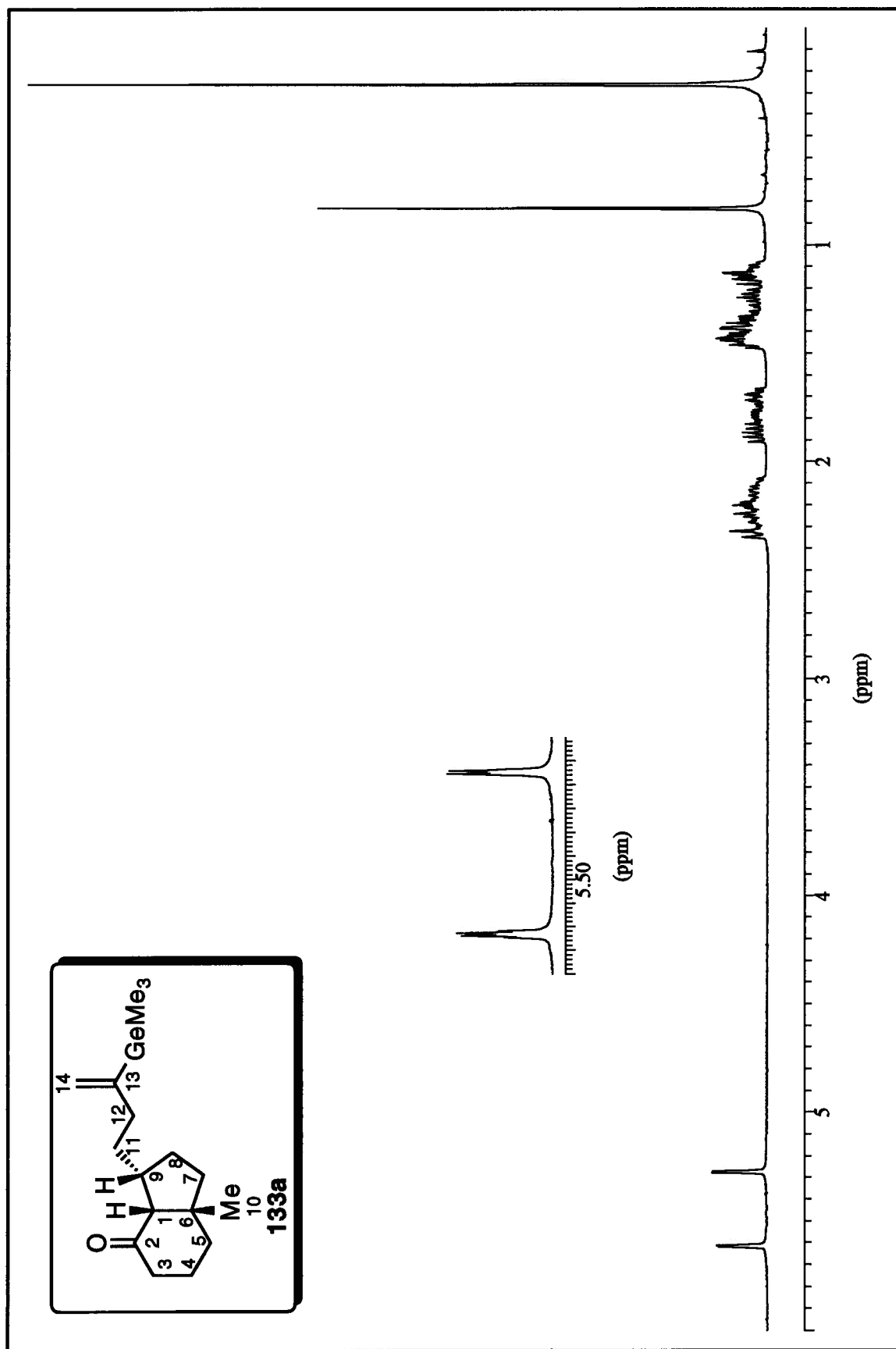
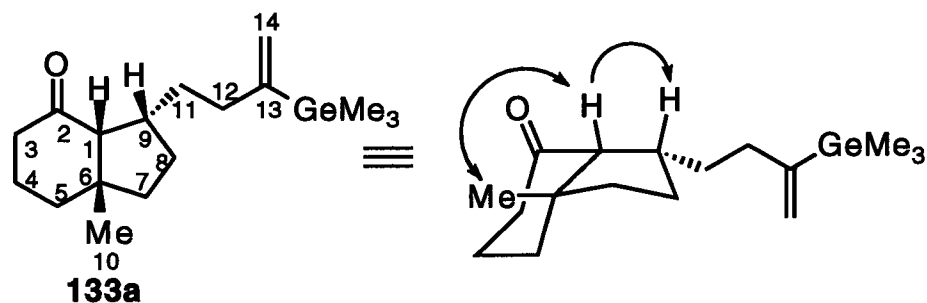


Figure 1: The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Cis-Fused Vinylgermane 133a

quaternary carbons and to methylene (CH₂) carbons from those associated with methine (CH) and methyl (CH₃) carbons (see **Table 27**, experimental, page 195). Most of the signals of the ¹H nmr and ¹³C nmr spectra were assigned through the use of ¹H, ¹H-homonuclear correlation and ¹H, ¹³C-heteronuclear correlation 2D nmr spectra (COSY and HMQC experiments, respectively; see **Tables 26** and **27**, experimental, pages 194 and 195). A HMBC experiment provided evidence that the signal at δ 45.4 was due to the quaternary angular carbon (C-6), as indicated by the long range heteronuclear coupling between C-6 and H-1, H-4', H-5', H-7, H-7', and Me-10. The following NOE difference experiments were consistent with the assigned relative configuration at each of the carbons 1, 6 and 9.



Irradiation of the signal at δ 0.83 (Me-10) caused an enhancement of the signal at δ 2.33 (H-1). Irradiation of the signal at δ 2.33 (H-1) caused an enhancement of the signals at δ 0.83 (Me-10) and 2.10-2.15 (H-9). These results were consistent with the assigned cis-fused ring junction stereochemistry as well as the assigned stereochemistry at C-9 (i.e. the cuprate reagent **15** was introduced *trans* to the angular methyl group).

The ¹H nmr spectrum (400 MHz, C₆D₆) of the trans-fused adduct **133b** is illustrated in **Figure 2** and revealed a signal due to the Me₃Ge group at δ 0.30 (s), a signal due to the tertiary methyl group (Me-10) at δ 0.56 (s), a signal due to the angular proton H-1 at δ 1.75 (d, J = 10 Hz), and two signals due to the vinyl protons at δ 5.31 (br d, J = 1 Hz) and 5.70 (m). The COSY spectrum allowed the assignment of H-9 (part of the m at δ 2.28-2.39) through the correlation of its signal to that of the angular proton H-1 and the homoallylic protons H-11 and H-11' (see **Table 25**, experimental, page 192).

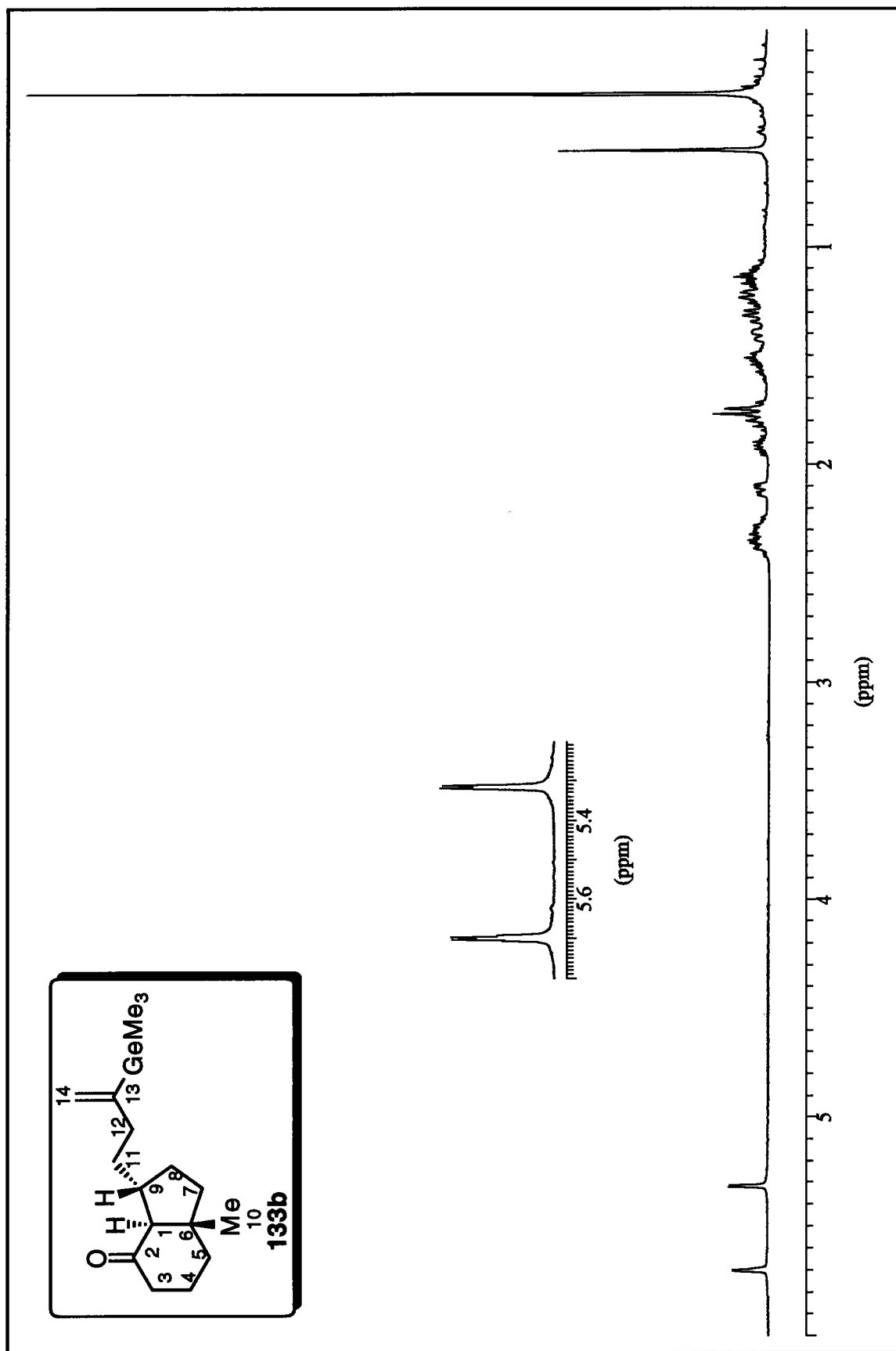
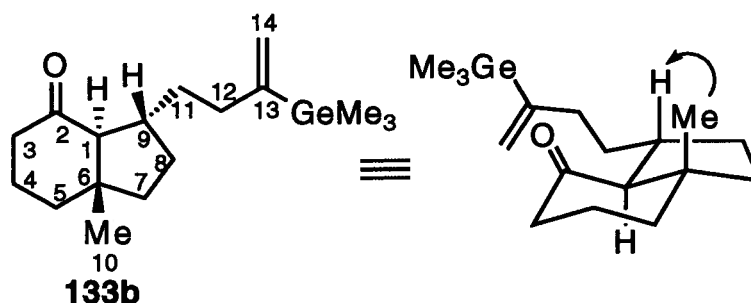


Figure 2: The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Trans-Fused Vinylgermane 133b



The stereochemistry at the ring junction was confirmed by an NOE difference experiment. Irradiation of the signal at δ 0.56 (Me-10) caused an enhancement of the signal at δ 2.29-2.34 (H-9). Molecular models indicate that a positive NOE result between Me-10 and H-9 could only result when there is a trans-fused ring junction. This NOE result also confirms the stereochemistry of the conjugate addition reaction.

The relative stereochemistries of the conjugate addition adducts **130a-133b** were consistent with the results of the NOE difference experiments, as discussed above. There was, however, added empirical evidence to distinguish the cis- and trans-fused epimers for a given reaction. For instance, in all cases, the cis-fused epimer was more polar than the corresponding trans-fused adduct and was always the second compound to be eluted from a silica gel chromatographic column. Upon examination of the IR spectra for each compound, it was found that the positions of the carbonyl absorbances for the trans-fused epimers are consistently at a wavenumber higher than those for the corresponding cis-fused epimers (see **Table 9**, page 69). The differences in the position of the carbonyl absorbances in the trans- and cis-fused epimers ranged from 11 cm^{-1} (entry 3, **Table 9**) to 22 cm^{-1} (entry 2, **Table 9**).

Moreover, in the ^1H nmr spectra (CDCl_3 or C_6D_6), the angular proton H-1 in the cis-fused adducts is more deshielded by the adjacent carbonyl group than the same proton in the corresponding trans-fused adducts. Thus, the ^1H nmr signal for H-1 in the cis-fused adducts appeared downfield in comparison to the H-1 signal for the trans-fused epimer (**Table 9**, Δ ppm for H-1 (cis-fused vs. trans-fused) ranged from 0.10 ppm (entry 2) to 0.58 ppm (entry 4)).

In the case of the cis- and trans-fused epimers **133a** and **133b**, further evidence for the stereochemistry of the ring junction was obtained by comparing the ^{13}C nmr signals for the angular methyl groups. The ^{13}C nmr signal for the angular methyl carbon (Me-10) of the cis-fused adduct **133a** appeared at δ 28.4 ppm, considerably downfield from that of the trans-fused epimer **133b**, which appeared at δ 18.7 ppm ($\Delta\delta = 28.4 - 18.7 = 9.7$ ppm). Literature precedent for the determination of ring junction stereochemistry based on the shielding of angular methyl carbons is well established and one such example is illustrated below.⁶²

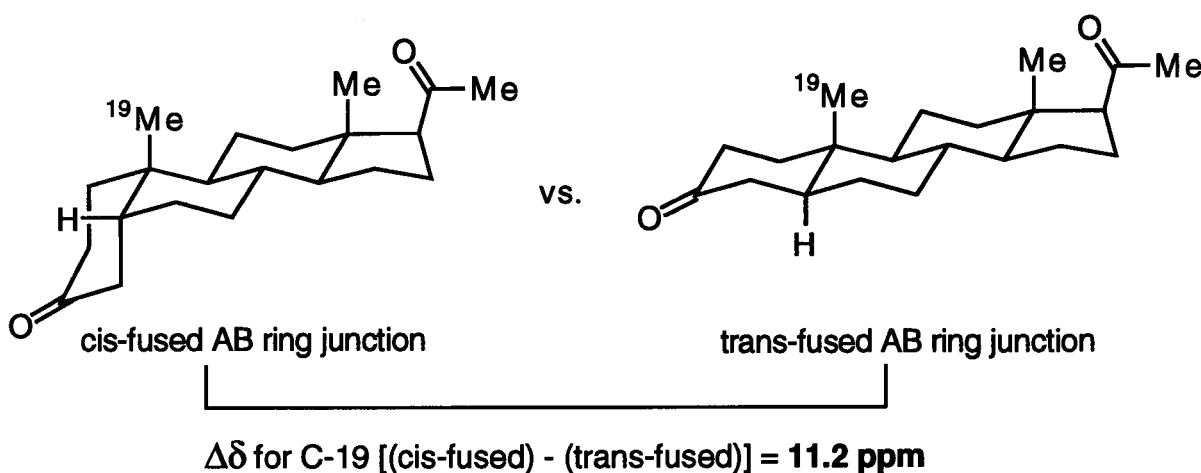


Table 9: Consistent IR and ^1H nmr Differences Between the Cis-Fused and Trans-Fused Vinylgermane Epimers

Entry	R	R'	Compound #	Compound #
			IR (cm^{-1}) carbonyl absorbance	IR (cm^{-1}) carbonyl absorbance
			^1H nmr shift for H-1	^1H nmr shift for H-1
1	Me	H	130a	130b
			1694 cm^{-1}	1713 cm^{-1}
			δ 2.34 (d, $J = 9.5$ Hz) ^a	δ 1.85 (d, $J = 12.5$ Hz) ^a
2	Me	Me	131a	131b
			1695 cm^{-1}	1717 cm^{-1}
			δ 2.05 (br s) ^b	δ 1.95 (br s) ^b
3	H	H	132a	132b
			1703 cm^{-1}	1714 cm^{-1}
			δ 2.68-2.72 (dd, $J = 8, 8$ Hz) ^a	— ^c
4	H	Me	133a	133b
			1698 cm^{-1}	1714 cm^{-1}
			δ 2.33 (d, $J = 10.5$ Hz) ^b	δ 1.75 (d, $J = 10$ Hz) ^b

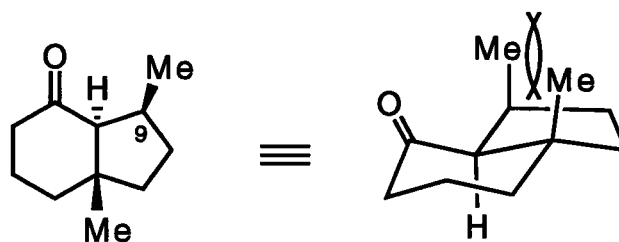
a- This signal was obtained from the ^1H nmr spectrum (400 MHz) using CDCl_3 as the solvent.

b- This signal was obtained from the ^1H nmr spectrum (400 MHz) using C_6D_6 as the solvent.

c- The H-1 proton was not identifiable in the ^1H nmr spectrum (400 MHz, CDCl_3) of compound **132b**.

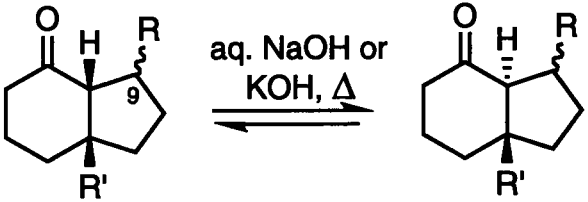
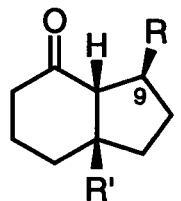
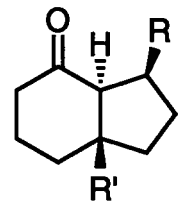
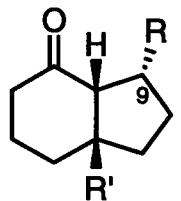
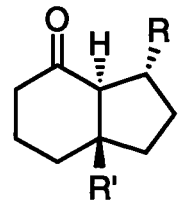
As seen in **Table 8** (page 58), the cis-fused adducts **130a-133a** were the major epimers obtained in the conjugate addition reactions of the cuprate reagent **15** to the enones **74**, **75**, **95**, and **96**, respectively. The hydrolysis of the silyl enol ether intermediates is presumed to be a kinetically controlled process, since, under the conditions of the workup, no equilibration of the products would be expected to take place. Thus, protonation of the enolate from the side cis to the angular group (to form the cis-fused ring junction) must involve an energy of activation lower than that leading to the trans-fused isomer. We were interested in examining the thermodynamically controlled equilibration of the cis- and trans-fused epimers. Before describing the results of this study, literature precedent for the equilibration of cis- and trans-fused bicyclo[4.3.0]nonan-2-ones will be discussed.

The cis- and trans-fused ratio of bicyclo[4.3.0]nonan-2-ones obtained upon a thermodynamically controlled equilibration reaction is greatly dependent on the location and configuration of the substituents in the ring system. Dana and coworkers⁶³ have shown that when the R substituent at C-9 is cis to the angular group R' (i.e. both R and R' are on the same face of the molecule), the cis-fused isomer predominates in the equilibrium mixture (see entries 1-3, **Table 10**). This is particularly evident when both R and R' = Me, as seen by the > 99: < 1 ratio in favor of the cis-fused epimer (entry 1, **Table 10**). This result can be explained in terms of the disfavored pseudo 1,3-diaxial interaction between R and R' that would be present in the trans-fused epimer (see below).



Conversely, when the R substituent at C-9 is trans to the angular group R', the trans-fused isomer predominates as seen in the 1:15.7 and 1:2.2 ratios (entries 4 and 5, respectively, **Table 10**).

Table 10: The Thermodynamically Controlled Equilibration of the Cis- and Trans-fused Bicyclo[4.3.0]nonan-2-ones⁶³

				
Entry	R	R'	CIS-FUSED ^a	TRANS-FUSED ^a
				
1	Me	Me	> 99	: < 1
2	H	H	3.2	: 1
3	H	Me	11.5	: 1
				
4	Me	H	1	: 15.7
5	Me	Me	1	: 2.2

a- The ratios were determined either by ¹H nmr spectroscopic analysis or VPC analysis.

Another example of the thermodynamically controlled equilibration of functionalized bicyclo[4.3.0]nonanes was reported by Paquette *et al.*⁶⁴ (equation 26). The trans-fused epimer **134** is the thermodynamically more stable compound of the two possible isomers.

This result is in accord with Dana's findings, since the ethyl substituent at C* is trans to the angular proton at C# (compare with entry 4, Table 10).

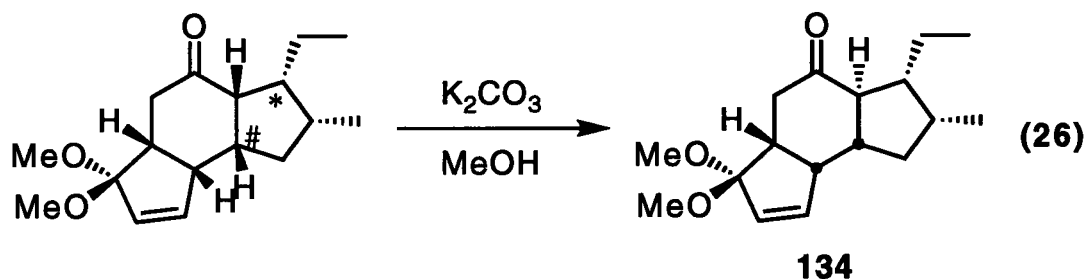


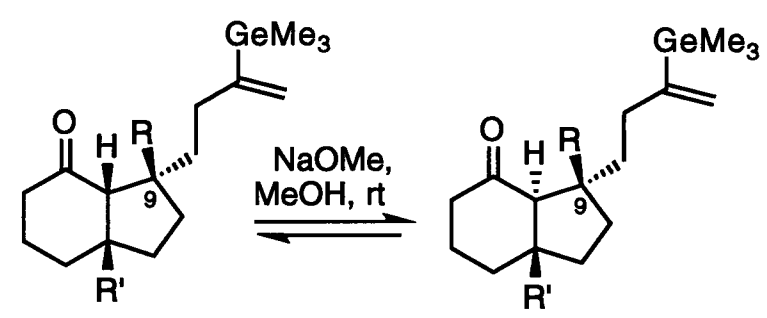
Table 11 summarizes our equilibration studies on the bicyclic keto vinylgermanes **130a** and **130b**, **131a** and **131b**, **132a** and **132b**, and **133a** and **133b**. In all cases, except entry 2, the trans-fused isomer is the thermodynamically more stable epimer. The cis- and trans-fused isomers were separated and each epimer was subjected to identical equilibration conditions (NaOMe/MeOH, rt). Thus, when compound **130a** (entry 1) was equilibrated, a 1:3 ratio of **130a** and **130b** was obtained, as determined by ^1H nmr spectroscopic analysis. Similarly, when the trans-fused epimer **130b** was equilibrated, the same 1:3 ratio was obtained, thereby verifying that this ratio is, in fact, the equilibrium ratio. This 1:3 ratio is in the same direction as Dana's result in entry 4, Table 10 (1:15.7 ratio in favor of the trans-fused epimer).

In entry 2, Table 11 (both R and R' = Me) the cis-fused isomer **131a** is favored by a ratio of > 99 : < 1. This result is comparable with that observed by Dana and coworkers⁶³ (see entry 1, Table 10). Upon examination of molecular models, it is obvious why, in this case, the cis-fused epimer **131a** is the thermodynamically more stable isomer. The two tertiary methyl groups in the trans-fused isomer **131b** experience a pseudo 1,3-diaxial interaction (see page 61) which is alleviated upon epimerization to the cis-fused isomer **131a**.

The findings summarized in entries 3 and 4 (Table 11), in which R = H, are very similar to Dana's results (entries 4 and 5, Table 10). In these cases, the substituents at C-9 are trans to the angular group R' and the trans-fused epimers are favored. In entry 3, Table

11 ($R = R' = H$), the equilibrium ratio is 1:30 in favor of the trans-fused epimer **132b**. It is not surprising that this result is comparable to the 1:15.7 ratio observed by Dana (entry 4, **Table 10**) since the substituents at C-9 are similar in both entries. In entry 4, **Table 11** ($R = H$, $R' = Me$), the equilibrium ratio is 1:5 in favor of the trans-fused epimer **133b** (compare to the 1:2.2 ratio observed by Dana in entry 6, **Table 10**).

Table 11: Equilibration Studies of the Vinylgermane Bicyclo[4.3.0]nonan-2-ones

			
Entry	R	R'	<div style="display: flex; justify-content: space-between;"> <div>CIS-FUSED</div> <div>RATIO^a</div> <div>TRANS-FUSED</div> </div>
1	Me	H	<div style="display: flex; justify-content: space-between;"> <div>130a 1</div> <div>:</div> <div>130b 3</div> </div>
2	Me	Me	<div style="display: flex; justify-content: space-between;"> <div>131a >99</div> <div>:</div> <div>131b <1</div> </div>
3	H	H	<div style="display: flex; justify-content: space-between;"> <div>132a 1</div> <div>:</div> <div>132b 30</div> </div>
4	H	Me	<div style="display: flex; justify-content: space-between;"> <div>133a 1</div> <div>:</div> <div>133b 5</div> </div>

a- For entries 1, 3 and 4, the ratio was determined by the 1H nmr spectroscopic analysis of the crude product mixture. For entry 2, the cis-fused isomer **131a** was the only isomer evident in the 1H nmr spectrum of the crude oil.

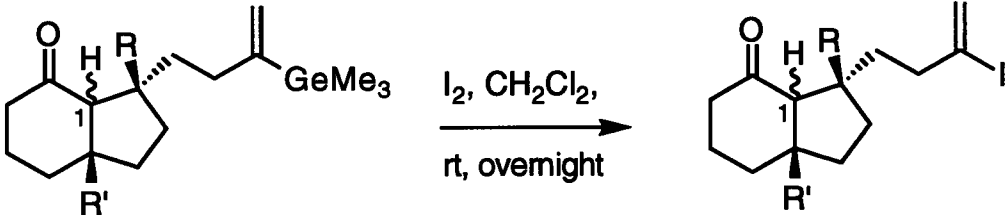
2.3.4. PREPARATION OF THE KETO VINYL IODIDES

The next step in the preparation of the cyclization precursors was the conversion of the vinylgermane adducts **130a-133b** into the corresponding vinyl iodides **135a-138b**. This was accomplished by treating a mixture of the cis- and trans-fused vinylgermane adducts with iodine in CH₂Cl₂ at room temperature. The results, summarized in **Table 12**, indicate that the yields for these conversions are excellent (91% - 99%). Partial epimerization at C-1 (i.e. equilibration of the ring junction stereochemistry) was found to occur during most of the reactions. For example, in entry 1, a 9:1 mixture of **130a** and **130b** was converted to a 1.5:1 mixture of the cis- and trans-fused vinyl iodides **135a** and **135b**, respectively. The epimeric mixtures of the cis- and trans-fused vinyl iodides could be separated, either partially or completely, via column chromatography on silica gel. As was the case with the keto vinylgermane epimers, the cis-fused vinyl iodides were always eluted from the silica gel column after the corresponding trans-fused vinyl iodides.

Spectroscopic evidence for the conversion of the keto vinylgermanes into the vinyl iodides was obtained from ¹H nmr spectroscopic analysis. For example, the ¹H nmr spectrum (400 MHz, C₆D₆) of the cis-fused vinyl iodide **138a** (entry 4, **Table 12**) is illustrated in **Figure 3** and revealed resonances for the vinyl protons at δ 5.54 (m) and 5.70-5.71 (br d, J = 1.5 Hz), significantly downfield from the values for the corresponding protons in the starting material **133a** (see **Figure 1**). This supported the replacement of the Me₃Ge moiety with the more electronegative iodine atom. Similarly, the ¹H nmr spectrum (400 MHz, C₆D₆) of the trans-fused epimer **138b**, illustrated in **Figure 4**, revealed resonances for the vinyl protons at δ 5.56 (m) and 5.78-5.79 (m).

The epimers could also be differentiated by comparing the positions of the carbonyl absorbances in the IR spectra of the cis- and trans-fused compounds. As reported in **Table 13** (page 78), the carbonyl absorbances for the trans-fused epimers are consistently at a wavenumber higher than those for the corresponding cis-fused epimers.

Table 12: Conversion of the Keto Vinylgermanes into the Corresponding Keto Vinyl Iodides

<div></div>							
Entry	Substrate(s)		R	R'	Yield ^b	Vinyl Iodide Product(s)	
	Cis-Fused	Trans-Fused				Cis-Fused	Trans-Fused
	RATIO ^a					RATIO ^c	
1	130a 9	: 130b 1	Me	H	91%	135a 1.5	: 135b 1
2 ^d	131a		Me	Me	99%	136	
3	132a 19	: 132b 1	H	H	98%	137a 5	: 137b 1
4	133a 1	: 133b 4	H	Me	92%	138a 1	: 138b 5

a- The ratio of the cis- and trans-fused keto vinylgermane adducts was determined by ¹H nmr spectroscopic analysis of the mixture.

b- Except for entry 2, the yield refers to the combined isolated yield of the cis- and trans-fused vinyl iodides.

c- For entry 1, the ratio of the cis- and trans-fused vinyl iodides was determined by ¹H nmr spectroscopic analysis of the crude mixture. For entries 3 and 4, the ratio of the cis- and trans-fused vinyl iodides was determined by glc analysis of the crude mixture.

d- In this case, only the cis-fused isomer was available for conversion to the corresponding cis-fused vinyl iodide.

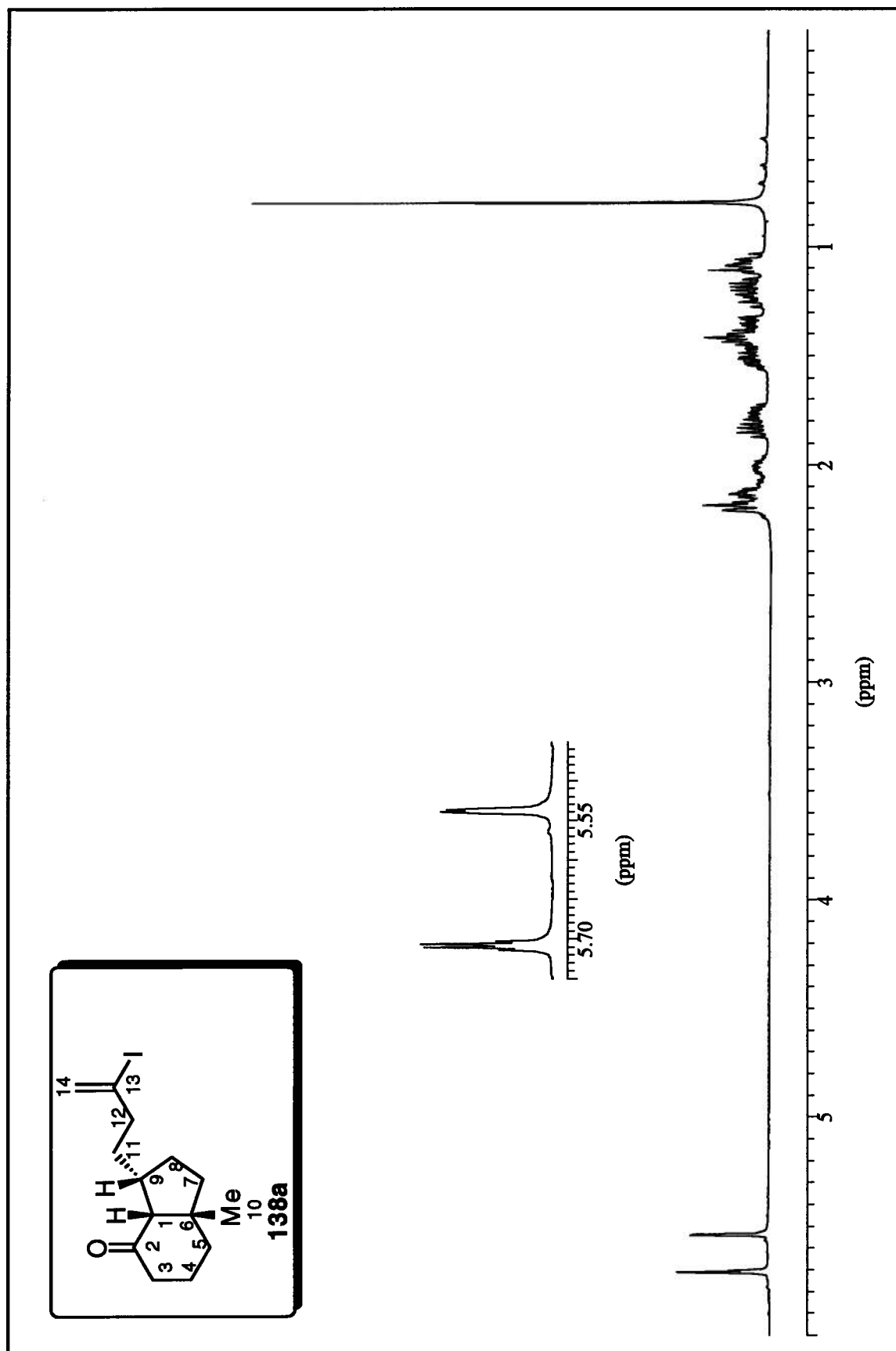


Figure 3: The ^1H nmr Spectrum (400 MHz, C_6D_6) of the Cis-Fused Vinyl Iodide 138a

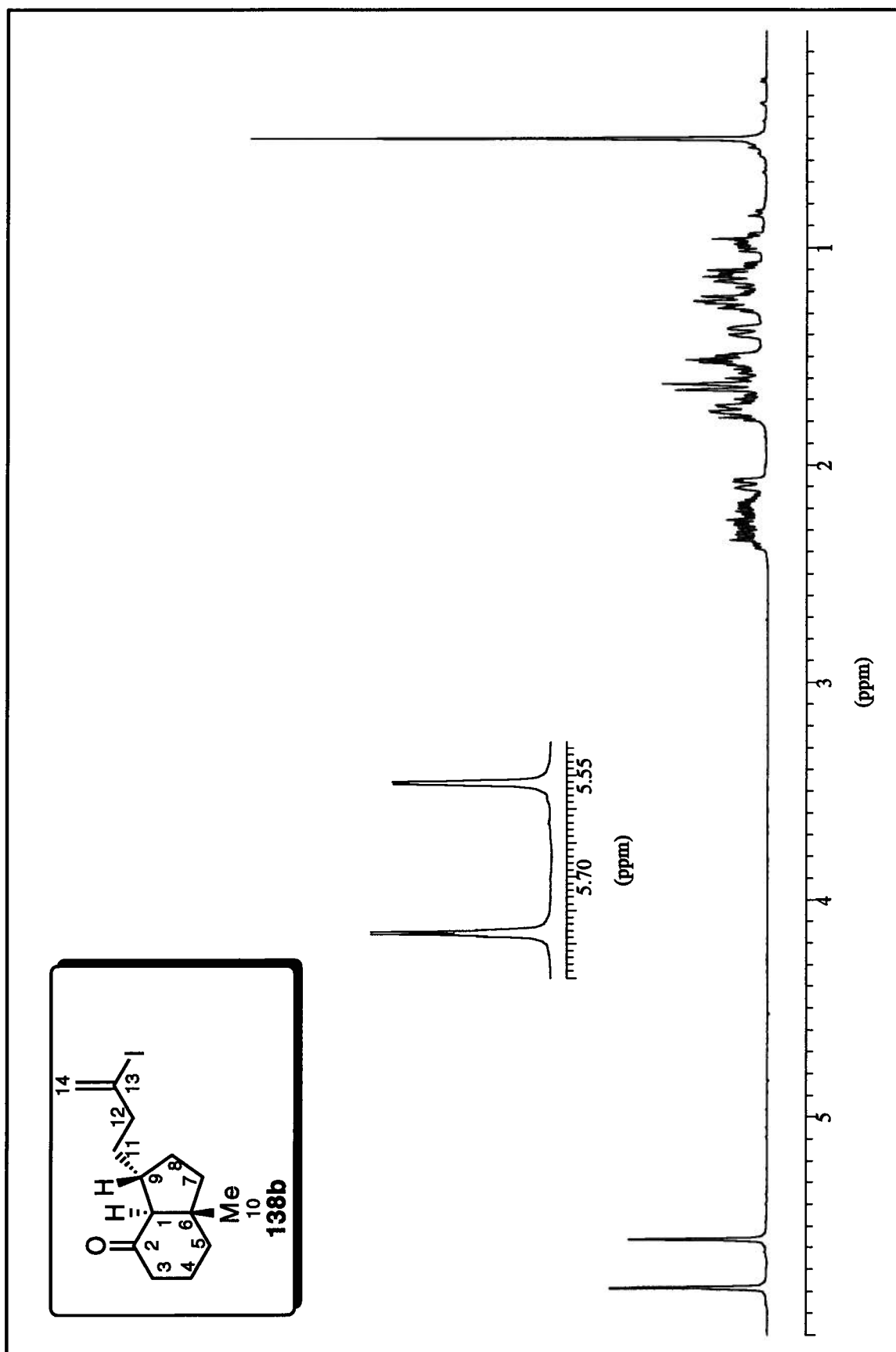
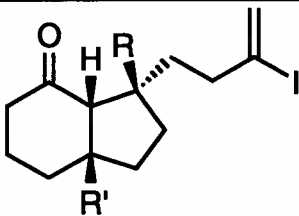
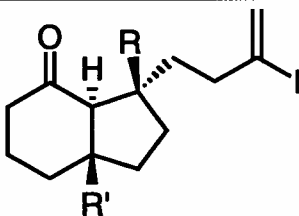


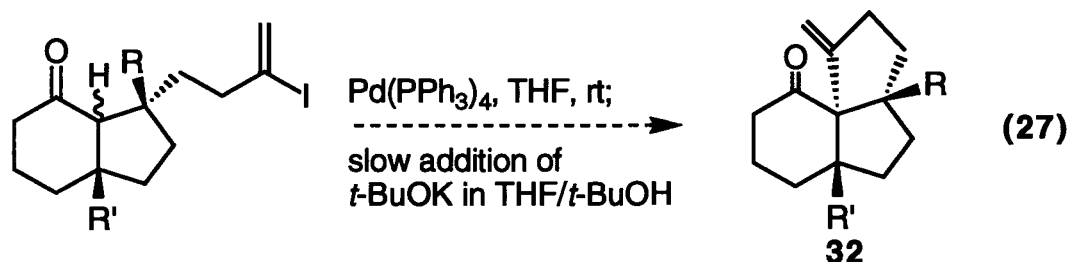
Table 13: Differences in the Position of the Carbonyl Absorbances in the Cis- and Trans-Fused Vinyl Iodides

				
Entry	R	R'	Compound #	Compound #
			IR (cm ⁻¹) carbonyl absorbance	IR (cm ⁻¹) carbonyl absorbance
1	Me	H	135a	135b
			1694 cm ⁻¹	1710 cm ⁻¹
2	Me	Me	136	
			1692 cm ⁻¹	— ^a
3	H	H	137a	137b
			1707 cm ⁻¹	1713 cm ⁻¹
4	H	Me	138a	138b
			1698 cm ⁻¹	1708 cm ⁻¹

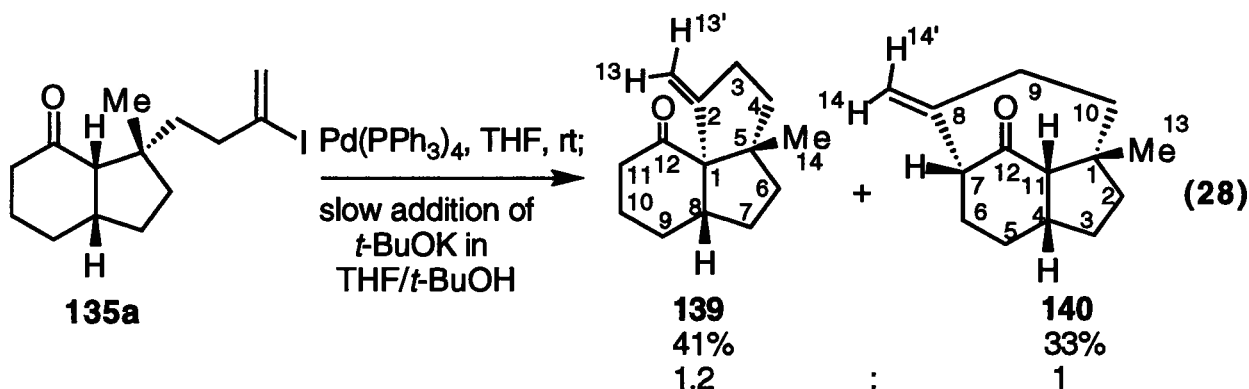
a- The corresponding trans-fused vinyl iodide was not obtained.

2.3.5. CYCLIZATION STUDIES

With the bicyclic keto vinyl iodide precursors in hand, we were now ready to attempt the Pd(0)-catalyzed cyclization reactions to form the tricyclic keto alkenes of general structure **32** (equation 27).



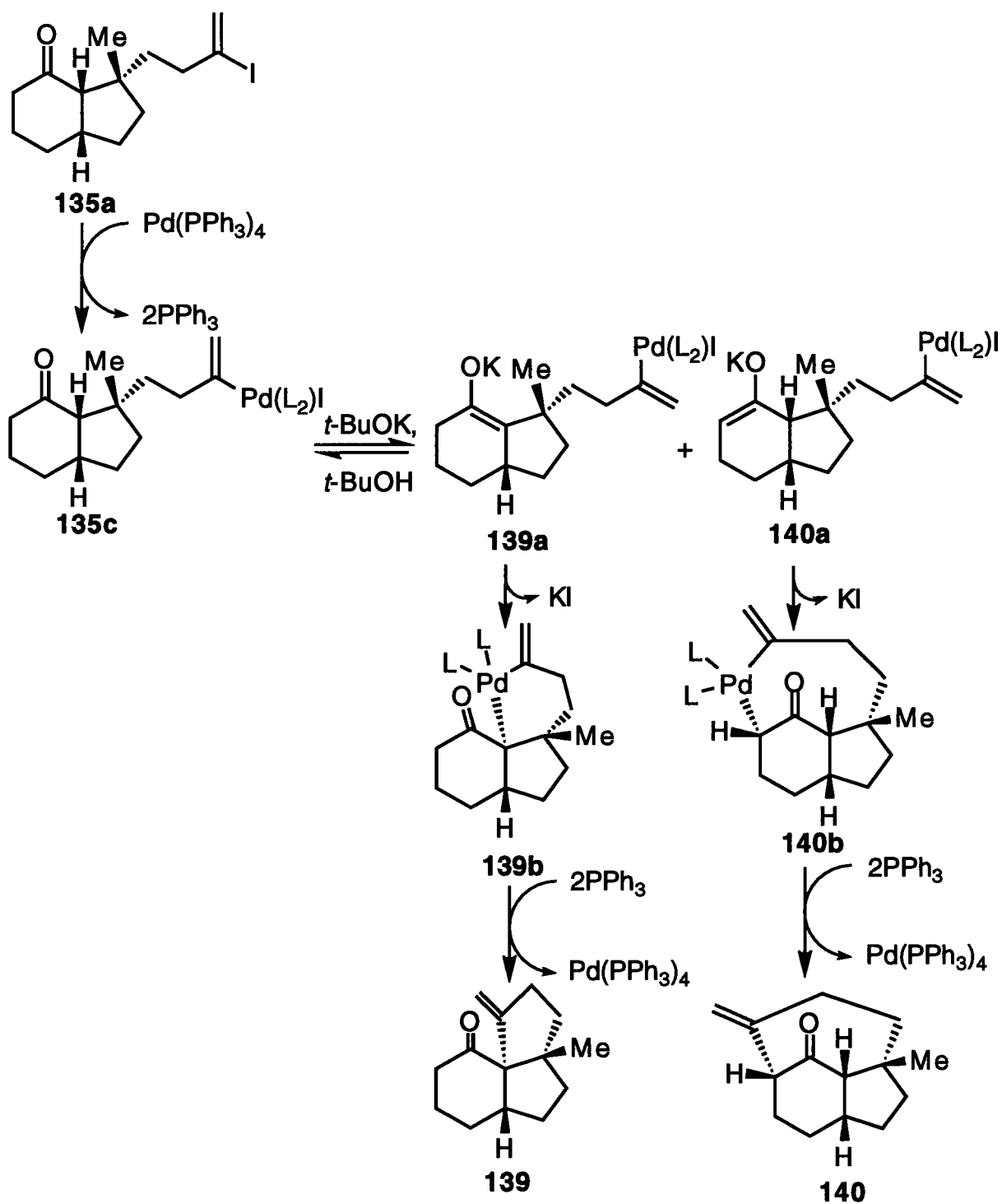
The cis-fused vinyl iodide **135a** was treated with $\text{Pd(PPh}_3)_4$ (24 mol%), followed by a slow addition of $t\text{-BuOK}$ in a 4:1 mixture of dry THF and dry $t\text{-BuOH}$ (equation 28). Upon completion of the reaction, glc and tlc analysis of the crude reaction mixture indicated that the reaction had yielded two products. ^1H nmr spectroscopic analysis revealed that both products lacked the vinyl iodide moiety. The two products were readily separated by flash chromatography and were subsequently subjected to ^1H nmr and mass spectroscopic analysis, which revealed that cyclization had occurred to yield two constitutional isomers.



The first product eluted was the expected fused tricyclic keto alkene **139** which was obtained in 41% yield (equation 28). To our surprise, the other product was determined to be (*vide infra*) the seven-membered ring bridged compound **140**, obtained in 33% yield (equation 28). This seven-membered ring bridged moiety is quite exceptional since its synthesis requires the

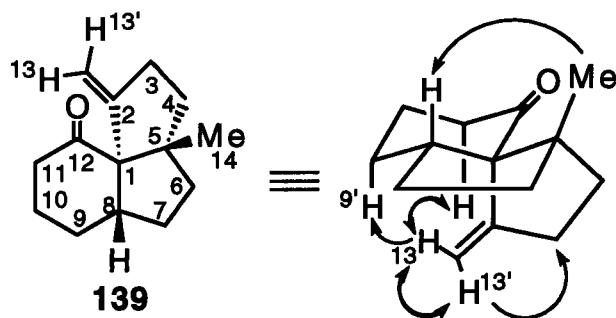
formation of an eight-membered ring palladacycle (see intermediate **140b**, **Scheme 26**). The proposed pathway for the formation of **139** and **140** from **135a** is detailed in **Scheme 26**.

As shown in **Scheme 26**, oxidative addition of the Pd(0) catalyst forms the organopalladium(II) species **135c**. The added base can generate two enolates, **139a** and **140a**, and, under the reaction conditions, these should be in equilibrium with each other. The order of the two steps (i.e. oxidative addition and enolate formation) is not known with certainty but has been arbitrarily portrayed as shown in **Scheme 26**. The more highly substituted of the two possible enolates, **139a**, proceeds to form the six-membered ring palladacycle **139b**, which undergoes reductive elimination of Pd(0) to produce the fused compound **139**. On the other hand, enolate **140a** generates the eight-membered ring palladacycle **140b**, which will subsequently form the bridged product **140**. The spectroscopic evidence for the assigned structures of these two cyclized products, **139** and **140**, will now be discussed in detail.



Scheme 26

The IR spectrum of the fused tricyclic compound **139** revealed absorbances at 1703 and 1636 cm^{-1} , indicative of carbonyl and olefinic moieties. The ^1H nmr spectrum (400 MHz, CDCl_3), illustrated in **Figure 5**, revealed a signal at δ 1.16 (s) for the tertiary methyl group (Me-14), and two signals for the vinyl protons at δ 5.08 (br s, H-13) and 5.16 (br s, H-13'). The COSY spectrum allowed the assignment of nearly all the proton signals (see **Table 28**, experimental, page 206). Confirmation that the cyclization had occurred to generate 5-methyl-2-methylenetricyclo[6.4.0.0^{1,5}]dodecan-12-one (**139**) was obtained by NOE difference experiments. Irradiation of the signal at δ 1.16 (Me-14) caused an enhancement of the signal at δ 2.05-2.12 (H-8). Irradiation of the signal at δ 2.57-2.64 (H-11') caused an enhancement of the signal at δ 5.08 (H-13). Irradiation of the signal at δ 5.08 (H-13) caused an enhancement of the signals at δ 1.83-1.95 (H-9'), 2.57-2.64 (H-11'), and 5.16 (H-13'). Irradiation of the signal at δ 5.16 (H-13') caused an enhancement of the signals at δ 2.39-2.45 (H-3 and H-3') and 5.08 (H-13).



It is highly doubtful that the stereochemistry at C-1 is epimeric with that shown in **139** (see formula **141**, page 84). To form **141**, approach of the side chain would have to occur on the top face of the molecule. This is unlikely due to steric hindrance from the adjacent tertiary methyl group (Me-14). However, the NOE results obtained for compound **139** could not rule out this possibility (i.e. the NOE results could also apply to structure **141**, see below).

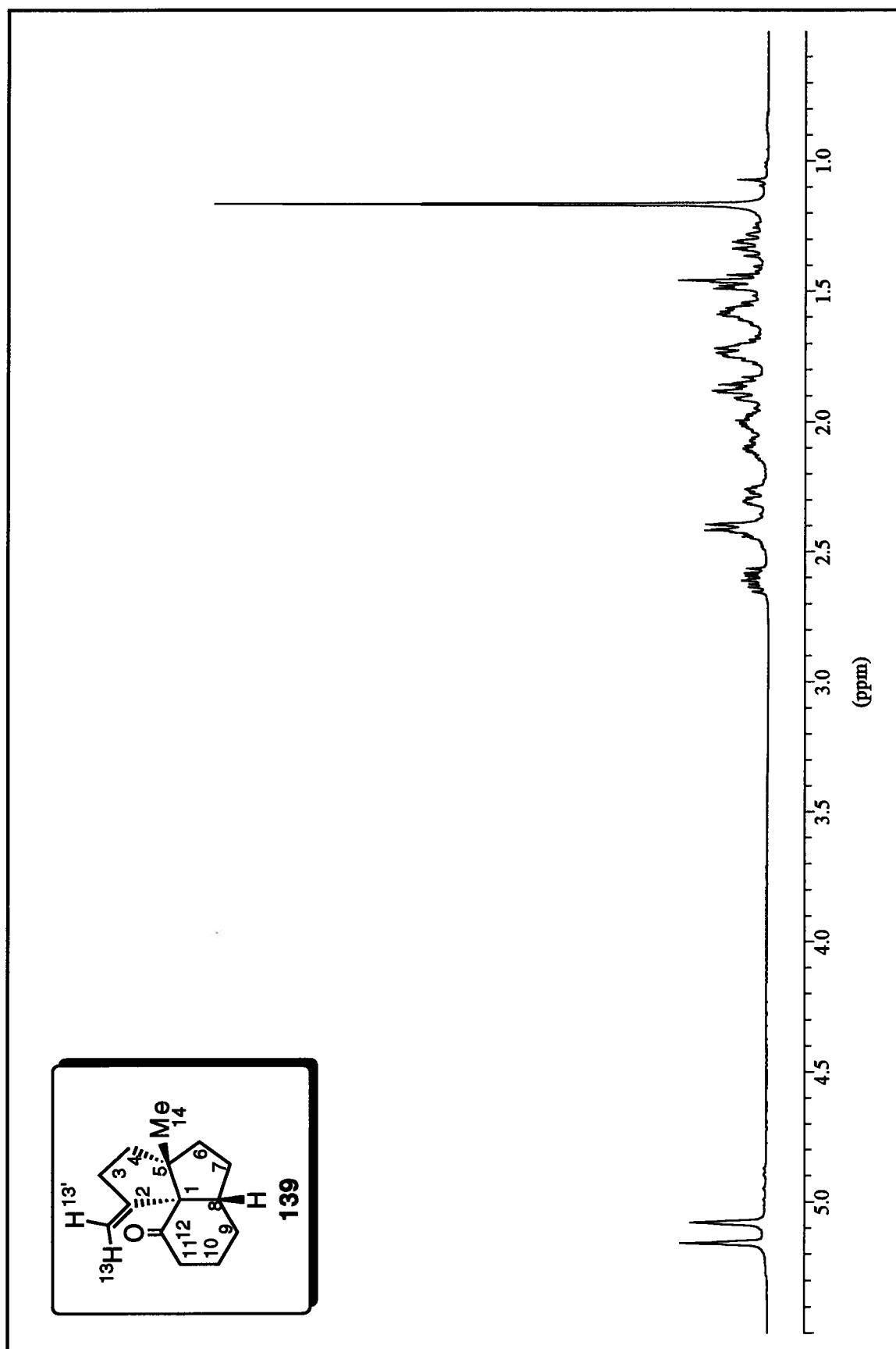
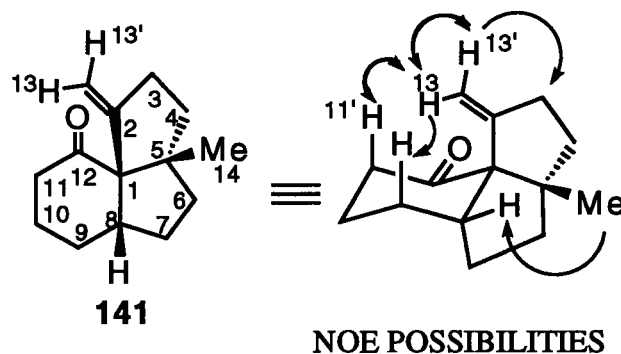
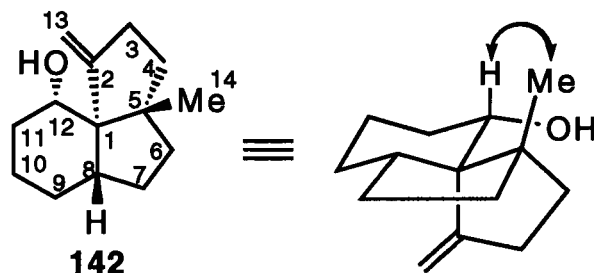


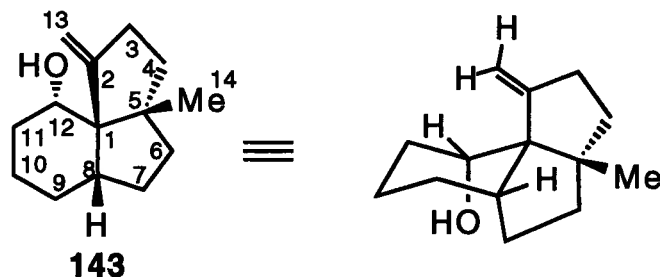
Figure 5: The ^1H NMR Spectrum (400 MHz, CDCl_3) of the Fused Keto Alkene 139



Therefore, in order to distinguish between compounds **139** and **141**, the ketone function of **139** was reduced with DIBAL. A single alcohol **142** was obtained in 90% yield. The hydroxyl moiety was evident in the IR spectrum by absorbances at 3467 and 3394 cm^{-1} . The ^1H nmr spectrum (400 MHz, CDCl_3) revealed the proton H-12 at δ 3.58-3.65 (m). Irradiation of the signal at δ 1.14 (Me-14) caused an enhancement of the signal at δ 3.58-3.65 (H-12) and vice versa.



These NOE difference experiments indicated the following: the reduction of **139** had occurred stereoselectively by attack of the reducing agent from the less hindered beta face of the molecule and the stereochemistry at C-1 could only be assigned as shown in compounds **139** and **142**. If the tricyclic alcohol had possessed the stereochemistry depicted in **143**, an NOE between Me-14 and H-12 would not be possible (see the conformational drawing of **143** below).



The structural assignment of the bridged tricyclic compound **140** was accomplished by examining the ^1H nmr spectrum, as well as by carrying out COSY, NOE, HMQC, and HMBC experiments. The relative stereochemistry was confirmed by X-ray crystallographic analysis of a derivative (*vide infra*). The IR spectrum of **140** revealed absorbances at 1700 and 1633 cm^{-1} , indicative of ketone and olefinic functions. The ^1H nmr spectrum (400 MHz, CDCl_3) of **140**, illustrated in **Figure 6**, indicated the presence of a methyl group (Me-13) at δ 1.10 (s), an angular proton H-11 at δ 2.38 (br d, $J = 8.5\text{ Hz}$), and two vinyl protons at δ 4.81 (br s) and 4.95 (br s). There was a significantly deshielded proton at δ 3.26 (br s) which was not present in the ^1H nmr spectrum of the other isomer **139**. The COSY spectrum allowed the assignment of this signal to H-7 through the correlation of its signal to that of H-14, H-14', H-6, H-6', and H-11 (w-coupling) (see **Table 29**, experimental, page 208). The chemical shift of H-7 can be explained by its close proximity to the deshielding cones of both the carbonyl and olefinic functions. The COSY spectrum also allowed the assignment of all the protons of compound **140**, including H-9 and H-9' (through correlation of their signals to that of the vinyl proton H-14') and H-10 and H-10' (through the correlation of their signals to those of H-9 and H-9'). The carbon signals in the ^{13}C nmr spectrum (500 MHz, CDCl_3) were assigned on the basis of their heteronuclear correlation to the proton signals (HMQC and HMBC experiments, see **Table 30**, experimental, page 209). For example, the signal at δ 55.3 showed a one-bond correlation to its attached proton H-7 (HMQC experiment) and two three-bond correlations to the vinylic protons H-14 and H-14' (HMBC experiment) and was thus assigned to C-7. The signal at δ 45.4 was assigned to the quaternary carbon C-1 on the basis of its long range correlation to H-9' and/or H-11⁶⁵ and Me-13. The HMQC and HMBC correlations also helped to confirm the proton assignments, particularly those that were imbedded in multiplets (i.e. protons H-2, H-2', H-3, H-3', H-5, H-5', H-6, H-6', H-10, and H-10'). With these assignments in hand, NOE difference experiments were conducted to determine the relative configuration at each of the carbons 1, 4, 7, and 11.

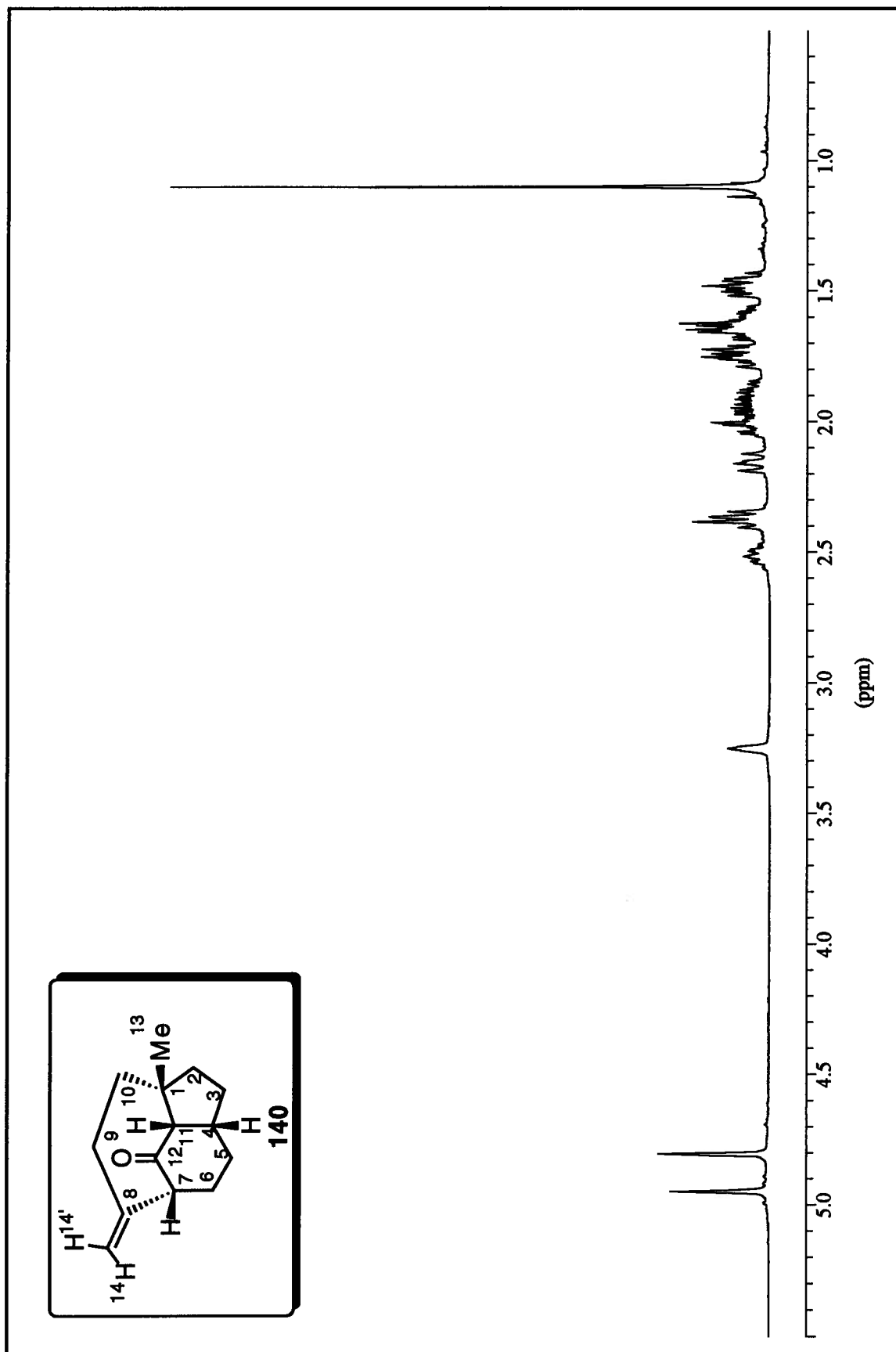
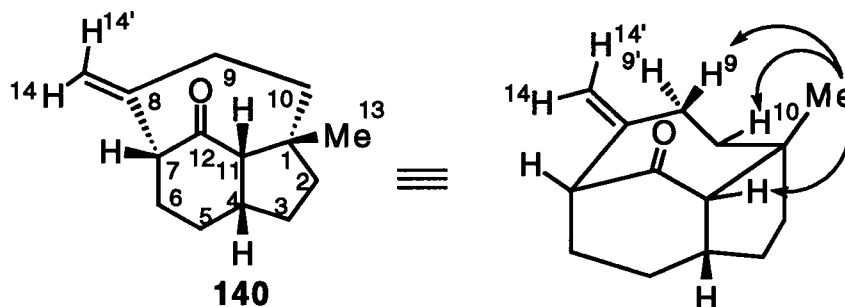


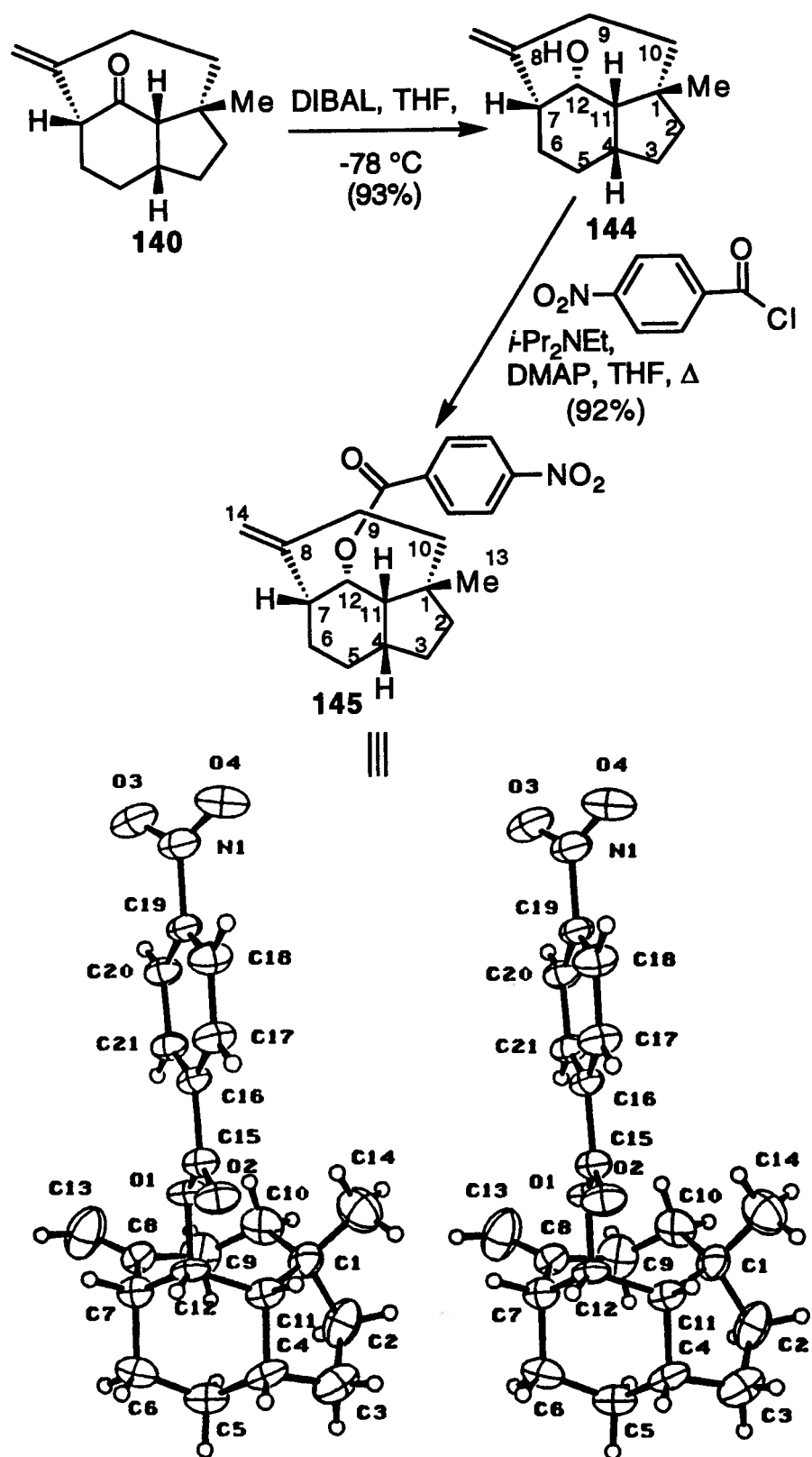
Figure 6: The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Bridged Keto Alkene 140



Irradiation of the signal at δ 1.10 (Me-13) caused an enhancement of the signals at δ 1.43-1.52 (H-10), 2.12-2.19 (H-9), and 2.36 (H-11). The NOE between Me-13 and H-11 confirmed that the 5,6 ring junction was cis-fused. In order to unambiguously verify this unique structure, the ketone **140** was reduced to the alcohol **144** which, in turn, was derivatized to the *p*-nitrobenzoate **145** (Scheme 27). X-ray crystallographic analysis of the crystalline compound **145** was carried out. The stereoview of this substance is shown in Scheme 27.

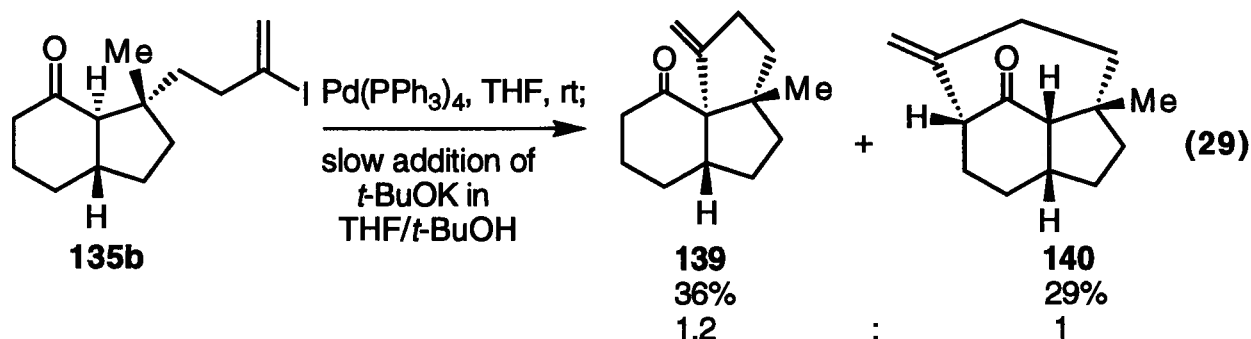
The IR spectrum of **144** revealed absorbances at 3468 and 3420 cm^{-1} , characteristic of a hydroxyl moiety. The ^1H nmr spectrum (400 MHz, CDCl_3) of the alcohol **144** revealed a signal at δ 1.14 (s) for the methyl group (Me-13), a signal at δ 1.51-1.72 for the OH (which disappeared upon the addition of D_2O), a signal at δ 3.99 (br s, which collapsed to a dd ($J = 6, 6$ Hz) upon the addition of D_2O) for the proton H-12, and two signals at δ 4.77 (br d, $J = 2.5$ Hz) and 4.84 (br s) for the vinyl protons H-14 and H-14'. The COSY spectrum allowed the assignment of H-7 (δ 2.68) and H-11 (part of the m at δ 2.01-2.14) through the correlation of their signals to that of H-12 (see Table 31, experimental, page 214).

The *p*-nitrobenzoate **145** was recrystallized from MeOH- H_2O to afford thin colourless plates. X-ray crystallographic analysis⁶⁶ of this material confirmed the constitution and relative configuration of **145** (Scheme 27). This data also provided definitive evidence for the stereochemistry of the conjugate addition reaction (i.e. the vinylgermane side chain had been introduced *trans* to the angular group in the conjugate addition of reagent **15** to enone **74**).



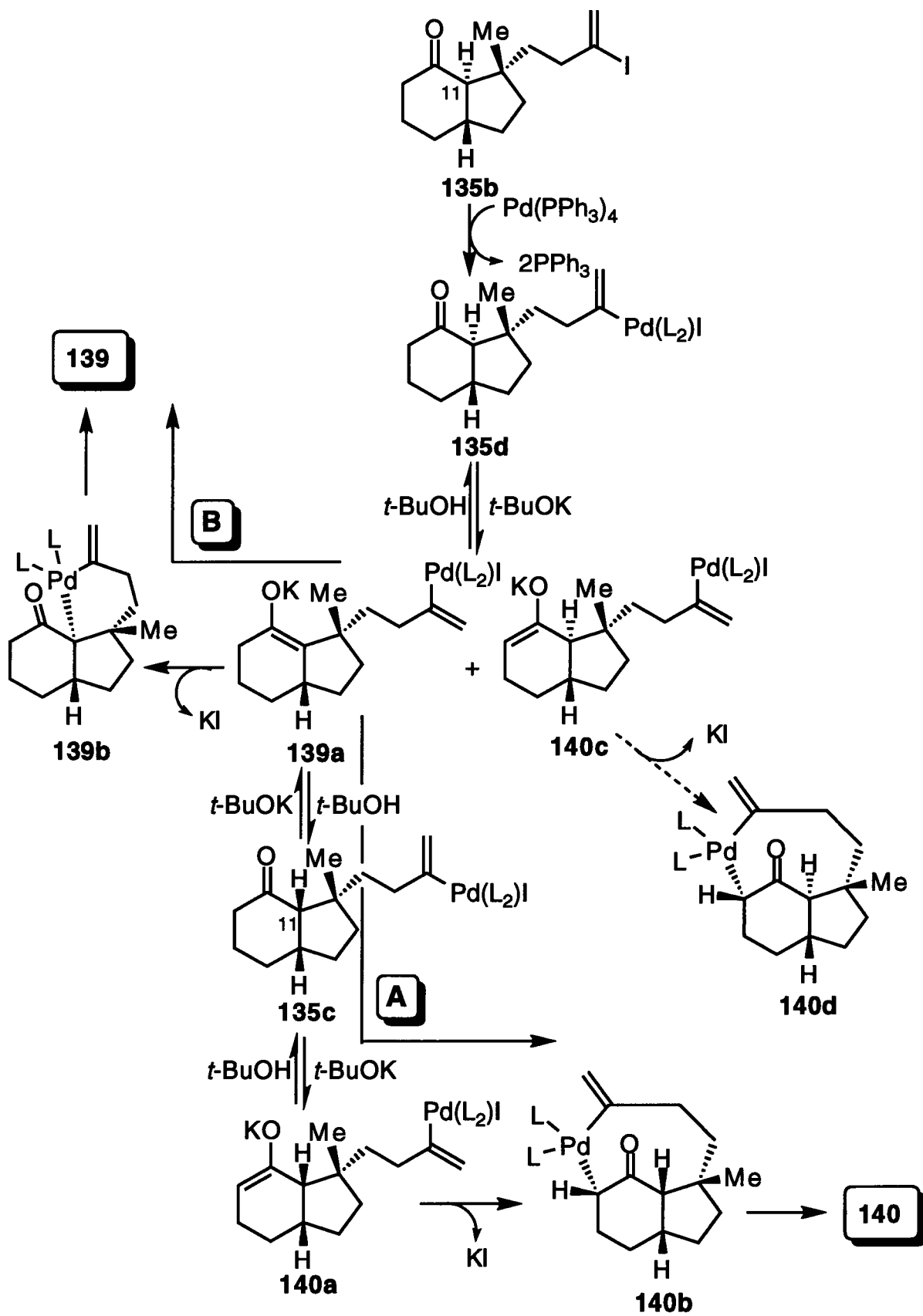
Scheme 27

The trans-fused vinyl iodide **135b** was subjected to the Pd(0)-catalyzed cyclization conditions in order to examine the effects of the trans-fused ring junction on the ratio of fused to bridged cyclized products (equation 29).



The overall yield of the two cyclized products **139** and **140** was slightly lower than that obtained using the cis-fused epimer **135a** as the starting material (65% (equation 29) vs. 74% (equation 28, page 79)). However, the ratio of the fused to bridged compounds **139** and **140** was 1.2:1, which was identical with that observed using the cis-fused epimer **135a**. The proposed pathway for the formation of compounds **139** and **140** from the trans-fused vinyl iodide **135b** is detailed in Scheme 28.

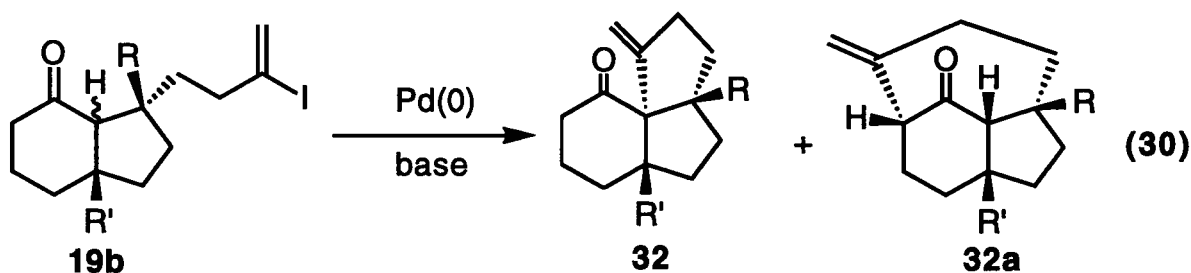
As in Scheme 26 (page 81), the oxidative addition in Scheme 28 (**135b** → **135d**) is shown to occur prior to enolate formation. The reaction of the ketone **135d** with base proceeds to yield two enolates, **139a** and **140c**. Enolate **139a** can generate the fused compound **139** via the palladacycle **139b** (see route B, Scheme 28). The cyclization of the other enolate **140c** to the intermediate **140d** is highly unlikely since the examination of molecular models indicated that the palladacycle **140d** is very strained. Under the thermodynamically controlled base equilibration conditions, enolate **139a** can epimerize to the enolate **140a** via the cis-fused ketone **135c** (see route A, Scheme 28). Enolate **140a** can then proceed to form the bridged keto alkene **140**. Thus, the formation of compound **140** from the trans-fused epimer **135b** necessitates epimerization at C-11, followed by the cyclization reaction. In order to obtain similar fused to bridged



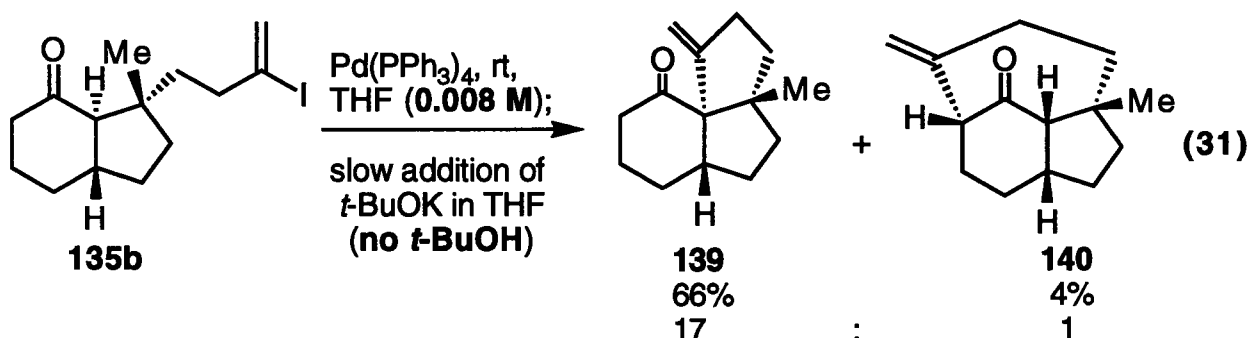
Scheme 28

product ratios from **135a** and **135b** (see Schemes 26 (page 81) and 28, respectively), it follows that the rate of epimerization must be fast compared with the rate of cyclization.

There were two questions which needed to be addressed. First of all, could we modify the reaction conditions to change the product ratio and secondly, what effect do the substituents R and R' (see compound **19b**) have on the ratio of fused (general structure **32**) to bridged (general structure **32a**) product formation (equation 30)?



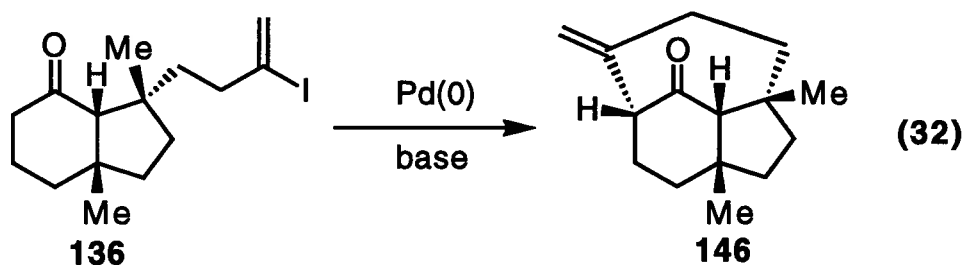
In an experiment related to the first question, the trans-fused epimer **135b** was subjected to a cyclization procedure employing the following modifications: the reaction was conducted at a higher dilution (i.e. the concentration of **135b** in the reaction mixture was diluted from 0.05 M to 0.008 M) and the *t*-BuOH was omitted from the base mixture (equation 31).



As shown in Scheme 28, the enolate **139a** can proceed directly to form the fused compound **139** via the intermediate palladacycle **139b** (route B) or enolate **139a** can epimerize to the enolate **140a** via the cis-fused ketone **135c** (route A). The bridged product

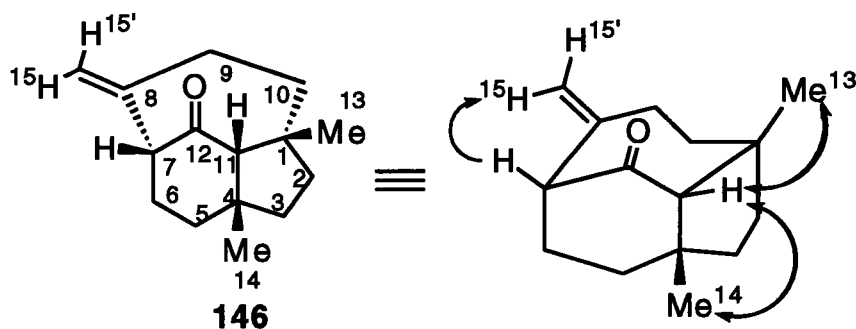
140 can then be generated from the enolate **140a**. If the epimerization rate is slowed somewhat compared to the rate of cyclization, we would expect to obtain less of the bridged compound **140**, since its synthesis requires epimerization of **135d** prior to cyclization. As discussed in Section 2.1. (page 27), the modifications described in equation **31** can be assumed to slow both the rate of epimerization at the ring junction and the equilibration of the two possible enolates. As predicted, the modified reaction conditions produced more of the fused product **139** than the bridged compound **140**; the reaction yielded a 17:1 ratio of products **139** and **140** (equation **31**). Thus, we were able to control the reaction conditions to selectively generate more of the fused compound **139**.

With respect to the second question posed above, the effects of the substituents R and R' on the outcome of the cyclization reaction are summarized in **Table 14** (page 94). The cis-fused vinyl iodide **136** (entry 2) was cyclized employing the Pd(0)-catalyzed conditions (equation **32**). Only one cyclized product was evident in the ^1H nmr spectrum of the crude reaction mixture. The sole cyclized product was isolated in 63% yield and was determined to be the bridged compound **146**.



The ^1H nmr spectrum (400 MHz, C_6D_6) of **146** revealed resonances at δ 0.86 (s) and 1.01 (br s) for the tertiary methyl groups (Me-14 and Me-13, respectively), δ 2.16 (br s) for the angular proton H-11, δ 3.28 (br s) for the bridgehead proton H-7, and δ 4.68 (br s) and 4.71 (br d, $J = 1$ Hz) for the vinyl protons (H-15 and H-15', respectively). The COSY

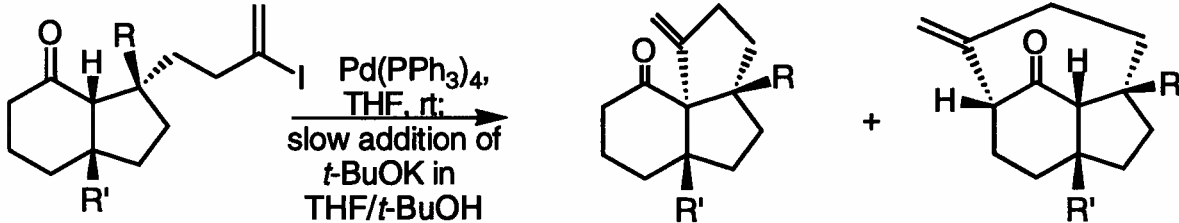
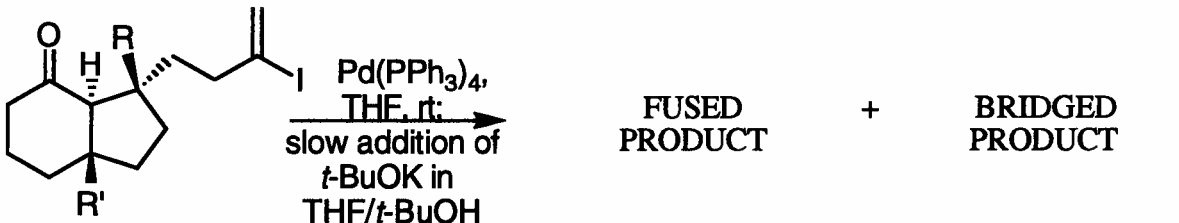
spectrum allowed the assignment of H-6' (δ 1.71-1.84) through correlation of its signal to that of H-7 (see **Table 32**, experimental, page 219).



The stereochemistry was confirmed by the following NOE difference experiments. Irradiation of the signal at δ 0.86 (Me-14) caused an enhancement of the signal at δ 2.16 (H-11). Irradiation of the signal at δ 1.01 (Me-13) also caused an enhancement of the signal at δ 2.16 (H-11) while irradiation of the signal at δ 2.16 (H-11) caused enhancement of the signals at δ 0.86 (Me-14) and 1.01 (Me-13). Irradiation of the signal at δ 3.28 (H-7) caused an enhancement of the signal at δ 4.68 (H-15). These experiments confirm that H-11, Me-13 and Me-14 must be on the same face of the molecule.

The cyclization reaction was not performed on the trans-fused counterpart of the vinyl iodide **136** since this substrate was not synthesized (i.e. when $R = R' = \text{Me}$, the cis-fused compound **136** was not only the kinetically formed epimer in the hydrolysis of the silyl enol ether intermediate but was also the thermodynamically more stable of the two possible epimers, see pages 60 and 73, respectively).

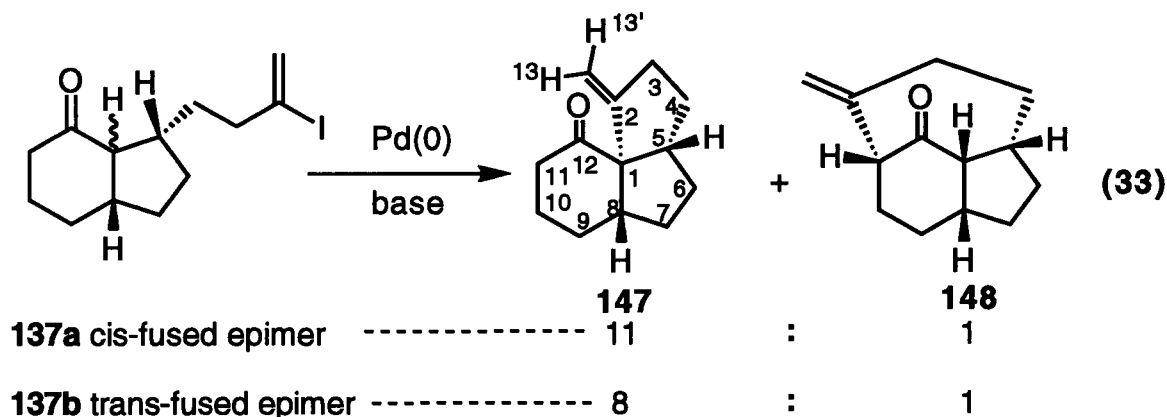
Table 14: Cyclization Studies in Forming Fused and Bridged Tricyclic Keto Alkenes

						
Entry	Vinyl Iodide	R	R'	Total Yield ^a	FUSED PRODUCT	BRIDGED PRODUCT RATIO ^b
1	135a	Me	H	74%	139 1.2	: 140 1
2	136	Me	Me	63%	< 1	: 146 > 99
3	137a	H	H	45%	147 11	: 148 1
4	138a	H	Me	41%	< 1	: 149 > 99
						
5	135b	Me	H	65%	139 1.2	: 140 1
6 ^c	135b	Me	H	70%	139 17	: 140 1
7	137b	H	H	52%	147 8	: 148 1
8	138b	H	Me	38%	< 1	: 149 > 99

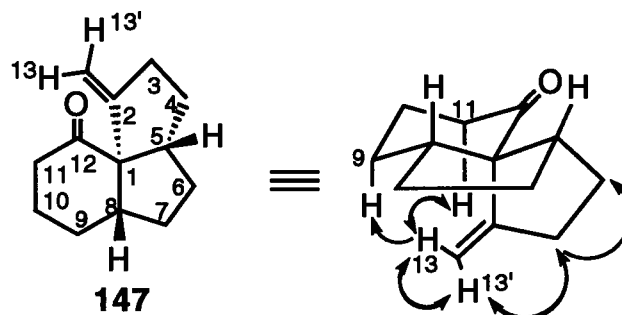
a- Isolated yield of both the fused and bridged cyclized products.

b- This ratio refers to the isolated product ratio.

c- This cyclization reaction was carried out using modified reaction conditions (0.008 M dilution and no *t*-BuOH in the base mixture).

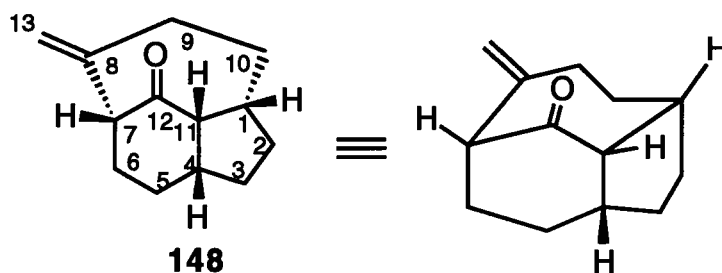


Entries 3 and 7 (**Table 14**, page 94) describe the results of the cyclization of the cis- and trans-fused vinyl iodides **137a** and **137b**, respectively. The ratio of fused to bridged products **147** and **148** was similar in both cases (~11:1 and ~8:1, respectively, see equation **33**). The major product in each case was the fused tricyclic compound **147**. The ^1H nmr spectrum (400 MHz, CDCl_3) of **147** revealed two signals at δ 5.15 (br s) and 5.26 (br s) for the vinyl protons (H-13 and H-13', respectively). The COSY spectrum allowed the assignment of H-3 and H-3' (δ 2.39-2.48, m) through the correlation of their signal to that of H-13 and H-13' (see **Table 33**, experimental, page 222). The signals H-4 (δ 1.52-1.56, m) and H-4' (δ ~1.80-1.85, m) were assigned due to their correlations with H-3 and H-3'. The signals H-11 (δ 2.27-2.33, m) and H-11' (part of the m at δ 2.74-2.83) were assigned on the basis of their chemical shift (deshielding due to the adjacent carbonyl group). The signals due to H-10 (δ ~1.61-1.75, m) and H-10' (δ ~2.06-2.11) were assigned due to their correlations to H-11 and H-11'. In turn, one of the protons at C-9 (δ ~1.85-1.88, m, H-9) was assigned through its correlation to H-10 and H-10'. The following NOE difference experiments verified the relative configuration of **147** and also allowed the assignment of the vinyl protons H-13 and H-13'.

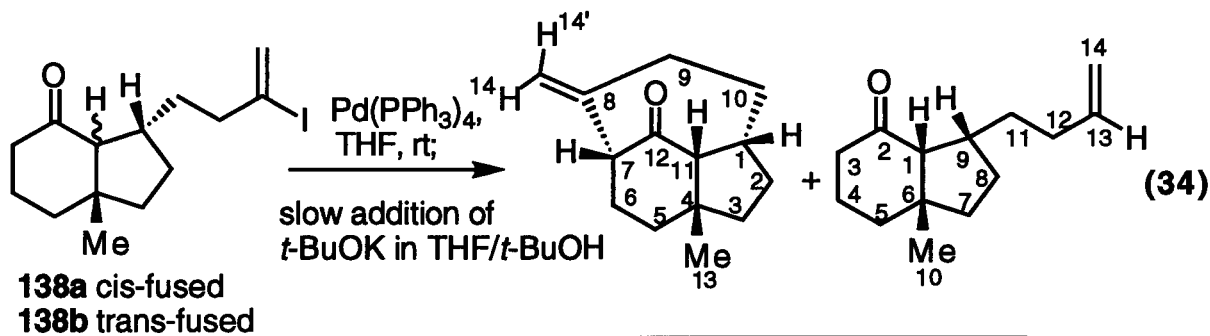


Irradiation of the signal at δ 2.39-2.48 (H-3 and H-3') caused an enhancement of the signals at δ 1.52-1.56 (H-4), 1.61-2.11 (H-4'), and 5.26 (H-13'). Irradiation of the signal at δ 2.74-2.83 (H-11') caused an enhancement of the signals at δ 2.27-2.33 (H-11) and 5.15 (H-13). Irradiation of the signal at δ 5.15 (H-13) caused an enhancement of the signals at δ 1.61-2.11 (H-9), 2.74-2.83 (H-11'), and 5.26 (H-13'). Irradiation of the signal at δ 5.26 (H-13') caused an enhancement of the signals at δ 2.39-2.48 (H-3 and H-3') and 5.15 (H-13).

The minor cyclized product was determined to be the bridged compound **148**. The ^1H nmr spectrum (400 MHz, CDCl_3) of **148** revealed a signal at δ 2.74-2.29 (dd, $J = 8.5, 8.5$ Hz) corresponding to the angular proton H-11, a signal at δ 3.29 (br s) indicative of the bridgehead proton H-7, and two signals at δ 4.82-4.83 (dd, $J = 1.5, 1.5$ Hz) and 4.94-4.95 (dd, $J = 1.5, 1.5$ Hz) for the vinyl protons H-13 and H-13'.



Entries 4 and 8 (**Table 14**, page 94) describe the results of the cyclization of the cis- and trans-fused vinyl iodides **138a** and **138b**, respectively (see equation 34). In both cases, the bridged product **149** was the sole cyclized product. In each case, however, there was produced a small amount of uncyclized reduced byproduct **150**.

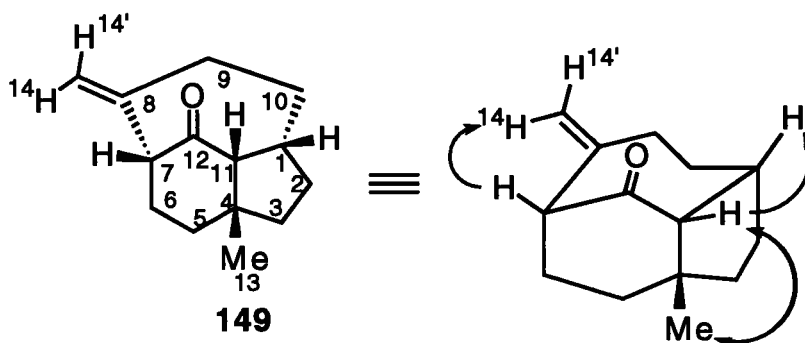


Vinyl Iodide	149	150
138a	41% 5	8% 1
138b	38% 10	4% 1

The IR spectrum of the minor product **150** revealed absorbances at 1698 and 1641 cm^{-1} , indicative of carbonyl and olefinic moieties. The ^1H nmr spectrum (400 MHz, CDCl_3) revealed three vinyl protons (δ 4.90-4.93 (dddd, $J = 10, 1.5, 1.5, 1.5$ Hz, H-14); δ 4.94-5.00 (dddd, $J = 17, 1.5, 1.5, 1.5$ Hz, H-14'); and δ 5.69-5.79 (dddd, $J = 17, 10, 7, 7$ Hz, H-13)) whose multiplicities and coupling constants are indicative of a monosubstituted double bond. Thus, the reduced byproduct was assigned structure **150**.

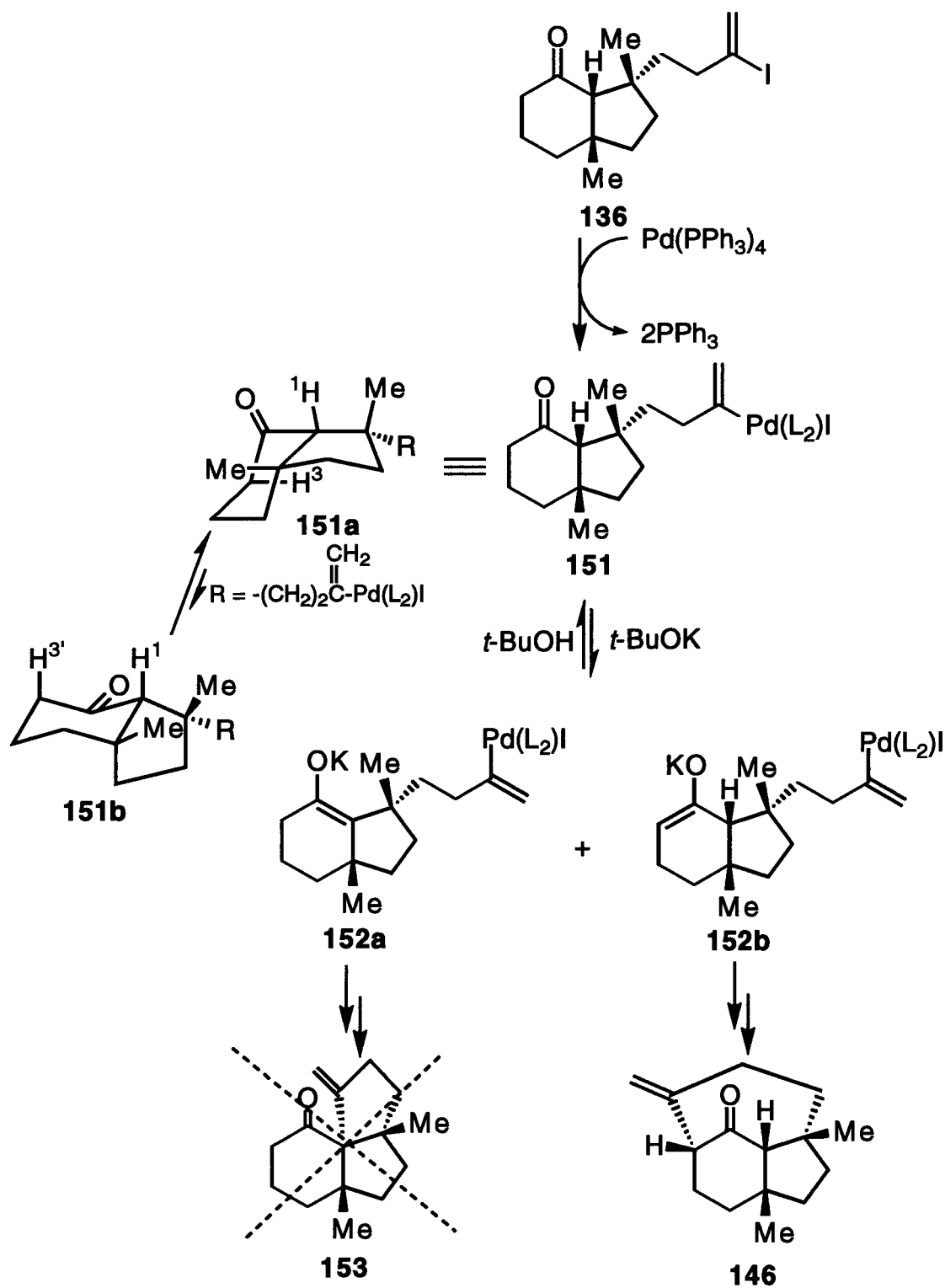
The major product was determined to be the bridged compound **149**. The ^1H nmr spectrum (400 MHz, C_6D_6) of **149** had signals at δ 0.86 (s) for the tertiary methyl group (Me-13), δ 2.49 (br d, $J = 10.5$ Hz) for the angular proton H-11, δ 3.31 (br s) for the bridgehead proton H-7, and δ 4.69 (br dd, $J = 1, 1$ Hz) and 4.75 (br d, $J = 1$ Hz) for the vinyl protons H-14 and H-14', respectively. The COSY spectrum allowed the assignment of H-1 (part of the m at δ 2.22-2.34) through the correlation of its signal to that of H-11 (see **Table**

34, experimental, page 226). The assignment of H-6 (δ ~1.60-1.68, m) and H-6' (δ 1.78-1.86, m) was made on the basis of their correlations to the signal H-7. The assignment of H-9 (δ 1.97-2.03, br dd, J = 15, 9 Hz) and H-9' (δ 2.22-2.34, m) was made on the basis of their correlations to the signal H-14'. Based on these assignments, we were able to confirm the stereochemistry with NOE difference experiments.



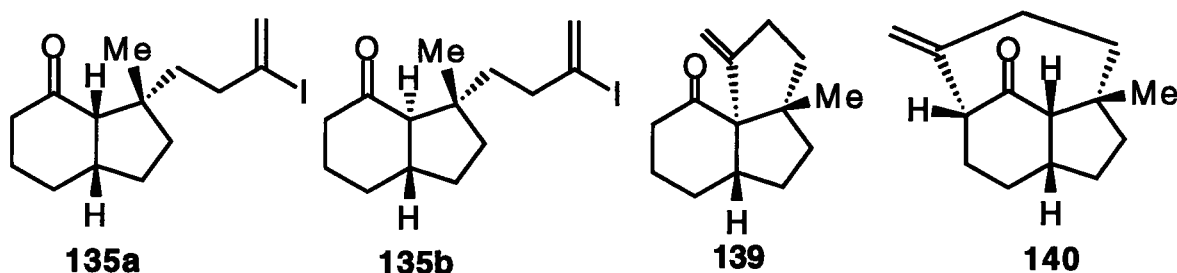
Irradiation of the signal at δ 0.86 (Me-13) caused an enhancement of the signal at δ 2.49 (H-11). Irradiation of the signal at δ 2.49 (H-11) caused an enhancement of the signals at δ 0.86 (Me-13) and 2.22-2.34 (H-1). This result confirmed that H-1, H-11, and Me-13 must be on the same face of the molecule. Irradiation of the signal at δ 3.31 (H-7) caused an enhancement of the signal at δ 4.69 (H-14), confirming the assignment of the vinyl protons H-14 and H-14'.

It is apparent from the results in **Table 14** (page 94) that the ratio of fused to bridged products does not depend on the nature of the ring junction of the starting material but rather on the nature of the substituents R and R'. When both R and R' = Me (vinyl iodide **136**, entry 2, **Table 14**, page 94), only the bridged product **146** was obtained. **Scheme 29** (page 99) illustrates a possible rationalization for the sole formation of compound **146**. The formation of the more highly substituted enolate **152a** involves removal (by base) of the sterically hindered angular proton of compound **151** (i.e. the angular proton is adjacent to two quaternary centers). Moreover, this deprotonation probably occurs from the less stable



Scheme 29

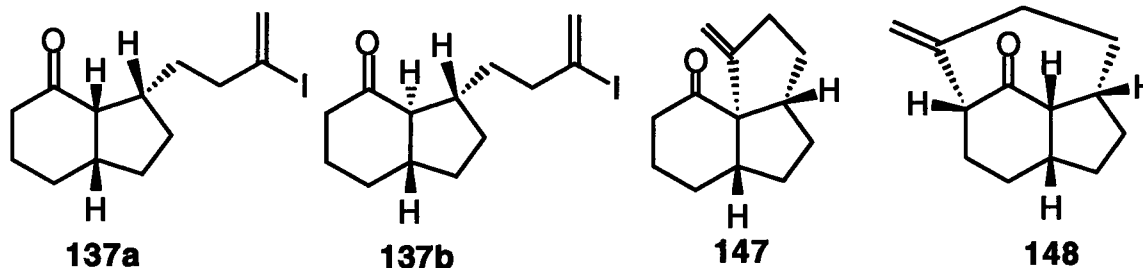
of the two conformers **151a** and **151b** (i.e. the conformer **151b**), in which the axial angular proton H-1 is nearly perpendicular to the plane of the ketone function. The formation of the kinetically favored enolate, **152b**, involves removal of H-3 from conformer **151a** or H-3' from conformer **151b**. It is likely that the deprotonation occurs mainly from conformer **151b**, in which H-3' is sterically much more accessible than H-3 in conformer **151a** (see **Scheme 29**). The abstraction of H-1 from conformer **151b** is much more sterically hindered than the abstraction of H-3' from conformer **151b**. Thus, the enolate **152b** is formed preferentially over the enolate **152a**, thereby accounting for the preferential formation of the bridged compound **146** (none of the fused compound **153** was obtained).



When $R' = H$ and $R = Me$ (vinyl iodides **135a** and **135b**, entries 1 and 5, **Table 14**, page 94), an intermediate result is obtained with the formation of a 1.2:1 ratio of fused to bridged compounds **139** and **140**. The proposed pathways for the formation of compounds **139** and **140** from the cis- and trans-fused vinyl iodides **135a** and **135b** are shown in **Schemes 26** (page 81) and **28** (page 90), respectively. The product ratio could be manipulated by modifying the cyclization conditions (see entry 6, **Table 14**, page 94).

It is difficult to rationalize the results obtained from the experiments summarized in entries 3, 4, 7, and 8 (**Table 14**, page 94). First of all, the mass balance and overall yields obtained from these reactions were poor (i.e. the yields ranged from 38% to 52%). Since the mass balance was poor, it is difficult to speculate on where the remaining material went. Secondly, several reactions are occurring concurrently (i.e. deprotonation, enolate equilibration, and cyclization) and without further study, one cannot predict which reaction is

controlling the product ratio. It was observed that when the angular group (R') is a methyl group (entries 2, 4, and 8, **Table 14**, page 94), only the bridged product is obtained, regardless of the configuration of the ring junction (i.e. compare entries 4 and 8, **Table 14**).



At the other extreme, when $R = R' = H$ (vinyl iodides **137a** and **137b**, entries 3 and 7, **Table 14**, page 94), the fused product **147** is favored by ratios of 11:1 and 8:1 over the bridged product **148**. In this case ($R = R' = H$), it is likely that the rate of epimerization is fast relative to the rate of cyclization. Thus, the cyclization to form the six-membered ring palladacycle (which leads to the formation of the fused product **147**) must be faster than the cyclization to form the eight-membered ring palladacycle (which leads to the formation of the bridged product **148**).

2.3.6. CONCLUSION

The conjugate addition of the organocopper(I) reagent **15** to the bicyclic enones **74**, **75**, **95**, and **96** was shown to proceed stereoselectively to give cis- and trans-fused vinylgermane adducts. These adducts were converted into the corresponding vinyl iodide precursors, which were subsequently subjected to the Pd(0)-catalyzed cyclization conditions. These cyclizations provided us with the expected fused tricyclic compounds **139** and **147** as well as the structurally unique bridged compounds **140**, **148**, and **149**.

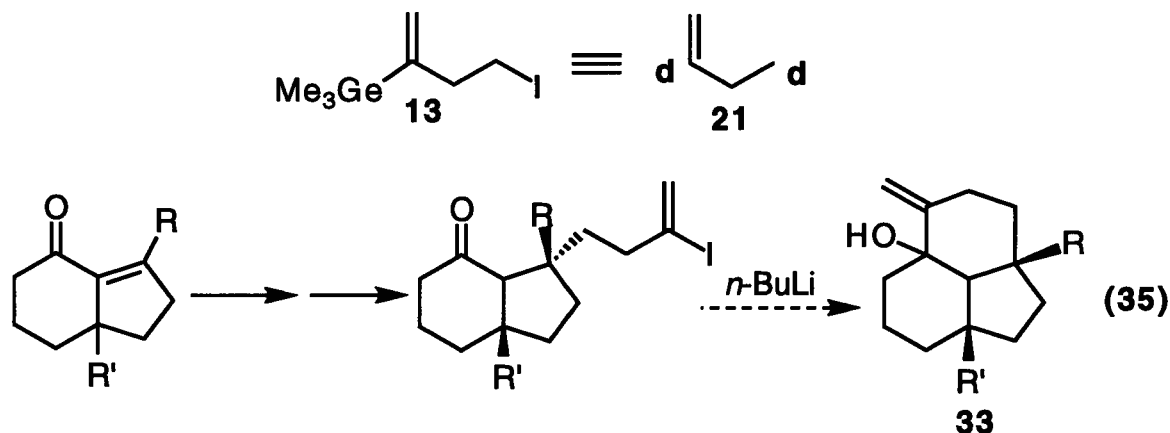
Although the nature of the two substituents R and R' did not affect the stereochemistry of the conjugate addition reaction, they did influence the ratio of the cis- and trans-fused vinylgermane adducts obtained upon thermodynamically controlled equilibration

reactions. Moreover, the substituents R and R' had a significant effect on the fused to bridged product ratio of the cyclization reactions as discussed above.

2.4. THE FORMATION OF TRICYCLIC COMPOUNDS BEARING AN ALLYLIC, ANGULAR HYDROXYL GROUP VIA A METAL-HALOGEN EXCHANGE REACTION

2.4.1. INTRODUCTORY REMARKS

In Sections 2.1. and 2.3., the vinylgermane bifunctional reagent **13** was employed in annulation sequences as the synthetic equivalent of an a^2,d^4 -synthon. Reagent **13** can also serve as the synthetic equivalent of a 1-butene d^2,d^4 -synthon **21**, as depicted in equation 35. The first two steps in this sequence are identical with those described in Sections 2.3.3.4. and 2.3.4. (i.e. the stereoselective conjugate addition of the organocopper(I) reagent **15** to bicyclo[4.3.0]non-9-en-2-ones, followed by the conversion of the vinylgermane adducts to the corresponding vinyl iodides). The proposed ring closure step involves conversion of the vinyl iodide moiety into a donor center via a lithium-iodine exchange reaction. In this way, we hoped to gain access to tricyclic allylic alcohols of general structure **33**. Examination of the stereochemical outcome of such a reaction was also a motivating factor for these studies.



2.4.2. CYCLIZATION STUDIES

The cyclization reactions were performed on the bicyclic trans-fused vinyl iodides **135b**, **137b**, and **138b** (Table 15, page 104) and the cis-fused vinyl iodides **135a**, **136**, **137a**, and **138a** (Table 17, page 110). The results of the cyclization reactions of the trans-fused vinyl iodides are summarized in Table 15 and indicate that the lithium-iodine exchange reaction and subsequent closure of the vinyl lithium species onto the carbonyl carbon

proceeded cleanly and in good yield in all cases. Upon examination of molecular models, it was clear that the approach of the vinyl lithium moiety to the carbonyl carbon from the alpha direction is much more favorable than approach from the beta face of the molecule (see **154a**). Nonetheless, the stereochemistry of each cyclization reaction was confirmed by ^1H nmr experiments (*vide infra*).

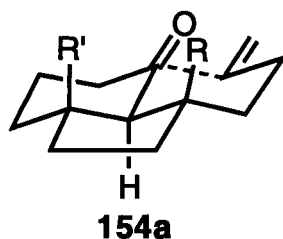
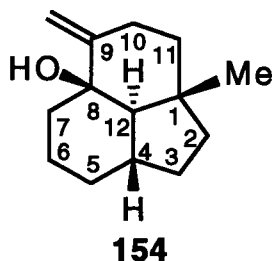


Table 15: Cyclization Reactions of the Trans-Fused Vinyl Iodides to Yield Tricyclic Compounds Bearing an Allylic, Angular Hydroxyl Group

Entry	Vinyl Iodide	R	R'	Cyclized Product (Isolated Yield)
1	135b	Me	H	154 (95%)
2	137b	H	H	155 (83%)
3	138b	H	Me	156 (85%)



The trans-fused vinyl iodide **135b** (entry 1, **Table 15**) was treated with 2.6 equivalents of *n*-BuLi at -78 °C to provide, after workup and purification, the crystalline tricyclic compound **154** in 95% yield. Interestingly, nucleophilic attack of *n*-BuLi on the carbonyl function does not compete with the lithium-iodine exchange and intramolecular cyclization reactions. The IR spectrum of **154** revealed absorbances at 3568, 3449, 3079, and 1646 cm⁻¹, typical of hydroxyl and olefinic moieties. The ¹H nmr spectrum (400 MHz, CDCl₃), illustrated in part a of **Figure 7** (page 106), revealed a signal at δ 0.78 (d, J = 12.5 Hz) for the angular proton H-12, a signal at δ 1.08 (s) for the tertiary methyl group, and two signals at δ 4.80 (dd, J = 2, 2 Hz) and 4.86 (dd, J = 2, 2 Hz) for the vinyl protons. The COSY spectrum allowed the assignment of the protons H-4, H-7, H-7', H-10, H-10', H-11, and H-11' (see **Table 35**, experimental, page 231). The relative configuration at each of the carbons 1, 4, and 12 was known from the starting keto vinyl iodide. Therefore, the only unknown stereochemistry was at C-8 (i.e. the carbon bearing the angular hydroxyl group). Attempts at observing a nuclear Overhauser enhancement of the hydroxyl proton failed. For this reason, we needed to utilize a technique other than NOE difference experiments to verify the C-8 stereochemistry of the tricyclic alcohols.

Pyridine-d₅ has been used as a non-invasive shift reagent to establish both the location and stereochemical orientation of protons situated in the vicinity of hydroxyl functions.⁶⁷ Demarco *et al.*⁶⁷ report that protons occupying positions 1,3-diaxial, vicinal, or geminal to a hydroxyl function are deshielded on the order of 0.15 - 0.40 ppm in pyridine relative to chloroform. Pyridine is believed to complex to the alcohol moiety via a hydrogen bonding association (**Scheme 30**, page 107).

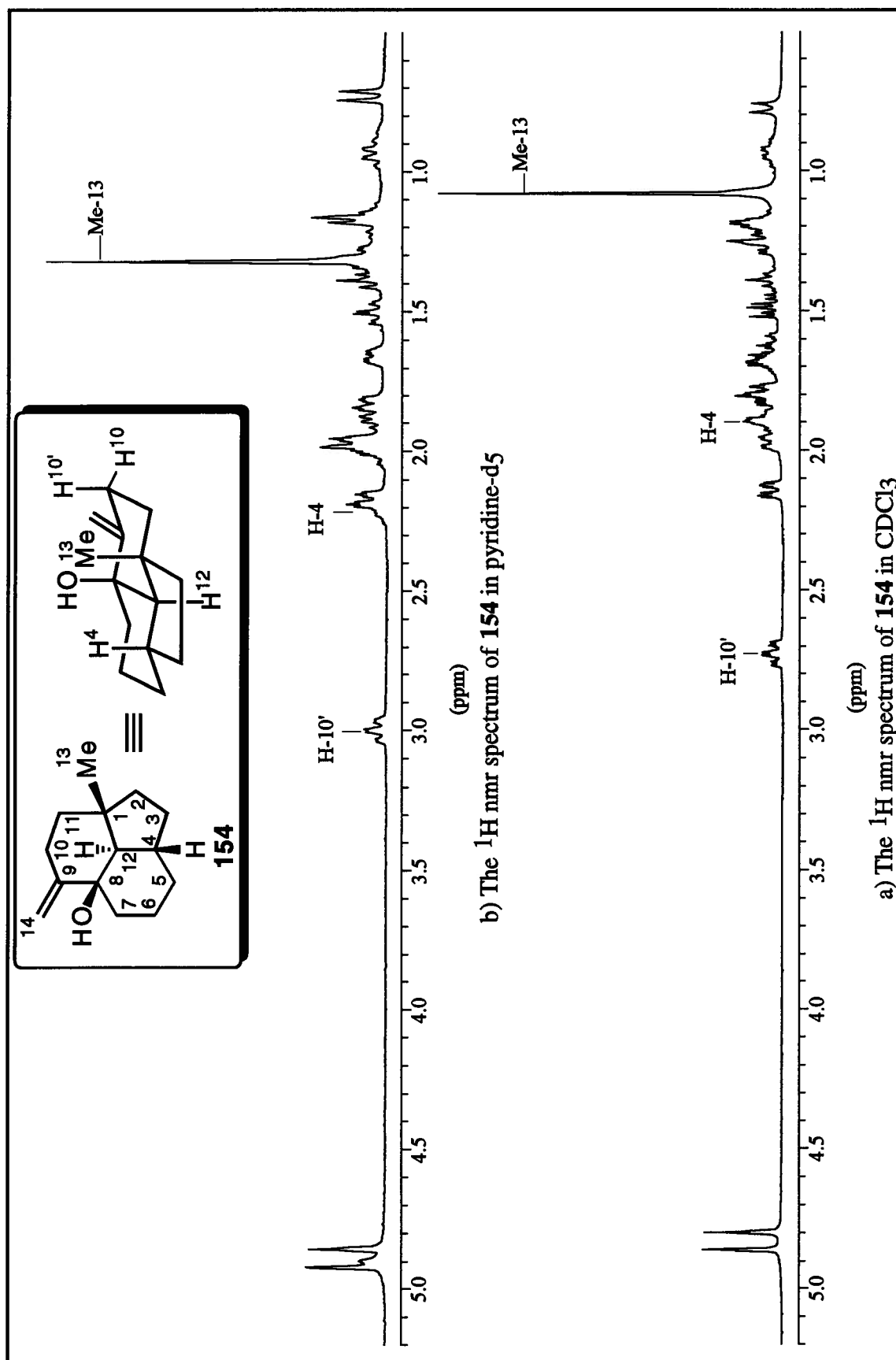
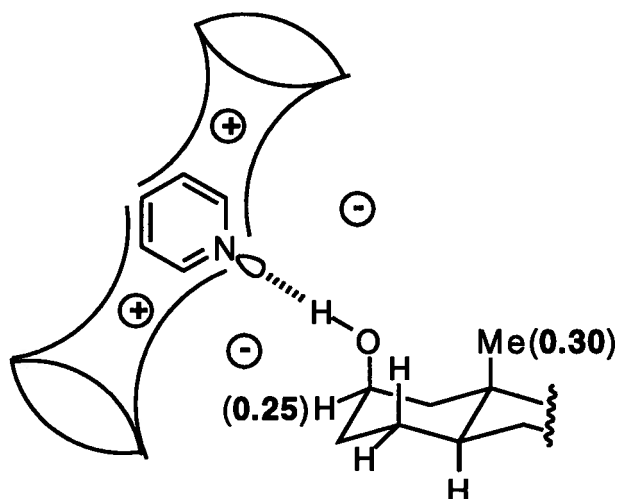


Figure 7: The ^1H NMR Spectrum (400 MHz) of the Allylic Alcohol **154 in a) CDCl_3 and b) pyridine- d_5**



Scheme 30⁶⁷

In the case of hydrogen bonding of a hydroxyl proton to pyridine, it is assumed that the N...H-O bond is co-linear (i.e. the O-H bond lies along the axis of symmetry of the nitrogen lone-pair electrons). For steric reasons, this association must take place from the side of the ring away from the axial methyl group. Thus, in light of the known mechanism by which deshielding can occur, the geometrical relationship, illustrated in **Scheme 30**, explains the Δ values ($\Delta = \delta(\text{pyridine-d}_5) - \delta(\text{CDCl}_3)$) reported for the axial methyl group ($\Delta = 0.30$) and the geminal proton ($\Delta = 0.25$).⁶⁷

In order to verify the stereochemical result of the cyclization reaction, we investigated the effects of pyridine-d₅ on the chemical shifts of the protons of the tricyclic compound **154**. The ¹H nmr spectrum (400 MHz) of **154** in pyridine-d₅ (see part b of **Figure 7**, page 106) revealed the following characteristic signals: δ 0.73 (d, $J = 13$ Hz) for H-12, δ 1.32 (s) for the tertiary methyl group, and δ 4.85-4.86 (dd, $J = 2, 2$ Hz) and 4.92-4.93 (dd, $J = 2, 2$ Hz) for the vinyl protons. The COSY spectrum allowed the identification of many of the other protons (see **Table 36**, experimental, page 231).

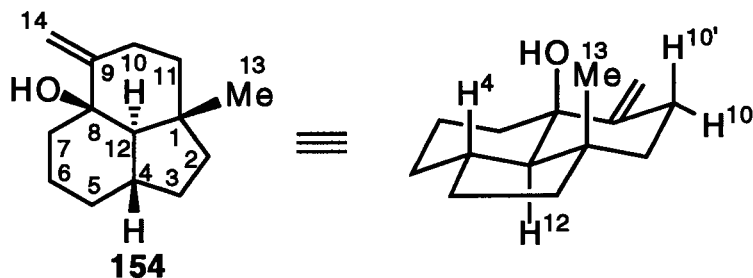
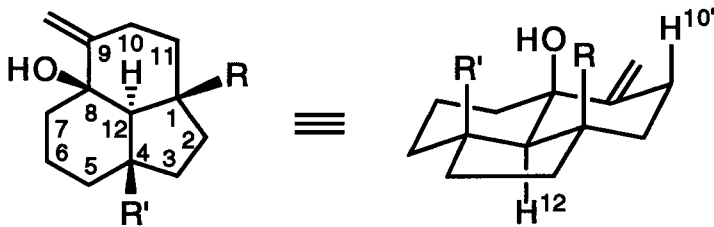


Figure 7 (page 106) compares the ^1H nmr spectra of **154** in CDCl_3 versus that in pyridine- d_5 . Three signals, H-4 ($\Delta = 0.36$), H-10' ($\Delta = 0.26$), and Me-13 ($\Delta = 0.24$), were significantly shifted downfield in pyridine- d_5 relative to CDCl_3 (see **Table 37**, experimental, page 232). Since the relative configuration at carbons 1 and 4 is known, it follows that the hydroxyl group must be on the same face of the molecule as H-4 and Me-13, thereby verifying the stereochemistry at C-8. The protons H-4, H-10', and Me-13 exist in a 1,3-diaxial relationship to the hydroxyl group, thus explaining the downfield shifts observed for these protons in pyridine- d_5 relative to CDCl_3 . As indicated in **Table 37** (experimental, page 232), the chemical shifts of all the other assigned protons did not change significantly in pyridine- d_5 relative to CDCl_3 .

The remaining two trans-fused vinyl iodides **137b** and **138b** were cyclized to yield the tricyclic alcohols **155** and **156** in 83% and 85% yield, respectively (entries 2 and 3, **Table 15**, page 104). The stereochemistry of the cyclization reaction was verified by comparing the ^1H nmr spectra of **155** and **156** in pyridine- d_5 versus those in CDCl_3 (see **Tables 49** and **56**, experimental, pages 249 and 259, respectively). As with compound **154**, those protons in a 1,3-diaxial relationship to the angular hydroxyl group were shifted downfield in pyridine- d_5 relative to CDCl_3 (see **Table 16**). The downfield shifts ranged from 0.22 ppm (entry 3, **Table 16**) to 0.88 ppm (entry 2, **Table 16**). Thus, the *n*-BuLi mediated cyclization of the trans-fused vinyl iodides provided a stereoselective route to the synthesis of the tricyclic alcohols **154-156**.

Table 16: Δ^a ppm for those Protons in a 1,3-Diaxial Relationship with the Angular Hydroxyl Group

						
Entry	Tricyclic Alcohol	R	R'	Δ^a for R' (ppm)	Δ^a for R (ppm)	Δ^a for H-10' (ppm)
1 ^b	154	Me	H	0.36	0.24	0.26
2 ^c	155	H	H	0.88	0.40	0.34
3 ^d	156	H	Me	0.22	0.28	0.34

a - $\Delta = \delta$ (pyridine- d_5) - δ ($CDCl_3$).

b- Data from **Table 37**, experimental, page 232.

c- Data from **Table 49**, experimental, page 249.

d- Data from **Table 56**, experimental, page 259.

The results of the cyclization of the cis-fused vinyl iodides **135a**, **136**, **137a**, and **138a**, summarized in **Table 17**, were not as straightforward as those obtained with the trans-fused vinyl iodides. Upon examination of molecular models, it was evident that the vinyl lithium species, obtained from the reaction of the cis-fused vinyl iodides with *n*-BuLi, could approach the carbonyl carbon from two different directions (i.e. attack from either the alpha or beta face of the molecule).

Table 17: Cyclization Reactions of the Cis-Fused Vinyl Iodides to Yield Tricyclic Compounds Bearing an Allylic, Angular Hydroxyl Group

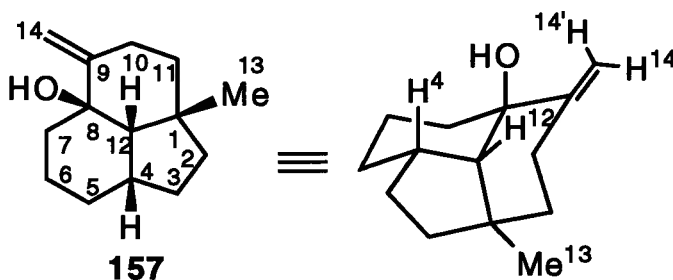
Entry	Vinyl Iodide	R	R'	Beta-OH Products (Yield) ^a	Alpha-OH Products (Yield) ^a	Uncyclized Byproduct (Yield) ^a	Total Yield
				RATIO ^b			
1	135a	Me	H	157 24% 1	158 51% 2.1	159 8%	83%
2	136	Me	Me	160 65% > 99	— ^c < 1	161 35%	100%
3	137a	H	H	162 26% 1	163 37% 1.4	164 11%	74%
4	138a	H	Me	165 40% 1.1	166 35% 1	167 20%	95%

a- Yield refers to the isolated yield.

b- This is the ratio between the two cyclized products.

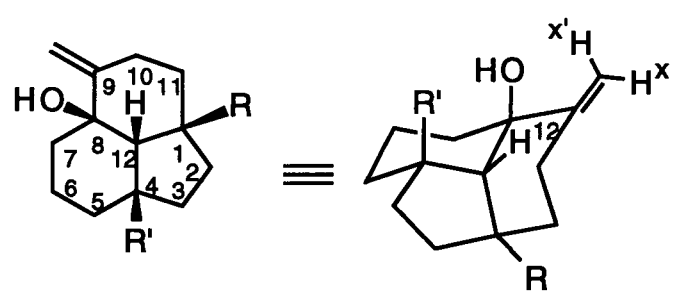
c- None of this product was obtained.

The cyclization of the cis-fused vinyl iodide **135a** provided, after workup and purification, products **157**, **158**, and **159** in yields of 24%, 51%, and 8%, respectively (entry 1, **Table 17**). The two major products, **157** and **158**, were determined to be epimeric tricyclic alcohols, whereas the minor compound **159** was found to be an uncyclized byproduct in which the iodine moiety had been replaced by a proton. The spectroscopic evidence for these three products will now be discussed.



The IR spectrum of the cyclized product **157** revealed absorbances at 3472, 3387, 3087, and 1642 cm^{-1} , characteristic of hydroxyl and olefinic moieties. The ^1H nmr spectrum (400 MHz, CDCl_3) revealed signals at δ 1.01 (s) for the tertiary methyl group (Me-13), δ 1.41 (d, $J = 7$ Hz) for the angular proton H-12, and δ 4.81–4.82 (m) and 5.10 (br d, $J = 1$ Hz) for the vinyl protons H-14 and H-14'. The COSY spectrum allowed the assignment of several other protons (see **Table 39**, experimental, page 237). The ^1H nmr spectrum (400 MHz) of **157** in pyridine- d_5 was also examined, and a comparison of the chemical shifts of the assigned protons in pyridine- d_5 relative to CDCl_3 was made (see **Table 41**, experimental, page 238). Upon examination of molecular models, it was clear that one of the six-membered rings must exist in either a boat or twist-boat conformation. The conformation depicted above explains why the protons H-4, H-12, and H-14' were all significantly shifted downfield in pyridine- d_5 relative to CDCl_3 (entry 1, **Table 18**). The angular proton H-4 ($\Delta = 0.16$) is in a 1,3-diaxial relationship with the OH group, while proton H-12 ($\Delta = 0.37$) is in a cis vicinal position, and the vinyl proton H-14' ($\Delta = 0.48$) is in very close proximity to the hydroxyl group. As was previously observed, the chemical shift of the other assigned protons did not change significantly in pyridine- d_5 relative to CDCl_3 .

Table 18: Δ^a ppm for those Protons in Close Proximity to the Angular Hydroxyl Group in the Beta-OH Products

						
Entry	Tricyclic Alcohol	R	R'	Δ^a for R' (ppm)	Δ^a for H-12 (ppm)	Δ^a for H-x' (ppm)
1 ^b	157	Me	H	0.16	0.37	0.48
2 ^c	160	Me	Me	0.19	0.39	0.49
3 ^d	162	H	H	0.16	0.38	0.49
4 ^{e,f}	165	H	Me	0.18	0.52	0.50

a - $\Delta = \delta$ (pyridine- d_5) - δ ($CDCl_3$).

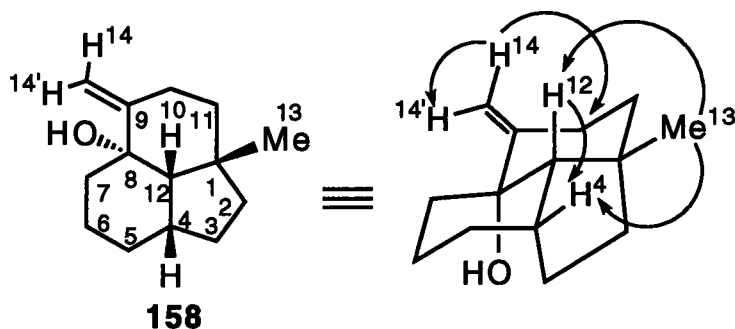
b- Data from **Table 41**, experimental, page 238.

c- Data from **Table 44**, experimental, page 243.

d- Data from **Table 53**, experimental, page 255.

e- Data from **Table 60**, experimental, page 265.

f- In this compound, H-x was also deshielded by 0.16 ppm in pyridine- d_5 relative to $CDCl_3$.



The IR spectrum of the other cyclized product **158** revealed absorbances at 3600, 3494, 3079, and 1639 cm^{-1} , indicative of hydroxyl and olefinic functions. The 1H nmr

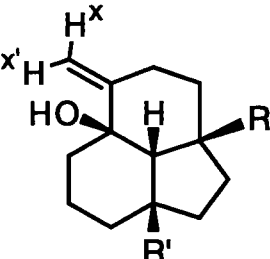
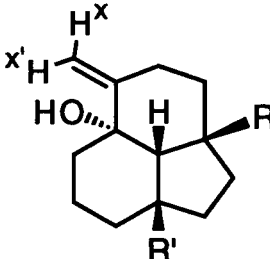
spectrum (400 MHz, CDCl₃) possessed signals at δ 0.71 (s) due to the hydroxyl proton (which disappeared upon the addition of D₂O), δ 0.99 (s) for the tertiary methyl group (Me-13), δ 1.14 (d, J = 7 Hz) for the angular proton H-12, and δ 4.71-4.72 (m) and 4.89 (br d, J = 1 Hz) for the vinyl protons H-14 and H-14', respectively. The COSY spectrum allowed the assignment of H-4 (δ ~2.31-2.38, m) through the correlation of its signal to that of H-12 (see **Table 38**, experimental, page 234). The allylic protons H-10 (δ ~ 2.26-2.31, m) and H-10' (δ ~2.38-2.43, m) were identified via their correlations to the vinyl protons H-14 and H-14'. Similarly, the protons H-11 (δ ~1.42-1.50, m) and H-11' (δ 2.00-2.07, ddd, J = 12.5, 12.5, 4.5 Hz) were assigned through their correlations to H-10 and H-10'.

The following NOE difference experiments were consistent with the assigned relative configuration at carbons 1, 4, and 12. Irradiation of the signal at δ 0.99 (Me-13) caused an enhancement of the signals at δ 1.14 (H-12) and ~2.31-2.38 (H-4). Irradiation of the signal at δ 1.14 (H-12) caused an enhancement of the signal at δ ~2.31-2.38 (H-4). These experiments established that H-4, H-12, and Me-13 are on the same face of the molecule. Irradiation of the signal at δ 4.71-4.72 (H-14) caused an enhancement of the signals at δ ~2.38-2.43 (H-10') and 4.89 (H-14'), thus allowing the assignment of the vinyl protons H-14 and H-14'.

Comparison of the ¹H nmr spectra of **158** in pyridine-d₅ versus CDCl₃ did not provide conclusive evidence for the stereochemical assignment at C-8. Nonetheless, compound **158** is epimeric to the corresponding alcohol **157**, and must thus possess the relative configuration shown above. Moreover, it was found that the alpha-OH products **158**, **163**, and **166** were readily differentiated from the corresponding beta-OH products **157**, **160**, **162**, and **165** on the basis of their polarity in column chromatography. The alcohols **158**, **163**, and **166** were much less polar than their corresponding epimers **157**, **162**, and **165** (the difference in R_f (using 9:1 petroleum ether - diethyl ether) was ~0.5). The difference in polarity can be explained by the fact that the hydroxyl groups of compounds **158**, **163**, and **166** are buried in the concave face of the molecules and are thus much less accessible than the hydroxyl groups of compounds **157**, **162**, and **165**.

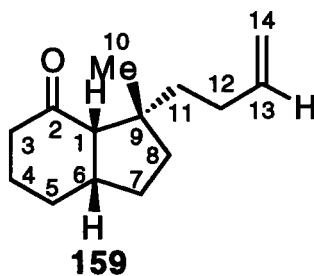
Other evidence that distinguished the epimeric tricyclic alcohols was obtained from the chemical shifts of the vinylic protons H-x'. **Table 19** lists the chemical shifts of H-x' for the tricyclic alcohols obtained in the cyclization reactions of the cis-fused vinyl iodides. The chemical shifts of H-x' in the beta-OH products **157**, **160**, **162**, and **165** were more downfield in comparison to those shifts for the corresponding alpha-OH products. The hydroxyl group in the beta-OH products is situated very close to H-x' and thus deshields this proton, as was further confirmed in the pyridine-d₅ studies.

Table 19: Differences in the Chemical Shift of the Vinyl Proton H-x' Between the Beta-OH and Alpha-OH Products

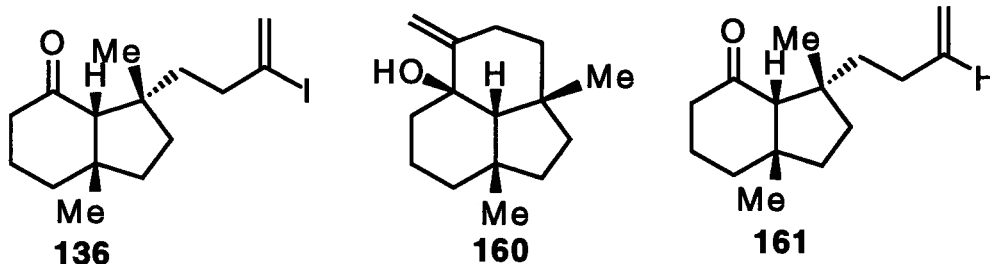
			 Beta-OH Products	 Alpha-OH Products
Entry	R	R'	Compound #	Compound #
			¹ H nmr shift for H-x' a	¹ H nmr shift for H-x' a
1	Me	H	157	158
			δ 5.10	δ 4.89
2	Me	Me	160	
			δ 5.09	— b
3	H	H	162	163
			δ 5.10-5.11	δ 4.86
4	H	Me	165	166
			δ 5.08	δ 4.90

a- CDCl₃ was the solvent used in these ¹H nmr spectra.

b- This compound was not obtained.

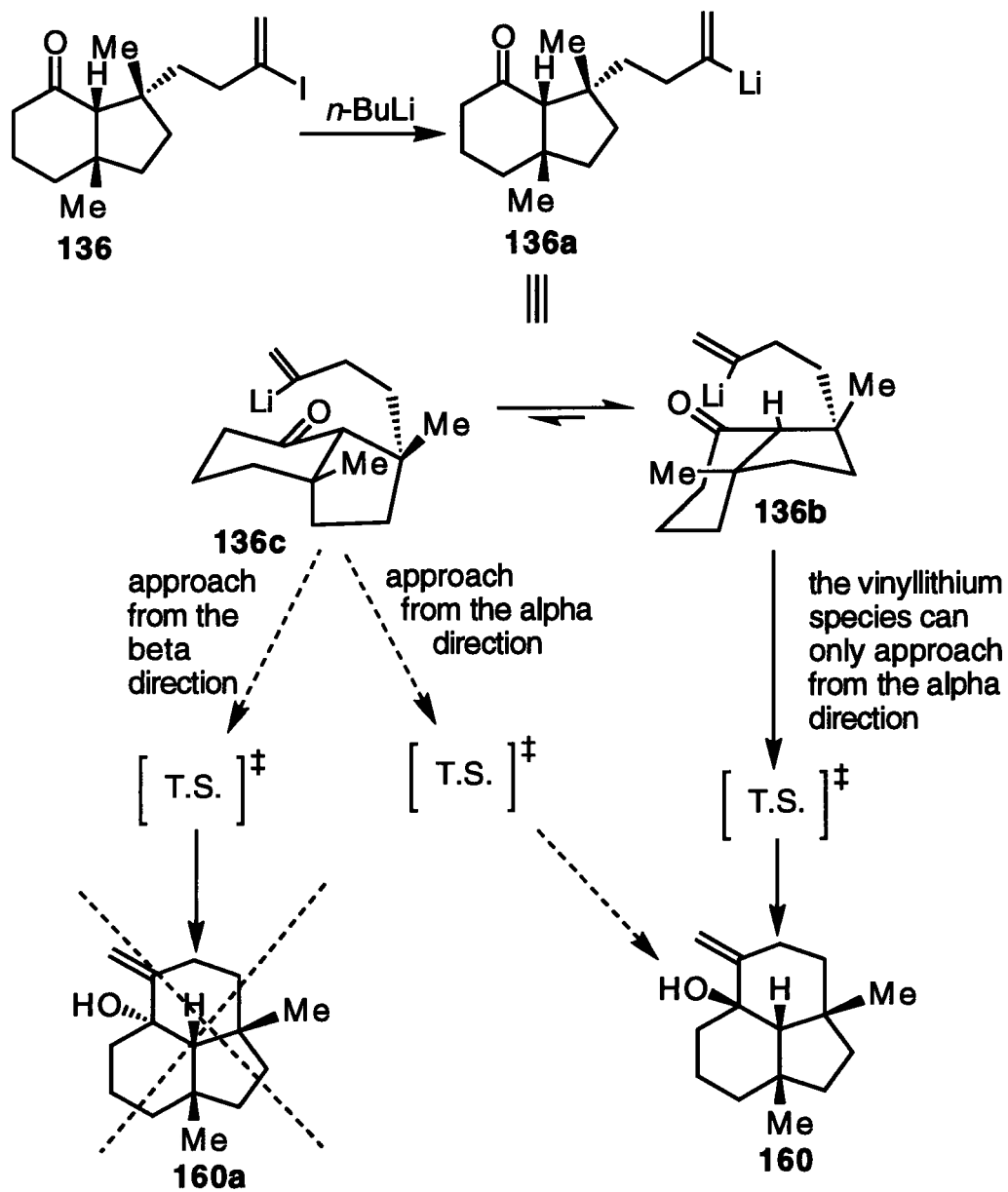


The IR spectrum of the byproduct **159** revealed absorbances at 3076, 1694, and 1641 cm^{-1} , typical of ketone and olefinic moieties. The ^1H nmr spectrum (400 MHz, CDCl_3) possessed three signals at δ 4.90-4.92 (br d, $J = 10$ Hz, H-14), 4.95-5.00 (dddd, $J = 17, 2, 2, 2$ Hz, H-14'), and 5.72-5.82 (dddd, $J = 17, 10, 6.5, 6.5$ Hz, H-13), indicative of a monosubstituted double bond.

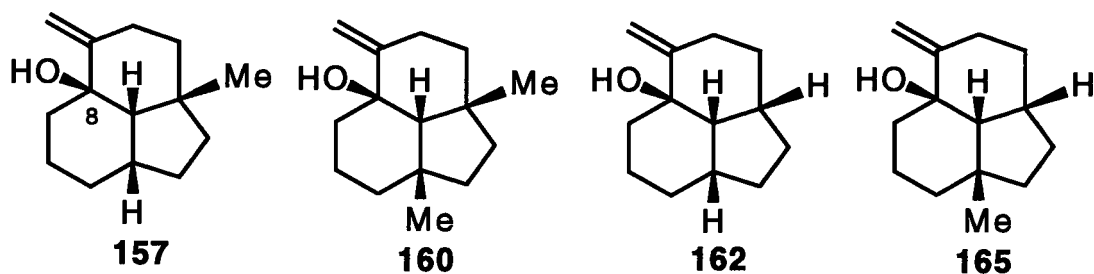


Of the remaining three cis-fused vinyl iodides **136**, **137a**, and **138a**, the latter two substrates were cyclized to yield a product composition similar to that obtained from **135a** (see entries 3 and 4, **Table 17**, page 110). On the other hand, iodide **136** (entry 2) yielded only two products upon treatment with *n*-BuLi, **160** and **161**. The only cyclized product, **160**, was determined to be that obtained from alpha attack of the vinyl lithium species onto the carbonyl carbon (i.e. the beta-OH product). The other compound was the uncyclized byproduct **161**. The assignments of the tricyclic structures in **Table 17** were based on analyses of the ^1H nmr spectra of each compound. The relative configuration at C-8 for the beta-OH products (**157**, **160**, **162**, and **165**) was confirmed by analyzing the ^1H nmr spectra of these compounds in pyridine- d_5 relative to that in CDCl_3 (**Table 18**, page 112).

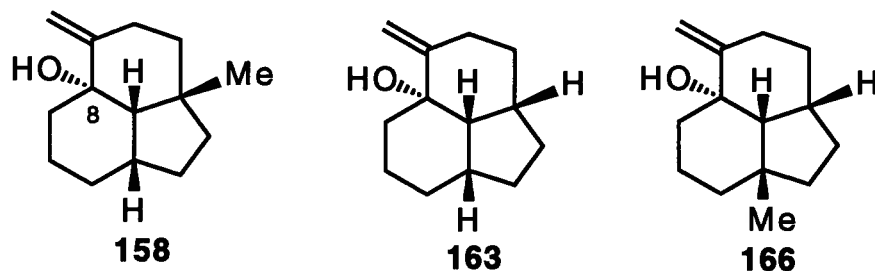
In the cyclization of the *cis*-fused vinyl iodides, the nature of the substituents R and R' influences the ratio of the products obtained. For example, the formation of the α -OH product was slightly favored when R' = H (entries 1 and 3, **Table 17**, page 110). An approximately equal amount of epimeric alcohols was obtained when R = H and R' = Me (entry 4, **Table 17**). When both R and R' = Me, the approach of the vinylolithium species occurred exclusively from the α face of the molecule, resulting in the sole formation of the β -OH product **160** (entry 2, **Table 17**). This latter result can be rationalized by examining the two possible conformations, **136b** and **136c**, of the vinylolithium species **136a** (see **Scheme 31**). Upon examination of molecular models, it was concluded that the vinylolithium side chain in conformer **136b** can approach the carbonyl carbon only from the α face of the molecule, resulting in the formation of the β -OH product **160**. In the other conformer, **136c**, the vinylolithium side chain can approach the carbonyl carbon from either direction (leading to the formation of the alcohols **160a** and **160**). However, conformer **136c** is significantly less stable than **136b** due to a pseudo 1,3-diaxial interaction between the two tertiary methyl groups. Thus, one can conclude that the cyclization reaction proceeds via conformer **136b**, resulting in the sole formation of product **160**.



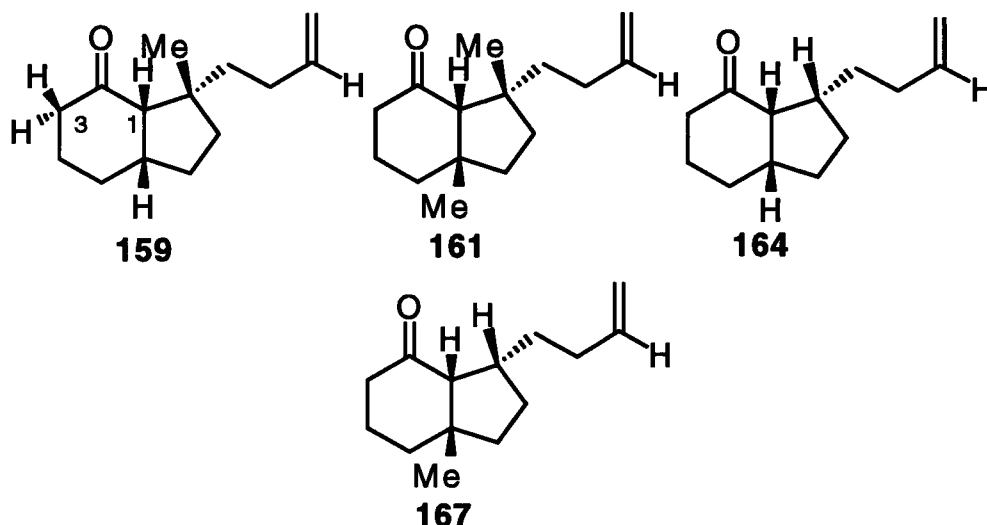
Scheme 31



The beta-OH products (**157**, **160**, **162**, and **165**) were obtained in yields varying from 24% to 65% (see **Table 17**, page 110). The chemical shifts of those protons in close proximity to the hydroxyl group (R', H-12, and H-x') were all shifted downfield in pyridine- d_5 relative to $CDCl_3$ (see **Table 18**, page 112). The shifts, which ranged from 0.16 ppm to 0.52 ppm, verified the stereochemistry at C-8.



The alpha-OH products were obtained in yields varying from 35% to 51% (see **Table 17**, page 110), depending on the nature of the R and R' substituents. The configuration at C-8 for compounds **158**, **163**, and **166** was confirmed by examining the chemical shifts of the vinyl protons H-x' in comparison to the shifts of H-x' for the corresponding epimeric alcohols (see **Table 19**, page 114). Also, the relative polarity of the alpha-OH and beta-OH products in column chromatography was indicative of the relative configuration at C-8 (*vide supra*).



In the reactions of the *cis*-fused vinyl iodides with *n*-BuLi, bicyclic byproducts (**159**, **161**, **164**, and **167**) were also obtained (Table 17, page 110). Increasing the reaction time did not decrease the amount of byproduct formed. This indicated that the byproduct is probably formed by protonation of the vinyl lithium species by the acidic protons adjacent to the carbonyl carbon, rather than by quenching of the reaction during workup. Since the configuration at the ring junction (C-1) does not epimerize (i.e. only *cis*-fused byproducts were obtained), it follows that the protonation of the vinyl lithium species probably occurs by transfer of one of the acidic protons at C-3.

2.4.3. CONCLUSION

The cyclization of the *cis*- and *trans*-fused vinyl iodides via a lithium-iodine exchange reaction provided an excellent route to the synthesis of tricyclic compounds bearing an allylic, angular hydroxyl group. In this way, the annulation sequence utilized the vinylgermane reagent **13** as the synthetic equivalent of a 1-butene d^2,d^4 -synthon. The cyclization of the *trans*-fused vinyl iodides proceeded stereoselectively; the nature of the

substituents R and R' did not affect the stereochemistry of the addition (i.e. the stereochemistry at C-8). On the other hand, the cyclization of the cis-fused vinyl iodides provided an epimeric mixture of alcohols, the composition of which depended on the substituents R and R'.

III. EXPERIMENTAL

3.1. GENERAL

3.1.1. DATA ACQUISITION AND PRESENTATION

Infrared (IR) spectra were recorded as films between sodium chloride plates (liquid samples) or as potassium bromide pellets (solid compounds), employing either a Perkin-Elmer 1710 FT-IR or a Bomem Michelson 100 FT-IR Spectrophotometer, both with internal calibration.

Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Bruker model AC-200, WH-400, or AMX-500 spectrometer using deuteriochloroform (CDCl_3) as the solvent, unless otherwise noted. Signal positions (δ) are given in parts per million from tetramethylsilane and were measured relative to the signals of chloroform (δ 7.26), benzene (δ 7.15), acetone (δ 2.04), or pyridine (δ 8.71, C-2 proton). Coupling constants (J values) are given in Hertz (Hz). The spectral data are reported in the following format: chemical shift (ppm), (multiplicity, number of protons, coupling constant(s), and assignments (when known)). Abbreviations used are: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad. In the ^1H nmr spectra, H-x and H-x' have been used to designate protons on the same carbon, with H-x' being the proton resonating at lower field. In some cases, the proton assignments were supported by COSY (^1H - ^1H homonuclear correlation spectroscopy) and/or NOE (nuclear Overhauser enhancement) difference experiments. These experiments were carried out using a Bruker model WH-400 spectrometer.

Carbon nuclear magnetic resonance (^{13}C nmr) spectra and the attached proton test experiments (APT) were recorded on a Varian XL-300 spectrometer at 75.3 MHz or on a Bruker model AM-400 (100.4 MHz) or AMX-500 (125.8 MHz) spectrometer, using deuteriochloroform as the solvent, unless otherwise noted. Signal positions (δ values) are given in parts per million from tetramethylsilane and were measured relative to the signals of chloroform-d (δ 77.0), benzene-d₆ (δ 128.0), or pyridine-d₅ (δ 149.9, C-2). Signals with negative phase in the attached proton test are so indicated in brackets (-ve) following the

chemical shift. The ^1H - ^{13}C heteronuclear multiple quantum coherence experiments (HMQC)⁶⁸ and the ^1H - ^{13}C heteronuclear multiple bonds connectivity experiments (HMBC)⁶⁸ were recorded on a Bruker model AMX-500 spectrometer.

Low and high resolution electron impact mass spectra were recorded on a Kratos MS50 mass spectrometer (70 eV). Desorption chemical ionization mass spectra were recorded with a Delsi Nermag R-10-10 C mass spectrometer. Gas-liquid chromatography-low resolution mass spectrometry (GLCLRMS) was accomplished using a combination of a Carlo Erba model 4160 capillary gas chromatograph (15 m x 0.25 m fused silica column coated with DB-5) and a Kratos/RFA MS 80 mass spectrometer, interfaced with a hollow capillary tube. The following atomic masses were used to calculate the mass of fragments observed in the HRMS: ^1H 1.007825; ^{12}C 12.00000; ^{14}N 14.00307; ^{16}O 15.99491; ^{28}Si 27.97693; ^{74}Ge 73.921177; ^{127}I 126.9044. All compounds subjected to high resolution mass measurements were homogeneous by glc and/or tlc analysis. For some of the compounds containing trimethylgermyl groups, the high resolution mass spectrometry molecular mass determinations were based on the ($\text{M}^+ - \text{Me}$) peak.

Elemental analyses were performed on a CARLO ERBA CHN elemental analyzer, model 1106, by the UBC Microanalytical Laboratory.

Specific rotations at the sodium D line (589.3 nm) and the temperature t ($[\alpha]_D^t$) were measured on a JASCO J710 spectropolarimeter using spectroscopic grade chloroform as the solvent.

Gas-liquid chromatography (glc) analyses were performed on a Hewlett-Packard model 5880A or 5890 gas chromatograph, both equipped with flame ionization detectors and fused silica capillary columns, either ~20 m x 0.21 mm coated with cross-linked SE-54 or ~25 m x 0.20 mm coated with 5% phenylmethyl silicone. Chiral gas-liquid chromatography (glc) analyses were performed on a Hewlett-Packard model 5880A gas chromatograph using an Altech Chirasil-Val III capillary column, 25 m x 0.25 mm x 0.16 μm .

Thin layer chromatography (tlc) was carried out on commercial aluminum-backed silica gel 60 plates (E. Merck, type 5554, 0.2 mm). Reverse phase tlc was performed on commercially available, glass-backed plates (Whatman, type KC18/KC18F). Visualization was accomplished with either ultraviolet light (254 nm) and/or iodine followed by heating the plates after staining with an appropriate reagent. The stains used were (a) phosphomolybdic acid (PMA) in EtOH (20% w/v, Aldrich), (b) ammonium molybdate and cerium sulfate in 10% aqueous sulfuric acid (5% ammonium molybdate w/v and 0.1% $\text{Ce}(\text{SO}_4)_2$ w/v), (c) vanillin in a sulfuric acid-EtOH mixture (6% vanillin w/v, 4% sulfuric acid v/v, and 10% water v/v in EtOH), or (d) anisaldehyde in a sulfuric acid-EtOH mixture (5% anisaldehyde v/v and 5% sulfuric acid v/v). Conventional (drip) and flash chromatography⁶⁹ were performed using 230-400 mesh silica gel (E. Merck, Silica Gel 60). Tlc grade silica chromatography⁷⁰ was performed on 10-50 μm Type H silica (S-6628, Sigma). Radial chromatography⁷¹ was performed on a Chromatotron[®] Model 7924 using 1 or 2 mm thick radial plates (silica gel 60, PF254, with calcium sulfate, E. Merck #7749).

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures refer to air-bath temperatures of Kugelrohr (bulb-to-bulb) distillations and are uncorrected. Viscous and/or high molecular weight compounds were often heated under reduced pressure (vacuum pump) to remove residual solvent; this was accomplished using a Kugelrohr distillation apparatus.

Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame and/or oven ($\sim 140^\circ\text{C}$) dried. The glass syringes, Teflon[®] cannulae and needles used for handling anhydrous solvent and reagents were oven dried, while plastic syringes were flushed with dry argon prior to use. Gas-tight syringes (Hamilton series 1700) were placed under reduced pressure (vacuum pump) for 10 min and flushed with dry argon prior to use. The small and large Teflon[®] cannulae were purchased from Canlab (Mississauga, ON.) and have the following dimensions: the small cannula (catalogue # R5360-111) has an inner diameter of 0.38 mm

and a wall thickness of 0.23 mm; the large cannula (catalogue # R5360-117) has an inner diameter of 0.97 mm and a wall thickness of 0.30 mm.

Concentration, evaporation, or removal of solvent under reduced pressure (water aspirator) refer to solvent removal via a Büchi rotary evaporator at ~15 Torr.

Cold temperatures were maintained by the use of the following baths: 0 °C, ice/water; -20 °C, -35 °C, and -48 °C, aqueous calcium chloride/CO₂ (27, 39, and 47 g CaCl₂/100 mL H₂O, respectively);⁷² -78 °C, acetone/CO₂; -98 °C, MeOH/liquid nitrogen.

3.1.2. SOLVENTS AND REAGENTS

All solvents and reagents were purified and dried using established procedures.⁷³ Benzene and dichloromethane were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. The four aforementioned solvents were distilled under an atmosphere of dry argon and used immediately. Acetonitrile, *N,N*-diisopropylethylamine, *N,N*-dimethylformamide, dimethylsulfoxide, HMPA (WARNING: carcinogenic), 2-methyl-2-propanol (*t*-BuOH), pyridine, triethylamine, and trimethylsilyl chloride were refluxed over and then distilled from calcium hydride. *N,N*-Dimethylformamide, HMPA, and 2-methyl-2-propanol (*t*-BuOH) were stored over 4Å molecular sieves. Trimethylsilyl bromide was distilled from calcium hydride using a Kugelrohr distillation apparatus and was used immediately. Magnesium was added to MeOH and, after refluxing the mixture, the MeOH was distilled from the resulting solution of magnesium methoxide and was stored over 4Å molecular sieves. Acetic anhydride and carbon tetrachloride were refluxed over and then distilled from phosphorous pentoxide. Petroleum ether refers to a hydrocarbon mixture with a boiling range of 30-60 °C. All other solvents were obtained commercially and were used without purification.

Boron trifluoride-etherate was purified by distillation from calcium hydride under reduced pressure (60 °C/20 Torr).

Solutions of methyllithium (as a complex with LiBr) in diethyl ether, *n*-butyllithium in hexanes, and *tert*-butyllithium in pentane were obtained from Aldrich Chemical Co., Inc. and standardized using the procedure of Kofron and Baclawski.⁷⁴

Hexamethylditin was obtained from Organometallics Inc. (East Hampstead, N.H.) and was distilled at aspirator pressure prior to use.

A solution of NaOMe in dry MeOH was prepared in the following manner: to a cold (-78 °C) flask containing dry NaH was added the appropriate amount of dry MeOH. The mixture was stirred at -78 °C for 10 min, warmed to rt, and used immediately.

Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts⁷⁵ and was stored in a dessicator under an atmosphere of dry argon. Copper(I) chloride (99%) and copper(I) cyanide were purchased from Aldrich Chemical Co., Inc. and were used without purification.

Tetrakis(triphenylphosphine)palladium(0) was either purchased from Aldrich Chemical Co., Inc. and used without purification or was prepared by the method described by Coulson.⁷⁶

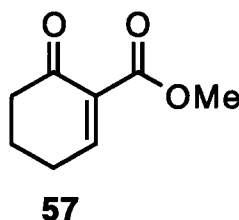
Chloroform and deuteriochloroform were dried by filtration through a short column of basic alumina (activity I), which had been dried in an oven (~140 °C) overnight and then allowed to cool in a dessicator prior to use.

All other reagents are commercially available and were used without purification.

Aqueous ammonium chloride-ammonium hydroxide (NH₄Cl-NH₄OH, pH 8-9) solution was prepared by the addition of ~50 mL of aqueous ammonium hydroxide (58%) to 950 mL of a saturated aqueous ammonium chloride solution.

3.2. SYNTHESIS OF BICYCLIC COMPOUNDS VIA THE FIVE-MEMBERED RING ANNULATION SEQUENCE

3.2.1. SYNTHESIS OF 2-(CARBOMETHOXY)-2-CYCLOHEXEN-1-ONE (57):



A solution of PhSeBr in THF was prepared as follows: to a stirred solution of Ph₂Se₂ (1.70 g, 5.50 mmol, 1.2 equiv.) in dry THF (5.5 mL) at rt was added Br₂ (0.80 g, 5.0 mmol, 1.1 equiv.). The resultant solution (containing ~10 mmol of PhSeBr) was stirred at rt for 10 min and used immediately in the following reaction.

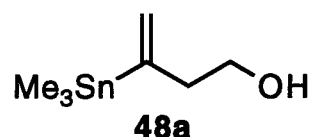
To a cold (0 °C), stirred solution of 2-(carbomethoxy)cyclohexanone⁷⁷ (737 mg, 4.72 mmol, 1 equiv.) in dry THF (18 mL) was added, in one portion, sodium hydride (226 mg, 9.42 mmol, 2 equiv.). The suspension was stirred at 0 °C for 40 min. A solution of PhSeBr in dry THF (1.8 M, 3.9 mL, 7.0 mmol, 1.5 equiv.) was added, dropwise, to the enolate solution. The mixture was stirred at 0 °C for 40 min and was poured into a stirred suspension of diethyl ether (20 mL), petroleum ether (20 mL), and saturated aqueous NaHCO₃ (15 mL). The layers were separated and the aqueous layer was extracted with diethyl ether - petroleum ether (1:1, 3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL), and concentrated under reduced pressure.

The crude selenide was dissolved in CH₂Cl₂ (15 mL) at rt and a solution of H₂O₂ (1.2 mL of 30% aqueous H₂O₂, ~2.5 equiv.) in water (2.5 mL) was added to the mixture in three equal portions at intervals of 10 min. Occasional cooling in an ice-water bath ensured that the mixture remained at rt. Saturated aqueous NaHCO₃ (50 mL) and CH₂Cl₂ (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic extracts were washed with brine (1 x 50 mL), dried over

anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product thus obtained was distilled (air-bath temperature 90-100 °C/0.15 Torr) to afford 670 mg (92%) of 2-(carbomethoxy)-2-cyclohexen-1-one (**57**),⁷⁸ as a colourless oil.

3.2.2. SYNTHESIS OF 4-iodo-2-trimethylgermyl-1-butene (**13**) VIA THE CORRESPONDING VINYLSTANNANE REAGENT

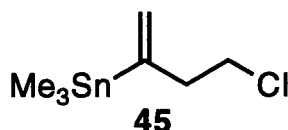
3.2.2.1. Synthesis of 3-Trimethylstannyl-3-buten-1-ol (**48a**):



To a cold (-20 °C), stirred solution of hexamethylditin (77.2 g, 236 mmol, 1.5 equiv.) in dry THF (600 mL) was added a solution of methyllithium in diethyl ether (1.52 M, 155 mL, 236 mmol, 1.5 equiv.). The yellow solution was stirred at -20 °C for 25 min. The reaction mixture was cooled to -78 °C and solid CuBr•Me₂S (48.7 g, 236 mmol, 1.5 equiv.) was added in one portion. The red/brown mixture was stirred at -78 °C for 30 min. A solution of 3-buten-1-ol (11.0 g, 156 mmol, 1 equiv.) in dry THF (10 mL) was added, dropwise, to the mixture. Methanol (318 mL, 7.80 x 10³ mmol, 50 equiv., unpurified HPLC grade) was added and the mixture was stirred at -78 °C for 3.5 h and was warmed to 0 °C for 3h. Aqueous NH₄Cl - NH₄OH (pH 8-9, 400 mL) and diethyl ether (400 mL) were added and the mixture was opened to the atmosphere and stirred vigorously until the aqueous phase became bright blue in colour. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 300 mL). The combined organic extracts were washed with brine (1 x 300 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude oil thus obtained was divided into two equal portions and subjected to drip column chromatography on two separate columns (~500 g silica gel for each column, 200 mL petroleum ether followed by 750 mL of 9:1 petroleum ether - diethyl ether, and finally 4:1

petroleum ether - diethyl ether). The vinylstannane alcohol fractions obtained from both columns were combined, concentrated under reduced pressure, and distilled (air-bath temperature 60 °C/20 Torr) to yield 19.1 g (52%) of 3-trimethylstannyl-3-buten-1-ol (**48a**),⁷⁹ as a colourless oil.

3.2.2.2. Synthesis of 4-Chloro-2-trimethylstannyl-1-butene (**45**):



To a stirred solution of 3-trimethylstannyl-3-buten-1-ol (**48a**) (19.1 g, 81.3 mmol, 1 equiv.) in dry CCl₄ (400 mL) at rt was added dry triethylamine (17.0 mL, 122 mmol, 1.5 equiv.) and triphenylphosphine (32.0 g, 122 mmol, 1.5 equiv.). The mixture was heated to reflux for 17 h, cooled to rt, and diluted with hexanes (2 L) to precipitate triphenylphosphine oxide. The slurry was filtered through Florisil (500 g) using water aspirator pressure. The filtrate was concentrated under reduced pressure and flash chromatographed (400 g silica gel, petroleum ether). The oil thus obtained was distilled (air-bath temperature 50-60 °C/20 Torr) to yield 19.4 g (95%) of 4-chloro-2-trimethylstannyl-1-butene (**45**),⁸⁰ as a colourless oil.

3.2.2.3. Synthesis of 4-Iodo-2-trimethylgermyl-1-butene (**13**):



To a cold (-78 °C), stirred solution of 4-chloro-2-trimethylstannyl-1-butene (**45**) (3.80 g, 15.0 mmol, 1 equiv.) in dry THF (75 mL) was added a solution of methyllithium in diethyl ether (1.46 M, 13.3 mL, 19.4 mmol, 1.3 equiv.). The solution was stirred at -78 °C for 0.5 h.

Bromotrimethylgermane (4.14 g, 21.0 mmol, 1.4 equiv.) was cannulated into the solution and the resulting mixture was stirred at -78 °C for 2 h. Aqueous NH₄Cl - NH₄OH (pH 8-9, 50 mL) and diethyl ether (60 mL) were added, the mixture was warmed to rt, and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed with brine (1 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude 4-chloro-2-trimethylgermyl-1-butene (**50**) was used immediately in the following step without further purification.

To a solution of the crude 4-chloro-2-trimethylgermyl-1-butene (**50**) (~15.0 mmol based on the theoretical amount) in acetone (75 mL, unpurified HPLC grade) at rt was added sodium iodide (34.0 g, 225 mmol, 15 equiv. based on the vinylstannane chloride **45**). The suspension was heated to reflux for 65 h and then cooled to rt. The acetone was removed by rotary evaporation and the residual material was dissolved in diethyl ether (75 mL) and water (75 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (4 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was subjected to flash chromatography (125 g silica gel, petroleum ether) and the oil thus obtained was distilled (air-bath temperature 80-90 °C/15 Torr) to afford 3.75 g (84% from the vinylstannane chloride) of 4-iodo-2-trimethylgermyl-1-butene (**13**),⁸¹ as a colourless oil.

¹H nmr (400 MHz) δ : 0.23 (s, 9H, -GeMe₃), 2.73-2.78 (tt, 2H, J = 8, 1 Hz, allylic methylene protons), 3.18-3.22 (t, 2H, J = 8 Hz, ICH₂CH₂-), 5.32 (m, 1H, vinyl proton), 5.59 (m, 1H, vinyl proton).

¹³C nmr (75.3 MHz) δ : -2.0 (-ve, -Ge(CH₃)₃), 4.3, 41.4, 123.6 (CH₂=C-), 152.6 (CH₂=C-).

Anal. calcd. for C₇H₁₅GeO: C 28.14, H 5.06, I 42.48; found: C 28.16, H 5.07, I 42.31.

3.2.3. SYNTHESIS OF 4-IODO-2-TRIMETHYLGGERMYL-1-BUTENE (13) VIA A PLATINUM CATALYZED HYDROGERMYLATION REACTION

3.2.3.1. Synthesis of 3-Trimethylgermyl-3-buten-1-ol (52):



To a stirred solution of 4-trimethylsilyloxy-1-trimethylsilyl-1-butyne (**51**)⁸² (2.89 g, 13.5 mmol, 1 equiv.) in dry CH₂Cl₂ (14 mL) at rt was added hydrogen hexachloroplatinate(IV) hydrate (H₂PtCl₆·xH₂O, 108 mg, 0.207 mmol, 1.5 mol%). The resulting heterogeneous orange solution became a cloudy orange suspension within minutes. The suspension was cooled to 0 °C and trimethylgermane⁸³ (2.4 mL, 20 mmol, 1.5 equiv.) was added via a gas-tight syringe. The orange precipitate dissipated soon after the addition of Me₃GeH. The solution was warmed to rt and stirred for 15 h. The reaction mixture was filtered (100 g silica gel, 300 mL diethyl ether as eluant) and the filtrate was concentrated under reduced pressure. The residual material was dissolved in CH₂Cl₂ (135 mL). To the stirred solution was added *p*-TsOH·H₂O (3.08 g, 16.2 mmol, 1.2 equiv.). The mixture was warmed to 30 °C for 1 h. Saturated aqueous NaHCO₃ (100 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 300 mL) and ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual crude product was chromatographed⁸⁴ (150 g tlc grade silica gel, 4:1 petroleum ether - ethyl acetate) and the oil thus obtained was distilled (air-bath temperature 80 °C/20 Torr) to afford 1.8 g (71%) of 3-trimethylgermyl-3-buten-1-ol (**52**), as a colourless oil.

IR (film): 3365, 1606, 1047, 825 cm⁻¹.

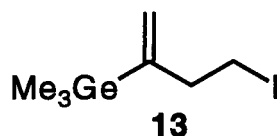
^1H nmr (400 MHz) δ : 0.23 (s, 9H, $-\text{GeMe}_3$), 1.40 (br s, 1H, $-\text{OH}$; this signal exchanges upon treatment with D_2O), 2.47-2.50 (br t, 2H, $J = 6.5$ Hz, allylic methylene protons), 3.65-3.69 (q, 2H, $J = 6.5$ Hz, $\text{HOCH}_2\text{CH}_2-$; this signal collapses to a triplet upon treatment with D_2O), 5.34 (m, 1H, vinyl proton), 5.63 (m, 1H, vinyl proton).

^{13}C nmr (75.3 MHz) δ : 1.9 (-ve, $-\text{Ge}(\text{CH}_3)_3$), 40.4, 61.1, 124.6 ($\text{CH}_2=\text{C}-$), 150.3 ($\text{CH}_2=\text{C}-$).

Exact Mass calcd. for $\text{C}_6\text{H}_{13}\text{GeO}$ ($\text{M}^+ - \text{Me}$): 175.0178; found: 175.0179.

Anal. calcd. for $\text{C}_7\text{H}_{16}\text{GeO}$: C 44.53, H 8.54; found: C 44.64, H 8.70.

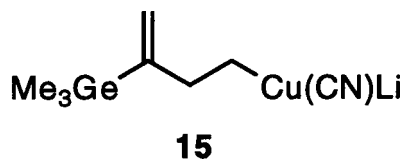
3.2.3.2. Synthesis of 4-Iodo-2-trimethylgermyl-1-butene (**13**):



To a cold (0 °C), stirred solution of triphenylphosphine (7.65 g, 29.2 mmol, 3.1 equiv.) in dry diethyl ether (70 mL) and dry acetonitrile (23 mL) was added iodine (7.41 g, 29.2 mmol, 3.1 equiv.) in two portions. A solution of the vinylgermane alcohol **52** (1.78 g, 9.37 mmol, 1 equiv.) in dry diethyl ether (5 mL) was cannulated into the yellow suspension. The suspension was warmed to rt and stirred for 15 min. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) and diethyl ether (100 mL) were added and the layers were separated. The organic phase was washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 75 mL), 10% aqueous CuSO_4 (2 x 75 mL), and water (1 x 75 mL). The combined aqueous layers were extracted with diethyl ether (3 x 75 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was flash chromatographed (150 g silica gel, petroleum ether) and the oil thus obtained was distilled (air-bath

temperature 85-92 °C/15 Torr) to provide 2.58 g (92%) of 4-iodo-2-trimethylgermyl-1-butene (**13**), as a colourless oil (spectral data are identical with those reported above).

3.2.4. PREPARATION OF THE CUPRATE REAGENT **15**:



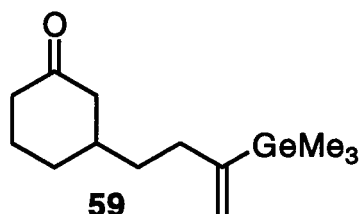
To a cold (-98 °C), stirred solution of freshly distilled 4-iodo-2-trimethylgermyl-1-butene (**13**) (886 mg, 2.97 mmol, 1 equiv.) in dry THF (40 mL) was rapidly added a solution of *tert*-butyllithium in pentane (1.7 M, 3.4 mL, 5.8 mmol, 1.95 equiv.). The resultant clear yellow solution was stirred at -98 °C for 10 min and was warmed to -78 °C. Copper(I) cyanide (279 mg, 3.12 mmol, 1.05 equiv.) was added in one portion and the suspension became colourless. Brief warming (2-4 min) of the reaction mixture at -35 °C provided a light tan homogeneous solution containing the cuprate reagent **15**, which was cooled to -78 °C and used immediately. CAUTION: While it is necessary for the solution to become homogeneous, prolonged warming will result in the decomposition of the cuprate reagent.

3.2.5. GENERAL PROCEDURE 1: PREPARATION OF THE KETO VINYLGERMANES⁸⁵

To a cold (-78 °C), stirred solution of the cuprate reagent **15** (1.3 - 2 equiv., prepared as described above) in dry THF was added, dropwise, dry trimethylsilyl bromide (3 - 8 equiv.). This was followed by the dropwise addition (via a large cannula) of a solution of enone (1 equiv.) in dry THF (~1 mL per mmol of enone). The yellow-orange solution was stirred at -78 °C until the reaction was complete, as determined by glc and/or tlc analysis of

an aliquot. In some cases, warming of the solution was required for the reaction to reach completion. Water (~2 mL per mmol of enone) was added and the reaction mixture was warmed to rt and stirred vigorously, open to the atmosphere, for ~1 h until the hydrolysis of the silyl enol ether was complete (as indicated by tlc analysis). Aqueous NH_4Cl - NH_4OH (pH 8-9, 15 mL per mmol of enone) and diethyl ether (20 mL per mmol of enone) were added and the mixture was stirred vigorously until the aqueous layer became bright blue in colour. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x (~30 mL per mmol of enone)). The combined organic extracts were washed with brine (1 x (~30 mL per mmol of enone)), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was flash chromatographed and the acquired liquid was distilled to provide the desired keto vinylgermane.

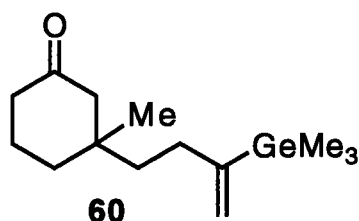
3.2.5.1. Synthesis of 3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (**59**):



Following general procedure 1, a solution of the cuprate reagent **15** (2.97 mmol, 1.4 equiv.) in dry THF (40 mL) was treated sequentially with trimethylsilyl bromide (1.00 g, 6.53 mmol, 3 equiv.) and a solution of 2-cyclohexen-1-one (209 mg, 2.17 mmol, 1 equiv.) in dry THF (2 mL). The reaction mixture was stirred at -78 °C for 4 h. The crude product was flash chromatographed (70 g silica gel, 5.7:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 120-130 °C/0.2 Torr) to provide 519 mg (89%) of the keto vinylgermane **59**,⁸⁶ as a colourless oil.

^1H nmr (400 MHz) δ : 0.20 (s, 9H, -GeMe₃), 1.21-2.09 (m, 8H), 2.18-2.48 (m, 5H), 5.19 (m, 1H, vinyl proton), 5.50 (m, 1H, vinyl proton).

3.2.5.2. Synthesis of 3-Methyl-3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (**60**):



Following general procedure 1, a solution of the cuprate reagent **15** (3.38 mmol, 1.5 equiv.) in dry THF (45 mL) was treated sequentially with trimethylsilyl bromide (1.00 g, 6.53 mmol, 3 equiv.) and a solution of 3-methyl-2-cyclohexen-1-one (243 mg, 2.21 mmol, 1 equiv.) in dry THF (2 mL). The reaction mixture was stirred at -78 °C for 4 h and subjected to the workup conditions described in general procedure 1. ^1H nmr spectroscopic analysis of the crude product revealed the presence of a silyl enol ether function. The crude oil was thus dissolved in a mixture of THF (20 mL) and 5% hydrochloric acid (2 mL) and the solution was stirred at rt for 10 min (at which point tlc analysis confirmed the hydrolysis of the silyl enol ether). Water (20 mL) and diethyl ether (40 mL) were added to the mixture and the layers were separated. The aqueous layer was extracted with diethyl ether (4 x 75 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 117-120 °C/0.2 Torr) to afford 543 mg (95%) of the keto vinylgermane **60**, as a colourless oil.

IR (film): 1714, 1600, 1234, 825 cm^{-1} .

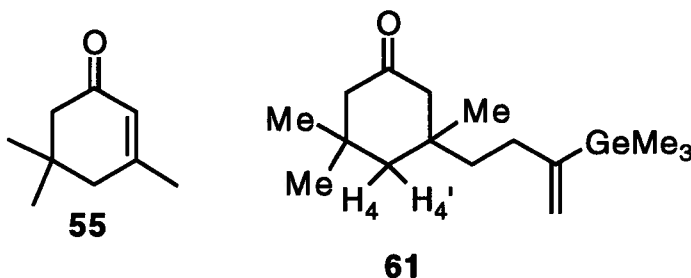
^1H nmr (400 MHz, C_6D_6) δ : 0.22 (s, 9H, $-\text{GeMe}_3$), 0.69 (s, 3H, Me), 1.07-1.28 (m, 4H), 1.41-1.48 (m, 2H), 1.87-2.10 (m, 6H), 5.23 (m, 1H, vinyl proton), 5.54 (m, 1H, vinyl proton).

^{13}C nmr (50.3 MHz, C_6D_6) δ : -1.7 (-ve, $-\text{Ge}(\underline{\text{CH}}_3)_3$), 21.1, 24.7 (-ve, Me), 31.5, 35.9, 38.2, 40.8, 41.8, 53.4, 122.1 ($\underline{\text{CH}}_2=\text{C}-$), 154.0 ($\text{CH}_2=\underline{\text{C}}-$), 208.7 ($-\underline{\text{C}}=\text{O}$).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{23}\text{GeO}$ ($\text{M}^+ - \text{Me}$): 269.0961; found: 269.0965.

Anal. calcd. for $\text{C}_{14}\text{H}_{26}\text{GeO}$: C 59.43, H 9.26; found: C 59.62, H 9.32.

3.2.5.3. Synthesis of 3,5,5-Trimethyl-3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (**61**):



a. Via Conjugate Addition of the Cuprate Reagent **15** to Isophorone (**55**) in the Presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$:

Following general procedure 1, a solution of the cuprate reagent **15** (1.28 mmol, 1.6 equiv.) in dry THF (12 mL) was treated sequentially with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (110 μL , 0.894 mmol, 1.1 equiv.) and a solution of isophorone (**55**) (111 mg, 0.803 mmol, 1 equiv.) in dry THF (1 mL). The yellow reaction mixture was stirred at -78°C for 8 h and was warmed to -30°C over a period of 1.5 h. The crude product was subjected to flash chromatography (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath

temperature 80-85 °C/0.2 Torr) to yield 47 mg (19%) of the keto vinylgermane **61**,⁸⁷ as a colourless oil.

¹H nmr (400 MHz) δ : 0.20 (s, 9H, -GeMe₃), 1.04, 1.05, 1.07 (s, s, s, 3H each, tertiary methyl groups), 1.30-1.48 (m, 2H), 1.55 (d, 1H, J = 14.5 Hz, H-4), 1.62 (d, 1H, J = 14.5 Hz, H-4'), 2.10-2.24 (m, 6H), 5.18 (m, 1H, vinyl proton), 5.50 (m, 1H, vinyl proton).

¹³C nmr (75.3 MHz) δ : -1.8 (-ve, -Ge(CH₃)₃), 27.1 (-ve, Me), 30.5 (-ve, Me), 31.3, 32.5 (-ve, Me), 36.1, 38.7, 44.6, 49.2, 53.0, 54.2, 122.0 (CH₂=C-), 154.0 (CH₂=C-), 212.3 (-C=O).

Anal. calcd. for C₁₆H₃₀GeO: C 61.78, H 9.72; found: C 61.96, H 9.68.

b. Via Conjugate Addition of the Cuprate Reagent 15 to Isophorone (55) in the Presence of TMSBr:

Following general procedure 1, a solution of the cuprate reagent **15** (2.25 mmol, 1.7 equiv.) in dry THF (19 mL) was treated sequentially with trimethylsilyl bromide (614 mg, 4.01 mmol, 3 equiv.) and a solution of isophorone (**55**) (185 mg, 1.34 mmol, 1 equiv.) in dry THF (2 mL). The yellow reaction mixture was stirred at -78 °C for 8 h and was warmed to -20 °C over the course of 2 h, at which point the solution became colourless. The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled to afford 245 mg (59%) of the keto vinylgermane **61** (spectral data are identical with those reported above).

c. Via Conjugate Addition of the Cuprate Reagent 15 to Isophorone (55) in the Presence of TMSCl and BF₃•Et₂O:

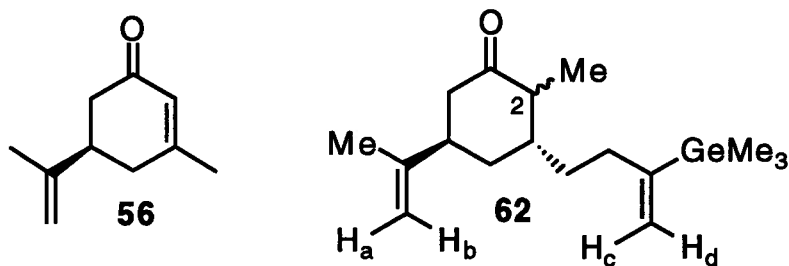
Following general procedure 1, a solution of the cuprate reagent **15** (1.81 mmol, 1.6 equiv.) in dry THF (16 mL) was treated sequentially with BF₃•Et₂O (150 μ L, 1.22 mmol, 1.1

equiv.), trimethylsilyl chloride (420 μ L, 3.31 mmol, 3 equiv.), and a solution of isophorone (**55**) (152 mg, 1.10 mmol, 1 equiv.) in dry THF (1 mL). The yellow solution was stirred at -78 °C for 8 h and was warmed to -30 °C over 1.5 h. The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled to yield 224 mg (66%) of the keto vinylgermane **61** (spectral data are identical with those reported above).

d. Via Conjugate Addition of the Cuprate Reagent **15** to Isophorone (**55**) in the Presence of TMSBr and $\text{BF}_3 \cdot \text{Et}_2\text{O}$:

Following general procedure 1, a solution of the cuprate reagent **15** (2.18 mmol, 1.7 equiv.) in dry THF (18 mL) was treated sequentially with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (170 μ L, 1.38 mmol, 1.1 equiv.), trimethylsilyl bromide (630 mg, 4.11 mmol, 3.2 equiv.), and a solution of isophorone (**55**) (175 mg, 1.27 mmol, 1 equiv.) in dry THF (1.5 mL). The yellow reaction mixture was stirred at -78 °C for 8 h and was warmed to -30 °C over a period of 1.5 h. The crude product was subjected to flash chromatography (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled to afford 283 mg (72%) of the keto vinylgermane **61** (spectral data are identical with those reported above).

3.2.5.4. Synthesis of (3*R*, 5*R*)-2-Methyl-5-(1-methylethenyl)-3-[3-(trimethylgermyl)-3-butenyl]-cyclohexanone (**62**):

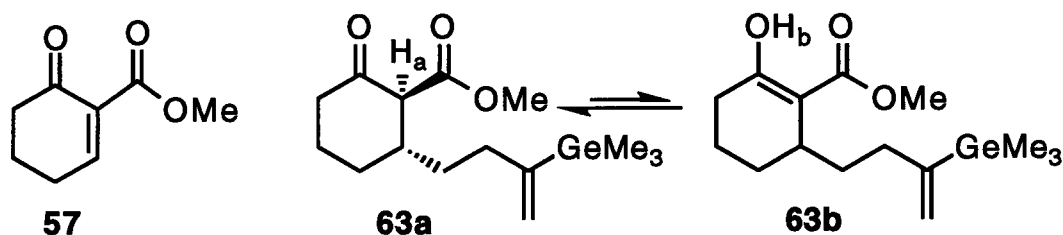


Following general procedure 1, a solution of the cuprate reagent **15** (2.45 mmol, 1.6 equiv.) in dry THF (33 mL) was treated sequentially with trimethylsilyl bromide (615 mg,

4.02 mmol, 2.6 equiv.) and a solution of (*R*)-(-)-carvone (**56**) (230 mg, 1.53 mmol, 1 equiv.) in dry THF (1.5 mL). The reaction mixture was stirred at -78 °C for 3 h. The crude product was subjected to flash chromatography (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 96-100 °C/0.2 Torr) to afford 471 mg (95%) of the keto vinylgermane **62**,⁸⁸ as a colourless oil. ¹H nmr spectroscopic analysis of the compound **62** revealed that it consisted of a ~4:1 mixture of epimers at carbon two.

¹H nmr (400 MHz) δ : 0.19, 0.20 (s, s, ratio undetermined, 9H, -GeMe₃), 1.00, 1.11 (d, d, ratio ~4:1, 3H, *J* = 7 Hz, secondary Me), 1.20-1.48 (m, 2H), 1.73 (br s, 3H, vinyl Me), 1.93-2.67 (m, 9H), 4.68, 4.72, 4.76, 4.80 (br s, br s, br s, br s, ratio ~1:4:4:1, 2H, H_a and H_b), 5.15 (m, 1H, H_c or H_d), 5.48 (m, 1H, H_c or H_d).

3.2.5.5. Synthesis of 2-Carbomethoxy-3-[3-(trimethylgermyl)-3-butenyl]cyclohexanone (**63**):



Following general procedure 1, a solution of the cuprate reagent **15** (1.28 mmol, 1.7 equiv.) in dry THF (15 mL) was treated sequentially with trimethylsilyl bromide (352 mg, 2.30 mmol, 3 equiv.) and a solution of 2-(carbomethoxy)-2-cyclohexen-1-one (**57**) (118 mg, 0.765 mmol, 1 equiv.) in dry THF (1 mL). The reaction mixture was stirred at -78 °C for 2 h. Flash chromatography of the crude oil (25 g silica gel, 5.7:1 petroleum ether - diethyl ether) and removal of trace amounts of residual solvent (vacuum pump) from the resultant oil afforded 224 mg (90%) of the keto vinylgermane **63**, as a colourless oil. The vinylgermane

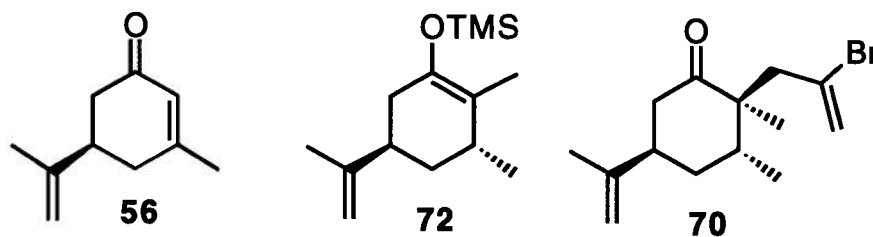
compound **63** is unstable to heat and thus distillation was avoided. Analysis of the ^1H nmr spectrum of compound **63** indicated a ~5:1 mixture of tautomers **63a** and **63b**, respectively.

IR (film): 1746, 1714, 1652, 1612, 1220, 1150, 827 cm^{-1} .

^1H nmr (400 MHz) δ : 0.20, 0.21 (s, s, ratio undetermined, 9H, $-\text{GeMe}_3$), 1.20-2.85 (m, 11H), 3.12, 8.18 (d, s, ratio ~5:1, 1H, $J = 11.5$ Hz, H_a and H_b , respectively), 3.69, 3.73 (s, s, ratio ~5:1, 3H, $-\text{C}(\text{O})\text{OMe}$), 5.13, 5.17 (m, m, ratio undetermined, vinyl protons), 5.48, 5.51 (m, m, ratio undetermined, vinyl protons).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{23}\text{GeO}_3$ ($\text{M}^+ - \text{Me}$): 313.0859; found: 313.0864.

3.2.5.6. Synthesis of (3*R*, 5*R*)-2,3-Dimethyl-5-(1-methylethenyl)-1-trimethylsiloxycyclohexene (**72**) and (2*S*, 3*R*, 5*R*)-2-(2-Bromo-2-propenyl)-2,3-dimethyl-5-(1-methylethenyl)-cyclohexanone (**70**):



To a cold ($-78\text{ }^{\circ}\text{C}$), stirred solution of methyllithium (1.53 M in diethyl ether, 4.4 mL, 6.7 mmol, 4 equiv.) in dry THF (17 mL) was added solid $\text{CuBr}\cdot\text{Me}_2\text{S}$ (686 mg, 3.34 mmol, 2 equiv.). The resultant pale yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 50 min. Trimethylsilyl chloride (0.64 mL, 5.1 mmol, 3 equiv.) was added, followed by the dropwise addition of a solution of (*R*)-(-)-carvone (**56**) (254 mg, 1.69 mmol, 1 equiv.) in dry THF (1 mL). The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 3.5 h and Et_3N (0.71 mL, 5.1 mmol, 3 equiv.) was added.

The solution was warmed to rt and pentane (20 mL) and aqueous NH_4Cl - NH_4OH (pH 8-9, 15 mL) were added. The layers were separated and the aqueous phase was extracted with pentane (3 x 50 mL). The combined organic layers were washed with 0.1 M aqueous citric acid (3 x 25 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The product was distilled under reduced pressure (high vacuum) to yield 401 mg (99%) of the silyl enol ether **72**, as a colourless oil. The silyl enol ether **72** was used immediately in the next step.

^1H nmr (400 MHz) δ : 0.19 (s, 9H, $-\text{SiMe}_3$), 1.04 (d, 3H, $J = 8$ Hz, secondary Me), 1.48-1.57 (m, 2H), 1.58 (br s, 3H, vinyl Me), 1.73 (s, 3H, vinyl Me), 1.97-2.07 (m, 2H), 2.15-2.21 (m, 1H), 2.36-2.43 (m, 1H), 4.69-4.72 (m, 2H, vinyl protons).

To a cold (0 °C), stirred solution of the silyl enol ether **72** (189 mg, 0.793 mmol, 1 equiv.) in dry THF (8 mL) was added a solution of methyllithium in diethyl ether (1.53 M, 0.58 mL, 0.89 mmol, 1.1 equiv.). The resultant solution was stirred at 0 °C for 1.5 h and cooled to -20 °C. Dry HMPA (0.41 mL, 2.4 mmol, 3 equiv.) was added followed by the addition of 2,3-dibromopropene (0.33 mL, 3.2 mmol, 4 equiv.). The solution was stirred at -20 °C for 2 h, 0 °C for 3.5 h, and was warmed to rt and left stirring overnight. Diethyl ether (50 mL) and saturated aqueous NH_4Cl (50 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 50 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was flash chromatographed (25 g silica gel, 1.2:1 petroleum ether - CH_2Cl_2) and the oil thus obtained was distilled (air-bath temperature 100-105 °C/0.15 Torr) to provide 105 mg (46%) of the alkylated product **70**, a single diastereomer by ^1H nmr spectroscopy.

^1H nmr (400 MHz) δ : 0.92 (d, 3H, J = 8 Hz, secondary Me), 1.05 (s, 3H, tertiary Me), 1.57-1.65 (m, 1H), 1.75 (s, 3H, vinyl Me), 2.01-2.10 (m, 1H), 2.15-2.23 (m, 1H), 2.35-2.42 (m, 1H), 2.52-2.61 (m, 1H), 2.68-2.75 (dd, 1H, J = 12, 12 Hz), 2.80 (d, 1H, J = 14 Hz, allylic proton), 3.05 (d, 1H, J = 14 Hz, allylic proton), 4.72 (s, 1H, vinyl proton), 4.79 (s, 1H, vinyl proton), 5.52 (m, 1H, vinyl proton), 5.56 (m, 1H, vinyl proton).

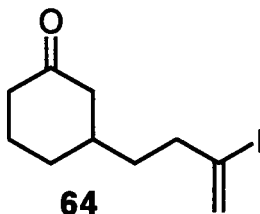
3.2.6. GENERAL PROCEDURE 2A: PREPARATION OF THE KETO VINYL IODIDES FROM THE CORRESPONDING KETO VINYLGERMANES

To a stirred solution of the appropriate keto vinylgermane (1 equiv.) in dry CH_2Cl_2 (21 mL per mmol of vinylgermane) at rt was added a solution of iodine in dry CH_2Cl_2 (0.04 M, 1.5 equiv.). The dark purple reaction mixture was stirred at rt until the reaction was determined to have reached completion (by glc and/or tlc analysis), usually overnight. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (~40 mL per mmol of product) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x (40 mL per mmol of product)) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was subjected to flash chromatography and the oil thus obtained was distilled, or the residual traces of solvent were removed (vacuum pump), to yield the required keto vinyl iodide.

3.2.7. GENERAL PROCEDURE 2B: PREPARATION OF THE KETO VINYL IODIDES FROM THE CORRESPONDING KETO VINYLGERMANES ⁸⁹

To a stirred solution of the appropriate keto vinylgermane (1 equiv.) in dry CH_2Cl_2 (25 mL per mmol of vinylgermane) at rt was added solid iodine (1.5 equiv.) in one portion. The remaining procedure is identical with that of general procedure 2a.

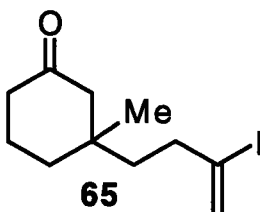
3.2.6.1. Synthesis of 3-(3-Iodo-3-butenyl)cyclohexanone (**64**):



Following general procedure 2a, the keto vinylgermane **59** (507 mg, 1.88 mmol) was converted into the keto vinyl iodide **64**. The crude product was flash chromatographed (73 g silica gel, 5.7:1 petroleum ether - diethyl ether) and the residual solvent was removed (vacuum pump) from the acquired oil to yield 494 mg (94%) of the vinyl iodide **64**,⁹⁰ as a colourless oil.

¹H nmr (400 MHz) δ : 1.30-1.40 (m, 1H), 1.45-1.70 (m, 3H), 1.73-1.95 (m, 2H), 1.98-2.06 (m, 2H), 2.20-2.45 (m, 5H), 5.69 (m, 1H, vinyl proton), 6.02 (m, 1H, vinyl proton).

3.2.7.1. Synthesis of 3-(3-Iodo-3-butenyl)-3-methylcyclohexanone (**65**):



Following general procedure 2b, the keto vinylgermane **60** (1.12 g, 3.96 mmol) was transformed into the corresponding keto vinyl iodide **65**. The crude product was flash chromatographed (90 g silica gel, 5.7:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 94-98 °C/0.09 Torr) to afford 1.13 g (98%) of the keto vinyl iodide **65**, as a colourless oil.

IR (film): 1713, 1618, 1229, 1102, 1050, 892 cm^{-1} .

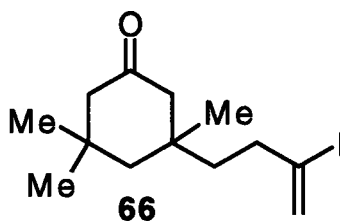
^1H nmr (400 MHz) δ : 0.94 (s, 3H, Me), 1.48-1.64 (m, 4H), 1.86-1.91 (m, 2H), 2.13 (d, 1H, J = 14 Hz, H-2), 2.20 (d, 1H, J = 14 Hz, H-2'), 2.29 (t, 2H, J = 7 Hz), 2.34-2.40 (m, 2H), 5.67 (br d, 1H, J = 1.5 Hz, vinyl proton), 6.02 (q, 1H, J = 1.5 Hz, vinyl proton).

^{13}C nmr (100.4 MHz) δ : 22.0, 24.8 (-ve, Me), 35.8, 38.1, 39.9, 40.9, 41.2, 53.6, 111.8 ($\text{CH}_2=\underline{\text{C}}$ -), 125.4 ($\underline{\text{C}}\text{H}_2=\text{C}$ -), 211.6 ($-\underline{\text{C}}=\text{O}$).

Exact Mass calcd. for $\text{C}_{11}\text{H}_{17}\text{IO}$: 292.0323; found: 292.0323.

Anal. calcd. for $\text{C}_{11}\text{H}_{17}\text{IO}$: C 45.22, H 5.87, I 43.44; found: C 45.18, H 5.93, I 43.22.

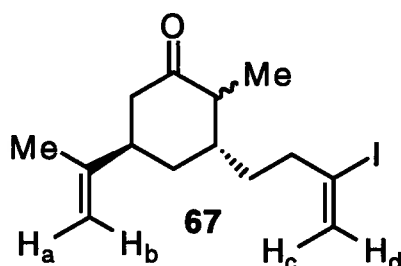
3.2.6.2. Synthesis of 3-(3-Iodo-3-butenyl)-3,5,5-trimethylcyclohexanone (**66**):



Following general procedure 2a, the keto vinylgermane **61** (399 mg, 1.28 mmol) was converted into the corresponding keto vinyl iodide **66**. The product was subjected to flash chromatography (35 g silica gel, 5.7:1 petroleum ether - diethyl ether) and removal of trace amounts of solvent (vacuum pump) from the acquired oil yielded 390 mg (95%) of the desired vinyl iodide **66**,⁹¹ as a pale yellow oil.

^1H nmr (400 MHz) δ : 1.03, 1.05, 1.06 (s, s, s, 3H each, tertiary Me groups), 1.45-1.69 (m, 4H), 2.11-2.25 (m, 4H), 2.35-2.47 (m, 2H), 5.67-5.68 (m, 1H, vinyl proton), 6.01-6.02 (m, 1H, vinyl proton).

3.2.6.3. Synthesis of (3*R*, 5*R*)-3-(3-Iodo-3-butenyl)-2-methyl-5-(1-methylethenyl)cyclohexanone (**67**):



Following general procedure 2a, the keto vinylgermane **62** (471 mg, 1.46 mmol) was converted into the corresponding keto vinyl iodide **67**. The crude product was flash chromatographed (35 g silica gel, 5.7:1 petroleum ether - diethyl ether) and removal of trace amounts of solvent (vacuum pump) from the resultant liquid afforded 464 mg (97%) of the keto vinyl iodide **67**.⁹² Analysis of the ^1H nmr spectrum revealed that the slightly yellow oil consisted of a ~1.5:1 mixture of epimers at carbon two.

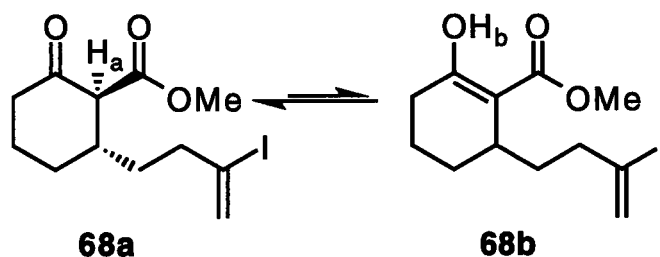
^1H nmr (400 MHz) δ : 1.05, 1.13 (d, d, ratio ~1.5:1, 3H, J = 8 Hz, secondary Me), 1.02-1.25 (m, 1H), 1.42-1.51 (m, 1H), 1.55-1.75 (m, 2H), 1.74, 1.76 (br s, br s, ratio undetermined, 3H, vinyl methyl protons), 1.87-2.02 (m, 1H), 2.07-2.65 (m, 6H), 4.66, 4.73, 4.75, 4.78 (br s, br s, br s, br s, ratio ~1:1.5:1.5:1, 2H, H_a and H_b), 5.68 (m, 1H, H_c or H_d), 6.01 (m, 1H, H_c or H_d).

^{13}C nmr (75.3 MHz) δ : 11.7 (-ve), 14.1 (-ve), 20.6 (-ve), 21.5 (-ve), 26.3, 31.2, 32.9, 33.1, 38.6 (-ve), 39.3 (-ve), 40.4 (-ve), 40.8 (-ve), 42.4, 42.8, 43.6, 46.1, 48.4 (-ve), 49.4 (-ve),

110.0, 110.1, 111.4, 111.5, 125.8, 125.9, 146.8, 147.2, 212.5, 213.3.

Anal. calcd. for C₁₄H₂₁IO: C 50.61, H 6.37, I 38.20; found: C 50.69, H 6.35, I 38.38.

3.2.6.4. Synthesis of 2-Carbomethoxy-3-(3-iodo-3-butenyl)cyclohexanone (**68**):



Following general procedure 2a, a mixture of the keto vinylgermanes **63a** and **63b** (292 mg, 0.893 mmol) was converted into the corresponding mixture of keto vinyl iodides **68a** and **68b**. The crude product was flash chromatographed (25 g silica gel, 5.7:1 petroleum ether - diethyl ether) to yield, after removal of residual solvent (vacuum pump) from the resultant liquid, 283 mg (94%) of the keto vinyl iodides **68a** and **68b**. Analysis of the ¹H nmr spectrum of the product indicated a ~2.5:1 mixture of the tautomers **68a** and **68b**, respectively.

IR (film): 1746, 1713, 1653, 1615, 1440, 1260, 1221, 1149 cm⁻¹.

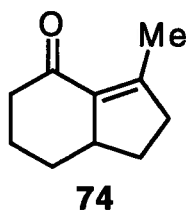
¹H nmr (400 MHz) δ: 1.40-2.83 (m, 11H), 3.12, 8.16 (d, s, ratio ~2.5:1, 1H, *J* = 11.5 Hz, H_a and H_b respectively), 3.69, 3.61 (s, s, ratio ~2.5:1, 3H, -C(O)OMe), 5.68, 5.70 (m, m, ratio undetermined, 1H, vinyl proton), 5.90, 6.10 (m, m, ratio undetermined, 1H, vinyl proton).

Exact Mass calcd. for C₁₂H₁₇IO₃: 336.0222; found: 336.0220.

3.2.8. GENERAL PROCEDURE 3: Pd(0)-CATALYZED CYCLIZATION REACTION OF THE KETO VINYL IODIDES⁹³

To a stirred solution of the appropriate keto vinyl iodide (1 equiv.) in dry THF (10 mL per mmol of vinyl iodide) at rt was added solid tetrakis(triphenylphosphine)palladium(0)⁹⁴ (20-30 mol% with respect to the starting vinyl iodide). The reaction mixture was stirred for 10 min until a light brown homogeneous solution resulted. A solution of *t*-BuOK (commercial, Aldrich) in a 4:1 mixture of dry THF and dry *t*-BuOH (~0.24 M, 1.15 equiv.) was added, via syringe pump, over the course of ~4 h. Potassium iodide precipitated from the mixture as the reaction proceeded. After the mixture had been stirred for an additional 1-2 h at rt, diethyl ether (25 mL per mmol of the vinyl iodide) and brine (20 mL per mmol of the vinyl iodide) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x (30 mL per mmol of the vinyl iodide)). The combined organic extracts were washed with brine (1 x (30 mL per mmol of the vinyl iodide)), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude material was flash chromatographed and distilled to give the desired bicyclic product.

3.2.8.1. Synthesis of 9-Methylbicyclo[4.3.0]non-9-en-2-one (**74**):



a. Via the Pd(0)-Catalyzed Cyclization Reaction Described in General Procedure 3:

Following general procedure 3, the keto vinyl iodide **64** (479 mg, 1.72 mmol) was converted to the bicyclic enone **74** by employing 475 mg of Pd(PPh₃)₄ (0.411 mmol, 24 mol%). The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 125-135 °C/20 Torr) to afford 166 mg (64%) of the bicyclic enone **74**.⁹⁵

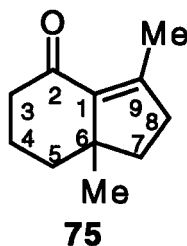
^1H nmr (400 MHz) δ : 1.20-1.31 (dq, 1H, J = 3, 13 Hz), 1.41-1.52 (m, 1H), 1.68-1.81 (m, 1H), 1.93-2.32 (m, 5H), 2.08 (br s, 3H, vinyl Me), 2.39-2.50 (m, 2H), 2.81-2.92 (m, 1H).

b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (high dilution (0.008 M)):

To a stirred solution of the keto vinyl iodide **64** (130 mg, 0.47 mmol, 1 equiv.) in dry THF (58 mL, 0.008 M dilution) at rt was added Pd(PPh₃)₄ (141 mg, 0.122 mmol, 26 mol%). A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.20 M, 2.7 mL, 0.54 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 3.5 h. The mixture was stirred for an additional 15 min at rt and then subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 125-135 °C/20 Torr) to yield 37 mg (52%) of the bicyclic enone **74** (spectral data are identical with those reported above).

c. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (high dilution (0.008 M) and no *t*-BuOH present in the base mixture):

To a stirred solution of the keto vinyl iodide **64** (146 mg, 0.525 mmol, 1 equiv.) in dry THF (65 mL, 0.008 M dilution) at rt was added Pd(PPh₃)₄ (135 mg, 0.117 mmol, 22 mol%). A solution of *t*-BuOK in dry THF (0.20 M, 3.0 mL, 0.60 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 3.5 h. The mixture was stirred for an additional 4 h at rt and was then subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 125-135 °C/20 Torr) to yield 33 mg (42%) of the bicyclic enone **74** (spectral data are identical with those reported above).

3.2.8.2. Synthesis of 6,9-Dimethylbicyclo[4.3.0]non-9-en-2-one (**75**):

Following general procedure 3, the keto vinyl iodide **65** (153 mg, 0.524 mmol) was converted into the bicyclic enone **75** by employing 138 mg of $\text{Pd}(\text{PPh}_3)_4$ (0.119 mmol, 23 mol%). The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 64-68 °C/0.1 Torr) to yield 56 mg (65%) of the bicyclic enone **75**, as a colourless oil.

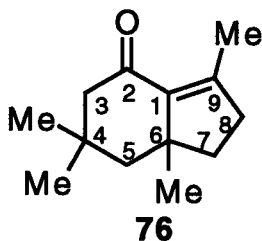
IR (film): 1679, 1627, 1454, 1216, 1124 cm^{-1} .

^1H nmr (400 MHz, C_6D_6) δ : 0.83 (s, 3H, angular Me), 1.21-1.28 (dt, 1H, $J = 2.5, 13$ Hz), 1.40-1.63 (m, 5H), 1.81-1.88 (dd, 1H, $J = 18, 9$ Hz), 1.93-2.02 (m, 1H), 1.99 (br s, 3H, vinyl Me), 2.21-2.30 (m, 1H), 2.31-2.37 (m, 1H).

^{13}C nmr (75.3 MHz, C_6D_6) δ : 16.0 (-ve), 21.5, 24.3 (-ve), 36.4, 38.8, 40.7, 41.6, 48.7, 140.6, 148.2, 198.9 (C-2).

Exact Mass calcd. for $\text{C}_{11}\text{H}_{16}\text{O}$: 164.1201; found: 164.1198.

Anal. calcd. for $\text{C}_{11}\text{H}_{16}\text{O}$: C 80.44, H 9.82; found: C 80.57, H 9.88.

3.2.8.3. Synthesis of 4,4,6,9-Tetramethylbicyclo[4.3.0]non-9-en-2-one (**76**):

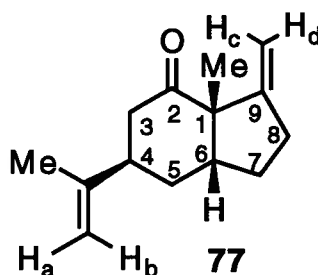
Following general procedure 3, the keto vinyl iodide **66** (328 mg, 1.02 mmol) was converted into the corresponding bicyclic enone **76** by employing 236 mg of Pd(PPh₃)₄ (0.204 mmol, 20 mol%). The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 135-140 °C/20 Torr) to afford 164 mg (83%) of the bicyclic enone **76**,⁹⁶ as a colourless oil.

¹H nmr (400 MHz) δ : 0.93, 1.03, 1.10 (s, s, s, 3H each, tertiary Me groups), 1.58-1.90 (m, 4H), 2.08 (br s, 3H, vinyl Me), 2.13-2.28 (m, 3H), 2.49-2.59 (m, 1H).

¹³C nmr (75.3 MHz) δ : 16.4 (-ve, Me), 28.8 (-ve, Me), 29.4 (-ve, Me), 31.6 (-ve, Me), 32.9, 37.1, 43.2, 46.7, 51.6, 53.6, 139.1, 152.0, 200.5 (C-2).

Anal. calcd. for C₁₃H₂₀O: C 81.20, H 10.48; found: C 80.96, H 10.47.

3.2.8.4. Synthesis of (1*S*, 4*R*, 6*R*)-1-Methyl-9-methylene-4-(1-methylethenyl)bicyclo[4.3.0]-nonan-2-one (**77**):



a. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 19 mol% Pd(PPh₃)₄:

Following general procedure 3, the keto vinyl iodide **67** (88 mg, 0.265 mmol) was converted into the bicyclic ketone **77** by employing 58 mg of Pd(PPh₃)₄ (0.050 mmol, 19 mol%). Flash chromatography (15 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude product and distillation (air-bath temperature 130-135 °C/20 Torr) of the oil thus obtained provided 43 mg (80%) of the bicyclic ketone **77**,⁹⁷ as a colourless oil.

¹H nmr (400 MHz) δ : 1.22 (s, 3H, angular Me), 1.45-1.57 (m, 1H), 1.70-1.90 (m, 3H), 1.73 (br s, 3H, vinyl Me), 2.09-2.17 (dt, 1H, $J = 12, 6$ Hz), 2.35-2.53 (m, 4H), 2.58-2.63 (m, 1H), 4.68 (br s, 1H, H_a or H_b), 4.82 (m, 2H, H_a or H_b and H_c or H_d), 5.00 (t, 1H, $J = 2$ Hz, H_c or H_d).

b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 15 mol% Pd(PPh₃)₄:

Following general procedure 3, the keto vinyl iodide **67** (98 mg, 0.29 mmol, 1 equiv.) was converted into the bicyclic enone **77** by employing 53 mg of Pd(PPh₃)₄ (0.046 mmol, 15 mol%). The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 130-135 °C/20 Torr) to afford 44 mg (73%) of the bicyclic enone **77** (spectral data are identical with those reported above).

c. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 10 mol% Pd(PPh₃)₄:

Following general procedure 3, the keto vinyl iodide **67** (94 mg, 0.28 mmol, 1 equiv.) was converted into the bicyclic enone **77** by employing 35 mg of Pd(PPh₃)₄ (0.030 mmol, 10 mol%). The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 130-135 °C/20 Torr) to afford 40 mg (70%) of the bicyclic enone **77** (spectral data are identical with those reported above).

d. Via the Pd(0)-Catalyzed Cyclization Reaction Employing 5 mol% Pd(PPh₃)₄:

Following general procedure 3, the keto vinyl iodide **67** (93 mg, 0.28 mmol, 1 equiv.) was converted into the bicyclic enone **77** by employing 15 mg of Pd(PPh₃)₄ (0.013 mmol, 5 mol%). The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 130-135 °C/20 Torr) to afford 30 mg (52%) of the bicyclic enone **77** (spectral data are identical with those reported above).

e. Via the Pd(0)-Catalyzed Cyclization Reaction Employing CuCl as an Additive:

To a stirred solution of the keto vinyl iodide **67** (83 mg, 0.25 mmol, 1 equiv.) in dry THF (2.5 mL) at rt was added sequentially Pd(PPh₃)₄ (14 mg, 0.012 mmol, 5 mol%) and CuCl (1.3 mg, 0.013 mmol, 5 mol%). A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.2 mL, 0.29 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 3 h. After the mixture was stirred for an additional 6 h at rt, tlc analysis indicated that the keto vinyl iodide **67** had not been consumed. An additional 14 mg of Pd(PPh₃)₄ (5 mol%), 1.4 mg of CuCl (5 mol%), and 0.3 mL of the *t*-BuOK solution (0.3 equiv., added over 1 h via syringe pump) were added and the mixture was stirred at rt overnight. Analysis (tlc) confirmed that the vinyl iodide **67** had been consumed and the mixture was subjected to the workup conditions as described in general procedure 3. The crude product was flash

chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 130-135 °C/20 Torr) to afford 16 mg (32%) of the bicyclic enone **77** (spectral data are identical with those reported above).

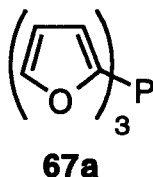
f. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd₂(dba)₃/PPh₃ as the Catalyst:

To a stirred solution of Pd₂(dba)₃⁹⁸ (21 mg, 0.048 mmol of Pd, 20 mol%) in dry THF (1.2 mL) at rt was added solid PPh₃ (24 mg, 0.092 mmol, 38 mol%, ~2:1 ratio of PPh₃:Pd). The red solution was stirred for 10 min and a solution of the keto vinyl iodide **67** (80 mg, 0.24 mmol, 1 equiv.) in dry THF (1.2 mL) was added via a large cannula. A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.2 mL, 0.28 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 3 h. The reaction mixture was stirred for an additional 1 h at rt and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 130-135 °C/20 Torr) to provide 32 mg (65%) of the bicyclic ketone **77** (spectral data are identical with those reported above).

g. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd₂(dba)₃/Ph₃As as the Catalyst:

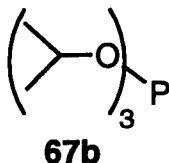
To a stirred solution of Pd₂(dba)₃⁹⁸ (24 mg, 0.052 mmol of Pd, 20 mol%) in dry THF (1.2 mL) at rt was added solid Ph₃As (32 mg, 0.10 mmol, 40 mol%, ~2:1 ratio of Ph₃As:Pd). The yellowish brown solution was stirred for 10 min and a solution of the keto vinyl iodide **67** (85 mg, 0.26 mmol, 1 equiv.) in dry THF (1 mL) was added via a large cannula. A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.09 M, 3.0 mL, 0.27 mmol, 1.05 equiv.) was added, via syringe pump, over the course of 3 h. The reaction mixture was stirred at rt for an additional 43 h and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum

ether - diethyl ether) to provide 4 mg (8%) of the bicyclic ketone **77** (spectral data are identical with those reported above).



h. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd₂(dba)₃/Tri(2-furyl)-phosphine (**67a**) as the Catalyst:

To a stirred solution of Pd₂(dba)₃⁹⁸ (17 mg, 0.037 mmol of Pd, 20 mol%) in dry THF (1 mL) at rt was added solid tri(2-furyl)phosphine⁹⁹ (**67a**) (17 mg, 0.074 mmol, 38 mol%, ~2:1 ratio of tri(2-furyl)phosphine: Pd). The yellowish brown solution was stirred for 10 min and a solution of the keto vinyl iodide **67** (63 mg, 0.19 mmol, 1 equiv.) in dry THF (1.2 mL) was added via a large cannula. A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 0.9 mL, 0.22 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 2.5 h. The reaction mixture was stirred at rt for an additional 8 h and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) to provide 13 mg (34%) of the bicyclic ketone **77** (spectral data are identical with those reported above).



i. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd₂(dba)₃/Triisopropylphosphite (**67b**) as the Catalyst:

To a stirred solution of Pd₂(dba)₃⁹⁸ (24 mg, 0.052 mmol of Pd, 20 mol%) in dry THF (0.8 mL) at rt was added triisopropylphosphite¹⁰⁰ (**67b**) (26 μL, 0.10 mmol, 40 mol%, ~2:1 ratio of triisopropylphosphite: Pd). The yellowish green solution was stirred for 10 min and a

solution of the keto vinyl iodide **67** (88 mg, 0.26 mmol, 1 equiv.) in dry THF (1.8 mL) was added via a large cannula. A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.3 mL, 0.31 mmol, 1.2 equiv.) was added, via syringe pump, over the course of 3.5 h. The reaction mixture was stirred at rt for an additional 10 h and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) to provide 9 mg (16%) of the bicyclic ketone **77** (spectral data are identical with those reported above).

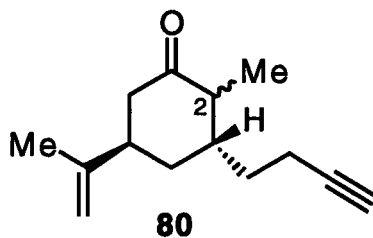
j. Via the Pd(0)-Catalyzed Cyclization Reaction Employing PdCl₂(dppf) as the Catalyst:

To a stirred solution of PdCl₂(dppf)¹⁰¹ (39 mg, 0.053 mmol, 18 mol%) in dry THF (1.0 mL) at rt was added a solution of the keto vinyl iodide **67** (97 mg, 0.29 mmol, 1 equiv.) in dry THF (2.0 mL). A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.4 mL, 0.34 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 4 h. The reaction mixture was stirred at rt for an additional 50 h and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) to provide 4 mg (6%) of the bicyclic ketone **77** (spectral data are identical with those reported above).

k. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd(OAc)₂/PPh₃ as the Catalyst:

To a stirred solution of the keto vinyl iodide **67** (77 mg, 0.23 mmol, 1 equiv.) in dry THF (2.3 mL) was added solid Pd(OAc)₂ (11 mg, 0.05 mmol, 20 mol%) and PPh₃ (26 mg, 0.10 mmol, 40 mol%). A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.1 mL, 0.27 mmol, 1.15 equiv.) was added, via syringe pump, over the course of 4 h. The reaction mixture was stirred at rt for an additional 48 h and was subjected to the workup conditions as described in general procedure 3. ¹H nmr spectroscopic analysis of the

crude product indicated that there was only a trace amount of the desired bicyclic ketone **77** present.



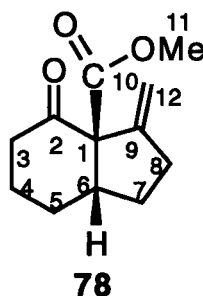
1. Via the Cyclization Reaction Employing a Stoichiometric Amount of Ni(COD)₂:

To a flask containing Ni(COD)₂¹⁰² (75 mg, 0.27 mmol, 1.1 equiv.) was added a solution of the vinyl iodide **67** (84 mg, 0.25 mmol, 1 equiv.) in dry THF (3.5 mL). To the resultant black solution was added, via syringe pump (3 h), a solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.1 mL, 0.27 mmol, 1.15 equiv.). The reaction mixture was stirred at rt overnight and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) to provide, after removal of trace amounts of solvent from the resultant oil, 36 mg (70%) of the keto acetylene **80**, as a colourless oil. None of the desired bicyclic ketone **77** was obtained. ¹H nmr spectroscopic analysis of the acetylene **80** revealed that it consisted of a ~1:1 mixture of epimers at carbon two.

IR (film): 3296, 2117, 1709, 1646, 1455, 1217, 896 cm⁻¹.

¹H nmr (400 MHz) δ: 1.04, 1.15 (d, d, ratio ~1:1, 3H, *J* = 7.5 Hz, secondary Me), 1.16-1.30 (m, 2H), 1.42-1.70 (m, 2H), 1.77 (br s, 3H, vinyl Me), 1.77-1.83 (m, 1H), 1.97 (br s, 1H, acetylenic proton), 2.00-2.71 (m, 6H), 4.71, 4.75, 4.79, 4.83 (s, s, s, s, ratio ~1:1:1:1, 2H, vinyl protons).

3.2.8.5. Synthesis of (1*R**, 6*S**)-1-Carbomethoxy-9-methylenebicyclo[4.3.0]nonan-2-one (**78**):



a. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Pd(PPh₃)₄ as the Catalyst and Cs₂CO₃ as the Base:

To a stirred suspension of flame dried Cs₂CO₃¹⁰³ (330 mg, 1.01 mmol, 5.1 equiv.) in dry THF (1 mL) at rt was added a solution of the vinyl iodide **68** (67 mg, 0.20 mmol, 1 equiv.) in dry THF (1 mL). Pd(PPh₃)₄ (66 mg, 0.057 mmol, 28 mol%) was added to the mixture in one portion and the suspension was heated to 50-60 °C for 6 h. The mixture was cooled to rt, and diethyl ether (15 mL) and water (15 mL) were added to the suspension. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (1 x 25 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was subjected to flash chromatography (14 g silica gel, 5.7:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 110-120 °C/20 Torr) to yield 18 mg (43 %) of the bicyclic keto ester **78**, as a colourless oil.

IR (film): 1719, 1653, 1435, 1250, 899 cm⁻¹.

¹H nmr (400 MHz) δ: 1.49-1.59 (m, 1H), 1.64-1.73 (m, 1H), 1.80-1.99 (m, 3H), 2.32-2.53 (m, 5H), 3.00-3.08 (br dt, 1H, *J* = 12, 6 Hz), 3.76 (s, 3H, Me-11), 4.96 (m, 1H, H-12), 5.24 (m, 1H, H-12').

^{13}C nmr (75.3 MHz) δ : 23.9, 26.0, 28.2, 29.7, 39.4, 47.7 (-ve), 52.7 (-ve), 71.9, 112.0 (C-12), 147.9 (C-9), 171.2 (C-10), 206.1 (C-2).

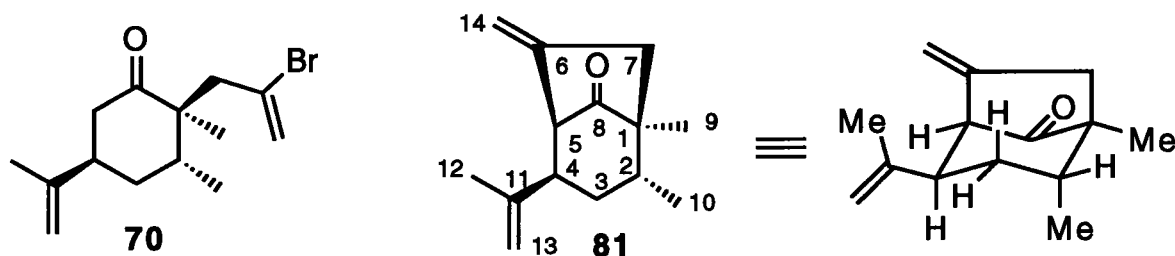
Exact Mass calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_3$: 208.1099; found: 208.1092.

Anal. calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_3$: C 69.21, H 7.74; found C 68.82, H 7.75.

b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing $\text{Pd}_2(\text{dba})_3/\text{PPh}_3$ as the Catalyst and Cs_2CO_3 as the Base:

To a flask containing flame dried Cs_2CO_3 (270 mg, 0.829 mmol, 5.3 equiv.) was added sequentially $\text{Pd}_2(\text{dba})_3$ ⁹⁸ (14 mg, 0.032 mmol, 20 mol%), dry THF (0.4 mL), and PPh_3 (16 mg, 0.061 mmol, 38 mol%, ~2:1 ratio of PPh_3 :Pd). The yellow/orange suspension was stirred at rt for 5 min and a solution of the vinyl iodide **68** (53 mg, 0.16 mmol, 1 equiv.) in dry THF (1.2 mL) was added. The mixture was heated to 52 °C for 5 h. As described in the above procedure, the reaction mixture was worked up and the crude product was purified to yield 15 mg (47%) of the bicyclic keto ester **78** (spectral data are identical with those reported above).

3.2.8.6. Synthesis of (1*S*, 2*R*, 4*R*, 5*S*)-1,2-Dimethyl-6-methylene-4-(1-methylethenyl)bicyclo-[3.2.1]heptan-8-one (**81**):



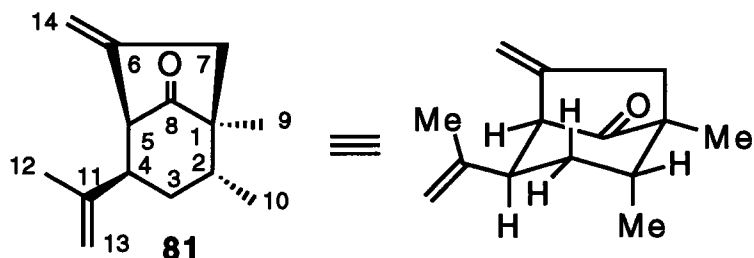
To a stirred solution of the vinyl bromide **70** (52 mg, 0.18 mmol, 1 equiv.) in dry THF (4 mL) at rt was added solid Pd(PPh₃)₄ (61 mg, 0.053 mmol, 29 mol%). The reaction mixture was stirred for 10 min until a light brown homogeneous solution resulted. A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.1 M, 1.8 mL, 0.18 mmol, 1 equiv.) was added, via syringe pump, over the course of 3 h. The reaction mixture was stirred at rt for an additional 1 h and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) to provide 2 fractions. The first compound eluted was the bicyclic product **81**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 115-120 °C/20 Torr) to yield 19 mg (51%) (70% based on consumed starting material) of the bridged bicyclic keto alkene **81**, as a colourless oil.

IR (film): 3089, 1752, 1654, 1454, 1096, 885 cm⁻¹.

¹H nmr (400 MHz) δ : 0.90 (d, 3H, *J* = 8 Hz, Me-10), 1.04 (s, 3H, Me-9), 1.22-1.29 (dd, 1H, *J* = 14, 6 Hz, H-3), 1.74 (br s, 3H, Me-12), 1.91-1.97 (m, 1H, H-3'), 2.00-2.05 (m, 1H, H-2), 2.49 (br d, 1H, *J* = 16 Hz, H-7), 2.52 (br d, 1H, *J* = 16 Hz, H-7'), 2.70 (br d, 1H, *J* = 12 Hz, H-4), 2.79 (br s, 1H, H-5), 4.65 (br s, 1H, H-13), 4.69 (br s, 1H, H-14), 4.78 (br s, 1H, H-13'), 5.13 (br s, 1H, H-14').

Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 20**.

Table 20: ^1H nmr Data (400 MHz, CDCl_3) for the Bridged Keto Alkene **81**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-10	0.90 (d, $J = 8$)	H-2	H-4
Me-9	1.04 (s)		H-2, H-7
H-3	1.22-1.29 (dd, $J = 14, 6$)	H-3' ^b , H-4	
Me-12	1.74 (br s)	H-13, H-13'	
H-3'	1.91-1.97 (m)	H-2, H-3, H-4	
H-2	2.00-2.05 (m)	Me-10	
H-7	2.49 (br d, $J = 16$)	H-7', H-14, H-14'	
H-7'	2.52 (br d, $J = 16$)	H-7, H-14, H-14'	
H-4	2.70 (br d, $J = 12$)	H-3, H-3', H-5	
H-5	2.79 (m)	H-4, H-14, H-14'	
H-13	4.65 (br s)	Me-12, H-13'	
H-14	4.69 (br s)	H-5, H-7, H-7', H-14'	
H-13'	4.78 (br s)	Me-12, H-13	
H-14'	5.13 (br s)	H-5, H-7, H-7', H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-3' is more downfield than H-3).

The second compound to be eluted from the column chromatography was the starting bromide **70**. The appropriate fractions were concentrated to afford 14 mg of compound **70**.

3.3. ATTEMPTS AT SYNTHESIS OF SIX-MEMBERED RINGS VIA A PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING REACTION

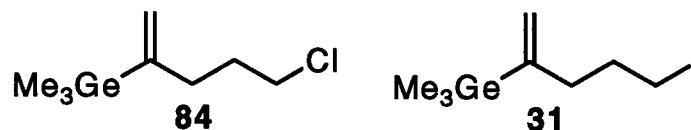
3.3.1. SYNTHESIS OF 5-iodo-2-trimethylgermyl-1-pentene (31) VIA THE CORRESPONDING VINYLSTANNANE COMPOUND

3.3.1.1. Synthesis of 5-Chloro-2-trimethylstannyl-1-pentene (83a):



To a cold (-20 °C), stirred solution of hexamethylditin (102 g, 0.311 mol, 1 equiv.) in dry THF (1.3 L) was added a solution of methyllithium in diethyl ether (1.27 M, 245 mL, 0.311 mol, 1 equiv.). The resultant yellow solution was stirred at -20 °C for 30 min and cooled to -78 °C. Solid CuBr•Me₂S (64.0 g, 0.311 mol, 1 equiv.) was added in one portion and the reddish brown mixture was stirred at -78 °C for 30 min. A solution of 5-chloro-1-pentyne (**82**) (33.0 g, 0.311 mol, 1 equiv.) in dry THF (10 mL) was added, via a dropping funnel, over the course of 40 min. The reaction mixture was stirred at -78 °C for 8 h and glacial acetic acid (89.0 mL, 1.55 mmol, 5 equiv.) was added. The resultant mixture was stirred at -78 °C for 20 min, was warmed to rt, and was poured into a stirred suspension of aqueous NH₄Cl - NH₄OH (pH 8-9, 1 L) and diethyl ether (1 L). The mixture was stirred, open to the atmosphere, overnight. The layers were separated and the bright blue aqueous phase was extracted with diethyl ether (2 x 1 L). The combined organic extracts were washed with aqueous NH₄Cl - NH₄OH (pH 8-9, 1 x 1 L) and brine (1 x 1 L), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude material was subjected to drip chromatography (1.75 Kg silica gel, petroleum ether) and the oil thus obtained was distilled (air-bath temperature 50-55 °C/20 Torr) to afford 55 g (66%) of 5-chloro-2-trimethylstannyl-1-pentene (**83a**).¹⁰⁴

3.3.1.2. Synthesis of 5-Iodo-2-trimethylgermyl-1-pentene (31):



To a cold (-78 °C), stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (**83a**) (2.27 g, 8.49 mmol, 1 equiv.) in dry THF (42 mL) was added a solution of methyllithium in diethyl ether (1.31 M, 8.10 mL, 10.6 mmol, 1.25 equiv.). The colourless solution was stirred at -78 °C for 0.5 h. Bromotrimethylgermane (2.48 g, 12.5 mmol, 1.47 equiv.) was cannulated into the solution and the resultant mixture was stirred at -78 °C for 2.5 h. Aqueous NH₄Cl - NH₄OH (pH 8-9, 30 mL) and diethyl ether (40 mL) were added to the solution and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude 5-chloro-2-trimethylgermyl-1-pentene (**84**) was used immediately in the following step without further purification.

To a solution of the crude 5-chloro-2-trimethylgermyl-1-pentene (**84**) (~8.5 mmol based on the theoretical amount) in acetone (42 mL, unpurified HPLC grade) at rt was added solid sodium iodide (19.0 g, 127 mmol, 15 equiv. based on the stannyl chloride). The suspension was heated to reflux for 13 h and then cooled to rt. The acetone was removed by rotary evaporation and the residual material was dissolved in diethyl ether (50 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (4 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was flash chromatographed (100 g silica gel, petroleum ether) and the oil thus obtained was distilled (air-bath temperature 50-55 °C/0.2 Torr) to afford 2.25 g (85% from the stannyl chloride **83a**) of 5-iodo-2-trimethylgermyl-1-pentene (**31**), as a colourless oil.

IR (film): 3046, 1604, 1426, 1235, 824, 601 cm^{-1} .

^1H nmr (400 MHz) δ : 0.20 (s, 9H, $-\text{GeMe}_3$), 1.89-1.96 (quintet, 2H, $J = 8.5$ Hz, $\text{ICH}_2\text{CH}_2\text{CH}_2-$), 2.30 (t, 2H, $J = 8.5$ Hz, allylic methylene protons), 3.28 (t, 2H, $J = 8.5$ Hz, ICH_2CH_2-), 5.26 (m, 1H, vinyl proton), 5.57 (m, 1H, vinyl proton).

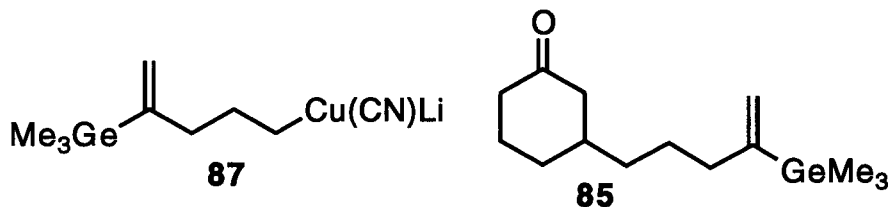
^{13}C nmr (75.3 MHz) δ : -1.9 (-ve, $-\text{Ge}(\text{CH}_3)_3$), 6.5, 32.4, 37.7, 122.7 ($\text{CH}_2=\text{C}-$), 152.0 ($\text{CH}_2=\text{C}$).

Exact Mass calcd. for $\text{C}_7\text{H}_{14}\text{GeI}$ ($\text{M}^+ - \text{Me}$): 298.9352; found: 298.9355.

Anal. calcd. for $\text{C}_8\text{H}_{17}\text{GeI}$: C 30.72, H 5.48, I 40.58; found: C 30.77, H 5.59, I 40.46.

3.3.2. SYNTHESIS OF THE CUPRATE REAGENT **87** AND THE KETO VINYLGERMANES

3.3.2.1. Synthesis of 3-[4-(Trimethylgermyl)-4-pentenyl]cyclohexanone (**85**):



To a cold ($-98\text{ }^\circ\text{C}$), stirred solution of *tert*-butyllithium (1.69 M in pentane, 3.4 mL, 5.7 mmol, 2.8 equiv.) in dry THF (51 mL) was added (over a period of 15 min) a solution of 5-iodo-2-trimethylgermyl-1-pentene (**31**) (915 mg, 2.93 mmol, 1.43 equiv.) in dry THF (2 mL). The resultant pale yellow solution was stirred at $-98\text{ }^\circ\text{C}$ for 10 min and was warmed to $-78\text{ }^\circ\text{C}$. Copper(I) cyanide (275 mg, 3.07 mmol, 1.5 equiv.) was added in one portion and the suspension became colourless. Brief warming (2-4 min) of the reaction mixture at $-35\text{ }^\circ\text{C}$

provided a light tan homogeneous solution containing the cuprate reagent **87** which was cooled to $-78\text{ }^{\circ}\text{C}$. To the solution of the cuprate reagent **87** was added trimethylsilyl bromide (1.10 g, 7.16 mmol, 3.5 equiv.) and a solution of 2-cyclohexen-1-one (197 mg, 2.05 mmol, 1 equiv.) in dry THF (1 mL). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h and was subjected to the workup conditions as described in general procedure 1. The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature $88\text{--}90\text{ }^{\circ}\text{C}/0.2\text{ Torr}$) to afford 433 mg (75%) of the keto vinylgermane **85**, as a colourless oil.

IR (film): 3044, 1714, 1604, 1421, 1235, 915, 825 cm^{-1} .

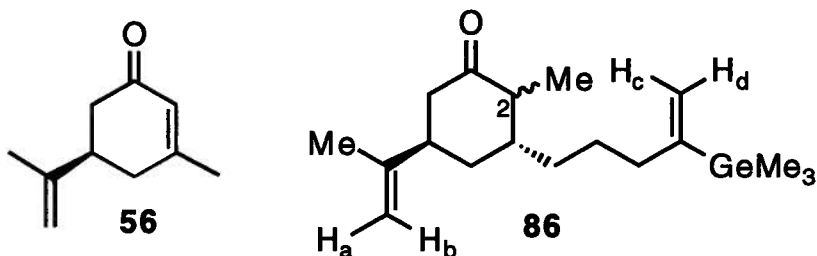
^1H nmr (400 MHz) δ : 0.19 (s, 9H, $-\text{GeMe}_3$), 1.23-1.44 (m, 5H), 1.55-1.78 (m, 2H), 1.84-1.88 (m, 1H), 1.93-2.04 (m, 2H), 2.14 (br t, 2H, $J = 7.5\text{ Hz}$), 2.17-2.26 (m, 1H), 2.29-2.35 (m, 1H), 2.36-2.41 (ddt, 1H, $J = 14, 4, 2\text{ Hz}$), 5.16-5.17 (m, 1H, vinyl proton), 5.47-5.48 (dt, 1H, $J = 2.5, 1.5\text{ Hz}$).

^{13}C nmr (75.3 MHz) δ : -1.9 (-ve, $-\text{Ge}(\underline{\text{CH}}_3)_3$), 25.3, 25.8, 31.3, 36.3, 37.3, 39.0 (-ve, C-3), 41.5, 48.2, 121.5 ($\underline{\text{CH}}_2=\text{C}-$), 153.8 ($\text{CH}_2=\underline{\text{C}}-$), 211.9 (C-1).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{26}\text{GeO}$: 284.1195; found: 284.1193.

Anal. calcd. for $\text{C}_{14}\text{H}_{26}\text{GeO}$: C 59.42, H 9.26; found: C 59.49, H 9.15.

3.3.2.2. Synthesis of (3*R*, 5*R*)-2-Methyl-5-(1-methylethenyl)-3-[4-(trimethylgermyl)-4-pentenyl]-cyclohexanone (**86**):



To a cold (-98 °C), stirred solution of *tert*-butyllithium (1.71 M in pentane, 0.82 mL, 1.4 mmol, 2.5 equiv.) in dry THF (12 mL) was added (over a period of 15 min) a solution of 5-iodo-2-trimethylgermyl-1-pentene (**31**) (226 mg, 0.723 mmol, 1.3 equiv.) in dry THF (2 mL). The resultant pale yellow solution was stirred at -98 °C for 10 min and was warmed to -78 °C. Copper(I) cyanide (68 mg, 0.76 mmol, 1.4 equiv.) was added in one portion and the suspension became colourless. Brief warming (2-4 min) of the reaction mixture at -35 °C provided a light tan homogeneous solution containing the cuprate reagent **87** which was cooled to -78 °C. To the solution of the cuprate reagent **87** was added trimethylsilyl bromide (335 mg, 2.19 mmol, 4 equiv.) and a solution of (*R*)-carvone (**56**) (84 mg, 0.56 mmol, 1 equiv.) in dry THF (1 mL). The reaction mixture was stirred at -78 °C for 6 h and was subjected to the workup conditions as described in general procedure 1. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 110-120 °C/0.15 Torr) to afford 132 mg (70%) of the keto vinylgermane **86**, as a colourless oil. ¹H nmr spectroscopic analysis indicated that the product consisted of an ~2:1 ratio of epimers at carbon two.

IR (film): 1713, 1646, 1453, 1220, 914, 825, 772 cm⁻¹.

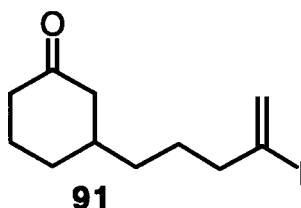
¹H nmr (400 MHz) δ: 0.18, 0.21 (s, s, ratio undetermined, 9H, -GeMe₃), 1.00, 1.11 (d, d, ratio ~2:1, 3H, *J* = 8 Hz for each d, secondary Me group), 1.72, 2.00 (s, s, ratio ~2:1, 3H,

vinyl Me group), 1.12-2.65 (m, 13H), 4.71, 4.73, 4.79, 4.80 (br s, br s, br s, br s, ratio undetermined, 2H, H_a and H_b), 5.19, 5.50 (m, m, 2H, H_c and H_d).

Exact Mass calcd. for C₁₈H₃₂GeO: 338.1665; found: 338.1661.

3.3.3. SYNTHESIS OF THE KETO VINYL IODIDES

3.3.3.1. Synthesis of 3-(4-Iodo-4-pentenyl)cyclohexanone (**91**):



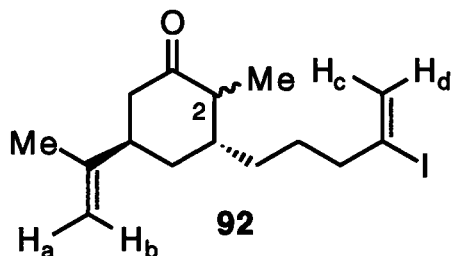
Following general procedure 2b, the keto vinylgermane **85** (419 mg, 1.48 mmol, 1 equiv.) was converted into the keto vinyl iodide **91**. The crude product was flash chromatographed (35 g silica gel, 9:1 petroleum ether - diethyl ether) and removal of trace amounts of solvent (vacuum pump) from the resultant oil yielded 418 mg (97%) of the vinyl iodide **91**, as a pale yellow oil.

IR (film): 1712, 1617, 1427, 1225, 894, 773 cm⁻¹.

¹H nmr (400 MHz) δ : 1.21-1.37 (m, 2H), 1.48-2.06 (m, 8H), 2.20-2.43 (m, 5H), 5.65 (m, 1H, vinyl proton), 5.98 (m, 1H, vinyl proton).

Exact Mass calcd. for C₁₁H₁₇IO: 292.0323; found: 292.0326.

3.3.3.2. Synthesis of (3*R*, 5*R*)-3-(4-Iodo-4-pentenyl)-2-methyl-5-(1-methylethenyl)cyclohexanone (**92**):



Following general procedure 2b, the keto vinylgermane **86** (217 mg, 0.644 mmol, 1 equiv.) was converted into the keto vinyl iodide **92**. The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum ether - diethyl ether) and removal of trace amounts of solvent (vacuum pump) from the resultant oil afforded 211 mg (95%) of the vinyl iodide **92**, as a pale yellow oil. ^1H nmr spectroscopic analysis revealed that the product consisted of a ~2:1 mixture of epimers at carbon two.

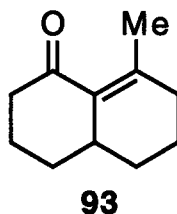
IR (film): 3074, 1709, 1646, 1618, 1429, 1164, 896 cm^{-1} .

^1H nmr (400 MHz) δ : 1.00, 1.13 (d, d, ratio ~2:1, 3H, J = 8 Hz for each d, secondary Me group), 1.25-1.70 (m, 5H), 1.63, 1.65 (s, s, ratio undetermined, 3H, vinyl Me group), 1.98-2.68 (m, 8H), 4.70, 4.75, 4.78, 4.82 (br s, br s, br s, br s, ratio ~1:2:2:1, 2H, H_a and H_b), 5.70, 6.00 (m, m, 2H, H_c and H_d).

Exact Mass calcd. for $\text{C}_{15}\text{H}_{23}\text{IO}$: 346.0793; found: 346.0786.

3.3.4. CYCLIZATION REACTIONS TO FORM SIX-MEMBERED RINGS

3.3.4.1. Synthesis of 10-Methylbicyclo[4.4.0]dec-10-en-2-one (**93**):



a. Via the Pd(0)-Catalyzed Cyclization Reaction Conditions Described in General Procedure 3:

To a stirred solution of the keto vinyl iodide **91** (105 mg, 0.359 mmol, 1 equiv.) in dry THF (3.6 mL, 0.1 M dilution) at rt was added Pd(PPh₃)₄ (143 mg, 0.123 mmol, 34 mol%). A solution of *t*-BuOK in a 4:1 mixture of dry THF and dry *t*-BuOH (0.24 M, 1.7 mL, 0.41 mmol, 1.1 equiv.) was added, via a syringe pump, over the course of 3 h. The reaction mixture was stirred for an additional 1 h at rt and was subjected to the workup conditions as described in general procedure 3. The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum ether - diethyl ether) and removal of trace amounts of solvent (vacuum pump) from the resultant oil provided 3 mg (5%) of the bicyclic enone **93**.

¹H nmr (400 MHz) δ : 1.17-1.49 (m, 3H), 1.62-1.77 (m, 2H), 1.85 (d, 3H, *J* = 2 Hz, vinyl Me group), 1.86-1.99 (m, 3H), 2.08-2.11 (m, 2H), 2.24-2.32 (m, 2H), 2.48 (br d, 1H, *J* = 15 Hz).

Exact Mass calcd. for C₁₁H₁₆O: 164.1201; found: 164.1203.

b. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (0.02 M dilution and no *t*-BuOH present in the base mixture):

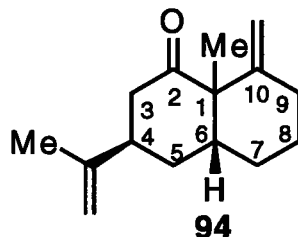
To a stirred solution of the keto vinyl iodide **91** (130 mg, 0.45 mmol, 1 equiv.) in dry THF (30 mL, 0.02 M dilution) at rt was added Pd(PPh₃)₄ (177 mg, 0.153 mmol, 34 mol%). A solution of *t*-BuOK in dry THF (0.24 M, 2.1 mL, 0.50 mmol, 1.1 equiv.) was added, via a

syringe pump, over the course of 3 h. The reaction mixture was stirred at rt overnight and was subjected to the workup conditions as described in general procedure 3. The crude product was subjected to flash chromatography (25 g silica gel, 9:1 petroleum ether - diethyl ether) and removal of trace amounts of solvent (vacuum pump) from the resultant oil yielded 20 mg (27%) of the bicyclic enone **93** (spectral data are identical with those reported above).

c. Via the Pd(0)-Catalyzed Cyclization Reaction Employing Modified Conditions (0.004 M dilution and no *t*-BuOH present in the base mixture):

To a stirred solution of the keto vinyl iodide **91** (71 mg, 0.24 mmol, 1 equiv.) in dry THF (60 mL, 0.004 M dilution) at rt was added Pd(PPh₃)₄ (101 mg, 0.087 mmol, 36 mol%). A solution of *t*-BuOK in dry THF (0.20 M, 1.4 mL, 0.28 mmol, 1.1 equiv.) was added, via a syringe pump, over the course of 5.5 h. The reaction mixture was stirred at rt overnight and was subjected to the workup conditions as described in general procedure 3. Flash chromatography (15 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude product and removal of trace amounts of solvent (vacuum pump) from the resultant oil afforded 16 mg (41%) of the bicyclic enone **93** (spectral data are identical with those reported above).

3.3.4.2. Synthesis of (4*R*, 6*R*)-1-Methyl-10-methylene-4-(1-methylethenyl)bicyclo[4.4.0]-decan-2-one (**94**):



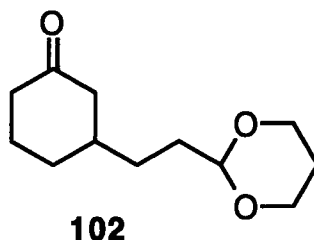
To a stirred solution of the keto vinyl iodide **92** (75 mg, 0.22 mmol, 1 equiv.) in dry THF (43 mL, 0.005 M dilution) at rt was added Pd(PPh₃)₄ (91 mg, 0.079 mmol, 36 mol%). A solution of *t*-BuOK in dry THF (0.20 M, 1.3 mL, 0.25 mmol, 1.1 equiv.) was added, via a syringe pump, over the course of 5.5 h. The reaction mixture was stirred at rt overnight and was subjected to the workup conditions as described in general procedure 3. Flash chromatography (15 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude product and removal of trace amounts of solvent (vacuum pump) from the resultant oil afforded 1 mg (2%) of the bicyclic enone **94**.

¹H nmr (400 MHz) δ : 1.27 (s, 3H, tertiary Me group), 1.75 (br s, 3H, vinyl Me group), 1.30-2.70 (m, 12H), 4.70, 4.75, 4.81, 4.94 (br s, br s, br s, br s, 1H each, vinyl protons).

3.4. THE FORMATION OF TRICYCLIC RING SYSTEMS EMPLOYING THE ANNULATION METHOD BASED ON THE PALLADIUM(0)-CATALYZED INTRAMOLECULAR COUPLING

3.4.1. SYNTHESIS OF THE BICYCLIC ENONES:

3.4.1.1. Synthesis of 3-[2-(1,3-Dioxan-2-yl)ethyl]cyclohexanone (**102**):



To a stirred suspension of freshly ground magnesium turnings (686 mg, 28.2 mmol, 2.7 equiv.) and iodine (a few crystals) in dry THF (1 mL) at rt was added dropwise (via a large cannula) a solution of 2-(2-bromoethyl)-1,3-dioxane (2.75 g, 14.1 mmol, 1.3 equiv.) in dry THF (5 mL). The bromide solution was added at such a rate that reflux of the mixture was maintained. After the addition was complete, the mixture was heated to reflux for 30 min. The mixture was cooled to rt, diluted with dry THF (19 mL), and cooled to -78 °C. Solid CuBr•Me₂S (443 mg, 2.15 mmol, 15 mol% with respect to the Grignard reagent) was added in one portion and the cloudy, colourless mixture was stirred at -78 °C for 1 h. Dry HMPA (4.6 mL, 26 mmol, 2.5 equiv.) was added and the mixture was stirred for 10 min. A solution of 2-cyclohexen-1-one (1.01 g, 10.5 mmol, 1 equiv.) and trimethylsilyl chloride (3.3 mL, 26 mmol, 2.5 equiv.) in dry THF (4 mL) was added dropwise, via a large cannula. The resultant pale yellow mixture was stirred at -78 °C for 3 h and warmed to -48 °C for 1 h. Water (15 mL) was added and the mixture was warmed to rt and stirred for 30 min. Aqueous NH₄Cl - NH₄OH (pH 8-9, 50 mL) and diethyl ether (75 mL) were added and the mixture was opened to the atmosphere and stirred vigorously until the aqueous phase became bright blue in colour. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 75 mL). The combined organic extracts were washed with water (4 x 75 mL),

dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was flash chromatographed (150 g silica gel, 2.3:1 petroleum ether - ethyl acetate) and the oil thus obtained was distilled (air-bath temperature 126-128 °C/0.15 Torr) to afford 2.0 g (88%) of the acetal compound **102**.

IR (film): 1714, 1406, 1240, 1139, 1006, 893 cm^{-1} .

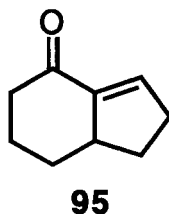
^1H nmr (400 MHz, C_6D_6) δ : 0.64-0.67 (dt, 1H, $J = 12.5, 1$ Hz), 0.75-0.84 (br q, 1H, $J = 11.5$ Hz), 1.10-1.86 (m, 11H), 2.10-2.14 (br d, 1H, $J = 14$ Hz), 2.28-2.32 (dt, 1H, $J = 14, 2$ Hz), 3.30-3.36 (br dd, 2H, $J = 11.5, 11.5$ Hz, axial protons of $-\text{OCH}_2-$), 3.79-3.83 (br dd, 2H, $J = 11.5, 5$ Hz, equatorial protons of $-\text{OCH}_2-$), 4.29-4.32 (t, 1H, $J = 5$ Hz, $-\text{OCH}_2-$).

^{13}C nmr (75.3 MHz, C_6D_6) δ : 25.1, 26.1, 30.9, 31.1, 32.8, 38.7 (-ve), 41.3, 48.0, 66.7, 102.3 (-ve, $-\text{OCHO}-$), 208.6 ($-\text{C}=\text{O}$).

Exact Mass calcd. for $\text{C}_{12}\text{H}_{20}\text{O}$: 212.1412; found: 212.1409.

Anal. calcd. for $\text{C}_{12}\text{H}_{20}\text{O}$: C 67.89, H 9.50; found: C 67.79, H 9.55.

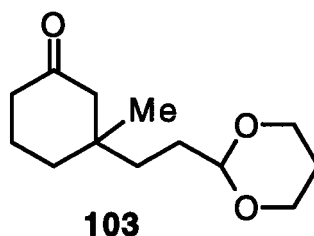
3.4.1.2. Synthesis of Bicyclo[4.3.0]non-9-en-2-one (**95**):



A solution of the acetal compound **102** (912 mg, 4.30 mmol, 1 equiv.) in a mixture of THF (29 mL) and 0.1 M hydrochloric acid (15 mL) was refluxed for 14 h. The resultant

brown solution was cooled to rt and cautiously neutralized with saturated aqueous NaHCO_3 . Diethyl ether (100 mL) and water (50 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 75 mL) and the combined organic extracts were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product thus obtained was subjected to radial chromatography (4 mm plate, 9:1 petroleum ether - diethyl ether) to yield 427 mg (73%) of the bicyclic enone **95**,^{105,106} as a colourless oil.

3.4.1.3. Synthesis of 3-[2-(1,3-Dioxan-2-yl)ethyl]-3-methylcyclohexanone (**103**):



To a stirred suspension of freshly ground magnesium turnings (570 mg, 23.4 mmol, 2.6 equiv.) and iodine (a few crystals) in dry THF (1 mL) at rt was added dropwise (via a large cannula) a solution of 2-(2-bromoethyl)-1,3-dioxane (2.29 g, 11.7 mmol, 1.3 equiv.) in dry THF (4 mL). The bromide solution was added at such a rate that reflux of the mixture was maintained. After the addition was complete, the mixture was heated to reflux for 30 min. The mixture was cooled to rt, diluted with dry THF (15 mL), and cooled to $-78\text{ }^{\circ}\text{C}$. Solid $\text{CuBr}\cdot\text{Me}_2\text{S}$ (389 mg, 1.89 mmol, 16 mol% with respect to the Grignard reagent) was added in one portion and the cloudy, colourless mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Dry HMPA (3.9 mL, 22 mmol, 2.5 equiv.) was added and the mixture was stirred for 10 min. A solution of 3-methyl-2-cyclohexen-1-one (978 mg, 8.88 mmol, 1 equiv.) and trimethylsilyl chloride (2.8 mL, 22 mmol, 2.5 equiv.) in dry THF (4 mL) was added dropwise, via a large cannula. The resultant pale yellow mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 h and warmed to -48

°C for 1 h. Water (7 mL) was added and the mixture was warmed to rt and was stirred for 45 min. Aqueous NH_4Cl - NH_4OH (pH 8-9, 40 mL) and diethyl ether (50 mL) were added and the mixture was opened to the atmosphere and stirred vigorously overnight. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water (4 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was flash chromatographed (160 g silica gel, 2.3:1 petroleum ether - ethyl acetate) and the oil thus obtained was distilled (air-bath temperature 132-136 °C/0.15 Torr) to afford 1.9 g (95%) of the acetal compound **103**.

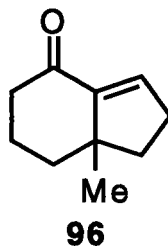
IR (film): 1708, 1461, 1148, 1081, 1007, 894 cm^{-1} .

^1H nmr (400 MHz, C_6D_6) δ : 0.76 (s, 3H, Me), 0.99-1.06 (m, 1H), 1.13-1.20 (ddd, 1H, J = 13.0, 8.5, 4.5 Hz), 1.29-1.98 (m, 12H), 3.30-3.36 (br dd, 2H, J = 11.5, 11.5 Hz, axial protons of $-\text{OCH}_2-$), 3.79-3.83 (br dd, 2H, J = 11.5, 5 Hz, equatorial protons of $-\text{OCH}_2-$), 4.28-4.30 (t, 1H, J = 5 Hz, $-\text{OCH}_2\text{O}-$).

^{13}C nmr (75.3 MHz, C_6D_6) δ : 22.0, 24.9 (-ve, Me), 26.1, 29.8, 35.3, 35.4, 37.7, 40.8, 53.7, 66.7, 102.7 (-ve, $-\text{OCH}_2\text{O}-$), 209.0 ($-\text{C}=\text{O}$).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_3$: 226.1569; found: 226.1562.

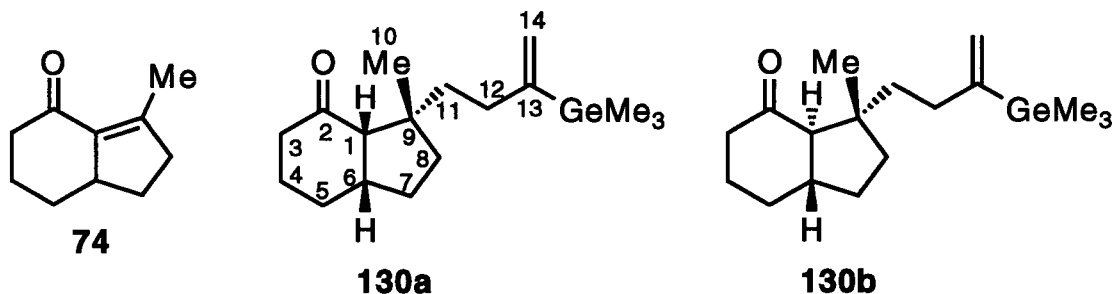
Anal. calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_3$: C 68.99, H 9.80; found: C 69.07, H 9.88.

3.4.1.4. Synthesis of 6-Methylbicyclo[4.3.0]non-9-en-2-one (**96**):

A solution of the acetal compound **103** (800 mg, 3.54 mmol, 1 equiv.) in a mixture of THF (28 mL) and 0.1 M hydrochloric acid (14 mL) was refluxed for 19 h. The resultant brown solution was cooled to rt and cautiously neutralized with saturated aqueous NaHCO₃. Diethyl ether (100 mL) and water (50 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 75 mL) and the combined organic extracts were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product thus obtained was subjected to flash chromatography (35 g silica gel, 49:1 CH₂Cl₂ - acetone) to afford 324 mg (61%) of the bicyclic enone **96**,¹⁰⁷ as a colourless oil.

3.4.2. SYNTHESIS AND EPIMERIZATION OF THE BICYCLIC KETO VINYLGERMANES

3.4.2.1. Synthesis of (1*S**, 6*S**, 9*S**)-9-Methyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (**130a**) and (1*R**, 6*S**, 9*S**)-9-Methyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (**130b**):



Following general procedure 1, a solution of the cuprate reagent **15** (1.49 mmol, 2 equiv.) in dry THF (15 mL) was treated sequentially with trimethylsilyl bromide (625 mg, 4.08 mmol, 5.3 equiv.) and a solution of the bicyclic enone **74** (115 mg, 0.766 mmol, 1 equiv.) in dry THF (1 mL). The reaction mixture was stirred at -78 °C for 9 h. ¹H nmr spectroscopic analysis of the crude product indicated a 9:1 ratio of the isomers **130a** and **130b**, as determined by the integration of their respective methyl proton signals. The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum ether - diethyl ether) to afford two compounds. The first compound to be eluted was the trans-fused product **130b**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 130-132 °C/0.8 Torr) to afford 22 mg (9%) of the minor trans-fused product **130b**, as a colourless oil.

IR (film): 1713, 1605, 1236, 1045, 825 cm⁻¹.

¹H nmr (400 MHz) δ : 0.19 (s, 9H, -GeMe₃), 1.09 (s, 3H, Me-10), 1.25-1.42 (m, 4H), 1.51-1.78 (m, 3H), 1.82-1.90 (m, 1H), 1.85 (d, 1H, *J* = 12.5 Hz, H-1), 1.99-2.28 (m, 7H), 5.12-

5.13 (m, 1H, H-14), 5.48-5.49 (m, 1H, H-14').

^1H nmr (400 MHz, C_6D_6) δ : 0.30 (s, 9H, $-\text{GeMe}_3$), 0.85-0.93 (dq, 1H, $J = 4$, 12.5 Hz), 0.99-1.07 (m, 1H, H-5), 1.24 (s, 3H, Me-10), 1.18-1.29 (m, 2H, one of which is H-4), 1.41-1.62 (m, 6H, five of which are H-1, H-4', H-5', H-6, and H-11), 1.66-1.79 (m, 2H, one of which is H-3), 1.98-2.06 (dt, 1H, $J = 4.5$, 13 Hz, H-11'), 2.11-2.13 (m, 1H, H-3'), 2.25-2.33 (br dt, 1H, $J = 4.5$, 13 Hz, H-12), 2.37-2.45 (br dt, 1H, $J = 4.5$, 13 Hz, H-12'), 5.30-5.31 (br d, 1H, $J = 2.5$ Hz, H-14), 5.68-5.69 (m, 1H, H-14').

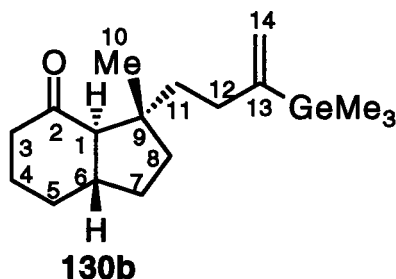
Detailed ^1H nmr data (C_6D_6), derived from a COSY experiment, are given in **Table 21**.

^{13}C nmr (100.4 MHz, C_6D_6) δ : -1.6 (-ve, $-\text{Ge}(\text{CH}_3)_3$), 22.2 (-ve, Me-10), 26.9, 29.1, 31.7, 33.7, 37.8, 42.3, 42.5, 42.7, 44.7 (-ve), 64.9 (-ve, C-1), 121.6 (C-14), 154.7 (C-13), 208.2 (C-2).

Exact Mass calcd. for $\text{C}_{17}\text{H}_{30}\text{GeO}$: 324.1508; found: 324.1511.

Anal. calcd. for $\text{C}_{17}\text{H}_{30}\text{GeO}$: C 63.21, H 9.36; found: C 63.11, H 9.19.

Table 21: ^1H nmr Data (400 MHz, C_6D_6) for the Trans-Fused Compound **130b**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
-GeMe ₃	0.30 (s)	
H-5	0.99-1.07 (m)	H-4, H-4' ^b , H-5'
Me-10	1.24 (s)	
H-4	Part of the m at 1.18-1.29	H-3, H-3', H-4', H-5, H-5'
H-1	Part of the m at 1.41-1.62	
H-4'	Part of the m at 1.41-1.62	H-3, H-3', H-4, H-5, H-5'
H-5'	Part of the m at 1.41-1.62	H-4, H-4', H-5
H-6	Part of the m at 1.41-1.62	
H-11	Part of the m at 1.41-1.62	H-11', H-12, H-12'
H-3	Part of the m at 1.66-1.79	H-3', H-4, H-4'
H-11'	1.98-2.06 (dt, J = 4.5, 13)	H-11, H-12, H-12'
H-3'	2.11-2.13 (m)	H-3, H-4, H-4'
H-12	2.25-2.33 (br dt, J = 4.5, 13)	H-11, H-11', H-12', H-14, H-14'
H-12'	2.37-2.45 (br dt, J = 4.5, 13)	H-11, H-11', H-12, H-14, H-14'
H-14	5.30-5.31 (br d, J = 2.5)	H-12, H-12', H-14'
H-14'	5.68-5.69 (m)	H-12, H-12', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-4' is more downfield than H-4)

The fractions containing the second compound to be eluted from the above column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 120-130 °C/0.28 Torr) to afford 198 mg (80%) of the major cis-fused compound **130a**, as a colourless oil.

IR (film): 1694, 1601, 1176, 1031, 824 cm⁻¹.

¹H nmr (400 MHz) δ: 0.20 (s, 9H, -GeMe₃), 1.16 (s, 3H, Me-10), 1.20-1.40 (m, 4H), 1.48-1.63 (m, 2H), 1.76-2.16 (m, 7H), 2.34 (d, 1H, *J* = 9.5 Hz, H-1), 2.40-2.46 (m, 2H), 5.13-5.14 (m, 1H, H-14), 5.47-5.48 (m, 1H, H-14').

¹H nmr (400 MHz, acetone-d₆) δ: 0.20 (s, 9H, -GeMe₃), 1.13 (s, 3H, Me-10), 1.25-1.41 (m, 4H, three of which are H-7, H-11, and H-11'), 1.43-1.53 (m, 1H, H-7'), 1.55-1.66 (m, 1H, H-4), 1.78-2.01 (m, 5H, three of which are H-4', H-8, and H-8'), 2.14-2.18 (br t, 2H, *J* = 8.5 Hz, H-12 and H-12'), 2.31 (d, 1H, *J* = 9 Hz, H-1), 2.31-2.34 (m, 1H, H-3'), 2.43-2.47 (m, 1H, H-6), 4.61 (d, 1H, *J* = 1 Hz, H-14), 4.96 (br s, 1H, H-14').

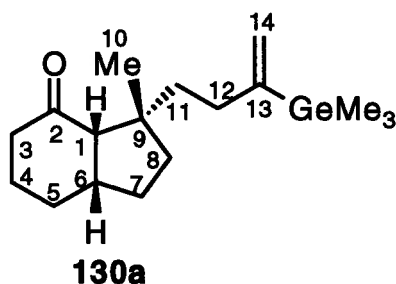
Detailed ¹H nmr data (acetone-d₆), derived from COSY and NOE experiments, are given in **Table 22**.

¹³C nmr (400 MHz, CDCl₃) δ: -1.7 (-ve, -Ge(CH₃)₃), 23.6, 27.0 (-ve), 30.6, 31.1, 32.7, 37.2, 37.4, 40.5 (-ve), 42.6, 47.3, 62.7 (-ve, C-1), 121.6 (C-14), 154.3 (C-13), 214.7 (C-2).

Exact Mass calcd. for C₁₇H₃₀GeO: 324.1508; found: 324.1512.

Anal. calcd. for C₁₇H₃₀GeO: C 63.21, H 9.36; found: C 63.39, H 9.37.

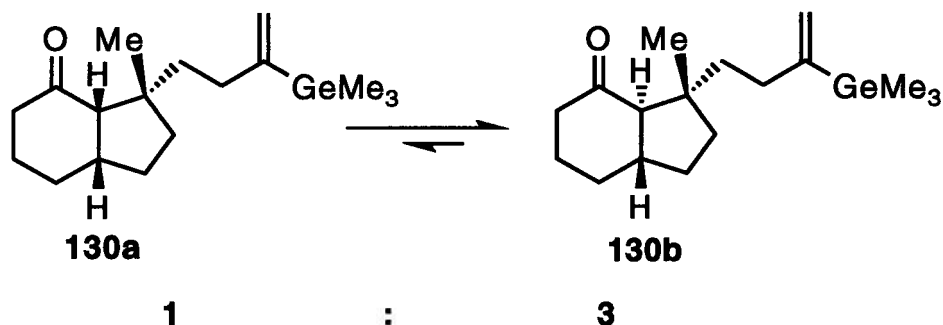
Table 22: ^1H nmr Data (400 MHz, acetone- d_6) for the Cis-Fused Compound **130a**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-GeMe ₃	0.20 (s)		
Me-10	1.13 (s)		H-1, H-8, H-8' ^b , H-12, H-12'
H-7	Part of the m at 1.25-1.41	H-6, H-7', H-8, H-8'	
H-11	Part of the m at 1.25-1.41	H-12, H-12'	
H-11'	Part of the m at 1.25-1.41	H-12, H-12'	
H-7'	1.43-1.53 (m)	H-7, H-8, H-8'	
H-4	1.55-1.66 (m)	H-3'	
H-4'	Part of the m at 1.78-2.01	H-3', H-4	
H-8	Part of the m at 1.78-2.01	H-7, H-7'	
H-8'	Part of the m at 1.78-2.01	H-7, H-7'	
H-12 and H-12'	2.14-2.18 (br t, $J = 8.5$)	H-11, H-11', H-14'	
H-1	2.31 (d, $J = 9$)	H-6	
H-3'	2.31-2.34 (m)	H-4, H-4'	
H-6	2.43-2.47 (m)	H-1, H-7	H-1
H-14	4.61 (d, $J = 1$)	H-14'	
H-14'	4.96 (br s)	H-12, H-12', H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

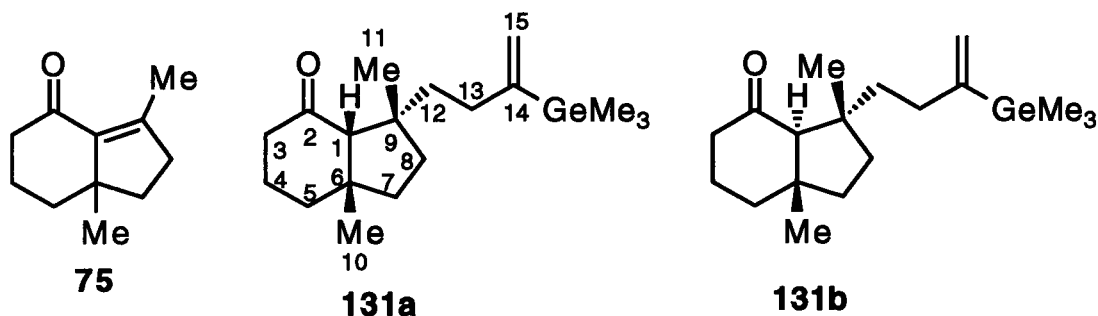
b- H' indicates the hydrogen of a pair which is more downfield (H-8' is more downfield than H-8)

3.4.2.2. Epimerization of compounds **130a** and **130b**:

To a cold (-78 °C), stirred solution of the cis-fused compound **130a** (11 mg, 0.034 mmol, 1 equiv.) in dry MeOH (3.4 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 100 μ L, 0.030 mmol, 0.9 equiv.). The yellow solution was warmed to rt and was stirred for 64 h. The MeOH was removed by rotary evaporation and water (5 mL) and diethyl ether (5 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The ^1H nmr spectroscopic analysis of the oil thus obtained indicated a 3:1 ratio¹⁰⁸ of the trans- to cis-fused compounds, **130b** and **130a**.

To a cold (-78 °C), stirred solution of the trans-fused compound **130b** (13.7 mg, 0.0423 mmol, 1 equiv.) in dry MeOH (4.2 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 130 μ L, 0.038 mmol, 0.9 equiv.). The yellow solution was warmed to rt and was stirred for 64 h. The MeOH was removed by rotary evaporation and water (5 mL) and diethyl ether (5 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The ^1H nmr spectroscopic analysis of the oil thus obtained indicated a 3:1 ratio¹⁰⁸ of the trans- to cis-fused compounds, **130b** and **130a**.

3.2.2.3. Synthesis of (1*S**, 6*S**, 9*S**)-6,9-Dimethyl-9-[3-(trimethylgermyl)-3-butenyl]-bicyclo[4.3.0]nonan-2-one (**131a**) and (1*R**, 6*S**, 9*S**)-6,9-Dimethyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (**131b**):



Following general procedure 1, a solution of the cuprate reagent **15** (0.877 mmol, 2 equiv.) in dry THF (9 mL) was treated sequentially with trimethylsilyl bromide (505 mg, 3.30 mmol, 7.5 equiv.) and a solution of the bicyclic enone **75** (72 mg, 0.44 mmol, 1 equiv.) in dry THF (0.5 mL). The reaction mixture was stirred at -78 °C for 9h. ¹H nmr spectroscopic analysis of the crude product indicated a 20:1 ratio¹⁰⁹ of the two epimeric compounds **131a** and **131b**. The crude product was flash chromatographed (25 g silica gel, 9:1 petroleum ether - diethyl ether) to provide two fractions. The first compound to be eluted was the trans-fused compound **131b**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 120-125 °C/0.2 Torr) to afford 6 mg (4%) of the minor trans-fused compound **131b**.

IR (film): 1717, 1608, 1460, 1235, 914, 825 cm⁻¹.

¹H nmr (400 MHz, C₆D₆) δ: 0.25 (s, 9H, -GeMe₃), 0.74 (s, 3H, Me), 1.08-1.22 (m, 1H), 1.32-1.59 (m, 9H), 1.55 (s, 3H, Me), 1.60-1.86 (m, 1H), 1.95 (s, 1H, H-1), 2.11-2.25 (m, 2H), 2.38-2.44 (m, 1H), 5.28-5.29 (m, 1H, H-15), 5.63-5.64 (m, 1H, H-15').

^1H nmr (400 MHz, acetone- d_6) δ : 0.19 (s, 9H, -GeMe₃), 0.92 (s, 3H, Me), 1.30 (s, 3H, Me), 1.35-1.53 (m, 3H), 1.55-1.70 (m, 4H), 1.74-1.80 (m, 1H), 1.87-1.97 (m, 2H), 2.05-2.12 (m, 2H), 2.17-2.33 (m, 2H), 2.28 (br s, 1H, H-1), 5.14 (br s, 1H, H-15), 5.50 (br s, 1H, H-15').

NOE difference experiments (in acetone- d_6): irradiation of the signal at δ 0.92 (Me) caused an enhancement of the signal at δ 1.30 (Me); irradiation of the signal at δ 1.30 (Me) caused an enhancement of the signal at δ 0.92 (Me).

^{13}C nmr (75.3 MHz, C_6D_6) δ : -1.7 (-ve, -Ge(CH₃)₃), 20.0 (-ve, Me), 23.5, 25.1 (-ve, Me), 30.2, 33.7, 39.2, 39.7, 40.5, 42.3, 46.5, 49.0, 67.1 (-ve, C-1), 121.5 (C-15), 154.6 (C-14), 208.6 (C-2).

Exact Mass calcd. for $\text{C}_{18}\text{H}_{32}\text{GeO}$: 338.1665; found: 338.1674.

Anal. calcd. for $\text{C}_{18}\text{H}_{32}\text{GeO}$: C 64.15, H 9.57; found: C 64.35, H 9.81.

The second product to be eluted was the cis-fused compound **131a**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 125-130 °C/0.1 Torr) to afford 120 mg (82%) of the major cis-fused compound **131a**.

IR (film): 1695, 1460, 1176, 824 cm^{-1} .

^1H nmr (400 MHz, C_6D_6) δ : 0.24 (s, 9H, -GeMe₃), 0.83 (s, 3H, Me), 1.20 (s, 3H, Me), 1.17-1.51 (m, 9H), 1.62-1.69 (q, 1H, J = 7 Hz), 1.90-1.97 (m, 1H), 2.05 (br s, 1H, H-1), 2.10-2.15 (m, 1H), 2.19-2.24 (m, 1H), 2.27-2.33 (m, 1H), 5.24 (br t, 1H, J = 1 Hz, H-15), 5.58-5.59 (m, 1H, H-15').

^1H nmr (400 MHz, acetone- d_6) δ : 0.20 (s, 9H, -GeMe3), 1.08 (br s, 3H, Me-10), 1.13 (br s, 3H, Me-11), 1.17-1.23 (m, 1H, H-12), 1.25-1.86 (m, 9H, three of which are H-4, H-4', and H-12'), 1.96 (br s, 1H, H-1), 2.06-2.10 (m, 1H, H-3), 2.11-2.18 (m, 2H, H-13 and H-13'), 2.24-2.31 (m, 1H, H-3'), 4.61-4.62 (m, 1H, H-15), 4.95-4.96 (m, 1H, H-15').

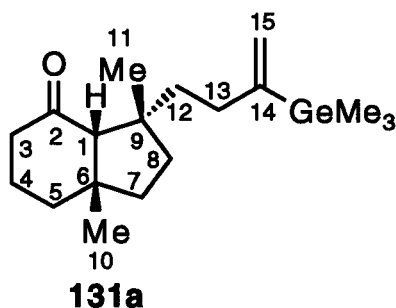
Detailed ^1H nmr data (acetone- d_6), derived from COSY and NOE experiments, are given in **Table 23**.

^{13}C nmr (100.4 MHz, C_6D_6) δ : -1.6 (-ve, -Ge(CH3)3), 21.0, 28.0 (-ve, Me), 29.4 (-ve, Me), 33.3, 36.1, 37.1, 38.0, 40.4, 42.2, 43.9, 48.1, 70.8 (-ve, C-1), 122.1 (C-15), 154.3 (C-14), 211.6 (C-2).

Exact Mass calcd. for $\text{C}_{18}\text{H}_{32}\text{GeO}$: 338.1665; found: 338.1660.

Anal. calcd. for $\text{C}_{18}\text{H}_{32}\text{GeO}$: C 64.15, H 9.57; found: C 64.45, H 9.69.

Table 23: ^1H nmr Data (400 MHz, acetone- d_6) for the Cis-Fused Vinylgermane Compound **131a**: COSY and NOE Experiments

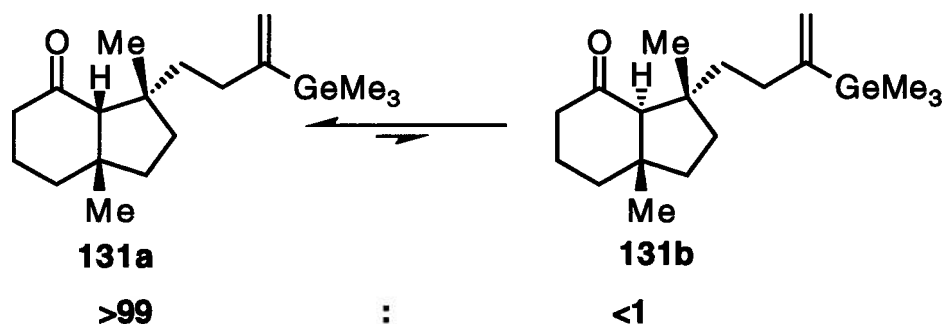


Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-GeMe ₃	0.20 (s)		
Me-10	1.08 (br s)	H-1	H-1
Me-11	1.13 (br s)	H-1	H-1, H-12' ^b , H-13, H-13'
H-12	1.17-1.23 (m)	H-12', H-13, H-13'	
H-12'	~1.25-1.51 (m), part of the m at 1.25-1.86	H-12, H-13, H-13'	
H-4	~1.65-1.73 (m), part of the m at 1.25-1.86	H-3, H-3', H-4'	
H-4'	~1.80-1.86 (m), part of the m at 1.25-1.86	H-3, H-3', H-4	
H-1	1.96 (br s)	H-3' ^c , Me-10, Me-11	Me-10, Me-11
H-3	2.06-2.10 (m)	H-3', H-4, H-4'	
H-13 and H-13'	2.11-2.18 (m)	H-12, H-12', H-15'	
H-3'	2.24-2.31 (m)	H-1 ^c , H-3, H-4, H-4'	
H-15	4.61-4.62 (m)	H-15'	
H-15'	4.95-4.96 (m)	H-13, H-13', H-15	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-12' is more downfield than H-12).

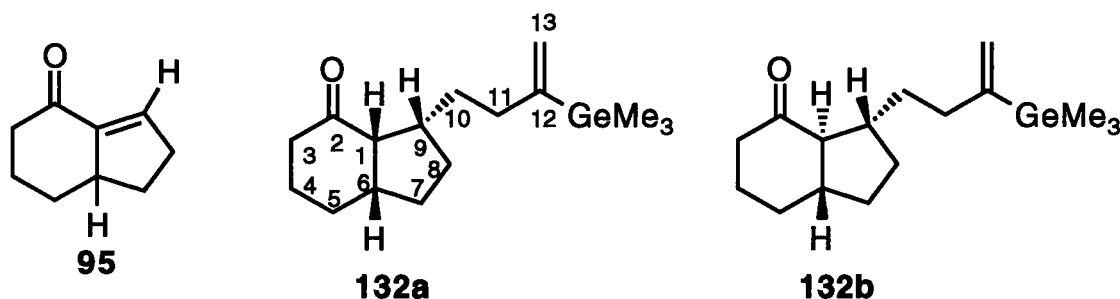
c- W coupling

3.4.2.4. Epimerization of compounds **131a** and **131b**:

To a cold (-78 °C), stirred solution of the cis-fused compound **131a** (42 mg, 0.12 mmol, 1 equiv.) in dry MeOH (2.5 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 0.37 mL, 0.11 mmol, 0.9 equiv.). The yellow solution was warmed to rt and was stirred for 48 h. The MeOH was removed by rotary evaporation and water (10 mL) and diethyl ether (10 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The cis-fused compound **131a** was the only isomer evident in the ^1H nmr spectrum of the crude oil.

To a cold (-78 °C), stirred solution of the trans-fused compound **131b** (10 mg, 0.030 mmol, 1 equiv.) in dry MeOH (1.0 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 90 μL , 0.027 mmol, 0.9 equiv.). The yellow solution was warmed to rt and was stirred for 48 h. The MeOH was removed by rotary evaporation and water (5 mL) and diethyl ether (5 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. ^1H nmr spectroscopic analysis of the crude oil indicated that the trans-fused compound **131b** had completely epimerized to the cis-fused compound **131a**, thereby verifying that the cis-fused compound **131a** is the thermodynamically more stable epimer.

3.4.2.5. Synthesis of (1*S**, 6*S**, 9*S**)-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (**132a**) and (1*R**, 6*S**, 9*S**)-9-[3-(trimethylgermyl)-3-butenyl]bicyclo[4.3.0]nonan-2-one (**132b**):



Following general procedure 1, a solution of the cuprate reagent **15** (2.18 mmol, 1.5 equiv.) in dry THF (29 mL) was treated sequentially with trimethylsilyl bromide (1.10 g, 7.18 mmol, 5 equiv.) and a solution of the bicyclic enone **95** (199 mg, 1.46 mmol, 1 equiv.) in dry THF (2 mL). The reaction mixture was stirred at -78 °C for 3 h. The crude product was flash chromatographed (35 g silica gel, 12.3:1 petroleum ether - diethyl ether) to afford 398 mg (88%) of a mixture of the cis- and trans-fused compounds, **132a** and **132b**. ¹H nmr spectroscopic analysis of this oil indicated a 5:1 ratio¹¹⁰ of compounds **132a** and **132b**. Further purification by column chromatography (25 g silica gel, 19:1 petroleum ether - diethyl ether) afforded a partial separation of compounds **132a** and **132b**. The first few fractions from the column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 90-92 °C/0.1 Torr) to provide the pure trans-fused compound **132b**, as a colourless oil.

IR (film): 1714, 1664, 1602, 1235, 914, 825 cm⁻¹.

¹H nmr (400 MHz) δ: 0.20 (s, 9H, -GeMe₃), 1.16-1.42 (m, 5H), 1.59-1.72 (m, 3H), 1.82-2.01 (m, 4H), 2.08-2.31 (m, 5H), 5.14 (br s, 1H, H-13), 5.50 (br s, 1H, H-13').

^{13}C nmr (75.3 MHz) δ : -1.8 (-ve, -Ge(CH₃)₃), 28.0, 28.7, 31.0, 31.2, 35.2, 35.9, 36.5 (-ve), 41.9, 50.0 (-ve), 63.6 (-ve, C-1), 121.0 (C-13), 154.3 (C-12), 211.3 (C-2).

Exact Mass calcd. for C₁₆H₂₈GeO: 310.1352; found: 310.1351.

Anal. calcd. for C₁₆H₂₈GeO: C 62.20, H 9.13; found: C 61.89, H 9.18.

A few late fractions eluted from the above column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 120-124 °C/0.25 Torr) to afford the pure cis-fused compound **132a**, as a colourless oil.

IR (film): 1703, 1605, 1452, 1235, 915, 825 cm⁻¹.

^1H nmr (400 MHz) δ : 0.18 (s, 9H, -GeMe₃), 1.34-1.85 (m, 9H, two of which are H-10 and H-10'), 1.88-1.95 (m, 1H), 2.01-2.08 (br ddd, 1H, H-11, J = 15.5, 10, 5.5 Hz, H-11), 2.08-2.15 (m, 2H, one of which is H-6), 2.18-2.24 (m, 1H, H-11'), 2.37-2.43 (m, 2H, one of which is H-9), 2.68-2.72 (dd, 1H, J = 8, 8 Hz, H-1), 5.13-5.14 (m, 1H, H-13), 5.46-5.47 (m, 1H, H-13').

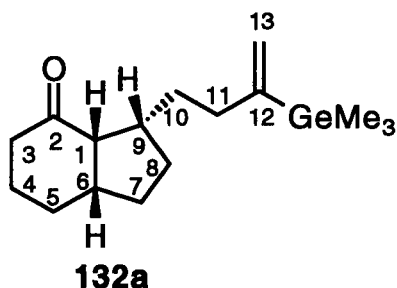
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 24**.

^{13}C nmr (75.3 MHz) δ : -1.8 (-ve, -Ge(CH₃)₃), 23.8, 28.7, 29.8, 30.5, 32.0, 36.8, 42.1 (-ve), 42.6 (-ve), 42.7, 55.4 (-ve, C-1), 121.5 (C-13), 153.9 (C-12), 214.8 (C-2).

Exact Mass calcd. for C₁₆H₂₈GeO: 310.1352; found: 310.1345.

Anal. calcd. for C₁₆H₂₈GeO: C 62.20, H 9.13; found: C 62.40, H 8.99.

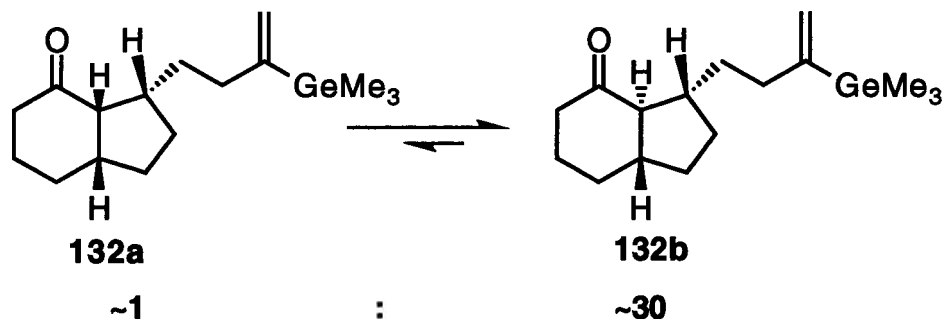
Table 24: ^1H nmr Data (400 MHz, CDCl_3) for the Cis-Fused Vinylgermane Compound **132a**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-GeMe ₃	0.18 (s)		
H-10	~1.34-1.43 (m), part of the m at 1.34-1.85	H-9, H-11, H-11' ^b	
H-10'	~1.61-1.69 (m), part of the m at 1.34-1.85	H-9, H-11, H-11'	
H-11	2.01-2.08 (br ddd, J = 15.5, 10, 5.5)	H-10, H-10', H-11', H-13, H-13'	
H-6	Part of the m at 2.08-2.15	H-1	H-1
H-11'	2.18-2.24 (m)	H-10, H-10', H-11, H-13, H-13'	
H-9	Part of the m at 2.37-2.43	H-1, H-10, H-10'	H-1, H-11
H-1	2.68-2.72 (dd, J = 8, 8)	H-6, H-9	H-6, H-9
H-13	5.13-5.14 (m)	H-11, H-11', H-13'	
H-13'	5.46-5.47 (m)	H-11, H-11', H-13	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

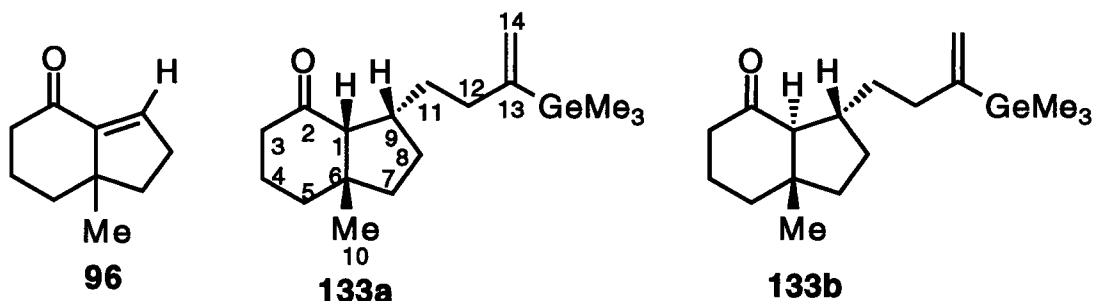
b- H' indicates the hydrogen of a pair which is more downfield (H-11' is more downfield than H-11).

3.4.2.6. Epimerization of compounds **132a** and **132b**:

To a cold (-78 °C), stirred solution of the cis-fused compound **132a** (13 mg, 0.042 mmol, 1 equiv.) in dry MeOH (1.4 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 130 μ L, 0.038 mmol, 0.9 equiv.). The yellow solution was warmed to rt and was stirred for 20 h. The MeOH was removed by rotary evaporation and water (5 mL) and diethyl ether (5 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. ^1H nmr spectroscopic analysis of the oil thus obtained indicated that the thermodynamic ratio of the compounds **132b** to **132a** was ~30:1.¹¹⁰

To a cold (-78 °C), stirred solution of the trans-fused compound **132b** (21 mg, 0.068 mmol, 1 equiv.) in dry MeOH (2.3 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 200 μ L, 0.061 mmol, 0.9 equiv.). The yellow solution was warmed to rt and was stirred for 20 h. The MeOH was removed by rotary evaporation and water (10 mL) and diethyl ether (10 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The ratio of the trans- to cis-fused compounds **132b** and **132a**, as judged by ^1H nmr spectroscopic analysis of the crude oil, was determined to be ~30:1.¹¹⁰

3.4.2.7. Synthesis of (1*R**, 6*S**, 9*S**)-6-Methyl-9-[3-(trimethylgermyl)-3-butenyl]bicyclo-[4.3.0]nonan-2-one (**133a**) and (1*S**, 6*S**, 9*S**)-6-Methyl-9-[3-(trimethylgermyl)-3-butenyl]-bicyclo[4.3.0]nonan-2-one (**133b**):



Following general procedure 1, a solution of the cuprate reagent **15** (2.35 mmol, 2 equiv.) in dry THF (25 mL) was treated sequentially with trimethylsilyl bromide (750 mg, 4.90 mmol, 4 equiv.) and a solution of the bicyclic enone **96** (181 mg, 1.20 mmol, 1 equiv.) in dry THF (1.5 mL). The reaction mixture was stirred at -78 °C for 5 h and warmed to -10 °C over the course of 3 h. ¹H nmr spectroscopic analysis of the crude oil indicated that the cis- and trans-fused addition products, **133a** and **133b**, were present in a ratio of 6:1.¹¹¹ Flash chromatography of the crude product (35 g silica gel, 9:1 petroleum ether - diethyl ether) provided, after removal of trace amounts of solvent (vacuum pump) from the resultant oil, 379 mg (98%) of a mixture of the compounds **133a** and **133b**. Further purification by column chromatography provided a partial separation of compounds **133a** and **133b**. The first few fractions eluted from the column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 145-150 °C/0.1 Torr) to afford the pure trans-fused compound **133b**, as a colourless oil.

IR (film): 1714, 1604, 1457, 1383, 1236, 1179, 914, 826 cm⁻¹.

¹H nmr (400 MHz, C₆D₆) δ: 0.30 (s, 9H, -GeMe₃), 0.56 (s, 3H, Me-10), 1.10-1.43 (m, 6H, one of which is H-11), 1.48-1.58 (m, 2H), 1.75 (d, 1H, *J* = 10 Hz, H-1), 1.72-1.82 (m, 2H,

one of which is H-3), 1.90-1.93 (m, 1H, H-11'), 2.09-2.14 (dd, 1H, $J = 13.5, 5$ Hz, H-3'), 2.28-2.39 (m, 3H, H-9, H-12, and H-12'), 5.31 (br d, 1H, $J = 1$ Hz, H-14), 5.70 (m, 1H, H-14').

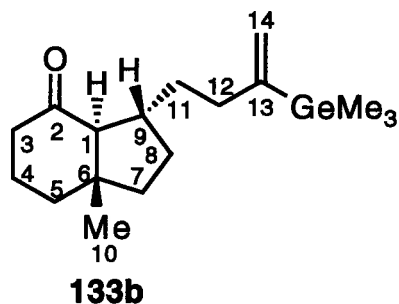
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 25**.

^{13}C nmr (75.3 MHz, C_6D_6) δ : -1.7 (-ve, $-\text{Ge}(\text{CH}_3)_3$), 18.7 (-ve, Me-10), 24.1, 27.7, 35.0 (-ve), 36.0, 36.7, 38.3, 39.6, 41.3, 48.6, 65.8 (-ve, C-1), 121.7 (C-14), 154.2 (C-13), 208.6 (C-2).

Exact Mass calcd. for $\text{C}_{17}\text{H}_{30}\text{GeO}$: 324.1508; found: 324.1506.

Anal. calcd. for $\text{C}_{17}\text{H}_{30}\text{GeO}$: C 63.21, H 9.36; found: C 63.11, H 9.22.

Table 25: ^1H nmr Data (400 MHz, C_6D_6) for the Trans-Fused Vinylgermane Compound **133b**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-GeMe ₃	0.30 (s)		
Me-10	0.56 (s)		H-9
H-11	Part of the m at 1.10-1.43	H-9, H-11' ^b , H-12, H-12'	
H-1	1.75 (d, J = 10)	H-9	
H-3	Part of the m at 1.72-1.82	H-3'	H-3'
H-11'	1.90-1.93 (m)	H-9, H-11, H-12, H-12'	H-11, H-12, H-12'
H-3'	2.09-2.14 (dd, J = 13.5, 5)	H-3	H-3
H-9	Part of the m at 2.28-2.39	H-1, H-11, H-11'	
H-12	Part of the m at 2.28-2.39	H-11, H-11', H-14'	
H-12'	Part of the m at 2.28-2.39	H-11, H-11', H-14'	
H-14	5.31 (br d, J = 1)	H-14'	
H-14'	5.70 (m)	H-12, H-12', H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-11' is more downfield than H-11).

The more polar cis-fused compound **133a** was also obtained in a pure form by concentrating the late fractions obtained from the above column chromatography. The oil thus obtained was distilled (air-bath temperature 92-94 °C/0.25 Torr) to provide compound **133a**, as a colourless oil.

IR (film): 1698, 1605, 1457, 1235, 915, 825 cm⁻¹.

¹H nmr (400 MHz, C₆D₆) δ: 0.26 (s, 9H, -GeMe₃), 0.83 (s, 3H, Me-10), 1.08-1.47 (m, 8H, H-7', H-7, H-3', H-11, H-4, H-5', H-5, H-3), 1.66-1.91 (m, 3H, H-8, H-11', H-4'), 2.09-2.30 (m, 4H, H-12', H-8', H-9, H-12), 2.33 (d, 1H, *J* = 10.5 Hz, H-1), 5.27 (br d, 1H, *J* = 2.5 Hz, H-14), 5.61-5.62 (m, 1H, H-14').

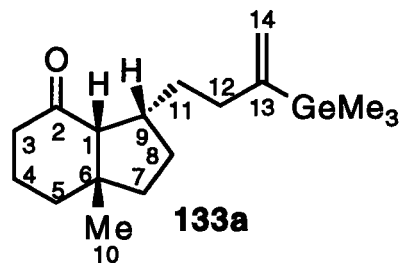
Detailed ¹H nmr data, derived from COSY and NOE experiments, are given in **Table 26**.

Detailed ¹³C nmr data, derived from HMQC and HMBC experiments, are given in **Table 27**.

Exact Mass calcd. for C₁₇H₃₀GeO: 324.1508; found: 324.1502.

Anal. calcd. for C₁₇H₃₀GeO: C 63.22, H 9.36; found: C 62.98, H 9.43.

Table 26: ^1H nmr Data (400 MHz, C_6D_6) for the Cis-Fused Vinylgermane Compound **133a**: COSY and NOE Experiments

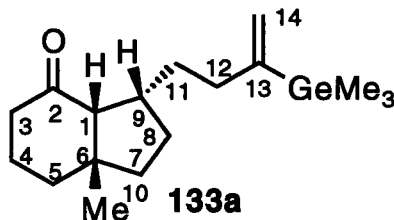


Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-GeMe ₃	0.26 (s)		
Me-10	0.83 (s)	H-5' ^b	H-1, H-5, H-5', H-7, H-7'
H-3	~1.08-1.11 (m), part of the m at 1.08-1.47	H-3', H-4, H-4'	
H-5	~1.11-1.20 (m), part of the m at 1.08-1.47	H-4'	
H-5'	~1.20-1.28 (m), part of the m at 1.08-1.47	Me-10	
H-4	~1.30-1.40 (m), part of the m at 1.08-1.47	H-3, H-3', H-4'	
H-11	~1.32-1.40 (m), part of the m at 1.08-1.47	H-9, H-11', H-12, H-12'	
H-3'	~1.35-1.42 (m), part of the m at 1.08-1.47	H-3	
H-7	~1.40-1.47 (m), part of the m at 1.08-1.47	H-8, H-8'	
H-7'	~1.40-1.47 (m), part of the m at 1.08-1.47	H-8, H-8'	
H-4'	~1.66-1.70 (m), part of the m at 1.66-1.91	H-3, H-3', H-4, H-5, H-5'	
H-11'	~1.70-1.80 (m), part of the m at 1.66-1.91	H-9, H-11, H-12, H-12'	H-11
H-8	~1.80-1.91 (m), part of the m at 1.66-1.91	H-7, H-7', H-8', H-9	
H-12	~2.09-2.10 (m), part of the m at 2.09-2.30	H-11, H-11', H-12', H-14, H-14'	
H-9	~2.10-2.15 (m), part of the m at 2.09-2.30	H-1, H-8, H-11, H-11'	
H-8'	~2.15-2.21 (m), part of the m at 2.09-2.30	H-7, H-7', H-8	
H-12'	~2.21-2.27 (m), part of the m at 2.09-2.30	H-11, H-11', H-12, H-14, H-14'	
H-1	2.33 (d, J = 10.5)	H-9	H-9, Me-10
H-14	5.27 (br d, J = 2.5)	H-12, H-12', H-14'	
H-14'	5.61-5.62 (m)	H-12, H-12', H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-5' is more downfield than H-5).

Table 27: ^1H nmr (500 MHz, C_6D_6) and ^{13}C nmr (125.8 MHz, C_6D_6) Data for the Cis-Fused Vinylgermane Compound **133a**: HMQC and HMBC Experiments



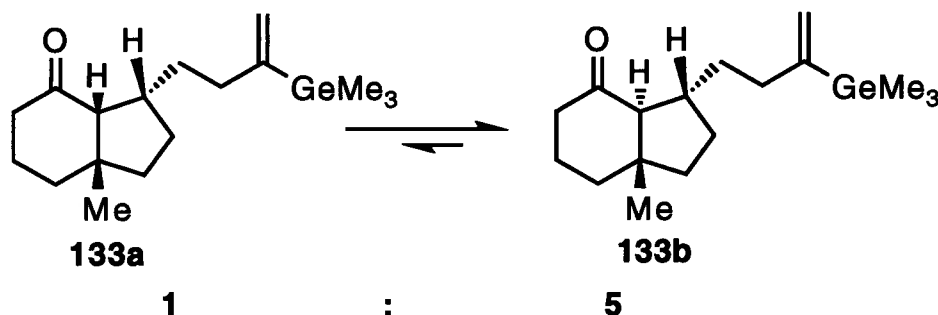
C-x	^{13}C nmr (125.8 MHz) δ ppm, APT ^a	HMQC ^{b,c} ^1H nmr Correlations δ ppm (assignment)	^1H - ^{13}C HMBC ^{b,c} Long-range Correlations H-x
-Ge(CH ₃) ₃	-1.7 (-ve)	0.26 (-GeMe ₃)	
C-7	21.6	Part of the m (8H) at 1.08-1.47 (H-7 and H-7' ^d)	H-5' (3 bond), H-8 (2 bond)
Me-10	28.4 (-ve)	0.83 (Me-10)	H-1 (3 bond), H-5 (3 bond), H-5' (3 bond)
C-4	31.0	Part of the m (8H) at 1.08-1.47 (H-4); part of the m (3H) at 1.66-1.91 (H-4')	H-1 (4 bond)
C-11	32.6	Part of the m (8H) at 1.08-1.47 (H-11); part of the m (3H) at 1.66-1.91 (H-11')	H-1 (3 bond), H-12 (2 bond)
C-5	34.9	Part of the m (8H) at 1.08-1.47 (H-5 and H-5')	H-1 (3 bond), H-3 (3 bond), H-7 and H-7' (3 bond), H-8 (4 bond), Me-10 (3 bond)
C-12	37.2	Part of the m (5H) at 2.09-2.30 (H-12 and H-12')	
C-3	40.1	Part of the m (8H) at 1.08-1.47 (H-3 and H-3')	H-4 (2 bond), H-5' (3 bond)
C-8	42.1	Part of the m (3H) at 1.66-1.91 (H-8); part of the m (5H) at 2.09-2.30 (H-8')	H-5' (4 bond)
C-9	42.3 (-ve)	Part of the m (5H) at 2.09-2.30 (H-9)	H-1 (2 bond), H-3' (4 bond), H-11' (2 bond)
C-6	45.4		H-1 (2 bond), H-4' (3 bond), H-5' (2 bond), H-7 and H-7' (2 bond), Me-10 (2 bond)
C-1	62.2 (-ve)	2.33 (H-1)	Me-10 (3 bond)
C-14	122.1	5.27 (H-14); 5.61-5.62 (H-14')	H-12 (3 bond)
C-13	153.8		H-12 (2 bond), H-14' (2 bond)
C-2	211.7		

a- The results of the APT experiment are given in parentheses (-ve for CH and CH₃ carbon signals).

b- The assignment and the chemical shifts of the ^{13}C nmr spectrum are listed in the first and second columns, respectively. The third column shows the ^1H nmr signal(s) which correlate(s) with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate(s) with the ^{13}C nmr signal of the first two columns as obtained from HMBC experiments (2, 3, and 4 bond correlations).

c- Only those HMQC and HMBC data that could be assigned are recorded.

d- H' indicates the hydrogen of a pair which is more downfield (H-7' is more downfield than H-7).

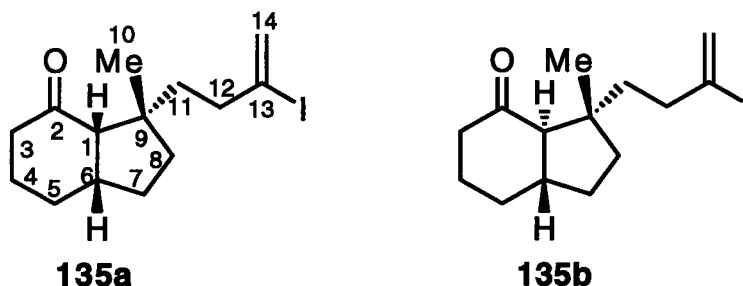
3.4.2.8. Epimerization of compounds **133a** and **133b**:

To a cold (-78 °C), stirred solution of the cis-fused compound **133a** (8.0 mg, 0.025mmol, 1 equiv.) in dry MeOH (2.5 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 150 μ L, 0.044 mmol, 1.8 equiv.). The yellow solution was warmed to rt and was stirred for 72 h. The MeOH was removed by rotary evaporation and water (5 mL) and diethyl ether (5 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Analysis of the crude oil by ^1H nmr spectroscopy indicated that the ratio of the trans- to cis-fused compounds (**133b**:**133a**) was 5:1.¹¹¹

To a cold (-78 °C), stirred solution of the trans-fused compound **133b** (5.0 mg, 0.015 mmol, 1 equiv.) in dry MeOH (1.5 mL) was added a solution of NaOMe in dry MeOH (0.30 M, 92 μ L, 0.028 mmol, 1.8 equiv.). The yellow solution was warmed to rt and was stirred for 72 h. The MeOH was removed by rotary evaporation and water (5 mL) and diethyl ether (5 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The ratio of the trans- to cis-fused compounds (**133b**:**133a**), as judged by ^1H nmr spectroscopic analysis of the crude oil, was determined to be 5:1.¹¹¹

3.4.3. CONVERSION OF THE BICYCLIC KETO VINYLGERMANES INTO THE CORRESPONDING KETO VINYL IODIDES

3.4.3.1. Synthesis of (1*S**, 6*S**, 9*S**)-9-(3-Iodo-3-butenyl)-9-methylbicyclo[4.3.0]nonan-2-one (**135a**) and (1*R**, 6*S**, 9*S**)-9-(3-Iodo-3-butenyl)-9-methylbicyclo[4.3.0]nonan-2-one (**135b**):



Following general procedure 2b, a mixture of the epimeric keto vinylgermanes **130a** and **130b** (160 mg, 0.50 mmol, 1 equiv., ratio of **130a**:**130b** was ~9:1¹⁰⁸) was converted into the corresponding mixture of the keto vinyl iodides **135a** and **135b**. Flash chromatography (15 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude product resulted in 150 mg (91%) of an epimeric mixture of the vinyl iodides **135a** and **135b**, in a ratio of ~1.5:1.¹¹² Further column chromatography (25 g silica gel, 9:1 petroleum ether - diethyl ether) resulted in the separation of the cis- and trans-fused vinyl iodides, **135a** and **135b**. The first compound to be eluted from the column chromatography was the trans-fused compound **135b**. Concentration of the appropriate fractions and distillation (air-bath temperature 119-121 °C/0.1 Torr) of the oil thus obtained, provided 60 mg of the pure trans-fused vinyl iodide **135b**, as a pale yellow oil.

IR (film): 1710, 1618, 1452, 1106, 1048 cm⁻¹.

¹H nmr (400 MHz) δ : 1.08 (s, 3H, Me-10), 1.27-1.42 (m, 3H), 1.46-1.69 (m, 3H), 1.82-1.91 (m, 3H), 1.99-2.09 (m, 3H), 2.14-2.48 (m, 4H), 5.63 (br s, 1H, H-14), 5.98 (br d, 1H, $J = 1$

Hz, H-14').

^{13}C nmr (75.3 MHz) δ : 21.9 (-ve, Me-10), 26.9, 28.9, 31.6, 37.7, 41.7, 41.8, 42.1, 42.4, 44.8 (-ve), 64.9 (-ve, C-1), 113.0 (C-13), 124.8 (C-14), 210.5 (C-2).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{21}\text{IO}$: 332.0636; found: 322.0633.

Anal. calcd. for $\text{C}_{14}\text{H}_{21}\text{IO}$: C 50.61, H 6.37, I 38.20; found: C 50.66, H 6.39, I 38.00.

The second compound to be eluted from the above column chromatography was the cis-fused compound **135a**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 80-90 °C/0.3 Torr) to provide 90 mg of the pure cis-fused vinyl iodide **135a**, as a pale yellow oil.

IR (film): 1694, 1618, 1457, 1101 cm^{-1} .

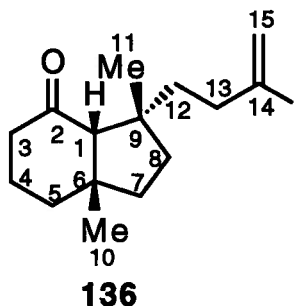
^1H nmr (400 MHz, C_6D_6) δ : 0.94-1.13 (m, 2H), 1.04 (s, 3H, Me-10), 1.14-1.32 (m, 2H), 1.43-1.63 (m, 6H), 1.80-1.88 (m, 1H), 1.98-2.20 (m, 4H), 2.24 (br d, 1H, $J = 13.5$ Hz, H-1), 5.48 (br s, 1H, H-14), 5.63 (br d, 1H, $J = 1$ Hz, H-14').

^{13}C nmr (75.3 MHz, C_6D_6) δ : 23.6, 27.2 (-ve, Me-10), 30.7, 30.9, 37.3, 37.4, 40.4 (-ve), 41.6, 42.5, 46.4, 62.0 (-ve, C-1), 113.4 (C-13), 125.3 (C-14), 211.5 (C-2).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{21}\text{IO}$: 332.0636; found: 332.0634.

Anal. calcd. for $\text{C}_{14}\text{H}_{21}\text{IO}$: C 50.61, H 6.37, I 38.20; found: C 50.77, H 6.38, I 38.00.

3.4.3.2. Synthesis of (1*S**, 6*S**, 9*S**)-6,9-Dimethyl-9-(3-iodo-3-butenyl)bicyclo[4.3.0]nonan-2-one (**136**):



Following general procedure 2b, the *cis*-fused keto vinylgermane **131a** (112 mg, 0.332 mmol, 1 equiv.) was converted into the *cis*-fused keto vinyl iodide **136**. Flash chromatography (15 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude product and distillation (air-bath temperature 140-144 °C/0.12 Torr) of the oil thus obtained, afforded 114 mg (99%) of the *cis*-fused vinyl iodide **136**, as a pale yellow oil.

IR (film): 1692, 1620, 1460, 1238, 893, 739 cm⁻¹.

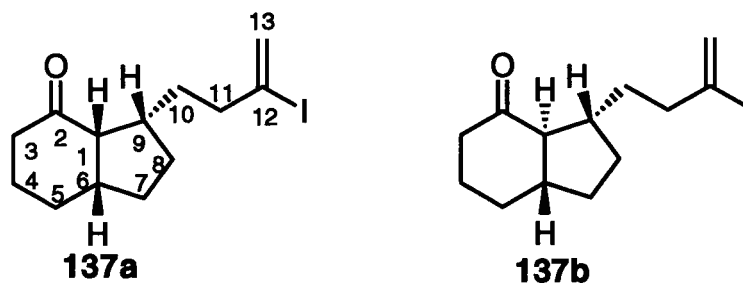
¹H nmr (400 MHz, C₆D₆) δ: 0.79 (s, 3H, Me), 1.04 (s, 3H, Me), 1.09-1.18 (m, 1H), 1.28-1.51 (m, 8H), 1.55-1.63 (dt, 1H, *J* = 4.5, 13 Hz), 1.87-1.96 (m, 1H), 1.98 (br s, 1H, H-1), 2.02-2.10 (dt, 1H, *J* = 4, 13.5 Hz), 2.12-2.17 (m, 1H), 2.25-2.30 (m, 1H), 5.47 (br d, 1H, *J* = 1 Hz, H-15), 5.61 (br d, 1H, *J* = 1 Hz, H-15').

¹³C nmr (100.4 MHz, C₆D₆) δ: 21.0, 28.1 (-ve, Me), 29.4 (-ve, Me), 36.1, 37.1, 37.3, 40.3, 40.5, 42.8, 46.4, 48.1, 70.6 (-ve, C-1), 114.4 (C-14), 125.3 (C-15), 211.5 (C-2).

Exact Mass calcd. for C₁₅H₂₃IO: 346.0793; found: 346.0792.

Anal. calcd. for C₁₅H₂₃IO: C 52.03, H 6.70, I 36.65; found: C 52.35, H 6.75, I 36.42.

3.4.3.3. Synthesis of (1*S**, 6*S**, 9*S**)-9-(3-Iodo-3-butenyl)bicyclo[4.3.0]nonan-2-one (**137a**) and (1*R**, 6*S**, 9*S**)-9-(3-Iodo-3-butenyl)bicyclo[4.3.0]nonan-2-one (**137b**):



Following general procedure 2b, a mixture of the cis- and trans-fused keto vinylgermanes **132a** and **132b** (205 mg, 0.663 mmol, 1 equiv., ratio of **132a**:**132b** was ~19:1¹¹⁰) was converted into the corresponding epimeric mixture of the keto vinyl iodides **137a** and **137b**. The crude product was subjected to radial chromatography (2 mm plate, 9:1 petroleum ether - diethyl ether) to provide, after removal of trace amounts of residual solvent (vacuum pump) from the resultant oil, 208 mg (98%) of a mixture of the cis- and trans-fused vinyl iodides **137a** and **137b**, in a ratio of ~5:1.¹¹³ Further column chromatography (25 silica gel, 9:1 petroleum ether - diethyl ether) resulted in a partial separation of the two epimeric iodides, **137a** and **137b**. The first few fractions eluted from the column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 126-130 °C/0.1 Torr) to afford 20 mg of the pure trans-fused vinyl iodide **137b**, as a pale yellow oil.

IR (film): 1713, 1617, 1448, 1227, 1155, 893 cm⁻¹.

¹H nmr (400 MHz) δ : 1.29-1.42 (m, 4H), 1.61-2.44 (m, 13H), 5.65 (br s, 1H, H-13), 6.02-6.03 (br d, 1H, $J = 1.5$ Hz, H-13').

^{13}C nmr (75.3 MHz) δ : 28.0, 28.8, 31.0, 31.1, 35.6 (-ve), 35.7, 41.8, 44.3, 50.0 (-ve), 63.5 (-ve, C-1), 112.3 (C-12), 125.0 (C-13), 211.1 (C-2).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{19}\text{IO}$: 318.0480; found: 318.0485.

Anal. calcd. for $\text{C}_{13}\text{H}_{19}\text{IO}$: C 49.07, H 6.02, I 39.88; found: C 48.76, H 5.95, I 39.90.

The late fractions eluted from the above column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 98-102 °C/0.13 Torr) to provide 88 mg of the pure cis-fused vinyl iodide **137b**, as a pale yellow oil.

IR (film): 1707, 1616, 1429, 1153, 892 cm^{-1} .

^1H nmr (400 MHz) δ : 1.41-1.94 (m, 10H), 2.05-2.15 (m, 2H), 2.30-2.47 (m, 4H), 2.68-2.72 (dd, 1H, $J = 8, 8$ Hz, H-1), 5.66 (br s, 1H, H-13), 5.99-6.00 (m, 1H, H-13').

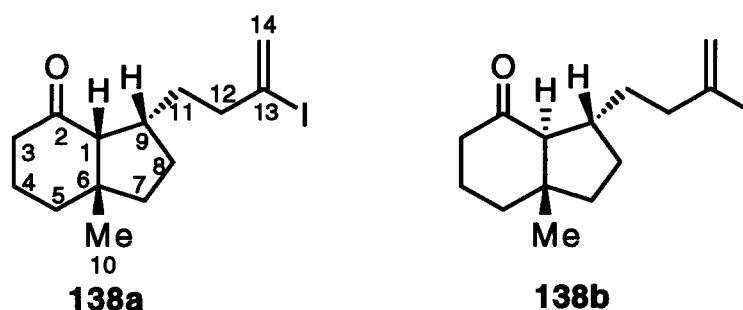
^{13}C nmr (75.3 MHz) δ : 23.7, 28.2, 29.5, 29.8, 31.8, 41.7 (-ve), 42.4 (-ve), 42.8, 44.7, 55.0 (-ve, C-1), 112.2 (C-12), 125.4 (C-13), 214.6 (C-2).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{19}\text{IO}$: 318.0480; found: 318.0482.

Anal. calcd. for $\text{C}_{13}\text{H}_{19}\text{IO}$: C 49.07, H 6.02, I 39.88; found: C 49.25, H 6.04, I 39.70.

The middle fractions eluted from the above column chromatography were concentrated to provide 100 mg of a mixture of the cis- and trans-fused vinyl iodides **137a** and **137b**.

3.4.3.4. Synthesis of (1*R**, 6*S**, 9*S**)-9-(3-Iodo-3-butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (**138a**) and (1*S**, 6*S**, 9*S**)-9-(3-Iodo-3-butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (**138b**):



Following general procedure 2b, an epimeric mixture of the keto vinylgermanes **133a** and **133b** (193 mg, 0.598 mmol, 1 equiv., the ratio of **133a**:**133b** was ~1:4¹¹¹) was converted into the corresponding mixture of the keto vinyl iodides **138a** and **138b**. The crude product was subjected to radial chromatography (2 mm plate, 9:1 petroleum ether - diethyl ether) to provide, after removal of trace amounts of solvent (vacuum pump) from the resultant oil, 182 mg (92%) of an epimeric mixture of the cis- and trans-fused vinyl iodides **138a** and **138b**, in a ratio of ~1:5.¹¹⁴ Further purification by column chromatography (25 silica gel, 19:1 petroleum ether - diethyl ether) resulted in a partial separation of the two iodides **138a** and **138b**. The first few fractions eluted from the column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 140-145 °C/0.25 Torr) to afford 83 mg of the pure trans-fused vinyl iodide **138b**, as a pale yellow oil.

IR (film): 1708, 1617, 1456, 1383, 1182, 892 cm⁻¹.

¹H nmr (400 MHz, C₆D₆) δ: 0.50 (s, 3H, Me-10), 0.94-1.80 (m, 12H), 2.07-2.39 (m, 4H), 5.56 (m, 1H, H-14), 5.78-5.79 (m, 1H, H-14').

¹³C nmr (75.3 MHz) δ: 18.6 (-ve, Me-10), 24.2, 27.5, 33.6 (-ve), 36.0, 38.3, 39.5, 41.4, 44.5,

49.2, 66.0 (-ve, C-1), 112.3 (C-13), 125.0 (C-14), 211.2 (C-2).

Exact Mass calcd. for C₁₄H₂₁IO: 332.0636; found: 332.0641.

Anal. calcd. for C₁₄H₂₁IO: C 50.61, H 6.37, I 38.20; found: C 50.53, H 6.37, I 38.00.

The late fractions eluted from the above column chromatography were concentrated and the oil thus obtained was distilled (air-bath temperature 125-130 °C/0.2 Torr) to afford 15 mg of the pure cis-fused vinyl iodide **138a**, as a pale yellow oil.

IR (film): 1698, 1616, 1456, 1187, 893 cm⁻¹.

¹H nmr (400 MHz, C₆D₆) δ: 0.80 (s, 3H, Me-10), 1.03-1.26 (m, 4H), 1.32-1.55 (m, 5H), 1.72-1.87 (m, 2H), 2.19 (d, 1H, *J* = 9.5 Hz, H-1), 1.96-2.21 (m, 4H), 5.54 (m, 1H, H-14), 5.70-5.71 (br d, 1H, *J* = 1.5 Hz, H-14').

¹³C nmr (75.3 MHz, C₆D₆) δ: 21.6, 28.7 (-ve, Me-10), 30.7, 32.5, 35.0, 39.4, 41.2 (-ve), 42.1, 44.8, 45.5, 61.8 (-ve, C-1), 112.4 (C-13), 125.5 (C-14), 211.7 (C-2).

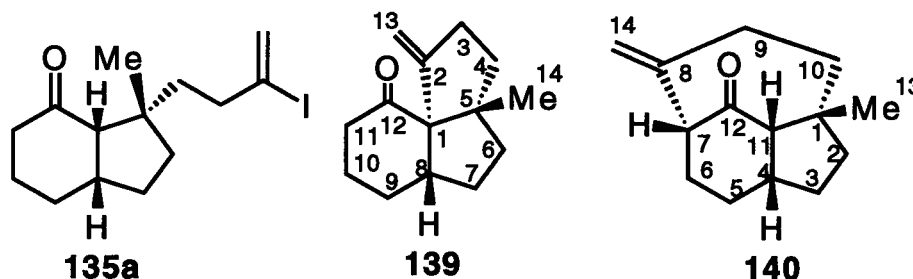
Exact Mass calcd. for C₁₄H₂₁IO: 332.0636; found: 332.0637.

Anal. calcd. for C₁₄H₂₁IO: C 50.61, H 6.37, I 38.20; found: C 50.58, H 6.38, I 38.08.

The middle fractions eluted from the above column chromatography were concentrated to provide 84 mg of a mixture of the cis- and trans-fused vinyl iodides **138a** and **138b**.

3.4.4. Pd(0)-CATALYZED CYCLIZATION REACTIONS OF THE BICYCLIC VINYL IODIDES TO PRODUCE TRICYCLIC RING SYSTEMS

3.4.4.1. Synthesis of (1*S**, 5*S**, 8*S**)-5-Methyl-2-methylenetricyclo[6.4.0.0^{1,5}]dodecan-12-one (**139**) and (1*S**, 4*S**, 7*R**, 11*S**)-1-Methyl-8-methylenetricyclo[5.3.2.0^{4,11}]dodecan-12-one (**140**):



a. Via a Pd(0)-Catalyzed Cyclization of the Cis-Fused Vinyl Iodide **135a**:

To a stirred solution of the cis-fused vinyl iodide **135a** (65 mg, 0.20 mmol, 1 equiv.) in dry THF (3.9 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (55 mg, 0.048 mmol, 24 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.1 M, 4:1 THF : *t*-BuOH, 2.3 mL, 0.22 mmol, 1.15 equiv.) was added, via a syringe pump, over 6.5 h. The reaction mixture was stirred at rt for an additional 3 h and worked up as described in general procedure 3. The crude product was flash chromatographed (15 g silica gel, 19:1 petroleum ether - diethyl ether) to yield two cyclized compounds, **139** and **140**. The first compound to be eluted was concentrated and the oil thus obtained was distilled (air-bath temperature 76-80 °C/0.05 Torr) to afford 17 mg (41%) of the fused tricyclic keto alkene **139**, as a colourless oil.

IR (film): 1703, 1636, 1462, 1222, 1010, 892 cm⁻¹.

¹H nmr (400 MHz) δ: 1.16 (s, 3H, Me-14), 1.26-1.36 (m, 1H), 1.40-1.63 (m, 4H, two of which are H-4 and H-7), 1.67-1.78 (m, 2H, H-9 and H-10), 1.83-2.12 (m, 4H, H-4', H-8, H-9',

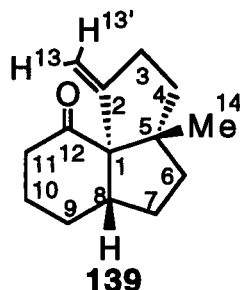
and H-10'), 2.25-2.32 (m, 1H, H-11), 2.39-2.45 (m, 2H, H-3 and H-3'), 2.57-2.64 (m, 1H, H-11'), 5.08 (br s, 1H, H-13), 5.16 (br s, 1H, H-13').

Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 28**.

^{13}C nmr (75.3 MHz) δ : 22.9, 23.8, 24.7 (-ve, Me-14), 27.8, 34.4, 38.4, 38.5, 38.6, 46.8 (-ve, C-8), 52.5, 69.0 (C-1), 110.0 (C-13), 153.9 (C-2), 210.5 (C-12).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.1514; found: 204.1514.

Table 28: ^1H nmr Data (400 MHz, CDCl_3) for the Fused Tricyclic Compound **139**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-14	1.16 (s)		H-8
H-7	Part of the m at 1.40-1.63	H-8	
H-4	Part of the m at 1.40-1.63	H-3, H-3' ^b , H-4'	
H-9	Part of the m at 1.67-1.78	H-8, H-9', H-10'	
H-10	Part of the m at 1.67-1.78	H-10', H-11, H-11'	
H-4'	~1.83-1.95 (m), part of the m at 1.83-2.21	H-3, H-3', H-4	
H-9'	~1.83-1.95 (m), part of the m at 1.83-2.21	H-8, H-9, H-10, H-10', H-11'	
H-10'	~1.95-2.05 (m), part of the m at 1.83-2.21	H-9, H-9', H-10, H-11, H-11'	
H-8	~2.05-2.12 (m), part of the m at 1.83-2.21	H-7, H-9, H-9'	
H-11	2.25-2.32 (m)	H-10, H-10', H-11'	H-11'
H-3 and H-3'	Part of the m at 2.39-2.45	H-4, H-4', H-13, H-13'	
H-11'	2.57-2.64 (m)	H-9', H-10, H-10', H-11	H-10', H-11, H-13
H-13	5.08 (br s)	H-3, H-3', H-13'	H-9', H-11', H-13'
H-13'	5.16 (br s)	H-3, H-3', H-13	H-3 and H-3', H-13

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-3' is more downfield than H-3)

The second compound to be eluted from the above column chromatography was the bridged keto alkene **140**. Concentration of the appropriate fractions and distillation (air-bath temperature 86-88 °C/0.25 Torr) of the oil thus obtained, provided 13 mg (33%) of the bridged tricyclic compound **140**, as a colourless oil.

IR (film): 1700, 1633, 1457, 1255, 894 cm^{-1} .

^1H nmr (400 MHz) δ : 1.10 (s, 3H, Me-13), 1.43-1.52 (m, 2H, H-3 and H-10), 1.56-1.68 (m, 3H, H-2, H-5, and H-5'), 1.71-1.79 (m, 2H, H-3' and H-10'), 1.84-2.04 (m, 3H, H-2', H-6, and H-6'), 2.12-2.19 (br dd, 1H, $J = 15, 11$ Hz, H-9), 2.38 (br d, 1H, $J = 8.5$ Hz, H-11), 2.34-2.40 (m, 1H, H-9'), 2.49-2.52 (dddd, 1H, $J = 8.5, 8.5, 8.5, 8.5, 3$ Hz, H-4), 3.26 (br s, 1H, H-7), 4.81 (br s, 1H, H-14), 4.95 (br s, 1H, H-14').

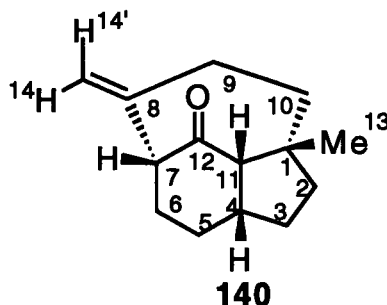
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 29**.

Detailed ^{13}C nmr data, derived from HMQC and HMBC experiments, are given in **Table 30**.

Exact Mass calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.1514; found: 204.1519.

Anal. calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C 82.30, H 9.87; found: C 82.12, H 10.10.

Table 29: ^1H nmr Data (400 MHz, CDCl_3) for the Bridged Tricyclic Compound **140**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-13	1.10 (s)		H-9, H-10, H-11
H-3	Part of the m at 1.43-1.52	H-2, H-2' ^b , H-3'	
H-10	Part of the m at 1.43-1.52	H-9, H-9', H-10'	
H-2	Part of the m at 1.56-1.68	H-2', H-3, H-3', H-4	
H-5	Part of the m at 1.56-1.68	H-4, H-6, H-6'	
H-5'	Part of the m at 1.56-1.68	H-4, H-6, H-6'	
H-3'	Part of the m at 1.71-1.79	H-2, H-2', H-3	
H-10'	Part of the m at 1.71-1.79	H-9, H-9', H-10	
H-2'	Part of the m at 1.84-2.04	H-2, H-3, H-3'	
H-6	Part of the m at 1.84-2.04	H-5, H-5', H-6', H-7	
H-6'	Part of the m at 1.84-2.04	H-5, H-5', H-6, H-7	
H-9	2.12-2.19 (br dd, J = 15, 11)	H-9', H-10, H-10', H-14'	H-9', H-10'
H-11 ^d	2.38 (br d, J = 8.5)	H-4, H-7 ^c	H-9, Me-13, H-14'
H-9' ^d	2.34-2.40 (m)	H-9, H-10, H-10', H-14'	H-9, Me-13, H-14'
H-4	2.49-2.52 (dddd, J = 8.5, 8.5, 8.5, 3)	H-2, H-5, H-5', H-11	
H-7	3.26 (br s)	H-6, H-6', H-11 ^c , H-14, H-14'	
H-14	4.81 (br s)	H-7, H-14'	
H-14'	4.95 (br s)	H-7, H-9, H-9', H-14'	

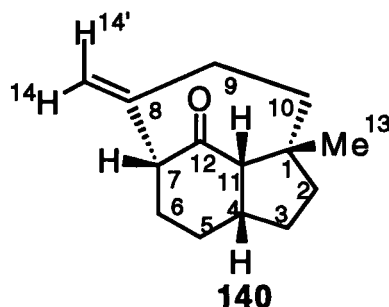
a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

c- W-coupling

d- The multiplet containing both H-9' and H-11 was irradiated in a NOE experiment.

Table 30: ^1H nmr (500 MHz, CDCl_3) and ^{13}C nmr (125.8 MHz, CDCl_3) Data for the Bridged Compound **140**: HMQC and HMBC Experiments



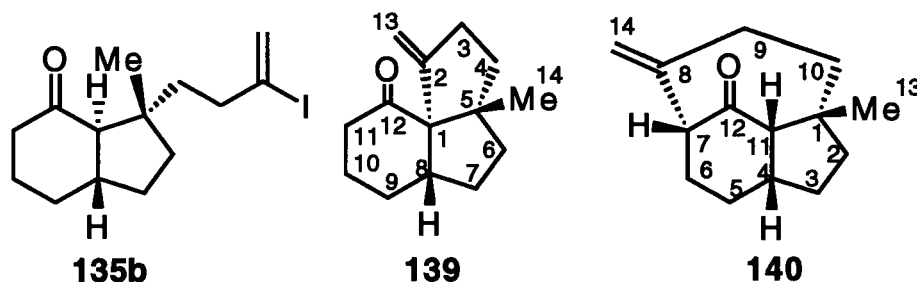
Assignment C-x	^{13}C nmr (125.8 MHz) δ ppm	HMQC a,b ^1H nmr Correlations (500 MHz) δ ppm (assignment)	^1H - ^{13}C HMBC a,b Long-range Correlations H-x
C-5	26.8	Part of the m (3H) at 1.52-1.63 (H-5 and H-5' ^b)	
Me-13	28.6	1.10 (Me-13)	
C-2	30.9	Part of the m (3H) at 1.56-1.68 (H-2); part of the m (3H) at 1.84-2.04 (H-2')	
C-9	33.2	2.12-2.19 (H-9); 2.34-2.40 (H-9')	H-14 (3 bond), H-14' (3 bond)
C-6	33.5	Part of the m (3H) at 1.84-2.04 (H-6 and H-6')	H-14 (4 bond), H-14' (4 bond)
C-10	38.8	Part of the m (2H) at 1.43-1.52 (H-10); part of the m (2H) at 1.71-1.79 (H-10')	H-9' (2 bond) and/or H-11 (3 bond) ^c , Me-13 (3 bond)
C-3	40.4	Part of the m (2H) at 1.43-1.52 (H-3); part of the m (2H) at 1.71-1.79 (H-3')	Me-13 (4 bond)
C-4	42.7	2.49-2.52 (H-4)	
C-1	45.4		H-9' (3 bond) and/or H-11 (2 bond) ^c , Me-13 (2 bond)
C-7	55.3	3.26 (H-7)	H-14 (3 bond), H-14' (3 bond)
C-11	63.4	2.38 (H-11)	Me-13 (3 bond)
C-14	112.7	4.81 (H-14); 4.95 (H-14')	
C-8	147.6		
C-12	214.2		H-11 (2 bond)

a- The assignment and the chemical shifts of the ^{13}C nmr spectrum are listed in the first and second columns, respectively. The third column shows the ^1H nmr signal(s) which correlate(s) with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate(s) with the ^{13}C nmr signal of the first two columns as obtained from HMBC experiments (2, 3, and 4 bond correlations).

b- Only those HMQC and HMBC data that could be assigned are recorded.

c- Since H-9' and H-11 have very similar chemical shifts, the correlations to the multiplet containing these two protons may be due to H-9' or H-11 or both signals.

d- H' indicates the hydrogen of a pair which is more downfield (H-5' is more downfield than H-5).



b. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide **135b**:

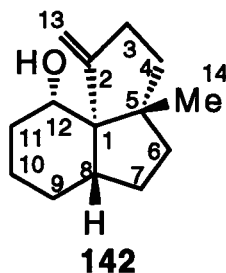
To a stirred solution of the trans-fused vinyl iodide **135b** (40 mg, 0.12 mmol, 1 equiv.) in dry THF (1.4 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (38 mg, 0.033 mmol, 25 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.1 M, 4:1 THF : *t*-BuOH, 1.4 mL, 0.14 mmol, 1.15 equiv.) was added, via a syringe pump, over 4 h. The mixture was stirred at rt for an additional 3.5 h and worked up as described in general procedure 3. The crude product was subjected to flash chromatography (8 g silica gel, 19:1 petroleum ether - diethyl ether) to provide 8.8 mg (36%) of the fused tricyclic compound **139** followed by 7.1 mg (29%) of the bridged compound **140** (the spectral data of compounds **139** and **140** are identical with those reported above).

c. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide **135b** employing modified reaction conditions:¹¹⁶

To a stirred solution of the trans-fused vinyl iodide **135b** (34 mg, 0.10 mmol, 1 equiv.) in dry THF (13.0 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (32 mg, 0.028 mmol, 28 mol%). A solution of *t*-BuOK in dry THF (0.1 M, 1.2 mL, 0.12 mmol, 1.15 equiv.) was added, via a syringe pump, over 5.5 h. The mixture was stirred at rt for an additional 1 h and subjected to the workup conditions as described in general procedure 3. Flash chromatography (8 g silica gel, 19:1 petroleum ether - diethyl ether) of the crude product afforded 14 mg (66%) of the fused tricyclic compound **139** followed by 1 mg (4%) of the bridged compound **140** (the spectral data of compounds **139** and **140** are identical with those reported above). The ratio of the fused to bridged compounds (**139**:**140**) in this modified cyclization experiment is

17:1,¹¹⁷ which is in sharp contrast to the 1.2:1 ratio¹¹⁸ observed in the two previous examples.

3.4.4.2. Synthesis of (1*S**, 5*S**, 8*S**, 12*S**)-5-Methyl-2-methylenetricyclo[6.4.0.0^{1,5}]-dodecan-12-ol (**142**):



To a cold (-78 °C), stirred solution of the fused tricyclic compound **139** (10 mg, 0.049 mmol, 1 equiv.) in dry THF (0.5 mL) was added a solution of DIBAL in hexanes (1 M, 89 μ L, 0.089 mmol, 1.8 equiv.). The solution was stirred at -78 °C for 1 h. Water (2 mL) was added and the solution was warmed to rt and was stirred for 30 min. Aqueous NH₄Cl - NH₄OH (pH 8-9, 2 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was flash chromatographed (2 g silica gel, 9:1 petroleum ether - diethyl ether) to afford 10 mg (90%) of the solid alcohol **142**, a single diastereomer (as indicated by ¹H nmr spectroscopic analysis). The alcohol **142** was recrystallized from petroleum ether - diethyl ether to provide a colourless crystalline solid, mp 53-55 °C.

IR (KBr): 3467, 3394, 1636, 1467, 1072, 896 cm⁻¹.

¹H nmr (400 MHz) δ : 1.14 (s, 3H, Me-14), 1.20-1.82 (m, 14H), 2.31-2.42 (m, 2H), 3.58-3.65

(m, 1H, H-12), 5.11 (br s, 1H, H-13), 5.28 (br s, 1H, H-13').

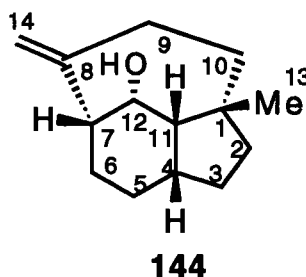
NOE difference experiments: irradiation of the signal at δ 1.14 (Me-14) caused an enhancement of the signal at δ 3.58-3.65 (H-12); irradiation of the signal at δ 3.58-3.65 (H-12) caused an enhancement of the signal at δ 1.14 (Me-14).

^{13}C nmr (75.3 MHz) δ : 23.9, 24.4, 24.8 (-ve, Me-14), 29.8, 30.9, 35.2, 39.2, 39.5, 47.2 (-ve, C-8), 53.0, 60.9, 73.2 (-ve, C-12), 111.7 (C-13), 154.6 (C-2).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1666.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.32, H 10.78.

3.4.4.3. Synthesis of (1*S**, 4*S**, 7*R**, 11*S**, 12*S**)-1-Methyl-8-methylenetricyclo-[5.3.2.0^{4,11}]dodecan-12-ol (**144**):



To a cold (-78 °C), stirred solution of the bridged tricyclic compound **140** (20 mg, 0.098 mmol, 1 equiv.) in dry THF (1 mL) was added a solution of DIBAL in hexanes (1 M, 171 μL , 0.171 mmol, 1.7 equiv.). The solution was stirred at -78 °C for 1.5 h. Water (4 mL) was added and the solution was warmed to rt and was stirred for 30 min. Aqueous NH_4Cl - NH_4OH (pH 8-9, 4 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was subjected to radial chromatography (1 mm plate, 9:1 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 65-70 °C/0.4 Torr) to provide 19 mg (93%) of the bridged alcohol **144**, a single diastereomer (as indicated by ^1H nmr spectroscopic analysis). The alcohol **144** subsequently solidified and was recrystallized from petroleum ether - diethyl ether to afford a translucent solid, mp 31-32 °C.

IR (KBr): 3468, 3420, 1630, 1457, 1259, 1067, 889 cm^{-1} .

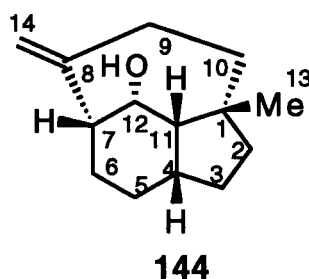
^1H nmr (400 MHz) δ : 1.14 (s, 3H, Me-13), 1.29-1.43 (m, 4H, H-2, H-4, H-5, and H-5'), 1.51-1.72 (m, 5H, four of which are -OH, H-6, H-10, and H-10'; this multiplet collapses to 4 protons upon the addition of D_2O), 1.79-1.87 (m, 2H, H-2' and H-6'), 2.01-2.14 (m, 2H, one of which is H-11), 2.35-2.40 (br dd, 1H, $J = 12.5, 6$ Hz, H-9), 2.45-2.51 (br dd, 1H, $J = 12.5, 12.5$ Hz, H-9'), 2.68 (br s, 1H, H-7), 3.99 (br s, 1H, H-12; this signal collapses to a dd ($J = 6, 6$ Hz) upon the addition of D_2O), 4.77 (br d, 1H, $J = 2.5$ Hz, H-14), 4.84 (br s, 1H, H-14').

Detailed ^1H nmr data, derived from a COSY experiment, are given in **Table 31**.

^{13}C nmr (75.3 MHz) δ : 24.1, 29.7, 30.7, 33.9, 35.7 (-ve), 38.2, 39.9, 41.3 (-ve), 42.6, 47.7 (-ve), 53.1 (-ve), 73.4 (-ve, C-12), 115.2 (C-14), 152.5 (C-8).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1670.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.25, H 10.58.

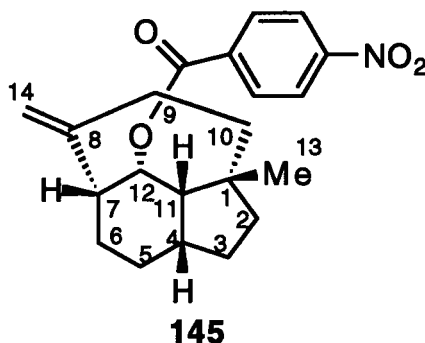
Table 31: ^1H nmr Data (400 MHz, CDCl_3) for the Bridged Alcohol **144**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
Me-13	1.14 (s)	
H-2	Part of the m at 1.29-1.43	H-2' ^b
H-4	Part of the m at 1.29-1.43	H-11
H-5	Part of the m at 1.29-1.43	H-6, H-6'
H-5'	Part of the m at 1.29-1.43	H-6, H-6'
H-6	Part of the m at 1.51-1.72	H-5, H-5', H-6', H-7
H-10	Part of the m at 1.51-1.72	H-9, H-9'
H-10'	Part of the m at 1.51-1.72	H-9, H-9'
-OH	Part of the m at 1.51-1.72; disappears upon the addition of D_2O	
H-2'	Part of the m at 1.79-1.87	H-2
H-6'	Part of the m at 1.79-1.87	H-5, H-5', H-6, H-7
H-11	Part of the m at 2.01-2.14	H-4, H-12
H-9	2.35-2.40 (br dd, $J = 12.5, 6$)	H-9', H-10, H-10', H-14'
H-9'	2.45-2.51 (br dd, $J = 12.5, 12.5$)	H-9, H-10, H-10', H-14, H-14'
H-7	2.68 (br s)	H-6, H-6', H-12
H-12	3.99 (br s); 3.99 (dd, $J = 6, 6$) upon the addition of D_2O	H-7, H-11
H-14	4.77 (br d, $J = 2.5$)	H-9', H-14'
H-14'	4.84 (br s)	H-9, H-9', H-14

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

3.4.4.4. Synthesis of (1*S**, 4*S**, 7*R**, 11*S**, 12*S**)-1-Methyl-8-methylene-12-*p*-nitrobenzoyloxy-tricyclo[5.3.2.0^{4,11}]dodecane (**145**):



To a stirred solution of the bridged alcohol **144** (14 mg, 0.068 mmol, 1 equiv.), dry *i*-Pr₂NEt (24 μL, 0.13 mmol, 2 equiv.), and DMAP (8 mg, 0.07 mmol, 1 equiv.) in dry THF (3.4 mL) at rt was added *p*-nitrobenzoyl chloride (62 mg, 0.33 mmol, 5 equiv.). The cloudy mixture was refluxed for 3 h; water (10 mL) and brine (10 mL) were added to the mixture and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) and the solid thus obtained was recrystallized from MeOH - H₂O to afford 22 mg (92%) of the ester **145**, as thin colourless plates, mp 86-87 °C. X-ray crystallographic analysis⁶⁶ of this material confirmed the constitution and relative configuration shown above.

IR (KBr): 3116, 1722, 1632, 1608, 1530, 1275, 1103, 720 cm⁻¹.

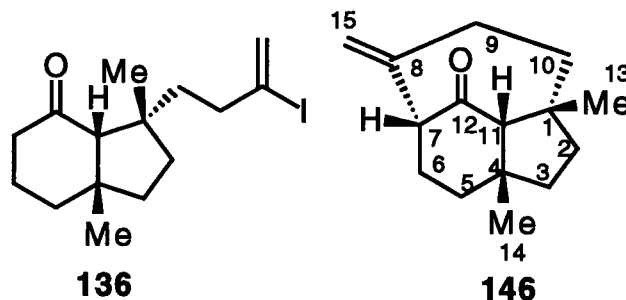
¹H nmr (400 MHz) δ: 1.06 (s, 3H, Me-13), 1.25 (br s, 1H), 1.35-1.50 (m, 3H), 1.60-1.66 (m, 1H), 1.72-1.92 (m, 5H), 2.24-2.30 (m, 2H), 2.47-2.52 (dd, 1H, *J* = 13, 7 Hz, H-9), 2.56-2.63 (dd, 1H, *J* = 13, 13 Hz, H-9'), 2.95-2.97 (m, 1H, H-7), 4.65 (br d, 1H, *J* = 2.5 Hz, H-14),

4.77 (br d, 1H, $J = 2.5$, H-14'), 5.42 (dd, 1H, $J = 5.5, 5.5$ Hz, H-12), 8.19-8.22 (br d, 2H, $J = 9$ Hz, aromatic protons), 8.29-2.31 (br d, 2H, $J = 9$ Hz, aromatic protons).

^{13}C nmr (75.3 MHz) δ : 24.3, 29.7, 29.8, 31.2, 34.0, 34.7 (-ve), 38.2, 39.3, 41.5 (-ve), 42.9, 44.0 (-ve), 50.5 (-ve), 78.1 (-ve, C-12), 114.2 (C-14), 123.6 (-ve), 130.6 (-ve), 151.6 (C-8).

Exact Mass calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_4$: 355.1783; found: 355.1777.

3.4.4.5. Synthesis of (1*R**, 4*S**, 7*R**, 11*S**)-1,4-Dimethyl-8-methylenetricyclo[5.3.2.0^{4,11}]-dodecan-12-one (**146**):



To a stirred solution of the cis-fused vinyl iodide **136** (43 mg, 0.12 mmol, 1 equiv.) in dry THF (2.5 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (36 mg, 0.031 mmol, 25 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.2 M, 4:1 THF : *t*-BuOH, 0.71 mL, 0.14 mmol, 1.15 equiv.) was added, via a syringe pump, over 4 h. The reaction mixture was stirred at rt for an additional 2 h and subjected to the workup conditions as described in general procedure 3. ¹H nmr spectroscopic analysis of the crude oil indicated that the sole cyclized product was the bridged compound **146** (i.e. no fused tricyclic compound was observed in the ¹H nmr spectrum of the crude oil). Flash chromatography (8 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude product and distillation (air-bath temperature 92-94 °C/0.15 Torr) of the oil thus obtained, provided 17 mg (63%) of the bridged tricyclic compound **146**, as a colourless oil.

IR (film): 1697, 1633, 1459, 1257, 894 cm⁻¹.

¹H nmr (400 MHz, C₆D₆) δ: 0.86 (s, 3H, Me-14), 0.97-1.00 (m, 1H, H-5), 1.01 (br s, 3H, Me-13), 1.12-1.38 (m, 4H, one of which is H-10), 1.40-1.55 (m, 3H, one of which is H-10'), 1.63-1.69 (m, 1H, H-6), 1.71-1.84 (m, 1H, H-6'), 2.06-2.12 (br dd, 1H, *J* = 15, 9.5 Hz, H-9), 2.16 (br s, 1H, H-11), 2.21-2.28 (br dd, 1H, *J* = 15, 10 Hz, H-9'), 3.28 (br s, 1H, H-7), 4.68 (br s, 1H, H-15), 4.78 (br d, 1H, *J* = 1 Hz, H-15').

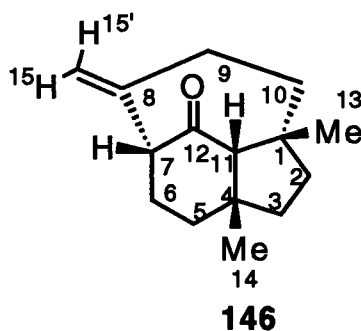
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 32**.

^{13}C nmr (75.3 MHz, C_6D_6) δ : 28.5 (-ve, Me), 30.9 (-ve, Me), 31.1, 32.0, 33.3, 38.9, 39.0, 40.1, 45.6, 47.2, 56.2 (-ve, C-11), 70.9 (-ve, C-7), 112.9 (C-15), 148.6 (C-8), 210.6 (C-12).

Exact Mass calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$: 218.1671; found: 218.1669.

Anal. calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$: C 82.52, H 10.16; found: C 82.30, H 10.19.

Table 32: ^1H nmr Data (400 MHz, C_6D_6) for the Bridged Compound **146**: COSY and NOE Experiments

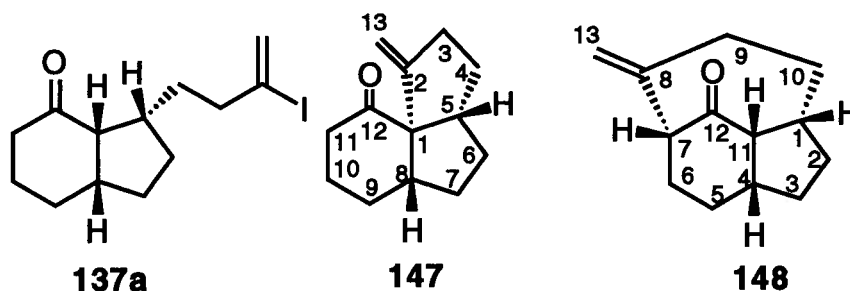


Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-14	0.86 (s)		H-6' ^b , H-11
H-5	0.97-1.00 (m)	H-6, H-6'	
Me-13	1.01 (br s)	H-10'	H-11
H-10	Part of the m at 1.12-1.38	H-9, H-9', H-10'	
H-10'	Part of the m at 1.40-1.55	H-9, H-9', H-10, Me-13	
H-6	1.63-1.69 (m)	H-5, H-6'	
H-6'	1.71-1.84 (m)	H-5, H-6	H-6, H-7, Me-14
H-9	2.06-2.12 (br dd, $J = 15$, 9.5)	H-9', H-10, H-10', H-15'	
H-11	2.16 (br s)	H-7	Me-13, Me-14
H-9'	2.21-2.28 (br dd, $J = 15$, 10)	H-9, H-10, H-10', H-15'	
H-7	3.28 (br s)	H-6, H-6', H-11, H-15	H-6', H-15
H-15	4.68 (br s)	H-7, H-15'	
H-15'	4.78 (br d, $J = 1$)	H-9, H-9', H-15	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-6' is more downfield than H-6).

3.4.4.6. Synthesis of (1*R**, 5*S**, 8*S**)-2-Methylenetricyclo[6.4.0.0^{1,5}]dodecan-12-one (**147**) and (1*S**, 4*R**, 7*R**, 11*S**)-8-Methylenetricyclo[5.3.2.0^{4,11}]dodecan-12-one (**148**):



a. Via a Pd(0)-Catalyzed Cyclization of the Cis-Fused Vinyl Iodide **137a**:

To a stirred solution of the cis-fused vinyl iodide **137a** (66 mg, 0.21 mmol, 1 equiv.) in dry THF (4.1 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (53 mg, 0.046 mmol, 22 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.1 M, 4:1 THF : *t*-BuOH, 2.4 mL, 0.24 mmol, 1.15 equiv.) was added, via a syringe pump, over 6 h. The mixture was stirred at rt for an additional 3 h and worked up as described in general procedure 3. Analysis (glc) of the crude oil indicated an 11:1 ratio of the fused to bridged cyclized products, **147** and **148**. Flash chromatography (8 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude oil provided two compounds. The first compound to be eluted was the fused tricyclic compound **147**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 84-88 °C/0.2 Torr) to afford 16 mg (41%) of the fused compound **147**, as a colourless oil.

IR (film): 3094, 1707, 1635, 1464, 1222, 894 cm⁻¹.

¹H nmr (400 MHz) δ: 1.20-1.43 (m, 2H), 1.52-1.56 (m, 1H, H-4), 1.61-2.11 (m, 8H, four of which are H-4', H-9, H-10, and H-10'), 2.27-2.33 (m, 1H, H-11), 2.39-2.48 (m, 2H, H-3 and H-3'), 2.74-2.83 (m, 2H, one of which is H-11'), 5.15 (br s, 1H, H-13), 5.26 (br s, 1H, H-13').

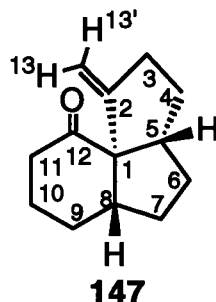
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 33**.

^{13}C nmr (75.3 MHz) δ : 23.2, 25.5, 29.7, 29.8, 31.2, 36.4, 37.1, 44.5 (-ve), 52.1 (-ve), 69.4 (C-1), 110.8 (C-13), 151.6 (C-2), 210.4 (C-12).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{18}\text{O}$: 190.1358; found: 190.1361.

Anal. calcd. for $\text{C}_{13}\text{H}_{18}\text{O}$: C 82.06, H 9.53; found: C 82.17, H 9.55.

Table 33: ^1H nmr Data (400 MHz, CDCl_3) for the Fused Tricyclic Compound **147**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
H-4	1.52-1.56 (m)	H-3, H-3' ^b , H-4'	
H-4'	~1.80-1.85 (m), part of the m at 1.61-2.11	H-3, H-3', H-4	
H-9	~1.85-1.88 (m), part of the m at 1.61-2.11	H-10, H-10'	
H-10	~1.61-1.75 (m), part of the m at 1.61-2.11	H-9, H-10', H-11, H-11'	
H-10'	~2.06-2.11 (m), part of the m at 1.61-2.11	H-9, H-10, H-11, H-11'	
H-11	2.27-2.33 (m)	H-10, H-10', H-11'	H-11'
H-3 and H-3'	2.39-2.48 (m)	H-4, H-4', H-13, H-13'	H-4, H-4', H-13'
H-11'	Part of the m at 2.74-2.83	H-10, H-10', H-11	H-11, H-13
H-13	5.15 (br s)	H-3, H-3', H-13'	H-9, H-11', H-13'
H-13'	5.26 (br s)	H-3, H-3', H-13	H-3 and H-3', H-13

a- Only those COSY correlations and NOE data that could be assigned are recorded.

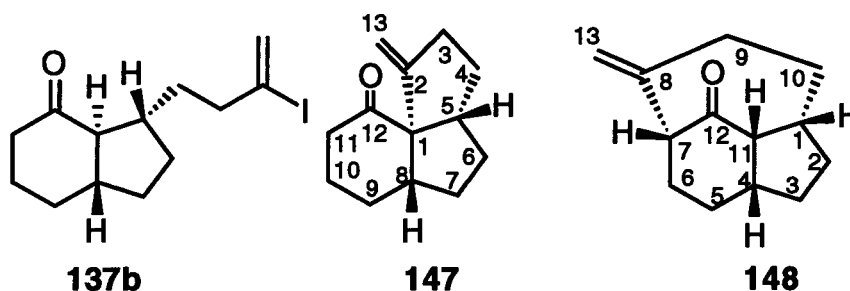
b- H' indicates the hydrogen of a pair which is more downfield (H-3' is more downfield than H-3).

The late fractions eluted from the above column chromatography were concentrated to provide, after removal of trace amounts of solvent (vacuum pump) from the resultant oil, 1.5 mg (4%) of the bridged compound **148**, as a colourless oil.

IR (film): 1710, 1632, 1447, 1276, 750 cm^{-1} .

^1H nmr (400 MHz) δ : 1.25-2.52 (m, 14H), 2.74-2.79 (dd, 1H, J = 8.5, 8.5 Hz, H-11), 3.29 (br s, 1H, H-7), 4.82-4.83 (dd, 1H, J = 1.5, 1.5 Hz, H-13), 4.94-4.95 (dd, 1H, J = 1.5, 1.5 Hz, H-13').

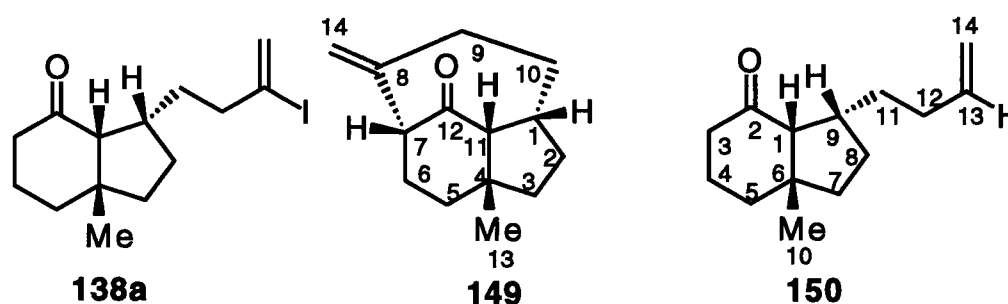
Exact Mass calcd. for $\text{C}_{13}\text{H}_{18}\text{O}$: 190.1358; found: 190.1353.



b. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide **137b:**

To a stirred solution of the trans-fused vinyl iodide **137b** (32 mg, 0.10 mmol, 1 equiv.) in dry THF (2 mL) at rt was added $\text{Pd}(\text{PPh}_3)_4$ ¹¹⁵ (34 mg, 0.029 mmol, 29 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.1 M, 4:1 THF : *t*-BuOH, 1.2 mL, 0.12 mmol, 1.15 equiv.) was added, via a syringe pump, over 5 h. The mixture was stirred at rt overnight and was worked up as described in general procedure 3. Analysis (glc) of the crude oil indicated an 8:1 ratio of the fused to bridged cyclized products, **147** and **148**. Flash chromatography (8 g silica gel, 9:1 petroleum ether - diethyl ether) of the crude oil yielded 9 mg (47%) of the fused tricyclic compound **147** followed by 1 mg (5%) of the bridged tricyclic compound **148** (the spectral data of compounds **147** and **148** are identical with those reported above).

3.4.4.7. Synthesis of (1*R**, 4*R**, 7*R**, 11*R**)-4-Methyl-8-methylenetricyclo[5.3.2.0^{4,11}]-dodecan-12-one (**149**) and (1*R**, 6*S**, 9*R**)-9-(3-Butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (**150**):



a. Via a Pd(0)-Catalyzed Cyclization of the Cis-Fused Vinyl Iodide **138a**:

To a stirred solution of the cis-fused vinyl iodide **138a** (39 mg, 0.12 mmol, 1 equiv.) in dry THF (2.3 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (38 mg, 0.033 mmol, 28 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.1 M, 4:1 THF : *t*-BuOH, 1.3 mL, 0.13 mmol, 1.15 equiv.) was added, via a syringe pump, over 6 h. The mixture was stirred at rt overnight and was subjected to the workup conditions as described in general procedure 3. Flash chromatography (8 g silica gel, 12.3:1 petroleum ether - diethyl ether) of the crude oil resulted in the isolation of two compounds, **149** and **150**. The first compound to be eluted was the uncyclized compound **150**. Concentration of the appropriate fractions provided, after removal of trace amounts of solvent (vacuum pump) from the resultant oil, 2 mg (8%) of the bicyclic compound **150**, as a colourless oil.

IR (film): 1698, 1641, 1456, 1232, 908 cm⁻¹.

¹H nmr (400 MHz) δ: 1.07 (s, 3H, Me-10), 1.27-1.31 (m, 1H), 1.41-1.69 (m, 6H), 1.81-1.96 (m, 4H), 2.04-2.13 (m, 2H), 2.34-2.43 (m, 3H), 4.90-4.93 (dddd, 1H, *J* = 10, 1.5, 1.5, 1.5 Hz, H-14), 4.94-5.00 (dddd, 1H, *J* = 17, 1.5, 1.5, 1.5 Hz, H-14'), 5.69-5.79 (dddd, 1H, *J* = 17, 10, 7, 7 Hz, H-13).

^{13}C nmr (75.3 MHz) δ : 21.3, 28.2 (-ve, Me-10), 31.0, 32.4, 33.0, 34.5, 40.5, 42.1, 42.3 (-ve), 45.4, 62.6 (-ve, C-1), 114.6 (C-14), 138.4 (-ve, C-13), 215.3 (C-2).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1672.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.43, H 10.83.

The second product to be eluted from the above column chromatography was the bridged tricyclic compound **149**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 98-102 °C/0.15 Torr) to afford 10 mg (41%) of the bridged compound **149**, as a colourless oil.

IR (film): 1699, 1632, 1459, 1257, 825 cm^{-1} .

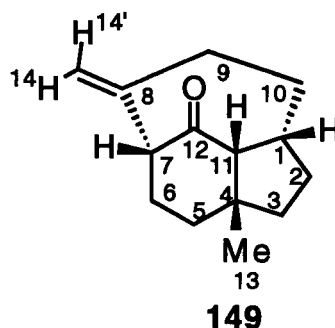
^1H nmr (400 MHz, C_6D_6) δ : 0.86 (s, 3H, Me-13), 0.93-0.98 (br dt, 1H, $J = 14.5, 4$ Hz, H-5), 1.12-1.19 (m, 1H), 1.24-1.68 (m, 7H, four of which are H-6, H-5', H-10', and H-10), 1.78-1.86 (m, 1H, H-6'), 1.97-2.03 (br dd, 1H, $J = 15, 9$ Hz, H-9), 2.22-2.34 (m, 2H, H-1 and H-9'), 2.49 (br d, 1H, $J = 10.5$ Hz, H-11), 3.31 (br s, 1H, H-7), 4.69 (br dd, 1H, $J = 1, 1$ Hz, H-14), 4.75 (br d, 1H, $J = 1$ Hz, H-14').

Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 34**.

^{13}C nmr (75.3 MHz, C_6D_6) δ : 27.3 (-ve, Me-13), 30.1, 31.1, 31.7, 31.8, 33.6, 40.6 (-ve), 41.1, 46.9, 56.9 (-ve), 63.9 (-ve), 113.4 (C-14), 148.1 (C-8), 211.1 (C-12).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.1514; found: 204.1517.

Table 34: ^1H nmr Data (400 MHz, C_6D_6) for the Bridged Compound **149**: COSY and NOE Experiments

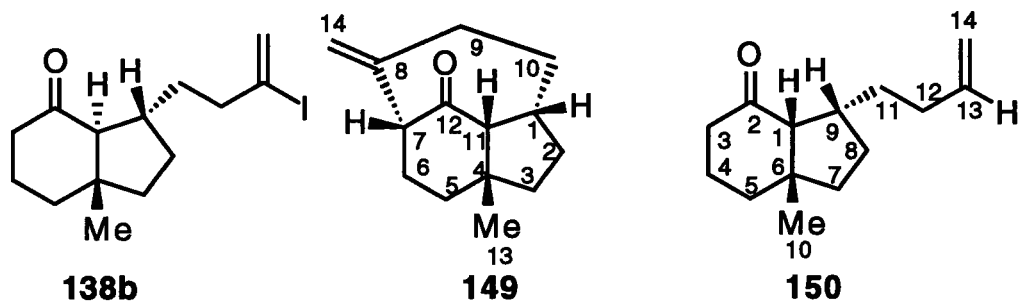


Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-13	0.86 (s)		H-6' ^b , H-11
H-5	0.93-0.98 (br dt, J = 14.5, 4)	H-5', H-6, H-6', H-11 ^c	
H-10	~1.24-1.32 (m), part of the m at 1.24-1.68	H-1, H-9, H-9'	
H-10'	~1.38-1.47 (m), part of the m at 1.24-1.68	H-1, H-9, H-9'	
H-5'	~1.50-1.58 (m), part of the m at 1.24-1.68	H-5, H-6'	
H-6	~1.60-1.68 (m), part of the m at 1.24-1.68	H-5, H-6', H-7	
H-6'	1.78-1.86 (m)	H-5, H-5', H-6, H-7	
H-9	1.97-2.03 (br dd, J = 15, 9)	H-9', H-10, H-10', H-14'	H-9', H-14'
H-1	Part of the m at 2.22-2.34	H-10, H-10', H-11	
H-9'	Part of the m at 2.22-2.34	H-9, H-10, H-10', H-14, H-14'	
H-11	2.49 (br d, J = 10.5)	H-1, H-5 ^c , H-7 ^c	H-1, Me-13
H-7	3.31 (br s)	H-6, H-6', H-11 ^c , H-14	H-6, H-6', H-14
H-14	4.69 (br dd, J = 1, 1)	H-7, H-9', H-14'	
H-14'	4.75 (br d, J = 1)	H-9, H-9', H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-6' is more downfield than H-6).

c- W coupling



b. Via a Pd(0)-Catalyzed Cyclization of the Trans-Fused Vinyl Iodide **138b**:

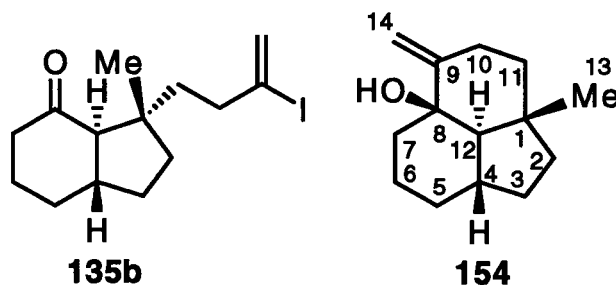
To a stirred solution of the trans-fused vinyl iodide **138b** (40 mg, 0.12 mmol, 1 equiv.) in dry THF (2.5 mL) at rt was added Pd(PPh₃)₄¹¹⁵ (39 mg, 0.034 mmol, 28 mol%). A solution of *t*-BuOK in dry THF and dry *t*-BuOH (0.1 M, 4:1 THF : *t*-BuOH, 1.4 mL, 0.14 mmol, 1.15 equiv.) was added, via a syringe pump, over 7 h. The mixture was stirred at rt overnight and was worked up as described in general procedure 3. Flash chromatography (8 g silica gel, 12.3:1 petroleum ether - diethyl ether) of the crude oil yielded 1 mg (4%) of the reduced bicyclic compound **150** followed by 9 mg (38%) of the bridged tricyclic compound **149** (the spectral data of compounds **149** and **150** are identical with those reported above).

3.5. SYNTHESIS OF TRICYCLIC COMPOUNDS BEARING AN ALLYLIC, ANGULAR HYDROXYL GROUP

3.5.1. GENERAL PROCEDURE 4: CYCLIZATION REACTIONS OF THE KETO VINYL IODIDES VIA A METAL-HALOGEN EXCHANGE REACTION¹¹⁹

To a cold (-78 °C), stirred solution of the appropriate vinyl iodide (1 equiv.) in dry THF (20 mL per mmol of vinyl iodide) was added a solution of *n*-butyllithium in hexanes (1.32 - 1.60 M, 2.5 equiv.). The resultant solution was stirred at -78 °C until the reaction reached completion, as determined by tlc analysis of an aliquot. Water (15 mL per mmol of the vinyl iodide) was added and the reaction mixture was warmed to rt. Diethyl ether (15 mL per mmol of the vinyl iodide) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x (100 mL per mmol of the vinyl iodide)) and ethyl acetate (2 x (100 mL per mmol of the vinyl iodide))). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude mixture was flash chromatographed and the product(s) thus obtained was (were) distilled or recrystallized to provide the corresponding cyclized product(s) bearing an allylic, angular hydroxyl group.

3.5.1.1. Synthesis of (1*S**, 4*S**, 8*R**, 12*R**)-1-Methyl-9-methylenetricyclo[6.3.1.0^{4,12}]-dodecan-8-ol (**154**):



Following general procedure 4, a solution of the trans-fused vinyl iodide **135b** (48 mg, 0.14 mmol, 1 equiv.) in dry THF (2.9 mL) was treated with a solution of *n*-butyllithium in hexanes (1.60 M, 0.23 mL, 0.36 mmol, 2.6 equiv.). The resultant solution was stirred at

-78 °C for 15 min. The crude product was flash chromatographed (8 g silica gel, 9:1 petroleum ether - diethyl ether) and the solid thus obtained was recrystallized from petroleum ether - diethyl ether to yield 28 mg (95%) of the tricyclic allylic alcohol **154**, a colourless crystalline solid, mp 65-68 °C.

IR (KBr): 3568, 3449, 3079, 1646, 1155, 1067, 904 cm^{-1} .

^1H nmr (400 MHz) δ : 0.78 (d, 1H, $J = 12.5$ Hz, H-12), 0.90-0.99 (m, 1H), 1.06 (s, 1H, -OH; this signal exchanges in the presence of D_2O), 1.08 (s, 3H, Me-13), 1.15-1.41 (m, 3H, one of which is H-11), 1.45-1.56 (m, 2H), 1.62-1.70 (m, 2H, one of which is H-7), 1.77-1.99 (m, 5H, three of which are H-7', H-4, and H-11'), 2.12-2.17 (ddd, 1H, $J = 14, 4, 2.5$ Hz, H-10), 2.69-2.78 (dddt, 1H, $J = 14, 14, 4.5, 2$ Hz, H-10'), 4.80 (dd, 1H, $J = 2, 2$ Hz, H-14), 4.86 (dd, 1H, $J = 2, 2$ Hz, H-14').

Detailed ^1H nmr data (CDCl_3), derived from a COSY experiment, are given in **Table 35**.

^1H nmr (400 MHz, pyridine- d_5) δ : 0.73 (d, 1H, $J = 13$ Hz, H-12), 0.89-0.98 (m, 1H), 1.13-1.28 (m, 1H), 1.32 (s, 3H, Me-13), 1.33-1.50 (m, 3H, one of which is H-11), 1.51-1.54 (m, 1H, H-7), 1.63-1.68 (m, 1H, H-7'), 1.81-2.04 (m, 5H, one of which is H-11'), 2.15-2.20 (ddd, 1H, $J = 14, 3, 3$ Hz, H-10), 2.20-2.30 (m, 1H, H-4), 2.96-3.03 (dddt, 1H, $J = 14, 14, 2, 2$ Hz, H-10'), 4.85-4.86 (dd, 1H, $J = 2, 2$ Hz, H-14), 4.92-4.93 (dd, 1H, $J = 2, 2$ Hz, H-14').

Detailed ^1H nmr data (pyridine- d_5), derived from a COSY experiment, are given in **Table 36**.

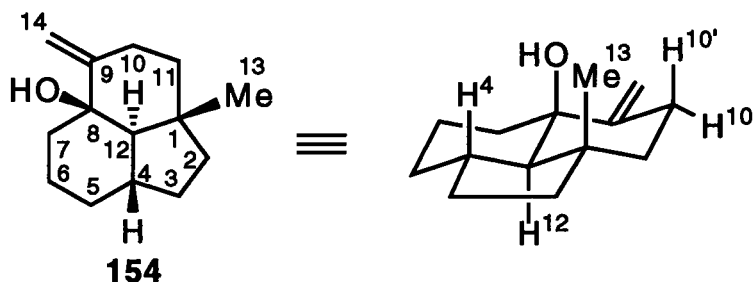
^1H nmr data comparing the chemical shifts in CDCl_3 versus those in pyridine- d_5 are given in **Table 37**.

^{13}C nmr (75.3 MHz) δ : 20.1 (-ve, Me-13), 22.6, 27.8, 30.0, 33.3, 33.8 (-ve), 36.2, 39.4, 40.0, 41.0, 59.7 (-ve, C-12), 72.7 (C-8), 107.4 (C-14), 153.8 (C-9).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1670.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.40, H 10.85.

Table 35: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **154**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-12	0.78 (d, $J = 12.5$)	H-4
-OH	1.06 (s)	
Me-13	1.08 (s)	
H-11	Part of the m at 1.15-1.41	H-10, H-10' ^b , H-11'
H-7	Part of the m at 1.62-1.70	H-7'
H-11'	~1.77-1.84 (m), part of the m at 1.77-1.99	H-10, H-10', H-11
H-4	~1.86-1.92 (m), part of the m at 1.77-1.99	H-12
H-7'	~1.93-1.99 (m), part of the m at 1.77-1.99	H-7
H-10	2.12-2.17 (ddd, $J = 14, 4, 2.5$)	H-10', H-11, H-11'
H-10'	2.69-2.78 (dddt, $J = 14, 14, 4.5, 2$)	H-10, H-11, H-11', H-14, H-14'
H-14	4.80 (dd, $J = 2, 2$)	H-10', H-14'
H-14'	4.86 (dd, $J = 2, 2$)	H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

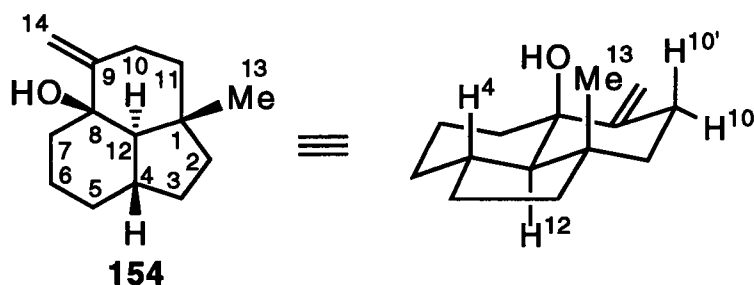
Table 36: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **154**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-12	0.73 (d, $J = 13$)	H-4
Me-13	1.32 (s)	
H-11	Part of the m at 1.33-1.50	H-10, H-10' ^b , H-11'
H-7	1.51-1.54 (m)	H-7'
H-7'	1.63-1.68 (m)	H-7
H-11'	~1.81-1.85 (m), part of the m at 1.81-2.04	H-10, H-10', H-11
H-10	2.15-2.20 (ddd, $J = 14, 3, 3$)	H-10', H-11, H-11'
H-4	2.20-2.30 (m)	H-12
H-10'	2.96-3.03 (dddt, $J = 14, 14, 2, 2$)	H-10, H-11, H-11', H-14, H-14'
H-14	4.85-4.86 (dd, $J = 2, 2$)	H-10', H-14'
H-14'	4.92-4.93 (dd, $J = 2, 2$)	H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 37: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **154** in CDCl_3 vs. Pyridine- d_5



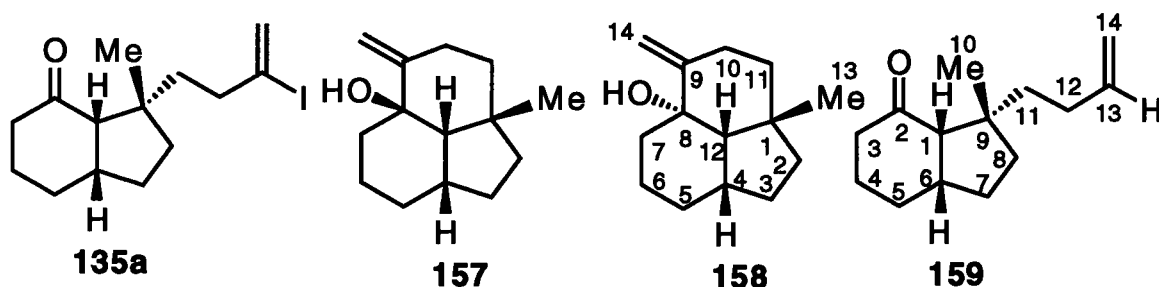
H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-4	~1.86-1.92	2.20-2.30	0.36
H-7	~1.62-1.70	1.51-1.54	-0.14
H-7' ^c	~1.93-1.99	1.63-1.68	-0.31
H-10	2.12-2.17	2.15-2.20	0.03
H-10'	2.69-2.78	2.96-3.03	0.26
H-11	~1.20-1.41	~1.33-1.50	0.11
H-11'	~1.76-1.84	~1.81-1.85	0.03
H-12	0.78	0.73	-0.03
Me-13	1.08	1.32	0.24
H-14	4.80	4.85-4.86	0.05
H-14'	4.86	4.92-4.93	0.06

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.20-2.30)/2 - (1.86+1.92)/2] = 0.36$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-7' is more downfield than H-7).

3.5.1.2. Synthesis of (1*S**, 4*S**, 8*R**, 12*S**)-1-Methyl-9-methylenetricyclo[6.3.1.0^{4,12}]-dodecan-8-ol (**157**), (1*S**, 4*S**, 8*S**, 12*S**)-1-Methyl-9-methylenetricyclo[6.3.1.0^{4,12}]-dodecan-8-ol (**158**), and (1*S**, 6*S**, 9*R**)-9-(3-Butenyl)-9-methylbicyclo[4.3.0]nonan-2-one (**159**):



Following general procedure 4, a solution of the cis-fused vinyl iodide **135a** (107 mg, 0.322 mmol, 1 equiv.) in dry THF (6.5 mL) was treated with a solution of *n*-butyllithium in hexanes (1.58 M, 0.51 mL, 0.81 mmol, 2.5 equiv.). The resultant solution was stirred at -78 °C for 3 h. The crude product mixture was subjected to radial chromatography (1 mm plate, 9:1 petroleum ether - diethyl ether) to give three fractions. The first compound to be eluted was the tricyclic compound **158**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 75-80 °C/0.08 Torr) to afford 34 mg (51%) of the tricyclic compound **158**, as a colourless oil.

IR (film): 3600, 3494, 3079, 1639, 1153, 1066, 896 cm⁻¹.

¹H nmr (400 MHz) δ: 0.71 (s, 1H, -OH; this signal exchanges in the presence of D₂O), 0.99 (s, 3H, Me-13), 1.14 (d, 1H, *J* = 7 Hz, H-12), 1.34-1.94 (m, 11H, one of which is H-11), 2.00-2.07 (ddd, 1H, *J* = 12.5, 12.5, 4.5 Hz, H-11'), 2.26-2.43 (m, 3H, H-10', H-4, and H-10), 4.71-4.72 (m, 1H, H-14), 4.89 (br d, 1H, *J* = 1 Hz, H-14').

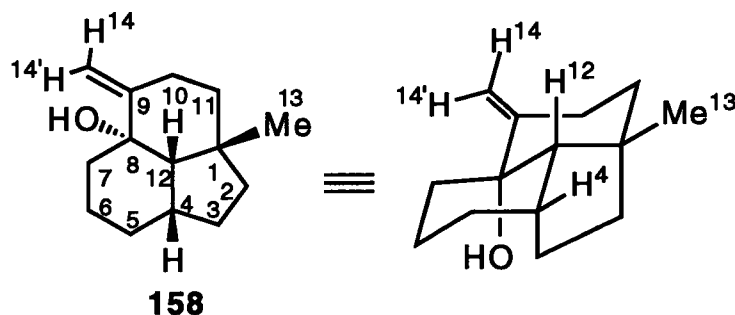
Detailed ¹H nmr data (CDCl₃), derived from COSY and NOE experiments, are given in Table 38.

^{13}C nmr (75.3 MHz) δ : 17.2, 26.1, 28.4, 30.2, 30.4 (-ve), 34.4, 35.8, 36.4 (-ve), 41.0, 41.6, 52.7 (-ve, C-12), 71.9 (C-8), 105.2 (C-14), 154.2 (C-9).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1669.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.50, H 10.78.

Table 38: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **158**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-OH	0.71 (s)		
Me-13	0.99 (s)		H-4, H-11, H-12
H-12	1.14 (d, $J = 7$)	H-4	H-4
H-11	~1.42-1.50 (m), part of the m at 1.34-1.94	H-10, H-10' ^b , H-11'	
H-11'	2.00-2.07 (ddd, $J = 12.5$, 12.5, 4.5)	H-10, H-10', H-11	H-11
H-10	~2.26-2.31 (m), part of the m at 2.26-2.43	H-10', H-11, H-11', H-14, H-14'	
H-4	~2.31-2.38 (m), part of the m at 2.26-2.43	H-12	
H-10'	~2.38-2.43 (m), part of the m at 2.26-2.43	H-10, H-11, H-11', H-14, H-14'	
H-14	4.71-4.72 (m)	H-10, H-10', H-14'	H-10', H-14'
H-14'	4.89 (br d, $J = 1$)	H-10, H-10', H-14	H-14

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

The second compound to be eluted was the bicyclic compound **159**. Concentration of the appropriate fractions and removal of trace amounts of solvent (vacuum pump) from the resultant oil, yielded 5.5 mg (8%) of the compound **159**, as a colourless oil.

IR (film): 3076, 1694, 1641, 1459, 1177, 908 cm^{-1} .

^1H nmr (400 MHz) δ : 1.14 (s, 3H, Me-10), 1.22-1.50 (m, 4H), 1.51-1.67 (m, 2H), 1.74-2.13 (m, 7H), 2.34 (d, 1H, $J = 9.5$ Hz, H-1), 2.40-2.47 (m, 2H), 4.90-4.92 (br d, 1H, $J = 10$ Hz, H-14), 4.95-5.00 (dddd, 1H, $J = 17, 2, 2, 2$ Hz, H-14'), 5.72-5.82 (dddd, 1H, $J = 17, 10, 6.5, 6.5$ Hz, H-13).

^{13}C nmr (100.4 MHz) δ : 23.5, 27.0 (-ve, Me-10), 29.2, 30.3, 30.9, 36.9, 37.4, 40.6 (-ve), 42.5, 47.1, 62.1 (-ve, C-1), 114.1 (C-14), 139.1 (-ve, C-13), 214.7 (C-2).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1662.

The last compound to be eluted was the tricyclic compound **157**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 90-95 $^{\circ}\text{C}/0.3$ Torr) to provide 16 mg (24%) of the compound **157**, as a colourless oil.

IR (film): 3472, 3387, 3087, 1642, 1470, 1103, 982 cm^{-1} .

^1H nmr (400 MHz) δ : 1.01 (s, 3H, Me-13), 1.12-1.25 (m, 2H), 1.40-1.78 (m, 12H, three of which are H-11', H-11, and H-12), 2.24-2.26 (m, 1H, H-4), 2.43-2.48 (m, 1H, H-10), 2.50-2.54 (m, 1H, H-10'), 4.81-4.82 (m, 1H, H-14), 5.10 (br d, 1H, $J = 1$ Hz, H-14').

Detailed ^1H nmr data (CDCl_3), derived from a COSY experiment, are given in **Table 39**.

^1H nmr (400 MHz, pyridine- d_5) δ : 1.04 (s, 3H, Me-13), 1.09-1.20 (dq, 1H, $J = 4, 13$ Hz), 1.31-1.81 (m, 11H, three of which are H-12 (d, $J = 7$ Hz), H-11', and H-11), 1.90-1.94 (m, 1H), 2.38-2.43 (m, 1H, H-4), 2.43-2.51 (m, 1H, H-10), 2.56-2.62 (m, 1H, H-10'), 4.95 (br d, 1H, $J = 1.5$ Hz, H-14), 5.58 (br s, 1H, H-14').

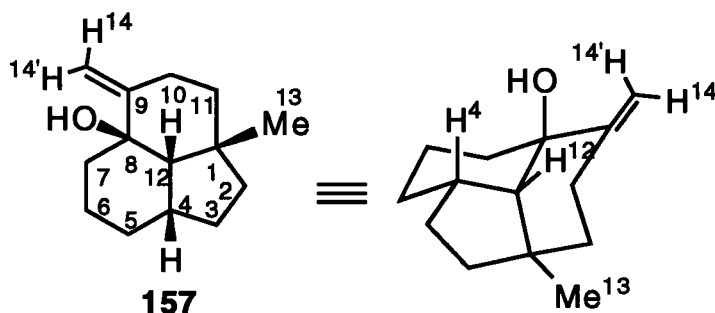
Detailed ^1H nmr data (pyridine- d_5), derived from a COSY experiment, are given in **Table 40**.

^1H nmr data comparing the chemical shifts in CDCl_3 versus those in pyridine- d_5 are given in **Table 41**.

^{13}C nmr (75.3 MHz) δ : 20.3, 27.2, 27.6, 30.4 (-ve, Me-13), 35.1, 35.4, 38.8 (-ve), 40.4, 40.8, 57.6 (-ve, C-12), 74.0 (C-8), 106.4 (C-14), 152.6 (C-9).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1666.

Table 39: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **157**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
Me-13	1.01 (s)	
H-12	1.41 (d, $J = 7$), part of the m at 1.37-1.78	H-4
H-11	~1.54-1.58 (m), part of the m at 1.37-1.78	H-10, H-10' ^b , H-11'
H-11'	~1.61-1.64 (m), part of the m at 1.37-1.78	H-10, H-10', H-11
H-4	2.24-2.26 (m)	H-12
H-10	2.43-2.48 (m)	H-10', H-11, H-11', H-14, H-14'
H-10'	2.50-2.54 (m)	H-10, H-11, H-11', H-14, H-14'
H-14	4.81-4.82 (m)	H-10, H-10', H-14'
H-14'	5.10 (br d, $J = 1$)	H-10, H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

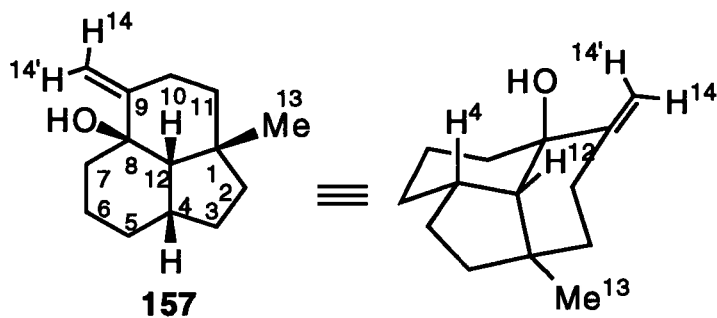
Table 40: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **157**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
Me-13	1.04 (s)	
H-11	~1.55-1.60 (m), part of the m at 1.31-1.81	H-10, H-10' ^b , H-11'
H-11'	~1.65-1.71 (m), part of the m at 1.31-1.81	H-10, H-10', H-11
H-12	1.78 (d, $J = 7$)	H-4
H-4	2.38-2.43 (m)	H-12
H-10	2.43-2.51 (m)	H-10', H-11, H-11', H-14, H-14'
H-10'	2.56-2.62 (m)	H-10, H-11, H-11', H-14, H-14'
H-14	4.95 (br d, $J = 1.5$)	H-10, H-10', H-14'
H-14'	5.58 (br s)	H-10, H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 41: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **157** in CDCl_3 vs. Pyridine- d_5



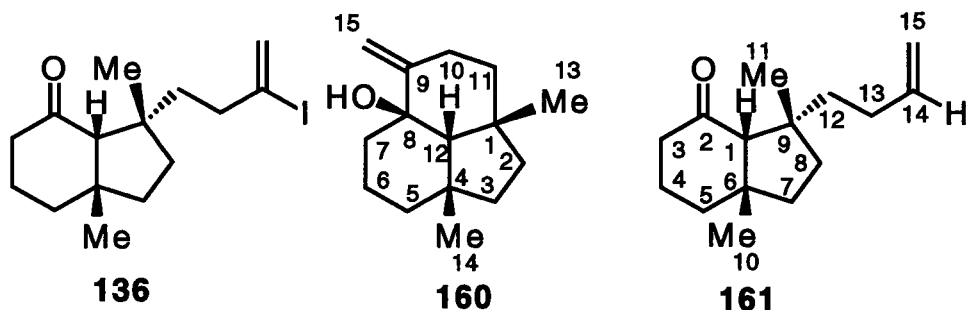
H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-4	2.24-2.26	2.38-2.43	0.16
H-10	2.43-2.48	2.43-2.51	0.02
H-10' ^c	2.50-2.54	2.56-2.62	0.07
H-11	~1.54-1.58	~1.55-1.60	0.02
H-11'	~1.61-1.64	~1.65-1.71	0.06
H-12	1.41	1.78	0.37
Me-13	1.01	1.04	0.03
H-14	4.81-4.82	4.95	0.14
H-14'	5.10	5.58	0.48

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.38+2.42)/2 - (2.24+2.26)/2] = 0.15$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

3.5.1.3. Synthesis of (1*S**, 4*S**, 8*R**, 12*S**)-1,4-Dimethyl-9-methylenetricyclo-[6.3.1.0^{4,12}]dodecan-8-ol (**160**) and (1*S**, 6*S**, 9*R**)-9-(3-Butenyl)-6,9-dimethylbicyclo-[4.3.0]nonan-2-one (**161**):



Following general procedure 4, a solution of the cis-fused vinyl iodide **136** (79 mg, 0.23 mmol, 1 equiv.) in dry THF (4.6 mL) was treated with a solution of *n*-butyllithium in hexanes (1.55 M, 0.37 mL, 0.57 mmol, 2.5 equiv.). The resultant solution was stirred at -78 °C for 1 h. The crude product mixture was subjected to radial chromatography (1 mm plate, 9:1 petroleum ether - diethyl ether) to provide two fractions. The first compound to be eluted was the bicyclic compound **161**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 92-94 °C/0.15 Torr) to afford 18 mg (35%) of the bicyclic compound **161**, as a colourless oil.

IR (film): 3077, 1693, 1641, 1460, 908 cm⁻¹.

¹H nmr (400 MHz) δ: 1.07 (s, 3H, Me), 1.14 (s, 3H, Me), 1.24-1.32 (m, 1H), 1.38-1.72 (m, 8H), 1.75-2.01 (m, 3H), 2.03 (br s, 1H, H-1), 2.09-2.16 (m, 1H), 2.36-2.41 (br d, 1H, *J* = 16.5 Hz), 4.90-4.92 (br d, 1H, *J* = 10 Hz, H-15), 4.95-5.00 (br dd, 1H, *J* = 17, 2 Hz, H-15'), 5.72-5.82 (dddd, 1H, *J* = 17, 10, 6.5, 6.5 Hz, H-14).

¹³C nmr (75.3 MHz) δ: 21.0, 28.0 (-ve, Me), 29.2 (-ve, Me), 29.4, 35.6, 37.3, 37.4, 40.2, 42.1, 44.5, 48.1, 71.0 (-ve, C-1), 114.2 (C-15), 139.1 (-ve, C-14), 214.8 (C-2).

Exact Mass calcd. for C₁₅H₂₄O: 220.1827; found: 220.1822.

Anal. calcd. for C₁₅H₂₄O: C 81.76, H 10.98; found: C 81.51, H 11.01.

The second compound to be eluted was the tricyclic compound **160**. Concentration of the appropriate fractions and distillation (air-bath temperature 90-94 °C/0.4 Torr) of the oil thus obtained, provided 33 mg (65%) of the compound **160**, as a colourless oil.

IR (KBr): 3446, 1644, 1451, 1129, 899 cm⁻¹.

¹H (400 MHz) δ: 1.01 (s, 3H, Me), 1.05 (s, 1H, H-12), 1.10 (br s, 1H, -OH; this signal exchanges in the presence of D₂O), 1.20 (s, 3H, Me), 1.21-1.26 (m, 1H), 1.38-1.60 (m, 8H, one of which is H-11), 1.69-1.89 (m, 3H, one of which is H-11'), 2.37-2.45 (m, 1H, H-10), 2.47-2.56 (m, 1H, H-10'), 4.79-4.81 (m, 1H, H-15), 5.09 (br s, 1H, H-15').

Detailed ¹H nmr data (CDCl₃), derived from a COSY experiment, are given in **Table 42**.

¹H nmr (400 MHz, pyridine-d₅) δ: 1.03 (s, 3H, Me-13), 1.21-1.25 (m, 1H, H-7), 1.31-1.57 (m, 8H, four of which are H-6, H-7', H-11, and H-12), 1.39 (s, 3H, Me-14), 1.65-1.79 (m, 3H, two of which are H-5 and H-11'), 2.07-2.14 (m, 1H, H-6'), 2.43-2.48 (m, 1H, H-10), 2.52-2.61 (m, 1H, H-10'), 4.95 (br d, 1H, *J* = 1.5 Hz, H-15), 5.58 (br s, 1H, H-15').

Detailed ¹H nmr data (pyridine-d₅), derived from COSY and NOE experiments, are given in **Table 43**.

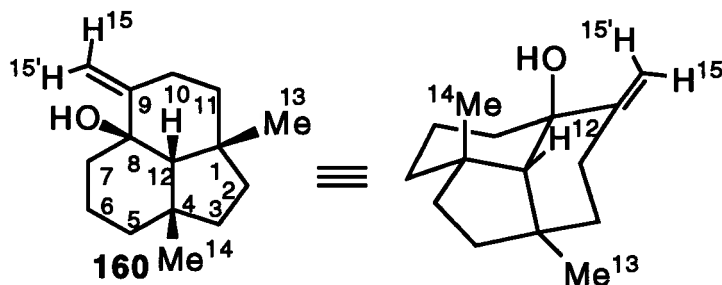
¹H nmr data comparing the chemical shifts in CDCl₃ versus those in pyridine-d₅ are given in **Table 44**.

Detailed ^{13}C nmr data (CDCl_3), derived from HMQC and HMBC experiments, are given in **Table 45**.

Detailed ^{13}C nmr data (pyridine- d_5), derived from HMQC and HMBC experiments, are given in **Table 46**.

Exact Mass calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: 220.1827; found: 220.1822.

Anal. calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: C 81.76, H 10.98; found: C 81.46, H 11.05.

Table 42: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **160**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
Me-13	1.01 (s)	
H-12	1.05 (s)	
-OH	1.10 (br s)	
Me-14	1.20 (s)	
H-11	~1.48-1.52 (m), part of the m at 1.38-1.60	H-10, H-10' ^b , H-11'
H-11'	~1.69-1.75 (m), part of the m at 1.69-1.89	H-10, H-10', H-11
H-10	2.37-2.45 (m)	H-10', H-11, H-11', H-15, H-15'
H-10'	2.47-2.56 (m)	H-10, H-11, H-11', H-15, H-15'
H-15	4.79-4.81 (m)	H-10, H-10', H-15'
H-15'	5.09 (br s)	H-10, H-10', H-15

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

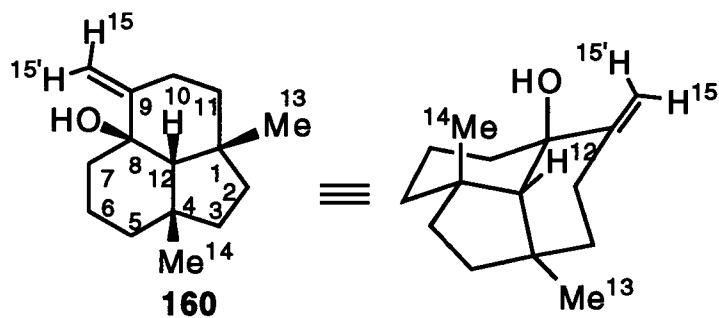
Table 43: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **160**: COSY and NOE Experiments

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-13	1.03 (s)		H-12
H-7	1.21-1.25 (m)	H-6, H-6' ^b , H-7'	H-6'
H-6	Part of the m at 1.31-1.57	H-5, H-6', H-7	
H-7'	Part of the m at 1.31-1.57	H-6', H-7	
H-11	Part of the m at 1.31-1.57	H-10, H-10', H-11'	
H-12	Part of the m at 1.31-1.57		
Me-14	1.39 (s)		
H-5	Part of the m at 1.65-1.79	H-6, H-6'	
H-11'	Part of the m at 1.65-1.79	H-10, H-10', H-11	
H-6'	2.07-2.14 (m)	H-5, H-6, H-7, H-7'	H-5, H-6
H-10	2.43-2.48 (m)	H-10', H-11, H-11', H-15, H-15'	
H-10'	2.52-2.61 (m)	H-10, H-11, H-11', H-15, H-15'	H-10, H-11, H-11', Me-13, H-15
H-15	4.95 (br d, $J = 1.5$)	H-10, H-10', H-15'	
H-15'	5.58 (br s)	H-10, H-10', H-15	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-6' is more downfield than H-6).

Table 44: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **160** in CDCl_3 vs. Pyridine- d_5



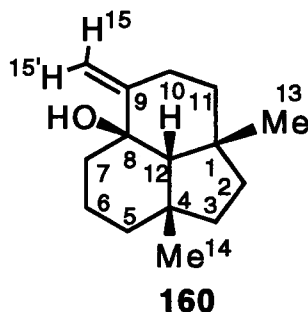
H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-10	2.37-2.45	2.43-2.48	0.04
H-10' ^c	2.47-2.56	2.52-2.61	0.05
H-11	~1.48-1.52	Part of m at 1.31-1.57	~ -0.06
H-11'	~1.69-1.75	Part of m at 1.65-1.79	~0.00
H-12	1.05	Part of m at 1.31-1.57	~ -0.39
Me-13	1.01	1.03	0.02
Me-14	1.20	1.39	0.19
H-15	4.79-4.81	4.95	0.15
H-15'	5.09	5.58	0.49

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.43+2.48)/2 - (2.37+2.45)/2] = 0.04$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 45: ^1H nmr (500 MHz, CDCl_3) and ^{13}C nmr (100.4 MHz, CDCl_3) Data for the Tricyclic Compound **160**: HMQC and HMBC Experiments



Assignment C-x ^a	^{13}C nmr (100.4 MHz) δ ppm, APT ^b	HMQC ^{c,d} ^1H nmr Correlations (500 MHz) δ ppm (assignment)	^1H - ^{13}C HMBC ^{c,d} Long-range Correlations H-x
	17.6		
C-10	27.5	H-10 (2.37-2.45); H-10' ^e (2.47-2.56)	H-15 (3 bond), H-15' (3 bond)
Me-14	28.7 (-ve)	Me-14 (1.20)	
Me-13	31.1 (-ve)	Me-13 (1.01)	
	32.4		
	34.9		
C-11	35.0	H-11 (1.48-1.52); H-11' (1.69- 1.75)	
	39.8		
	40.1		
C-1 and C-4	42.3 and 42.4		H-10 (3 bond) ^f , H-11 (2 bond) ^f , H-11' (2 bond) ^f , Me- 13 (2 bond) ^f , Me-14 (2 bond) ^g
C-12	63.3 (-ve)	H-12 (1.05)	
C-8	74.7		H-15 (3 bond), H-15' (3 bond)
C-15	106.4	H-15 (4.79-4.81); H-15' (5.09)	
C-9	153.2		

a- Only those assignments which could be assigned are recorded.

b- The results of the APT experiment are given in parentheses (-ve for CH and CH_3 carbon signals).

c- The assignment and the chemical shifts of the ^{13}C nmr spectrum are listed in the first and second columns, respectively. The third column shows the ^1H nmr signal(s) which correlate(s) with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate(s) with the ^{13}C nmr signal of the first two columns as obtained from HMBC experiments (2, 3, and 4 bond correlations).

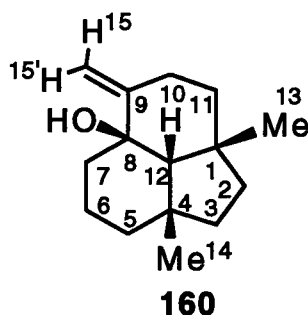
d- Only those HMQC and HMBC data that could be assigned are recorded.

e- H' indicates the hydrogen of a pair which is more downfield (H-7' is more downfield than H-7).

f- This long range correlation corresponds to C-1.

g- This long range correlation corresponds to C-4.

Table 46: ^1H nmr (500 MHz, pyridine- d_5) and ^{13}C nmr (125.8 MHz, pyridine- d_5) Data for the Tricyclic Compound **160**: HMQC and HMBC Experiments



Assignment C-x	^{13}C nmr (125.8 MHz) δ ppm	HMQC ^{a,b} ^1H nmr Correlations (500 MHz) δ ppm (assignment)	^1H - ^{13}C HMBC ^{a,b} Long-range Correlations H-x
C-6	18.2		
C-10	28.0		Me-13 (4 bond)
Me-14	29.2	Me-14 (1.39)	H-6 (4 bond)
Me-13	30.0	Me-13 (1.03)	H-11 (3 bond), H-11' ^c (3 bond)
C-7	31.4	H-7 (1.21-1.25); H-7' (1.31-1.57)	
C-5	33.1	H-5 (1.65-1.79)	
C-11	35.4	H-11 (1.31-1.57); H-11' (1.65-1.79)	Me-13 (3 bond)
C-2 or C-3	40.2		Me-13 (3 or 4 bond) ^d ; Me-14 (3 or 4 bond) ^d
C-2 or C-3	40.6		" " "
C-1 or C-4	42.4		
C-1 or C-4	42.7		
C-12	62.7	H-12 (1.31-1.57)	Me-13 (3 bond); Me-14 (3 bond)
C-8	74.1		
C-15	107.0	H-15 (4.95); H-15' (5.58)	H-10 (3 bond); H-10' (3 bond)
C-9	154.8		H-10 (2 bond); H-10' (2 bond)

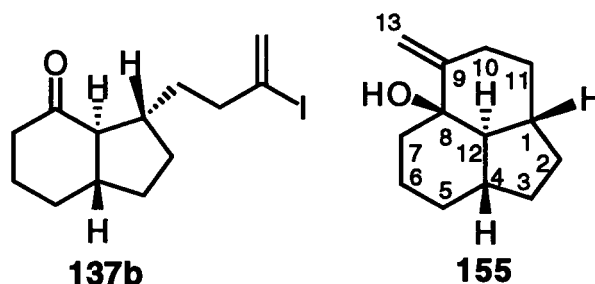
a- The assignment and the chemical shifts of the ^{13}C nmr spectrum are listed in the first and second columns, respectively. The third column shows the ^1H nmr signal(s) which correlate(s) with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate(s) with the ^{13}C nmr signal of the first two columns as obtained from HMBC experiments (2, 3, and 4 bond correlations).

b- Only those HMQC and HMBC data that could be assigned are recorded.

c- H' indicates the hydrogen of a pair which is more downfield (H-11' is more downfield than H-11).

d- These correlations correspond to either C-2 or C-3.

3.5.1.4. Synthesis of (1*S**, 4*S**, 8*R**, 12*R**)-9-Methylenetricyclo[6.3.1.0^{4,12}]dodecan-8-ol (**155**):



Following general procedure 4, a solution of the trans-fused vinyl iodide **137b** (35 mg, 0.11 mmol, 1 equiv.) in dry THF (2.2 mL) was treated with a solution of *n*-butyllithium in hexanes (1.32 M, 0.21 mL, 0.28 mmol, 2.5 equiv.). The resultant solution was stirred at -78 °C for 1 h. The crude product mixture was subjected to radial chromatography (1 mm plate, 1:1 CH₂Cl₂ - petroleum ether) and the solid thus obtained was recrystallized from petroleum ether - diethyl ether to afford 18 mg (83%) of the tricyclic compound **155**, a colourless crystalline solid, mp 35-37 °C.

IR (KBr): 3436, 3078, 1646, 1454, 1161, 1063, 902 cm⁻¹.

¹H nmr (400 MHz) δ: 0.58-0.64 (dd, 1H, *J* = 12, 12 Hz, H-12), 0.85-1.25 (m, 5H, two of which are H-4 and H-11), 1.46-2.00 (m, 10H, two of which are H-1 and H-11'), 2.18-2.23 (br ddd, 1H, *J* = 14, 4, 2.5 Hz, H-10), 2.47-2.55 (br ddd, *J* = 14, 14, 5 Hz, H-10'), 4.77 (br dd, 1H, *J* = 1.5, 1.5 Hz, H-13), 4.82-4.83 (dd, 1H, *J* = 1.5, 1.5 Hz, H-13').

Detailed ¹H nmr data (CDCl₃), derived from a COSY experiment, are given in **Table 47**.

¹H nmr (400 MHz, pyridine-*d*₅) δ: 0.54-0.60 (dd, 1H, *J* = 12, 12 Hz, H-12), 0.88-0.98 (dq, 1H, *J* = 3.5, 12 Hz), 1.04-1.20 (m, 2H, one of which is H-11), 1.47-1.56 (dt, 1H, *J* = 3.5, 13

Hz), 1.65-2.11 (m, 10H, three of which are H-1, H-4, and H-11'), 2.20-2.25 (ddd, 1H, $J = 13.5, 4, 2.5$ Hz, H-10), 2.81-2.89 (br ddd, 1H, $J = 13.5, 13.5, 5$ Hz, H-10'), 4.81-4.82 (m, 1H, H-13), 4.89 (br d, 1H, $J = 1.5$ Hz, H-13').

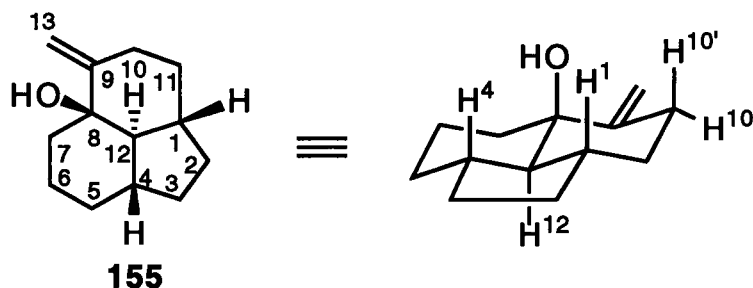
Detailed ^1H nmr data (pyridine- d_5), derived from a COSY experiment, are given in **Table 48**.

^1H nmr data comparing the chemical shifts in CDCl_3 versus those in pyridine- d_5 are given in **Table 49**.

^{13}C nmr (75.3 MHz) δ : 22.6, 28.3, 29.6, 32.2, 32.7, 33.5, 34.3, 37.1 (-ve, C-1 or C-4), 37.2 (-ve, C-1 or C-4), 59.5 (-ve, C-12), 71.7 (C-8), 107.0 (C-13), 153.3 (C-9).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: 192.1514; found: 192.1510.

Table 47: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **155**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-12	0.58-0.64 (dd, $J = 12, 12$)	H-1, H-4
H-11	~1.05-1.10 (m), part of the m at 0.85-1.25	H-10, H-10' ^b , H-11
H-4	~1.10-1.14 (m), part of the m at 0.85-1.25	H-12
H-1	~1.65-1.72 (m), part of the m at 1.46-2.00	H-11, H-11', H-12
H-11'	~1.93-2.00 (m), part of the m at 1.46-2.00	H-10, H-10', H-11
H-10	2.18-2.23 (br ddd, $J = 14, 4, 2.5$)	H-10', H-11, H-11', H-13
H-10'	2.47-2.55 (br ddd, $J = 14, 14, 5$)	H-10, H-11, H-11', H-13, H-13'
H-13	4.77 (br dd, $J = 1.5, 1.5$)	H-10, H-10', H-13'
H-13'	4.82-4.82 (dd, $J = 1.5, 1.5$)	H-10', H-13

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

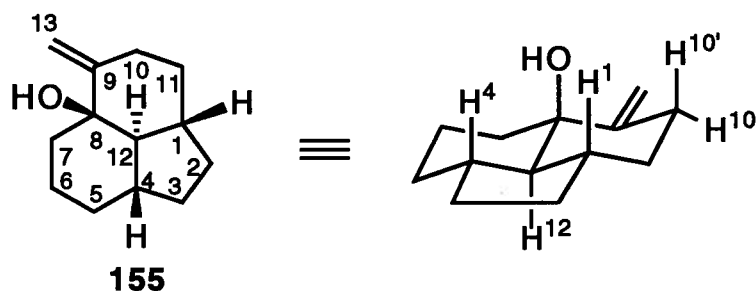
Table 48: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **155**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-12	0.54-0.60 (dd, $J = 12, 12$)	H-1, H-4
H-11	Part of the m at 1.04-1.20	H-1, H-10, H-10' ^b , H-11'
H-11'	~1.93-1.99 (m), part of the m at 1.65-2.11	H-10, H-10', H-11
H-4	~1.98-2.02 (m), part of the m at 1.65-2.11	H-12
H-1	~2.05-2.11 (m), part of the m at 1.65-2.11	H-11, H-12
H-10	2.20-2.25 (ddd, $J = 13.5, 4, 2.5$)	H-10', H-11, H-11'
H-10'	2.81-2.89 (br ddd, $J = 13.5, 13.5, 5$)	H-10, H-11, H-11', H-13, H-13'
H-13	4.81-4.82 (m)	H-10', H-13'
H-13'	4.89 (br d, $J = 1.5$)	H-10', H-13

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 49: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **155** in CDCl_3 vs. Pyridine- d_5



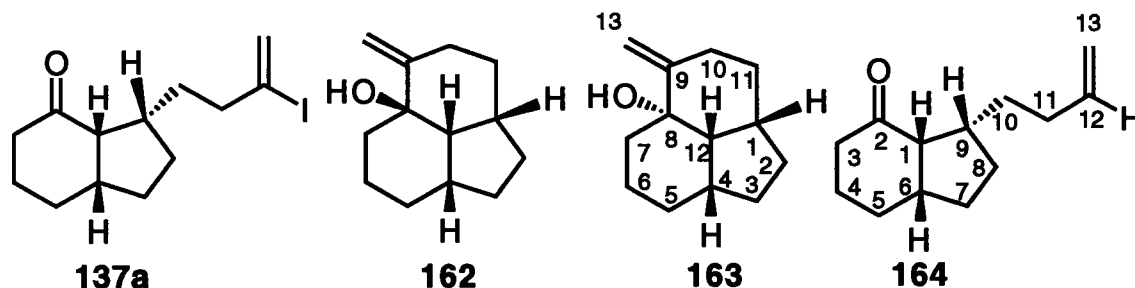
H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-1	~1.65-1.72	~2.05-2.11	0.40
H-4	~1.10-1.14	~1.98-2.02	0.88
H-10	2.18-2.23	2.20-2.25	0.02
H-10' ^c	2.47-2.55	2.81-2.89	0.34
H-11	~1.05-1.10	~1.04-1.20	0.04
H-11'	~1.93-2.00	~1.93-1.99	-0.01
H-12	0.58-0.64	0.54-0.60	-0.04
H-13	4.77	4.81-4.82	0.04
H-13'	4.82-4.83	4.89	0.06

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.05+2.11)/2 - (1.65+1.72)/2] = 0.40$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

3.5.1.5. Synthesis of (1*S**, 4*S**, 8*R**, 12*S**)-9-Methylenetricyclo[6.3.1.0^{4,12}]dodecan-8-ol (**162**), (1*S**, 4*S**, 8*S**, 12*S**)-9-Methylenetricyclo[6.3.1.0^{4,12}]dodecan-8-ol (**163**), and (1*S**, 6*S**, 9*R**)-9-(3-Butenyl)bicyclo[4.3.0]nonan-2-one (**164**):



Following general procedure 4, a solution of the cis-fused vinyl iodide **137a** (98 mg, 0.31 mmol, 1 equiv.) in dry THF (5 mL) was treated with a solution of *n*-butyllithium in hexanes (1.32 M, 0.58 mL, 0.77 mmol, 2.5 equiv.). The resultant solution was stirred at -78 °C for 30 min. The crude product mixture was flash chromatographed (15 g silica gel, 9:1 petroleum ether - diethyl ether) to afford three fractions. The first compound to be eluted was the tricyclic compound **163**. Concentration of the appropriate fractions and distillation (air-bath temperature 74-78 °C/0.22 Torr) of the oil thus obtained, provided 22 mg (37%) of the compound **163**, as a colourless oil.

IR (film): 3600, 3078, 1640, 1461, 1068, 900 cm⁻¹.

¹H nmr (400 MHz) δ: 0.71 (br s, 1H, -OH; this signal exchanges in the presence of D₂O), 1.32-1.97 (m, 13H, two of which are H-11 and H-11'), 2.06-2.11 (m, 1H), 2.18-2.28 (m, 2H, one of which is H-10), 2.45-2.51 (br ddd, 1H, *J* = 15.5, 5, 5 Hz, H-10'), 4.71-4.72 (m, 1H, H-13), 4.87 (br s, 1H, H-13').

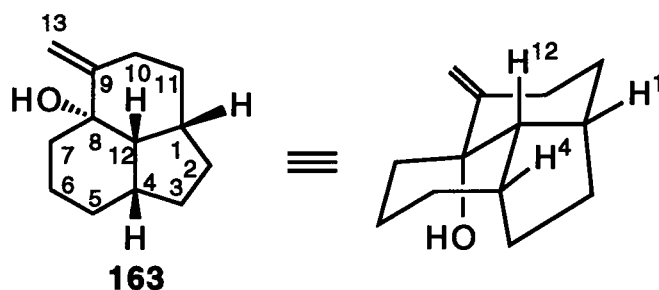
Detailed ¹H nmr data (CDCl₃), derived from a COSY experiment, are given in Table 50.

^{13}C nmr (75.3 MHz) δ : 17.4, 25.9, 27.8, 29.5, 30.0, 32.5, 34.4, 38.2 (-ve, C-1 or C-4), 38.8 (-ve, C-1 or C-4), 46.3 (-ve, C-12), 72.3 (C-8), 105.3 (C-13), 154.2 (C-9).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: 192.1514; found: 192.1519.

Anal. calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: C 81.20, H 10.48; found: C 81.31, H 10.38.

Table 50: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **163**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
-OH	0.71 (br s)	
H-11	~1.68-1.75 (m), part of the m at 1.32-1.97	H-10, H-10' ^b , H-11'
H-11'	~1.86-1.97 (m), part of the m at 1.32-1.97	H-10, H-10', H-11
H-10	~2.22-2.28 (m), part of the m at 2.18-2.28	H-10', H-11, H-11', H-13, H-13'
H-10'	2.45-2.51 (br ddd, J = 15.5, 5, 5)	H-10, H-11, H-11', H-13, H-13'
H-13	4.71-4.72 (m)	H-10, H-10', H-13'
H-13'	4.87 (br s)	H-10, H-10', H-13

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

The second compound to be eluted was the bicyclic compound **164**. The appropriate fractions were concentrated to provide, after removal of trace amounts of solvent (vacuum pump) from the resultant oil, 6.4 mg (11%) of the compound **164**, as a colourless oil.

IR (film): 3074, 1702, 1639, 1452, 994, 909 cm^{-1} .

^1H nmr (400 MHz) δ : 1.33-2.18 (m, 14H), 2.37-2.44 (m, 2H), 2.69-2.74 (dd, 1H, $J = 8.5$, 8 Hz, H-1), 4.90-4.93 (br ddd, 1H, $J = 10$, 1.5, 1.5 Hz, H-13), 4.95-5.01 (dddd, 1H, $J = 17$, 1.5, 1.5, 1.5 Hz, H-13'), 5.72-5.82 (dddd, 1H, $J = 17$, 10, 6.5, 6.5 Hz, H-12).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: 192.1514; found: 192.1517.

The last compound to be eluted was the tricyclic compound **162**. Concentration of the appropriate fractions and distillation (air-bath temperature 88-92 $^{\circ}\text{C}/0.1$ Torr) of the oil thus obtained, afforded 15 mg (26%) of the compound **162**, as a colourless oil.

IR (film): 3478, 3085, 1640, 991, 894 cm^{-1} .

^1H nmr (400 MHz) δ : 1.03-1.11 (m, 1H), 1.23 (s, 1H, $-\text{OH}$; this signal exchanges in the presence of D_2O), 1.31-1.76 (m, 10H, two of which are H-11 and H-11'), 1.80-1.89 (m, 2H, one of which is H-12), 2.09-2.18 (m, 2H, H-1 and H-4), 2.43-2.50 (m, 2H, H-10 and H-10'), 4.79-4.80 (m, 1H, H-13), 5.10-5.11 (m, 1H, H-13').

Detailed ^1H nmr data (CDCl_3), derived from a COSY experiment, are given in **Table 51**.

^1H nmr (400 MHz, pyridine- d_5) δ : 0.99-1.10 (dq, 1H, $J = 4$, 13 Hz), 1.22-1.81 (m, 10H, two of which are H-11 and H-11'), 1.92-1.96 (m, 1H), 2.08-2.11 (m, 1H, H-1), 2.22-2.27 (dd, 1H,

$J = 11, 11$ Hz, H-12), 2.30-2.34 (m, 1H, H-4), 2.49-2.53 (m, 2H, H-10 and H-10'), 4.93-4.95 (m, 1H, H-13), 5.59-5.60 (m, 1H, H-13').

Detailed ^1H nmr data (pyridine- d_5), derived from a COSY experiment, are given in **Table 52**.

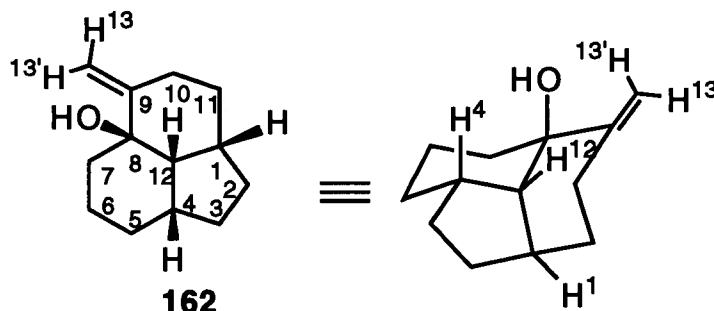
^1H nmr data comparing the chemical shifts in CDCl_3 versus those in pyridine- d_5 are given in **Table 53**.

^{13}C nmr (75.3 MHz) δ : 20.6, 27.9, 29.2, 29.6, 31.0, 32.0, 36.4, 37.1 (-ve, C-1 or C-4), 37.4 (-ve, C-1 or C-4), 50.2 (-ve, C-12), 73.7 (C-8), 106.2 (C-13), 153.7 (C-9).

Exact Mass calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: 192.1524; found: 192.1506.

Anal. calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: C 81.20, H 10.48; found: C 81.42, H 10.60.

Table 51: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **162**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
-OH	1.23 (s)	
H-11	~1.41-1.46 (m), part of the m at 1.31-1.76	H-4, H-10 and H-10' ^b , H-11'
H-11'	~1.71-1.75 (m), part of the m at 1.31-1.76	H-4, H-10 and H-10', H-11
H-12	~1.85-1.89 (m), part of the m at 1.80-1.89	H-1, H-4
H-1	~2.09-2.12 (m), part of the m at 2.09-2.18	H-11, H-11', H-12
H-4	~2.13-2.18 (m), part of the m at 2.09-2.18	H-12
H-10 and H-10'	2.43-2.50 (m)	H-11, H-11', H-13, H-13'
H-13	4.79-4.80 (m)	H-10 and H-10', H-13'
H-13'	5.10-5.11 (m)	H-10 and H-10', H-13

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

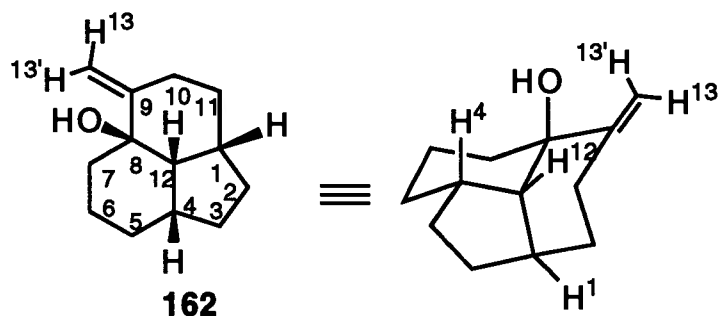
Table 52: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **162**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-11	~1.42-1.50 (m), part of the m at 1.22-1.81	H-1, H-10 and H-10' ^b , H-11'
H-11'	~1.63-1.71 (m), part of the m at 1.22-1.81	H-1, H-10 and H-10', H-11
H-1	2.08-2.11 (m)	H-11, H-11', H-12
H-12	2.22-2.27 (dd, $J = 11, 11$)	H-1, H-4
H-4	2.30-2.34 (m)	H-12
H-10 and H-10'	2.49-2.53 (m)	H-11, H-11', H-13, H-13'
H-13	4.93-4.95 (m)	H-10 and H-10', H-13'
H-13'	5.59-5.60 (m)	H-10 and H-10', H-13

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 53: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **162** in CDCl_3 vs. Pyridine- d_5



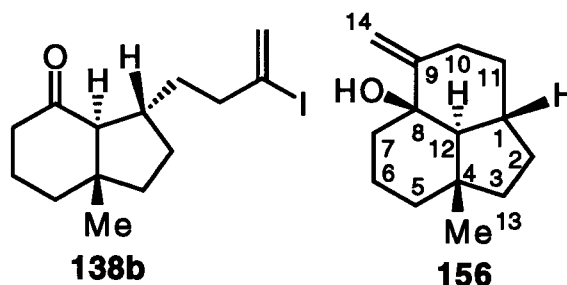
H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-1	~2.09-2.12	2.08-2.11	-0.01
H-4	~2.13-2.18	2.30-2.34	0.16
H-10 and H-10' ^c	2.43-2.50	2.49-2.53	0.04
H-11	~1.41-1.46	~1.42-1.50	0.02
H-11'	~1.71-1.75	~1.63-1.71	-0.06
H-12	~1.85-1.89	2.22-2.27	0.38
H-13	4.79-4.80	4.93-4.95	0.14
H-13'	5.10-5.11	5.59-5.60	0.49

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.08+2.11)/2 - (2.09+2.12)/2] = -0.01$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

3.5.1.6. Synthesis of (1*S**, 4*S**, 8*R**, 12*S**)-4-Methyl-9-methylenetricyclo[6.3.1.0^{4,12}]-dodecan-8-ol (**156**):



Following general procedure 4, a solution of the trans-fused vinyl iodide **138b** (42 mg, 0.13 mmol, 1 equiv.) in dry THF (2.5 mL) was treated with a solution of *n*-butyllithium in hexanes (1.51 M, 0.21 mL, 0.32 mmol, 2.5 equiv.). The resultant solution was stirred at -78 °C for 30 min. The crude product was subjected to radial chromatography (1 mm plate, 1:1 CH₂Cl₂ - petroleum ether), and the solid thus obtained was recrystallized from petroleum ether - diethyl ether to afford 22 mg (85%) of the tricyclic compound **156**, as a colourless crystalline solid, mp 60 °C.

IR (KBr): 3563, 3463, 3076, 1641, 1456, 1079, 900 cm⁻¹.

¹H nmr (400 MHz) δ: 0.72-0.76 (d, 1H, *J* = 13 Hz, H-12), 1.04 (s, 3H, Me-13), 1.06-1.17 (m, 4H, one of which is H-11), 1.20-1.28 (m, 1H), 1.40-1.46 (m, 1H), 1.51-1.64 (m, 2H), 1.73-2.07 (m, 6H, two of which are H-1 and H-11'), 2.16-2.21 (ddd, 1H, *J* = 14, 3.5, 2.5 Hz, H-10), 2.44-2.52 (br dd, 1H, *J* = 14, 14 Hz, H-10'), 4.71-4.72 (m, 1H, H-14), 4.80-4.81 (m, 1H, H-14').

Detailed ¹H nmr data (CDCl₃), derived from a COSY experiment, are given in Table 54.

^1H nmr (400 MHz, pyridine- d_5) δ : 0.68-0.71 (d, 1H, J = 13 Hz, H-12), 1.06-1.20 (m, 3H, one of which is H-11), 1.21-1.26 (m, 1H), 1.29 (s, 3H, Me-13), 1.40-1.42 (m, 1H), 1.54-1.61 (m, 2H), 1.76-1.85 (m, 2H), 1.98-2.04 (m, 2H, one of which is H-11'), 2.15-2.22 (m, 2H, one of which is H-10), 2.22-2.35 (m, 1H, H-1), 2.78-2.86 (br ddd, 1H, J = 13.5, 13.5, 4.5 Hz, H-10'), 4.75-4.76 (m, 1H, H-14), 4.86-4.87 (m, 1H, H-14).

Detailed ^1H nmr data (pyridine- d_5), derived from a COSY experiment, are given in **Table 55**.

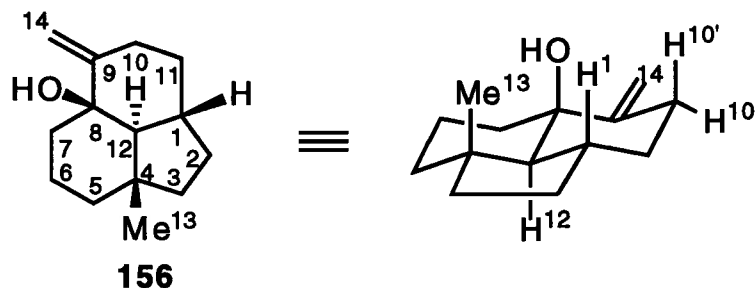
^1H nmr data comparing the chemical shifts in CDCl_3 versus those in pyridine- d_5 are given in **Table 56**.

^{13}C nmr (75.3 MHz) δ : 19.6, 20.7 (-ve, Me-13), 26.6, 32.8, 33.7 (-ve, C-1), 34.5, 35.4, 39.8, 39.9, 41.2, 59.6 (-ve, C-12), 73.0 (C-8), 106.4 (C-14), 154.1 (C-9).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1671.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.31, H 10.58.

Table 54: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **156**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-12	0.72-0.76 (d, $J = 13$)	H-1
Me-13	1.04 (s)	
H-11	~1.06-1.09 (m), part of the m at 1.06-1.17	H-1, H-10, H-10 ^b , H-11'
H-1	~2.00-2.02 (m), part of the m at 1.73-2.07	H-11, H-12
H-11'	~2.02-2.07 (m), part of the m at 1.73-2.07	H-10, H-10', H-11
H-10	2.16-2.21 (ddd, $J = 14, 3.5, 2.5$)	H-10', H-11, H-11'
H-10'	2.44-2.52 (br dd, $J = 14, 14$)	H-10, H-11, H-11', H-14, H-14'
H-14	4.71-4.72 (m)	H-10', H-14'
H-14'	4.80-4.81 (m)	H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

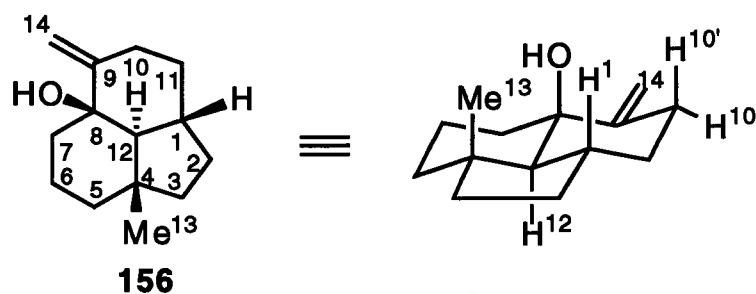
Table 55: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **156**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
H-12	0.68-0.71 (d, $J = 13$)	H-1
H-11	~1.06-1.13 (m), part of the m at 1.06-1.20	H-1, H-10, H-10 ^b , H-11'
Me-13	1.26 (s)	
H-11'	~2.01-2.04 (m), part of the m at 1.98-2.04	H-1, H-10, H-10', H-11
H-10	~2.18-2.22 (m), part of the m at 2.15-2.22	H-10', H-11, H-11'
H-1	2.22-2.35 (m)	H-11, H-11', H-12
H-10'	2.78-2.86 (br ddd, $J = 13.5, 13.5, 4.5$)	H-10, H-11, H-11', H-14, H-14'
H-14	4.75-4.76 (m)	H-10', H-14'
H-14'	4.86-4.87 (m)	H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 56: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **156** in CDCl_3 vs. Pyridine- d_5



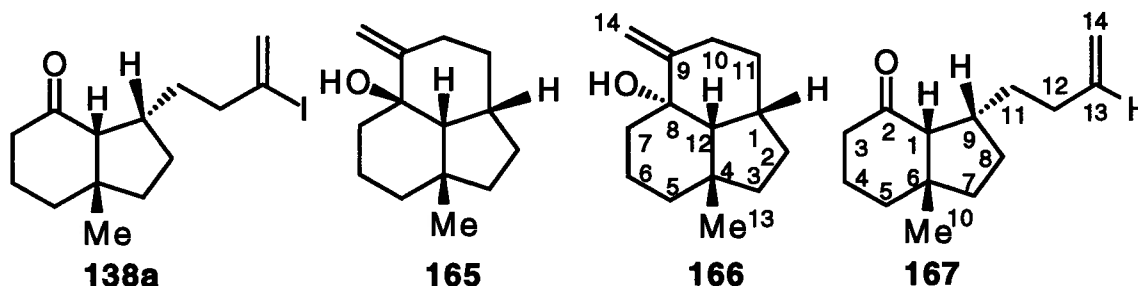
H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-1	~2.00-2.02	2.22-2.35	0.28
H-10	2.16-2.21	~2.18-2.22	0.02
H-10' ^c	2.44-2.52	2.78-2.86	0.34
H-11	~1.06-1.09	~1.06-1.13	0.02
H-11'	~2.02-2.07	~2.01-2.04	-0.02
H-12	0.72-0.76	0.68-0.71	-0.04
Me-13	1.04	1.26	0.22
H-14	4.71-4.72	4.75-4.76	0.04
H-14'	4.80-4.81	4.86-4.87	0.06

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.22+2.35)/2 - (2.00+2.02)/2] = 0.28$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

3.5.1.7. Synthesis of (1*S**, 4*S**, 8*R**, 12*R**)-4-Methyl-9-methylenetricyclo[6.3.1.0^{4,12}]-dodecan-8-ol (**165**), (1*S**, 4*S**, 8*S**, 12*R**)-4-Methyl-9-methylenetricyclo[6.3.1.0^{4,12}]-dodecan-8-ol (**166**), and (1*R**, 6*S**, 9*R**)-9-(3-Butenyl)-6-methylbicyclo[4.3.0]nonan-2-one (**167**):



Following general procedure 4, a solution of the cis-fused vinyl iodide **138a** (112 mg, 0.337 mmol, 1 equiv.) in dry THF (6.7 mL) was treated with a solution of *n*-butyllithium in hexanes (1.58 M, 0.53 mL, 0.84 mmol, 2.5 equiv.). The resultant solution was stirred at -78 °C for 1 h. The crude product mixture was subjected to radial chromatography (1 mm plate, 9:1 petroleum ether - diethyl ether) to provide three fractions. The first compound to be eluted was the tricyclic compound **166**. Concentration of the appropriate fractions and distillation (air-bath temperature 76-80 °C/0.1 Torr) of the oil thus obtained, afforded 24 mg (35%) of the compound **166**, as a colourless oil.

IR (film): 3549, 3079, 1640, 1457, 1140, 897 cm⁻¹.

¹H nmr (400 MHz) δ : 0.66 (s, 1H, -OH; this signal exchanges in the presence of D₂O), 0.91 (s, 3H, Me-13), 1.10-1.39 (m, 4H, one of which is H-12), 1.45-1.53 (m, 2H), 1.67-2.11 (m, 7H, two of which are H-11 and H-11'), 2.19-2.28 (dddd, 1H, *J* = 16, 16, 5, 2.5, 2.5 Hz, H-10), 2.36-2.42 (br ddd, 1H, *J* = 16, 4, 4 Hz, H-10'), 2.47-2.54 (sextet, 1H, *J* = 8 Hz, H-1), 4.69-4.71 (m, 1H, H-14), 4.90 (m, 1H, H-14').

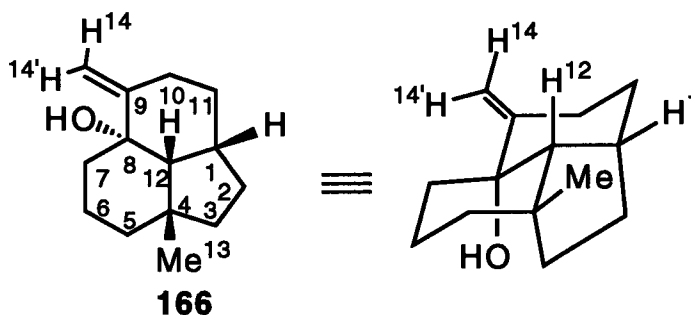
Detailed ¹H nmr data (CDCl₃), derived from a COSY experiment, are given in Table 57.

^{13}C nmr (75.3 MHz) δ : 17.8, 27.5, 29.5, 31.3 (-ve), 32.0, 34.5, 35.0, 35.8, 35.9 (-ve), 42.0, 51.7 (-ve, C-12), 72.1 (C-8), 105.6 (C-14), 154.0 (C-9).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1665.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.66, H 10.79.

Table 57: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **166**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
-OH	0.66 (s)	
Me-13	0.91 (s)	
H-12	1.19 (d, J = 8)	H-1
H-11	~1.76-1.81 (m), part of the m at 1.67-2.11	H-1, H-10, H-10' ^b , H-11'
H-11'	~1.85-1.92 (m), part of the m at 1.67-2.11	H-1, H-10, H-10', H-11
H-10	2.19-2.28 (ddddd, J = 16, 16, 5, 2.5, 2.5)	H-10', H-11, H-11', H-14, H-14'
H-10'	2.36-2.42 (br ddd, J = 16, 4, 4)	H-10, H-11, H-11', H-14, H-14'
H-1	2.47-2.54 (sextet, J = 8 Hz)	H-11, H-11', H-12
H-14	4.69-4.71 (m)	H-10, H-10', H-14'
H-14'	4.90 (m)	H-10, H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

The second compound to be eluted was the bicyclic compound **167**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 84-88 °C/0.15 Torr) to provide 14 mg (20%) of the compound **167**, as a colourless oil.

IR (film): 1698, 1641, 1456, 1232, 908 cm^{-1} .

^1H nmr (400 MHz) δ : 1.07 (s, 3H, Me-10), 1.27-1.31 (m, 1H), 1.41-1.69 (m, 6H), 1.81-1.96 (m, 4H), 2.04-2.13 (m, 2H), 2.34-2.43 (m, 3H), 4.90-4.93 (dddd, 1H, $J = 10, 1.5, 1.5, 1.5$ Hz, H-14), 4.94-5.00 (dddd, 1H, $J = 17, 1.5, 1.5, 1.5$ Hz, H-14'), 5.69-5.79 (dddd, 1H, $J = 17, 10, 7, 7$ Hz, H-13).

^{13}C nmr (75.3 MHz) δ : 21.3, 28.2 (-ve, Me-10), 31.0, 32.4, 33.0, 34.5, 40.5, 42.1, 42.3 (-ve), 45.4, 62.6 (-ve, C-1), 114.6 (C-14), 138.4 (-ve, C-13), 215.3 (C-2).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1672.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.43, H 10.83.

The last compound to be eluted was the tricyclic compound **165**. The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 84-87 °C/0.15 Torr) to provide 28 mg (40%) of the compound **165**, as a colourless oil.

IR (film): 3611, 3411, 1641, 1466, 1059, 898 cm^{-1} .

^1H nmr (400 MHz) δ : 1.15 (s, 1H, -OH; this signal exchanges in the presence of D_2O), 1.17 (s, 3H, Me-13), 1.19-1.46 (m, 9H, two of which are H-11 and H-12), 1.62-1.72 (m, 2H, one

of which is H-11'), 1.75-1.87 (m, 2H), 2.18-2.24 (m, 1H, H-1), 2.38-2.48 (m, 2H, H-10 and H-10'), 4.76-4.77 (m, 1H, H-14), 5.08 (m, 1H, H-14').

Detailed ^1H nmr data (CDCl_3), derived from a COSY experiment, are given in **Table 58**.

^1H nmr (400 MHz, pyridine- d_5) δ : 1.19-1.33 (m, 4H), 1.35 (s, 3H, Me-13), 1.37-1.54 (m, 3H, one of which is H-11), 1.58-1.69 (m, 1H, H-11'), 1.70-1.76 (m, 3H), 1.86 (d, 1H, $J = 11.5$ Hz, H-12), 2.10-2.19 (m, 2H, one of which is H-1), 2.45-2.52 (m, 2H, H-10 and H-10'), 4.92-4.94 (m, 1H, H-14), 5.57-5.59 (m, 1H, H-14').

Detailed ^1H nmr data (pyridine- d_5), derived from a COSY experiment, are given in **Table 59**.

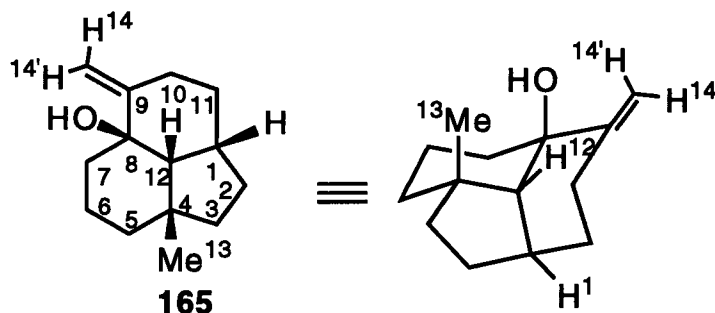
^1H nmr data comparing the chemical shifts in CDCl_3 versus those in pyridine- d_5 are given in **Table 60**.

^{13}C nmr (75.3 MHz) δ : 17.8, 28.4 (-ve, Me-13), 28.8, 29.5, 30.4, 33.2, 36.1, 38.5 (-ve, C-1), 41.0, 41.6, 55.4 (-ve, C-12), 74.3 (C-8), 106.2 (C-14), 154.2 (C-9).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1671; found: 206.1665.

Anal. calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$: C 81.50, H 10.75; found: C 81.54, H 10.65.

Table 58: ^1H nmr Data (400 MHz, CDCl_3) for the Tricyclic Compound **165**: COSY Experiment



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
-OH	1.15 (s)	
Me-13	1.17 (s)	
H-12	~1.32-1.37 (m), part of the m at 1.19-1.46	H-1
H-11	~1.45-1.51 (m), part of the m at 1.19-1.46	H-1, H-10 and H-10' ^b , H-11'
H-11'	Part of the m at 1.62-1.72	H-1, H-10 and H-10', H-11
H-1	2.18-2.24 (m)	H-11, H-11', H-12
H-10 and H-10'	2.38-2.48 (m)	H-11, H-11', H-14, H-14'
H-14	4.76-4.77 (m)	H-10 and H-10', H-14'
H-14'	5.08 (m)	H-10 and H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

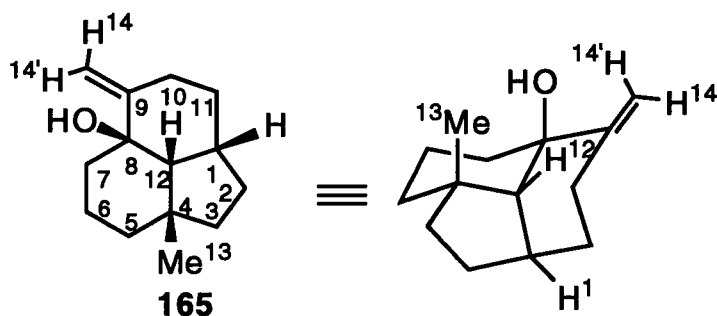
Table 59: ^1H nmr Data (400 MHz, pyridine- d_5) for the Tricyclic Compound **165**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
Me-13	1.35 (s)	
H-11	~1.48-1.53 (m), part of the m at 1.37-1.54	H-1, H-10 and H-10' ^b , H-11'
H-11'	1.58-1.69 (m)	H-1, H-10 and H-10', H-11
H-12	1.86 (d, $J = 11.5$)	H-1
H-1	~2.12-2.19 (m), part of the m at 2.10-2.19	H-11, H-11', H-12
H-10 and H-10'	2.45-2.52 (m)	H-11, H-11', H-14, H-14'
H-14	4.92-4.94 (m)	H-10 and H-10', H-14'
H-14'	5.57-5.59 (m)	H-10 and H-10', H-14

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

Table 60: Comparison of the ^1H nmr (400 MHz) Chemical Shifts of Compound **165** in CDCl_3 vs. Pyridine- d_5



H-x	δ ppm in CDCl_3	δ ppm in Pyridine- d_5	Δ a, b
H-1	2.18-2.24	~2.12-2.19	-0.06
H-10 and H-10' ^c	2.38-2.48	2.45-2.52	0.06
H-11	~1.45-1.51	~1.48-1.53	0.02
H-11'	Part of m at 1.62-1.72	1.58-1.69	~ -0.04
H-12	~1.32-1.37	1.86	0.52
Me-13	1.17	1.35	0.18
H-14	4.76-4.77	4.92-4.94	0.16
H-14'	5.08	5.57-5.59	0.50

a - $\Delta = \delta(\text{pyridine-}d_5) - \delta(\text{CDCl}_3)$; i.e. $[(2.12+2.19)/2 - (2.18+2.24)/2] = -0.06$.

b - Only those Δ 's > 0.15 are recorded in bold font.

c - H' indicates the hydrogen of a pair which is more downfield (H-10' is more downfield than H-10).

PART 2: TOTAL SYNTHESIS OF (-)-HOMALOMENOLS A AND B.

I. INTRODUCTION

1.1. GENERAL

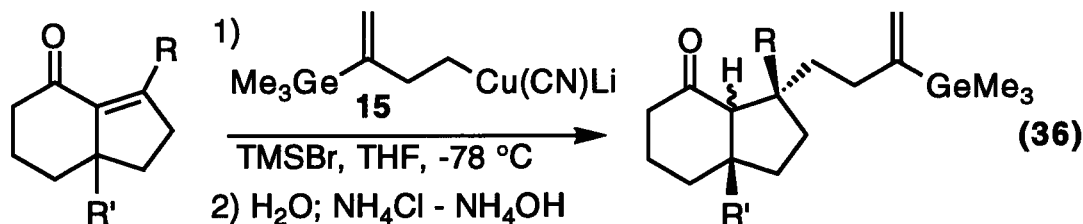
In the first century of organic chemistry, the focus was on chemical change in the direction of chemical reactions (i.e. reactant \rightarrow products). By the mid-1960's, a different and more systematic approach known as retrosynthetic analysis was developed. Corey¹²⁰ defines retrosynthetic analysis as a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The synthesis of complex organic molecules involves a number of steps:

- 1) choice of the molecule to be synthesized;
- 2) development of a synthetic strategy via retrosynthetic analysis;
- 3) the selection of specific individual steps and their ordering; and
- 4) the experimental execution of the synthesis.

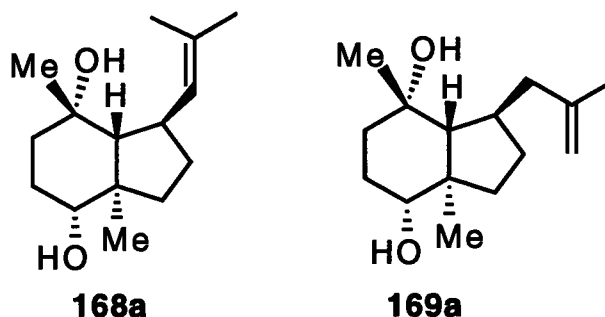
In the last decade, it has been increasingly crucial to design synthetic strategies that allow for the asymmetric synthesis of natural products.

1.2. PROPOSAL

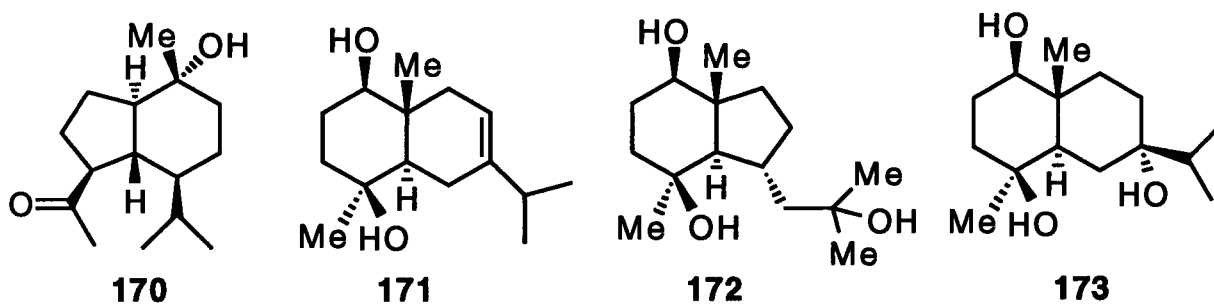
In Part 1 of this thesis, highly stereoselective conjugate addition reactions of the organocopper(I) reagent **15** to bicyclo[4.3.0]non-9-en-2-ones were studied in detail (equation **36**). How general is this reaction? Could other cuprate reagents be added stereoselectively to these enones?



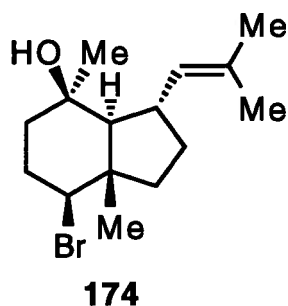
In order to provide at least a partial answer to these questions, it was decided to use this chemistry to develop a total synthesis of the recently isolated sesquiterpene alcohols, (+)-homalomenol A (**168a**) and (+)-homalomenol B (**169a**).

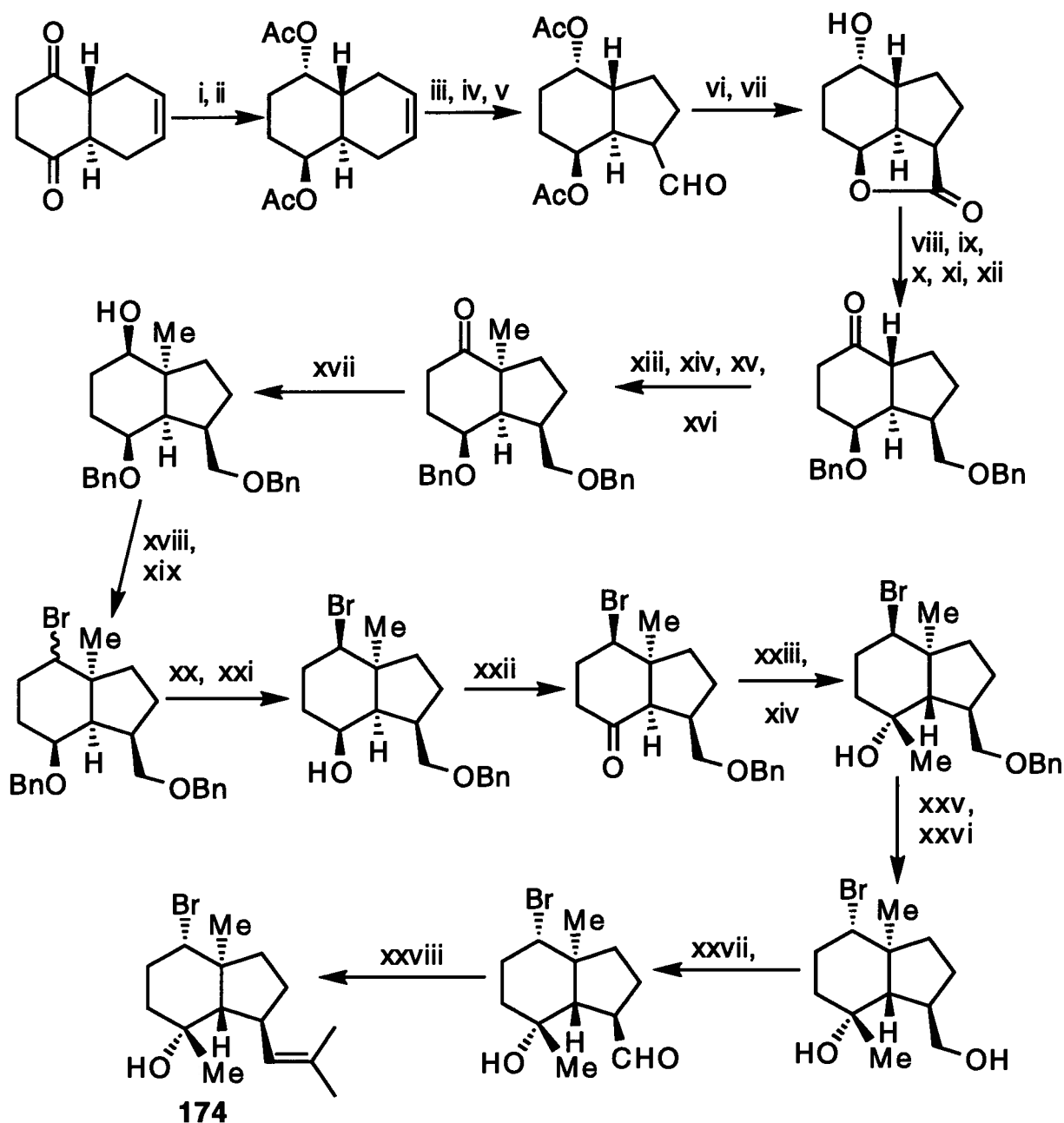


Sesquiterpenes **168a** and **169a** were isolated from the roots of *Homalomena aromatica* (Roxb.) Schott (Araceae) by Sung *et al.*¹²¹ and have not been previously synthesized. The roots of *Homalomena aromatica* are used in Vietnamese folk medicine as an anti-inflammatory agent, a tonic drug, and for the treatment of stomach diseases. The roots are also used in the aroma industry as a source of homalomenol oil which contains up to 80% linalool.¹²¹ The chloroform extract of the dried roots afforded six compounds, three of which were already known (oplopanone (**170**), oplodiol (**171**), and bullantantriol (**172**)). The three unknown sesquiterpenes were named homalomenol A (**168a**) and B (**169a**), and 1β , 4β , 7α -trihydroxyeudesmane (**173**). The absolute stereochemistry assigned to the homalomenols (shown above) was based on a positive Cotton effect observed for the ketone derived from the oxidation of the trihydroxyeudesmane sesquiterpene **173**. This assignment was later confirmed by our asymmetric synthesis.



There are several other natural products that are very similar in structure to homalomenals A (**168a**) and B (**169a**), one of which is the sesquiterpene oppositol (**174**). This compound was isolated from the marine epiphytic red alga *Laurencia subopposita* Setchell, and the absolute stereochemistry (shown below) was obtained from single-crystal X-ray diffraction analysis.¹²² The absolute stereochemistry of oppositol (**174**) is opposite to that of (+)-homalomenols A (**168a**) and B (**169a**). An extremely arduous 28 step racemic synthesis of oppositol (**174**) was carried out by Masamune and coworkers¹²³ (see **Scheme 32**).





i) LiAlH_4 , THF, rt; ii) Ac_2O , Pyridine, DMAP; iii) O_3 , CH_2Cl_2 , -78°C ; Zn, $\text{AcOH-H}_2\text{O}$; iv) $p\text{-TsOH}$, C_6H_6 , reflux; v) H_2 , 1-% Pd-C, EtOH, rt; vi) Jones reagent, acetone, 0°C ; vii) LiAlH_4 , THF, -20°C ; viii) EtOCH=CH_2 , PPTS, CH_2Cl_2 , rt; ix) LiAlH_4 , THF, 0°C ; x) BnBr , KH, DMF, rt; xi) 0.5 M HCl, rt; xii) PCC, CH_2Cl_2 , rt; xiii) HCOOEt , NaOEt, C_6H_6 , rt; xiv) BuSH , $p\text{-TsOH}$, MgSO_4 , C_6H_6 , rt; xv) MeI , $t\text{-BuOK}$, DME, -78°C ; xvi) KOH, DEG, reflux; xvii) NaBH_4 , MeOH, 0°C to rt; xviii) MsCl , Et_3N , CH_2Cl_2 , 0°C ; xix) Bu_4NBr , toluene, $95\text{--}97^\circ\text{C}$; xx) H_2 , 10% Pd-C, 1 M HCl, EtOH, rt; xxi) BnBr , NaH, DMF, -70°C ; xxii) PCC, CH_2Cl_2 , rt; xxiii) $p\text{-TsOH}$, CH_2Cl_2 , rt; xxiv) MeLi , ether, -20°C ; xxv) Bu_4NBr , toluene, 115°C ; xxvi) H_2 , Pd-C, 1 M HCl, EtOH, rt; xxvii) PDC, CH_2Cl_2 , rt; xxviii) $\text{Ph}_3\text{P=C(CH}_3)_2$, THF, 0°C .

Scheme 32¹²³

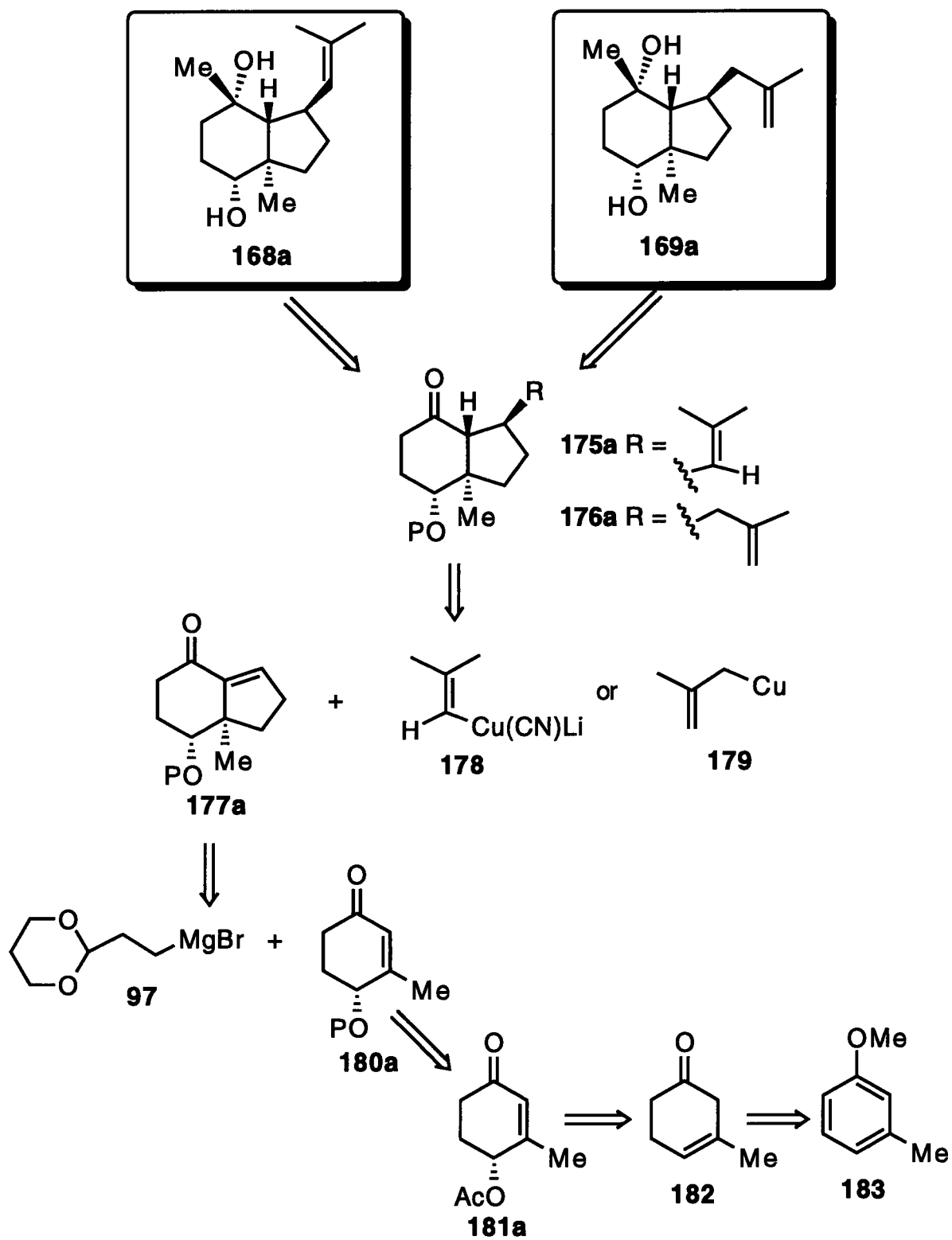
II. DISCUSSION

2.1. RETROSYNTHETIC ANALYSIS

Having chosen the target to be synthesized, the next step was to develop a synthetic strategy via retrosynthetic analysis. Our retrosynthetic plan towards the syntheses of (+)-homalomenols A (**168a**) and B (**169a**) is pictured in **Scheme 33**. Homalomenols A (**168b**) and B (**169b**) could, in principle, be obtained from the stereoselective methylation of the carbonyl moieties and deprotection of the secondary alcohols of the intermediates **175a** and **176a**, respectively. The functionalized bicyclo[4.3.0]nonan-2-ones **175a** and **176a** could, in turn, result from the stereoselective conjugate addition of the organocopper(I) reagents **178** and **179** to the bicyclic enone **177a**. In these key steps, the stereochemical results are predicted to resemble those obtained in the conjugate addition reactions of the organocopper(I) reagent **15** to the bicyclo[4.3.0]non-9-en-2-ones **74**, **75**, **95**, and **96** (see Section 2.3.3.4., page 56).

The bicyclic α,β -unsaturated ketone **177a** could be derived from the enone **180a** via a five-membered ring annulation process. The modified version of Helquist's annulation method utilized in Section 2.3.2. (pages 44-48) could be employed in the synthesis of **177a**. That is, the Grignard reagent **97** could be added in a conjugate fashion to the enone **180a**, and the resultant product could be converted, via an intramolecular aldol reaction, into the key bicyclic enone **177a**. The conditions for the aldol reaction would have to leave the protecting group intact.

The enone **180a** could be obtained from functional group manipulations of the allylic acetate **181a**. Acetate **181a** has been previously synthesized in an asymmetric fashion by Polla and Frejd¹²⁴ via a kinetically controlled enzymatic ester hydrolysis reaction. Polla and Frejd¹²⁴ report that the racemic acetate **181** could be obtained from epoxidation of the β,γ -unsaturated enone **182**, followed by base-promoted isomerization of the intermediate epoxide and acetylation of the resultant allylic alcohol. The β,γ -unsaturated enone **182** could, in turn, be derived from the Birch reduction of the commercially available 3-methylanisole (**183**).¹²⁵

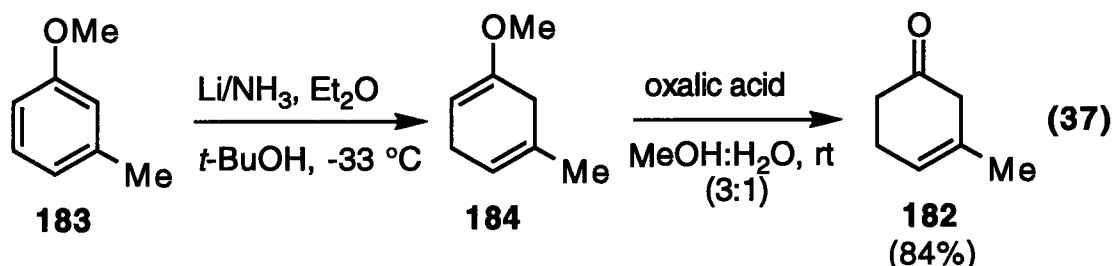


Scheme 33

2.2. SYNTHESIS OF (-)-HOMALOMENOL B (169b)

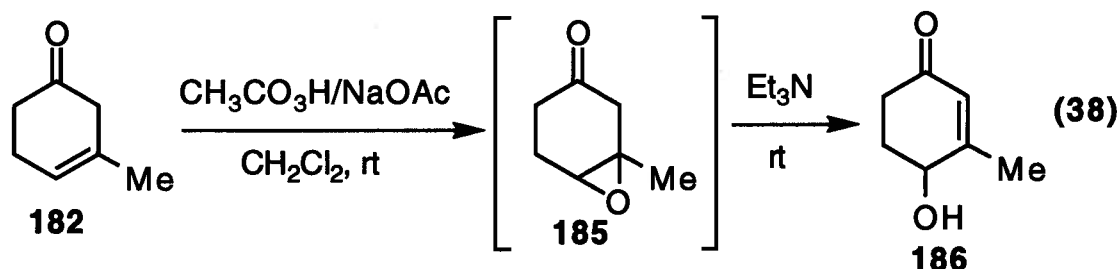
2.2.1. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS ALLYLIC ACETATE 181b

The method of Rubottom and Gruber¹²⁵ was used to prepare the β,γ -unsaturated enone **182**. Thus, treatment of 3-methylanisole (**183**) with Li/NH₃ and *tert*-butyl alcohol provided the enol ether **184** (equation 37). The crude enol ether **184** was then hydrolyzed with oxalic acid to yield, after workup and distillation, 3-methyl-3-cyclohexen-1-one (**182**) in 84% overall yield (equation 37).

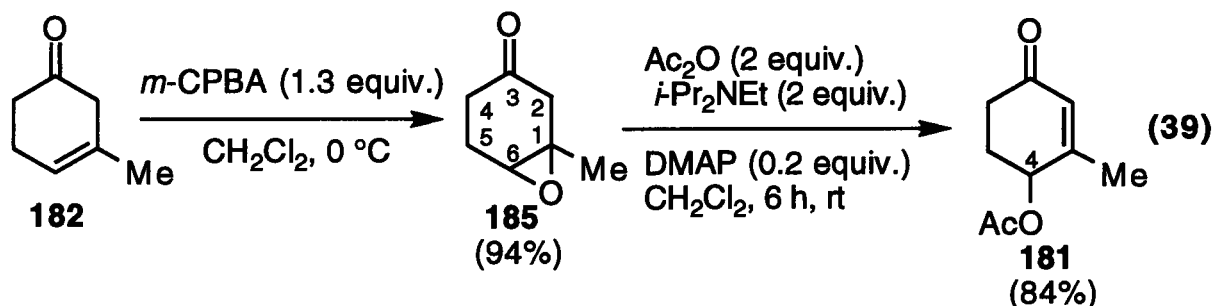


The ¹H nmr spectrum (400 MHz, C₆D₆) of **182** revealed a vinyl methyl signal at δ 1.35 (br s) and a vinyl proton signal at δ 5.17 (br s), identical with data reported for enone **182**.¹²⁵ Solutions of both the enol ether **184** and the β,γ -unsaturated enone **182** were concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column to avoid loss of product. The enone **182** was found to be stable when stored in the freezer under an atmosphere of argon.

According to Polla and Frejd,¹²⁴ the enone **182** could be transformed to the epoxide **185** with peracetic acid (equation 38). In the literature preparation, the crude epoxide **185** was immediately converted to the allylic alcohol **186** with Et₃N (equation 38).



We found that the allylic alcohol **186** was not very stable to purification and could not be stored for any length of time. We modified this procedure by using *m*-CPBA as the oxidizing agent instead of peracetic acid (equation 39). The epoxide **185** was isolated and was converted to the allylic acetate **181** directly (equation 39) to avoid having to isolate the intermediate alcohol **186**.

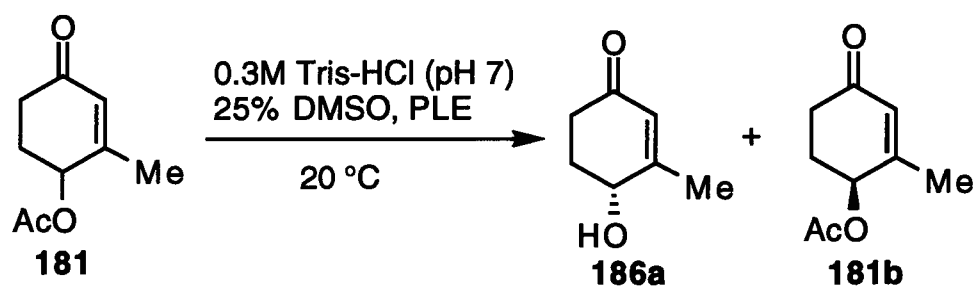


Upon workup and distillation, the epoxide **185** was obtained in 94% yield. The ^1H nmr spectrum (400 MHz, CDCl_3) of **185** indicated a signal at δ 1.36 (s) for the tertiary methyl group, signals at δ 2.56 (d, $J = 19$ Hz) and 2.78 (d, $J = 19$ Hz) for protons H-2 and H-2', and a signal at δ 3.20 (br d, $J = 2.5$ Hz) for H-6, thereby confirming that the epoxidation had taken place.

Epoxide **185** was treated with acetic anhydride, in the presence of *i*-Pr₂NEt and DMAP, to provide, after flash column chromatography and distillation, the racemic allylic acetate **181** in 84% yield (equation 39). The ^1H nmr spectrum (400 MHz, CDCl_3) of **181** indicated the following characteristic signals: δ 1.94 (br dd, $J = 1, 1$ Hz) corresponding to the vinyl methyl group; δ 2.13 (s) for the acetate methyl group; δ 5.54–5.58 (br dd, $J = 7.5, 5$ Hz) for the proton H-4; and δ 5.94 (br s) for the vinyl proton. The allylic acetate **181** could be stored indefinitely in the freezer under an atmosphere of argon with no signs of decomposition. It is interesting to note that Polla and Frejd¹²⁴ claim that the acetate **181** is unstable and must be used immediately in the next step.

Kinetic resolution of the racemic acetate **181** was accomplished with the enzyme, pig liver esterase (PLE), which was purchased as a suspension in 3.2 M $(\text{NH}_4)_2\text{SO}_4$, pH 8, from

Sigma. Polla and Frejd¹²⁴ report that the hydrolysis of **181** with PLE in the presence of a 0.3 M Tris-HCl buffer (pH 7) and 25% DMSO resulted in the isolation of the (*R*)-allylic alcohol **186a** with 90% ee (**Scheme 34**). The reaction was monitored by glc and was stopped at 45% conversion. Since we wished to obtain the alcohol **186a** in an enantiomeric excess of $\geq 95\%$, we ran this reaction allowing for only a 36% conversion (**Scheme 34**). The enantiomeric excess obtained for the (*R*)-allylic alcohol **186a** did not improve; in fact, the value obtained (88% ee) was slightly lower than that reported.

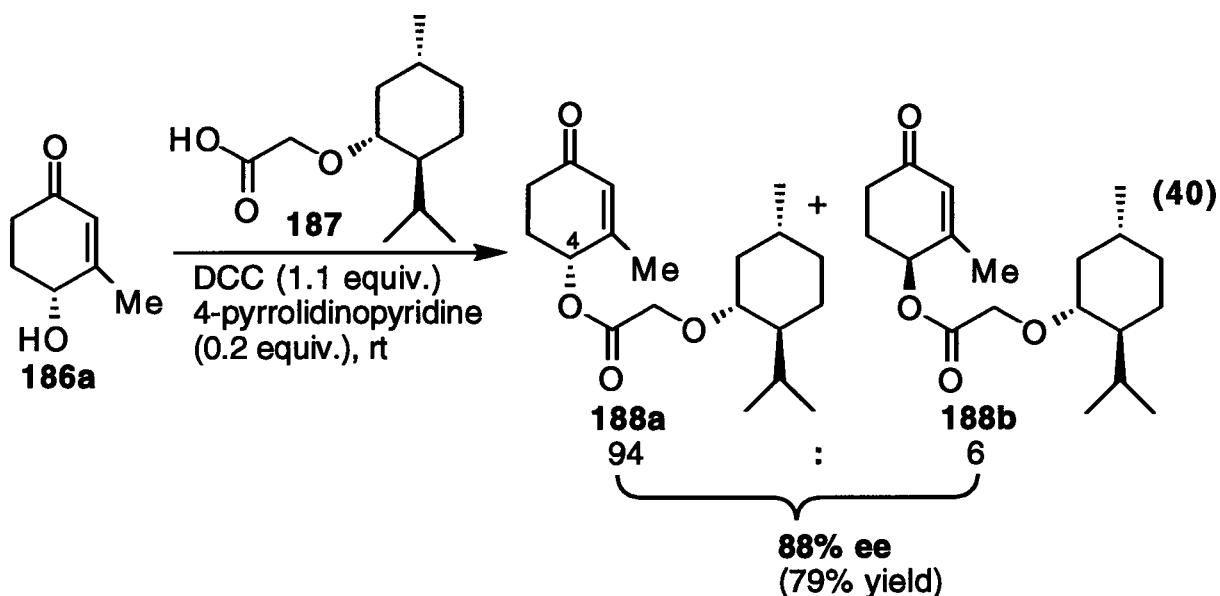


Conversion	182a % ee	177b % ee
45% ^a	90%	— ^b
36%	88%	84%

a- This reaction was reported by Polla and Frejd¹²⁴
b- This ee was not reported.

Scheme 34

The enantiomeric excess was determined by treating the allylic alcohol **186a** with (-)-menthoxyacetic acid (**187**) to afford a mixture of diastereomeric esters **188a** and **188b** (equation 40).¹²⁶ The ¹H nmr spectrum (400 MHz, CDCl₃) of this mixture revealed signals δ 0.79 (d, *J* = 7 Hz) for the secondary methyl group, δ 0.91 (d, *J* = 6.5 Hz) and 0.92 (d, *J* = 6.5 Hz) for the isopropyl methyl groups, δ 1.94 (dd, *J* = 1, 1 Hz) for the vinyl methyl group, δ 5.64–6.62 (dd, *J* = 7.5, 5 Hz) for the proton H-4, and δ 5.95 (br s) for the vinyl proton. In theory there should be two sets of signals for the diastereomers **188a** and **188b**; however, in the absence of a shift reagent, only one set of signals was observed.



The enantiomeric excess was determined by the ^1H nmr spectroscopic analysis of the mixture of the diastereomers in the presence of 0.1 - 0.2 equivalents of $\text{Eu}(\text{fod})_3$.¹²⁷ The 94:6 ratio shown in equation 40 was based on integration of the vinyl methyl signals. **Figure 8** shows the ^1H nmr spectra of a mixture of **188a** and **188b** in the absence and presence of $\text{Eu}(\text{fod})_3$. The vinyl methyl signals (part b, **Figure 8**), are very well resolved in the presence of the shift reagent $\text{Eu}(\text{fod})_3$ and were thus reliably integrated. The enantiomeric excess of the unreacted acetate **181b** was determined by converting the acetate to the alcohol (*vide infra*), forming the ester with (-)-menthoxyacetic acid (**187**), and analyzing the ^1H nmr spectrum of the diastereomeric mixture of esters in the presence of $\text{Eu}(\text{fod})_3$. In this way, the ee of the unreacted acetate was determined to be 84%.

Since the enantiomeric excess of the (*R*)-allylic alcohol **186a** was not synthetically acceptable (i.e. < 95% ee), we undertook to synthesize the (*S*)-enantiomer **186b** by allowing a greater enzymatic conversion (i.e. > 50% hydrolysis). The racemic acetate **181** was hydrolyzed with the PLE to an extent of 59% and the unreacted acetate **181b** was isolated in 40% yield (**Scheme 35**). A small portion of the acetate **181b** was hydrolyzed with Na_2CO_3 in MeOH, and the corresponding allylic alcohol **186b** was esterified with (-)-menthoxyacetic acid (**187**) (**Scheme 35**).

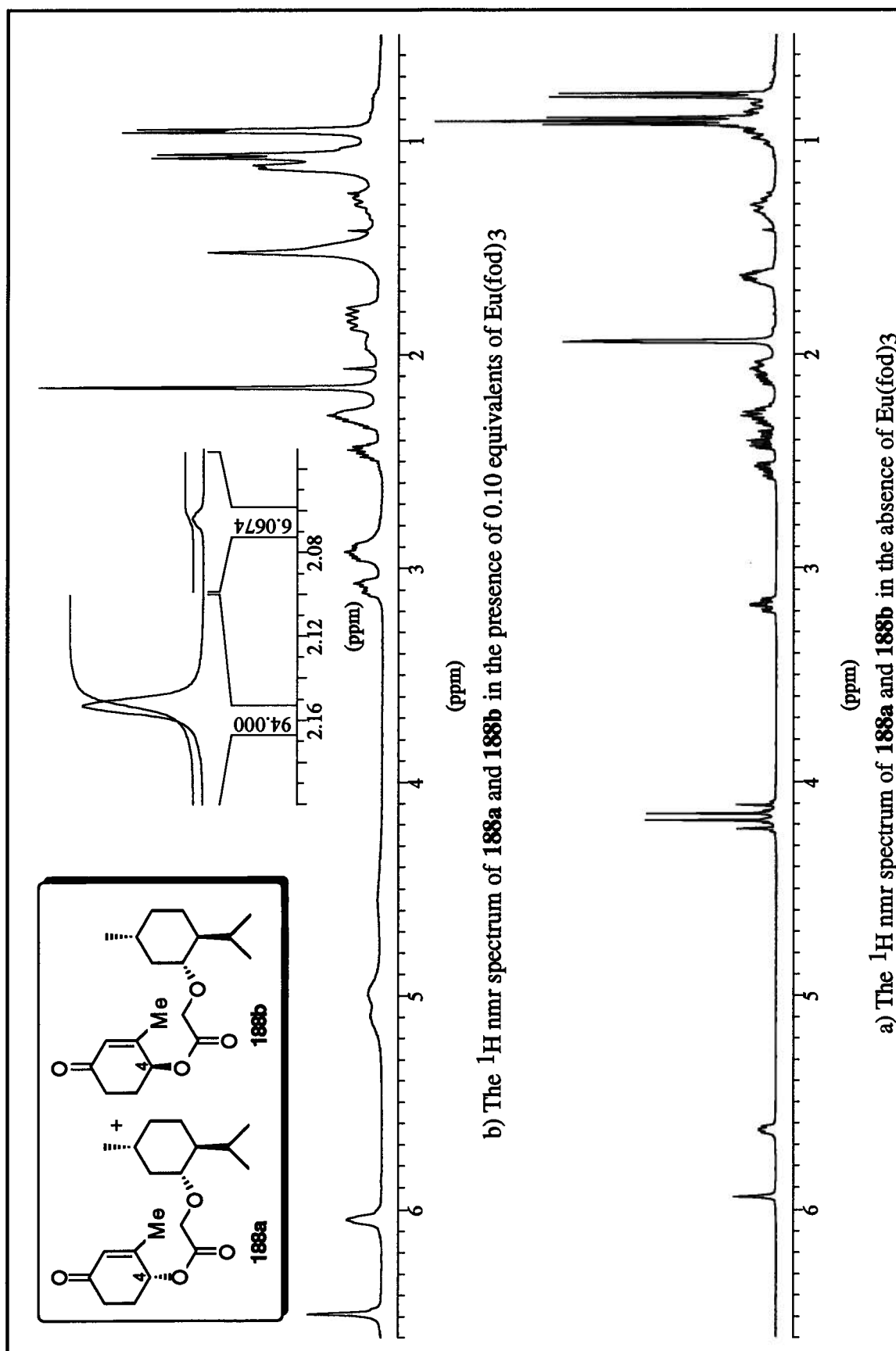
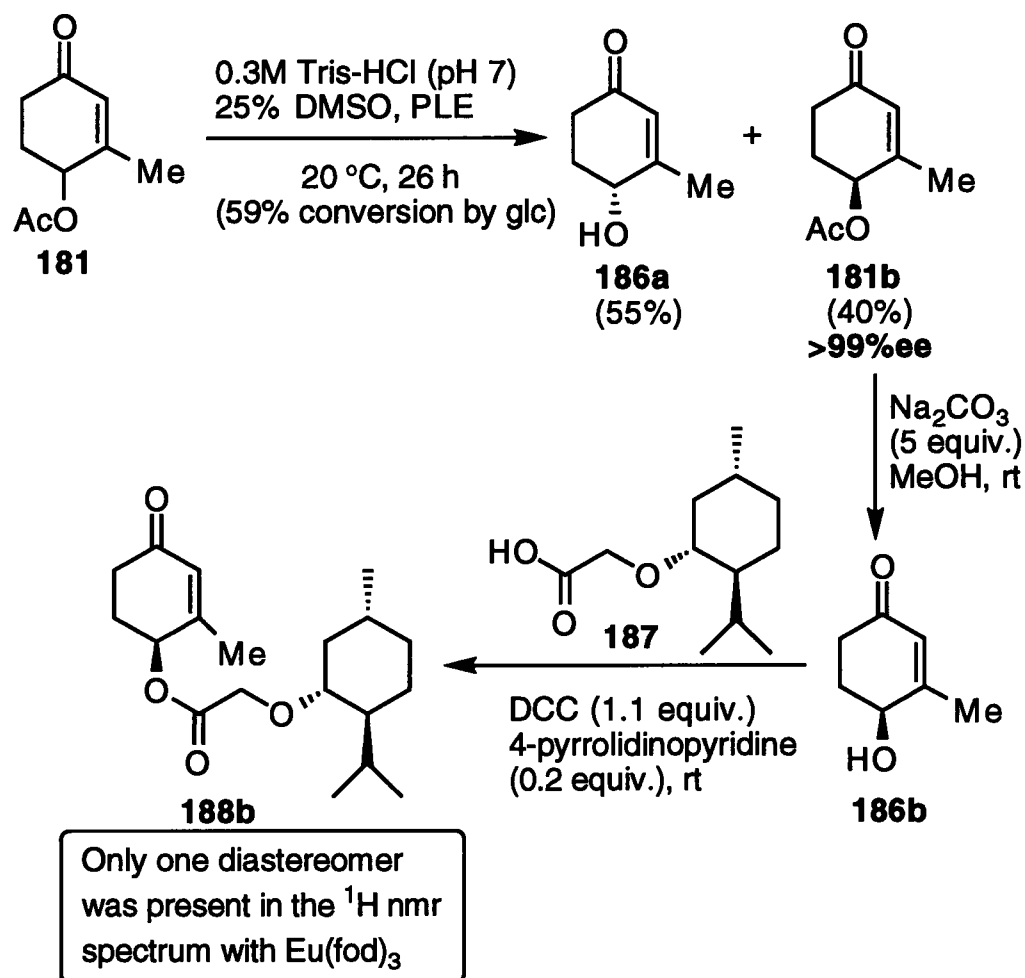
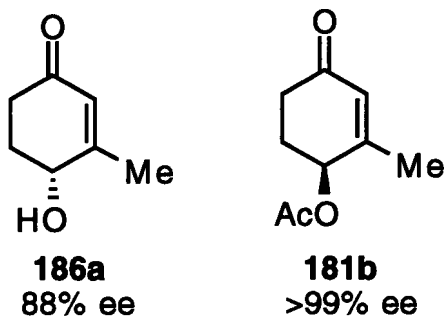


Figure 8: The ^1H NMR Spectra (400 MHz, CDCl_3) of **188a** and **188b** in a) the absence and b) presence of $\text{Eu}(\text{fod})_3$

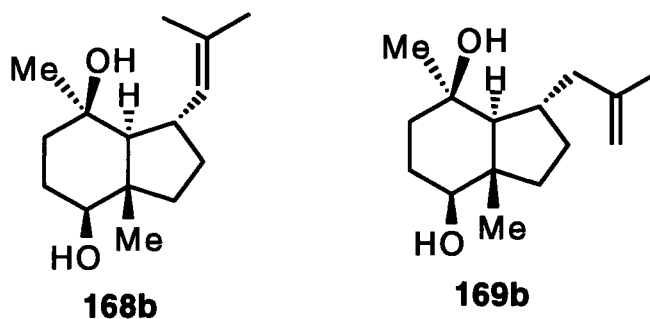


Scheme 35

The ¹H nmr spectrum (400 MHz, CDCl₃) of the ester **188b**, in the presence of 0.1 - 0.2 equivalents of Eu(fod)₃, revealed only one diastereomer (i.e. only one vinyl methyl group). Hence, the unreacted acetate **181b** in Scheme 35 was isolated in > 99% ee. This enantiomeric excess is in accord with that reported.¹²⁴

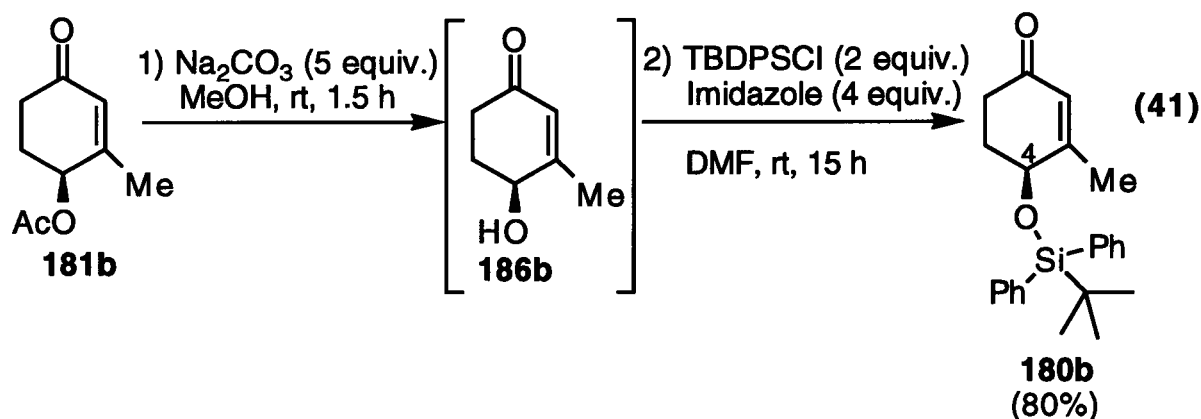


The (*R*)-allylic alcohol **186a** could be used to synthesize the naturally occurring (+)-homalomenols A (**168a**) and B (**169a**). However, since we could obtain the other enantiomeric series (i.e. (*S*)-allylic acetate **181b**) in a higher enantiomeric purity (> 99% ee versus 88% ee), we chose to synthesize the (-)-homalomenols A (**168b**) and B (**169b**).



2.2.2. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS BICYCLIC ENONE **177b**

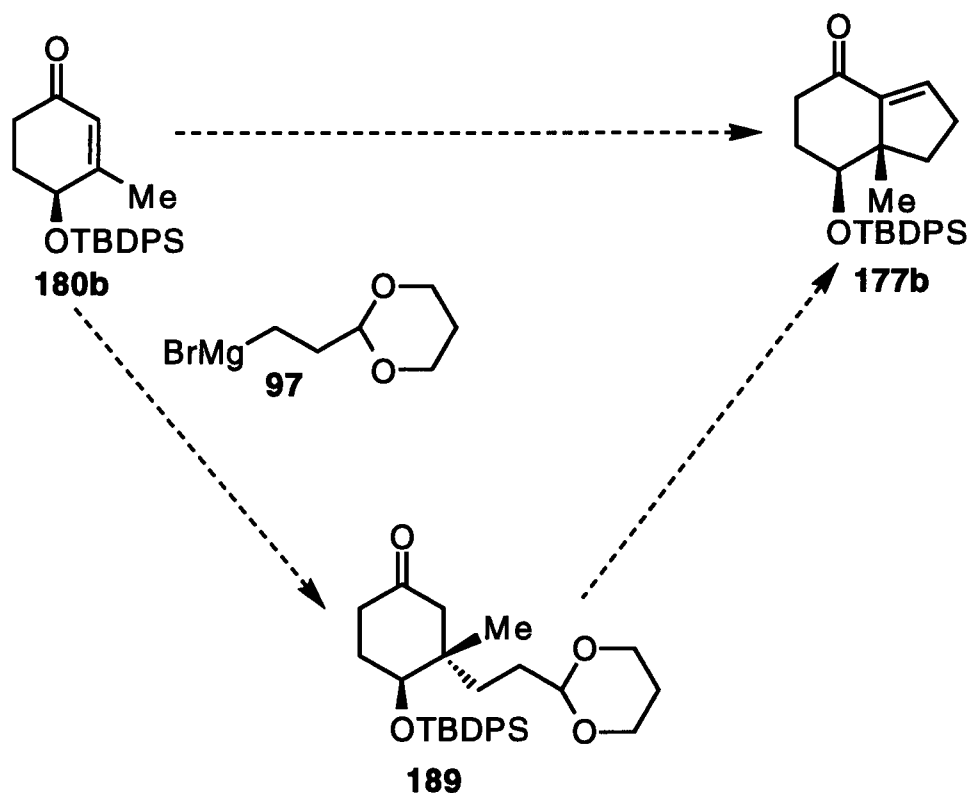
To continue with the synthesis of (-)-homalomenol B, the acetate function of **181b** needed to be replaced with a more chemoresistant group. Hence, the (-)-allylic acetate **181b** was converted to the TBDPS ether **180b** (equation 41). Conversion of **181b** to the corresponding alcohol **186b** was quickly accomplished with Na_2CO_3 and since the allylic alcohol **186b** was not very stable, it was used immediately in the next step. The alcohol function of **186b** was protected using TBDPSCl in the presence of imidazole to provide, after purification, the *tert*-butyldiphenylsilyl ether **180b** in 80% overall yield, as a highly viscous oil which could not be distilled (equation 41). Residual solvent was removed by heating compound **180b** to 75-80 °C/0.2 Torr using a Kugelrohr distillation apparatus.



The presence of the TBDPS group was evident in the ^1H nmr spectrum (400 MHz, CDCl_3) of **180b** via the signals at δ 1.08 (s, 9H, $-\text{CMe}_3$), 7.38-7.48 (m, 6H, aromatic protons), and 7.68-7.72 (m, 4H, aromatic protons). The signal at δ 1.94 (dd, $J = 1$, 1 Hz) was assigned to the vinyl methyl group; the signal at δ 4.34 (br dd, $J = 7.5$, 4.5 Hz) was assigned to the proton H-4; and the signal at δ 5.79 (br s) was assigned to the vinyl proton.

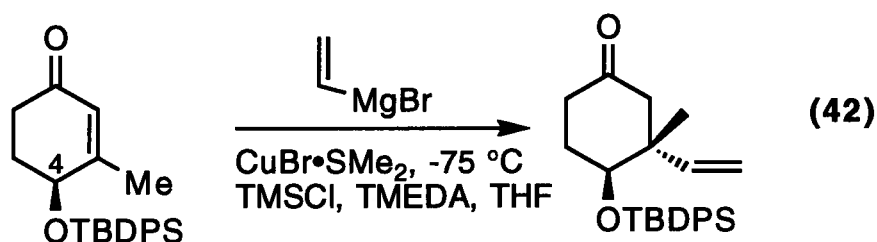
The next step in the synthetic plan was conversion of the enone **180b** to the bicyclic enone **177b** by employing a modified version of the five-membered ring annulation sequence reported by Helquist and coworkers^{4,46} (Scheme 36). The strongly acidic conditions

previously used for the intramolecular aldol cyclization (HCl/H₂O/THF/ Δ) would need to be modified to accommodate the TBDPS protecting group.



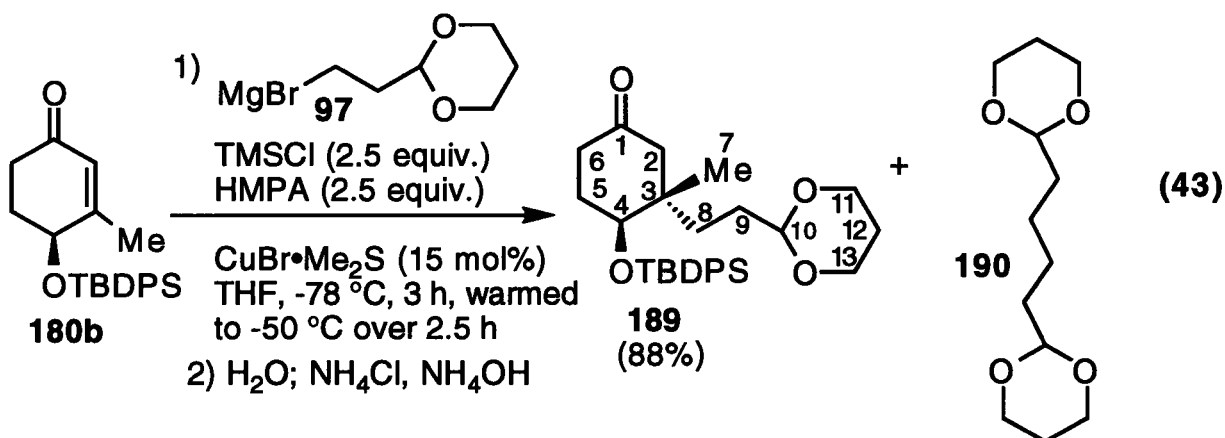
Scheme 36

A search of the literature revealed that conjugate addition to a six-membered ring enone will proceed anti to an oxygen substituent at C-4. One such example was reported by Polla and Frejd¹²⁴ and is illustrated in equation 42.



The conjugate addition of the Grignard reagent **97** to the enone **180b** proceeded, in the presence of $\text{CuBr}\cdot\text{Me}_2\text{S}$, TMSCl , and HMPA , to provide the keto acetal **189** in 88% yield

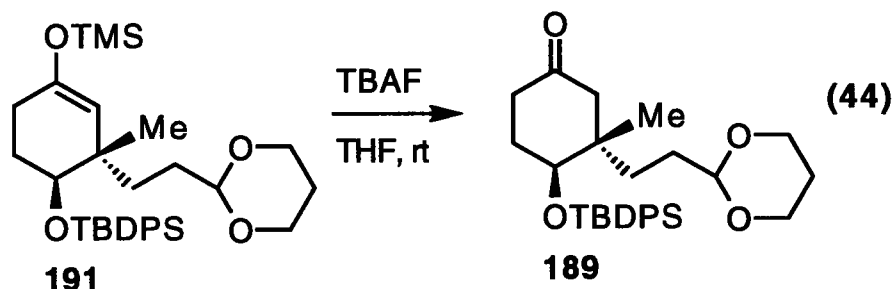
(equation 43). Only one stereoisomer was evident in the ^1H nmr spectrum of the crude product derived from the copper(I)-catalyzed Grignard addition. As expected, anti-addition relative to the oxygen substituent at C-4 was achieved; however, the stereochemistry was confirmed in a subsequent product (*vide infra*). A small amount of the coupled byproduct **190** was formed in this reaction and it was partially separated from the product **189** by flash column chromatography. The keto acetal **189** was subsequently crystallized from petroleum ether to completely separate it from the byproduct **190**.



The ^1H nmr spectrum (400 MHz, CDCl_3) of **189** revealed signals at δ 0.96 (s) for the tertiary methyl group, δ 1.09 (s) for the *tert*-butyl group, δ 3.65-3.72 and 3.66-3.73 (ddd, 1H each, $J = 12, 12, 2$ Hz for each ddd) for the axial protons on C-11 and C-13, δ 3.81-3.84 (dd, $J = 5, 5$ Hz) for the proton H-4, δ 4.03-4.07 (ddd, 2H, $J = 12, 5, 1$ Hz) for the equatorial protons on C-11 and C-13, δ 4.34-4.36 (dd, $J = 5, 4.5$ Hz) for the proton H-10, and δ 7.35-7.72 (m) and 7.66-7.72 (m) for the aromatic protons. The signal at δ 2.47-2.51 (br d, $J = 14$ Hz) was assigned to H-2' since only the protons at C-2 could exist as doublets. The COSY spectrum allowed the assignment of H-2 (part of the m at δ 1.96-2.07) through the correlation of its signal to that of H-2' (see **Table 63**, experimental, page 327). Various other protons, such as H-5, H-5', H-6, and H-6', were also assigned on the basis of COSY correlations.

It should be noted that the hydrolysis of the silyl enol ether intermediate **191** (formed after the conjugate addition reaction) proved to be somewhat troublesome. Typically, H_2O

was added to the reaction mixture and the resultant mixture was left stirring open to the atmosphere (~2 h to overnight). In most cases, the silyl enol ether **191** was completely hydrolyzed to the keto acetal **189** under these conditions. Occasionally, however, the hydrolysis of **191** did not proceed to completion; in these cases, the reaction mixture was worked up and the crude product was treated with one equivalent of TBAF in THF, which provided the keto acetal **189** (equation 44). The TBDPS protecting group was found to be stable to TBAF at room temperature.



In attempts to effect the conversion of the keto acetal **189** to the enone **177b**, the conditions reported by Helquist and coworkers^{4,46} (HCl/H₂O/THF) could not be employed because the TBDPS ether would, in all likelihood, be hydrolyzed.¹²⁸ The results of attempts to promote the aldol cyclization are summarized in **Table 61**. The conditions utilized in entries 1, 2, and 4 resulted in the nearly quantitative recovery of starting material **189**. Integration of the ¹H nmr spectrum of the crude product isolated in entry 3 indicated a ~1:1 mixture of starting material and product **177b**; however, there was also a significant amount of an unidentifiable byproduct.

Lavallée and Hanessian¹²⁸ have shown that TBDPS ethers are stable to 50% aqueous CF₃COOH in dioxane at room temperature (equation 45). Use of these conditions in our system (entry 4, **Table 61**) resulted in the recovery of only starting material. However, modification of these conditions (see entry 5, **Table 61**; 80% aqueous CF₃COOH vs. 50% CF₃COOH, and 70 °C vs. room temperature) resulted in a satisfactory formation of the desired enone **177b**.

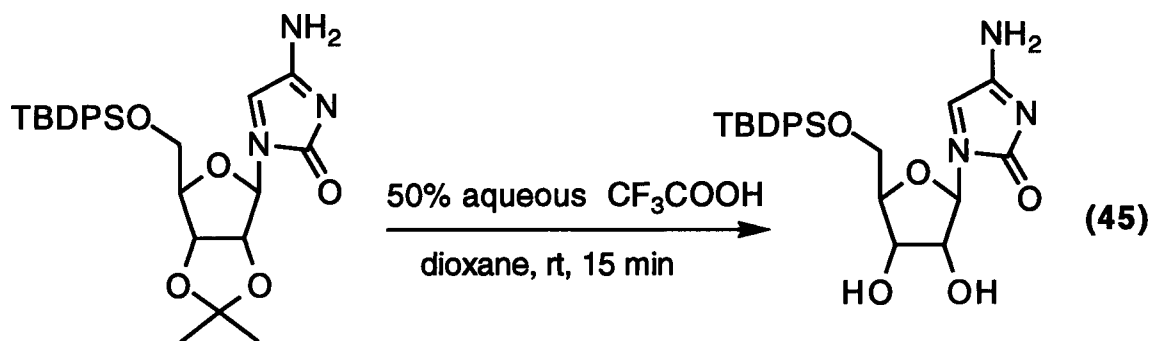


Table 61: Attempts to Cyclize Keto Acetal 189 to Form the Bicyclic Enone 177b

Entry	Conditions	Results
1 ^a	PPTS, aqueous acetone, Δ , overnight	Mostly starting material, a trace amount of 177b
2 ^b	80% aqueous acetic acid, THF, room temperature, 4 h	Mostly starting material
3 ^c	<i>p</i> -TsOH, CH ₂ Cl ₂ , Δ , 5 h	Starting material : Product 177b (~1:1 ratio) + unidentifiable byproduct
4 ^d	50% aqueous CF ₃ COOH/dioxane, room temperature, 4 h	Mostly starting material
5	80% aqueous CF ₃ COOH/dioxane (1:2), 70 °C, 16 h	82% Yield of 177b

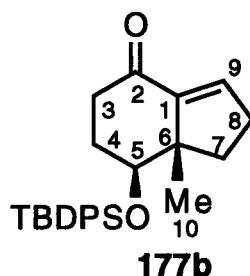
a- The conditions utilized were reported by Hagiwara and Uda¹²⁹ for the hydrolysis of 1,3-dioxolanes (i.e. 5-membered ring acetals).

b- The conditions utilized were reported by Babler *et al.*¹³⁰ for the hydrolysis of 1,3-dioxolanes.

c- The conditions utilized were reported by Baudin *et al.*¹³¹ for the hydrolysis of 1,3-dioxolanes.

d- The conditions utilized were reported by Lavallée and Hanessian¹²⁸ for the hydrolysis of 1,3-dioxolanes.

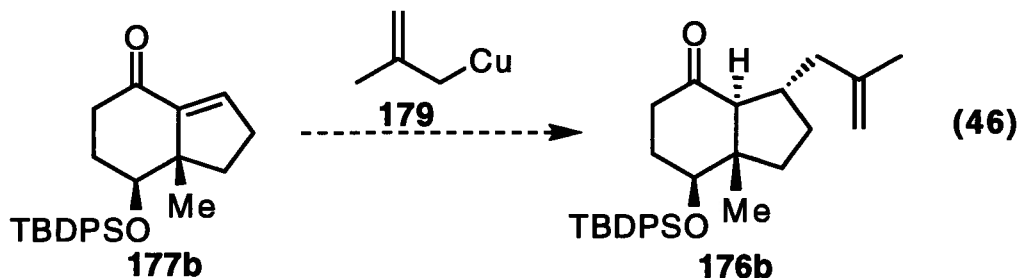
A few additional comments on the cyclization procedure (entry 5, **Table 61**) are necessary. The reaction mixture was heated at 70 °C for 16 h; after workup and flash column chromatography, the enone **177b** was isolated in 77% yield. The column was then flushed with diethyl ether and, after concentration, the residual material was resubjected to acidic conditions (100% CF₃COOH/dioxane (1:2), 70 °C) for 15 h. Upon workup and purification, an additional 5% of the enone **177b** was obtained, resulting in an overall yield of 82%. Presumably, the more polar compounds eluted with diethyl ether are intermediates in the cyclization sequence. Simply utilizing a longer reaction time (i.e. > 20 h) in the original reaction did not, however, improve the yield (i.e. ~ 77% yield of **177b** was obtained, regardless of the reaction time).



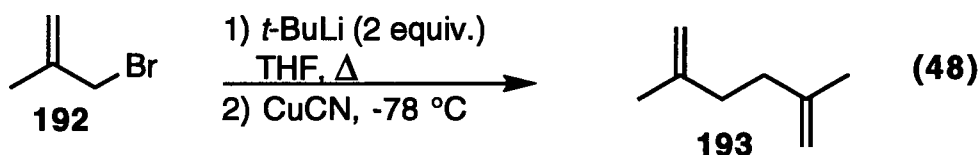
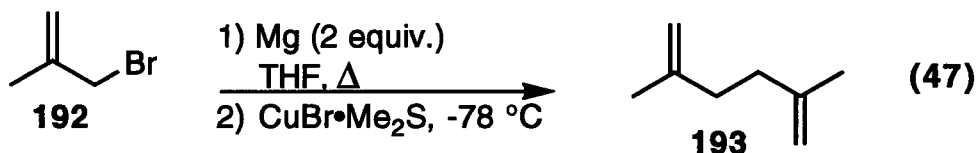
The IR spectrum of **177b** revealed absorbances at 1687 and 1618 cm⁻¹, characteristic of an α,β -unsaturated enone. The ¹H nmr spectrum (400 MHz, CDCl₃) revealed a signal at δ 1.20 (s) for the tertiary methyl group, a signal at δ 3.76-3.80 (dd, J = 11, 4 Hz) for proton H-5, and a signal at δ 6.42-6.63 (dd, J = 2.5, 2.5 Hz) for the vinyl proton H-9.

2.2.3. SYNTHESIS OF THE BICYCLIC KETONE 176b

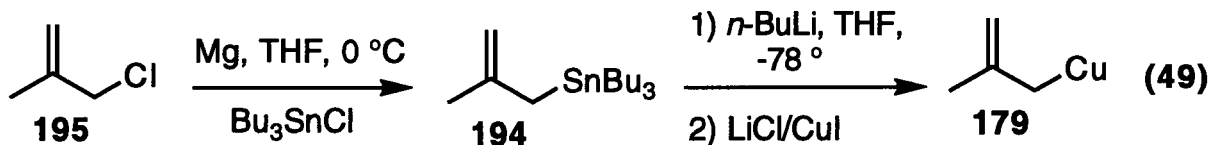
The next step in the synthesis of (-)-homalomenol B was the stereoselective conjugate addition of the organocopper(I) reagent **179** to the bicyclic enone **177b** (equation 46).



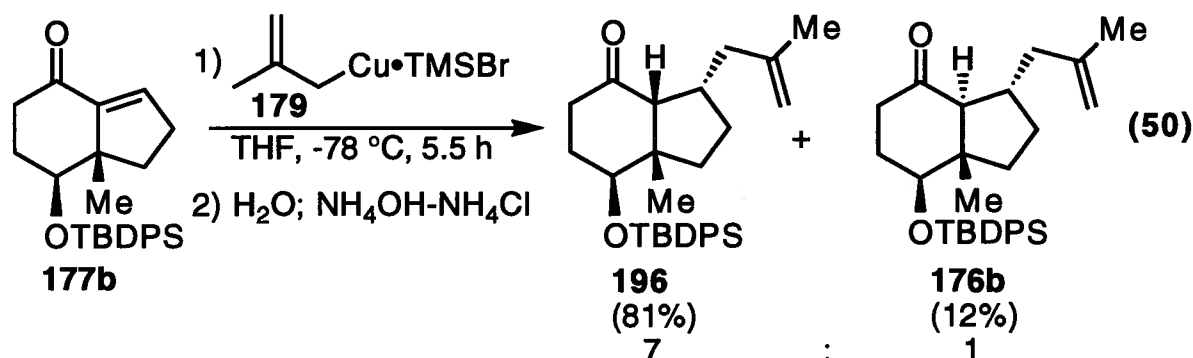
Our initial attempts to prepare **179** involved the reaction of methallyl bromide (**192**) with either magnesium (equation 47) or *t*-BuLi (equation 48). Both attempts failed, due to the sole formation of the coupled byproduct **193**. Allyl halides are known to be quite reactive, and thus, it was not surprising that **193** was formed.¹³²



Lipshutz and coworkers¹³³ have reported that the copper(I) reagent **179** can be prepared from 2-methyl-3-(tri-*n*-butylstannyl)propene (**194**) by sequential treatment of the latter substance with *n*-BuLi and LiCl/CuI (equation 49). In our work, it was found necessary to use freshly recrystallized CuI¹³⁴ for this preparation. The allylstannane **194** was prepared from 3-chloro-2-methylpropene (**195**) and tri-*n*-butylstannyl chloride, according to the procedure of Keck and Enholm¹³⁵ (equation 49).

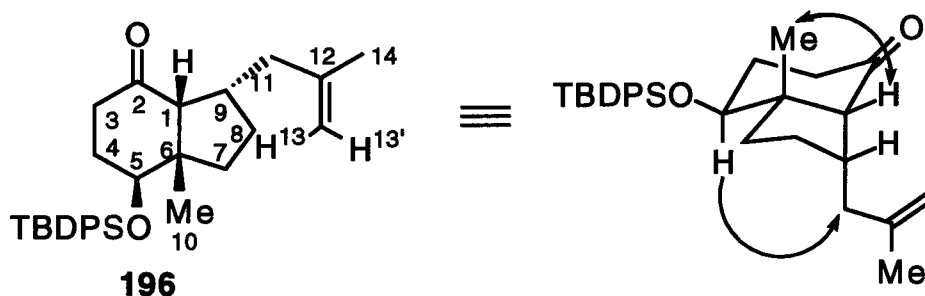


The conjugate addition of reagent **179** to the bicyclic enone **177b**, in the presence of TMSBr, resulted in the formation of a 7:1 mixture of epimers **196** and **176b** (equation 50).



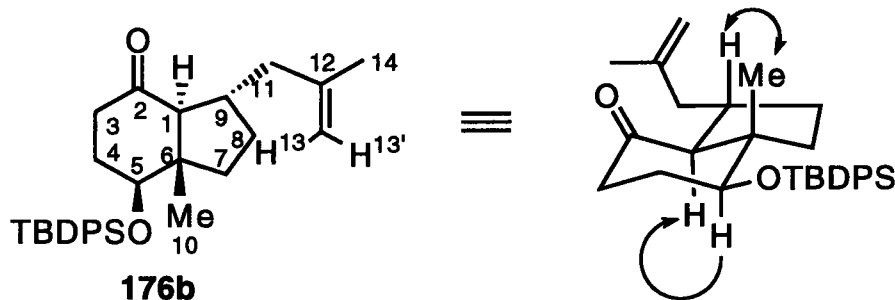
We were pleased to discover that the conjugate addition reaction had proceeded stereoselectively, as expected (see Section 2.3.3.4., page 56). The cis- and trans-fused epimers **196** and **176b** were easily separated by flash column chromatography and were isolated in 81% and 12% yield, respectively. When this reaction was performed in the presence of TMSCl (as reported in related chemistry by Lipshutz and coworkers¹³³) instead of TMSBr, the overall yield was decreased by 16%.

The ^1H nmr spectrum (400 MHz, CDCl_3) of the major cis-fused epimer **196** is illustrated in **Figure 9** and indicates signals at δ 1.18 (s) for the tertiary methyl group, δ 1.59 (s) for the vinyl methyl group, δ 2.49-2.52 (dd, $J = 10.5, 2$ Hz) for the angular proton H-1, δ 3.74-3.77 (dd, $J = 8.5, 3.5$ Hz) for the proton H-5, and δ 4.48 (br s) and 4.56 (br s) for the vinyl protons H-13 and H-13'. The COSY spectrum allowed the assignment of several other protons (see **Table 65**, experimental, page 335). For example, the signal at δ 1.41-1.47 (br dd, $J = 13, 10.5$ Hz) was assigned to H-9 through the correlation of its signal to that of H-1.



The relative stereochemistry of **196** was consistent with the following NOE difference experiments. Irradiation of the signal at δ 1.18 (Me-10) caused an enhancement of the signal at δ 2.49-2.52 (H-1) and vice versa. This confirmed the cis-fused nature of the ring junction. Irradiation of the signal at δ 3.74-3.77 (H-5) caused an enhancement of the signal at δ 1.56-1.70 (H-11), thereby verifying that reagent **179** had introduced the methallyl group *trans* to the angular methyl group, as predicted.

The ^1H nmr spectrum (400 MHz, CDCl_3) of the minor trans-fused epimer **176b** is illustrated in **Figure 10**. The tertiary methyl group (Me-10) was revealed as a singlet at δ 0.89; the vinyl methyl group was observed at δ 1.71 (s); the angular proton H-1 was evident as a doublet at δ 1.87-1.90 ($J = 11$ Hz); the proton H-5 was observed as a doublet of doublets at δ 3.33-3.44 ($J = 10.5, 5$ Hz); and the vinyl protons H-13 and H-13' were evident as broad singlets at δ 4.59 and 4.64, respectively. The COSY spectrum allowed the assignment of H-9 (δ 2.49-2.51, m) through the correlation of its signal to that of H-1 (see **Table 64**, experimental, page 333).



The following NOE difference experiments verified the stereochemistry of **176b**. Irradiation of the signal at δ 0.89 (Me-10) caused an enhancement of the signal at δ 2.44-2.51 (H-9) and vice versa. This not only confirmed the stereochemistry of the conjugate addition reaction, but also verified the trans-fused ring junction. Examination of molecular models indicated that an NOE between H-9 and Me-10 is only possible when the ring junction is trans-fused. Irradiation of the signal at δ 3.33-3.44 (H-5) caused an enhancement at δ 1.87-1.90 (H-1), further verifying the nature of the ring junction.

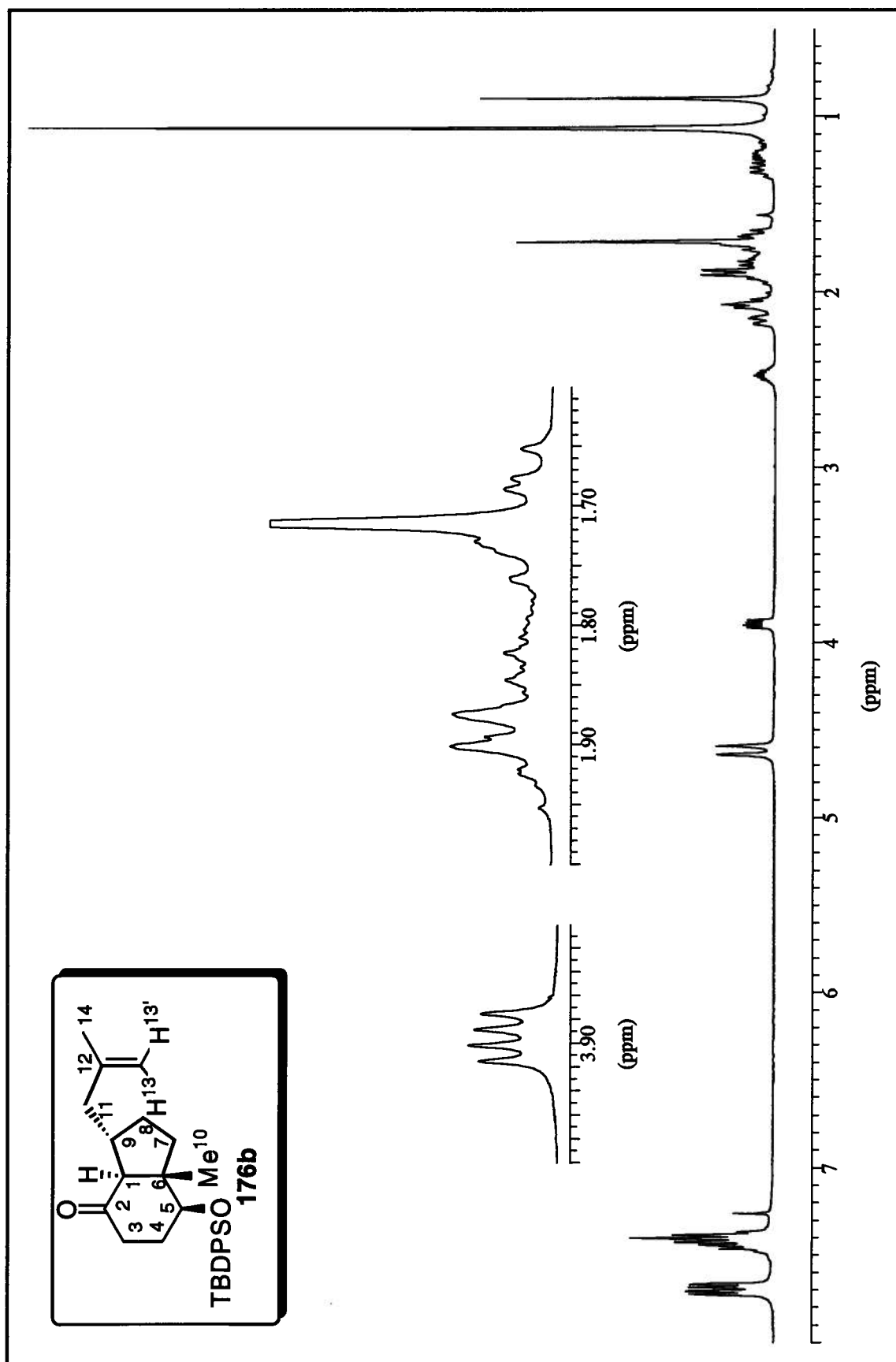
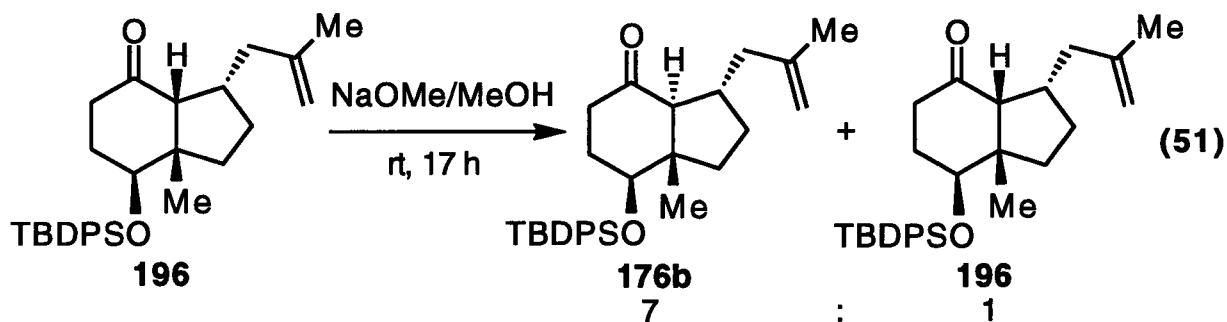
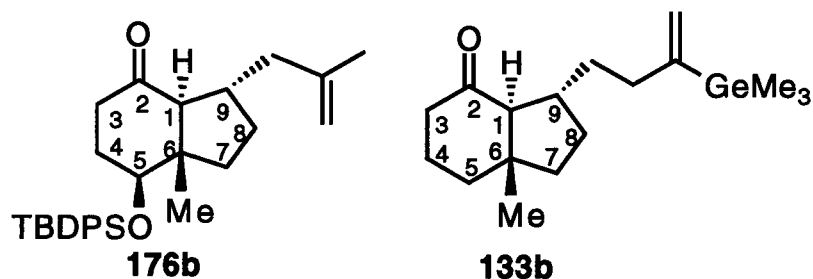


Figure 10: The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Trans-Fused Ketone 176b

The epimer required for the synthesis of (-)-homalomenol B is, in fact, the minor trans-fused isomer **176b**. According to our previous equilibration studies (see **Table 11**, page 73) and results reported by Dana and coworkers⁶³ (**Table 10**, page 71), the trans-fused epimer **176b** should be thermodynamically more stable than the corresponding cis-fused epimer **196**. In fact, treatment of **196** with NaOMe in MeOH resulted in a 7:1 mixture of **176b** and **196**, respectively (equation 51). The two epimers were separated by flash column chromatography, and the recovered cis-fused epimer **196** was resubjected to the epimerization conditions. The total yield of the trans-fused epimer **176b** after two such epimerizations was 94% (or 87% based on the enone **177b**).

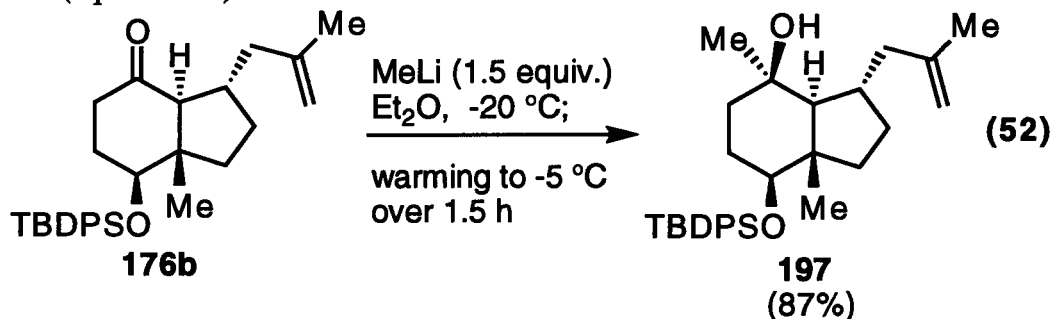


The 7:1 ratio of **176b**:**196**, obtained upon base equilibration, is similar to that observed in entry 4, **Table 11** (5:1 ratio of the trans- to cis-fused epimers **133b**:**133a**; page 73). The thermodynamically controlled base equilibrium ratio of trans- to cis-fused bicyclo[4.3.0]nonan-2-ones is very dependent on the nature and stereochemistry of the substituents at C-6 and C-9 (*vide supra*). Since **176b** and **133b** possess similar substituents in the same stereochemical orientation at carbons 6 and 9, it follows that they should have similar trans- to cis-fused ratios upon epimerization.

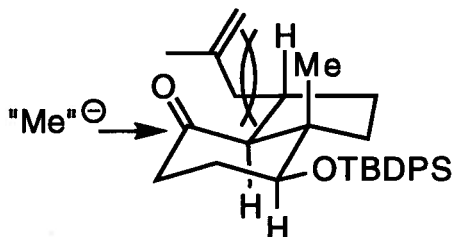


2.2.4. SYNTHESIS OF (-)-HOMALOMENOL B (**169b**)

The remaining two steps in the synthesis of (-)-homalomenol B involve the addition of a methyl carbanion to the bicyclic ketone **176b** and cleavage of the TBDPS ether function. The addition of MeLi to the carbonyl moiety of **176b** provided the tertiary alcohol **197** in 87% yield (equation 52).

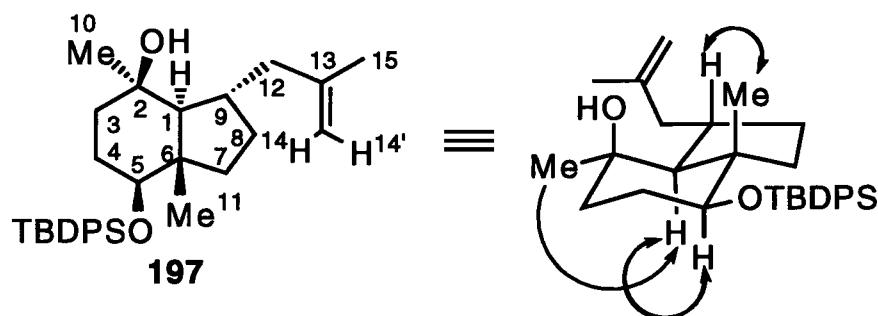


The stereochemical outcome of this conversion was based on the preferential equatorial approach of MeLi to the carbonyl carbon. Axial approach of MeLi would involve a 1,3-diaxial interaction between the angular methyl group and the incoming reagent (see below).

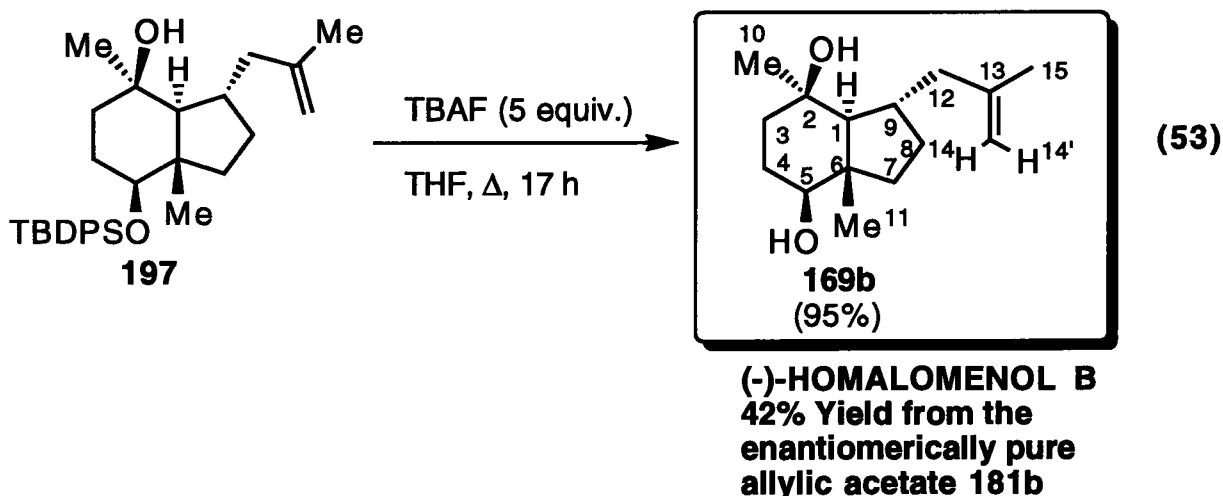


The IR spectrum of **197** indicated absorbances at 3583, 3481, 3071, and 1650 cm^{-1} , indicative of hydroxyl and olefinic moieties. The ^1H nmr spectrum (400 MHz, CDCl_3) revealed signals at δ 0.79 (br d, $J = 11$ Hz) for the angular proton H-1, δ 1.17 (s) for the newly-introduced tertiary methyl group (Me-10), δ 1.20 (d, $J = 0.6$ Hz) for the angular methyl group (Me-11), δ 3.37-3.41 (dd, $J = 11.5, 4.5$ Hz) for the proton H-5, and δ 4.66 (br s) and 4.71 (br s) for the vinyl protons H-14 and H-14', respectively. The COSY spectrum allowed the assignment of H-9 (δ 2.24-2.32, m) through the correlation of its signal to that of H-1 (see Table 66, experimental, page 339).

The following NOE difference experiments were consistent with the assigned structure **197**. Irradiation of the signal at δ 0.79 (H-1) caused an enhancement of the signal at δ 3.37-3.41 (H-5) and vice versa. Irradiation of the signal at δ 1.17 (Me-10) caused an enhancement of the signal at δ 0.79 (H-1); this result is consistent with the assigned stereochemistry of the MeLi addition. Irradiation of the signal at δ 1.20 (Me-11) caused an enhancement of the signal at δ 2.24-2.32 (H-9) and vice versa.



The final step, deprotection of the secondary alcohol, was accomplished with TBAF. The usual conditions for the cleavage of a TBDPS group involve treatment with TBAF in THF at room temperature.¹³⁶ However, the deprotection of **197** required reflux conditions for 17 hours to afford (-)-homalomenol B (**169b**) in 95% yield (equation 53). These more vigorous conditions are probably required because the secondary alcohol function is quite hindered.



(-)-Homalomenol B (**169b**) was recrystallized from ethyl acetate - petroleum ether to afford a colourless, crystalline solid, mp 94-95 °C (lit.¹²¹ mp 78-81 °C). The IR spectrum of **169b** revealed absorbances at 3632, 3371, 3070, and 1649 cm⁻¹, characteristic of hydroxyl and olefinic moieties. The ¹H nmr spectrum (400 MHz, CDCl₃) is shown in **Figure 11** and indicates signals at δ 0.92 (d, *J* = 11 Hz) for the angular proton H-1, 1.02 (br d, *J* = 0.9 Hz) for the angular methyl group (Me-11), 1.09 (br s, which disappears upon the addition of D₂O) for the tertiary alcohol proton, 1.25 (s) for the tertiary methyl group (Me-10), 1.70 (s) for the vinyl methyl group (Me-15), 3.34-3.38 (ddd, *J* = 11.5, 4.5, 4.5 Hz, which collapses to a dd (*J* = 11.5, 4.5 Hz) upon the addition of D₂O) for the proton H-5, and 4.66 (br s) and 4.71 (br s) for the vinyl protons H-14 and H-14', respectively. The results of the COSY and NOE experiments are listed in **Table 67** (experimental, page 342). The NOE difference experiments were very similar to those obtained with the precursor **197**. The IR, ¹H nmr, ¹³C nmr, and HRMS data for (-)-homalomenol B (**169b**) are consistent with those of the isolated compound (+)-homalomenol B.¹²¹ A comparison of the reported spectral data for (+)-homalomenol B (**169a**) with that of the synthetic (-)-homalomenol B (**169b**) is listed in **Table 68** (experimental, page 343). That the absolute stereochemistry of the synthetic (-)-homalomenol B is opposite to that of the natural product was confirmed by the sign of the specific optical rotation (observed [α]_D²⁰ -43.0 (*c* 1.710, CHCl₃) for the synthetic material; reported¹²¹ [α]_D²⁰ +20.4 (*c* 1.745, CHCl₃) for the natural product).

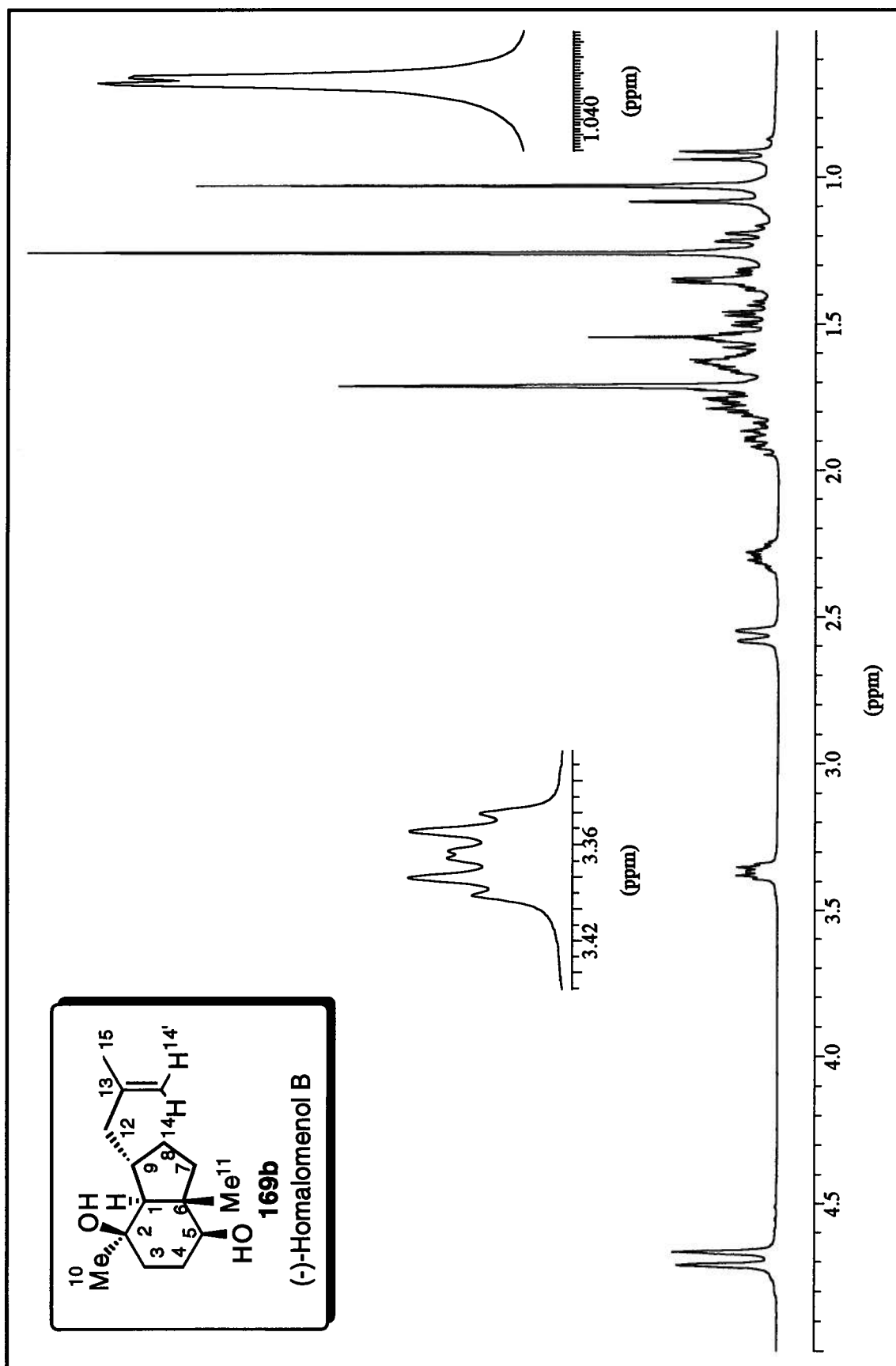


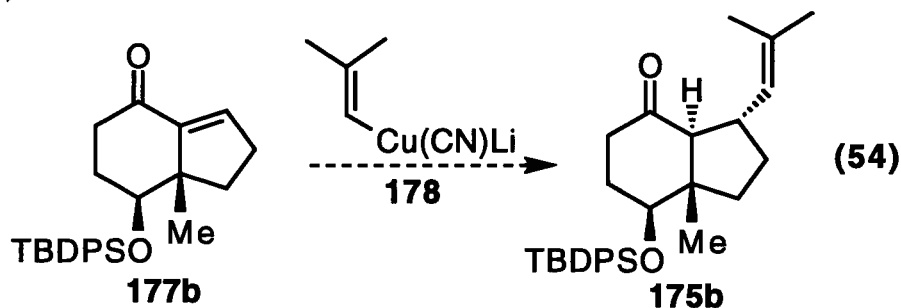
Figure 11: The ^1H nmr Spectrum (400 MHz, CDCl_3) of (-)-Homalomenol B (169b)

2.3. SYNTHESIS OF (-)-HOMALOMENOL A (**168b**)

2.3.1. PREPARATION OF THE BICYCLIC KETONE **175b**

2.3.1.1. Model Studies for the Preparation of Reagent **178**

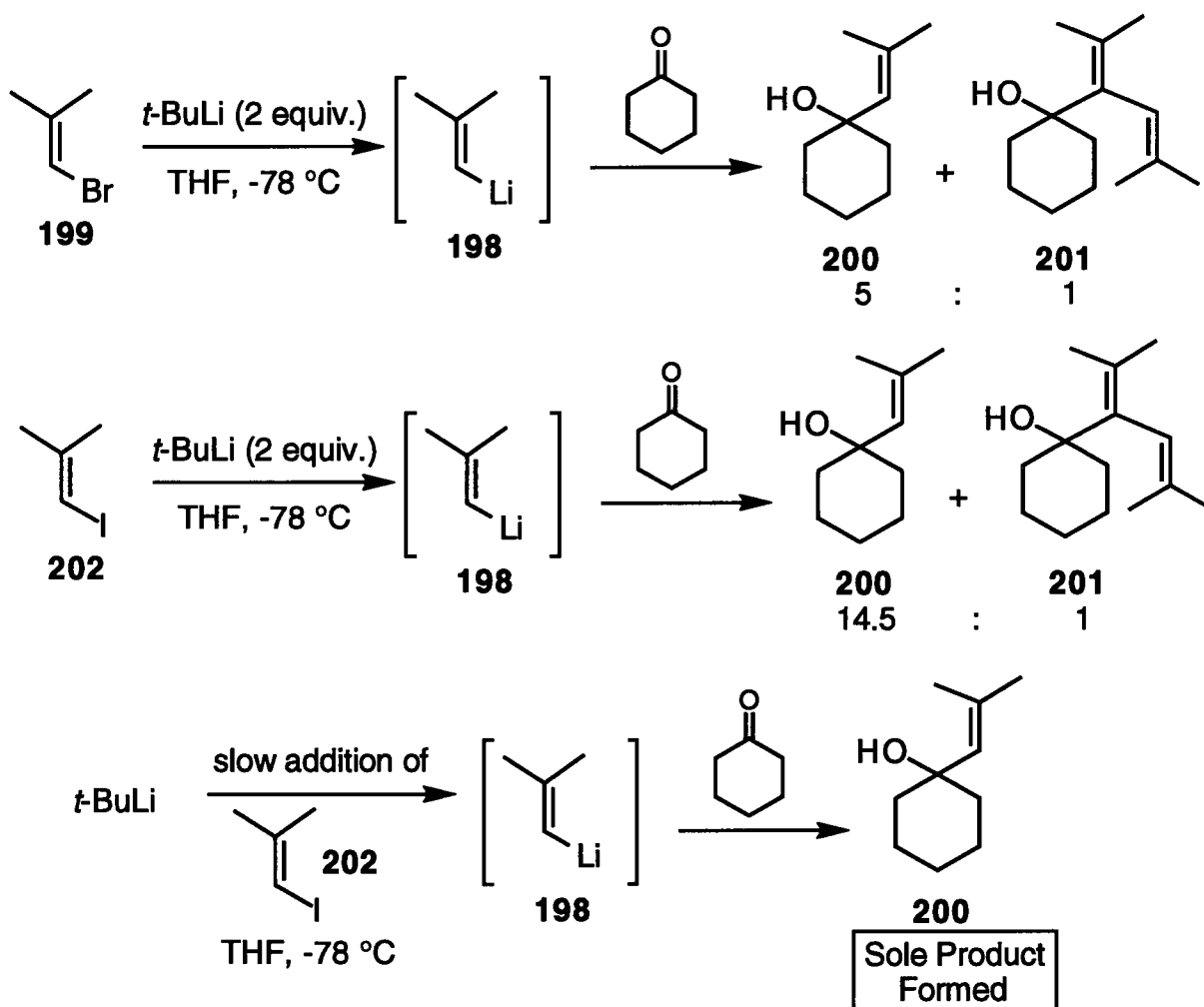
For the synthesis of (-)-homalomenol A (**168b**), we proposed the conjugate addition of the organocopper(I) reagent **178** to the enone **177b** to produce the desired ketone **175b** (equation 54).



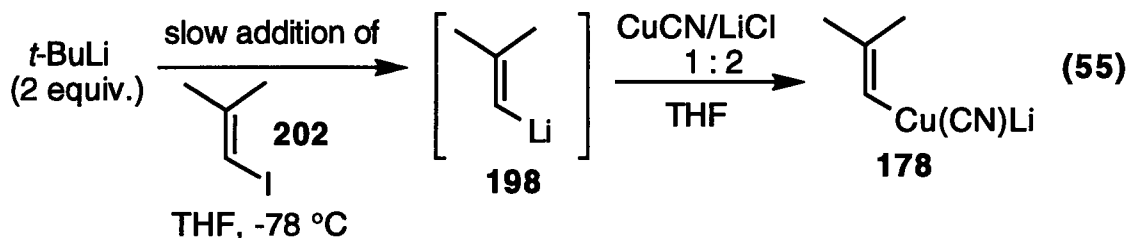
In order to prepare reagent **178**, we needed to first synthesize the vinyl lithium species **198**. The studies into the formation of **198**, using cyclohexanone as the acceptor reagent, are summarized in Scheme 36. The vinyl lithium species **198** is normally prepared from the reaction of *t*-butyllithium with 1-bromo-2-methylpropene (**199**).¹³⁷ However, our attempts at forming **198** from the reaction of *t*-butyllithium with 1-bromo-2-methylpropene (**199**) yielded a 5:1 mixture of the desired product **200** and the diene byproduct **201**, respectively. It is interesting to note there were no diene byproducts reported in any of the literature preparations and uses of **198**.¹³⁷ This problem was partially overcome by employing 1-iodo-2-methylpropene (**202**). The iodide **202** is not commercially available and was prepared according to the method of Inokawa *et al.*¹³⁸ The formation of the vinyl lithium species **198** from treatment of the iodide **202** with *tert*-butyllithium resulted in the formation of a 14.5:1 mixture of **200** and **201**, respectively. We were able to avoid the formation of diene byproduct **201** altogether by performing a slow addition of a solution of the vinyl iodide **202** in dry THF to a solution of *t*-BuLi in dry THF at -78 °C (see Scheme 36). It is at present unclear why these modifications avoid the formation of **201**; however, it should be noted that

the order of addition of the iodide **202** to *t*-BuLi is uniquely different from that reported for the formation of **198** from the bromide **199**.¹³⁷

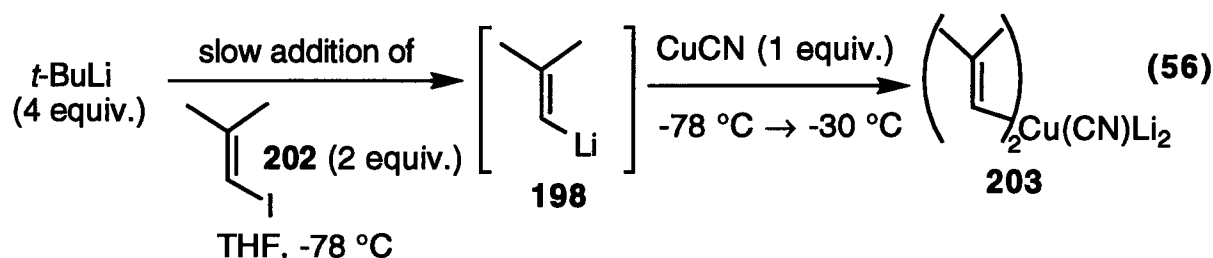
The next step in the formation of the organocopper(I) reagent **178** involved the addition of a copper(I) source to the vinyl lithium species **198**. The addition of solid CuCN to **198**, followed by warming the mixture to -35 °C, was not very effective since the copper(I) reagent decomposed at -30 to -40 °C. Thus, we opted to use a solubilized solution of CuCN (1 equiv.) and LiCl (2 equiv.) in THF¹³⁹ to avoid having to warm the organocopper(I) solution to allow for the dissolution of CuCN (equation 55).



Scheme 36



We also prepared the higher order copper(I) reagent **203** by adding one equivalent of CuCN to two equivalents of the vinyl lithium species **198** (equation 56). In this case, the solution could be warmed to -30°C to dissolve the CuCN without decomposition of the higher order organocopper(I) reagent.



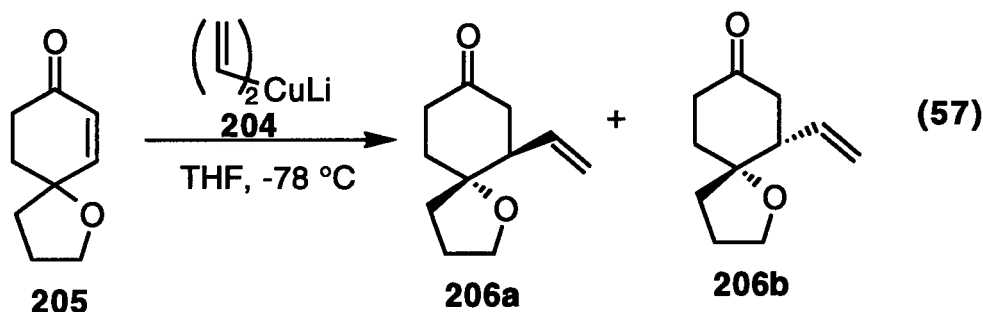
2.3.1.2. Literature Precedent on the Effects of Various Additives on the Stereoselectivity of Conjugate Addition Reactions

As will be discussed in Section 2.3.1.3. (page 300), the stereochemical outcome of the conjugate addition reaction of reagent **178** was dependent on the nature of the additives used. Thus, before examining the results of these studies, the literature precedent on the effects of various additives on the stereoselectivity of conjugate addition reactions will be outlined below.

In order to improve the chances for effecting a desired conjugate addition reaction, it is now common practice to mix either lower order (L.O.) or higher order (H.O.) cuprates with an additive such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or TMSCl , which often leads to spectacular increases in rates and yields of reactions.¹⁴⁰ It is well known that TMSX and/or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ affect the composition of H.O. organocuprates.^{140,141} For example, Lipshutz and coworkers have found that BF_3 sequesters RLi from the cuprate cluster.¹⁴¹ On the other hand, TMSX was

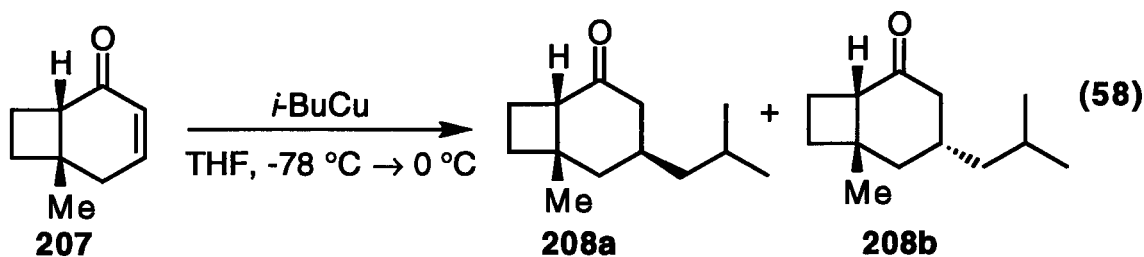
found to infiltrate the cuprate cluster by undergoing an irreversible reaction with the H.O. cuprate.¹⁴¹ The effects of these additives on the cuprate reagents must somehow be responsible for the stereochemical outcome of the addition reaction.

The effect of TMSCl on the stereochemical outcome of a conjugate addition reaction has been explored by Corey and Boaz.¹⁴² The addition of the L.O. organocopper(I) reagent **204** to the α,β -unsaturated enone **205** in the absence of TMSCl provided a 56:44 mixture of the adducts **206a** and **206b**, respectively (equation 57). In the presence of TMSCl, however, the trans isomer **206a** was the exclusive product.¹⁴³



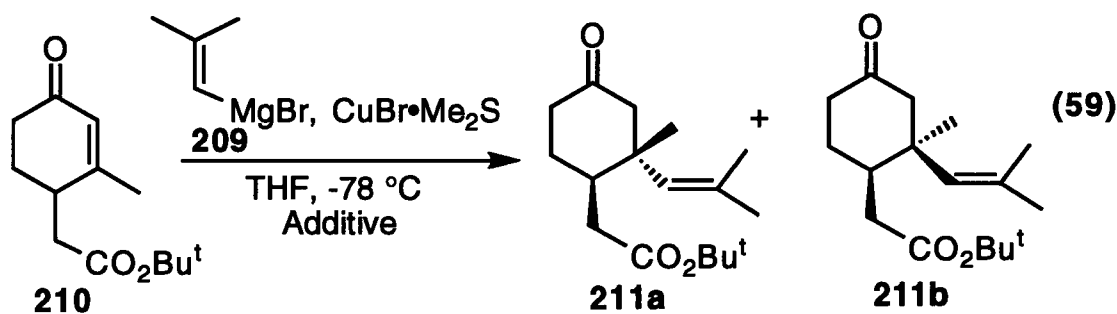
ADDITIVE	RATIO		
none	56	:	44
TMSCl	> 99	:	< 1

Helquist and Zhao¹⁴⁴ report that the stereoselectivity of the conjugate addition of an isobutyl group to the enone **207** was very sensitive to the reaction parameters. The desired isomer **208a** was obtained with a selectivity as high as 5:1 when the organocopper(I) reagent was employed in the presence of TMSCl (equation 58). On the other hand, **208b** was favored, by a factor as large as 3:1, when HMPA was also present. These results cannot, as yet, be explained but they do serve to indicate that care must be taken in choosing conditions for effecting stereoselective conjugate additions.



ADDITIVE	RATIO		
none	1	:	2.5
TMSCl	5	:	1
TMSCl + HMPA	1	:	3
BF ₃ •Et ₂ O	1.3	:	1

Another example was reported by Kuwajima and coworkers.¹⁴⁵ The use of BF₃•Et₂O as an additive changed the stereochemical outcome of the copper(I)-catalyzed addition of the Grignard reagent **209** to the enone **210**. In the absence of BF₃•Et₂O, there was no stereoselectivity observed, whereas in the presence of BF₃•Et₂O, a > 95:< 5 mixture of adducts **211a** and **211b** was obtained (see equation 59).¹⁴⁵



ADDITIVE	RATIO		
none	1	:	1
BF ₃ •Et ₂ O	> 95	:	< 5

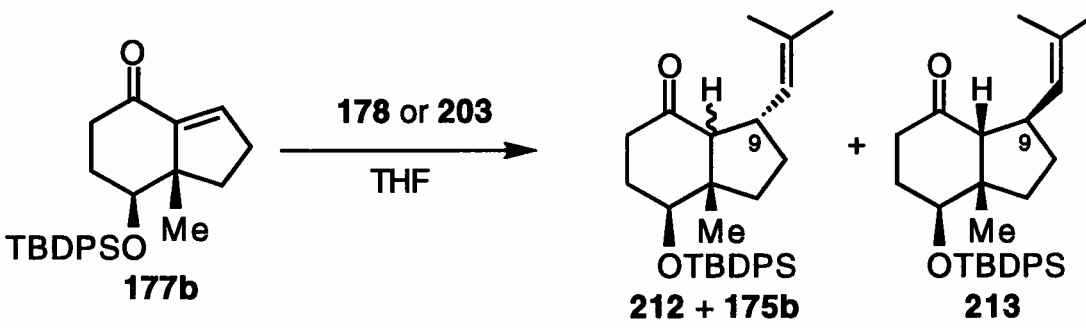
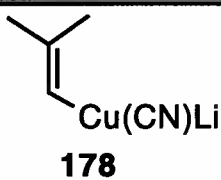
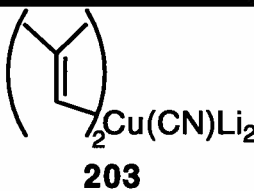
With these results in mind, we proceeded to study the conjugate addition of reagents **178** and **203** to the enantiomerically homogeneous bicyclic enone **177b**.

2.3.1.3. Conjugate Addition of the Organocopper(I) Reagents **178** and **203** to the Bicyclic Enone **177b**

Table 62 summarizes the results of the conjugate addition of reagents **178** and **203** to the enone **177b** in the presence of various additives. In entries 1-4, the L.O. organocopper(I) reagent **178** was used and a mixture of three isomers resulted. The cis- and trans-fused epimers **212** and **175b** possessed the desired stereochemistry at C-9. However, the undesired cis-fused isomer **213** was also formed, in which the configuration at C-9 was opposite to that present in compounds **212** and **175b**. The ratios of the desired adducts (**212** and **175b**) to the undesired adduct (**213**) were influenced both by the nature of the additive and the organocopper(I) reagent used. In entry 1, a 4:1 ratio was obtained; however, the reaction did not go to completion at -78 °C. When this reaction was allowed to warm to -10 °C (entry 2, **Table 62**), the reaction proceeded to completion but the ratio of the desired to undesired stereoisomers was changed from 4:1 to 1:1.4. Hence, subsequent L.O. cuprate additions were maintained at -78 °C. The use of BF₃•Et₂O and TMSBr (entry 3) forced the reaction to completion and provided a 1.9:1 mixture of desired to undesired adducts. This reaction will be discussed in more detail following the discussion of the results in **Table 62**. The use of BF₃•Et₂O alone (entry 4) provided a similar 1.8:1 ratio. The starting material was consumed but other unidentifiable byproducts were also formed.

The use of the H.O. organocopper(I) reagent **203** is detailed in entries 5-7 in **Table 62**. Inclusion of the additive TMSBr (entry 5) provided a 1:2 mixture of the desired to undesired adducts. This ratio is quite different from that obtained using the L.O. cuprate (entry 1), although it should be noted that the reaction conditions were slightly different. However, as was the case in entry 1, this reaction also did not proceed to completion. The use of BF₃•Et₂O (entries 6 and 7) allowed the reaction to proceed to completion to provide ratios ranging from 2.5:1 (entry 6) to 4.2:1 (entry 7). However, these reactions were not clean, and unidentifiable byproducts were observed in the crude ¹H nmr spectra.

Table 62: The Effects of Additives on the Conjugate Addition of Reagents **178** or **203** to the Enone **177b**

				
Entry	Organocopper(I) Reagents	Additive	Temp. and Time	RATIO ^a
1b	 178	TMSBr	-78 °C, 9.5 h	4 : 1
2	178	TMSBr	-78 °C, 6.5 h; -10 °C, 2 h	1 : 1.4
3	178	TMSBr + BF ₃ •Et ₂ O	-78 °C, 6.5 h	1.9 : 1
4 ^c	178	BF ₃ •Et ₂ O	-78 °C, 5.5 h	1.8 : 1
5d	 203	TMSBr	-78 °C, 2.5 h; -48 °C, 1 h	1 : 2
6 ^c	203	TMSBr + BF ₃ •Et ₂ O	-78 °C, 5 h; -60 °C, 4 h	2.5 : 1
7 ^c	203	BF ₃ •Et ₂ O	-78 °C, 5.5 h	4.2 : 1

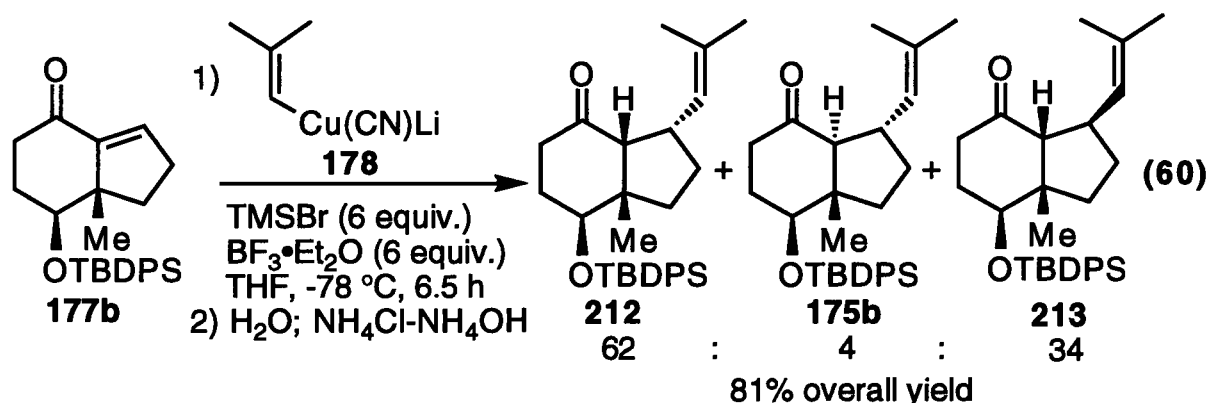
a- The ratios were determined by ¹H nmr spectroscopic analysis.

b- This reaction did not go to completion, approximately 33% starting material was recovered.

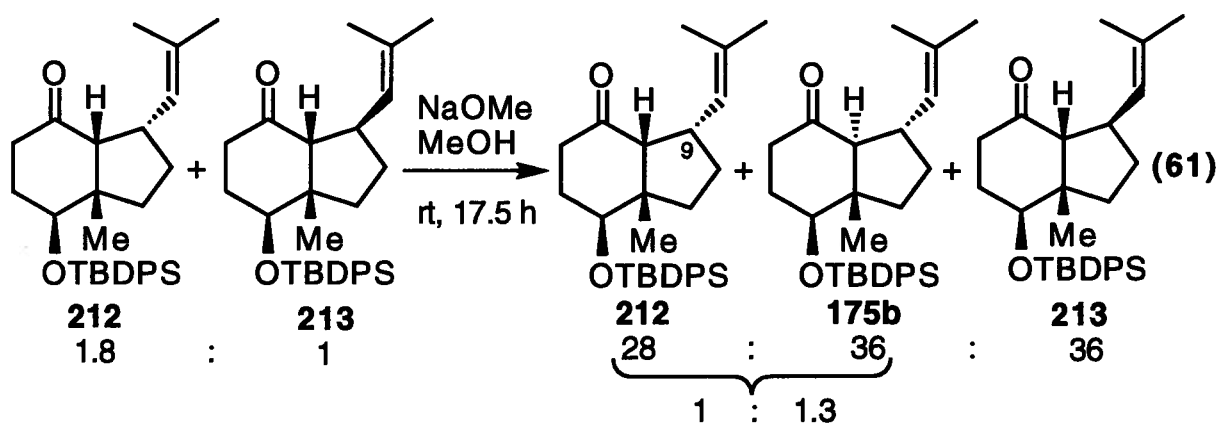
c- This reaction was not clean; other unidentifiable byproducts were observed in the crude ¹H nmr spectrum.

d- This reaction did not proceed to completion.

It is difficult to rationalize the stereochemical results summarized in **Table 62**. The conditions listed in entry 3 were found to be optimum; the reaction was clean and proceeded to completion to provide a mixture of products **212**, **175b** and **213** (62:4:34, respectively) in 81% overall yield (equation 60).

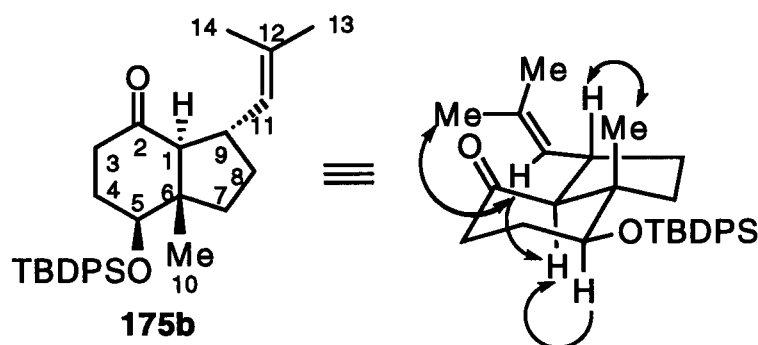


Flash column chromatography of this mixture provided compound **175b** in 3.4% yield and a mixture of the cis-fused compounds **212** and **213** in 78% yield. Fortunately, compound **212** could be epimerized to a mixture of **212** and **175b**, whereas compound **213** did not equilibrate under basic conditions. Not unexpectedly, compound **213** is thermodynamically more stable than its corresponding trans-fused epimer. Upon examination of molecular models, it is evident that the trans-fused epimer of compound **213** would be destabilized by a pseudo 1,3-diaxial interaction between the 2-methyl-1-propenyl group and the angular methyl group. Thus, when the mixture of adducts **212** and **213** was treated with NaOMe in MeOH, a 28:36:36 mixture of compounds **212**, **175b**, and **213** was produced (equation 61).



The trans-fused adduct **175b** was only slightly more stable than the cis-fused adduct **212**, as indicated by the 1.3:1 ratio obtained upon equilibration. This is in contrast to the 7:1 ratio observed for the trans- and cis-fused adducts **176b** and **196** used in the synthesis of (-)-homalomenol B (see page 290). Obviously, the nature of the substituent at C-9 has a significant effect on the thermodynamically controlled base equilibrium ratio of bicyclo[4.3.0]nonan-2-ones. The trans-fused adduct **175b** obtained upon equilibration was readily separated from the mixture by column chromatography. The remaining mixture of cis-fused adducts **212** and **213** was resubjected to the equilibration conditions and the desired isomer **175b** was obtained by chromatography. After three such epimerizations, the overall yield of the desired trans-fused epimer **175b** was 43%, based on the enone **177b**.

The ^1H nmr spectrum (400 MHz, CDCl_3) of desired epimer **175b** is illustrated in **Figure 12** and reveals signals at δ 0.91 (s) for the angular methyl group (Me-10), 1.60 (br s) and 1.70 (br s) for the vinyl methyl groups (Me-13 and Me-14, respectively), 3.03-3.10 (dddd, $J = 10.5, 10.5, 10.5, 6.5$ Hz) for the allylic proton H-9, 3.87-3.91 (dd, $J = 10.5, 5$ Hz) for the proton H-5, and 4.78 (br d, $J = 10.5$ Hz) for the vinyl proton H-11. The COSY spectrum allowed the assignment of the angular proton H-1 ($\delta \sim 2.01$, d, $J = 10.5$ Hz) through the correlation of its signal with that of H-9 (see **Table 69**, experimental, page 350).



The following NOE difference experiments were consistent with the above stereochemical assignments. Irradiation of the signal at δ 0.91 (Me-10) caused an enhancement of the signal at δ 3.03-3.10 (H-9) and vice versa, thus confirming the stereochemistry of the conjugate addition at C-9.

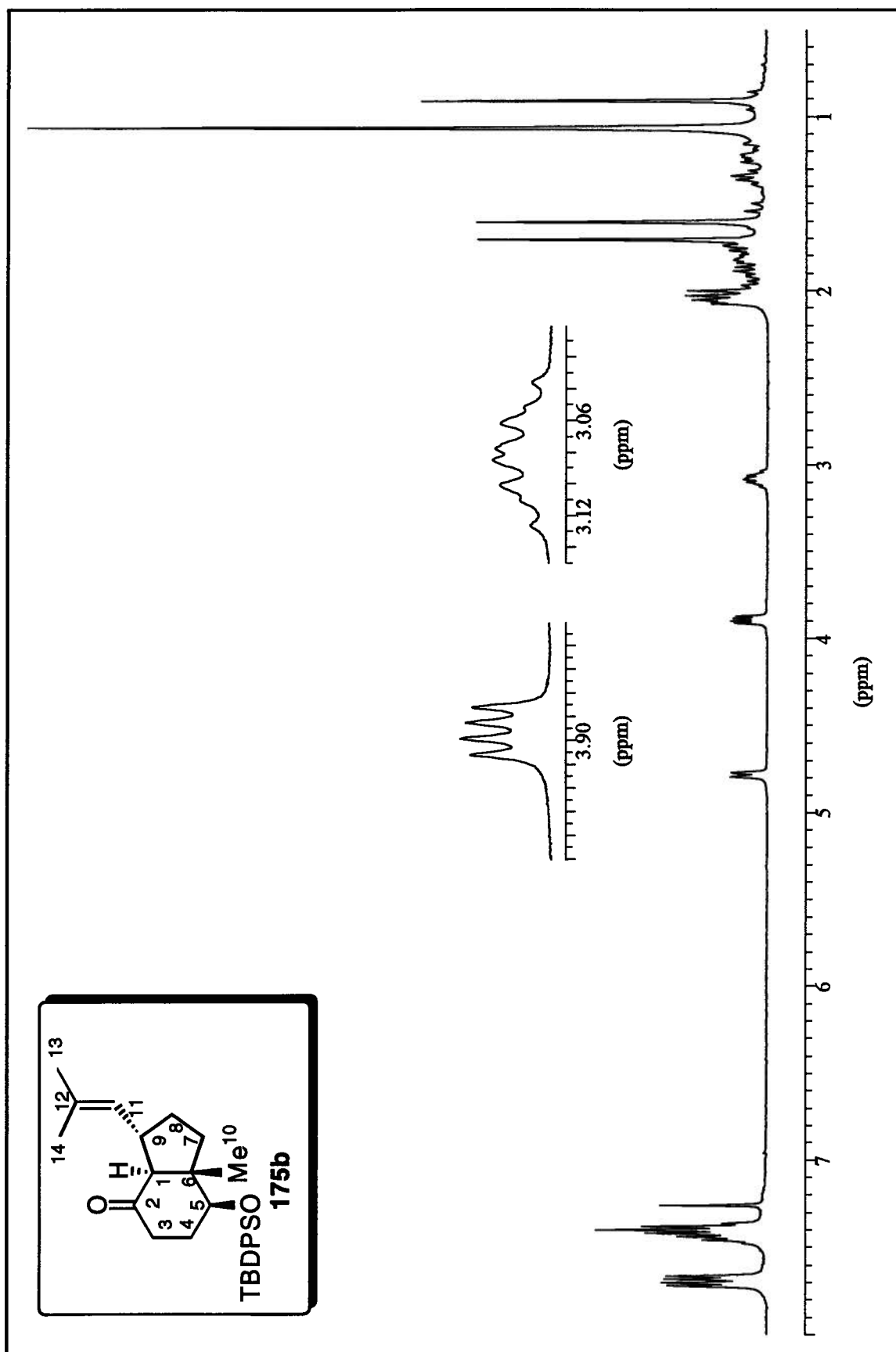
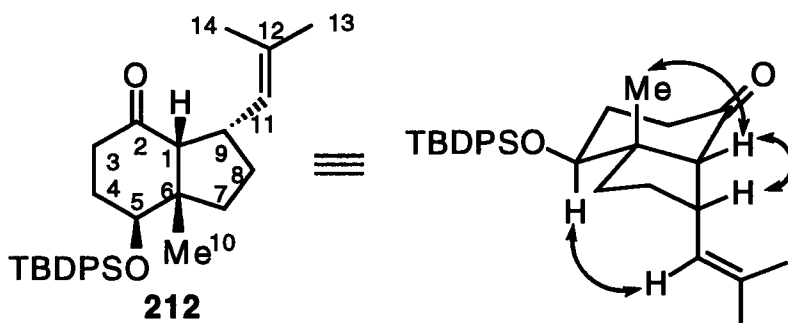


Figure 12: The ^1H nmr Spectrum (400 MHz, CDCl_3) of the Trans-Fused Ketone 175b

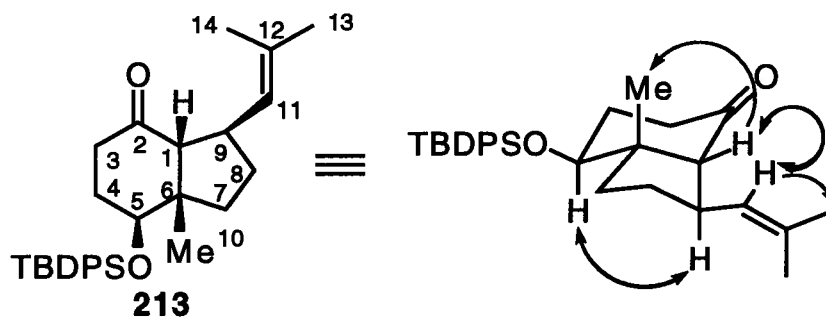
Irradiation of the signal at δ 3.87-3.91 (H-5) caused an enhancement of the signal at δ 2.01 (H-1). Irradiation of the signal at δ 4.78 (H-11) also caused an enhancement of the signal at δ 2.01 (H-1). These results are consistent with the trans-fused nature of the ring junction as well the stereochemical assignment at C-9. Irradiation of the signal at δ 1.60 (Me-13) caused an enhancement of the signal at δ 4.78 (H-11) and vice versa, thereby confirming the assignment of the vinyl methyl signals.

Column chromatography of the initial mixture of compounds **212**, **175b**, and **213** provided small amounts of pure cis-fused adducts **212** and **213**. The ^1H nmr spectrum (400 MHz, CDCl_3) of **212** possessed signals at δ 1.17 (s) for the angular methyl group (Me-10), 1.43 (d, $J = 0.8$ Hz) and 1.50 (br s) for the vinyl methyl groups (Me-14 and Me-13, respectively), 2.48-2.51 (br dd, $J = 10, 2$ Hz) for the angular proton H-1, 3.12-3.21 (m) for the allylic proton H-9, 3.77-3.81 (br dd, $J = 10.5, 5$ Hz) for the proton H-5, and 4.51 (br d, $J = 10$ Hz) for the vinyl proton H-11.

The stereochemical assignments were consistent with the following NOE difference experiments. Irradiation of the signal at δ 1.17 (Me-10) caused an enhancement of the signal at δ 2.48-2.51 (H-1), verifying the cis-fused nature of this compound. Irradiation of the signal at δ 2.48-2.51 (H-1) caused an enhancement of the signals at δ 1.17 (Me-10) and 3.12-3.21 (H-9) and vice versa. This result was consistent with the assigned stereochemistries at C-6, C-1, and C-9. Irradiation of the signal at δ 3.77-3.81 (H-5) caused an enhancement of the signal at δ 4.51 (H-11) and vice versa.



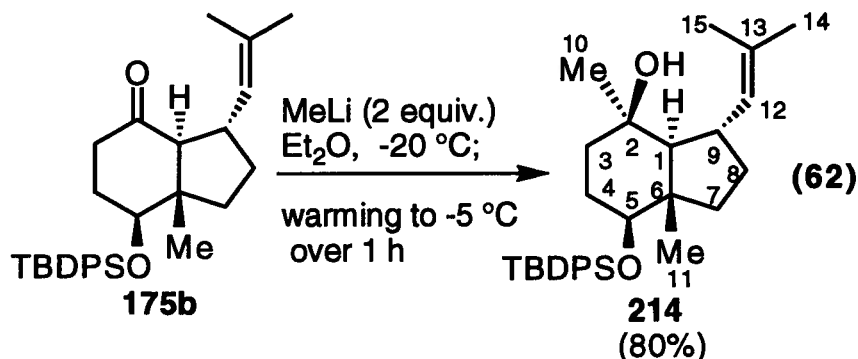
The ^1H nmr spectrum (400 MHz, CDCl_3) of the remaining isomer **213** revealed signals at δ 1.16 (s) for the angular methyl group (Me-10), 1.42 (d, $J = 1$ Hz) and 1.61 (d, $J = 1$ Hz) for the vinyl methyl groups (Me-14 and Me-13, respectively), 2.00 (d, $J = 11.5$ Hz) for the angular proton H-1, 2.79-2.88 (m) for the allylic proton H-9, 3.86-3.91 (dd, $J = 10.5$, 4 Hz) for the proton H-5, and 4.92 (br d, $J = 9$ Hz) for the vinyl proton H-11.



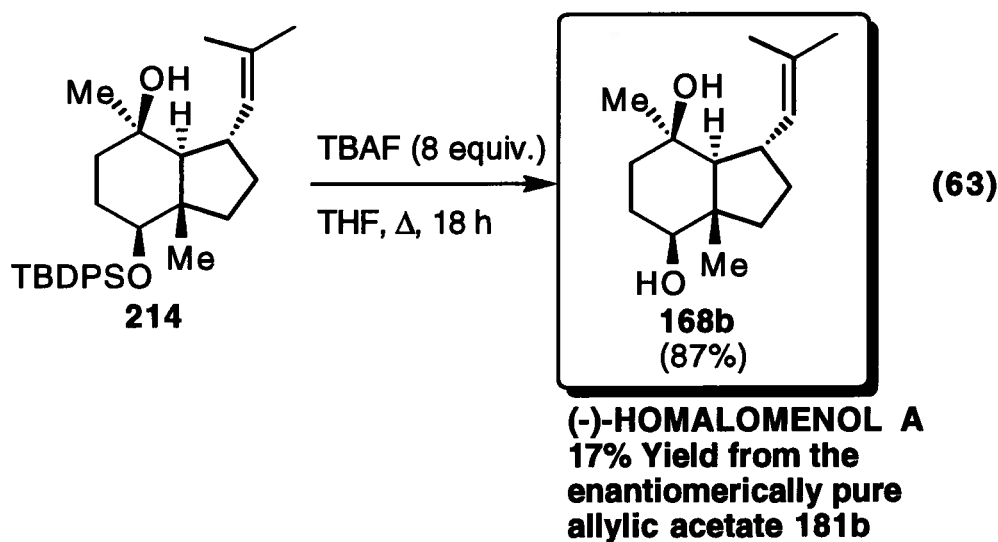
The following NOE difference experiments were consistent with the stereochemistry depicted above. Irradiation of the signal at δ 2.00 (H-1) caused an enhancement of the signals at δ 1.16 (Me-10) and 4.92 (H-11). Irradiation of the signal at δ 4.92 (H-11) caused an enhancement of the signals at δ 1.61 (Me-13) and 2.00 (H-1). Irradiation of the signal at δ 3.86-3.91 (H-5) caused an enhancement of the signal at δ 2.79-2.88 (H-9). These experiments were consistent with the assignment of the cis-fused ring junction as well as the assignment of the stereochemistry of the conjugate addition at C-9 (i.e. the 2-methyl-1-propenyl group had been introduced cis to the angular methyl group).

2.3.2. SYNTHESIS OF (-)-HOMALOMENOL A (**168b**)

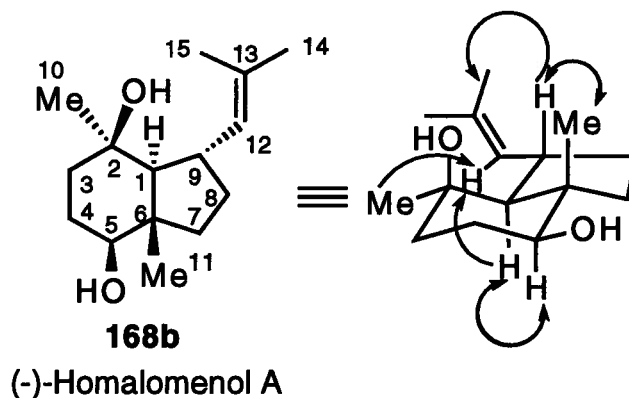
The next step in the synthesis of (-)-homalomenol A (**168b**) involved the stereoselective addition of MeLi to the carbonyl moiety of **175b** to provide the tertiary alcohol **214** in 80% yield (equation **62**).



The stereochemical outcome of this transformation was based on the preferential equatorial approach of MeLi to the carbonyl carbon (see page 291). The ^1H nmr spectrum (400 MHz, CDCl_3) of **214** revealed signals at δ 0.86 (d, $J = 11.5$ Hz) for the angular proton H-1, 0.97 (s, which exchanges upon treatment with D_2O) for the tertiary hydroxyl proton, 1.01 (s) for the angular methyl group (Me-11), 1.21 (s) for the newly introduced tertiary methyl group (Me-10), 1.62 (d, $J = 1$ Hz) and 1.63 (d, $J = 1$ Hz) for the vinyl methyl groups Me-13 and Me-14, 2.86-2.95 (m) for the allylic proton H-9, 3.35-3.39 (dd, $J = 11.5, 4$ Hz) for the proton H-5, and 5.00 (br d, $J = 9.5$ Hz) for the vinyl proton H-12.



In the final step, the deprotection of the secondary alcohol was accomplished by refluxing a solution of **214**, TBAF (8 equivalents), and THF for 17 h (equation **63**). (-)-Homalomenol A (**168b**) was obtained in 87% yield and was recrystallized from diethyl ether - petroleum ether to provide thin, needle-like plates, mp 99-100 °C (lit.¹²¹ reports (+)-homalomenol A as an oil). The IR spectrum of **168b** revealed absorbances at 3617, 3434, and 1581 cm^{-1} , characteristic of hydroxyl and olefinic moieties. The ^1H nmr spectrum (400 MHz, CDCl_3) is illustrated in **Figure 13** and indicates signals at δ 0.99 (br d, $J = 11.5$ Hz) for the angular proton H-1, 1.04 (d, $J = 0.7$ Hz) for the angular methyl group (Me-11), 1.10 (s) for the tertiary methyl group Me-10, 1.63 (d, $J = 1.5$ Hz) and 1.64 (d, $J = 1.5$ Hz) for the vinyl methyl groups Me-14 and Me-15, 2.88-2.98 (m) for the allylic proton H-9, 3.35-3.38 (dd, $J = 11.4, 4.1$ Hz) for the proton H-5, and 5.05 (br d, $J = 9.5$ Hz) for the vinyl proton H-12.



The following NOE difference experiments were consistent with the assigned stereochemistry of (-)-homalomenol A (**168b**). Irradiation of the signal at δ 0.99 (H-1) caused an enhancement of the signals at 3.35-3.38 (H-5) and 5.05 (H-12). Irradiation of the signal at δ 1.04 (Me-11) caused an enhancement of the signal at δ 2.88-2.98 (H-9) and vice versa. Irradiation of the signal at δ 1.10 (Me-10) caused an enhancement of the signal at δ 5.05 (H-12). Irradiation of the signal at δ 2.88-2.98 (H-9) caused an enhancement of the signals at δ 1.04 (Me-11) and 1.64 (Me-15). Irradiation of the signal at δ 3.35-3.38 (H-5) caused an enhancement of the signal at δ 0.99 (H-1).

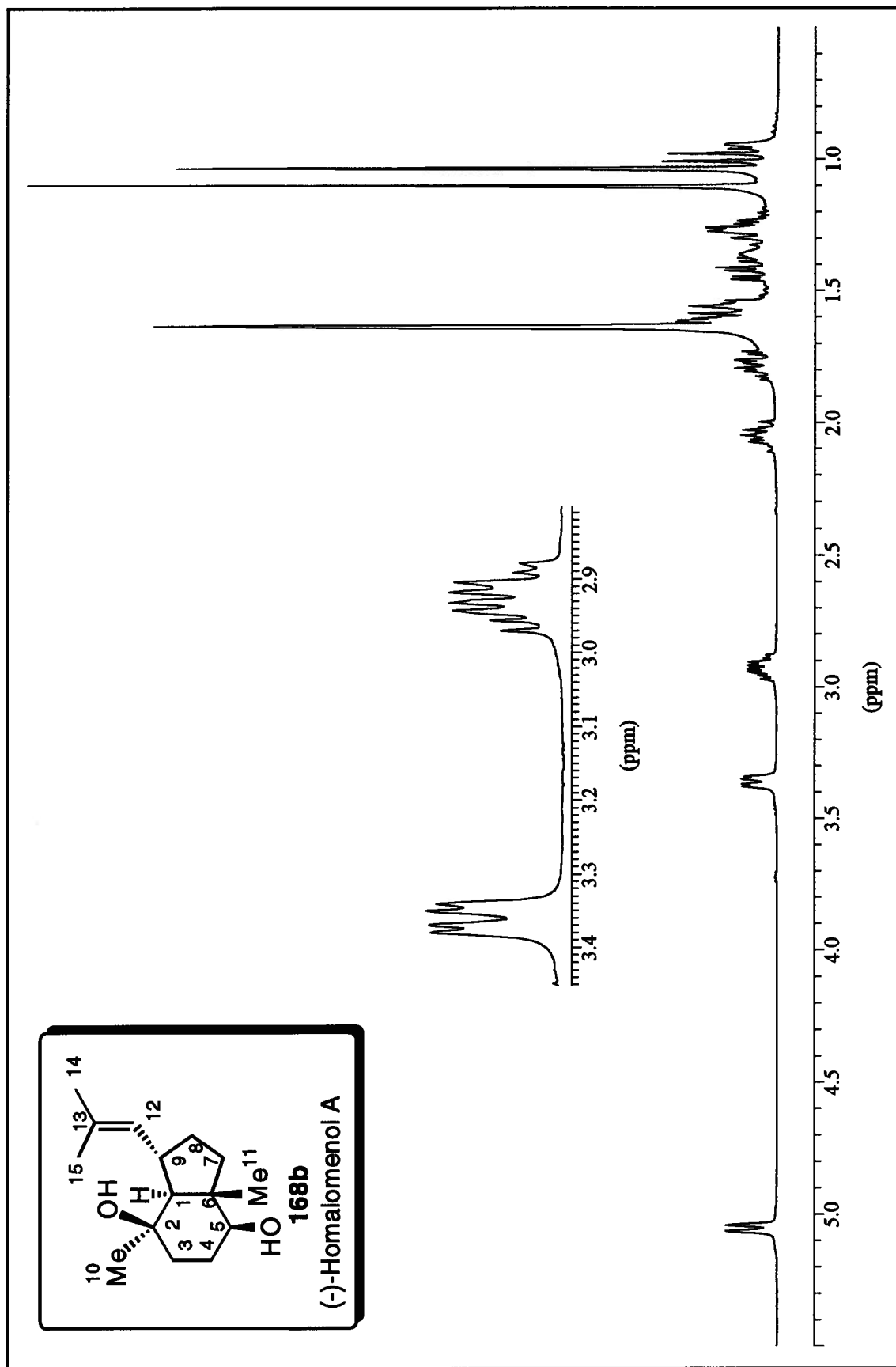
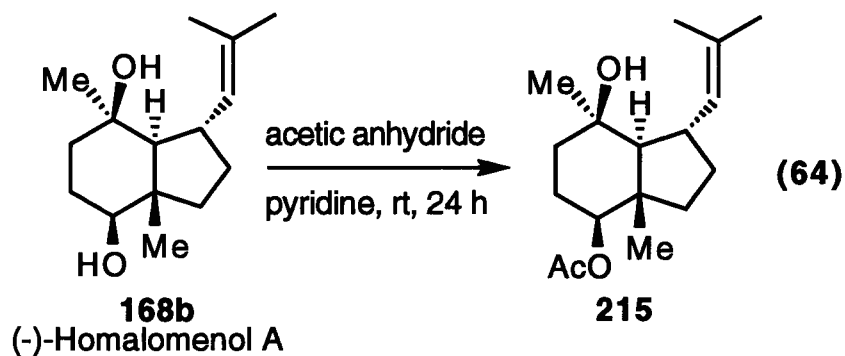


Figure 13: The ^1H nmr Spectrum (400 MHz, CDCl_3) of (-)-Homalomenol A (168b)

The IR, ^1H nmr, ^{13}C nmr, and HRMS data for (-)-homalomenol A (**168b**) are consistent with those of the isolated (+)-homalomenol A (**168a**).¹²¹ A comparison of the reported spectral data for (+)-homalomenol A with that of the synthetic (-)-homalomenol A is listed in **Table 72** (experimental, page 360). The absolute stereochemistry of the synthetic (-)-homalomenol A is opposite to that of the natural product. This was confirmed by the sign of the specific optical rotation (observed $[\alpha]_{\text{D}}^{20}$ -51.5 (c 1.30, CHCl_3) for the synthetic material; reported¹²¹ $[\alpha]_{\text{D}}^{20}$ +33.2 (c 1.205, CHCl_3) for the natural product).

2.3.3. SYNTHESIS OF THE (-)-MONOACETATE **215**

The conversion of (-)-homalomenol A (**168b**) to the monoacetate **215** was accomplished in 98% yield by reaction with acetic anhydride and pyridine (equation 64). The ^1H nmr spectrum (400 MHz, CDCl_3) of the synthetic **215** is illustrated in **Figure 14** and reveals a signal at δ 2.01 (s) for the newly introduced acetoxy methyl group. The ^1H nmr spectrum (200 MHz, CDCl_3) of the (+)-monoacetate **215** derived from the natural product is shown in **Figure 15**¹⁴⁶ and is similar to the spectrum of the synthetic monoacetate **215**.



A comparison of the reported spectral data for the (+)-monoacetate **215** with that of the synthetic (-)-monoacetate **215** is listed in **Table 73** (experimental, page 362) and indicates that these two products are enantiomers.

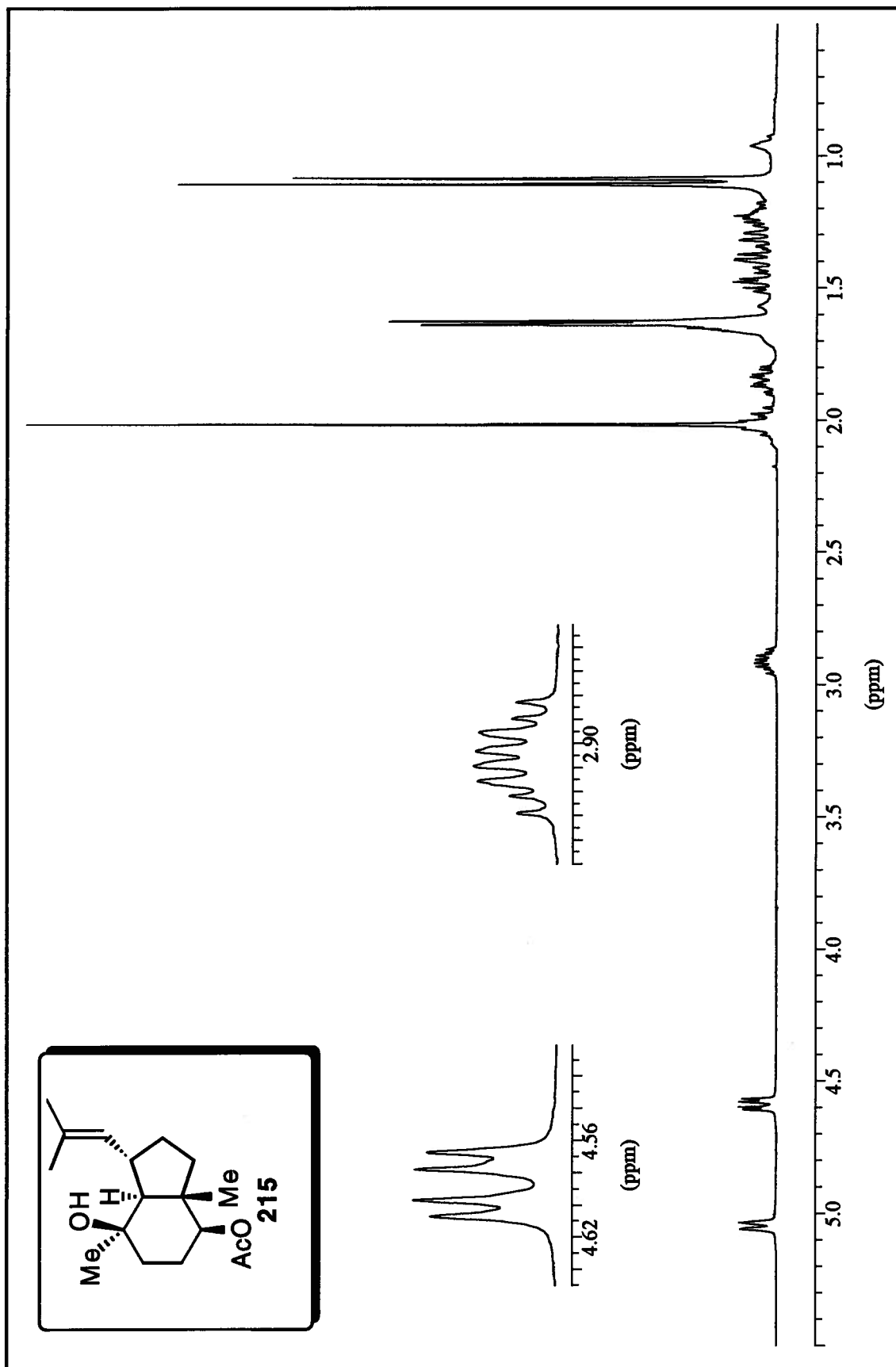


Figure 14: The ^1H nmr Spectrum (400 MHz, CDCl_3) of the (-)-Monoacetate 215

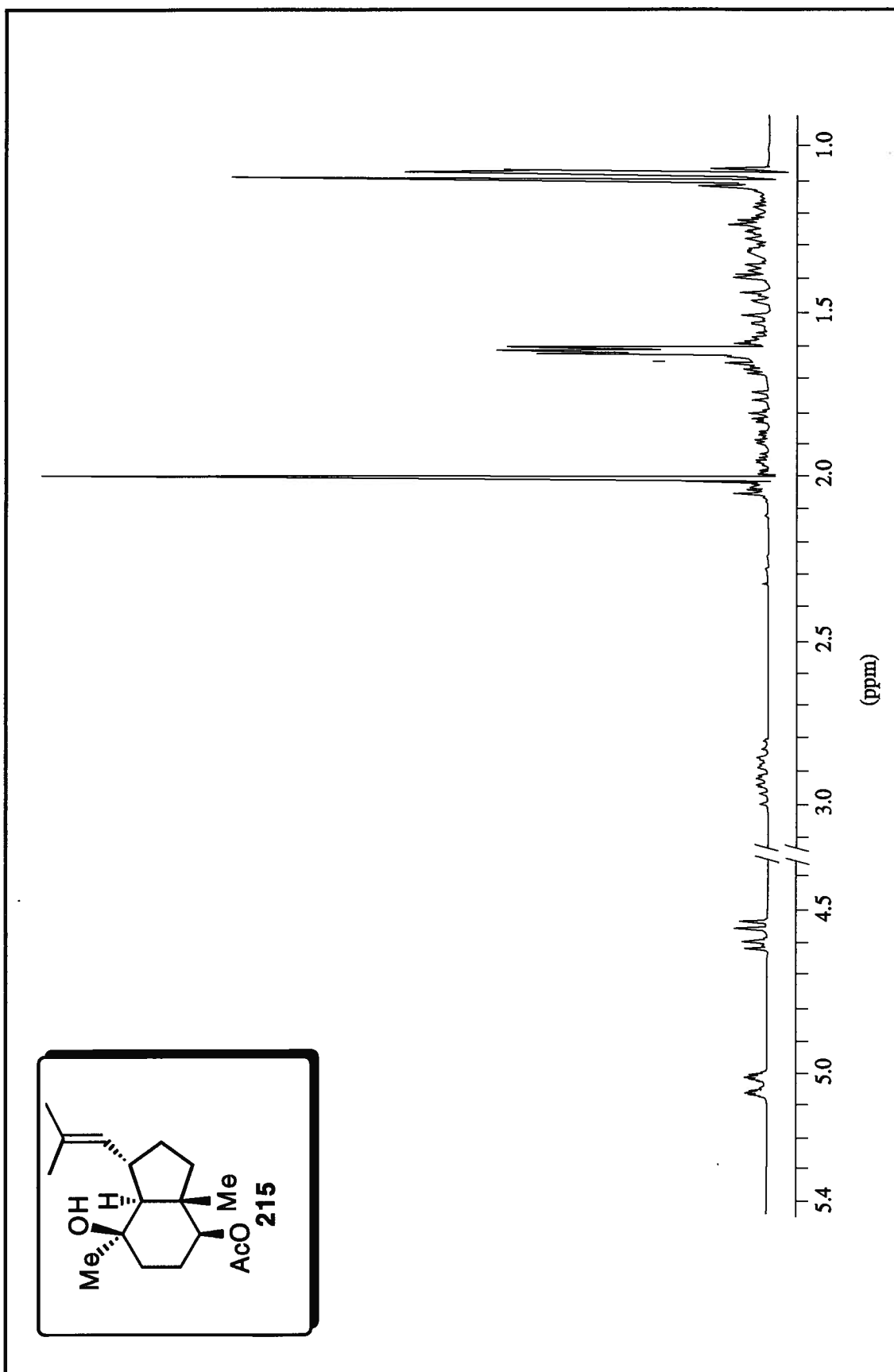
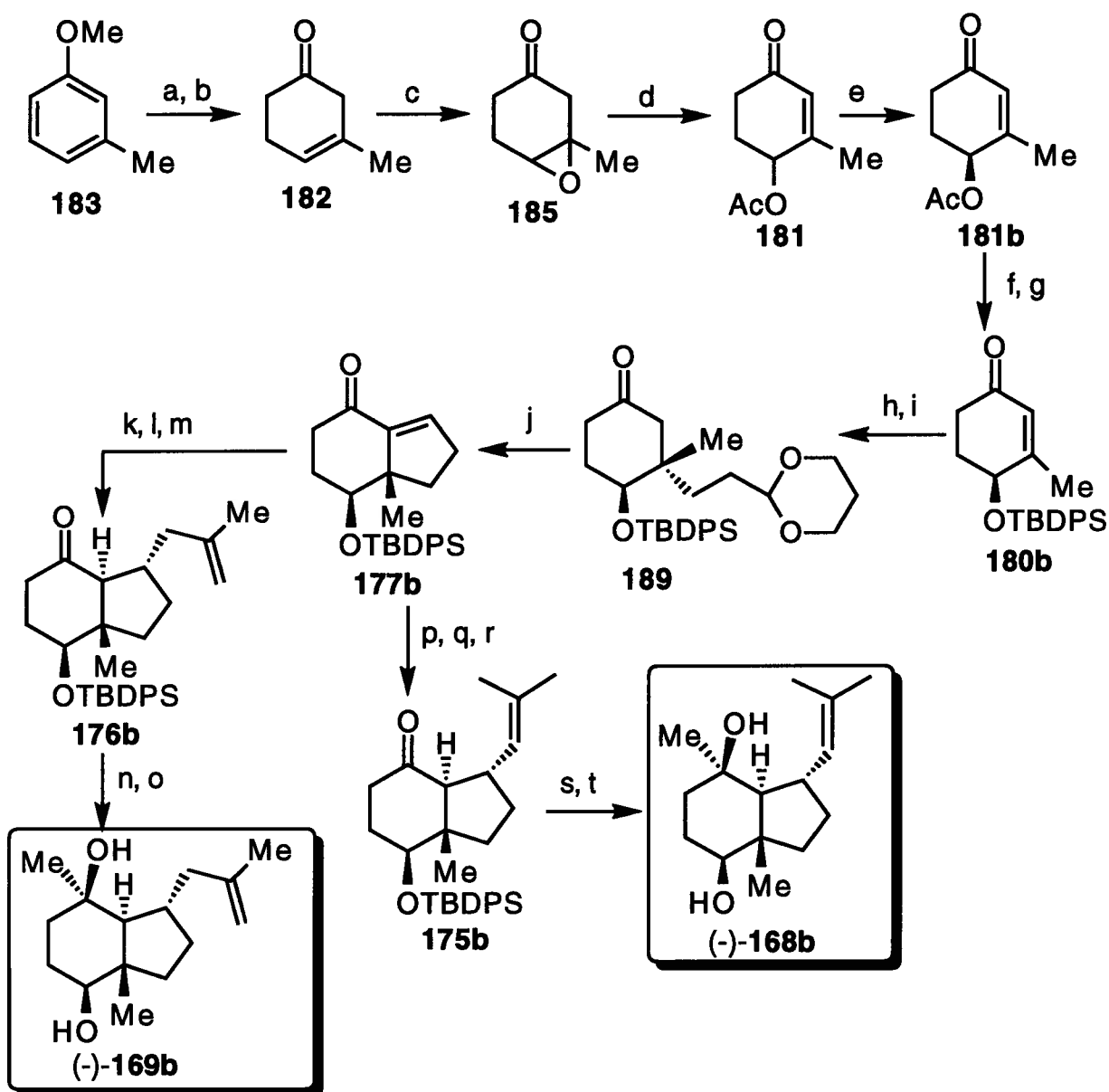


Figure 15: The ^1H nmr Spectrum (200 MHz, CDCl_3) of the (+)-Monoacetate 215 from Dr. T. V. Sung

2.4. CONCLUSION

The work described in Part 2 of this thesis culminated in the first total syntheses of two sesquiterpene alcohols, (-)-homalomenol A (**168b**) and (-)-homalomenol B (**169b**). The key steps of the overall synthetic sequences involved the conjugate addition of the organocopper(I) reagents **178** and **179** to the enantiomerically homogeneous bicyclic enone **177b**. In the synthesis of (-)-homalomenol B (**169b**), this conjugate addition reaction proceeded stereoselectively to provide the desired adduct **176b** in excellent yield. However, in the synthesis of (-)-homalomenol A (**168b**), the stereochemical outcome of the conjugate addition of **178** to the enone **177b** proved to be dependent on the nature of the additive. Nonetheless, the desired adduct **175b** was obtained, albeit in moderate yield, and the synthesis of **168b** was successfully completed. A summary of the syntheses of **168b** and **169b** is displayed in **Scheme 37**.



(a) Li/NH₃, Et₂O, *t*-BuOH, -33 °C; (b) oxalic acid, MeOH:H₂O (3:1), rt, 84%; (c) *m*-CPBA (1.3 equiv.), CH₂Cl₂, 0 °C, 94%; (d) (AcO)₂O (2 equiv.), *i*-Pr₂EtN (2 equiv.), DMAP (0.2 equiv.), CH₂Cl₂, 6 h, rt, 84%; (e) 0.3 M Tris-HCl (pH 7), 25% DMSO, PLE, 20 °C, 26 h (59% conversion), 40%, > 99% ee; (f) Na₂CO₃ (5 equiv.), MeOH, rt, 1.5 h; (g) TBDPSCl (2 equiv.), imidazole (4 equiv.), DMF, rt, 15 h, 80%; (h) reagent **97**, TMSCl (2.5 equiv.), HMPA (2.5 equiv.), CuBr·Me₂S (15 mol%), THF, -78 °C, 3 h, warming to -50 °C over 2.5 h; (i) H₂O; NH₄Cl-NH₄OH, 88%; (j) 80% aqueous CF₃COOH/dioxane (1:2), 70 °C, 16 h, 82%; (k) reagent **179**, TMSBr (7 equiv.), -78 °C, 5.5 h; (l) H₂O; NH₄Cl-NH₄OH; (m) NaOMe/MeOH, rt, 17 h, 87%; (n) MeLi (1.5 equiv.), Et₂O, -20 °C, warming to -5 °C over 1.5 h, 87%; (o) TBAF (5 equiv.), THF, Δ, 17 h, 95%; (p) reagent **178**, TMSBr (6 equiv.), BF₃·Et₂O (6 equiv.), THF, -78 °C, 6.5 h; (q) H₂O; NH₄Cl-NH₄OH; (r) NaOMe/MeOH, rt, 17.5 h, 43%; (s) MeLi (1.5 equiv.), Et₂O, -20 °C, warming to -5 °C over 1 h, 80%; (t) TBAF (8 equiv.), THF, Δ, 18 h, 87%.

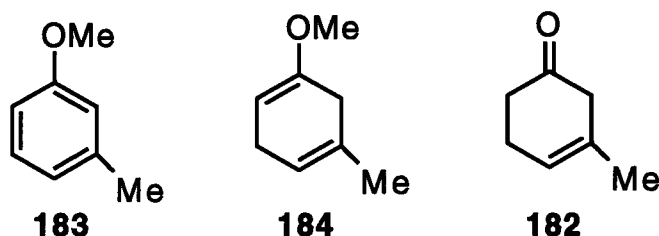
Scheme 37

III. EXPERIMENTAL

3.1. SYNTHESIS OF (-)-HOMALOMENOL B (169b)

3.1.1. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS ALLYLIC ACETATE **181b**

3.1.1.1. Synthesis of 3-Methyl-3-cyclohexen-1-one (**182**):¹⁴⁷

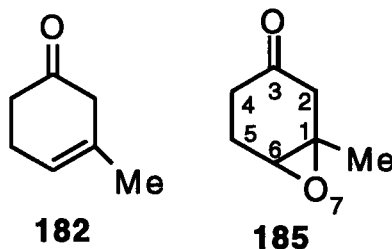


To cold (-78 °C), stirred liquid ammonia (200 mL, distilled from sodium) was added a solution of 3-methylanisole (**183**) (8.3 mL, 66 mmol, 1 equiv.) in dry diethyl ether (50 mL). This was followed by the addition of *tert*-butyl alcohol (62 mL, 660 mmol, 10 equiv.). Lithium metal (2.3 g, 330 mmol, 5 equiv.) was added in small portions over a period of 15 min. The blue solution was refluxed at -33 °C for 3.5 h. The reaction mixture was cooled to -78 °C and the excess lithium metal was destroyed by the portion-wise addition of solid ammonium chloride (52 g, 970 mmol, 15 equiv.). The cloudy white suspension was opened to the atmosphere via an air cooled condenser and the ammonia was allowed to evaporate. Pentane (150 mL) was added and the flask was warmed in a water bath to drive off any residual ammonia. Water (150 mL) was added and the layers were separated. The aqueous layer was extracted with pentane (2 x 90 mL) and the combined organic extracts were washed with water (4 x 100 mL) until no change in the volume of the water extract was noted. The organic extracts were dried over anhydrous magnesium sulfate and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm) to avoid loss of product.

The crude enol ether **184** was dissolved in 130 mL of methanol-water (3:1); to the mixture was added oxalic acid dihydrate (412 mg, 3.30 mmol, 5 mol% with respect to 3-methylanisole) and the resultant mixture was stirred at rt for 1.5 h. Water (200 mL) was added and the suspension was extracted with CH₂Cl₂ (6 x 100 mL) until the extracts no longer contained any product, as indicated by glc analysis. The combined organic extracts were washed with water (1 x 100 mL), dried over anhydrous magnesium sulfate, and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm). The oil thus obtained was distilled (88 °C/50 Torr) to give 6.0 g (84%) of 3-methyl-3-cyclohexen-1-one (**182**)¹⁴⁸ (lit.¹⁴⁹ bp 61-62 °C/14 Torr). This compound is stable when stored in the freezer under an atmosphere of argon.

¹H nmr (400 MHz, C₆D₆) δ: 1.35 (br s, 3H, Me), 1.90 (br s, 2H), 2.07 (t, 2H, *J* = 8 Hz), 2.42 (br s, 2H), 5.17 (br s, 1H, vinyl proton).

¹³C nmr (75.3 MHz, C₆D₆) δ: 22.6 (-ve, Me), 25.1, 38.1, 44.3, 121.0 (-ve, C-4), 132.3 (C-3), 207.6 (C-1).

3.1.1.2. Synthesis of 1-Methyl-7-oxabicyclo[4.1.0]heptan-3-one (**185**):^{150,124}

To a cold (0 °C), stirred solution of *m*-CPBA (purity 50-60%, 4.30 g, 12.5 mmol, 1.3 equiv.) in dry CH₂Cl₂ (90 mL) was added, via a large cannula, a solution of 3-methyl-3-cyclohexen-1-one (**182**) (1.05 g, 9.53 mmol) in dry CH₂Cl₂ (5 mL). After the mixture had been stirred at 0 °C for 2.5 h, excess *m*-CPBA was destroyed by the addition of saturated aqueous Na₂S₂O₃ (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (5 x 100 mL, to extract the 3-chlorobenzoic acid byproduct), dried over anhydrous magnesium sulfate, and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm). The oil thus obtained was distilled (80 °C/32 Torr) to afford 1.12 g (94%) of the epoxide **185**.

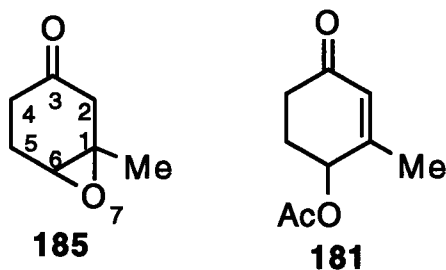
IR (film): 1713, 1198, 1044 cm⁻¹.

¹H nmr (400 MHz) δ: 1.36 (s, 3H, Me), 2.14-2.19 (m, 2H), 2.34-2.40 (m, 2 H), 2.56 (d, 1 H, *J* = 19 Hz, H-2), 2.78 (d, 1H, *J* = 19 Hz, H-2'), 3.20 (br d, 1 H, *J* = 2.5 Hz, H-6).

¹³C nmr (75.3 MHz) δ: 22.1, 22.3 (-ve, Me), 33.8, 43.8, 56.7, 58.1 (-ve, C-6), 207.7 (C-3).

Exact Mass calcd. for C₇H₁₀O: 126.0681; found: 126.0677.

Anal. calcd. for C₇H₁₀O: C 66.64, H 7.99; found: C 66.51, H 8.03.

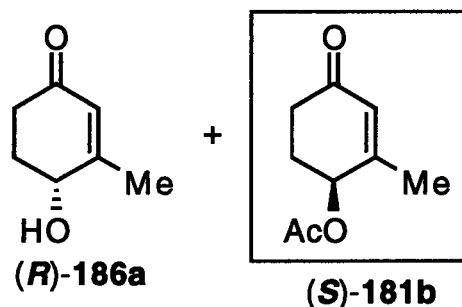
3.1.1.3. Synthesis of 4-Acetoxy-3-methyl-2-cyclohexen-1-one (**181**):¹⁵¹

To a stirred solution of the epoxide **185** (4.19 g, 33.2 mmol, 1 equiv.) in dry CH_2Cl_2 (110 mL) at rt was added dry acetic anhydride (6.3 mL, 66 mmol, 2 equiv.), DMAP (812 mg, 6.6 mmol, 0.2 equiv.), and dry *i*-Pr₂NEt (11.6 mL, 66.5 mmol, 2 equiv.). The mixture was stirred at rt for 6 h. Ethyl acetate (100 mL) and saturated aqueous NaHCO_3 (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 75 mL) and the combined organic extracts were washed with saturated aqueous NaHCO_3 (2 x 100 mL) and water (1 x 100 mL). The organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was flash chromatographed (300 g silica gel, 1:1 petroleum ether - CH_2Cl_2) and the oil thus obtained was distilled (air-bath temperature 90-94 °C/0.2 Torr) to provide 4.7 g (84%) of the allylic acetate **181**.¹⁵²

¹H nmr (400 MHz) δ : 1.94 (br dd, 3H, $J = 1, 1$ Hz, vinyl Me), 1.95-2.12 (m, 1H), 2.13 (s, 3H, -OC(O)CH₃), 2.21-2.31 (m, 1H), 2.36-2.44 (ddd, 1H, $J = 17, 10, 5$ Hz, H-6), 2.52-2.59 (ddd, 1H, $J = 17, 7, 5$ Hz, H-6'), 5.54-5.58 (br dd, 1H, $J = 7.5, 5$ Hz, -CHO-), 5.94 (br s, 1 H, vinyl proton).

¹³C nmr (75.3 MHz) δ : 20.4 (-ve, Me), 20.9 (-ve, Me), 28.4, 34.3, 69.8 (-ve, C-4), 128.7 (-ve, C-2), 158.1 (C-3), 170.3, 197.8.

3.1.1.4. Synthesis of (*R*)-(+)-4-Hydroxy-3-methyl-2-cyclohexen-1-one (**186a**) and (*S*)-(-)-4-Acetoxy-3-methyl-2-cyclohexen-1-one (**181b**):¹⁵³



To a stirred solution of the racemic allylic acetate **181** (4.57 g, 27.2 mmol) in Tris•HCl buffer,¹⁵⁴ pH 7 (0.3 M, 600 mL) and DMSO (200 mL) at rt was added PLE¹⁵⁵ (6 mL of enzyme suspension, 100 mg of protein, $\sim 1.7 \times 10^4$ units of activity). The above materials were dispensed with glass pipettes or with eppendorf plastic tips. In order to avoid inactivation of the enzyme, metal needles were not used. The pH of the solution was monitored using a pH meter (Fischer Accumet pH meter, model 140) and was kept at pH 7 by the appropriate addition of 0.1 M aqueous NaOH. A total of 155 mL of 0.1 M aqueous NaOH was used, indicating that the reaction had proceeded to the extent of 57% (i.e. 57% of the racemic acetate had been hydrolyzed to the corresponding alcohol). Analysis (glc) at this time (26 h) confirmed that $\sim 59\%$ of the acetate had been hydrolyzed. The solution was extracted with ethyl acetate (4 x 600 mL) and the combined organic extracts were washed with brine (1 x 200 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Flash chromatography (275 g silica gel, 3:2 petroleum ether - diethyl ether to elute the unreacted allylic acetate, followed by 100% ethyl acetate to elute the allylic alcohol) provided fractions containing the allylic acetate followed by fractions containing the more polar alcohol. Concentration of the first set of fractions provided 1.81 g (40%) of (-)-4-acetoxy-3-methyl-2-cyclohexen-1-one (**181b**) as a colourless oil ($[\alpha]_D^{25}$ -46.7 (*c* 1.69, CHCl₃); lit.,¹²⁴ -35.1 (*c* 0.61, CDCl₃)). The spectral data are identical with those derived

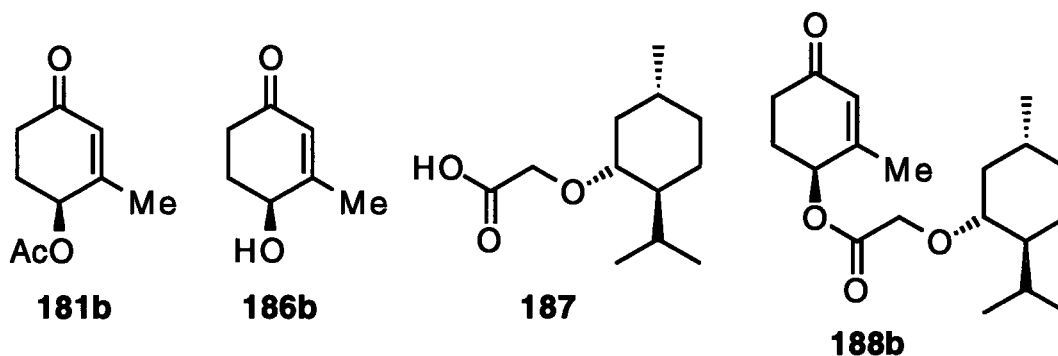
from the racemic acetate. Concentration of the late fractions afforded 2.0 g (58%) of 4-hydroxy-3-methyl-2-cyclohexen-1-one (**186a**).¹⁵⁶ The alcohol **186a** could be distilled (air-bath temperature 120-130 °C/0.38 Torr) to afford a colourless oil which exhibited the following spectral data:

¹H nmr (400 MHz) δ : 1.96-2.04 (m, 1H), 2.05 (dd, 3H, $J = 1, 1$ Hz, vinyl Me), 2.17 (d, 1H, $J = 6$ Hz), 2.25-2.39 (m, 2H), 2.53-2.60 (m, 1H), 4.36 (br dd, 1H, $J = 4.5, 4.5$ Hz, -CH₂OH), 5.85 (br s, 1H, vinyl proton).

¹³C nmr (75.3 MHz) δ : 20.6 (-ve, Me), 31.8, 34.8, 68.5 (-ve, C-4), 126.8 (-ve, C-2), 163.8 (C-3), 199.2 (C-1).

The enantiomeric excess of the desired (*S*)-(-)-4-acetoxy-3-methyl-2-cyclohexen-1-one (**181b**) was ascertained by converting the acetate to the corresponding alcohol,¹²⁴ forming the ester with (-)-menthoxyacetic acid (**187**),¹⁵⁷ and recording the ¹H nmr spectrum of this ester in the presence of 0.1-0.2 equivalents of Eu(fod)₃. Only one diastereomer was observed, hence an ee > 99% was obtained. The absolute configuration of the (*S*)-(-)-4-hydroxy-3-methyl-2-cyclohexen-1-one (**186b**) has been determined by Polla and Frejd¹²⁴ using the exciton chirality method.

To obtain (*R*)-(+)-4-hydroxy-3-methyl-2-cyclohexen-1-one (**186a**), the reaction was stopped at 36% conversion (~9 h reaction time). The enantiomeric excess of the alcohol thus obtained was determined (via the manner described above) to be 88%, and as a result we chose to synthesize (-)-homalomenol A and B using the higher purity (*S*)-(-)-4-acetoxy-3-methyl-2-cyclohexen-1-one (**181b**) (see discussion).

3.1.1.5. Synthesis of the ester **188b**:

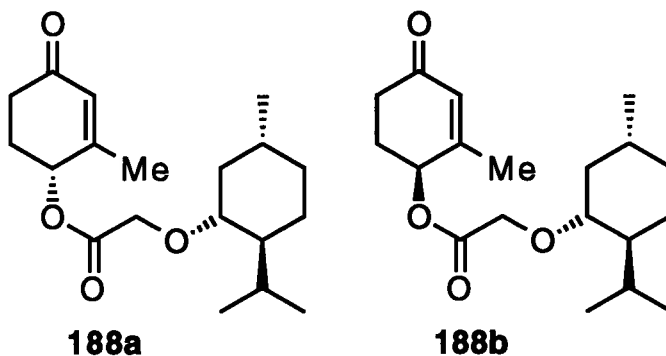
To a solution of the (-)-allylic acetate **181b** (24 mg, 0.14 mmol, 1 equiv.) in dry MeOH (2.8 mL) at rt was added solid sodium carbonate (76 mg, 0.71 mmol, 5 equiv.). The heterogeneous reaction mixture was stirred at rt for 1 h, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (3 g silica gel, 3:1 ethyl acetate - petroleum ether) to afford 16 mg (89%) of (*S*)-(-)-4-hydroxy-3-methyl-2-cyclohexen-1-one (**186b**) ($[\alpha]_D^{25}$ -38.2 (*c* 1.88, CHCl₃); lit.,¹²⁴ -48.8 (*c* 0.98, CDCl₃)). The spectral data are identical with those of 4-hydroxy-3-methyl-2-cyclohexen-1-one reported above.

To a stirred solution of the (-)-allylic alcohol **186b** (9 mg, 0.07 mmol, 1 equiv.) in dry diethyl ether (2.3 mL) at rt was added (-)-menthoxyacetic acid (**187**) (16 mg, 0.075 mmol, 1.1 equiv.), 4-pyrrolidinopyridine (2 mg, 0.01 mmol, 0.2 equiv.), and finally DCC (15 mg, 0.073 mmol, 1.1 equiv.). The mixture was stirred at rt for 2 h, at which time water (5 mL) and diethyl ether (10 mL) were added. The organic phase was washed with water (2 x 5 mL), 5% aqueous acetic acid (2 x 5 mL), water (2 x 5 mL), and saturated aqueous NaHCO₃ (1 x 5 mL). The organic layer was dried, concentrated under reduced pressure, and the crude oil thus obtained was flash chromatographed (8 g silica gel, 5.7:1 petroleum ether - ethyl acetate) to yield 17 mg (79%) of the ester **188b** as a colourless oil.

¹H nmr (400 MHz) δ : 0.79 (d, 3H, *J* = 7 Hz, secondary Me), 0.83-1.02 (m, 3H), 0.91, 0.92 (d, d, 3H each, *J* = 6.5, 6.5 Hz, isopropyl Me groups), 1.27-1.36 (m, 1H), 1.56-1.67 (m, 2H),

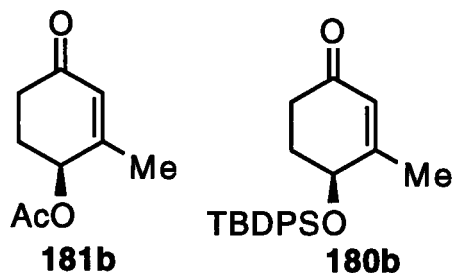
1.94 (dd, 3H, $J = 1, 1$ Hz, vinyl Me), 2.03-2.15 (m, 3H), 2.26-2.34 (m, 2H), 2.36-2.44 (ddd, 1H, $J = 17, 10, 4.5$ Hz), 2.52-2.58 (m, 1H), 3.15-3.21 (ddd, 1H, $J = 10.5, 10.5, 4$ Hz, $-\text{CH}\text{OCH}_2-$), 4.11 (d, 1H, $J = 16.5$ Hz, one of $-\text{C}(\text{O})-\text{CH}_2-\text{O}-$), 4.21 (d, 1H, $J = 16.5$ Hz, one of $-\text{C}(\text{O})-\text{CH}_2-\text{O}-$), 5.64-5.67 (dd, 1H, $J = 7.5, 5$, Hz, $-\text{CH}\text{OC}(\text{O})-$), 5.95 (br s, 1H, vinyl proton).

To a solution of the ester **188b** in CDCl_3 was added 0.15 equivalents of a $\text{Eu}(\text{fod})_3$ solution in CDCl_3 . The ^1H nmr of this mixture indicated only one signal corresponding to the vinyl methyl group, indicating an ee >99%. A similar experiment was performed on a mixture of esters **188a** and **188b** and two distinct, baseline resolved vinyl methyl signals were obtained for the two diastereomers.



3.1.2. PREPARATION OF THE ENANTIOMERICALLY HOMOGENEOUS BICYCLO[4.3.0] ENONE **177b**

3.1.2.1. Synthesis of (*S*)-(+)-4-(*tert*-Butyldiphenylsiloxy)-3-methyl-2-cyclohexen-1-one (**180b**):¹⁵⁸



To a solution of the (-)-allylic acetate **181b** (717 mg, 4.26 mmol, 1 equiv.) in dry MeOH (43 mL) at rt was added solid sodium carbonate (2.26 g, 21.3 mmol, 5 equiv.). The heterogeneous reaction mixture was stirred at rt for 1.5 h. The resultant pink mixture was filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography (35 g silica gel, 3:1 ethyl acetate - petroleum ether) to afford 538 mg (quantitative yield) of the colourless (-)-allylic alcohol **186b** which was used immediately in the next step.

To a solution of the (-)-allylic alcohol **186b** (538 mg, 4.26 mmol, 1 equiv.) in dry DMF (8.5 mL) at rt was added sequentially imidazole (1.16 g, 17.1 mmol, 4 equiv.) and *tert*-butyldiphenylsilyl chloride (2.2 mL, 8.5 mmol, 2 equiv.). The reaction mixture was stirred at rt for 15 h, at which time water (10 mL) was added. The aqueous phase was separated and extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with water (5 x 30 mL, in order to extract the DMF), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product mixture was subjected to flash chromatography (50 g silica gel, 9:1 petroleum ether - ethyl acetate) and the viscous oil thus obtained was heated to 70 °C/0.2 Torr for 1 h (to remove any residual solvent) to provide 1.2

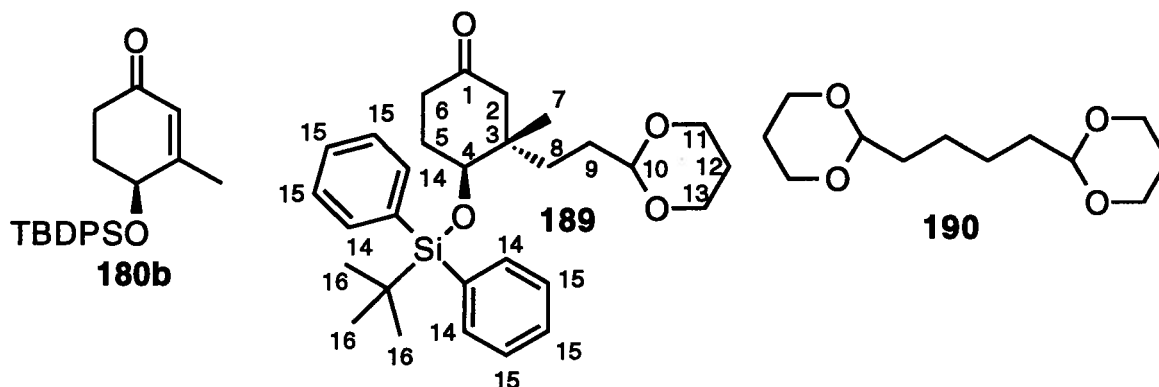
g (80%, based on allylic acetate **181b**) of the (+)-TBDPS ether **180b**¹⁵⁹ ($[\alpha]_{\text{D}}^{25} +8.7$ (c 2.05, CHCl₃); lit.,¹²⁴ +4.7 (c 1.03, CDCl₃)).

IR (film): 1674, 1627, 1590, 1111, 974, 704 cm⁻¹.

¹H nmr (400 MHz) δ : 1.08 (s, 9H, -CMe₃), 1.94 (dd, 3H, $J = 1$, 1 Hz, vinyl Me), 1.91-2.04 (m, 2H), 2.08-2.16 (m, 1H), 2.46-2.53 (ddd, 1H, $J = 17$, 6.5, 4.5 Hz, one of H-6), 4.34 (br dd, 1H, $J = 7.5$, 4.5 Hz, -CHO-), 5.79 (br s, 1H, vinyl proton), 7.38-7.48 (m, 6H, aromatic protons), 7.68-7.72 (m, 4H, aromatic protons).

¹³C nmr (75.3 MHz) δ : 19.4, 21.5 (-ve), 27.0 (-ve, -C(CH3)₃), 32.2, 34.8, 70.5 (-ve, -CO-), 126.7 (-ve, C-2), 127.6 (-ve), 127.8 (-ve), 129.9 (-ve), 130.0 (-ve), 132.9, 133.6, 135.8 (-ve), 135.9 (-ve), 163.6 (C-3), 198.7 (C-1).

3.1.2.2. Synthesis of (3*S*, 4*S*)-(+)-4-(*tert*-Butyldiphenylsiloxy)-3-[2-(1,3-dioxan-2-yl)ethyl]-3-methyl-cyclohexanone (**189**):



To a stirred suspension of freshly ground magnesium turnings (1.01 g, 41.7 mmol, 5 equiv.) and iodine (a few crystals) in dry THF (5 mL) at rt was added dropwise (via a large cannula) a solution of 2-(2-bromoethyl)-1,3-dioxane (4.06 g, 20.8 mmol, 2.5 equiv.) in dry THF (5 mL). Formation of the Grignard reagent began immediately and the bromide solution was added at such a rate that reflux of the reaction mixture was maintained. After the addition was complete, the mixture was heated to reflux for an additional 35 min. The mixture was cooled to rt, diluted with THF (90 mL), and further cooled to -78 °C. Solid CuBr•Me₂S (1.07 g, 5.20 mmol, 25 mol% with respect to the Grignard reagent) was added and the resultant cloudy mixture was stirred at -78 °C for 1 h. Addition of dry HMPA (3.7 mL, 21 mmol, 2.5 equiv.) was followed by the dropwise addition (via a large cannula over 10 min) of a solution of the (+)-enone **180b** (3.08 g, 8.45 mmol, 1 equiv.) and trimethylsilyl chloride (2.7 mL, 21 mmol, 2.5 equiv.) in dry THF (8 mL). The resultant bright yellow solution was stirred at -78 °C for 3 h and was then warmed to -50 °C over a period of 2.5 h, at which point the solution became colourless. Water (20 mL) was added and the mixture was stirred at rt for 2 h, open to the atmosphere, to hydrolyze the silyl enol ether. Aqueous NH₄Cl-NH₄OH (pH 8-9, 50 mL) and diethyl ether (50 mL) were added and the mixture was stirred vigorously until the aqueous phase became bright blue in colour. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 100 mL). The

combined organic extracts were washed with water (5 x 75 mL, to extract the HMPA), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.¹⁶⁰ The crude oil thus obtained was subjected to chromatography¹⁶¹ (50 g tlc grade silica gel, 5.7:1 petroleum ether - ethyl acetate) which yielded 3.0 g of the solid (+)-acetal **189** as well as a mixture of the acetal **189** and the byproduct **190**. The acetal **189** was separated from this mixture by crystallization from petroleum ether. The combined acetal fractions were then recrystallized from petroleum ether to yield 3.6 g (88%) of the (+)-acetal **189**, as a colourless crystalline solid, mp 99-101 °C, $[\alpha]_D^{25} +15.72$ (*c* 1.62, CHCl₃).

IR (KBr): 1704, 1588, 1145, 1111, 1088, 706 cm⁻¹.

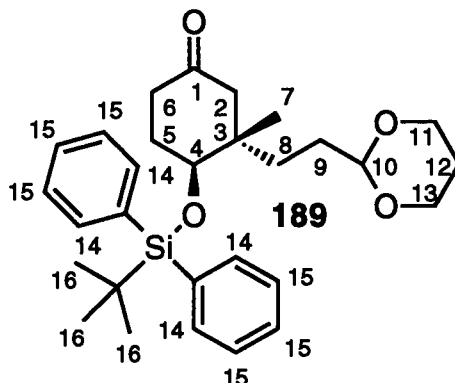
¹H nmr (400 MHz) δ : 0.96 (s, 3H, Me-7), 1.09 (s, 9H, Me-15), 1.27-1.47 (m, 5H, one of which is H-12), 1.74-1.79 (br ddd, 2H, *J* = 7.5, 7.5, 5 Hz, H-5 and H-5'), 1.96-2.07 (m, 3H, H-2, H-6, and H-12'), 2.38-2.43 (br dt, 1H, *J* = 14, 7.5 Hz, H-6'), 2.47-2.51 (br d, 1H, *J* = 14 Hz, H-2'), 3.65-3.72, 3.66-3.73 (ddd, 1H each, *J* = 12, 12, 2 Hz for each ddd, axial protons on C-11 and C-13), 3.81-3.84 (dd, 1H, *J* = 5, 5 Hz, H-4), 4.03-4.07 (br ddd, 2H, *J* = 12, 5, 1 Hz, equatorial protons on C-11 and C-13), 4.34-4.36 (dd, 1H, *J* = 5, 4.5 Hz, H-10), 7.35-7.72 (m, 6H, H-15), 7.66-7.72 (m, 4H, H-14).

Detailed ¹H nmr data, derived from a COSY experiment, is given in **Table 63**.

¹³C nmr (75.3 MHz) δ : 19.6, 21.2 (-ve, C-7), 25.7, 27.2 (-ve C-16), 28.8, 29.0, 33.1, 36.8, 42.7, 49.2, 66.8, 73.9 (-ve, C-4), 102.4 (-ve, C-10), 127.5 (-ve), 127.6 (-ve), 129.7 (-ve), 129.8 (-ve), 133.4, 134.3, 135.9 (-ve), 136.0 (-ve), 211.4 (C-1).

Exact Mass calcd. for C₂₉H₄₀O₄Si: 480.2696; found: 480.2668.

Anal. calcd. for C₂₉H₄₀O₄Si: C 72.46, H 8.39; found: C 72.57, H 8.52.

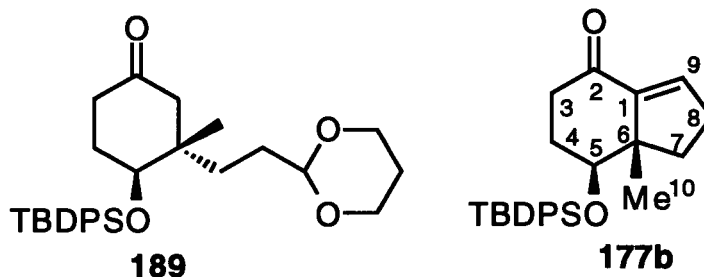
Table 63: ^1H nmr Data (400 MHz, CDCl_3) for the Keto Acetal **189**: COSY Experiment

Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a
Me-7	0.96 (s)	
Me-16	1.09 (s)	
H-12	~1.30-1.40 (m), part of the m (5H) at 1.27-1.47	H-11, H-11', H-12', H-13, H-13'
H-5 and H-5'	2.38-2.43 (br ddd, $J = 7.5, 7.5, 5$)	H-4, H-6, H-6'
H-2	Part of m (3H) at 1.96-2.07	H-2'
H-6	Part of m (3H) at 1.96-2.07	H-5, H-5', H-6'
H-12'	Part of m (3H) at 1.96-2.07	H-11, H-11', H-12, H-13, H-13'
H-6'	2.38-2.43 (dt, $J = 14, 7.5$)	H-5, H-5', H-6
H-2'	2.47-2.51 (br d, $J = 14$)	H-2
axial protons on C-11 and C-13	3.65-3.72, 3.66-3.73 (ddd, 1H each, $J = 12, 12, 2$)	equatorial protons on C-11 and C-13, H-12, H-12'
H-4	3.81-3.84 (dd, $J = 5, 5$)	H-5, H-5'
equatorial protons on C-11 and C-13	4.03-4.07 (ddd, 2H, $J = 12, 5, 1$)	axial protons on C-11 and C-13, H-12, H-12'
H-10	4.34-4.36 (dd, $J = 5, 4.5$)	
H-15	7.35-7.72 (m)	H-14
H-14	7.66-7.72 (m)	H-15

a- Only those COSY correlations that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-2' is more downfield than H-2).

3.1.2.3. Synthesis of (5*S*, 6*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-6-methylbicyclo[4.3.0]non-9-en-2-one (**177b**):¹⁶²



To a stirred solution of the (+)-acetal **189** (2.04 g, 4.24 mmol, 1 equiv.) in 1,4-dioxane (57 mL) at rt was added 80% aqueous trifluoroacetic acid (28 mL: 5.5 mL H₂O + 22.5 mL of 100% CF₃COOH). The mixture was heated to 80 °C for 16.5 h. The dark brown solution was neutralized by the careful, dropwise addition (via the condenser) of saturated aqueous NaHCO₃. The aqueous phase was separated and extracted with diethyl ether (3 x 75 mL) and ethyl acetate (1 x 75 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the brown oil thus obtained (125 g silica gel, 4:1 petroleum ether - diethyl ether) afforded 1.33 g (77%) of the (-)-enone **177b** as a viscous, yellow oil.

After recovery of the (-)-enone **177b**, the column was flushed with diethyl ether (600 mL). The eluate was concentrated, the residue was dissolved in a mixture of dioxane (16 mL) and 100% CF₃COOH (8 mL), and the solution was heated to 75 °C for 16 h. The reaction mixture was neutralized with saturated aqueous NaHCO₃. The aqueous layer was separated and extracted with diethyl ether (3 x 25 mL) and ethyl acetate (1 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual material was flash chromatographed (25 g silica gel, 4:1 petroleum ether - diethyl ether) to yield a further 81 mg (5%) of the (-)-enone **177b**. The residual solvent was removed by heating the enone to 80 °C/0.2 Torr for 1 h; the total yield of the (-)-enone **177b** was 2.14 g (82%), [α]_D²⁵ -22.2 (*c* 0.92, CHCl₃).

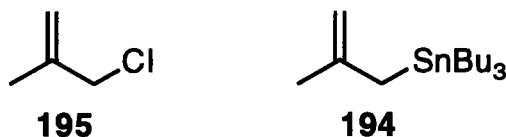
IR (neat): 1687, 1618, 1428, 1111, 1069, 703 cm^{-1} .

^1H nmr (400 MHz) δ : 1.09 (s, 9H, $-\text{CMe}_3$), 1.20 (s, 3H, Me-10), 1.70-1.75 (m, 2H), 1.99-2.08 (m, 3H), 2.26-2.50 (m, 3H), 3.76-3.80 (dd, 1H, $J = 11, 4$ Hz, H-5), 6.42-6.43 (dd, 1H, $J = 2.5, 2.5$ Hz, H-9), 7.37-7.47 (m, 6H, aromatic protons), 7.68-7.72 (m, 4H, aromatic protons).

^{13}C nmr (75.3 MHz) δ : 17.6 (-ve, Me-10), 19.4, 27.0 (-ve, $-\text{C}(\text{CH}_3)_3$), 29.2, 30.0, 38.1, 40.6, 52.4, 78.2 (-ve, C-5), 127.5 (-ve), 127.6 (-ve), 129.6 (-ve), 129.8 (-ve), 133.4, 134.5, 135.8 (-ve), 135.9 (-ve), 138.3 (-ve, C-9), 147.7 (C-1), 198.7 (C-2).

Exact Mass calcd. for $\text{C}_{26}\text{H}_{32}\text{O}_2\text{Si}$: 404.2171; found: 404.2178.

Anal. calcd. for $\text{C}_{26}\text{H}_{32}\text{O}_2\text{Si}$: C 77.18, H 7.97; found: C 76.88, H 7.91.

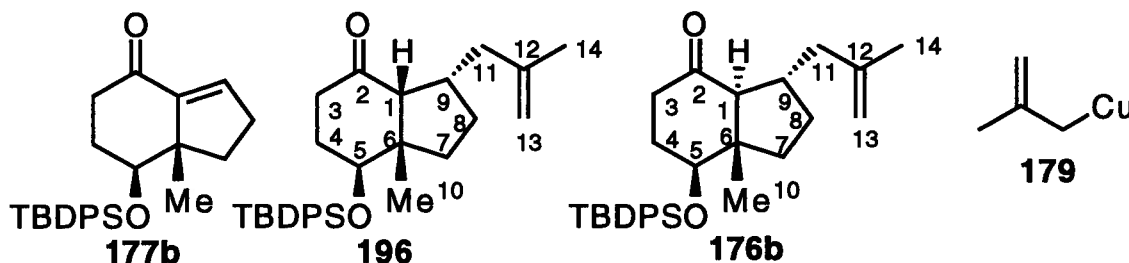
3.1.2.4. Synthesis of 2-methyl-3-(tri-*n*-butylstannyl)propene (**194**):^{163,164}

To a cold (0 °C), stirred suspension of freshly ground magnesium turnings (4.10 g, 169 mmol, 2.2 equiv.) in dry THF (20 mL) was added dropwise, over a period of 1 h, a solution of 3-chloro-2-methylpropene (**195**) (15.2 mL, 154 mmol, 2 equiv.) and tri-*n*-butylstannyl chloride (20.9 mL, 77.0 mmol, 1 equiv.) in dry THF (50 mL). The gray slurry was refluxed for 2 h, cooled to 0°C, and saturated aqueous ammonium chloride (10 mL) was added. The suspension was filtered (using water aspirator pressure) through Celite (10 g). The filter cake was washed with diethyl ether (700 mL) and the combined filtrates were concentrated. The concentrate was taken up in diethyl ether (500 mL) and the mixture was washed with water (2 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the oil thus obtained was distilled (100 °C/0.45 Torr) to provide 23.6 g (89%) of 2-methyl-3-(tri-*n*-butylstannyl)propene (**194**).¹⁶⁵

¹H nmr (400 MHz) δ : 0.80-0.95 (m, 15H), 1.28-1.55 (m, 12H), 1.70 (s, 3H, vinyl Me), 1.78 (s, 2H, -CH₂SnBu₃), 4.42-4.50 (m, 2H, vinyl protons).

3.1.3. PREPARATION OF THE BICYCLIC KETONE **176b**

3.1.3.1. Synthesis of (1*R*, 5*S*, 6*S*, 9*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(methallyl)-bicyclo-[4.3.0]nonan-2-one (**196**) and (1*S*, 5*S*, 6*S*, 9*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(methallyl)bicyclo[4.3.0]nonan-2-one (**176b**):¹⁶⁶



A suspension of flame dried lithium chloride¹⁶⁷ (267 mg, 6.30 mmol, 3.1 equiv.) and freshly recrystallized copper(I) iodide¹⁶⁸ (1.20 g, 6.30 mmol, 3.1 equiv.) in dry THF (35 mL) was stirred at rt for 15 min until a clear yellow solution resulted. The mixture was cooled to -78 °C. To a cold (-78 °C), stirred solution of 2-methyl-3-(tri-*n*-butylstannyl)propene (**194**) (2.12 g, 6.14 mmol, 3 equiv.) in dry THF (10 mL) was added a solution of *n*-butyllithium in hexanes (1.61 M, 3.6 mL, 5.8 mmol, 2.8 equiv.). The resultant yellow solution was stirred at -78 °C for 25 min and was quickly cannulated (via a large cannula) into the LiCl/CuI/THF solution to produce a clear red solution containing the organocopper(I) reagent **179**. Cannulation of trimethylsilyl bromide (2.20 g, 14.4 mmol, 7 equiv.) into the red solution was followed by the addition of a solution of the (-)-enone **177b** (829 mg, 2.05 mmol, 1 equiv.) in dry THF (5 mL). The reaction mixture was stirred at -78 °C for 5.5 h. Water (20 mL) was added and the mixture was stirred at rt, open to the atmosphere, for 45 min. Analysis by thin layer chromatography confirmed the hydrolysis of the silyl enol ether products. Aqueous NH₄Cl-NH₄OH (pH 8-9, 50 mL) was added and the mixture was stirred rapidly until the aqueous layer became bright blue in colour. The phases were separated and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. ¹H nmr spectroscopic analysis of the crude oil thus obtained

indicated a 5:1 ratio of the two isomers **196** and **176b**, as determined by the integration of their respective vinyl proton signals. The two isomers were easily separated by flash chromatography (125 g silica gel, 11.5:1 petroleum ether - diethyl ether). The first compound to be eluted was the addition product **176b** bearing the trans ring junction. Concentration of the appropriate fractions, followed by recrystallization (from diethyl ether - petroleum ether) of the solid thus obtained provided 113 mg (12%) of the (-)-trans-fused compound **176b**, a colourless crystalline solid, mp 98-99 °C, $[\alpha]_D^{25}$ -37.1 (*c* 1.27 in CHCl₃).

IR (KBr): 1716, 1649, 1590, 1112, 1094, 704 cm⁻¹.

¹H nmr (400 MHz) δ : 0.89 (s, 3H, Me-10), 1.06 (s, 9H, -CMe₃), 1.14-1.34 (m, 2H, one of which is H-8), 1.65-1.80 (m, 1H, H-11), 1.71 (s, 3H, Me-14), 1.81-1.95 (m, 5H, one of which is H-1 (d, *J* = 11 Hz), one of which is H-4, and one of which is H-4'), 2.01-2.19 (m, 2H), 2.14-2.19 (br dd, 1H, *J* = 14, 4.5 Hz, H-11'), 2.44-2.51 (m, 1H, H-9), 3.33-3.40 (dd, 1H, *J* = 10.5, 5 Hz, H-5) 4.59 (br s, 1H, H-13), 4.64 (br s, 1H, H-13'), 7.36-7.52 (m, 6H, aromatic protons), 7.66-7.73 (m, 4H, aromatic protons).

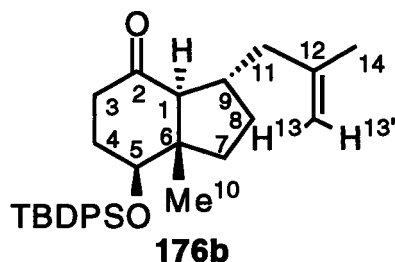
Detailed ¹H nmr data, derived from COSY and NOE experiments, are given in **Table 64**.

¹³C nmr (75.3 MHz) δ : 13.3 (-ve, Me-6), 19.4, 22.4 (-ve), 27.0 (-ve, -C(CH₃)₃), 27.1, 32.0, 32.6 (-ve), 38.4, 39.5, 44.5, 52.4, 62.9 (-ve), 78.8 (-ve, C-5), 110.6 (C-13), 127.5 (-ve), 127.6 (-ve), 129.6 (-ve), 129.8 (-ve), 133.6, 134.5, 135.9 (-ve), 136.0 (-ve), 145.2 (C-12), 209.7 (C-2).

Exact Mass calcd. for C₃₀H₄₀O₂Si: 460.2798; found: 460.2792.

Anal. calcd. for C₃₀H₄₀O₂Si: C 78.21, H 8.75; found: C 78.25, H 8.78.

Table 64: ^1H nmr Data (400 MHz, CDCl_3) for the Trans-Fused Compound **176b**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-10	0.89 (s)		H-9
-C(Me ₃)	1.06 (s)		
H-8	Part of the m at 1.14-1.34	H-9	
H-11	1.65-1.80 (m)	H-9, H-11' ^b , H-13, H-13'	
Me-14	1.71 (s)		H-9, H-11', H-13'
H-4	Part of the m at 1.81-1.95	H-5	
H-4'	Part of the m at 1.81-1.95	H-5	
H-1	~1.87-1.90 (d, J = 11), part of the m at 1.81-1.95	H-9	
H-11'	2.14-2.19 (br dd, J = 14, 4.5)	H-9, H-11, H-13	H-11, Me-14
H-9	2.44-2.51 (m)	H-1, H-8, H-11, H-11'	H-11', Me-10, Me-14
H-5	3.33-3.44 (dd, J = 10.5, 5)	H-4, H-4'	H-1
H-13	4.59 (br s)	H-11, H-11', H-13'	H-13'
H-13'	4.64 (br s)	H-11, H-13	H-13, Me-14

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-11' is more downfield than H-11).

The second compound to be eluted was the conjugate addition product **196** bearing the cis ring junction. Concentration of the appropriate fractions, followed by removal of traces of solvent (vacuum pump) from the oil thus obtained, provided 763 mg (81%) of the (-)-cis-fused product **196**, as a colourless oil, $[\alpha]_{\text{D}}^{25} -73.0$ (c 1.79, CHCl_3).

IR (neat): 1702, 1648, 1590, 1112, 704 cm^{-1} .

^1H nmr (400 MHz) δ : 1.02-1.21 (m, 1H), 1.07 (s, 9H, $-\text{CMe}_3$), 1.18 (s, 3H, Me-10), 1.30-1.38 (m, 1H), 1.41-1.47 (br dd, 1H, $J = 13, 10.5$ Hz, H-9), 1.59 (s, 3H, Me-14), 1.56-1.70 (m, 1H, H-11), 1.79-1.95 (m, 5H, two of which are H-4 and H-11'), 2.29-2.38 (m, 1H, H-4'), 2.40-2.48 (m, 1H), 2.49-2.52 (dd, 1H, $J = 10.5, 2$ Hz, H-1), 3.74-3.77 (dd, 1H, $J = 8.5, 3.5$ Hz, H-5), 4.48 (br s, 1H, H-13), 4.65 (br s, 1H, H-13'), 7.28-7.50 (m, 6H, aromatic protons), 7.66-7.73 (m, 4H, aromatic protons).

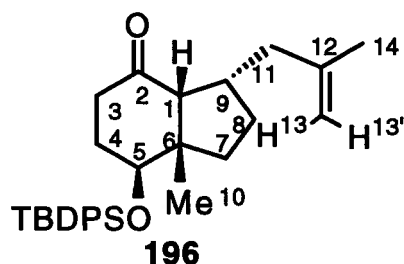
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 65**.

^{13}C nmr (75.3 MHz) δ : 19.4, 21.9 (-ve), 23.5 (-ve), 27.1 (-ve, $-\text{C}(\text{CH}_3)_3$), 27.9, 30.2, 37.9, 39.3, 40.4 (-ve), 40.7, 49.5, 62.8 (-ve), 74.1 (-ve), 111.4 (C-13), 127.5 (-ve), 127.7 (-ve), 129.7 (-ve), 129.8 (-ve), 133.3, 134.4, 135.9 (-ve), 136.0 (-ve), 143.9 (C-12), 213.5 (C-2).

Exact Mass calcd. for $\text{C}_{30}\text{H}_{40}\text{O}_2\text{Si}$: 460.2797; found: 460.2804.

Anal. calcd. for $\text{C}_{30}\text{H}_{40}\text{O}_2\text{Si}$: C 78.21, H 8.75; found: C 77.88, H 8.68.

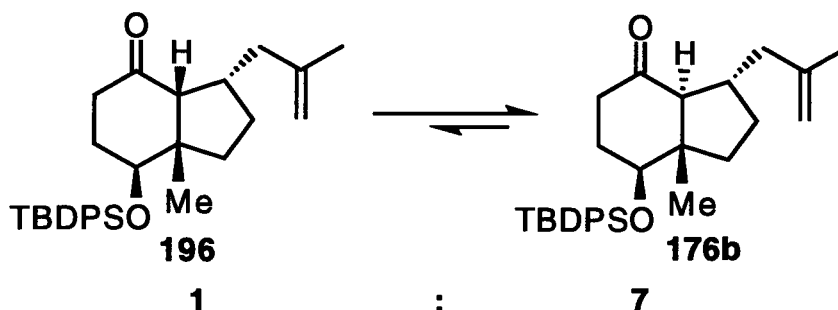
Table 65: ^1H nmr Data (400 MHz, CDCl_3) for the Cis-Fused Compound **196**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
-CMe ₃	1.07 (s)		
Me-10	1.18 (s)		H-1
H-9	1.41-1.47 (br dd, $J = 13, 10.5$)	H-1, H-11 ^b	H-11', H-13
Me-14	1.59 (s)		H-13'
H-11	1.56-1.70 (m)	H-11', H-13, H-13'	
H-4	Part of the m at 1.79-1.95	H-4', H-5	
H-11'	Part of the m at 1.79-1.95	H-11, H-13, H-13'	
H-4'	2.29-2.38 (m)	H-4, H-5	H-4
H-1	2.49-2.52 (dd, $J = 10.5, 2$)	H-9	Me-10
H-5	3.74-3.77 (dd, $J = 8.5, 3.5$)	H-4, H-4'	H-4, H-11
H-13	4.48 (br s)	H-11, H-11', H-13'	H-9
H-13'	4.56 (br s)	H-11, H-11', H-13	H-13, Me-14

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-11' is more downfield than H-11).

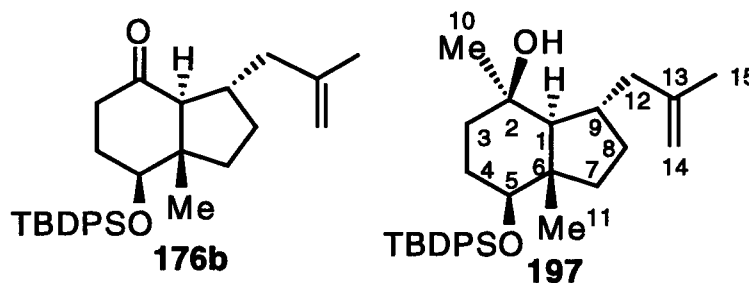
3.1.3.2. Epimerization of compound **196**:

To a cold ($-78\text{ }^{\circ}\text{C}$), stirred solution of the (-)-cis-fused compound **196** (264 mg, 0.573 mmol, 1 equiv.) in dry MeOH (11.5 mL) was added a solution of NaOMe in MeOH (0.4 M, 1.1 mL, 0.44 mmol, 0.8 equiv.). The pale yellow solution was warmed to rt and stirred for 19 h. The MeOH was removed by rotary evaporation and water (10 mL) and diethyl ether (20 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. ^1H nmr spectroscopic analysis of the oil thus obtained indicated a 7:1 ratio¹⁶⁹ of trans- to cis-fused compounds (**176b** and **196**, respectively). Flash chromatography of the crude oil (25 g silica gel, 19:1 petroleum ether - diethyl ether) yielded 223 mg (84%) of the (-)-trans-fused compound **176b**, followed by 35 mg (13%) of the (-)-cis-fused compound **196**.

The recovered (-)-cis-fused compound **196** (35 mg, 0.076 mmol) was subjected to the above epimerization conditions (2.0 mL MeOH, 0.15 mL of a 0.4 M NaOMe/MeOH solution, 0.8 equiv.). Flash chromatography (8 g silica gel, 19:1 petroleum ether - diethyl ether) of the crude product provided a further 24 mg of the (-)-trans-fused compound **176b**. After two such epimerizations, 247 mg (94%) of the crystalline (-)-trans-fused compound **176b** was obtained.

3.1.4. SYNTHESIS OF (-)-HOMALOMENOL B (**169b**)

3.1.4.1. Synthesis of (1*S*, 2*R*, 5*S*, 6*S*, 9*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-2,6-dimethyl-9-(methallyl)-bicyclo[4.3.0]nonan-2-ol (**197**):¹⁷⁰



To a cold (-20 °C), stirred solution of the (-)-trans-fused compound **176b** (61 mg, 0.13 mmol, 1 equiv.) in dry diethyl ether (2.6 mL) was added a solution of methyllithium in diethyl ether (1.4 M, 140 μ L, 0.20 mmol, 1.5 equiv.). The solution was warmed to -5 °C over the course of 1.5 h. A few drops of water were added to quench the excess methyllithium. The solution was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed (8 g silica gel, 9:1 petroleum ether - diethyl ether) and after removal of trace amounts of solvent (vacuum pump) from the resultant oil, there was obtained 55 mg (87%) of the (-)-tertiary alcohol **197**, as a colourless oil, $[\alpha]_D^{25}$ -75.2 (*c* 0.04, CHCl₃).

IR (film): 3583, 3481, 3071, 1650, 1590, 1111, 1052, 703 cm⁻¹.

¹H nmr (400 MHz) δ : 0.79 (br d, 1H, *J* = 11 Hz, H-1), 1.05 (s, 9H, -CMe₃), 1.00-1.10 (m, 1H), 1.11-1.20 (m, 2H, one of which is H-3), 1.17 (s, 3H, Me-10), 1.20 (d, 3H, *J* = 0.6 Hz, Me-11), 1.23-1.36 (m, 2H, H-4 and H-8), 1.42-1.47 (m, 1H, H-3'), 1.61-1.73 (m, 2H, one of which is H-12), 1.71 (s, 3H, Me-15), 1.80-1.93 (m, 2H, one of which is H-4'), 2.24-2.32 (m, 1H, H-9), 2.52 (br d, 1H, *J* = 14 Hz, H-12'), 3.37-3.41 (dd, 1H, *J* = 11.5, 4.5, H-5), 4.66 (br

s, 1H, H-14), 4.71 (br s, 1H, H-14'), 7.34-7.45 (m, 6H, aromatic protons), 7.65-7.71 (m, 4H, aromatic protons).

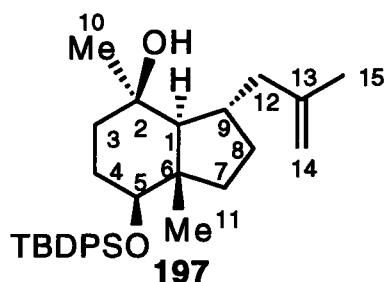
Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 66**.

^{13}C nmr (75.3 MHz) δ : 15.2 (-ve), 19.5, 22.6 (-ve), 27.0 (-ve, $-\text{C}(\text{CH}_3)_3$), 27.9, 28.2, 31.6 (-ve), 33.4 (-ve), 39.1, 40.9, 45.8, 48.4, 58.8 (-ve), 71.8 (C-2), 81.0 (-ve, C-5), 110.7 (C-14), 127.3 (-ve), 127.4 (-ve), 129.3 (-ve), 129.5 (-ve), 134.1, 135.2, 135.9 (-ve), 136.0 (-ve), 145.5 (C-13).

Exact Mass calcd. for $\text{C}_{27}\text{H}_{35}\text{O}_2\text{Si}$ ($\text{M}^+ - \text{C}(\text{CH}_3)_3$) : 419.2406; found: 419.2409.

Anal. calcd. for $\text{C}_{31}\text{H}_{44}\text{O}_2\text{Si}$: C 78.10, H 9.30; found: C 78.12, H 9.41.

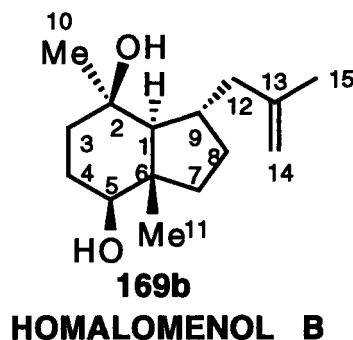
Table 66: ^1H nmr Data (400 MHz, CDCl_3) for the Tertiary Alcohol **197**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
H-1	0.79 (br d, $J = 11$)	H-9	H-5
Me-3	1.05 (s)		
H-3	Part of the m at 1.10-1.20	H-3' ^b , H-4, H-4'	
Me-10	1.17 (s)		H-1, H-3', H-9, H-12'
Me-11	1.20 (d, $J = 0.6$)		H-9
H-8	Part of the m at 1.23-1.36	H-9	
H-4	Part of the m at 1.23-1.36	H-3, H-3', H-4', H-5	
H-3'	1.42-1.47 (m)	H-3, H-4, H-4'	
H-12	Part of the m at 1.61-1.73	H-9, H-12', H-14, H-14'	
Me-15	1.71 (s)		
H-4'	Part of the m at 1.80-1.93	H-3, H-3', H-4	
H-9	2.24-2.32 (m)	H-1, H-8, H-12, H-12'	Me-10, Me-11, H-14, Me-15
H-12'	2.52 (br d, $J = 14$)	H-9, H-12, H-14	H-9, Me-10, H-12
H-5	3.37-3.41 (dd, $J = 11.5, 4.5$)	H-4, H-4'	H-1
H-14	4.66 (br s)	H-12, H-12', H-14'	
H-14'	4.71 (br s)	H-12, H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-3' is more downfield than H-3).

3.1.4.2. Synthesis of (-)-Homalomenol (**169b**):

To a stirred solution of the (-)-tertiary alcohol **197** (52 mg, 0.11 mmol, 1 equiv.) in dry THF (2.2 mL) at rt was added a solution of TBAF in THF (1 M, 550 μ L, 0.55 mmol, 5 equiv.). The mixture was refluxed for 17 h. The solution was cooled to rt and water (5 mL) and diethyl ether (10 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL) and ethyl acetate (2 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the oil thus obtained was flash chromatographed (8 g silica gel, 3:2 petroleum ether - ethyl acetate). Concentration of the appropriate fractions and recrystallization (from ethyl acetate - petroleum ether) of the solid thus obtained yielded 25 mg (95%) of (-)-homalomenol B (**169b**), a colourless crystalline solid, mp 94-95 $^{\circ}$ C, $[\alpha]_{\text{D}}^{20}$ -43.0 (*c* 1.71, CHCl₃); lit.¹²¹ $[\alpha]_{\text{D}}^{20}$ of (+)-homalomenol B (**169a**) +20.4 (*c* 1.745, CHCl₃). (-)-Homalomenol B (**169b**) was sublimed at 80 $^{\circ}$ C/0.2 Torr to afford needle-like crystals, mp 94-95 $^{\circ}$ C.

IR (KBr): 3632, 3371, 3070, 1649, 1194, 1024, 894 cm^{-1} .

^1H nmr (400 MHz, referenced at δ 7.24) δ : 0.92 (d, 1H, *J* = 11 Hz, H-1), 1.02 (br d, 3H, *J* = 0.9 Hz, Me-11), 1.09 (br s, 1H, 3 $^{\circ}$ OH; this signal exchanges upon treatment with D₂O), 1.15-1.27 (m, 2H), 1.25 (s, 3H, Me-10), 1.30-1.37 (m, 2H, H-8 and 2 $^{\circ}$ OH; this signal

exchanges upon treatment with D₂O), 1.41-1.66 (m, 3H, one of which is H-4), 1.70 (s, 3H, Me-15), 1.72-1.83 (m, 2H, H-4' and H-12), 1.84-1.94 (m, 1H), 2.24-2.34 (m, 1H, H-9), 2.56 (br d, 1H, $J = 14$ Hz, H-12'), 3.34-3.38 (ddd, 1H, $J = 11.5, 4.5, 4.5$ Hz, H-5; this signal collapses to a dd ($J = 11.5, 4.5$ Hz) upon treatment with D₂O), 4.66 (br s, 1H, H-14), 4.71 (br s, H-14').

Detailed ¹H nmr data, derived from COSY and NOE experiments, are given in **Table 67**.

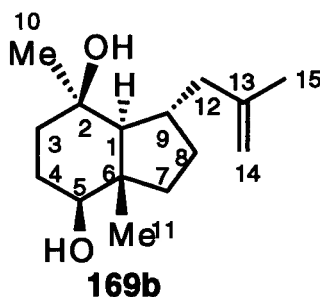
¹³C nmr (75.3 MHz) δ : 14.5 (-ve), 22.6 (-ve), 27.7, 28.0, 31.7 (-ve), 33.3 (-ve), 38.3, 41.0, 45.8, 47.7, 59.1 (-ve), 71.8 (C-2), 79.7 (-ve, C-5), 110.8 (C-14), 145.4 (C-13).

Exact Mass calcd. for C₁₅H₂₆O₂: 238.1933; found: 238.1927.

Anal. calcd. for C₁₅H₂₆O₂: C 75.58, H 10.99; found: C 75.80, H 11.14.

Comparison of the reported spectral data for (+)-homalomenol B (**169a**) with that of the synthetic (-)-homalomenol B (**169b**) is shown in **Table 68**.

Table 67: ^1H nmr Data (400 MHz, CDCl_3) for (-)-Homalomenol B (**169b**): COSY and NOE Experiments



Assignment H-x	^1H nmr Data (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
H-1	0.92 (d, $J = 11$)	H-9	H-5, Me-10, H-12
Me-11	1.02 (br d, $J = 0.9$)		H-9
3° OH	1.09 (br s)		
Me-10	1.25 (s)		H-1, H-12 ^b
H-8	Part of the m at 1.30-1.37	H-9	
2° OH	Part of the m at 1.30-1.37	H-5	
H-4	Part of the m at 1.41-1.66	H-4', H-5	
Me-15	1.70 (s)		
H-4'	Part of the m at 1.72-1.83	H-4, H-5	
H-12	Part of the m at 1.72-1.83	H-9, H-12', H-14, H-14'	
H-9	2.24-2.34 (m)	H-1, H-8, H-12, H-12';	Me-11, H-12', H-14, Me-15
H-12'	2.56 (br d, $J = 14$)	H-9, H-12, H-14, H-14'	H-9, Me-10, H-12
H-5	3.34-3.38 (ddd, $J = 11.5, 4.5,$ 4.5)	2° OH	H-1
H-14	4.66 (br s)	H-12, H-12', H-14'	
H-14'	4.71 (br s)	H-12, H-12', H-14	

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-12' is more downfield than H-12).

Table 68: Comparison of the Reported Spectral Data for (+)-Homalomenol B (**169a**) with that of the Synthetic (-)-Homalomenol B (**169b**)

Data	Synthetic	Reported ^a
MP	94-95 °C	78-81 °C
IR (cm ⁻¹)	3632	3610
	3371	3460
	3070	3080
	1649	1650
	1194	–
	1024	–
	894	900
¹ H NMR ^b (δ)	1.02 (br d, 3H, J = 0.9 Hz)	1.03 (d, 3H, J = 0.9 Hz)
	1.25 (s, 3H)	1.27 (s, 3H)
	1.70 (s, 3H)	1.71 (m, 3H)
	2.24-2.34 (m, 1H)	2.30 (m, 1H)
	2.56 (br d, 1H, J = 14 Hz)	2.57 (br d, 1H, J = 15 Hz)
	3.34-3.38 (dd, 1H, J = 11.5, 4.5, 4.5 Hz)	3.37 ^c (dd, 1H, J = 10.8, 4.5 Hz)
	4.66 (br s, 1H)	4.67 (m, 1H)
	4.71 (br s)	4.72 (m, 1H)
¹³ C NMR (δ)	14.5	14.6
	22.6	22.7
	27.7	27.8
	28.0	28.1
	31.7	31.2
	33.3	33.4
	38.3	38.4
	41.0	41.0
	45.8	45.9
	47.7	47.8
	59.1	51.9
	71.8	71.9
	79.7	79.8
	110.8	110.9
	145.5	145.5
HRMS (238.1933) ^d	238.1927	238.1926
Elemental Analysis	C ₁₅ H ₂₆ O ₂	– ^e
[α] _D ²⁰ (CHCl ₃)	-43.0 (c 1.71)	+20.4 (c 1.745)

a- Spectral data for (+)-homalomenol B as reported in reference 121.

b- Only the selected ¹H nmr signals for the synthetic (-)-homalomenol B which correspond to those reported for the natural (+)-homalomenol B are listed.

c- Reference 121 lists this signal at 4.62 ppm; however, the spectrum of (+)-homalomenol B provided by Dr. Sung indicates that this signal appears at 3.37 ppm.

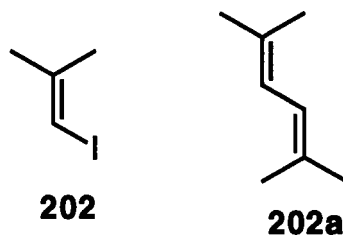
d- Calculated value for C₁₅H₂₆O₂.

e- Not reported.

3.2. ROUTE TO THE SYNTHESIS OF (-)-HOMALOMENOL A (168b)

3.2.1. PREPARATION OF THE BICYCLIC KETONE 175b

3.2.1.1. Synthesis of 1-Iodo-2-methylpropene (**202**):¹⁷¹



To 2.0 g of zinc dust in a cintered glass funnel was added 10 mL of 1.0 M hydrochloric acid. The resultant flocculent solid was triturated with a glass rod and the acid solution was removed using water aspirator pressure. This was repeated twice. The zinc dust was then washed with water (3 x 10 mL), MeOH (3 x 10 mL), and diethyl ether (3 x 10 mL) to provide ~2.0 g of activated zinc dust.

To a stirred, colourless solution of 1-bromo-2-methylpropene (19.0 mL, 185 mmol, 1 equiv.) in HMPA (135 mL) at rt was added solid potassium iodide (77.0 g, 464 mmol, 2.5 equiv.). The suspension turned dark orange. Cannulation of a solution of NiBr₂ in DMF (0.3 M, 50.0 mL, 14.8 mmol, 8 mol%) into the suspension was followed by the addition of freshly activated zinc dust (1.21 g, 18.5 mmol, 10 mol%). The dark green slurry was cooled to -20 °C and purged with an argon stream for 10 min. The mixture was heated to 70 °C and stirred at this temperature for 48 h. Diethyl ether (100 mL) and 5% hydrochloric acid (50 mL) were added. The organic layer was separated, washed with aqueous Na₂S₂O₇ (2 x 100 mL) and water (2 x 100 mL), dried over anhydrous sodium sulfate, and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm). The product was fractionally distilled at 61 °C/90 Torr to afford 23.7 g (70%) of 1-iodo-2-methylpropene (**202**). ¹H nmr spectroscopic analysis of the product revealed a 12:1 mixture of the desired compound **202** and 2,5-dimethyl-2,4-hexadiene (**202a**), as determined

by the integration of the respective vinyl proton signals. Since the latter compound does not interfere with the subsequent conjugate addition reaction, the mixture was used as obtained.

^1H nmr (400 MHz) of a mixture of 1-iodo-2-methylpropene (**202**) and 2,5-dimethyl-2,4-hexadiene (**202a**):

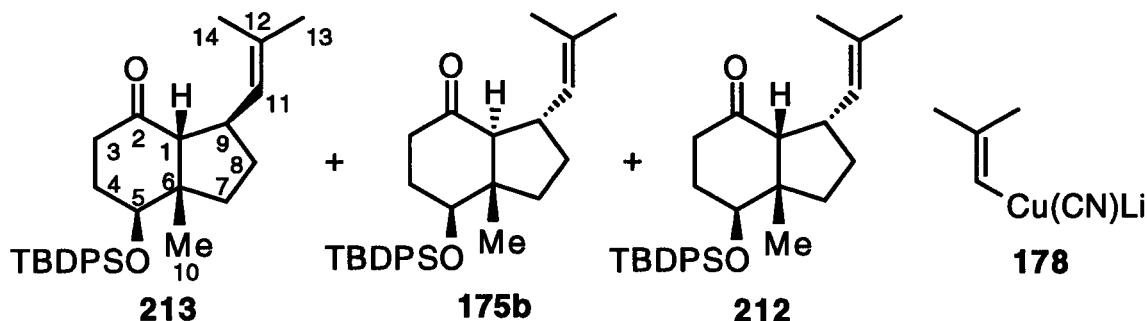
Signals attributed to 1-iodo-2-methylpropene (**202**)¹⁷² δ : 1.83 (s, 3H, vinyl Me), 1.91 (s, 3H, vinyl Me), 5.82 (s, 1H, vinyl proton).

Signals attributed to 2,5-dimethyl-2,4-hexadiene (**202a**) δ : 5.98 (s, 2H, vinyl proton), 1.72 (s, 6H, vinyl Me), 1.78 (s, 6H, vinyl Me).

Analysis of the mixture by glc-mass spectrometry showed:

M^+ (1-iodo-2-methylpropene (**202**)): 182; M^+ (2,5-dimethyl-2,4-hexadiene (**202a**)): 110.

3.2.1.2 Synthesis of (1*R*, 5*S*, 6*S*, 9*R*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (**213**), (1*S*, 5*S*, 6*S*, 9*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (**175b**), and (1*R*, 5*S*, 6*S*, 9*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (**212**):



a. Via Conjugate Addition of the Cuprate Reagent **178** to the Enone **177b** in the Presence of TMSBr and $\text{BF}_3 \cdot \text{Et}_2\text{O}$; General Procedure 5:

To a cold (-78°C), stirred solution of *tert*-butyllithium (1.62 M in pentane, 4.8 mL, 7.8 mmol, 12.8 equiv.) in dry THF (40 mL) was added slowly (over ~ 1 h via a small cannula) a solution of 1-iodo-2-methylpropene (**202**) (701 mg, 3.85 mmol, 6.4 equiv.) in dry THF (8 mL). The clear yellow solution became a cloudy, colourless mixture. To the cold (-78°C), stirred mixture was added (via a large cannula) a clear yellow solution of LiCl (326 mg, 7.69 mmol, 12.8 equiv.) and CuCN (345 mg, 3.85 mmol, 6.4 equiv.) in dry THF (13 mL).¹³⁹ $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (450 μL , 3.6 mmol, 6 equiv.) was added to the resultant orange/red solution containing the organocopper(I) reagent **178**. Cannulation of trimethylsilyl bromide (558 mg, 3.64 mmol, 6 equiv.) into the red solution was followed by the addition of a solution of the (-)-enone **177b** (245 mg, 0.605 mmol, 1 equiv.) in dry THF (5 mL). The mixture was stirred at -78°C for 6.5 h. The solution was quenched at -78°C with water (15 mL) and the mixture was stirred, open to the atmosphere, for 1 h. Aqueous NH_4Cl - NH_4OH (pH 8-9, 50 mL) and diethyl ether (50 mL) were added and the mixture was stirred vigorously until the aqueous layer became bright blue in colour. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with

brine (1 x 75 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The ^1H nmr spectrum of the crude oil thus obtained indicated that the starting material had been consumed and that the ratio of isomers **213**:**175b**:**212** was 34:4:62.¹⁷³

$$\begin{array}{ccccccc}
 \mathbf{213} & + & \mathbf{175b} & + & \mathbf{212} & & \\
 34 & : & 4 & : & 62 & & \\
 & & \underbrace{\hspace{1.5cm}} & & & & \\
 1 & & & : & 1.9 & &
 \end{array}$$

Flash chromatography (25 g silica gel, 19:1 petroleum ether - diethyl ether) of the crude oil provided 9.4 mg (3.4%) of compound **175b** and 220 mg (78%) of a mixture of compounds **213** and **212**. The mixture of addition products (218 mg, 0.47 mmol, 1 equiv.) was dissolved in MeOH (9 mL) and the solution was cooled to -78 °C. A solution of NaOMe in MeOH (0.4 M, 1.2 mL, 0.48 mmol, 1 equiv.) was added and the solution was warmed to rt and stirred for 17.5 h. The mixture was worked up (see epimerization procedure on page 180) and analysis of the ^1H nmr spectrum of the crude product indicated that the ratio of isomers **213**:**175b**:**212** was 36:36:28.¹⁷³ Flash chromatography (15 g silica gel, 19:1 petroleum ether - diethyl ether) of the crude product provided 64 mg (23 % with respect to the (-)-enone **177b**) of compound **175b** and 140 mg of a mixture of compounds **213** and **212**. The remaining mixture (140 mg of compounds **213** and **212**) was resubjected to the epimerization conditions and the desired isomer **175b** was derived by flash chromatography of the mixture. This process was repeated twice (i.e. three epimerizations in total). The overall yield of the desired (-)-isomer **175b**, based on the (-)-enone substrate **177b**, was 120 mg (43%). It is interesting to note that the compound **213** does not undergo epimerization (i.e. compound **213** is thermodynamically more stable than the corresponding trans-fused epimer).

The original mixture of compounds **213** and **212** was further purified by flash chromatography and the first few fractions eluted from the column chromatography were concentrated to provide pure compound **213**, a solid. The solid thus obtained was recrystallized from petroleum ether - diethyl ether to provide compound **213** as a colourless crystalline solid, mp 72-74 °C, $[\alpha]_D^{25}$ -30.0 (*c* 1.94, CHCl₃).

IR (KBr): 1709, 1589, 1109, 1093, 704 cm⁻¹.

¹H nmr (400 MHz) δ : 1.02-1.16 (m, 1H), 1.07 (s, 9H, -CMe₃), 1.16 (s, 3H, Me-10), 1.23-1.40 (m, 1H), 1.42 (d, 3H, *J* = 1 Hz, Me-14), 1.61 (d, 3H, *J* = 1 Hz, Me-13), 1.57-1.70 (m, 1H), 1.82-1.96 (m, 3H), 2.00 (d, 1H, *J* = 11.5 Hz, H-1), 2.12-2.28 (m, 2H), 2.79-2.88 (m, 1H, H-9), 3.86-3.91 (dd, 1H, *J* = 10.5, 4 Hz, H-5), 4.92 (br d, 1H, *J* = 9 Hz, H-11), 7.36-7.48 (m, 6H, aromatic protons), 7.66-7.73 (m, 4H, aromatic protons).

NOE difference experiments: irradiation of the signal at δ 2.00 (H-1) caused an enhancement of the signals at δ 1.16 (Me-10) and 4.92 (H-11); irradiation at δ 4.92 (H-11) caused an enhancement of signals at δ 1.61 (Me-13) and 2.00 (H-1); irradiation of the signal at δ 3.86-3.91 (H-5) caused an enhancement of the signal at δ 2.79-2.88 (H-9).

¹³C nmr (75.3 MHz) δ : 18.0 (-ve), 19.5, 21.2 (-ve), 25.6 (-ve), 27.0 (-ve, -C(CH₃)₃), 29.7, 31.6, 35.9, 37.6, 42.9 (-ve), 51.7, 67.8 (-ve), 73.1 (-ve, C-5), 127.5 (-ve), 127.7 (-ve), 129.6 (-ve), 129.8 (-ve), 132.1 (C-12), 133.4, 134.4, 135.9 (-ve), 136.0 (-ve), 212.2 (C-2).

Exact Mass calcd. for C₃₀H₄₀O₂Si: 460.2797; found: 460.2799.

Anal. calcd. for C₃₀H₄₀O₂Si: C 78.21, H 8.75; found: C 78.28, H 8.64.

Compound **175b** was the first compound to be eluted from the flash chromatography of the epimerization mixture. The oil thus obtained was heated at 80-100 °C/0.2 Torr for 1 h to remove any residual solvent, thereby providing pure compound **175b**, $[\alpha]_{\text{D}}^{25} -8.0$ (*c* 1.05, CHCl₃).

IR (film): 1723, 1590, 1112, 1064, 703 cm⁻¹.

¹H nmr (400 MHz) δ : 0.91 (s, 3H, Me-10), 1.06 (s, 9H, -CMe₃), 0.97-1.48 (m, 4H, one of which is H-8), 1.60 (br s, 3H, Me-13), 1.70 (br s, 3H, Me-14), 1.73-2.07 (m, 5H, three of which are H-1 (d, *J* = 10.5 Hz), H-4, and H-4'), 3.03-3.10 (dddd, 1H, *J* = 10.5, 10.5, 10.5, 6.5 Hz, H-9), 3.87-3.91 (dd, 1H, *J* = 10.5, 5 Hz, H-5), 4.78 (br d, 1H, *J* = 10.5 Hz, H-11), 7.36-7.48 (m, 6H, aromatic protons), 7.66-7.72 (m, 4H, aromatic protons).

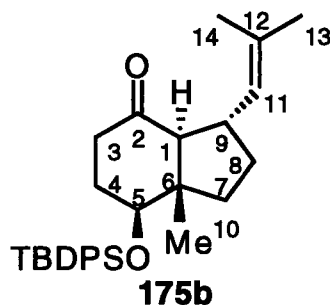
Detailed ¹H nmr data, derived from COSY and NOE experiments, are given in **Table 69**.

¹³C nmr (75.3 MHz) δ : 13.4 (-ve), 18.2 (-ve), 19.4, 25.8 (-ve), 27.0 (-ve, -C(CH₃)₃), 28.9, 32.1, 33.8 (-ve), 38.7, 39.6, 52.5, 63.5 (-ve), 78.8 (-ve, C-5), 127.5 (-ve), 127.6 (-ve), 128.7 (-ve, C-11), 129.6 (-ve), 129.8 (-ve), 131.5 (C-12), 133.6, 134.5, 135.9 (-ve), 136.0 (-ve), 209.4 (C-2).

Exact Mass calcd. for C₃₀H₄₀O₂Si: 460.2797; found: 460.2793.

Anal. calcd. for C₃₀H₄₀O₂Si: C 78.21, H 8.75; found: C 78.15, H 8.81.

Table 69: ^1H nmr Data (400 MHz, CDCl_3) for Compound **175b**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., (Hz))	COSY Correlations ^a	NOE Correlations ^a
Me-10	0.91 (s)		H-9
-CMe ₃	1.06 (s)		
H-8	Part of the m at 0.97-1.48	H-9	
Me-13	1.60 (br s)	H-11	H-11
Me-14	1.70 (br s)	H-11	
H-1	~2.01 (d, $J = 10.5$), part of the m at 1.37-2.07	H-9	H-5, H-11
H-4	Part of the m at 1.37-2.07	H-5	
H-4' ^b	Part of the m at 1.37-2.07	H-5	
H-9	3.03-3.10 (dddd, $J = 10.5$, 10.5, 10.5, 6.5)	H-1, H-8, H-11	Me-10, Me-14
H-5	3.87-3.91 (dd, $J = 10.5$, 5)	H-4, H-4'	H-1, -CMe ₃
H-11	4.78 (br d, $J = 10.5$)	H-9, Me-13, Me-14	H-1, Me-13

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-4' is more downfield than H-4)

Compound **212** was obtained in a pure form from further purification (flash chromatography) of the original mixture of compounds **213** and **212**. The late fractions eluted from the column chromatography were concentrated and the oil thus obtained was heated at 80-100 °C/0.2 Torr for 1 hour (to remove any residual solvent) to provide pure compound **212**, $[\alpha]_{\text{D}}^{25} -33.5$ (*c* 0.84, CHCl₃).

IR (film): 1704, 1590, 1112, 1089, 704 cm⁻¹.

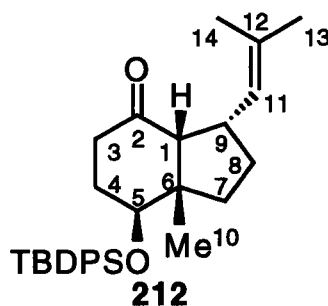
¹H nmr (400 MHz) δ : 1.08 (s, 9H, -CMe₃), 1.08-1.17 (m, 1H), 1.17 (s, 3H, Me-10), 1.31-1.39 (m, 1H), 1.43 (d, 3H, *J* = 0.8 Hz, Me-14), 1.50 (br s, 3H, Me-13), 1.74-2.00 (m, 5H, three of which are H-3, H-4, H-4'), 2.15-2.19 (m, 1H, H-3'), 2.48-2.51 (br dd, 1H, *J* = 10, 2 Hz, H-1), 3.12-3.21 (m, 1H, H-9), 3.77-3.81 (br dd, 1H, *J* = 10.5, 4 Hz, H-5), 4.51 (br d, 1H, *J* = 10 Hz, H-11), 7.37-7.49 (m, 6H, aromatic protons), 7.66-7.75 (m, 4H, aromatic protons).

Detailed ¹H nmr data, derived from COSY and NOE experiments, are given in **Table 70**.

¹³C nmr (75.3 MHz) δ : 18.0 (-ve), 19.4, 21.6 (-ve), 25.7 (-ve), 27.0 (-ve, -C(CH₃)₃), 29.0, 31.8, 38.5, 39.6, 41.4 (-ve), 49.5, 64.8 (-ve), 73.6 (-ve, C-5), 126.6 (-ve, C-11), 127.4 (-ve), 127.7 (-ve), 129.6 (-ve), 129.8 (-ve), 133.4, 133.5, 134.5, 135.9 (-ve), 136.0 (-ve), 212.7 (C-2).

Exact Mass calcd. for C₃₀H₄₀O₂Si: 460.2797; found: 460.2797.

Table 70: ^1H nmr Data (400 MHz, CDCl_3) for Compound **212**: COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., (Hz))	COSY Correlations ^a	NOE Correlations ^a
-CMe ₃	1.08 (s)		
Me-10	1.17 (s)		H-1
Me-14	1.43 (d, $J = 0.8$)	H-11	
Me-13	1.50 (br s)	H-11	
H-3	Part of the m at 1.74-2.00	H-3' ^b	
H-4	Part of the m at 1.74-2.00	H-3'	
H-4'	Part of the m at 1.74-2.00	H-3'	
H-3'	2.15-2.19 (m)	H-1 ^c , H-3, H-4, H-4', H-5	
H-1	2.48-2.51 (br dd, $J = 10, 2$)	H-3' ^c , H-9	H-9, Me-10
H-9	3.12-3.21 (m)	H-1, H-11	H-1, Me-14
H-5	3.77-3.81 (br dd, $J = 10.5, 5$)	H-3', H-4, H-4'	H-11
H-11	4.51 (br d, $J = 10$)	H-9, Me-13, Me-14	H-5, Me-13

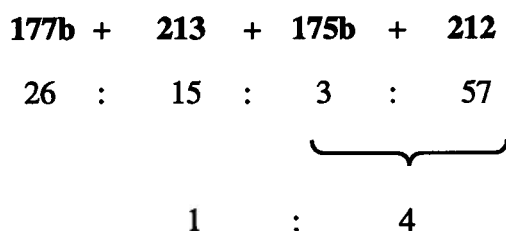
a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-3' is more downfield than H-3).

c-W coupling

b. Via Conjugate Addition of the Cuprate Reagent **178** to the Enone **177b** in the Presence of TMSBr at -78 °C:

Following the general procedure 5, the enone **177b** (224 mg, 0.553 mmol) was subjected to the cuprate addition reaction in the presence of TMSBr (i.e. BF₃•Et₂O was not used as a co-additive). The reaction mixture was stirred at -78 °C for 9.5 h. ¹H nmr spectroscopic analysis of the crude product indicated that ~25% of the starting material remained and that the ratio of compounds **213**:**175b**:**212** was 15:3:57.¹⁷⁴



Flash chromatography (25 g silica gel, 12.3:1 petroleum ether - diethyl ether) of the crude product produced 7.2 mg (3%) of compound **175b**, 137 mg (54%) of a mixture of compounds **213** and **212**, and 73 mg (33%) of recovered starting material **177b**. The mixture of addition products **213** and **212** was subjected to three epimerizations with NaOMe/MeOH (workup and column chromatography were performed after each epimerization to isolate the desired trans-fused isomer **175b**) to afford 97 mg (38% or 56% based on recovered starting material) of the desired epimer **175b**.

c. Via Conjugate Addition of the Cuprate Reagent **178** to the Enone **177b** in the Presence of TMSBr at -78 °C to -10 °C:

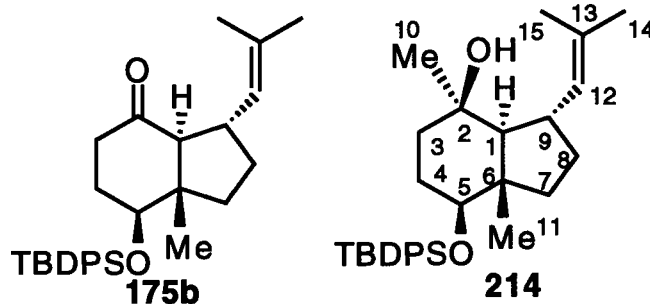
Following the general procedure 5, the enone **177b** (278 mg, 0.687 mmol) was subjected to the conjugate addition reaction employing trimethylsilyl bromide as the sole additive. The reaction mixture was stirred at -78 °C for 6.5 h and then was warmed to -10 °C over the course of 2 h. After the workup described in general procedure 5, the ¹H nmr spectrum of the crude product indicated that all of the starting enone **177b** had been

consumed, but that the product ratio now favored the undesired isomer **213**. The ratio of the addition products **213:175b:212** was found to be 59:3:38.¹⁷³

$$\begin{array}{rcccl}
 \mathbf{213} & + & \mathbf{175b} & + & \mathbf{212} \\
 59 & : & 3 & : & 38 \\
 & & \underbrace{\hspace{1.5cm}} & & \\
 1.4 & : & & & 1
 \end{array}$$

3.2.2. SYNTHESIS OF (-)-HOMALOMENOL A (**168b**)

3.2.2.1. Synthesis of (1*S*, 2*R*, 5*S*, 6*S*, 9*S*)-(-)-5-(*tert*-Butyldiphenylsiloxy)-2,6-dimethyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-ol (**214**):¹⁷⁰



To a cold (-20 °C), stirred solution of the (-)-trans-fused compound **175b** (170 mg, 0.369 mmol, 1 equiv.) in dry diethyl ether (7 mL) was added a solution of methyllithium in diethyl ether (1.4 M, 530 μ L, 0.74 mmol, 2 equiv.). The solution was warmed to -5 °C over the course of 1 h. Water (10 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude oil thus obtained was flash chromatographed (8 g silica gel, 9:1 petroleum ether - diethyl ether) to afford, after recrystallization of the acquired solid from diethyl ether - petroleum ether, 141 mg (80%) of the desired (-)-tertiary alcohol **214**, as a colourless crystalline solid, mp 98-100 °C, $[\alpha]_{\text{D}}^{25}$ -43.0 (*c* 1.71, CHCl₃).

IR (KBr): 3602, 3072, 1590, 1111, 703 cm⁻¹.

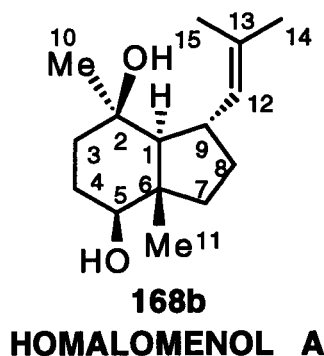
¹H nmr (400 MHz) δ : 0.86 (d, 1H, *J* = 11.5 Hz, H-1), 0.97 (s, 1H, -OH; this signal exchanges upon treatment with D₂O), 1.01 (s, 3H, Me-11), 1.04 (s, 9H, -CMe₃), 1.01-1.20 (m, 3H), 1.21 (s, 3H, Me-10), 1.26-1.35 (m, 1H), 1.41-1.45 (ddd, 1H, *J* = 14.5, 4.5, 2.5 Hz), 1.62-1.65 (m, 1H), 1.62, 1.63 (d, d, 3H each, *J* = 1 Hz for each d, Me-13 and Me-14), 1.79-1.90 (ddd, 1H, *J* = 18, 14, 4.5 Hz), 1.98-2.08 (m, 1H), 2.86-2.95 (m, 1H, H-9), 3.35-3.39 (dd,

1H, $J = 11.5$, 4 Hz, H-5), 5.00 (br d, 1H, $J = 9.5$ Hz, H-12), 7.34-7.42 (m, 6H, aromatic protons), 7.68-7.70 (m, 4H, aromatic protons).

^{13}C nmr (75.3 MHz) δ : 14.9 (-ve), 18.1 (-ve), 19.5, 25.7 (-ve), 27.0 (-ve, $-\text{C}(\text{CH}_3)_3$), 28.4, 29.5, 30.5 (-ve), 35.0 (-ve), 39.4, 40.4, 47.8, 58.8 (-ve), 71.7 (C-2), 81.3 (-ve, C-5), 127.3 (-ve), 127.4 (-ve), 128.4 (C-13), 129.3 (-ve), 129.5 (-ve), 132.4 (-ve, C-12), 134.1, 135.3, 135.9 (-ve), 136.0 (-ve).

Exact Mass calcd. for $\text{C}_{31}\text{H}_{44}\text{O}_2\text{Si}$: 476.3110; found: 476.3103.

Anal. calcd. for $\text{C}_{31}\text{H}_{44}\text{O}_2\text{Si}$: C 78.10, H 9.30; found: C 78.12, H 9.34.

3.2.2.2. Synthesis of (-)-Homalomenol A (**168b**):

To a stirred solution of the (-)-tertiary alcohol **214** (141 mg, 0.296 mmol, 1 equiv.) in dry THF (6 mL) at rt was added a solution of TBAF in THF (1 M, 2.4 mL, 2.4 mmol, 8 equiv.). The mixture was refluxed for 18 h. The solution was cooled to rt; water (25 mL) and diethyl ether (25 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL) and ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude oil was flash chromatographed (8 g silica gel, 3:2 petroleum ether - ethyl acetate) to yield 61 mg (87%) of (-)-homalomenol A (**168b**), a white solid. Recrystallization of the solid from diethyl ether - petroleum ether provided (-)-homalomenol A (**168b**) as thin, needle-like plates, mp 99-100 °C, $[\alpha]_{\text{D}}^{20}$ -51.5 (*c* 1.30, CHCl₃); lit.¹²¹ for (+)-homalomenol A (**168a**): oil, $[\alpha]_{\text{D}}^{20}$ +33.2 (*c* 1.205, CHCl₃).

IR (KBr): 3617, 3434, 1581, 1023 cm⁻¹.

¹H nmr (400 MHz, referenced at δ 7.24) δ : 0.93 (s, 1H, -OH; this signal exchanges upon treatment with D₂O), 0.99 (d, 1H, *J* = 11.5 Hz, H-1), 1.04 (d, 3H, *J* = 0.7 Hz, Me-11), 1.10 (s, 3H, Me-10), 1.19-1.39 (m, 3H, one of which is H-8), 1.41-1.46 (dd, 1H, *J* = 14, 5 Hz), 1.52-1.64 (m, 3H, one of which is H-4), 1.63, 1.64 (d, d, 3H each, *J* = 1.5 Hz for each d, Me-

14 and Me-15), 1.73-1.84 (m, 1H, H-4'), 2.00-2.11 (m, 1H, H-8'), 2.88-2.98 (m, 1H, H-9), 3.35-3.38 (dd, 1H, $J = 11.4, 4.1$ Hz, H-5), 5.05 (br d, 1H, $J = 9.5$ Hz, H-12).

Detailed ^1H nmr data, derived from COSY and NOE experiments, are given in **Table 71**.

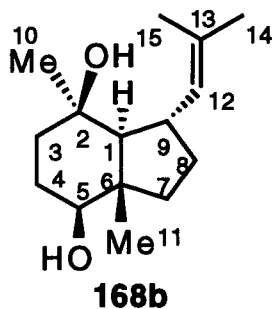
^{13}C nmr (75.3 MHz) δ : 14.1 (-ve), 18.1 (-ve), 25.7 (-ve), 27.9, 29.6, 30.7 (-ve), 34.9 (-ve), 38.6, 40.6, 47.1, 59.0 (-ve), 71.7 (C-2), 80.0 (-ve, C-5), 128.7 (C-13), 132.1 (-ve, C-12).

Exact Mass calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_2$: 238.1933; found: 238.1930.

Anal. calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_2$: C 75.58, H 10.99; found: C 75.29, H 11.12.

Comparison of the reported spectral data for (+)-homalomenol A (**168a**) with that of the synthetic (-)-homalomenol A (**168b**) is shown in **Table 72**.

Table 71: ^1H nmr Data (400 MHz, CDCl_3) for (-)-Homalomenol A (**168b**): COSY and NOE Experiments



Assignment H-x	^1H nmr (400 MHz) δ ppm (mult., J (Hz))	COSY Correlations ^a	NOE Correlations ^a
H-1	0.99 (br d, $J = 11.5$)	H-9	H-5, H-12
Me-11	1.04 (d, $J = 0.7$)		H-9
Me-10	1.10 (s)		H-12
H-8	Part of the m at 1.19-1.39	H-8' ^b , H-9	
H-4	Part of the m at 1.52-1.64	H-4', H-5	
Me-14	1.63 (d, $J = 1.5$)	H-12	
Me-15	1.64 (d, $J = 1.5$)	H-12	
H-4'	1.73-1.84 (m)	H-4, H-5	
H-8'	2.00-2.11 (m)	H-8, H-9	H-8, H-9
H-9	2.88-2.98 (m)	H-1, H-8, H-8', H-12	H-8', Me-11, Me-15
H-5	3.35-3.38 (dd, $J = 11.4, 4.1$)	H-4, H-4'	H-1
H-12	5.05 (br d, $J = 9.5$)	H-9, Me-14, Me-15	Me-14

a- Only those COSY correlations and NOE data that could be assigned are recorded.

b- H' indicates the hydrogen of a pair which is more downfield (H-8' is more downfield than H-8).

Table 72: Comparison of the Reported Spectral Data for (+)-Homalomenol A (**168a**) with that of the Synthetic (-)-Homalomenol A (**168b**)

Data	Synthetic	Reported ^a
MP	99-100 °C	— ^b
IR (cm ⁻¹)	3617	3600
	3434	3450
	1581	—
	1023	—
¹ H NMR ^c (δ)	1.04 (d, 3H, <i>J</i> = 0.7 Hz)	1.03 (d, 3H, <i>J</i> = 0.9 Hz)
	1.10 (s, 3H)	1.10 (s, 3H)
	1.63 (d, 3H, <i>J</i> = 1.5 Hz)	1.63 (m, 3H)
	1.64 (d, 3H, <i>J</i> = 1.5 Hz)	1.63 (m, 3H)
	2.88-2.98 (m, 1H)	2.92 (16 lines, 1H)
	3.35-3.38 (dd, 1H, <i>J</i> = 11.4, 4.1 Hz)	3.36 (dd, 1H, <i>J</i> = 11, 4.1 Hz)
	5.05 (br d, 1H, <i>J</i> = 9.5 Hz)	5.05 (d sp ^d , 1H, <i>J</i> = 9.3, 1.4 Hz)
¹³ C NMR (δ)	14.1	14.2
	18.1	18.1
	25.7	25.8
	27.9	28.0
	29.6	29.6
	30.7	30.7
	34.9	35.0
	38.6	36.7
	40.6	40.7
	47.1	47.2
	59.0	59.1
	71.7	71.8
	80.0	80.0
	128.7	128.7
	132.1	132.2
HRMS (238.1933) ^e	238.1930	238.1933
Elemental Analysis	C ₁₅ H ₂₆ O ₂	— ^f
[α] _D ²⁰ (CHCl ₃)	-51.5 (<i>c</i> 1.30)	+33.2 (<i>c</i> 1.205)

a- Spectral data for (+)-homalomenol A as reported in reference 121.

b- Reported as an oil.

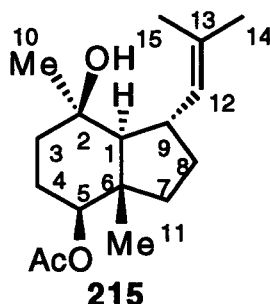
c- Only the selected ¹H nmr signals for the synthetic (-)-homalomenol A which correspond to those reported for the natural (+)-homalomenol A are listed.

d- d sp: doublet of septets

e- Calculated value for C₁₅H₂₆O₂

f- Not reported

3.2.3. SYNTHESIS OF (1*S*, 2*R*, 5*S*, 6*S*, 9*S*)-(-)-5-ACETOXY-2,6-DIMETHYL-9-(2-METHYL-1-PROPENYL)-BICYCLO[4.3.0]NONAN-2-OL (**215**):



To a stirred solution of homalomenol A (**168b**) (13 mg, 0.054 mmol, 1 equiv.) in dry pyridine (0.30 mL, 3.7 mmol, 68 equiv.) at rt was added acetic anhydride (0.30 mL, 3.2 mmol, 59 equiv.). The resultant solution was stirred at rt for 24 h and 0.1 M hydrochloric acid (5 mL) was then added. Diethyl ether was added (10 mL) and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (2 x 10 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was flash chromatographed (3 g silica gel, 9:1 petroleum ether - ethyl acetate) to provide 15 mg (98%) of the monoacetate **215**,¹⁷⁵ a solid. The monoacetate **215** was recrystallized from petroleum ether - ethyl acetate to provide a colourless crystalline solid, mp 89-92 °C.

IR (KBr): 3498, 1717, 1455, 1262, 1027 cm⁻¹.

¹H nmr (400 MHz, referenced at δ 7.24) δ: 1.08 (br s, 3H, Me), 1.11 (s, 3H, Me), 1.18-1.51 (m, 6H), 1.62 (br d, 3H, *J* = 1 Hz, vinyl Me), 1.63 (br d, 3H, *J* = 1 Hz, vinyl Me), 1.57-1.66 (m, 2H), 1.80-1.90 (m, 1H), 1.95-2.05 (m, 1H), 2.01 (s, 3H, -OC(O)Me), 2.87-2.96 (m, 1H, H-9), 4.57-4.61 (dd, 1H, *J* = 11.5, 4 Hz, H-5), 5.06 (br d, 1H, *J* = 9.5 Hz, H-12).

¹³C nmr (75.3 MHz) δ: 15.2 (-ve), 18.1 (-ve), 21.3 (-ve), 24.5, 25.7 (-ve), 29.3, 30.7 (-ve), 34.8 (-ve), 38.5, 40.3, 45.9, 59.1 (-ve), 71.6, 81.1 (-ve, C-5), 128.8 (C-13), 131.9 (-ve, C-12), 170.9 (-OC(=O)Me).

Exact Mass calcd. for C₁₇H₂₈O₃: 280.2039; found: 280.2035.

Anal. calcd. for C₁₇H₂₈O₃: C 72.82, H 10.06; found: C 72.70, H 9.91.

Table 73: Comparison of the Reported Spectral Data for the (+)-Monoacetate **215** with that of the Synthetic Monoacetate **215**

Data	Synthetic	Reported ^a
MP	89-92 °C	92-95 °C
IR (cm ⁻¹)	3498	3600
	1717	1720
	1455	—
	1262	1260
¹ H NMR ^b (δ)	1.08 (br s, 3H)	1.09 (d, 3H, <i>J</i> = 0.8 Hz)
	1.11 (s, 3H)	1.11 (s, 3H)
	1.62 (br d, 3H, <i>J</i> = 1Hz)	1.62 (d, 3H, <i>J</i> = 1.5 Hz)
	1.63 (br d, 3H, <i>J</i> = 1Hz)	1.63 (d, 3H, <i>J</i> = 1.5 Hz)
	2.01 (s, 3H)	2.02 (s, 3H)
	2.87-2.96 (m, 1H)	2.91 (16 lines, 1H)
	4.57-4.61 (dd, 1H, <i>J</i> = 11.5, 4 Hz)	4.58 (dd, 1H, <i>J</i> = 11.4, 4 Hz)
	5.06 (br d, 1H, <i>J</i> = 9.5 Hz)	5.04 (d sp ^c , 1H, <i>J</i> = 9.6, 1.5 Hz)
¹³ C NMR (δ)	15.2	15.2
	18.1	18.2
	21.3	21.4
	24.5	24.6
	25.7	25.8
	29.3	29.4
	30.7	30.7
	34.8	34.8
	38.5	38.5
	40.3	40.4
	45.9	46.0
	59.1	59.1
	71.6	71.7
	81.1	81.2
	128.8	128.8
	131.9	132.0
	170.9	171.0
HRMS (280.2039) ^d	280.2035	280.2042
Elemental Analysis	C ₁₇ H ₂₈ O ₃	— ^e

a- Spectral data for the monoacetate **215** as reported in reference 121.

b- Only the selected ¹H nmr signals for the synthetic monoacetate **215** which correspond to those reported for the (+)-monoacetate **215** are listed.

c- d sp: doublet of septets

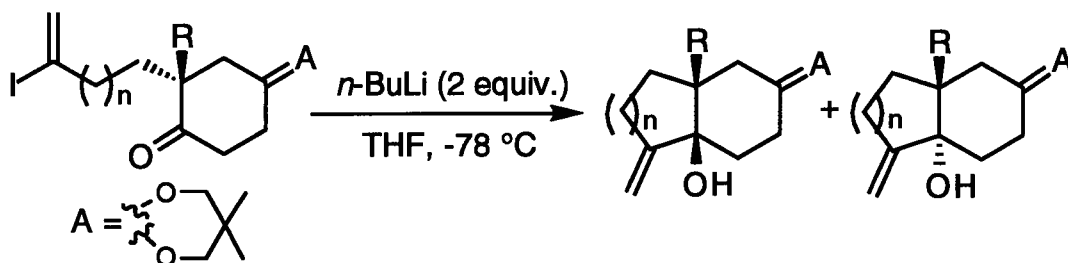
d- Calculated value for C₁₇H₂₈O₃

e- Not reported

IV. REFERENCES AND FOOTNOTES

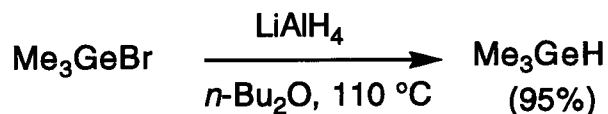
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2. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
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8. Seebach states that reactivity umpolung is present in a reagent in which acceptor and donor centers are reversed. See reference 2. For example, route A employs a d²,a⁴-synthon whereas route B employs an a²,d⁴-synthon.
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14. The average carbon-tin bond length is 2.18 Å while the average carbon-germanium bond length is 1.98 Å (Weast, R. C. (Ed.) "CRC Handbook of Chemistry and Physics", CRC Press, Boca Raton, 66th Edition, 1985, p F-165.). Since shorter bonds are associated with higher bond dissociation energies (Jackson, R. A. *J. Organomet. Chem.* **1979**, *166*, 17.), the trimethylgermyl functionality should be more resistant to transmetallation than the corresponding trimethylstannyl moiety.
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trimethylstannyl-1-pentene vs. 5-iodo-2-trimethylgermyl-1-pentene), the final ring closure step is identical with that described in reference 9. As a result, the product resulting from this annulation sequence is a bicyclic compound bearing a tertiary allylic alcohol. See below.



n=1, R=H	1	:	1
n=1, R=Me	> 99	:	< 1
n=2, R=H	1	:	15
n=2, R=Me	> 99	:	1

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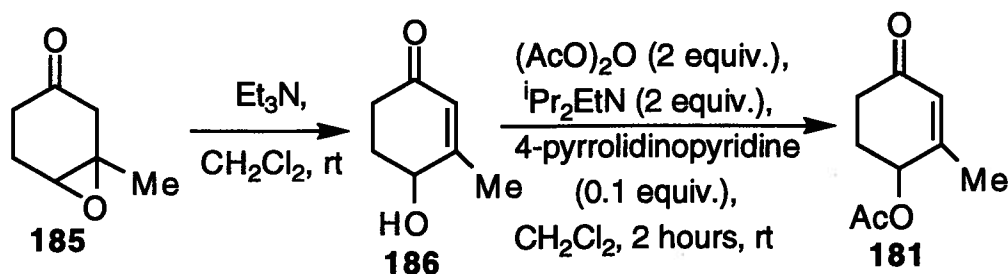
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79. The spectral data of 3-trimethylstannyl-3-buten-1-ol (**48a**) are identical with those reported in reference 10.

80. The spectral data of 4-chloro-2-trimethylstannyl-1-butene (**45**) are identical with those reported in reference 10.
81. The spectral data of 4-iodo-2-trimethylgermyl-1-butene (**13**) are identical with those reported in: Marais, P. C. Ph. D. Thesis, University of British Columbia, April 1990, page 124.
82. René Lemieux is thanked for a generous sample of 1-trimethylsilyl-4-trimethylsilyloxy-1-butyne (**51**).
83. René Lemieux is thanked for a generous sample of Me₃GeH. This volatile compound is stored in the freezer and should be transferred while still cold. The barrel of the gas-tight syringe (used in the transferring procedure) is cooled with ice water just prior to syringing the trimethylgermane.
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89. This procedure has been modified from that described in: Marais, P. C. Ph. D. Thesis, University of British Columbia, April 1990, page 147.
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92. The spectral data of the vinyl iodide **67** are identical with those reported in: Marais, P. C. Ph. D. Thesis, University of British Columbia, April 1990, page 150.
93. This procedure has been modified from that described in: Marais, P. C. Ph. D. Thesis, University of British Columbia, April 1990, page 152.
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98. The $\text{Pd}_2(\text{dba})_3$ used in this reaction was purchased from Aldrich Chemical Co., Inc.
99. Tri(2-furyl)phosphine was synthesized according to the following procedure: Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc., Perkin Trans. II* **1972**, 63.
100. The triisopropylphosphite used in this reaction was purchased from Aldrich Chemical Co., Inc.
101. $\text{PdCl}_2(\text{dppf})$ was synthesized according to the following procedure: Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
102. $\text{Ni}(\text{COD})_2$ was synthesized according to the following procedure: Mackenzie, P. B.; Krysan, D. J. *J. Org. Chem.* **1990**, *55*, 4229.
103. Cs_2CO_3 was dried by the following method: A round bottom flask containing solid Cs_2CO_3 was placed under reduced pressure (vacuum pump) and flame dried using a Bunsen burner. The flask was then filled with argon and cooled to rt.
104. The spectral data of 5-chloro-2-trimethylstannyl-1-pentene (**83a**) are identical with those reported in reference 10.
105. The spectral data of compound **95** are identical with those reported in reference 106.
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108. The ratio of compounds was determined by the integration of the methyl proton signals of compounds **130b** and **130a**, respectively.
109. The ratio of compounds was determined by the integration of the methyl proton signals of compounds **131a** and **131b**, respectively.
110. The ratio of compounds **132a** to **132b** was determined by comparing the integration of H-1 (pertaining to compound **132a**) to the integration of H-13 (pertaining to both compounds **132a** and **132b**).
111. The ratio was determined by the integration of the methyl proton signals of compounds **133a** and **133b**, respectively.
112. The ratio of **135a**:**135b** was determined by the integration of the vinyl methyl signals of compounds **135a** and **135b**, respectively.
113. The ratio of **137a**:**137b** was determined by glc analysis of the mixture.
114. The ratio of **138a**:**138b** was determined by glc analysis of the mixture.
115. The $\text{Pd}(\text{PPh}_3)_4$ used in this cyclization reaction was synthesized according to the following procedure: Coulson, D. R. *Inorganic Synthesis* **1972**, *13*, 121.

116. The dilution used in this reaction was 0.008M as opposed to the 0.05 M dilution described in general procedure 3 (page 146). Also, no *t*-BuOH was present in the base mixture.
117. The 17:1 ratio is based on the isolated amounts of the two cyclized products, **139** and **140**.
118. The 1.2:1 ratio is based on the isolated amounts of the two cyclized products, **139** and **140**.
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147. 3-Methyl-3-cyclohexen-1-one (**182**) was synthesized according to the following procedure: Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051.
148. The spectral data of 3-methyl-3-cyclohexen-1-one (**182**) are identical with those reported in the following paper: Noyce, D. S.; Evett, M. *J. Org. Chem.* **1972**, *37*, 394.
149. Acheson, R. M.; *J. Chem. Soc.* **1956**, 4232.
150. The original procedure for the synthesis of the epoxide **185** is described in reference 124. We have modified this procedure due to the fact that *m*-CPBA is much more readily available than is peracetic acid.
151. The original procedure for the synthesis of the acetate **181**, described in reference 124, is shown below:



We found that the allylic alcohol **186** in the above sequence was not very stable to purification and could not be stored for any length of time. Therefore, we modified the procedure to allow for the opening of the epoxide and protection to the acetate in one step.

152. The spectral data of the allylic acetate **181** are identical with those reported in reference 124.
153. The procedure for the kinetic resolution of the racemic allylic acetate **181** is reported in reference 124.
154. The Tris•HCl buffer was prepared by adding 0.3 M aqueous tris(hydroxymethyl)aminomethane to a stirred aqueous solution of 0.3 M tris(hydroxymethyl)aminomethane hydrochloride until the pH of the solution reached 7.
155. The pig liver esterase was purchased from Sigma as a suspension in 3.2 M (NH₄)₂SO₄, pH 8.
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157. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1987**, 46, 4475.
158. The original procedure (see reference 124) for the synthesis of the (+)-TBDPS ether **180b** was modified slightly.
159. The spectral data of the (+)-TBDPS ether **180b** are identical with those reported in reference 124.
160. In the event that the silyl enol ether failed to hydrolyze, the crude oil was dissolved in THF (1 mL per mmol of starting material) and treated with 1 equivalent of TBAF in THF. The mixture was stirred at rt for ~10 min. Water (10 mL per mmol of starting material) and ether (20 mL per mmol of starting material) were added to the mixture and the layers were separated. The aqueous layer was extracted thoroughly with diethyl ether and the combined organic extracts were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The keto acetal **189** was purified as described.
161. Taber, D. F. *J. Org. Chem.* **1982**, 47, 1351.
162. The procedure used for the acetal hydrolysis and subsequent intramolecular aldol condensation was modified from that described in the following paper: Lavallée, P.; Hanessian, S. *Can. J. Chem.* **1975**, 53, 2975.

163. 2-Methyl-3-(tri-*n*-butylstannyl)propene (**194**) was synthesized according to the procedure reported in reference 164.
164. Keck, G. E.; Enholm, E. J. *Tetrahedron* **1985**, *41*, 4079.
165. The spectral data of 2-methyl-3-(tri-*n*-butylstannyl)propene (**194**) are identical with those reported in reference 164.
166. The conjugate addition procedure used to synthesize compounds **196** and **176b** was modified somewhat from that described in reference 133.
167. LiCl was flame dried according to the following procedure: A round bottom flask containing solid LiCl was placed under reduced pressure (vacuum pump) and flame dried using a Bunsen burner. The flask was then filled with argon and cooled to rt.
168. The copper(I) iodide was recrystallized according to reference 134.
169. The ratio of compounds **176b**:**196** was determined by the integration of the respective vinyl proton signals in the ^1H nmr spectrum.
170. The procedure for the synthesis of a tertiary alcohol was modified somewhat from that described in the following paper: Masamune, T.; Sato, H.; Fukuzawa, A. *Tetrahedron Lett.* **1987**, *28*, 4303.
171. 1-Iodo-2-methylpropene (**202**) was synthesized according to the following procedure: Inokawa, S.; Takage, K.; Hayama, N. *Chem. Lett.* **1978**, 1435.
172. The reported ^1H nmr signals corresponding to 1-iodo-2-methylpropene (**202**) are identical to those reported in the following paper: Newman, M. S.; Beard, C. D. *J. Am. Chem. Soc.* **1970**, *92*, 4309.
173. The ratio of isomers was determined by the integration of the respective vinyl proton signals in the ^1H nmr spectrum.
174. The ratio of the starting material **177b** and compounds **213**, **175b**, and **212** was determined by the integration of the respective vinyl proton signals in the ^1H nmr spectrum. It was later found that 33% of the starting material **177b** was recovered (the ^1H nmr indicated that 25% of the starting material remained), indicating that the relaxation time for the vinyl proton of the starting material is longer than that observed for the vinyl proton signals of the addition products **213**, **175b**, and **212**.
175. The spectral data of the monoacetate **215** are identical with those reported in reference 121.

V. APPENDIX

5.1. APPENDIX 1: X-RAY CRYSTALLOGRAPHIC DATA

Compound	Ester 145
formula	$\text{C}_{21}\text{H}_{25}\text{NO}_4$
crystal system	monoclinic
space group	$p2_1/c$
a (Å)	12.019(2)
b (Å)	7.368(2)
c (Å)	21.572(2)
β°	98.82(1)
v (Å ³)	1887.7(6)
Z	4
number of reflections used in refinement	1442
R	0.052
R_w	0.044