METHYLENECYCLOHEXANE ANNULATIONS.
TOTAL SYNTHESES OF AXANE-TYPE SESQUITERPENOIDS

BY

BIK WAH ANISSA YEUNG

B.Sc., The Chinese University of Hong Kong, 1979

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

THE FACULTY OF GRADUATE STUDIES

(DEPARTMENT OF CHEMISTRY)

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

October 1986

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Chemistry

The University of British Columbia
1956 Main Mall
Vancouver, Canada
V6T 1Y3

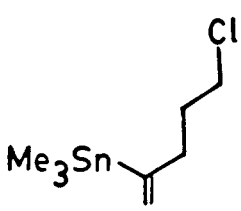
Date 15th December, 1986.

ABSTRACT

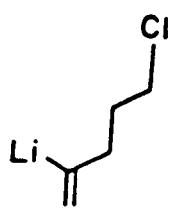
This thesis describes the preparation of 5-chloro-2-trimethylstannyl-1-pentene (111) and its conversion into 5-chloro-2-lithio-1-pentene (112). The latter reagent, which reacts smoothly with cyclohexanone at -78°C to give 5-chloro-2-(1-hydroxycyclohexyl)-1-pentene (132), was found to be thermally unstable at temperatures higher than -63°C.

Reagent (112) was transformed into the Grignard reagent (144) and the organocopper-phosphine complex reagent (145). Conjugate addition of reagents (144) and/or (145) to cyclic enones under appropriate conditions followed by cyclization of the resultant products, effected useful methylenecyclohexane annulation sequences [(104) → (116)].

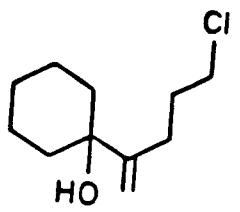
This methylenecyclohexane annulation method served as one of the two key steps in the syntheses of (±)-axamide-1 (174), (±)-axisonitrile-1 (173), and the corresponding C-10 epimers. Thus, copper(I)-catalyzed addition of the Grignard reagent (144) to 2-methyl-2-cyclopenten-1-one (152), followed by cyclization of the resultant chloro ketone (159), gave the annulation product (170), which was converted into the enone (203). The other key step in the projected synthesis, which involved $TiCl_4$-catalyzed conjugate addition of the bis(trimethylsilyl) ketene acetal (226) to the enone (203), provided a mixture of the keto acids (222) and (223). With appropriate functional group manipulations, (222) was converted into (±)-axamide-1 (174) and (±)-axisonitrile (173), while (223) was converted into (±)-10-epi-axamide-1 (224) and (±)-10-epi-axisonitrile-1 (225).



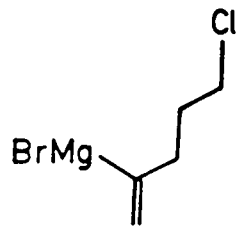
111



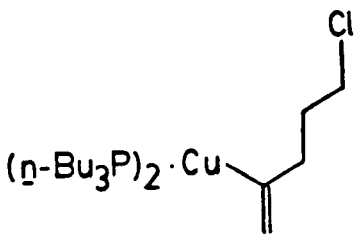
112



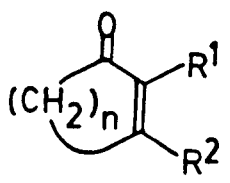
132



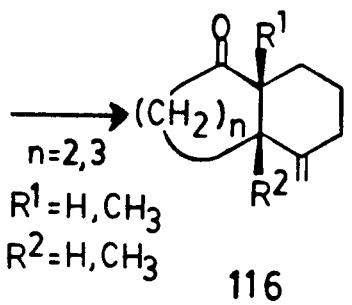
144



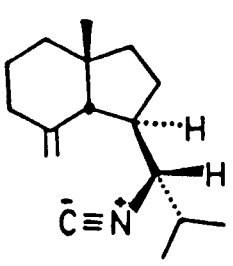
145



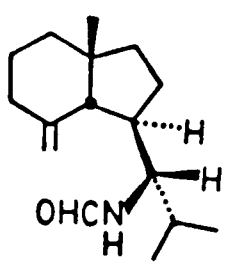
104



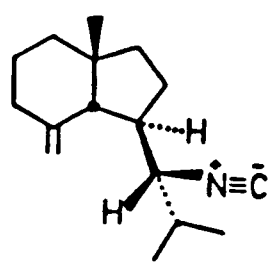
116



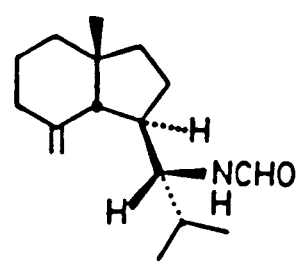
173



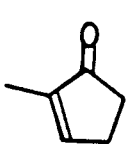
174



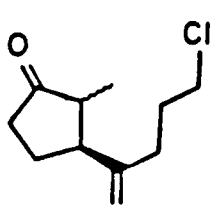
225



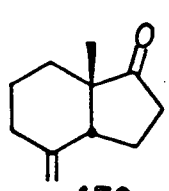
224



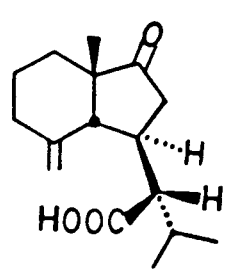
152



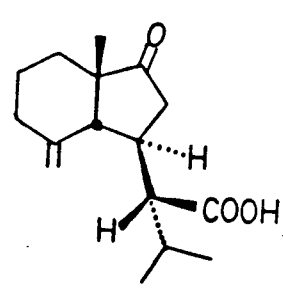
159



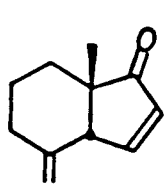
170



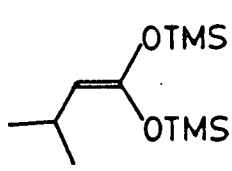
222



223



203



226

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

The following abbreviations have been used throughout this thesis.

Ac	=	acetyl
AIBN	=	2,2'-azobisisobutyronitrile
br	=	broad
Bu	=	butyl
CD	=	circular dichroism
d	=	doublet
DEG	=	diethylene glycol
DME	=	1,2-dimethoxyethane
DMF	=	N,N-dimethylformamide
equiv	=	equivalent(s)
Et	=	ethyl
glc	=	gas-liquid chromatography
h	=	hour(s)
HMPA	=	hexamethylphosphoramide
ir	=	infrared
LAH	=	lithium aluminum hydride
LDA	=	lithium diisopropylamide
LHMDS	=	lithium hexamethyldisilazide
m	=	multiplet
MCPBA	=	meta-chloroperbenzoic acid
Me	=	methyl

min	=	minute(s)
mp	=	melting point
Ms	=	methanesulfonate
NBS	=	N-bromosuccinimide
nmr	=	nuclear magnetic resonance
nOe	=	nuclear Overhauser effect
Ph	=	phenyl
Pr	=	propyl
py	=	pyridine
q	=	quartet
s	=	singlet
t	=	triplet
TBAF	=	tetra-n-butylammonium fluoride
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TMS	=	trimethylsilyl
tlc	=	thin-layer chromatography
p-TsOH	=	para-toluenesulfonic acid

ACKNOWLEDGEMENTS

I would like to thank Professor Edward Piers for his excellent guidance and encouragement throughout the course of my studies. It is a pleasure to work with him.

I would also like to thank the members of Professor Piers' research group for their helpful discussions and shared ideas.

I am indebted to Yee Fung Lu, Peter Marrs, and John Wai for their careful proofreading.

Thanks are also extended to the various services in the department for their efficient cooperation and to Mrs. Rani Theeparajah for her careful and efficient typing of this thesis.

To My Parents

with affection

CHAPTER I

INTRODUCTION

INTRODUCTION

A. General

Ring annulation* is a demanding and an important process in organic synthesis. The term "annulation"[1] is used to describe the process of building a ring onto a pre-existing system, cyclic or non-cyclic. The two new carbon-carbon bonds involved in annulation can be formed simultaneously, consecutively in a one-pot process, or separately. The added ring may be of any size although five- and six-membered rings are most commonly formed. In a broad sense, the methods of annulation include Diels-Alder reactions,[2] acid-catalyzed olefinic cyclizations,[3] and radical,[4] photochemical[5] and thermal[6] cyclizations. However, in a general sense, alkylations or Michael additions followed by cyclizations are more often thought of as the methods of annulation.

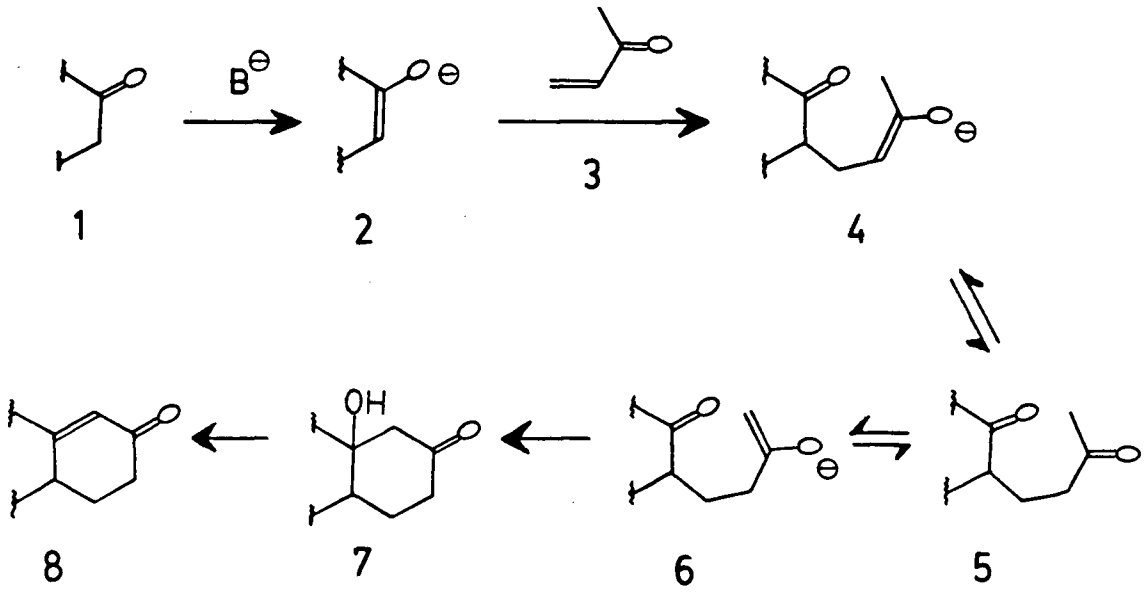
Considering the formation of a six-membered ring** which is a common structural unit in terpenes, steroids, and alkaloids, the

---

* The incorrectly spelled word annelation has been used quite often in the literature. Here, the less used but correctly spelled word annulation will be used (see reference 1).

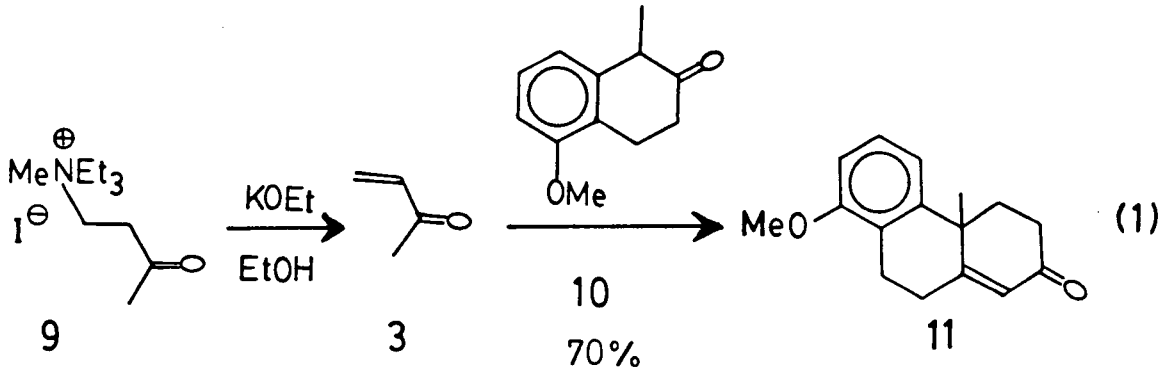
** Since five-membered ring annulations are not the primary interest of this thesis, no discussion about them will be given here. However, a few excellent reviews concerning five-membered ring annulations are available for consultation (see reference 7).

Robinson annulation reaction is commonly evoked. This process involves base catalyzed Michael addition of a ketone enolate (2) to an alkyl vinyl ketone [e.g. (3)] followed by acid- or base-catalyzed aldol condensation, as illustrated in Scheme 1.[1,8a] Different functionality patterns on the cyclohexenone products (8) can be derived by modifying the structures of the starting materials. This salient feature increases the utility of the Robinson annulation reaction.



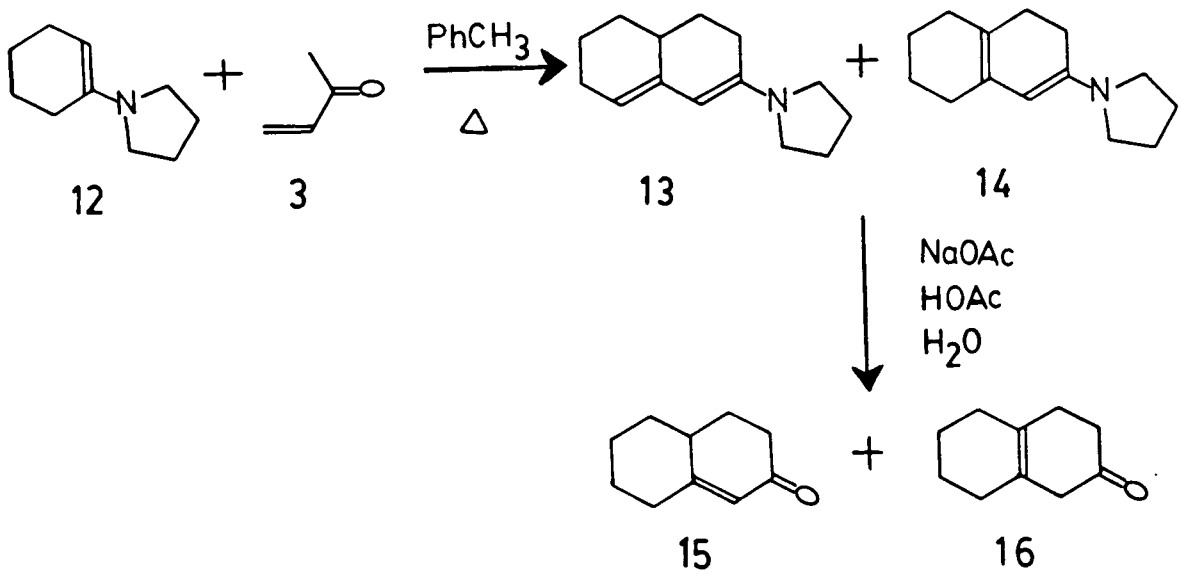
Scheme 1

However, the polymerization of the vinyl ketones, which leads to lower yields of the desired cyclohexenone products, constitutes a serious drawback of the Robinson annulation. The problem of polymerization was partly overcome by the use of a quaternized Mannich base [e.g. (9)][9] in place of the vinyl ketone (equation 1). Treatment of



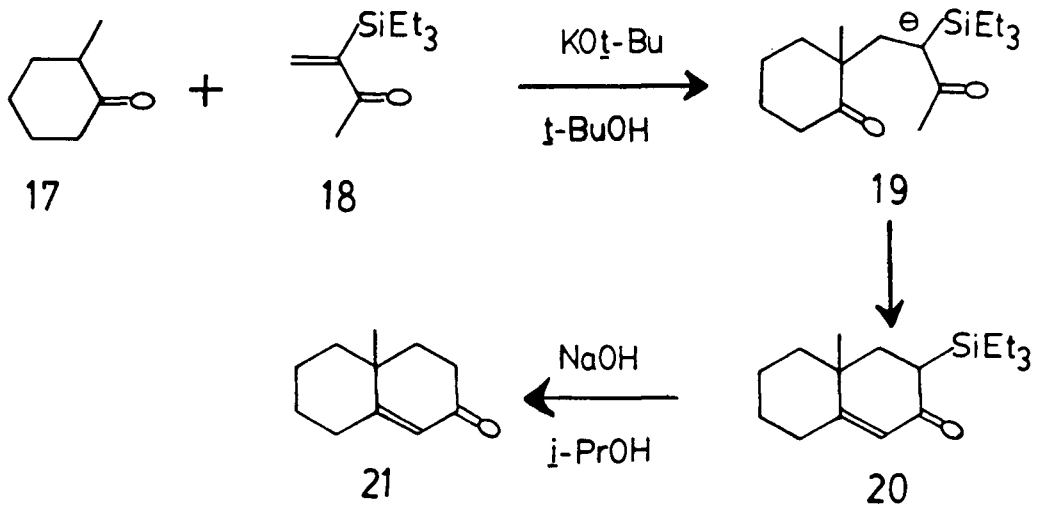
this Mannich base with strong base converts it into the corresponding vinyl ketone [e.g. (3)] in situ. Using this procedure, the yield of the product is usually improved.

The use of enamines[10] has also produced good yields in annulation reactions. For example, the enamine of cyclohexanone (12) reacts with methyl vinyl ketone (3) to give a mixture of (13) and (14). After hydrolysis of the latter substance, a mixture of isomers (15) and (16) was produced in 67% yield (Scheme 2).



Scheme 2

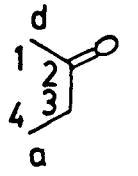
α-Trialkylsilyl enones [e.g. (18)] have also been used to react with ketone enolates[11] (Scheme 3). The triethylsilyl group in (19) stabilizes somewhat the initial negative charge formed by addition of the enolate ion to the enone, and, more importantly, provides steric hindrance which slows down anionic polymerization. The triethylsilyl group can be removed from the α'-triethylsilyl enone (20) with base after the annulation process is complete.



Scheme 3

Besides the annulation methods mentioned above, numerous modified reaction conditions and reagents related to (1) and (3) have been developed and used.[1,8] They serve to improve the yields and to produce various structural patterns for the products from the Robinson annulation reactions.

Reagents (3), (9) and (18) can be classified as bifunctional conjunctive* reagents containing both a donor and an acceptor** site and can be considered as synthetic equivalents to the synthon*** (22).



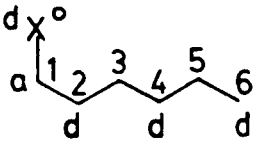
d^1, a^4 synthon

22

---

* Conjunctive reagents are those reagents that are incorporated in whole or in part into a more complex system. The term "conjunctive" is used to differentiate these reagents from those that react with but are not normally incorporated into a substrate (see reference 12).

** Heteroatoms, present in many organic molecules, impose an alternating acceptor and donor reactivity pattern upon the carbon skeleton, i.e. acceptor properties (attack by donor reagents) at carbons $C^{1.3.5\cdots}$, and donor properties (attack by acceptor reagents) at carbons $C^{2.4.6\cdots}$. The heteroatom X itself is a donor center (d^o) (see reference 13).

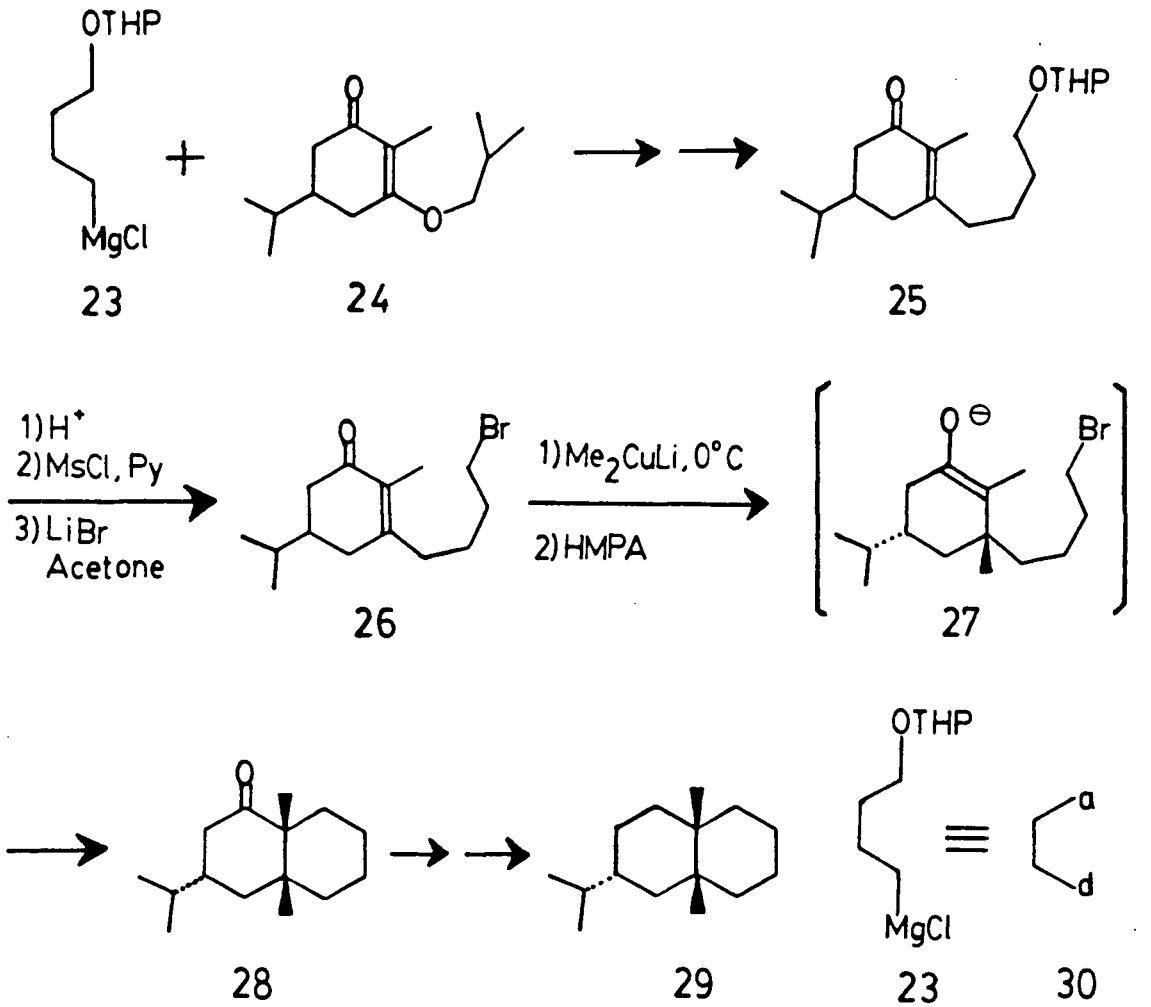


X=O,N

*** Corey defines synthons as "structural units within a molecule which are related to possible synthetic operations" (see reference 14).

A related annulation method, also making use of the Michael reaction, involves the addition of an organometallic reagent, usually a cuprate, to an enone, followed by cyclization. This method can be carried out in two ways, depending on whether the site necessary for cyclization is incorporated into the enone or into the organometallic reagent before the conjugate addition.

In the synthesis of valerane (29) reported by Posner et al.[15] (Scheme 4), addition of the Grignard reagent (23), a synthetic equiva-

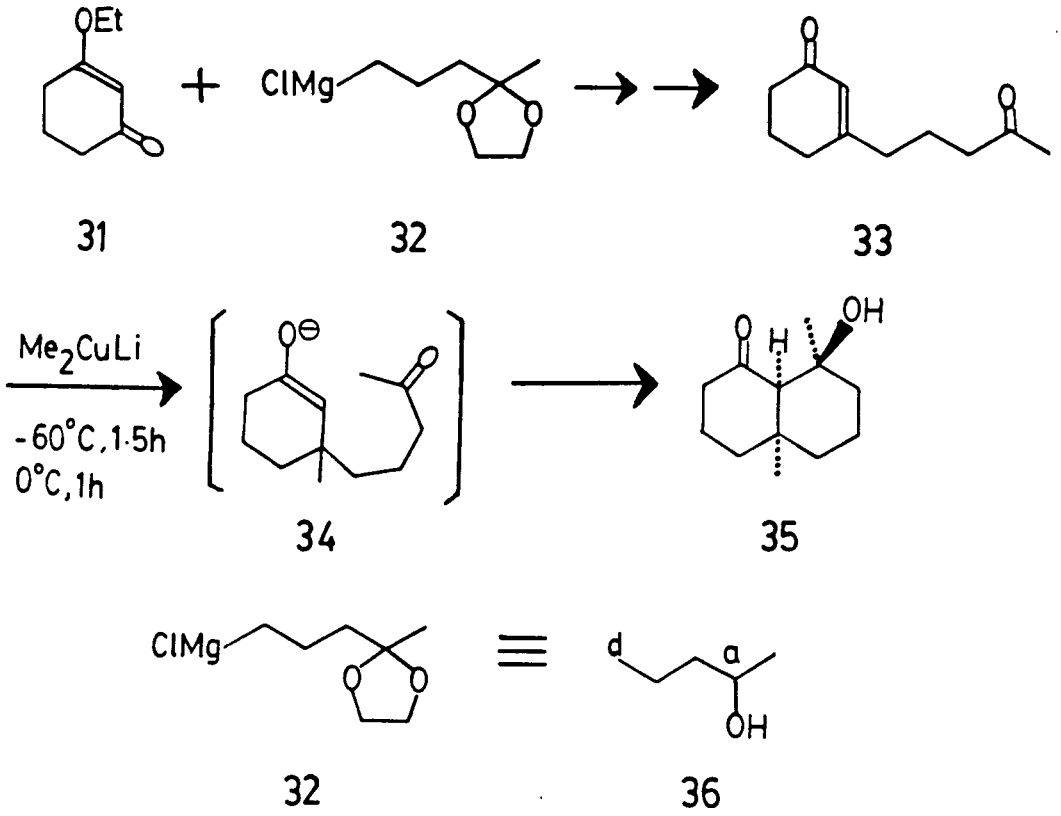


Scheme 4

lent to the butane d^4,a^1 synthon (30), to the keto enol ether (24) gave, after acid hydrolysis, the enone (25). Deprotection of the alcohol, mesylation, and displacement of the mesylate anion with bromide provided (26). Conjugate addition of lithium dimethylcuprate to the enone (26), followed by intramolecular alkylation in the presence of HMPA, afforded the bicyclic ketone (28). Deoxygenation of this bicyclic ketone produced valerane (29). In this synthesis, the acceptor site (the carbon bearing Br) involved in cyclization was incorporated into the enone molecule before conjugate addition of the cuprate. Two interesting features have to be mentioned here. Firstly, the methyl group from the cuprate reagent was introduced trans to the isopropyl group. Secondly, the cyclization highly favored the cis-1-decalone system.[50] In the light of these two points, the product was formed with the desired stereoselectivity.

A similar strategy has been described by Naf et al.[16] (Scheme 5). Treatment of the keto enol ether (31) with the Grignard reagent (32), a synthetic equivalent to the d^4,a^1 synthon (36), followed by acid hydrolysis, provided the enone (33). Lithium dimethylcuprate was added to the enone (33) at -60°C and the mixture was stirred at that temperature for 90 min and then at 0°C for a further 1 h. After workup of the mixture, the hydroxydecalone (35) was produced. Thus, again, the site (the carbonyl group) necessary for cyclization was present in the conjugate addition substrate prior to the addition reaction. The stereochemistry of the ring junction in the decalone product was cis.

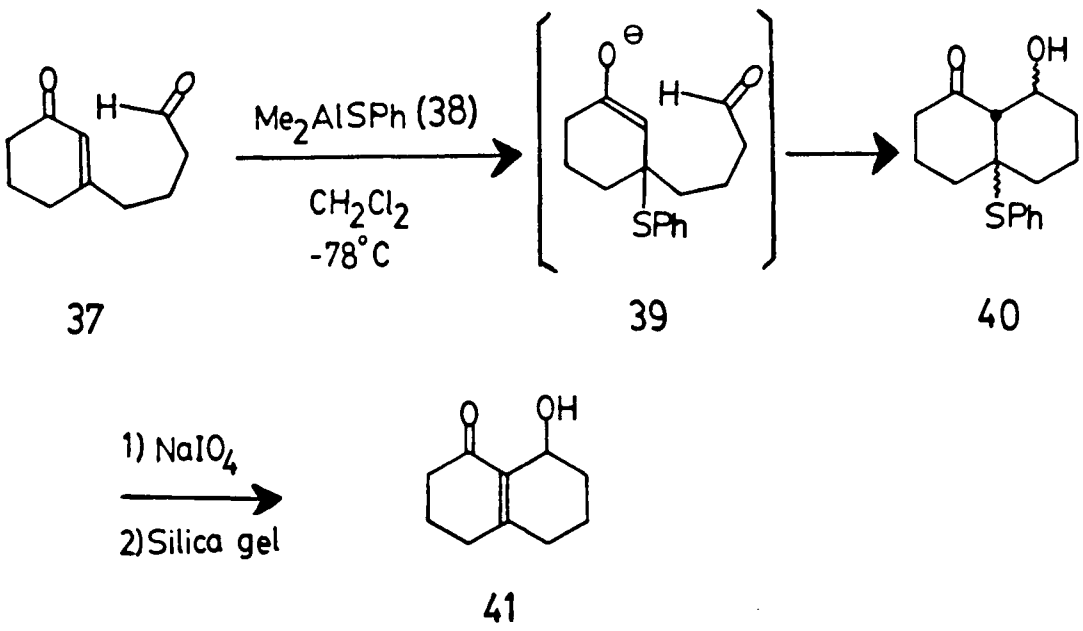
A closely related reaction sequence has been reported by Oshima[17]



Scheme 5

(Scheme 6). Here, the organoaluminum reagent (38) conjugately transferred the PhS moiety to the enone (37). Subsequent aldolization of the resultant intermediate (39) afforded (40). Conversion of (40) into (41) was achieved by oxidative elimination of the phenylthio group.

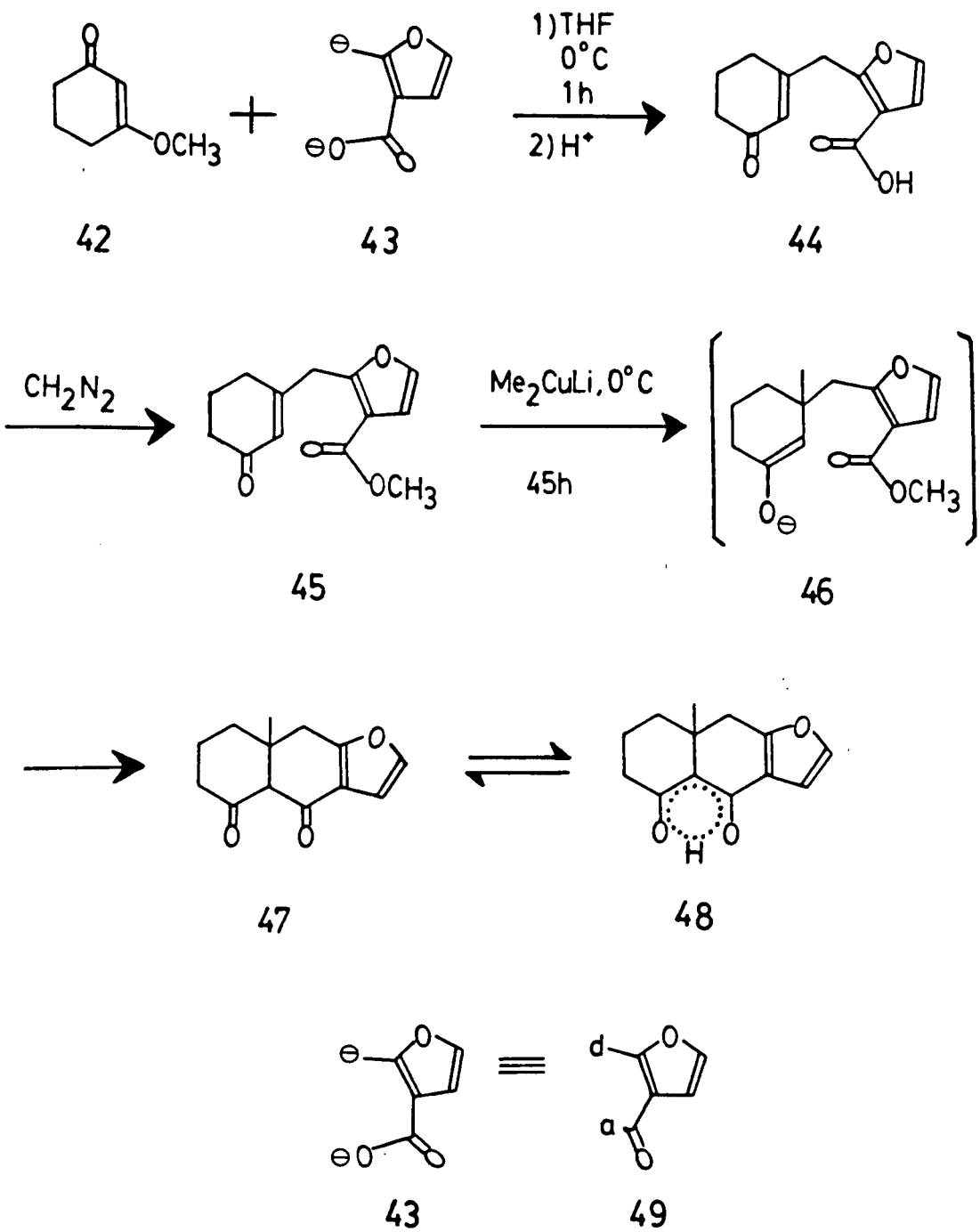
The dianion (43), synthetically equivalent to the d^4,a^1 synthon (49), has been employed by Takahashi[18] in his synthesis of (±)-14-norfuranoeudesmane-4,6-dione (47) (Scheme 7). The dianion (43) was allowed to react with 3-methoxy-2-cyclohexen-1-one (42) and the resultant product was subjected to acid hydrolysis to give the acid



Scheme 6

(44). Treatment of the ester (45), derived from (44), with lithium dimethylcuprate at 0°C for 45 h gave (±)-14-norfuranoeudesmane-4,6-dione (47). The ^{1}H nmr spectrum of this material showed that it consisted of an equilibrium mixture of the tautomers (47) and (48), in a ratio of 3:7, respectively. Once more, the site (the ester) involved in cyclization was present in the enone before conjugate addition of the cuprate.

Heathcock[19] has synthesized the dithiane (50) and used it as an equivalent of the d^{1},a^{4} synthon (53) (Scheme 8). The anion of (50) was added conjugately to 4-methyl-2-cyclohexen-1-one in the presence of HMPA to provide (51). The latter substance, upon treatment with acid, underwent hydrolysis and aldolization-dehydration to give the enone



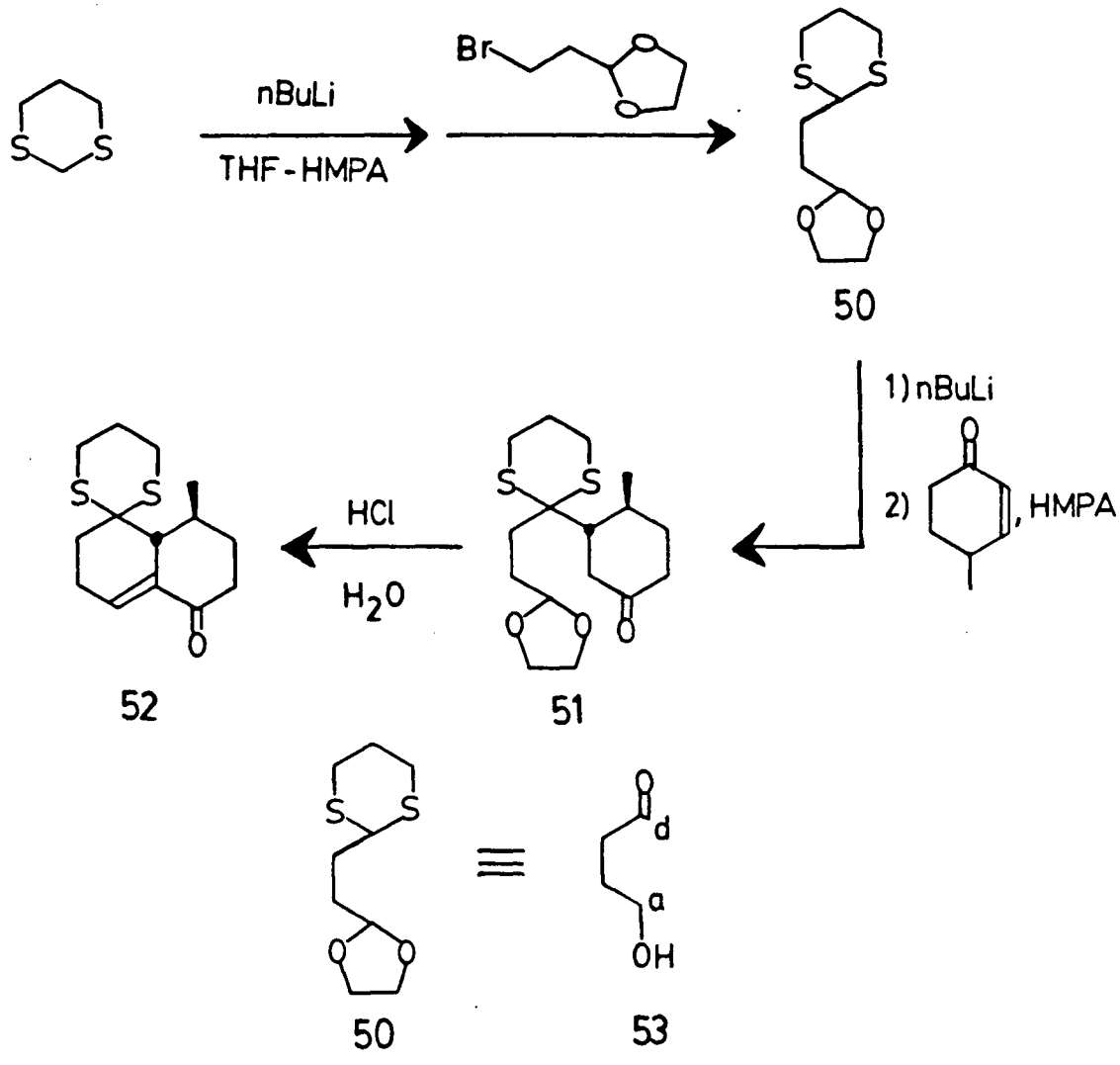
42 43 44

45 46

47 48

43 49

Scheme 7

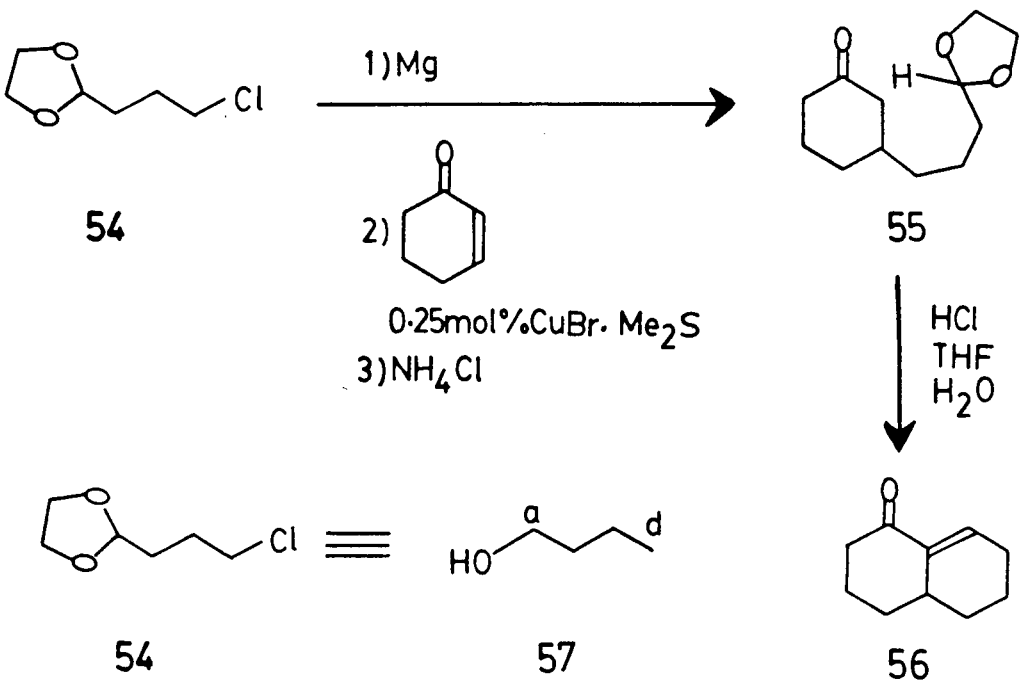


Scheme 8

(52). In this case, the site (the aldehyde carbonyl group) for cyclization was incorporated into the bifunctional conjunctive reagent (50) before conjugate addition to the substrate.

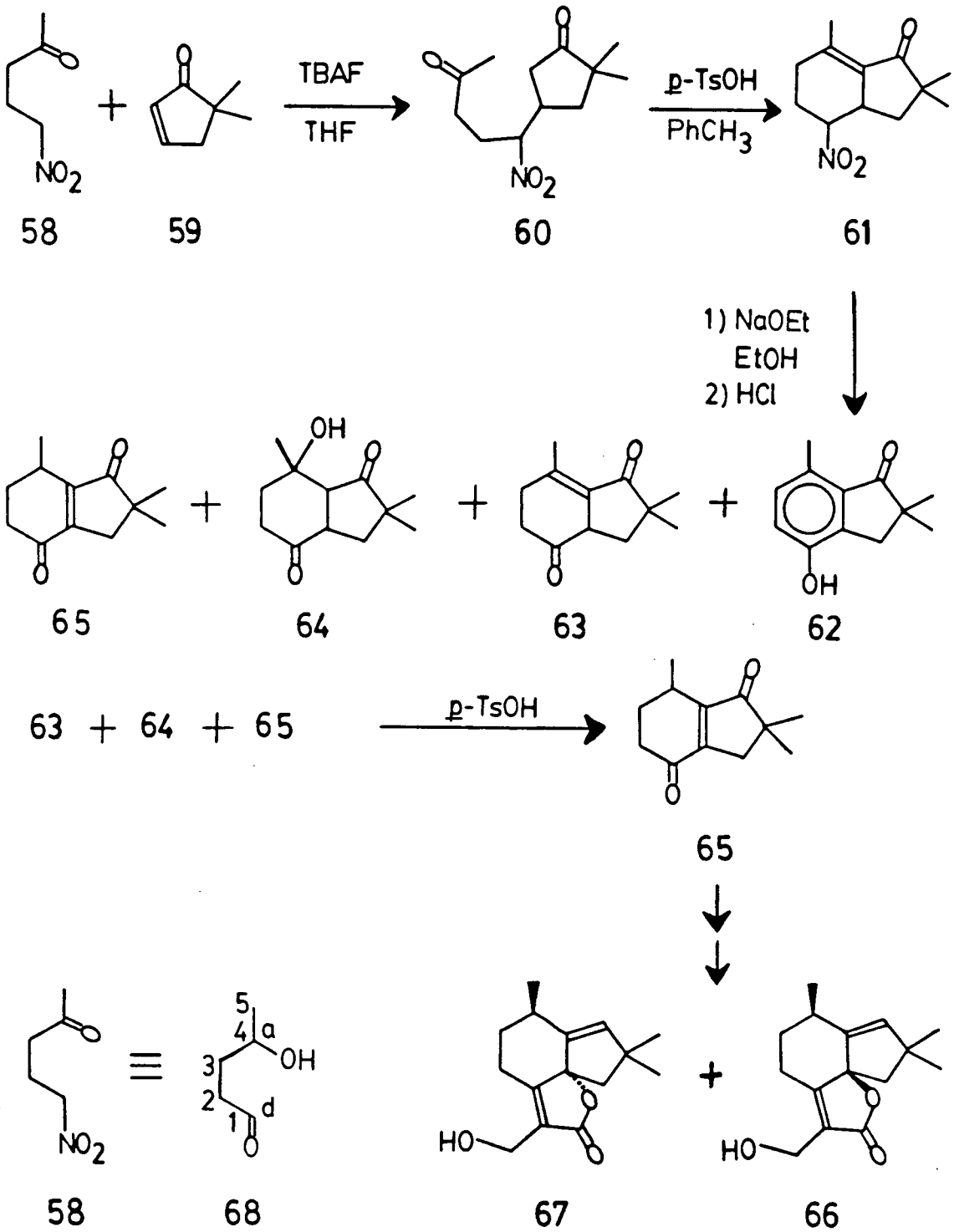
Helquist[20] has employed the reagent (54) [synthetically equivalent to the d^4,a^1 synthon (57)], which also contained a site (carbonyl group)

suitable for cyclization (Scheme 9). Compound (54) was converted into the corresponding Grignard reagent and the latter species was added conjugately to 2-cyclohexen-1-one in the presence of a copper(I) salt to produce the acetal ketone (55). Acid hydrolysis of (55) with concommitant aldolization-dehydration gave the enone (56).



Scheme 9

In the synthesis of (±)-8,9-deoxyalliacol B (66) reported by Raphael et al.,[21] 5-nitro-2-pentanone (58) was used as an equivalent of the d^1,a^4 synthon (68) (Scheme 10). Conjugate addition of the anion of (58) to 5,5-dimethyl-2-cyclopenten-1-one (59), followed by acid catalyzed aldol condensation and dehydration, produced the bicyclic nitro ketone (61). Subjection of (61) to the Nef reaction gave the four


TBAF
THF
p-TsOH
PhCH3
1) NaOEt
EtOH
2) HCl
p-TsOH
63 + 64 + 65
58
59
60
61
65
64
63
62
58
68
67
66

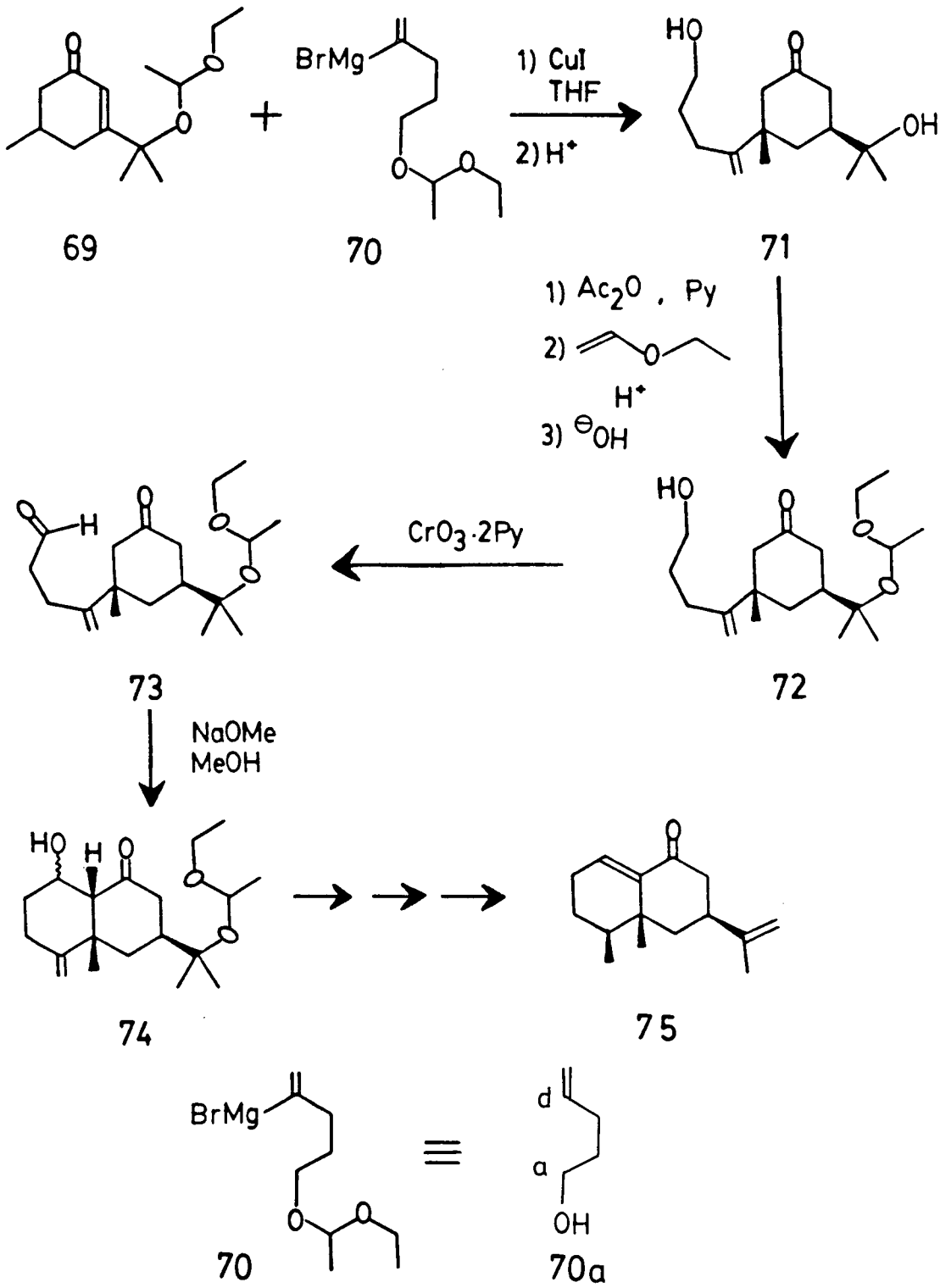
Scheme 10

products (62), (63), (64) and (65). Heating the mixture of (63), (64) and (65) with p-toluenesulfonic acid gave the single required conjugated diketone product (65). This diketone was converted, via a series of transformations, into (±)-8,9-deoxyalliacol B (66) and the diastereomeric lactone (67) in a ratio of 1:3, respectively. Incorporation of the carbonyl group (site for cyclization) into the bifunctional conjunctive reagent (58) was once again employed in this synthesis.

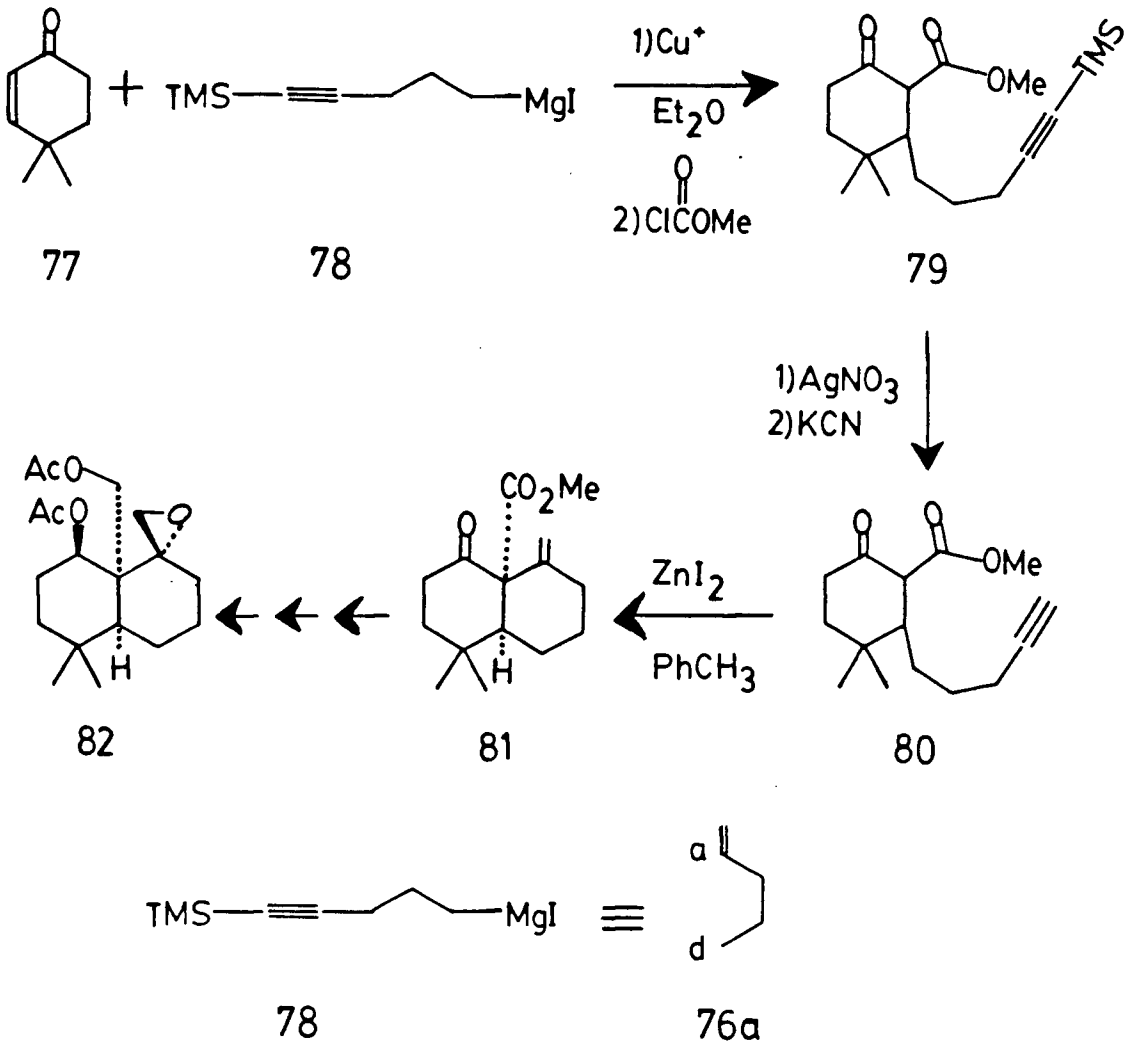
In each of the examples given above, the Michael reaction played a key role in the overall annulation sequence. Since the primary focus of the work described in this thesis was the development of a methylenecyclohexane annulation method via a Michael-type reaction, a section concerning previous achievements in methylenecyclohexane annulations is necessary.

The Grignard reagent (70), a synthetic equivalent to a d^4,a^1 synthon (70a), was used by Ficini in her synthesis of eremophilone (75).[22] Addition of (70) to the enone (69) in the presence of a copper(I) salt produced, after acid hydrolysis of the resultant product, the ketone (71) with the stereochemistry as shown (see Scheme 11). Appropriate functional group manipulations were employed to convert (71) into (72). Oxidation of (72) followed by base-catalyzed aldol condensation gave the aldol (74). Conversion of (74) into (75) was carried out via a few synthetic steps.

In his synthesis of the substituted cis-decalin (82), Ley[23] used a different Grignard reagent (78) as a synthetic equivalent to the 1-pentene d^5,a^2 synthon (76a) (Scheme 12). Addition of (78) to the enone (77) in the presence of a copper(I) salt, followed by trapping of


BrMg
1) CuI
THF
2) H+
HO
OH
69
70
71
1) Ac2O , Py
2)
H+
3) ⊖OH
HO
CrO3·2Py
H
73
72
NaOMe
MeOH
HO
H
74
75
BrMg
≡
d
a
OH
70
70a

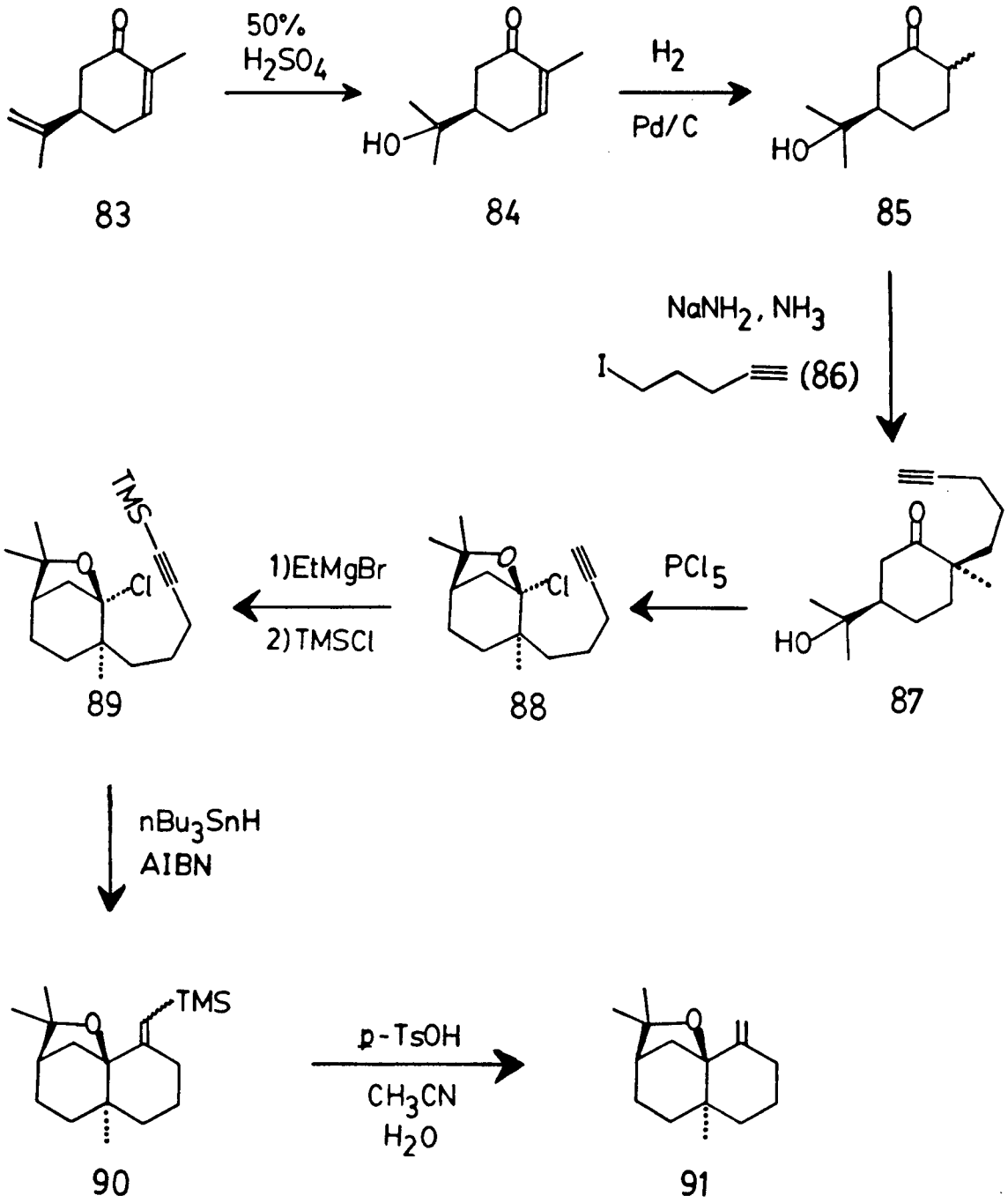
Scheme 11



Scheme 12

the resultant enolate anion with methyl chloroformate, provided the keto ester (79). Desilylation of (79) and subsequent cyclization of the resultant product (80) in the presence of zinc iodide produced the keto ester (81). Keto ester (81) was converted into (82) via a sequence of transformations.

In Buchi's[24] synthesis of β-agarofuran (91), 5-iodo-1-pentyne (86) was employed to effect the methylenecyclohexane annulation (Scheme 13).


50%
H_2SO_4
H_2
Pd/C
HO
83
84
85
$NaNH_2$, NH_3
I
(86)
87
PCl_5
1)EtMgBr
2)TMSCl
TMS
Cl
88
89
nBu_3SnH
AIBN
TMS
p-TsOH
CH_3CN
H_2O
90
91

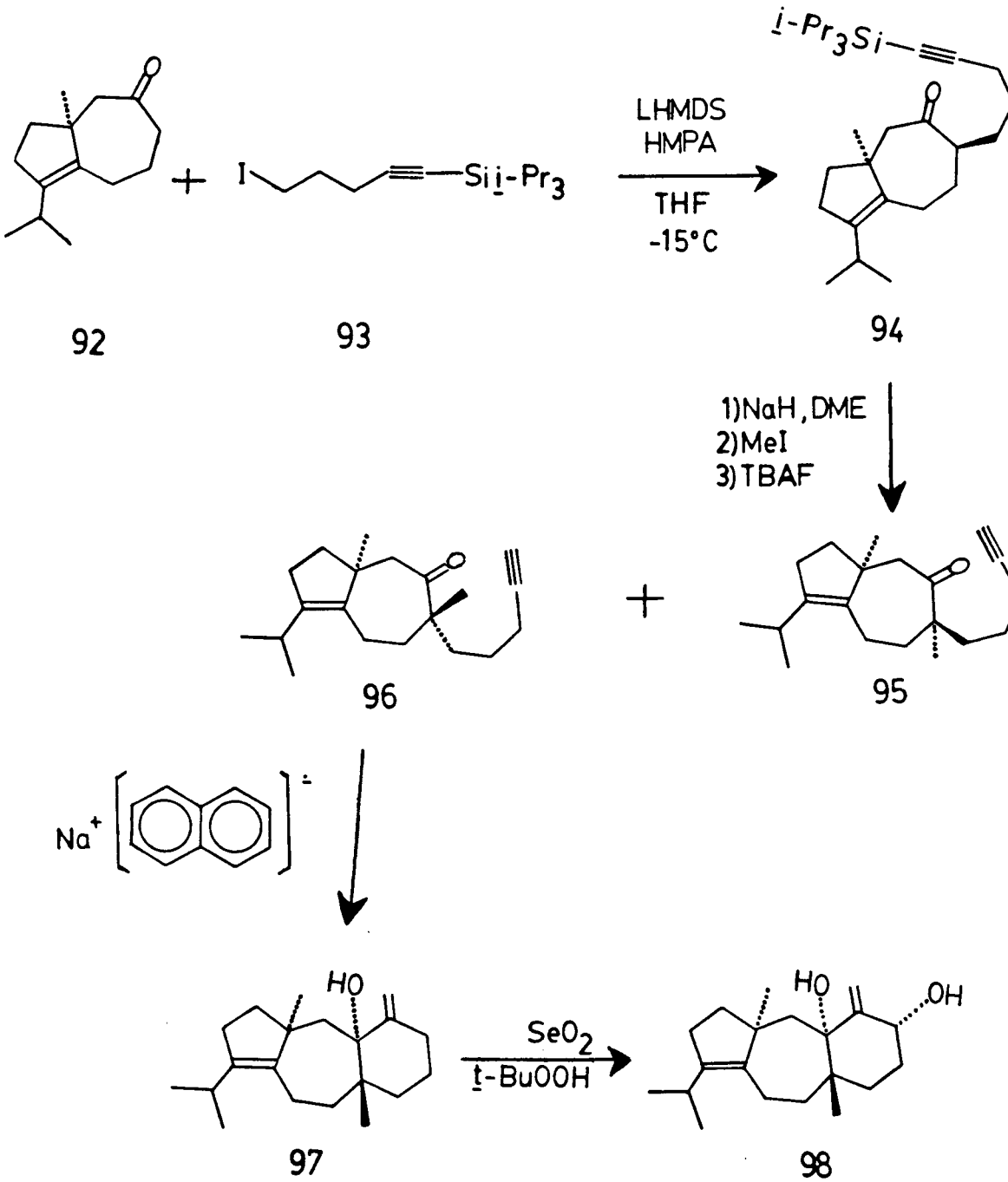
Scheme 13

(-)-Carvone (83) was subjected to successive hydration and hydrogenation to obtain the hydroxy ketone (85). Alkylation of the latter substance with the iodide (86) produced the hydroxy ketone (87) which, upon treatment with phosphorus pentachloride, provided the chloro ether (88). Trimethylsilylation of the terminal acetylene of (88), followed by ring closure of the resultant product (89) via a free radical process, yielded the tricyclic ether (90). Desilylation of (90) afforded β-agarofuran (91).

A recent synthesis of (±)-isoamijiol (98) by Pattenden[25] disclosed another method for methylenecyclohexane annulation (Scheme 14). Alkylation of the bicyclic ketone (92) with the iodide (93), followed by methylation and desilylation, provided a 4:1 mixture of (96) and (95), respectively. Intramolecular reductive coupling of the terminal acetylenic ketone (96) in the presence of sodium naphthalenide afforded the tricyclic alcohol (97). Treatment of (97) with selenium dioxide in the presence of t-butylhydroperoxide gave (±)-isoamijiol (98).

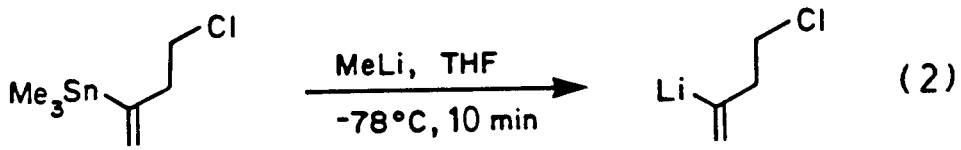
B. Problem

Previous work in our laboratory had shown[26a] that 4-chloro-2-lithio-1-butene (100), obtained by the transmetalation of 4-chloro-2-trimethylstannyl-1-butene (99) with methyllithium (equation 2), can be used as an equivalent to the 1-butene d^2,a^4 synthon (103). The cuprate reagents (101) and (102) derived from (100) have been shown to be useful species in a five-membered ring annulation sequence.[26b] Thus, conjugate

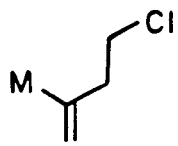


92 93 94 96 95 97 98

Scheme 14



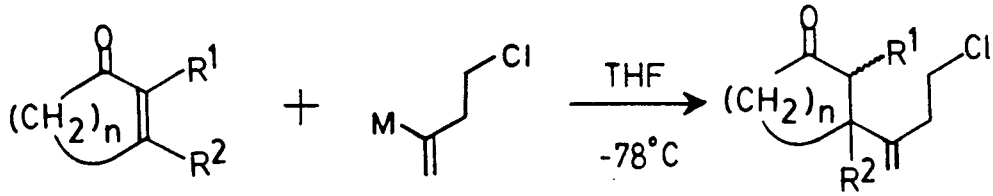
99 100 (2)



101 M = [CuSPh] Li
102 M = [CuCN] Li

103

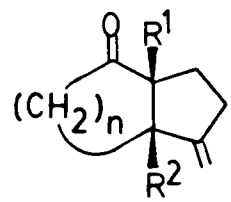
addition of the cuprates (101) and/or (102) to cyclic enones (104) provided the chloro ketones (105). The latter substances could be cyclized readily to the bicyclic ketones (106) by treatment with potassium hydride in THF (equation 3). Application of this annulation



104 101 M = [CuSPh] Li
102 M = [CuCN] Li
105

KH
THF

n=2,3
R^1=H, CH_3
R^2=H, CH_3

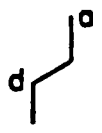


(3)

106

method to the synthesis of the structurally interesting sesquiterpenoids (±)-$\Delta^{9(12)}$-capnellene[27] and (±)-pentalenene[28] has further demonstrated the utility of the process. In fact, in these syntheses, reagents derived from (100) served as efficient synthetic equivalents to the three donor-acceptor synthons (103), (107) and (108).

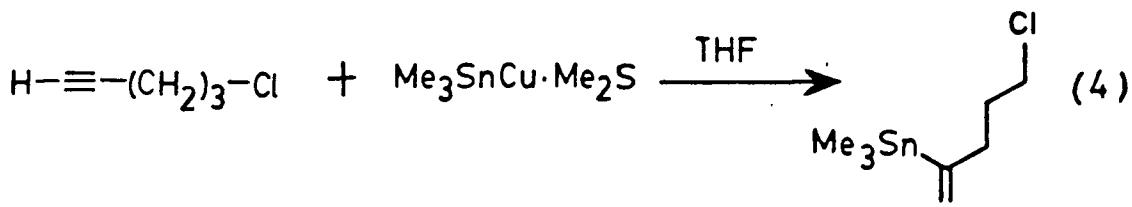
103



107

108

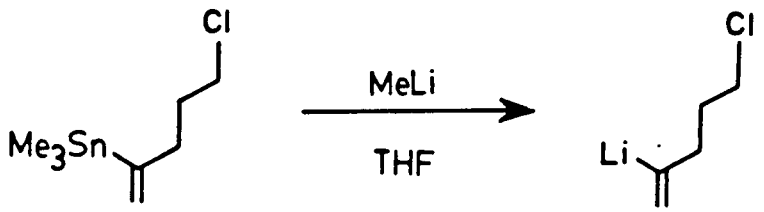
A potentially important extension to the methodology outlined above is to prepare homologs of the reagents (100)-(102). If the above sequences could be carried out with these homologs, bicyclic ring systems with varying ring sizes and with different substituent patterns would be obtained. One of the homologs of compound (99) is 5-chloro-2-trimethylstannyl-1-pentene (111). This material had been prepared in our laboratory <u>via</u> the addition of the (trimethylstannyl)copper reagent (110) to 5-chloro-1-pentyne (109) (equation 4).[29]



(4)

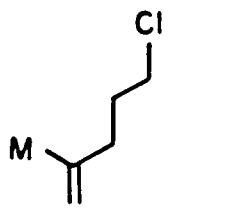
109 110 111

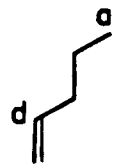
Since the reagent (111) is readily accessible, it was of interest to determine whether or not (111) could be transmetalated to give the lithio species (112) (equation 5). If this transmetalation were to be successful, the conversion of (112) into reagents (113) and (114) could



(5)

111 112

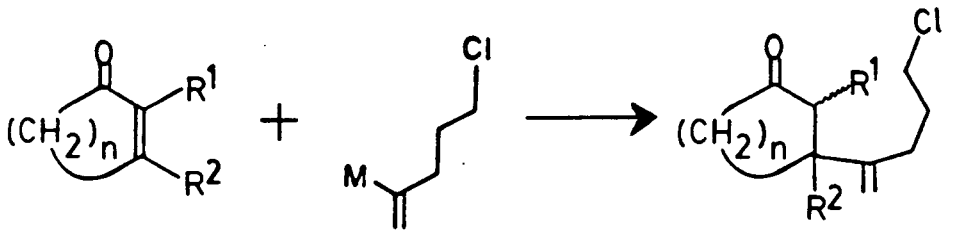




113 M=[CuSPh]Li
114 M=[CuCN]Li

76

be studied. Conjugate addition of (113) and/or (114) to cyclic enones, followed by intramolecular alkylation of the resultant products as shown in equation 6, would constitute an efficient methylenecyclohexane

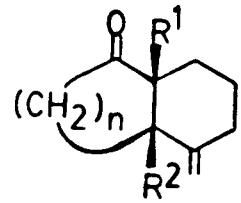


104

113 M=[CuSPh]Li
114 M=[CuCN]Li

115

n=2,3
R^1=H,CH_3
R^2=H,CH_3



(6)

116

annulation process. Thus, reagents (113) and (114) would serve as the synthetic equivalents to the 1-pentene d^2,a^5 synthon (76).

Since the methylenecyclohexane structural unit is quite common in natural products, particularly in terpenoids, the development of an efficient method to give this type of ring system is important. The proposed sequence, conjugate addition of the reagents (114) and/or (115) to enones, followed by cyclization, could serve as an efficient and a stereoselective methylenecyclohexane annulation method.

CHAPTER II

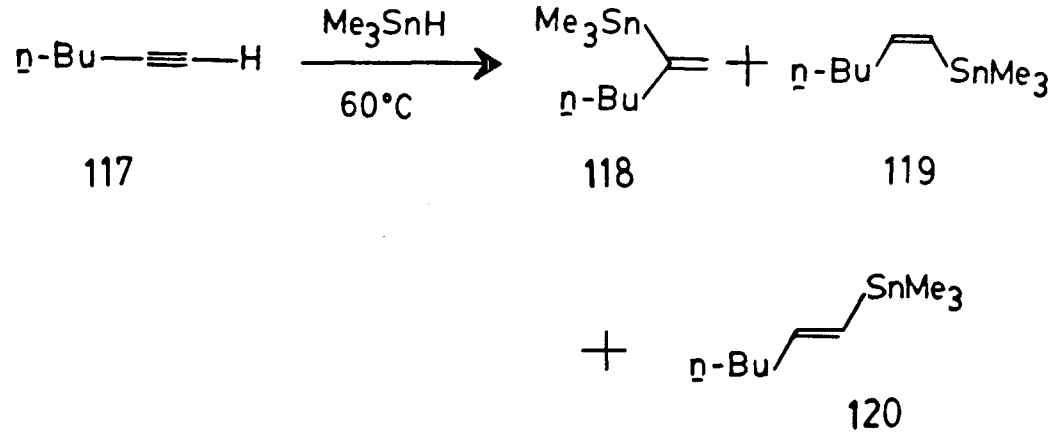
DISCUSSION

DISCUSSION

I. Preparation and Transmetalation of 5-Chloro-2-trimethylstannyl-1-pentene (111): Reaction of 5-Chloro-2-lithio-1-pentene (112) with Cyclohexanone

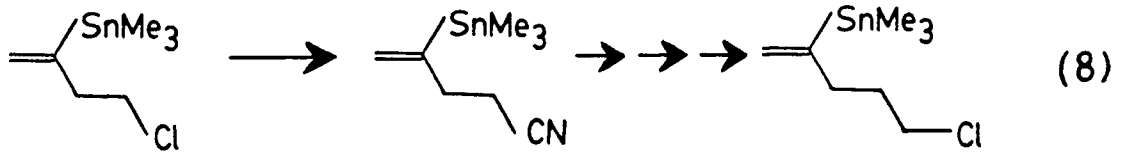
A. Preparation of 5-Chloro-2-trimethylstannyl-1-pentene (111)

When the work described in this thesis was begun, it was not obvious how the preparation of 5-chloro-2-trimethylstannyl-1-pentene (111) was to be accomplished. Hydrostannation of a 1-alkyne, a widely used method for preparing vinylstannanes, nearly always gives a mixture of products with the 2-trialkylstannyl-1-alkene as a minor product.[30] For example, reaction of 1-hexyne (117) with trimethyltin hydride affords a 2:29:69 mixture of the alkenes (118), (119), and (120), respectively (equation 7).[30]



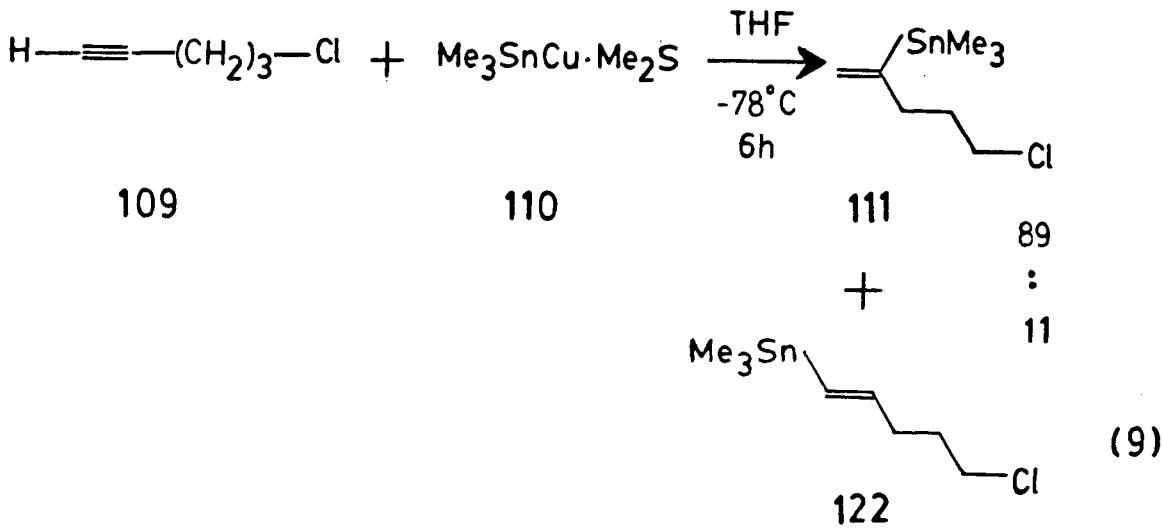
117 118 119 120 (7)

Since 4-chloro-2-trimethylstannyl-1-butene (99) had been prepared in our laboratory *via* a 4-step reaction sequence,[26a] one possible method for preparing (111) would be to homologate (99) (equation 8). However, the use of a multistep sequence to prepare a "starting material" is not a desirable mode of operation in organic synthesis.



99 121 111 (8)

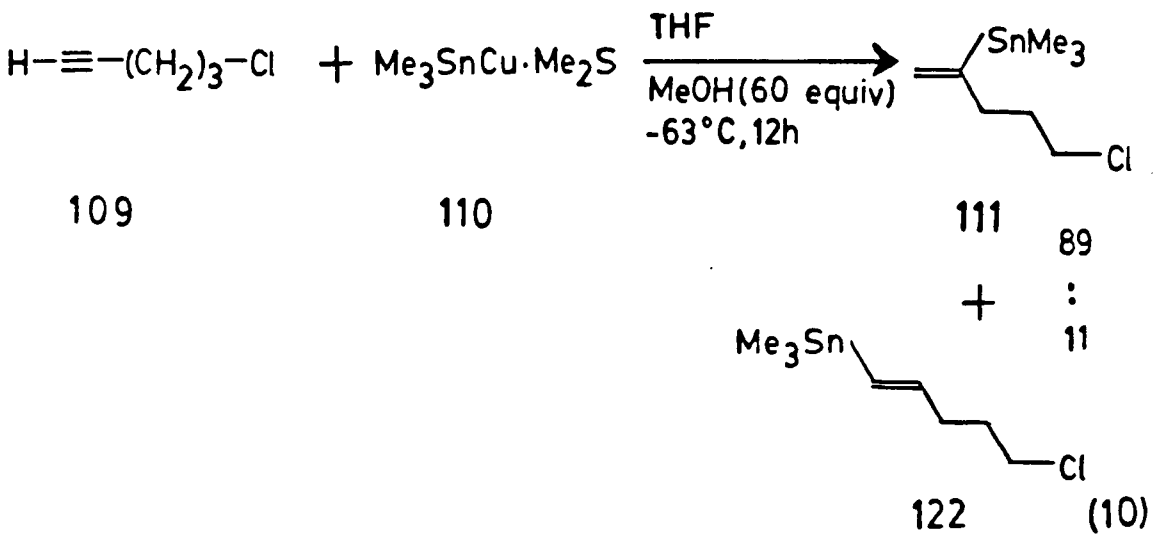
Fortunately, during the course of studying the reactions of (trialkylstannyl)copper reagents with acetylenic compounds, simple methods leading to the chloro vinylstannane (111) were established.[29] The first method involved the reaction of the (trimethylstannyl)copper reagent (110) (1.3 equiv) with 5-chloro-1-pentyne (109) (1 equiv) at -78°C for 6 h to provide, in 58% yield, the desired compound (111) (equation 9).[29]



109 110 111 122 (9)

In this reaction, the isomeric chloride (122) was produced together with the chloride (111) in a ratio of about 11:89, respectively.

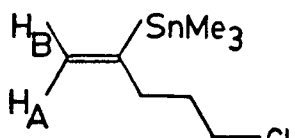
Another procedure with improved yield of (111) was found later.[29] Thus, reaction of the copper reagent (110) (2 equiv) with 5-chloro-1-pentyne (109) (1 equiv) in the presence of methanol (60 equiv) at -63°C for 12 h produced the desired chloride (111) in 79% yield (equation 10). A small amount of the isomer (122) was also produced.



Although the latter procedure has the advantage of producing (111) in higher yield, its utility is deterred by the necessity of operating at a low temperature (-63°C) for a prolonged period of time (12 h), a cumbersome task especially with large scale reactions. Consequently, the former procedure was adopted for large scale preparations of 5-chloro-2-trimethylstannyl-1-pentene (111). The (trimethylstannyl)-copper reagent (110) (38.3 mmol) was allowed to react with 5-chloro-1-pentyne (109) (30.2 mmol) in THF at -78°C for 6 h to produce, on the basis of a glc analysis, a mixture of the desired chloride (111) and the isomeric chloride (122) in a ratio of 85:15, respectively. The mixture

was subjected to (slow) column chromatography on silica gel to afford the desired chloride (111) in 68% yield. The isomeric chloride (122) was not recovered from the chromatography column even though a more polar solvent was employed for elution. Thus, it appeared that when the chromatography was carried out slowly (dropwise elution), compound (122) was destroyed on the silica gel column. Interestingly, if the mixture was subjected to flash column chromatography, the two isomeric compounds (111) and (122) were both recovered from the column, but were not separated cleanly.

The isolated, pure chloride (111) exhibited spectral data in full agreement with the structural assignment. The ^1H nmr spectrum of (111) showed a quintet at δ 1.85 ($\underline{J}$ = 7 Hz) for the $-CH_2C\underline{H}_2CH_2Cl$ protons, a broad triplet at δ 2.40 ($\underline{J}$ = 7 Hz) for the allylic protons, and a triplet at δ 3.50 ($\underline{J}$ = 7 Hz) for the $-C\underline{H}_2Cl$ protons. The two olefinic protons H_B and H_A appeared as a pair of doublet of triplets at δ 5.20 ($\underline{J}$ = 2.5, 1 Hz, $\underline{J}_{Sn-H}$ = 70 Hz) and 5.70 ($\underline{J}$ = 2.5, 1.5 Hz, $\underline{J}_{Sn-H}$ = 150 Hz),* respectively.



111

---

* It is known that with organotin compounds in which a tin atom and a hydrogen atom are vicinal on an olefinic linkage, $\underline{J}_{Sn-H}$ is much larger when they are <u>trans</u> to each other than when they are <u>cis</u> to each other.[31]

B. Transmetalation of 5-Chloro-2-trimethylstannyl-1-pentene (111): the Reaction of 5-Chloro-2-lithio-1-pentene (112) with Cyclohexanone

Gilman[32] first showed that the reaction of tetraphenyltin and excess n-butyllithium could be used to prepare tetra-n-butyltin (equation 11). Later, Seyferth and Weiner[33] prepared vinyllithium, which had been inaccessible until that time, by reaction of phenyllithium with tetravinyltin (equation 12).

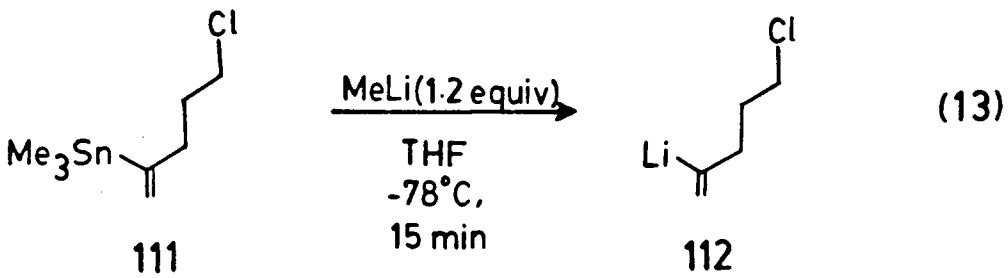
$$Ph_4Sn + 4n\text{-}BuLi \longrightarrow n\text{-}Bu_4Sn + 4PhLi \quad (11)$$

$$(CH_2{=}CH)_4Sn + 4PhLi \longrightarrow Ph_4Sn + 4(CH_2{=}CH)Li \quad (12)$$

A large number of vinyllithium reagents, prepared *via* the transmetalation of vinylstannanes with alkyllithiums, have been reported[34] since the work of Seyferth and Weiner.[33] Thus, the transmetalation process has become a valuable tool for organic synthesis, especially for the synthesis of vinyllithium reagents inaccessible by other routes. There are several features of the transmetalation process that contribute to its usefulness: (a) the reaction usually proceeds efficiently at low temperatures (below -50°C), (b) the reaction is completely stereospecific and (c) the by-product of the reaction is a coordinately saturated tetraalkyltin which does not interfere with the reactions of the vinyllithium species. For example, the two vinylstannanes (125) and (126), obtained by stereospecific retro- Diels-Alder reactions of (123) and (124), respectively, could be transmetalated with n-butyl-

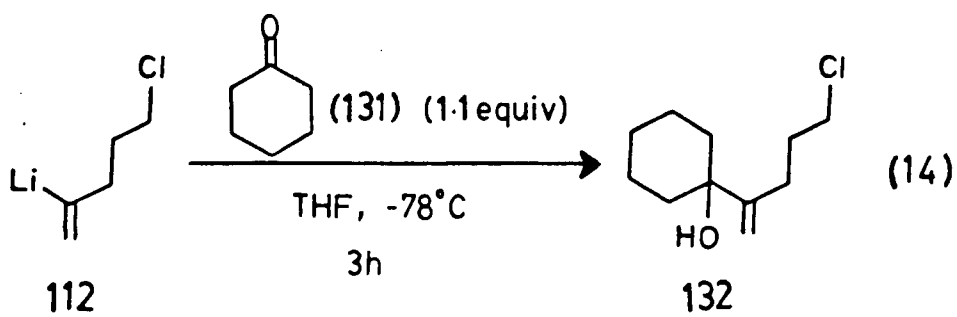
lithium at -78°C without loss of stereochemistry.[35] The resultant lithium species (127) and (128) could be trapped with 2-methylpropanal to give the alcohols (129) and (130), respectively (Scheme 15).

With the readily accessible 5-chloro-2-trimethylstannyl-1-pentene (111) at hand, the transmetalation reaction of this material was carried out. The vinylstannane (111) was allowed to react with methyllithium (1.2 equiv) at -78°C for 15 min. A clear, colorless solution of 5-chloro-2-lithio-1-pentene (112) was produced (equation 13).

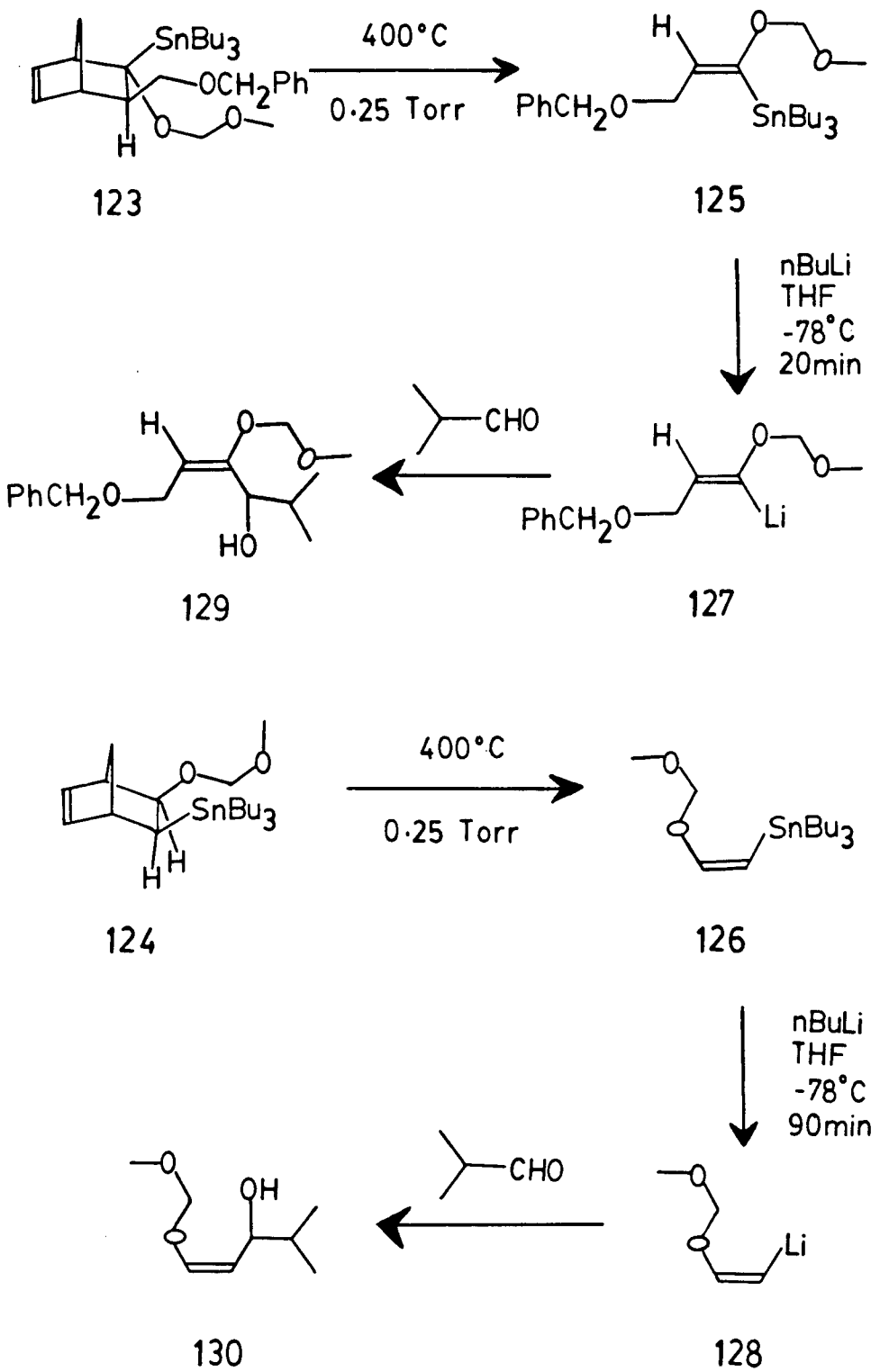


111 112 (13)

The vinyl reagent (112) was allowed to react with cyclohexanone (131) (1.1 equiv) at -78°C to give 5-chloro-2-(1-hydroxycyclohexyl)-1-pentene (132) as a single product (equation 14). The crude product,



112 132 (14)


SnBu3
OCH2Ph
H
400°C
0·25 Torr
H
PhCH2O
SnBu3
123
125
nBuLi
THF
-78°C
20min
CHO
H
PhCH2O
HO
H
PhCH2O
Li
129
127
400°C
0·25 Torr
SnBu3
H
H
SnBu3
124
126
nBuLi
THF
-78°C
90min
CHO
OH
Li
130
128

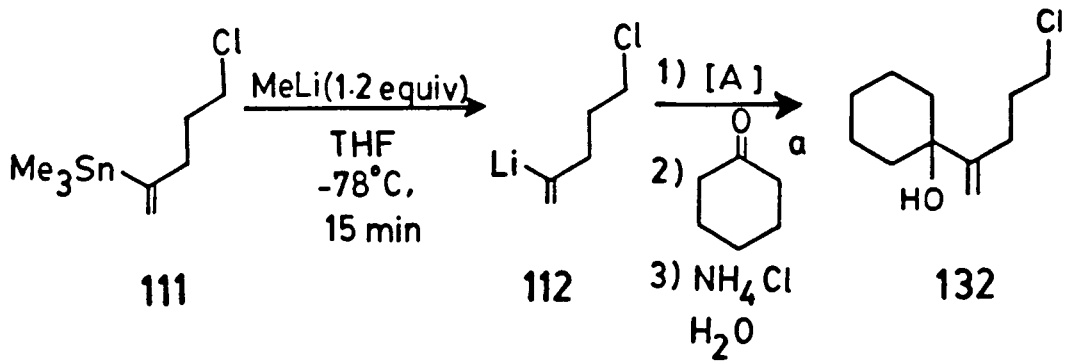
Scheme 15

which contained a small amount of the starting material (131), was subjected to column chromatography on silica gel to afford the pure alcohol (132) in 84% yield. The spectroscopic data obtained from the chloro alcohol (132) fully confirmed the structural assignment. The ir spectrum of (132) showed an O-H stretching absorption at 3431 cm^{-1}, and an absorption due to the $C = CH_2$ moiety at 902 cm^{-1}. The ^1H nmr spectrum of (132) contained a quintet at δ 1.98 ($\underline{J}$ = 7 Hz) due to the $-C\underline{H}_2CH_2Cl$ protons, a triplet at δ 2.24 ($\underline{J}$ = 7 Hz) due to the allylic methylene protons, and a triplet at δ 3.56 ($\underline{J}$ = 7 Hz) due to the $-C\underline{H}_2Cl$ protons. The olefinic protons gave rise to two singlets at δ 4.82 and 5.14.

Since the lithio species (112) seemed to be quite stable at -78°C, it was of interest to determine its stability at higher temperatures. Therefore, three additional experiments were carried out. In these experiments, the solutions of the lithio reagent (112) were stirred at -63°C, -48°C, and -20°C for 30 minutes. Each solution was then recooled to -78°C, and cyclohexanone was added. After a period of 3 h, each mixture was subjected to a standard workup procedure. The results of these experiments are summarized in Table I. From a perusal of the data given in Table I, it can be seen that the vinyllithium species (112) is not particularly stable at temperatures higher than approximately -60°C. At -48°C, (112) appears to decompose slowly, while at -20°C, it decomposes completely within 30 minutes.

The fate of the lithio species (112) at higher temperatures was not explicitly determined. However, ($\underline{Z}$)-5-chloro-3-lithio-2-pentene (134), which has been prepared in our laboratory *via* transmetalation of reagent

Table I: The Thermal Stability of 5-Chloro-2-lithio-1-pentene (112)



111 112 132

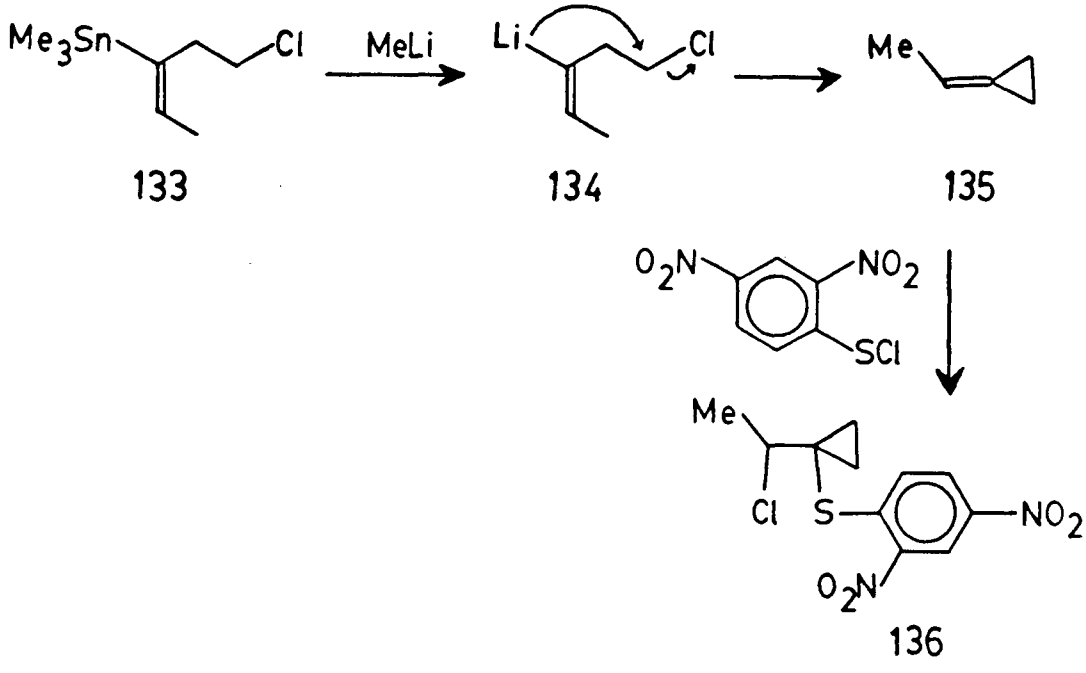
Entry	Condition, [A]	Yield (%)[b]
1	-	84
2	-63°C, 30 min	76
3	-48°C, 30 min	58
4	-20°C, 30 min	0[c]

a 1.1 equiv of cyclohexanone was used and the resultant mixture was stirred at -78°C for 3 h.

b Yield of isolated, pure (132).

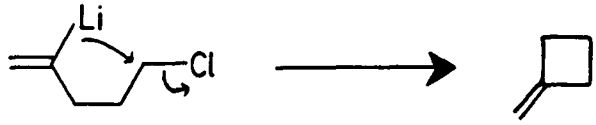
c Only cyclohexanone was recovered.

(133) with methyllithium, was found to cyclize rapidly even at -78°C to give ethylidenecyclopropane (135). The latter substance was trapped with 2,4-dinitrophenylsulfenyl chloride to give compound (136) (Scheme 16).[36]



Scheme 16

It seems likely that, at higher temperatures, the lithio species (112) would cyclize to give methylenecyclobutane (137) (equation 15). The latter substance (bp 42°C)[37] is very volatile and vigorous proof for its formation was not carried out.



112 137 (15)

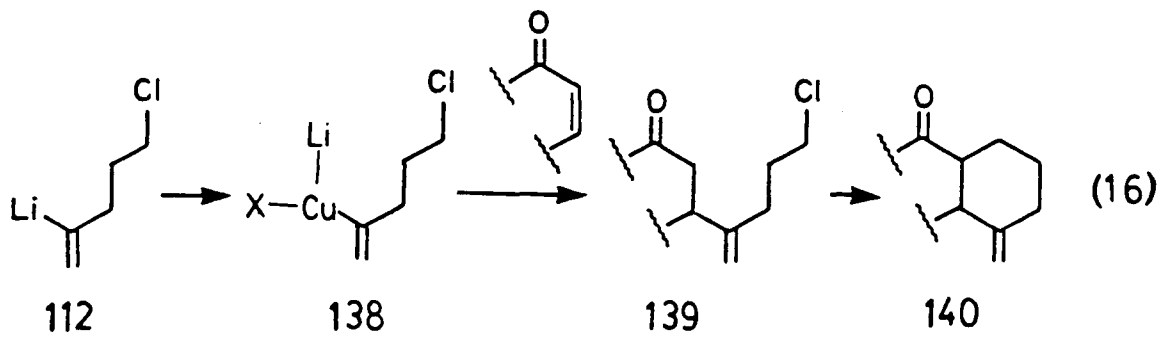
II. Conjugate Addition of Cuprate Species Derived from 5-Chloro-2-lithio-1-pentene (112) to Cyclic Enones: An Efficient Methylenecyclohexane Annulation Sequence

Organocopper reagents are a very important and useful class of organometallic reagents for carbon-carbon bond formation in natural product syntheses.[38] The usefulness of these reagents is due to their ease of preparation and their ability to effect certain transformations which are difficult or impossible to accomplish effectively with any other reagents. There are two general types of reactions of organocopper reagents: (a) additions to carbon-carbon double and triple bonds,[39] and (b) substitution of organic halides and alcohol derivatives.[40] These reactions are usually highly stereoselective, regioselective, and chemoselective.

Despite their widespread applications in organic synthesis, organocopper reagents are not without limitations:[41] (a) homocuprates,

R_2CuLi,* usually waste one R group in reactions, (b) heterocuprates, RCuXLi (X = ligand bonded to copper via a heteroatom), are often thermally unstable and must be used at low temperatures,[42] (c) the acetylenic mixed cuprates, RCuR'Li (R' = 1-alkynyl ligand), are less reactive than the homocuprates, R_2CuLi.[43] To circumvent these limitations, a number of new organocopper reagents,[46] e.g. dicyclohexylphosphido ligand based heterocuprates [$RCu(Pcy_2)Li$][44] and higher order cuprates [$RR'Cu(CN)Li_2$][45], have been prepared and shown to be of higher stability and reactivity.

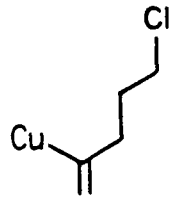
After the transmetalation of 5-chloro-2-trimethylstannyl-1-pentene (111) with methyllithium had been shown to be successful, the next important task was to prepare cuprate reagents derived from 5-chloro-2-lithio-1-pentene (112), in order to perform the methylenecyclohexane annulation sequence as shown in equation 16.



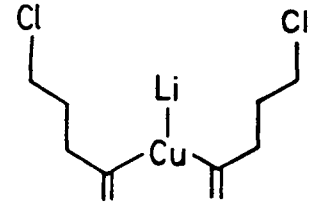
---

* This formulation, and those of other organocopper reagents, are not meant to imply actual structures but are used to show stoichiometry and for convenience.

The generation and use of either a heterocuprate with the general structure (138) or a stoichiometric organocopper compound with the structure (141) would be more desirable than formation and use of the bishomocuprate (142). If the latter reagent were to be employed, one



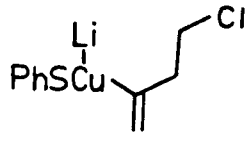
141



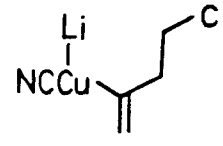
142

equivalent of the reagent (112) would be lost. It was equally important to choose appropriate organocopper reagents that could be generated and added conjugately to enones at low temperatures, owing to the instability of reagent (112) at temperatures higher than -60°C.

Since the lithium phenylthio- and cyano[2-(4-chloro-1-butenyl)] cuprates (101) and (102) had been prepared and used successfully for



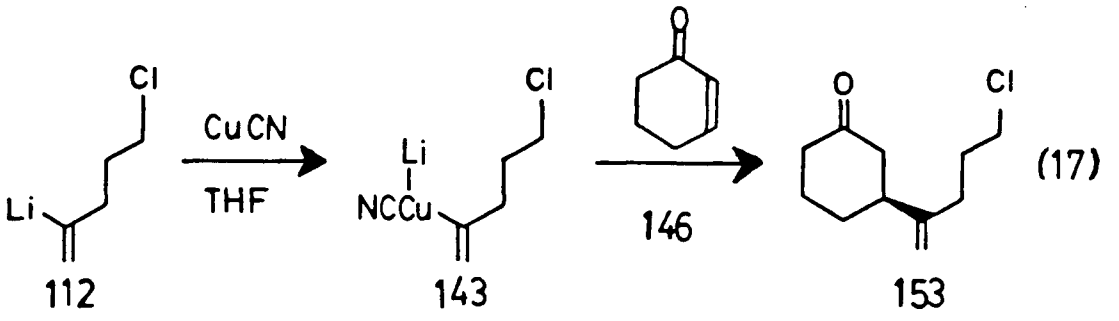
101



102

conjugate addition reactions with cyclic enones,[26b] it was expected that either phenylthio or cyano would be a suitable auxiliary ligand for the cuprate (138) (X = SPh or CN). Because of its non-hygroscopic and stable nature,[47] the commercially available cuprous cyanide was selected to prepare the cuprate (143).

Addition of cuprous cyanide (1 equiv) to a solution of 5-chloro-2-lithio-1-pentene (112) (1 equiv) in dry THF at -78°C, followed by the addition of 2-cyclohexen-1-one (146), gave 3-[2-(5-chloro-1-pentenyl)]-cyclohexanone (153) in 30% yield (equation 17). In attempts to improve



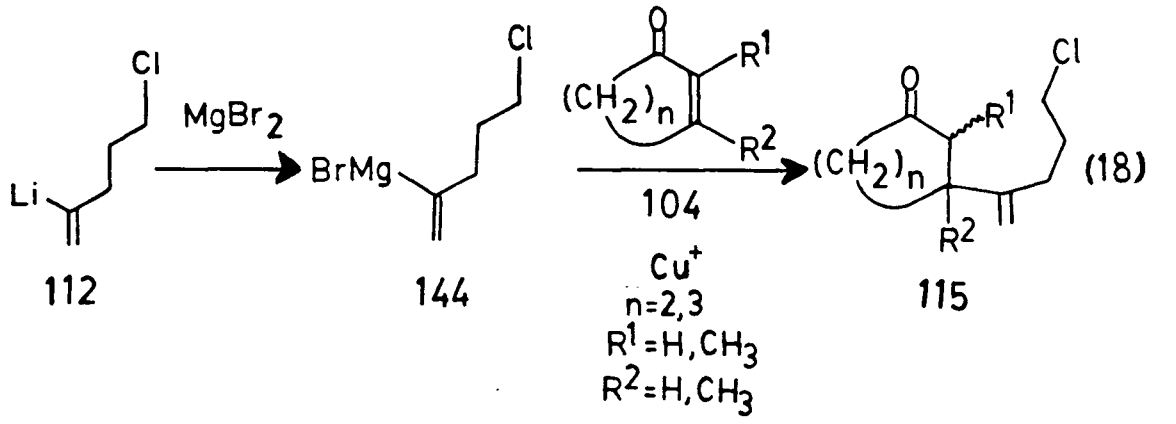
the yield of this reaction, the use of a number of different reaction conditions was investigated. All of these attempts, including the use of boron trifluoride-etherate to catalyze the reaction, failed to provide better yields of (153).

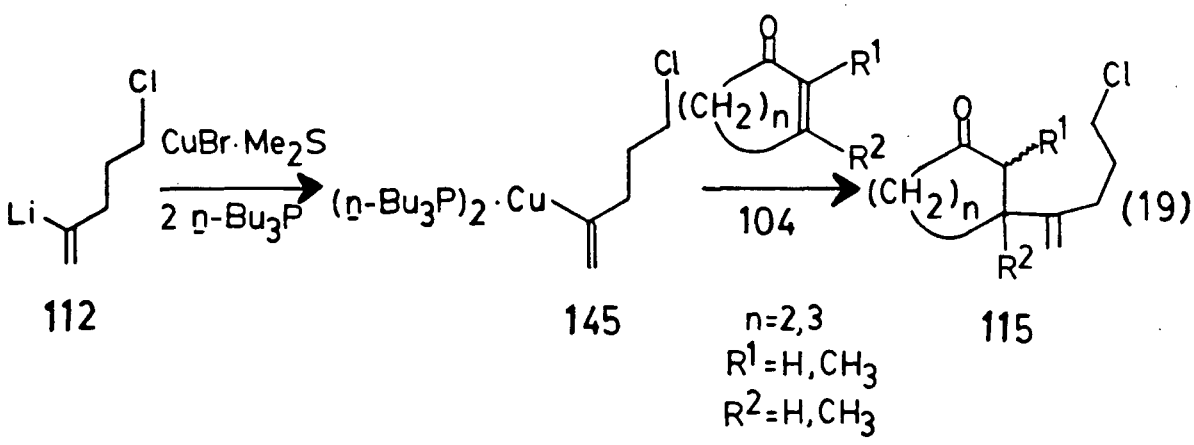
Therefore, different methods, e.g. use of different ligands and different types of organocopper reagents, to effect the conjugate transfer of the 2-(5-chloro-1-pentenyl) group to enones were studied. Eventually, two procedures were established as being reasonably satisfactory.

The first procedure (method A) involved copper(I)-catalyzed conjugate addition of the Grignard reagent obtained by the treatment of (112) with magnesium bromide-etherate (equation 18). Specifically, magnesium bromide-etherate (1.2 equiv) was added to a cold (-78°C), stirred solution of 5-chloro-2-lithio-1-pentene (112) (1 equiv) in dry THF and the resulting milky mixture was stirred at this temperature for 20 minutes to give the Grignard reagent (144). Solid copper bromide-

dimethyl sulfide complex (0.25 equiv) was added in one portion to give a pale yellow mixture. The cyclic enone (1 equiv) was added. The reaction mixture was stirred at -78°C for 3 h, and then was treated with saturated aqueous ammonium chloride. Further suitable workup provided the corresponding conjugate addition product.

The second procedure (method B) was modelled on work done by Noyori and co-workers[48] (equation 19). Solid copper bromide-dimethyl sulfide complex (1.1 equiv) was added to a stirred solution of tri-n-butylphosphine (2 equiv) in dry ether at room temperature. The mixture was stirred for 10 min to give a colorless solution. The solution was





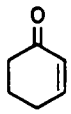
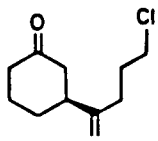
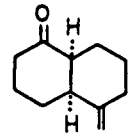
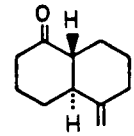
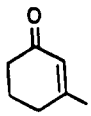
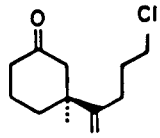
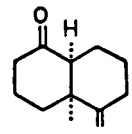
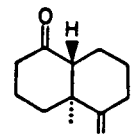
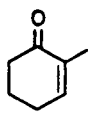
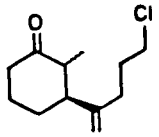
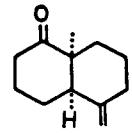
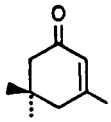
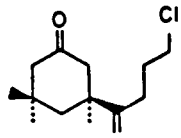
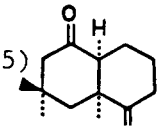
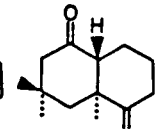
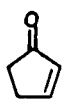
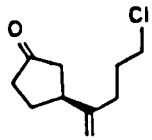
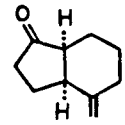
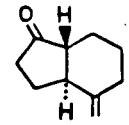
cooled to -78°C and then was transferred (cannula) to a cold (-78°C), stirred solution of 5-chloro-2-lithio-1-pentene (112) (1 equiv) in dry THF to provide a pale yellow solution of (145). The cyclic enone (1 equiv) was added and the resulting mixture was stirred at -78°C for 1 h and at -48°C for 2 h. A suitable workup procedure gave the desired conjugate addition product.

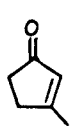
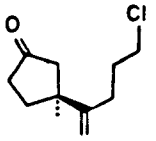
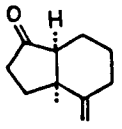
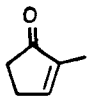
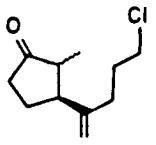
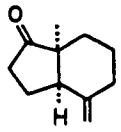
The results of conjugate additions via methods A and B are summarized in Table II. In general, the yields of the conjugate addition reactions [(146)-(152) → (153)-(159), respectively] using methods A and/or B were satisfactory, though not very high. For some hindered enones [e.g. 3,5,5-trimethyl-2-cyclohexen-1-one (149)], the addition of boron trifluoride-etherate (1.2 equiv)[49] immediately after the addition of the enones provided the corresponding chloro ketones [e.g. (156)] in yields higher than those derived from similar reactions without the Lewis acid.

In each case, the crude material obtained from the copper(I)-catalyzed conjugate addition of the Grignard reagent (144) to the enones (146)-(152) consisted essentially of the conjugate addition product and a small amount of the enone. The pure chloro ketone could be obtained by subjection of the mixture to column chromatography on silica gel.

On the other hand, the crude material obtained from addition of the reagent (145) to the enones (146)-(152) consisted, in each case, of the conjugate addition product, a small amount of enone and tri-n-butylphosphine. In each case, this mixture was subjected to chromatography on silica gel, using mixtures of petroleum ether and ether (20:1 to 7:1) as eluent. In this fashion, the pure chloro ketone was readily obtained.

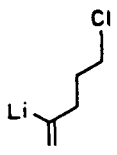
Table II: Methylenecyclohexane Annulation of Cyclic Enones

Entry	Enone	Conjugate addition product [method,[a] yield (%)[b]]		Cyclized product(s) [ratio,[c] yield (%)[b]]		
1	 146	 153	(A,81; B,61)	 160	 161	(1:2, 86)
2	 147	 154	(A[d],37; B,55)	 162	 163	(3.5:1,82)
3	 148	 155	(A[d],55; B,58)	 164		(78)
4	 149	 156	(A[d,e],45; B[d],65)	 165	 166	(8:1, 89)
5	 150	 157	(A,54; B,65)	 167	 168	(~5:1,84)

6			(A^d,54; B^d,38)		(88)
	151	158		169	
7			(A^d,33; B,67)		(90)
	152	159		170	

---

a Method A:

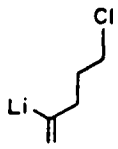


112

1) $MgBr_2$ (1.2 equiv), -78°C, 20 min
2) $CuBr \cdot Me_2S$ (0.25 equiv)
3) enone (1 equiv), -78°C, 3 h
4) NH_4Cl, H_2O

→ conjugate addition product

Method B:



112

1) n-Bu_3P (2 equiv), $CuBr \cdot Me_2S$ (1.1 equiv)
2) enone (1 equiv), -78°C, 1 h; -48°C, 2 h
3) NH_4Cl, H_2O

→ conjugate addition product

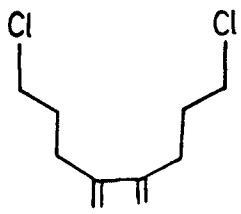
b Yield of distilled, purified product(s).

b Ratios were determined by gas-liquid chromatography.

d $BF_3.Et_2O$ (1.2 equiv) was added immediately after addition of the enone.

e The reaction time was 4.5 h.

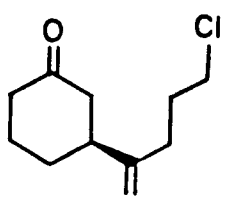
On rare occasions, a by-product (2-10%) was observed in the crude products. This material could be separated in pure form from the conjugate addition product by chromatography. On the basis of its spectral properties, this substance was assigned structure (171). The mass spectrum of this material (171) exhibited the molecular ion at m/e



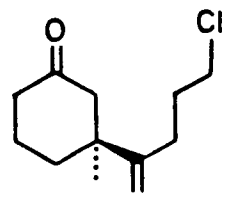
171

206 (based on ^{35}Cl). The ir spectrum showed peaks at 1570 and 890 cm^{-1}. The ^{1}H nmr spectrum of (171) showed a quintet of doublets ($\underline{J}$ = 7, 2 Hz) centered at δ 1.90 attributable to the $-C\underline{H}_2CH_2Cl$ protons, a broad triplet ($\underline{J}$ = 7 Hz) at δ 2.42 attributable to the allylic protons, and a triplet ($\underline{J}$ = 7 Hz) at δ 3.52 attributable to the $-C\underline{H}_2Cl$ protons. Furthermore, the olefinic protons gave rise to two broad singlets at δ 5.00 and 5.25.

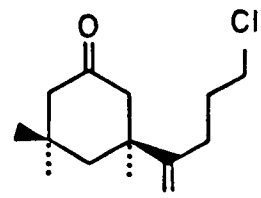
Analyses (glc, tlc) of the chloro ketones (153), (154), and (156)-(158) obtained from methods A and/or B indicated that each of them consisted of essentially one component. Furthermore, in each case, the spectra (ir, ^{1}H nmr, high resolution mass) agreed well with the assigned structure. For example, the ir spectrum of (154) showed a carbonyl absorption at 1700 cm^{-1} and a peak at 900 cm^{-1} for the $>C=CH_2$ absorption. The 400 MHz ^{1}H nmr spectrum of (154) exhibited a singlet at δ 1.11 due to the tertiary methyl proton, and a triplet at δ 3.59 ($\underline{J}$ = 7



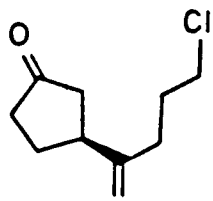
153



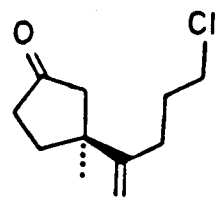
154



156



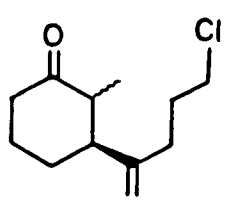
157



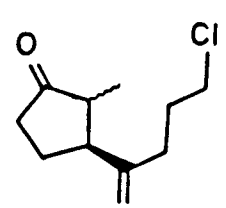
158

Hz) due to the -C$\underline{H}_2$Cl protons. Additionally, the olefinic protons gave rise to two singlets at δ 4.87 and 4.93.

As expected, each of the chloro ketones (155) and (159) was found to consist of two epimers. Thus on the basis of glc analyses, (155) derived from method A consisted of a 12:1 mixture of epimers, while (155) obtained from method B consisted of a 6:1 mixture of the same diastereomers. The ^{1}H nmr spectra of (155) supported these observations. Thus, the spectrum of (155) obtained from method A showed two doublets (ratio 12:1, $\underline{J}$ = 7 Hz in each case) at δ 0.95 and 1.00,



155



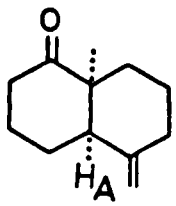
159

respectively, due to the secondary methyl groups. In the ^{1}H nmr spectrum of (155) obtained from method B, these two signals were in a ratio of 6:1.

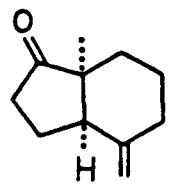
On the other hand, glc analyses of the chloro ketone (159) indicated that mixtures of epimers in ratios of 4:1 and 2:1 were obtained from methods A and B, respectively. The ^{1}H nmr spectrum of (159) obtained from method A exhibited two doublets (ratio 4:1, J = 7 Hz in each case) at δ 1.05 and 0.88, respectively, attributable to the secondary methyl groups. In the ^{1}H nmr spectrum of (159) obtained from method B, these two signals were in a ratio of 2:1.

The chloro ketones (153)-(159) were cyclized smoothly by treatment with potassium hydride (~2.5 equiv) in dry THF at room temperature for 2 h to give the annulated products (160)-(170). The results of these cyclizations are summarized in Table II. The yields of the cyclized products were excellent. As expected,[50] when no subsequent equilibration was possible (entries 3 and 7), the kinetic products [(164), (170)] having a cis-fused ring junction were produced as the sole products (glc analyses). The spectra (ir, ^{1}H nmr, high resolution mass) derived from compounds (164) and (170) agreed well with the structural assignments. For example, the ir spectrum of (164) exhibited a carbonyl absorption at 1695 cm^{-1} and a $>C=CH_2$ absorption at 895 cm^{-1}. The ^{1}H nmr spectrum of (164) exhibited a singlet at δ 1.10 due to the tertiary methyl protons, while the olefinic protons gave rise to two triplets at δ 4.69 (J = 1.5 Hz) and 4.72 (J = 2 Hz). The cis stereochemistry of the ring junction was confirmed by a nOe difference experiment.[51] Thus, irradiation at δ 1.10 (bridgehead methyl singlet)

caused enhancement of the one-proton signal at δ 2.25 (d of d, $\underline{J}$ = 12, 6 Hz). On the basis of the chemical shift and spin-spin coupling pattern, the latter resonance was assigned to H_A.

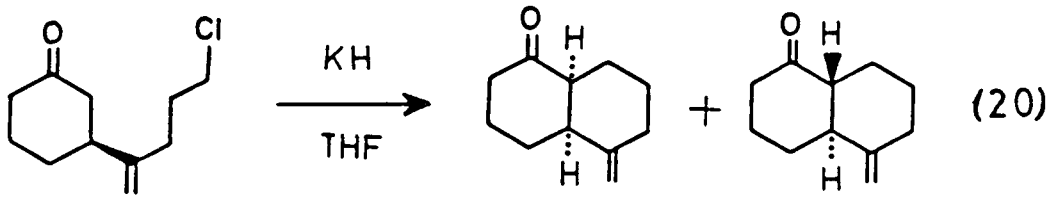


164



170

In other cases (entries 1, 2, 4-6) varying degrees of equilibration occurred under the conditions employed for ring closure. Thus, a mixture of (160) and (161) in a ratio of 1:2 (^{1}H nmr spectroscopy), respectively, was produced from the cyclization of compound (153) (equation 20). Subjection of this mixture to column chromatography on silica gel provided pure samples of (160) and (161). The ^{1}H nmr spectrum of (160) exhibited two signals due to olefinic protons, a one-proton triplet at δ 4.66 ($\underline{J}$ = 1.5 Hz) and a one-proton singlet at δ 4.69. In the ^{1}H nmr spectrum of (161), two singlets, one proton each, appeared at δ 4.69 and 4.75, due to the olefinic protons. However, no

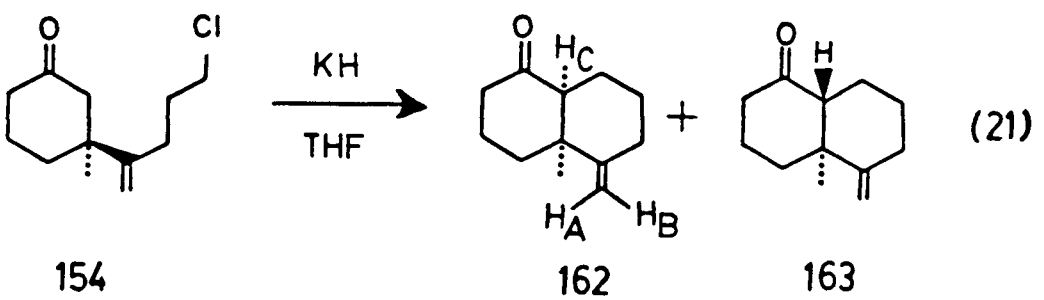


153 160 161 (20)

further information with respect to the stereochemistry at the ring junction of (160) and (161) could be obtained by means of ^1H nmr spectroscopy.

Fortunately, equilibration experiments involving compounds (160) and (161) did provide information regarding the stereochemistry at the ring junction of these substances. Thus, when a methanol solution of a mixture of (160) and (161) (ratio 1:2, respectively) was heated to reflux for 18 h in the presence of sodium methoxide, (161) was produced as the sole product. When each of (160) and (161) was equilibrated under the same conditions, (160) was completely converted into (161), while (161) was recovered unchanged. Therefore, the equilibrium (160) $\rightleftharpoons$ (161) favored exclusively (161). Since the trans-fused isomer would be expected to be more stable than the cis-fused isomer, these substances were assigned structures (161) and (160), respectively.

Cyclization of the compound (154) furnished a mixture of (162) and (163) in a ratio of 3.5:1, respectively (glc analysis) (equation 21). Compounds (162) and (163) were very difficult to separate by column chromatography on silica gel. However, partial separation was accomplished by subjection of the mixture to column chromatography on 25%



154 162 163

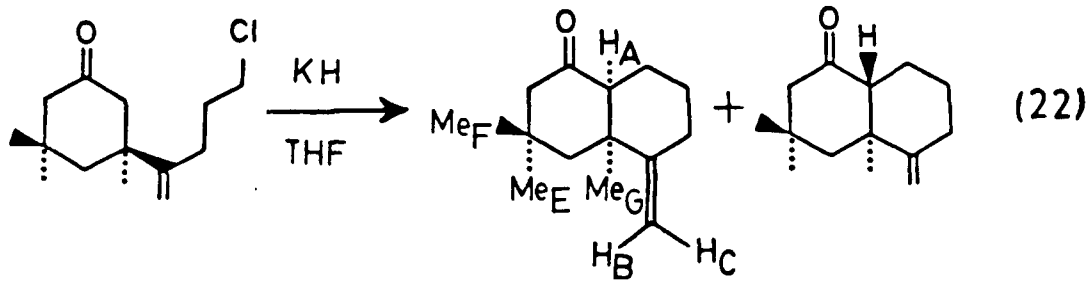
silver nitrate impregnated silica gel.[52] By this means, analytically pure samples of (162) and (163) were obtained.

The ^{1}H nmr spectrum of (162) showed the tertiary methyl singlet at δ 1.17, while the olefinic protons gave rise to two singlets at δ 4.73 and 4.76. In a nOe difference experiment, irradiation at δ 1.17 (bridgehead methyl singlet) caused enhancement of two one-proton signals at δ 4.73 (s) and at δ 2.15 (d of d, J = 10, 4 Hz). On the basis of the chemical shift and spin-spin coupling pattern, the signal at δ 2.15 was assigned to H_C. Furthermore, it was evident from the nOe experiment that the signal at δ 4.73 was derived from H_A, and therefore, the signal at δ 4.76 could be assigned to H_B. The nOe experiment also showed that (162) possessed a cis-fused ring junction.

In the ^{1}H nmr spectrum of (163), which should be the trans isomer, the tertiary methyl group gave rise to a singlet at δ 0.95, while the two olefinic protons appeared as a multiplet at δ 4.70-4.76.

The assignment of stereochemistry at the ring junction of compounds (162) and (163) was further verified by equilibration experiments. When each of (162) and (163) was equilibrated (MeONa/MeOH, reflux, 18 h) a mixture of (162) and (163) in a ratio of 1:2.8, respectively, (glc analysis) was obtained in each case. Thus, the equilibrium (162) $\rightleftharpoons$ (163) favored the more stable trans isomer (163).

A mixture of (165) and (166) in a ratio of 8:1 (glc analysis), respectively, was obtained from the cyclization of compound (156) (equation 22). Again, partial separation of (165) and (166) was achieved by subjection of this mixture to column chromatography on silica gel impregnated with 25% silver nitrate. Analytically pure



(22)

156 165 166

samples of (165) and (166) were obtained in this manner.

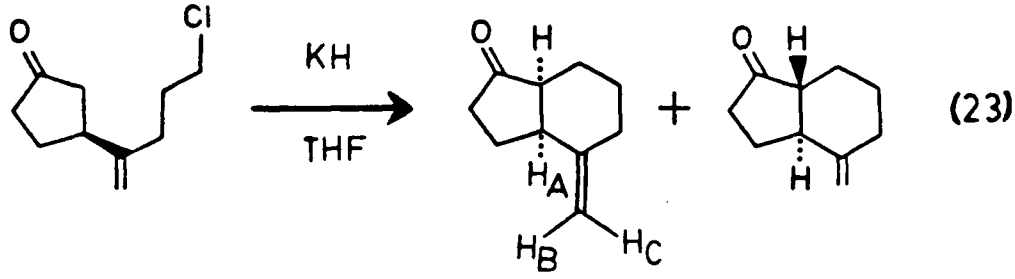
The ^1H nmr spectrum of (165) exhibited three tertiary methyl singlets at δ 1.05, 1.06 and 1.26, while the two olefinic protons gave rise to a quartet ($\underline{J}$ = 1.5 Hz) at δ 4.77 and a broad singlet at δ 4.80. In a nOe difference experiment, irradiation at δ 1.26 (a tertiary methyl singlet) caused enhancement of the signals at δ 1.06 (3H, s), 2.13 (d of d, 1H, $\underline{J}$ = 8, 4.5 Hz), and 4.80 (br s). Since only the bridgehead methyl group was close enough to cause nOe enhancement of the olefinic proton at δ 4.80, the signal at δ 1.26 was assigned to Me_G and the resonance at δ 4.80 was assigned to H_B. The other olefinic proton H_C was assigned to the signal at δ 4.77. Furthermore, the signals at δ 1.05 and 1.06 were attributed to Me_F and Me_E, respectively. Finally, the resonance at δ 2.13 could be assigned to H_A. From the nOe experiment, it was concluded that (165) contained a cis-cused ring junction.

In the ^1H nmr spectrum of (166), the trans isomer, three singlets due to the three tertiary methyl groups appeared at δ 1.04, 1.10 and 1.14, while the olefinic protons gave rise to two broad singlets at δ 4.70 and 4.73, respectively.

Equilibration experiments supported the stereochemistry assignments

for (165) and (166). Thus, when a methanol solution of the mixture of (165) and (166) (ratio 8:1, respectively) was heated to reflux for 18 h in the presence of sodium methoxide, a mixture of (165) and (166) in a ratio of 1:2, respectively, (glc analysis) was obtained. Therefore, the equilibrium (165) $\rightleftharpoons$ (166) favored the more stable trans isomer (166).

Cyclization of the compound (157) provided a mixture of (167) and (168) in a ratio of ~5:1, respectively (glc analysis) (equation 23). Column chromatography of this mixture on silica gel impregnated with 25% silver nitrate gave a small amount of pure (167). Compound (168) could not be separated in pure form by this method.



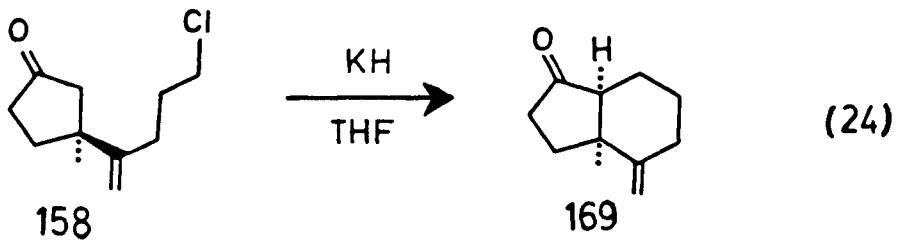
157 167 168

The ^1H nmr spectrum of (167) exhibited two singlets at δ 4.79 and 4.80, attributable to the olefinic protons. In a nOe difference experiment, irradiation of a one-proton signal at δ 2.95 (d of t, J = 7, 7 Hz) caused enhancement of the signal at δ 4.79 (s). On the basis of the chemical shifts, proximity in space and/or spin-spin coupling pattern, the resonances at δ 2.95 and 4.79 were assigned to H_A and H_B, respectively. Consequently, H_C was assigned to the signal at δ 4.80.

The ^1H nmr of a mixture of (167) and (168) showed that the alkene protons of (168) resonated at δ 4.66 (s) and 4.77 (br s).

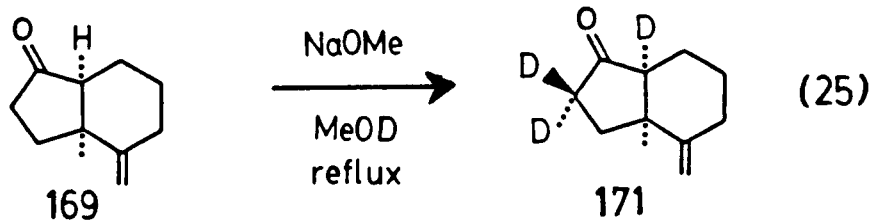
When a mixture of (167) and (168) (ratio 84:16, respectively) was equilibrated (MeONa/MeOH, reflux, 18 h), a mixture of (167) and (168) in a ratio of 82:18, respectively, (glc analysis) was obtained. When a pure sample of (167) was equilibrated under the same conditions, a 85:15 mixture of (167) and (168), respectively, (glc analysis) was obtained. On the basis of the results of the equilibration experiments and the fact that the cis-fused product would be the first-formed (kinetic) product from the ring closure reaction,[50] (167) was assigned to be the cis isomer and (168) was assigned to be the trans isomer.

Interestingly, the cyclization of compound (158) produced only one compound (169) (equation 24). The ^{1}H nmr spectrum of (169) showed a



158 169 (24)

singlet at δ 1.34 due to the tertiary methyl group while olefinic protons gave rise to two singlets at δ 4.77 and 4.81. Attempted equilibration of a methanol solution of (169) in the presence of sodium methoxide (reflux, 18 h) gave no detectable change in the crude product. Refluxing (18 h) a solution of (169) in MeOD in the presence of sodium methoxide gave a trideuterio compound (171) (equation 25) (mass spectrum molecular ion at m/e 167). The ^{1}H nmr spectrum of (171) also showed the tertiary methyl singlet at δ 1.34 and the signals due to the olefinic protons at δ 4.77 (s) and 4.81 (s). From the results of equilibration



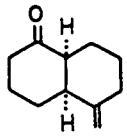
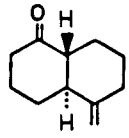
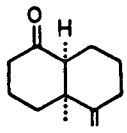
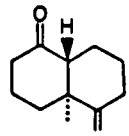
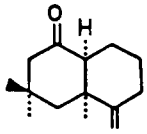
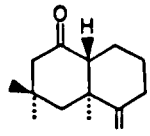
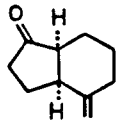
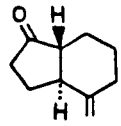
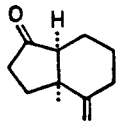
169 171 (25)

experiments and the fact that the kinetic product of the cyclization process would be the cis-fused bicyclic ketone,[50] the annulation product derived from (158) was assigned structure (169).

The results of the equilibration experiments described above are summarized in Table III. Not unexpectedly, the trans-fused compounds [(161), (163), (166)] were found to be more stable than the corresponding cis-fused epimers in the bicyclo[4.4.0]decalone series. On the other hand, the cis-fused isomers [(167), (169)] were found to be predominant for the bicyclo[4.3.0]nonanones.

In summary, the overall yields of the methylenecyclohexane annulation sequences summarized in Table II varied from 40% (entry 4) to 70% (entry 1). Considering the brevity of the reaction sequence and the fact that the methylenecyclohexane moiety is quite commonly found in members of the terpenoid family of natural products, the annulation process described above should find use in organic synthesis.

Table III: Equilibration of the Annulated Product(s)

Entry	Cyclized product(s)		ratio[a] after equilibration[b]
1	 160	 161	<1:>99
2	 162	 163	1:2.8
3	 165	 166	1:2
4	 167	 168	~5:1
5	 169		no change

a Ratios were determined by gas-liquid chromatography.

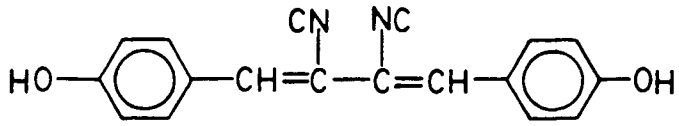
b Equilibration was carried out by refluxing (18 h) a methanol solution of the cyclized product(s) in the presence of sodium methoxide.

III. Total Syntheses of the Sesquiterpenoids (±)-Axamide-1, (±)-Axisonitrile-1, and the Corresponding C-10 Epimers

A. Introduction

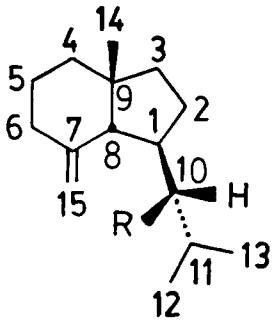
The isonitrile function is a very rare feature in nature. Most of the naturally occurring isonitriles discovered so far are of marine origin. In general, terpenoid isonitriles isolated from marine sources have carbon skeletons that are quite different from the carbon skeletons of terpenoids from terrestrial sources.

The first naturally occurring isonitrile, xanthocillin (172),[53] was isolated from cultures of penicillium notatum Westling by Rothe in 1950.



172

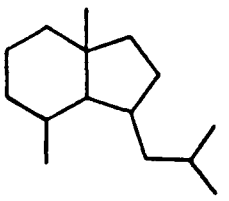
It was not until 1973 that a second natural isonitrile, (+)-axisonitrile-1 (173),[54] was isolated and characterized by Sica and co-workers. (+)-Axisonitrile-1 (173), the first isocyano-containing sesquiterpenoid isolated from marine sources, was obtained from the sponge Axinella cannabina. A number of isonitriles isolated from marine sources have been reported since that time.[55] Most of these are sesquiterpenoids while a few of them are diterpenoids; most of them are monofunctionalized while a few of them are polyfunctionalized.[55]



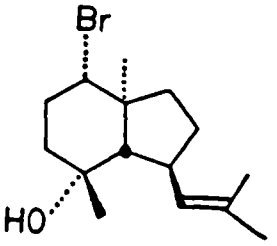
173 R= $\overset{+}{N}\equiv\bar{C}$

174 R= NCHO
H

175 R= N=C=S



176



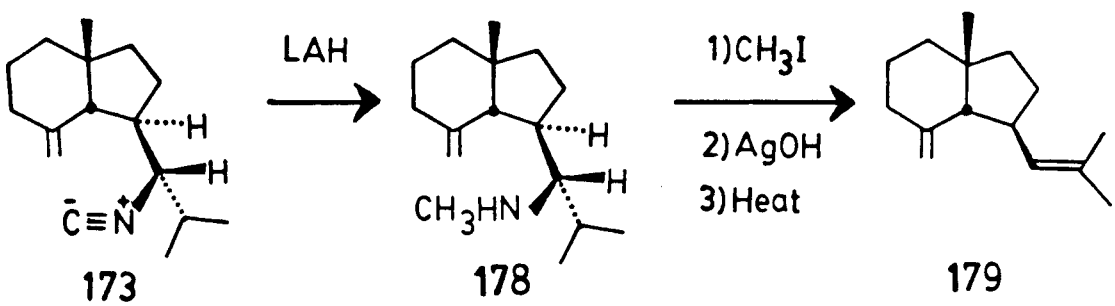
177

It is interesting to point out that most of the isonitriles found in nature co-occur with the corresponding isothiocyano and formamido derivatives. For example, (+)-axamide-1 (174)[56] and (+)-axisothiocyanate-1 (175)[54] were isolated from the same marine sponge that produced (+)-axisonitrile-1 (173).

(+)-Axisonitrile-1 (173)[54] was shown to possess an axane (176) carbon skeleton, which is also present in the natural product oppositol (177).[57] This carbon framework has not been encountered among terrestrial natural products. Compound (173) exhibited mp 43-45°C and $[\alpha]_D$ +22.6 ($CHCl_3$), and was found to have a structural formula $C_{16}H_{25}N$ (elemental analysis and mass spectrum). From the ir and ^1H nmr of (173), the following structure units were indicated: a secondary isonitrile function (ν_{max} 2130 cm^{-1} and a one-proton multiplet at δ 3.13, $\rangle$CH-NC), an exocyclic methylene unit (ν_{max} 3050, 1640, 895 cm^{-1}, a two-proton singlet at δ 4.75), a tertiary methyl group (a three-proton singlet at δ 0.99), and two secondary methyl groups probably

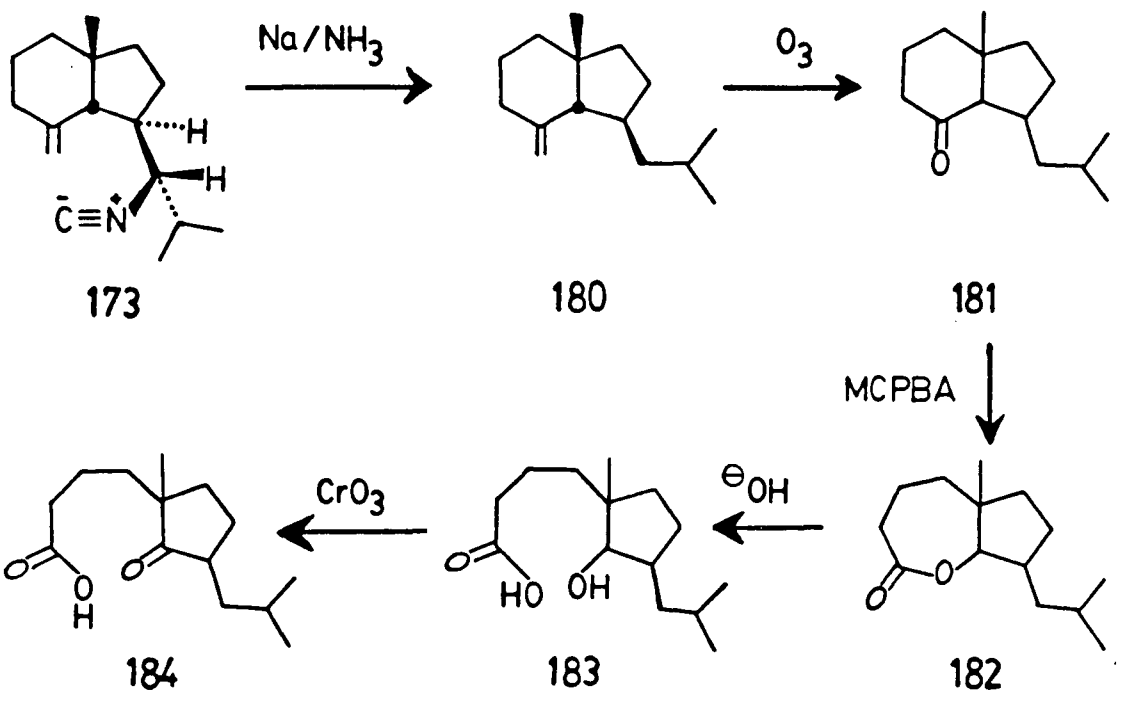
belonging to an isopropyl group (ν_{max} 1385 and 1375 cm^{-1}, two doublets at δ 0.85 and 1.03, $\underline{J}$ = 6 Hz in each case). From these facts, (+)-axisonitrile-1 should be a bicyclic sesquiterpenoid isonitrile.

Chemical transformations were carried out to provide further information concerning the structure of (+)-axisonitrile-1 (173) (Schemes 17 and 18).[54] Thus, (+)-axisonitrile-1 (173) was treated with lithium aluminum hydride to give the amine (178). Hofmann exhaustive methylation-elimination on (178) provided a diene (179), which was shown to contain a $\rangle$CH-CH = C$\begin{smallmatrix}\diagup Me\\ \diagdown Me\end{smallmatrix}$ unit by its ^{1}H nmr spectrum. Hence, the unit $\rangle$CH-CH(NC)-$CHMe_2$ should be present in (173).



Scheme 17

Removal of the isonitrile function could be achieved by treatment of (173) with sodium in liquid ammonia. The product of this reaction was compound (180). Ozonolysis of (180) gave the ketone (181), which was shown to have a ketone function on a six-membered ring (ν_{max} 1707 cm^{-1}). The ketone (181), upon being subjected to Baeyer-Villiger oxidation, afforded the lactone (182). In the ^{1}H nmr spectrum of (182),



173 180 181 182 183 184

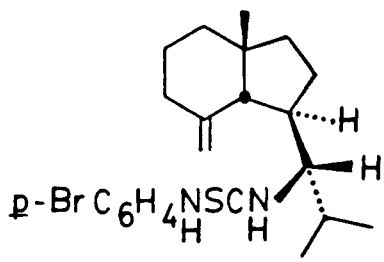
Scheme 18

a doublet at δ 3.72 (1H, $\underline{J}$ = 5 Hz, H-$\overset{|}{C}$-O) was present. Alkaline hydrolysis of (182) gave the hydroxy acid (183), which contained the unit H-$\overset{|}{C}$-OH (δ 3.25, 1H, $\underline{J}$ = 6.5 Hz). Jones' oxidation of (183) gave a cyclopentanone compound (184) (ν_{max} 1738 cm^{-1}).

On the basis of these results and those reported earlier, structure (173) was proposed for (+)-axisonitrile-1. However, at this stage, the stereochemistry of this natural product was not known.

The relative and absolute stereochemistry of (+)-axisonitrile-1 (173) were established by M. Adinolfi <u>et al</u>.[58] in 1977. (+)-Axiso-

nitrile-1 (173) was converted into the crystalline p-bromophenylthiourea derivative (185). The relative configuration of (185), as shown, was determined by X-ray diffractometric measurements. The absolute configuration of (+)-axisonitrile-1 was determined by means of a CD measurement performed on the ketone (181). This measurement showed that (+)-axisonitrile-1 possesses the absolute configuration shown in structure (173).

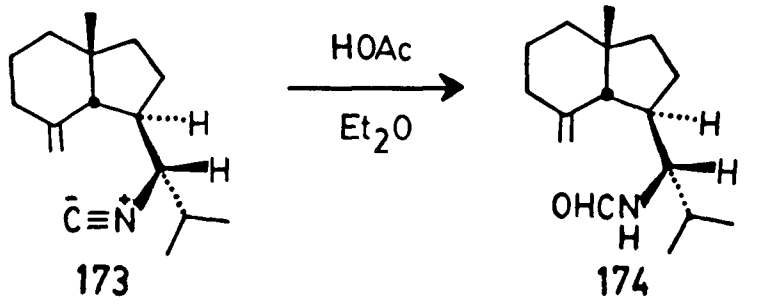


185

(+)-Axamide-1 (174) was isolated in relatively small amounts from the same sponge (Axinella cannabina) that produced (+)-axisonitrile-1 (173).[56] Compound (174) {$[\alpha]_D$ +10.0° ($CHCl_3$), η_D 1.5087} was obtained as a colorless oil, which was shown to have a structural formula $C_{16}H_{27}NO$ (mass spectrum and elemental analysis). The ir and ^1H nmr spectra of (174) showed that this material possessed the following structural units: a -NHCHO function (ν_{max} 3350-3150, 1687 cm^{-1}), an exocyclic methylene group [ν_{max} 3050, 1640, 895 cm^{-1}, δ 4.68 (2H, bm)], a tertiary methyl group (s, 3H, δ 0.94), and two secondary methyl groups, probably belonging to an isopropyl group (ν_{max} 1385 and 1375 cm^{-1}, two doublets at δ 0.88 and 0.80, 3H each, J = 6 Hz in each case).

All of these data indicated that there was a close structural relationship between (+)-axamide-1 and (+)-axisonitrile-1 (173). This

was confirmed by hydration of (173) to afford the corresponding formamide (equation 26), which showed physical, spectroscopic and chromatographic properties identical with those exhibited by (+)-axamide-1. Therefore, (+)-axamide-1 was shown to possess the structure (174).



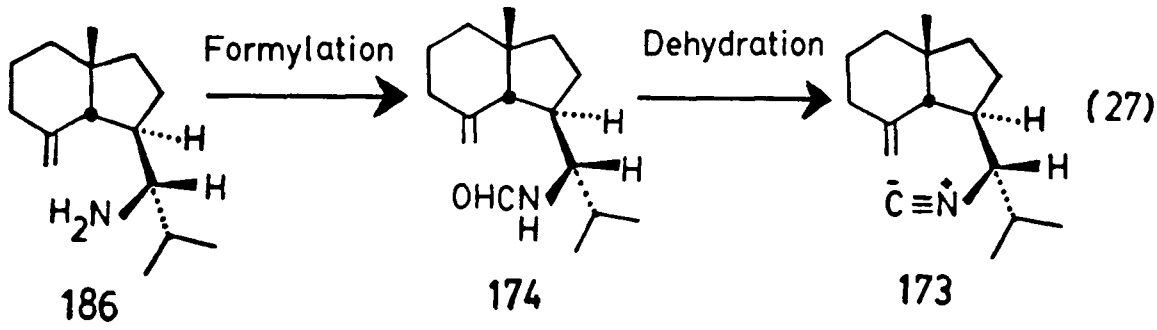
(26)

Naturally occurring isonitriles usually exhibit <u>in vitro</u> cytotoxic properties as well as antifeedant activities.[59] (+)-Axisonitrile-1 (173) has been shown to possess toxicity, but no antifeedant properties were detected.[55j,59b]

B. Total Syntheses of (±)-Axamide-1, (±)-Axisonitrile-1, and the Corresponding C-10 Epimers

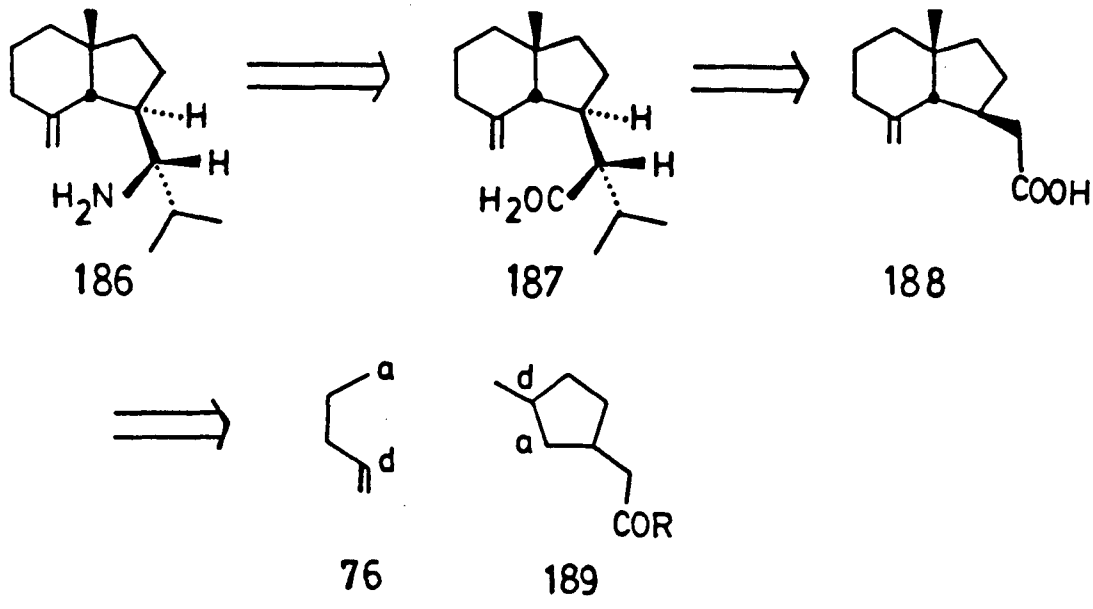
It is obvious that dehydration[60] of axamide-1 (174) would provide axisonitrile-1 (173), while the former substance could in turn be prepared by formylation[61] of the corresponding amine (186) (equation 27). Hence, the total syntheses of (±)-axamide-1 (174) and (±)-axisonitrile-1 (173) would be reduced to the synthesis of the racemic

amine (186).



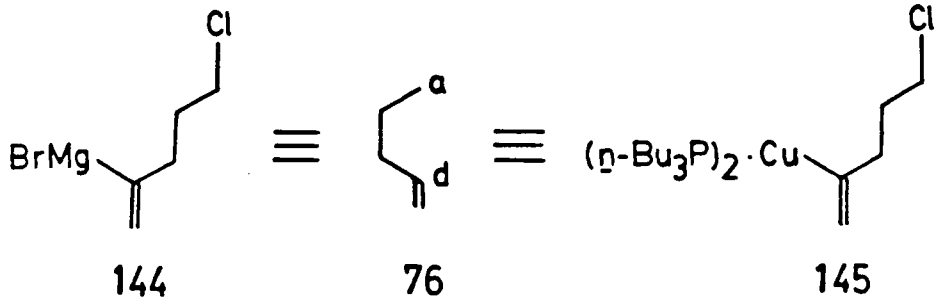
(27)

Retrosynthetic analyses revealed that two reasonable strategies could be envisaged to carry out the synthesis of the amine (186). Strategy A was based on the recognition that a major part of the molecule could be assembled by a synthetic combination of substances equivalent to synthons (76) and (189) (Scheme 19). As had already been shown, the Grignard reagent (144) or the organocopper reagent (145) could serve

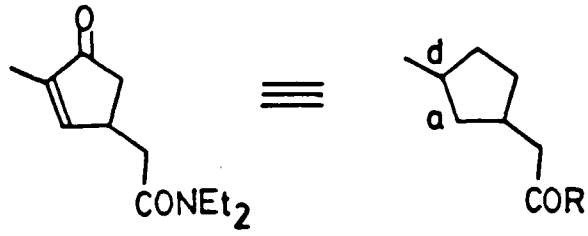


Scheme 19

as equivalents to the 1-pentene d^2,a^5 synthon (76). A potential equivalent to the synthon (189) would be the enone (190). Thus, the methyenecyclohexane annulation sequence described earlier would be used to prepare the necessary carbon skeleton. Explicitly, reaction of

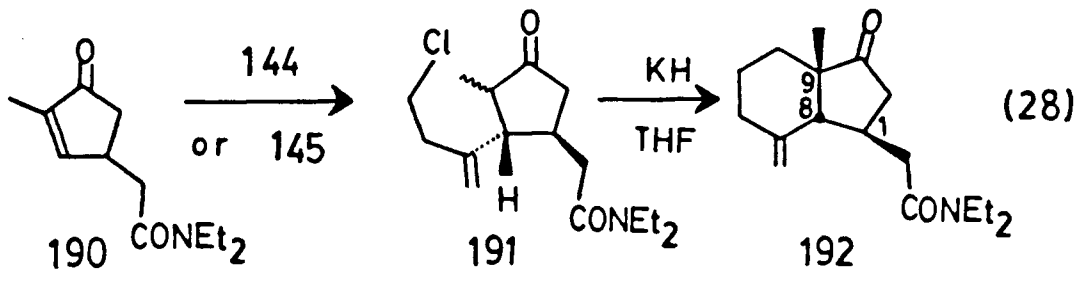


144 76 145



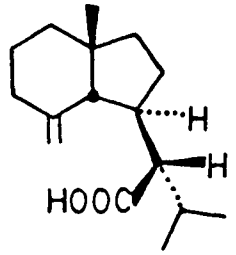
190 189

either reagent (144) or (145), under appropriate conditions, with the enone (190) would be expected to proceed in the desired stereochemical sense to give the corresponding conjugate addition product (191) (equation 28). Cyclization of the latter substance would furnish (192) with the same relative stereochemistry as that of (186) at the three

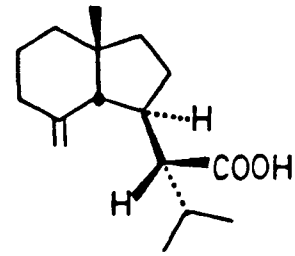


190 191 192 (28)

carbon centers, C-1, C-8 and C-9. Removal of the ketone function[62] from (192), with concommitant hydrolysis of the amide, followed by alkylation[63] of the resultant carboxylic acid with an isopropyl halide, would yield the acid (187) and, presumably, the corresponding epimer (193).

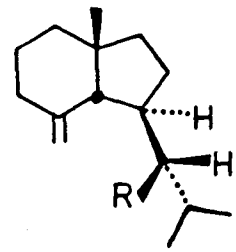


187



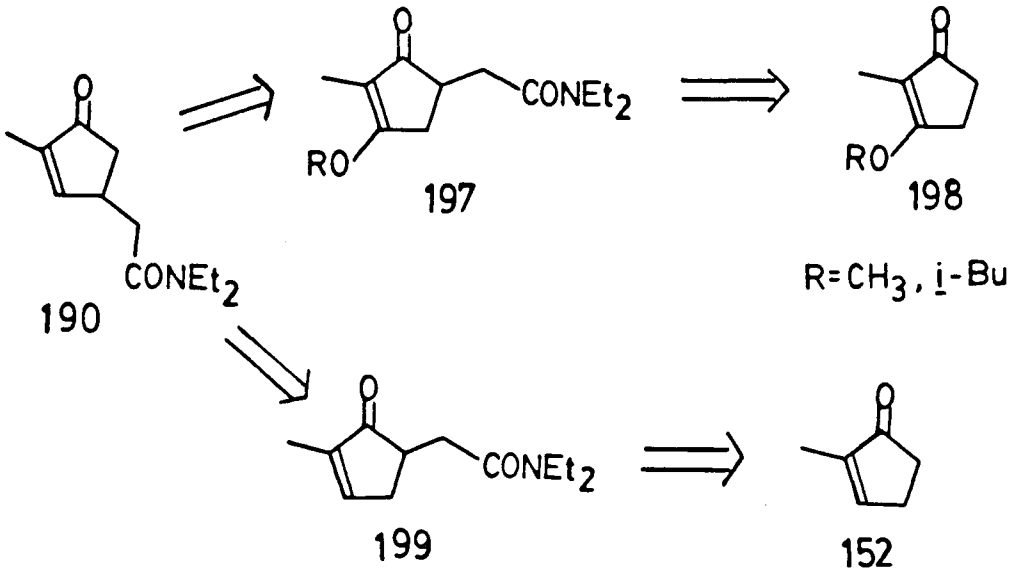
193

The acid (187) could be converted <u>via</u> the acid chloride (194) into the acyl azide (195). Curtius rearrangement of the latter substance would give, after appropriate manipulation of the resultant isocyanate (196), the amine (186).[64]



194 R= COCl
195 R= CON_3
196 R= N=C=O

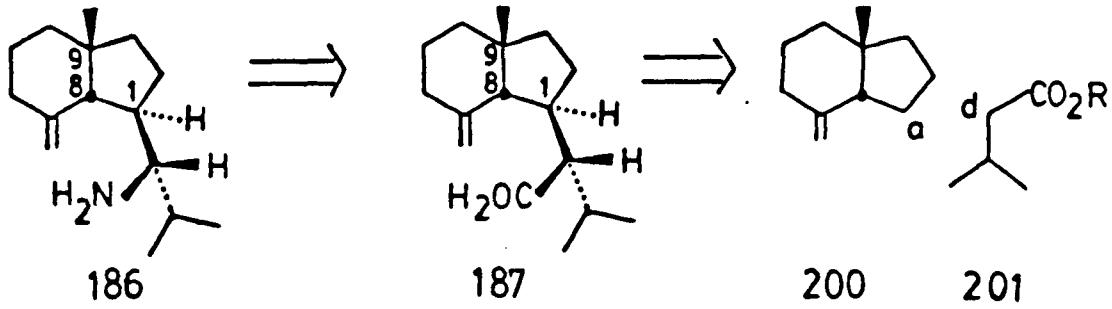
With respect to the synthesis of the enone (190), it was envisioned that this material could be prepared by α'-alkylation[65] of the unsaturated ketone (198), followed by hydride reduction-acid hydrolysis of the resultant product (197)[66] (Scheme 20). Alternatively,



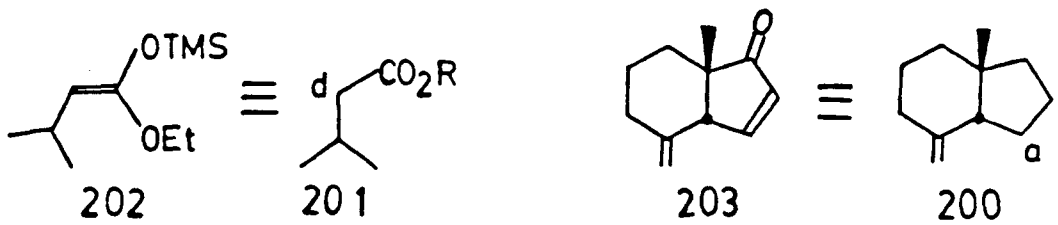
Scheme 20

α'-alkylation[67] of (152), followed by a 1,3-carbonyl transposition[68] on the resultant product (199) would also provide the enone (190) (Scheme 20).

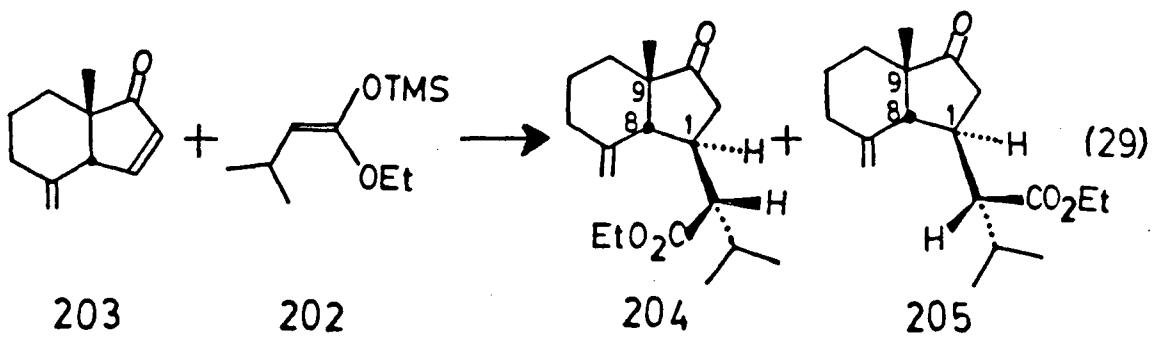
An alternative approach to the synthesis of the amine (186) (strategy B) would involve a sequence containing two key steps. One of the key steps would involve the synthetic combination of substances equivalent to the synthons (200) and (201) to assemble the carbon framework of (187) (Scheme 21). The O-trimethylsilyl ketene acetal (202) would serve as a synthetic equivalent to the synthon (201), while the enone (203) would correspond to the synthon (200). Michael addition[69] of (202) to the enone (203) would be expected to occur preferentially from the convex (β) face of compound (203) to provide a



Scheme 21

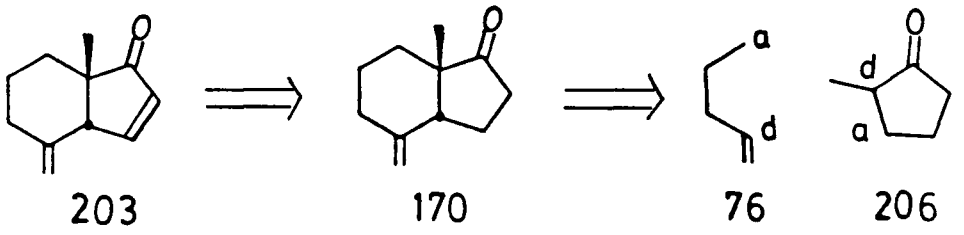


product (204) with the correct relative stereochemistry at C-1, C-8 and C-9 (equation 29). The corresponding epimer (205) would, presumably, be formed along with (204). Removal of the ketone function[62] from (204),



accompanied by hydrolysis of the ester, would give the acid (187). The acid (187) would be converted into the required amine (186) via the sequence of reactions outlined previously.

Compound (203) could be derived from the corresponding ketone (170), which could in turn be prepared by the other key conversion in the synthesis, the methylenecyclohexane annulation sequence described earlier (Scheme 22). Thus, it had already been shown that conjugate addition of either reagent (144) or (145) to the enone (152), followed by cyclization of the resultant product, provided the cis-fused bicyclic ketone (170).



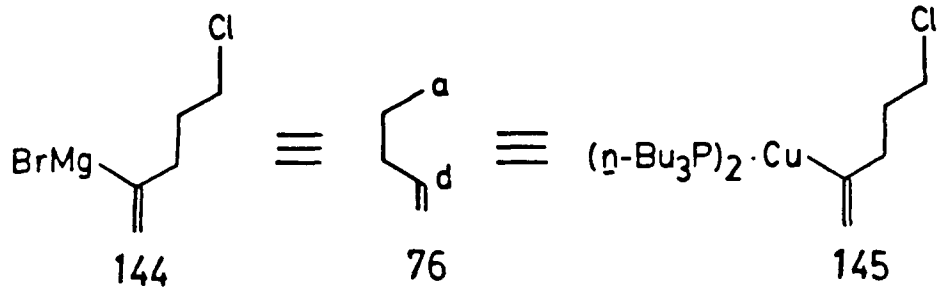
203 170 76 206

Scheme 22

All attempts to synthesize the amine (186) via strategy A (Schemes 19 and 20) failed. For examples, reaction of (207)* with diisobutylaluminum hydride in THF at -78°C, followed by acid hydrolysis of the

---

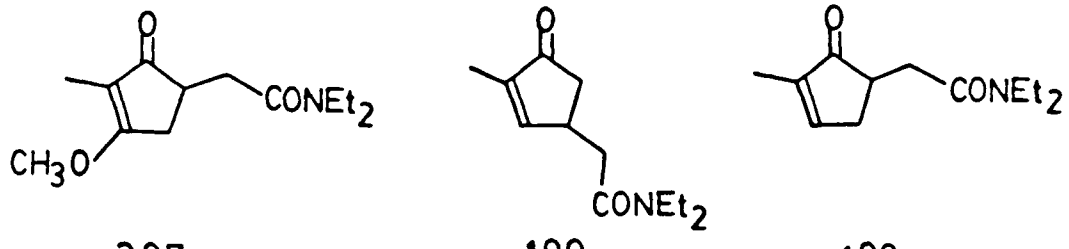
* Compound (207) was prepared (61%) by the α'-alkylation of 3-methoxy-2-methyl-2-cyclopenten-1-one (198) (R=CH_3) with N,N-diethylbromoacetamide in THF.[65]



144 76 145

152 206

resultant product mixture, provided the desired enone (190) in only 14% yield. Also produced was the isomer (199) (34%) and an inseparable mixture of uncharacterized compounds (19%). On the other hand, treatment of (207) with sodium borohydride in the presence of cerium trichloride hexahydrate in ethanol at 65°C,* [70] gave the enone (190) in only 18% yield. Some starting material (207) (24%) was recovered.



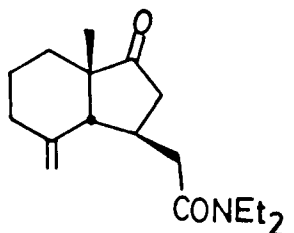
207 190 199

---

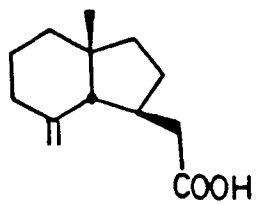
* No detectable reaction was observed at room temperature after 3 h.

Removal of the ketone function from (192)* ($NH_2NH_2 \cdot H_2O$, KOH, DEG)[71] with concommitant hydrolysis of the amide, provided (79%) two inseparable acids in a ratio of ~8:1 (glc analysis) [ir: ν_{max} 3400-2500 cm^{-1} (br), 1705 cm^{-1}]. The ^1H nmr spectrum of this mixture exhibited three multiplets at δ 4.62, 4.75 and 5.36, with relative areas of ~8:8:1, respectively. Thus, it appeared that the Wolff-Kishner reduction of (192) gave rise to a mixture of the desired acid (188) and the isomer (208), in a ratio of ~8:1, respectively. Furthermore, the relative amounts of (188) and (208) formed in the reduction-hydrolysis reaction varied from experiment to experiment. In fact, in most of the experiments, the ratio [(188):(208)] was considerably less than 8:1.

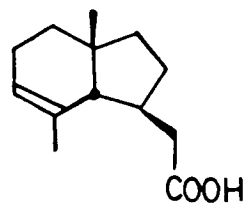
Finally, attempted alkylation (2.5 equivalents LDA, THF, HMPA; isopropyl iodide[63]) of the mixture of acids (188) and (208) (ratio 4:1, respectively) failed. The material recovered from the reaction mixture



192



188



208

---

* Compound (192) was prepared by the methylenecyclohexane annulation sequence described earlier. Thus, conjugate addition of 2-bromomagnesio-5-chloro-1-pentene (144) to the enone (190) in the presence of copper(I) salt and boron trifluoride-etherate followed by cyclization, provided (192) in 35% yield.

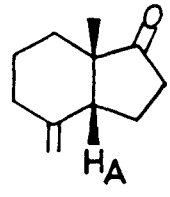
was a mixture of the acids (188) and (208) (ratio 4:1, respectively, 75%). On the other hand, when the dianions derived from the mixture of acids (188) and (208) (ratio 2:1, respectively) were quenched with deuterium oxide, a 2:1 mixture of products (glc analysis) was obtained in 71% yield. On the basis of spectral data [ir: ν_{max} 3400-2500 cm^{-1} (br), 1705 cm^{-1}; Exact Mass calcd. for $C_{13}H_{19}O_2D$: 209.1527; found: 209.1523], this mixture was concluded to consist largely of the corresponding mono-deuterated products of (188) and (208).

At this point strategy A for the synthesis of the amine (186) was abandoned and an investigation of strategy B (Schemes 21 and 22) was initiated.

At the outset, it was clear that the synthesis of (±)-axamide-1 (174) and (±)-axisonitrile-1 (173) rested heavily on the acquisition of relatively large quantities of the ketone (170). Of the two methods previously employed for effecting addition of the 5-chloro-[2-(1-pentenyl)] group to the enone (152), the modified Noyori procedure was discarded because, in large scale reactions, the necessary separation of tri-n-butylphosphine from the desired product proved to be quite tedious. On the other hand, in the earlier experiments, the yield of (170) from the copper(I)-catalyzed reaction of the Grignard reagent (144) (1 equiv) with the enone (152) (1 equiv) was quite low (33%). It was found, however, that this situation could be remedied by using an excess of the Grignard reagent (144).[72] Thus, when a 1.3:1 molar ratio of (144) to (152), respectively, was used for the conjugate addition reaction, the yield of the reaction was considerably improved.

Solid magnesium bromide-etherate (7.3 mmol) was added to a solution

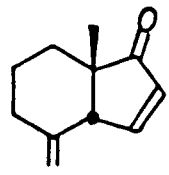
of 5-chloro-2-lithio-1-pentene (112) (7.3 mmol) in dry THF. Successive addition of copper bromide-dimethyl sulfide complex (1.8 mmol), 2-methyl-2-cyclopenten-1-one (152) (5.6 mmol), and boron trifluoride-etherate (7.3 mmol) gave a bright yellow solution which was stirred at -78°C for 3 h. Appropriate workup gave the chloro ketone (159) in 89% yield. Upon exposure to potassium hydride in THF, the chloro ketone (159) cyclized to produce the ketone (170) in 96% yield. Thus, the overall yield of the annulation sequence [(152) → (170)] had been increased to 85%. By repetition of this procedure, quantities of the ketone (170) sufficient to carry out the projected synthesis were obtained.



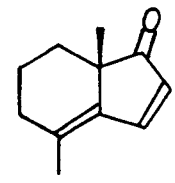
170

The ^1H nmr spectrum of (170) was consistent with the assigned structure. The tertiary methyl singlet appeared at δ 1.04 while the olefinic protons gave rise to a multiplet at δ 4.76-4.83. The cis ring junction of (170) was verified by a nOe difference experiment. Thus, irradiation at δ 1.04 (ring junction methyl singlet) caused enhancement of a one-proton signal at δ 2.49 (d of d, J = 12, 8 Hz). On the basis of chemical shift and the spin-spin coupling pattern, the latter resonance was assigned to H_A. The ir spectrum of (170) showed an absorption at 1730 cm^{-1}, indicating the presence of a carbonyl group.

In view of the presence of the exocyclic double bond in (170), the conversion of this material into the enone (203) was not expected to be straightforward. Thus, one might expect that exposure of the product (203) to acidic or basic medium could result in isomerization of the exocyclic double bond to give the fully conjugated product (209). A perusal of the literature indicated that three potential methods might be mild enough for conversion of the ketone (170) into the enone (203) without the complication mentioned above.



203



209

The first and commonly used method is the bromination of a trimethylsilyl enol ether with bromine or N-Bromosuccinimide to give the corresponding α-bromo ketone. The latter substance can be dehydrobrominated to produce the corresponding enone by treatment with a mixture of lithium bromide and lithium carbonate in refluxing N,N-dimethylformamide.[73]

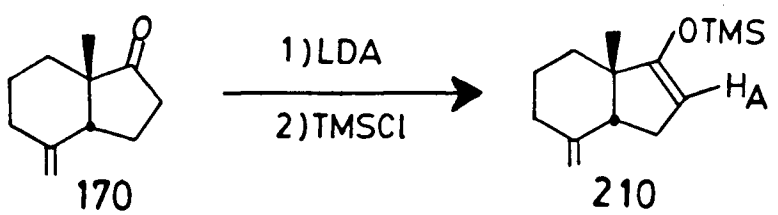
The second method makes use of organoselenium chemistry. Treatment of an enolate anion obtained from a ketone with phenylselenenyl chloride provides the corresponding α-phenylselenide. The latter substance can be oxidized with a suitable oxidant to the selenoxide, which undergoes an elimination reaction to produce the corresponding enone.[74]

The third and most recent method, reported by Saegusa, involves

reaction of a trimethylsilyl enol ether with palladium(II) acetate in acetonitrile to give the corresponding enone directly.[75]

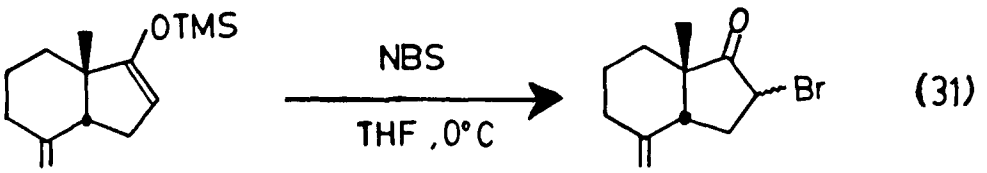
Initially, attempts were made to convert (170) into the enone (203) via the second and third methods. However, the yield of the enone (203) produced by the α-phenylselenide method was low (~20%). Furthermore, use of the Saegusa procedure provided, in only 15% yield, a 72:28 mixture of the ketone (170) and the enone (203) respectively. Since these two methods turned out to be unsatisfactory, the first method (bromination-dehydrobromination) was investigated.

Treatment of the ketone (170) with LDA in THF at -78°C followed by the addition of trimethylsilyl chloride gave, after a non-aqueous workup, the trimethylsilyl enol ether (210) in 99% yield (equation 30).[76a] The ^{1}H nmr spectrum of (210) showed a nine-proton singlet at δ 0.21 due to the trimethylsilyl (-$SiMe_3$) protons and a one-proton triplet at δ 4.48 (J = 2 Hz) due to the proton H_A.



(30)

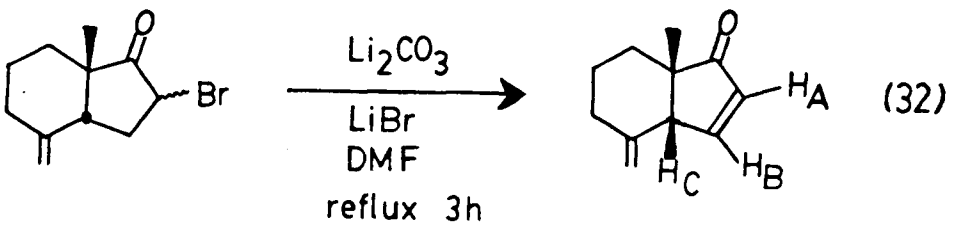
Reaction of the trimethylsilyl enol ether (210) with N-bromosuccinimide in dry THF at 0°C, gave the α-bromo ketone (211) (92%) as an 85:15 mixture (glc analysis) (equation 31).[73d] The ir spectrum of (211) exhibited an absorption at 1740 cm^{-1}, indicating the presence of a carbonyl group.



(31)

210 211

A solution-suspension of the α-bromo ketone (211), lithium bromide, and lithium carbonate in N,N-dimethylformamide was heated under reflux for 3 h to provide the enone (203) in 84% yield (equation 32).[73e]



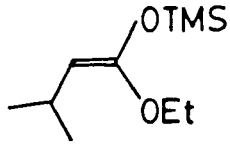
(32)

211 203

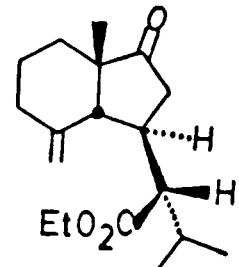
Interestingly, no isomerization of the exocyclic double bond was observed under the conditions employed. The ir spectrum of (203) showed an absorption at 1700 cm^{-1}, indicating the presence of a cyclopentenone-type carbonyl group. The ^1H nmr spectrum of (203) exhibited a singlet at δ 1.12 due to the tertiary methyl group, a one-proton broad singlet at δ 3.23 due to the proton H_C, and two one-proton signals at δ 6.20 (d of d, $\underline{J}$ = 5.5, 2 Hz) and 7.48 (d of d, $\underline{J}$ = 5.5, 2.5 Hz) due to the protons H_A and H_B, respectively. Additionally, the two exocyclic methylene protons gave rise to two singlets at δ 4.92 and 4.90. The cis ring junction of (203) was, again, confirmed by a nOe difference experiment, in which irradiation at δ 1.12 (tertiary methyl singlet)

caused enhancement of the signal at δ 3.23 (H_C).

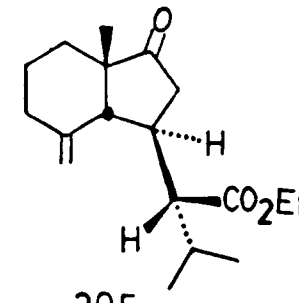
The next stage of the projected synthesis involved conjugate addition of the ketene acetal (202) to the enone (203) to give (204) and/or (205). It was evident from an examination of molecular models



202

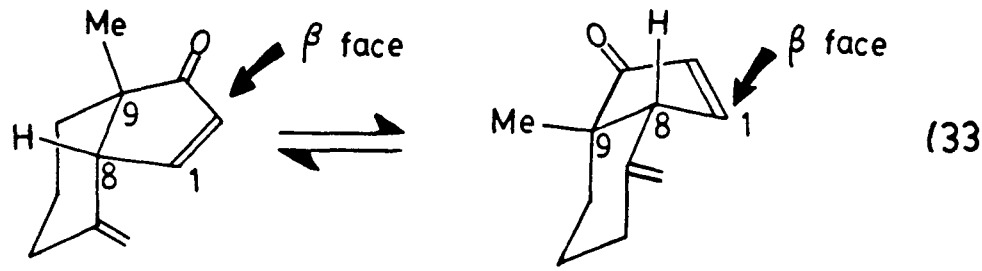


204



205

that this conjugate addition would occur preferentially from the convex (β) face of the enone molecule (equation 33). In this manner, each of the chiral centers C-1, C-8 and C-9 in the products (204) and/or (205) would possess the desired relative stereochemistry. Whether or not the preferential formation of (204) would be observed in this process was open to question.

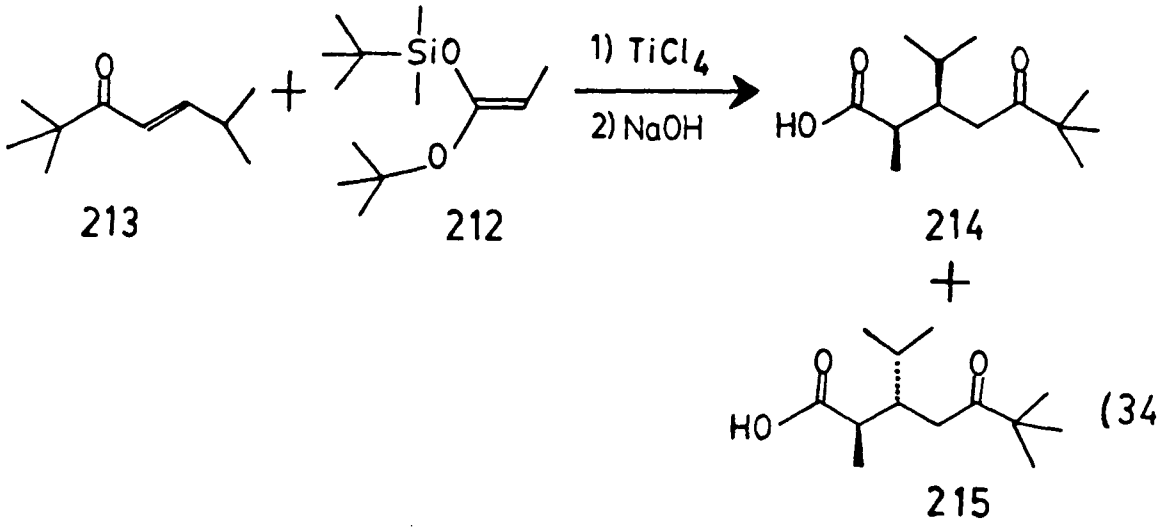


(33)

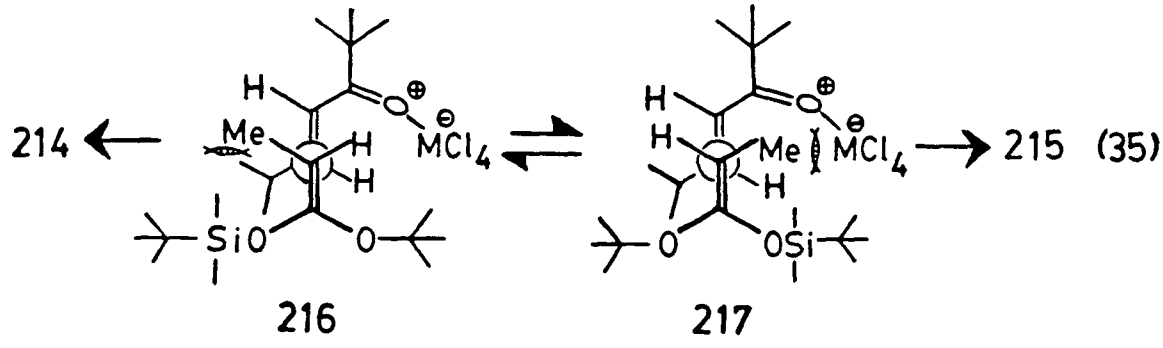
203 203

Recently, Heathcock[77] proposed an open transition state model to account for his observations of high stereoselectivity in Lewis acid

mediated Michael additions of silyl ketene acetals and/or enol silyl ethers to enones. For example, addition of the silyl ketene acetal (212) to the acyclic enone (213) in the presence of titanium tetrachloride produced, after base hydrolysis, a 96:4 mixture of (214) and (215), respectively (equation 34).[77a] The high stereoselective formation of



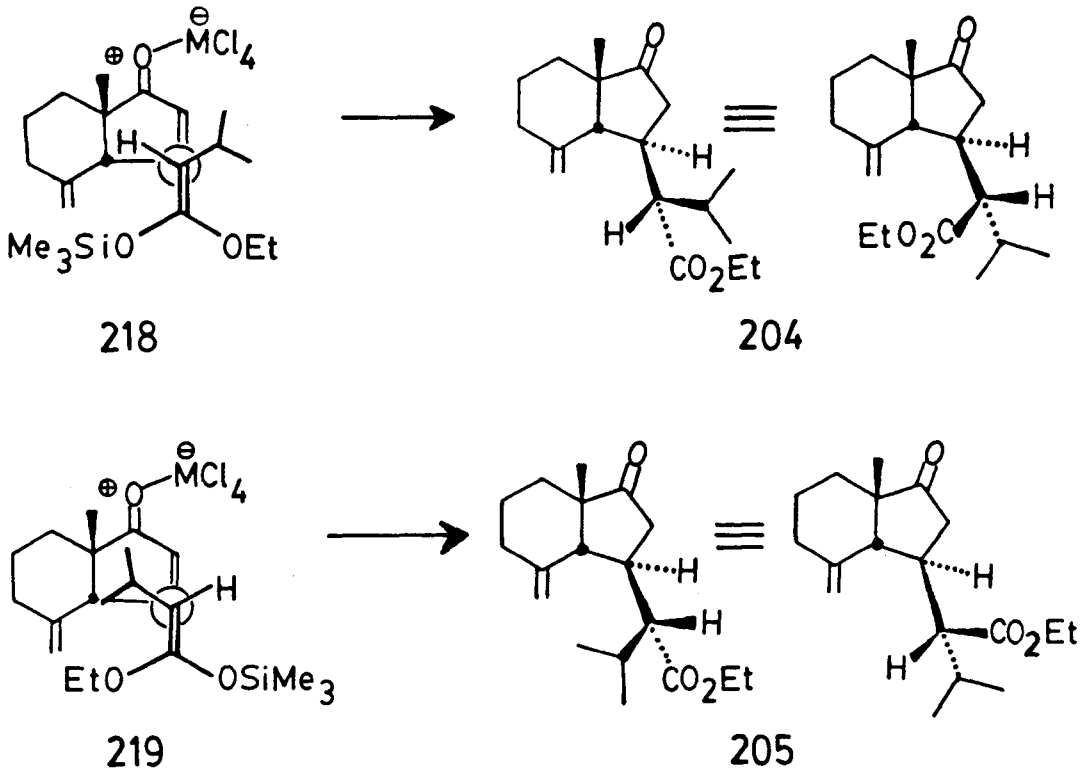
(214) was explained by postulating that the reaction proceeded primarily via a transition state derived from arrangement (216) rather than via a transition state derived from (217) (equation 35).



If one were to "apply" this transition-state model to the reaction of (203) with (202), one would anticipate that the desired substance

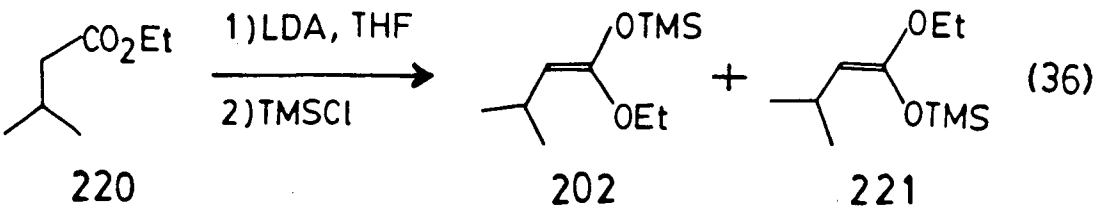
(204) would be the major product derived from this transformation. The preference for the formation of (204) relative to (205) would be due to the fact that the steric hindrance present in (219) would be greater than that present in (218) (Scheme 23). However, since most of the silyl ketene acetals and enones used by Heathcock were sterically quite demanding and since most of the enones he used were acyclic compounds that were quite different from compound (203), the validity of using this open transition state model for the addition summarized in equation 29 is questionable.

Treatment of the ester (220) with LDA in THF, followed by addition of trimethylsilyl chloride, provided a mixture of the (E)- and



Scheme 23

(Z)-trimethylsilyl ketene acetals, (202) and (221), in a ratio of 95:5, respectively (glc analysis) (equation 36).* The ^{1}H nmr spectrum of (202) exhibited a nine-proton singlet at δ 0.22 due to the trimethylsilyl (-$SiMe_3$) protons and a one-proton doublet at δ 3.62 (J = 9 Hz) due to the vinyl proton.

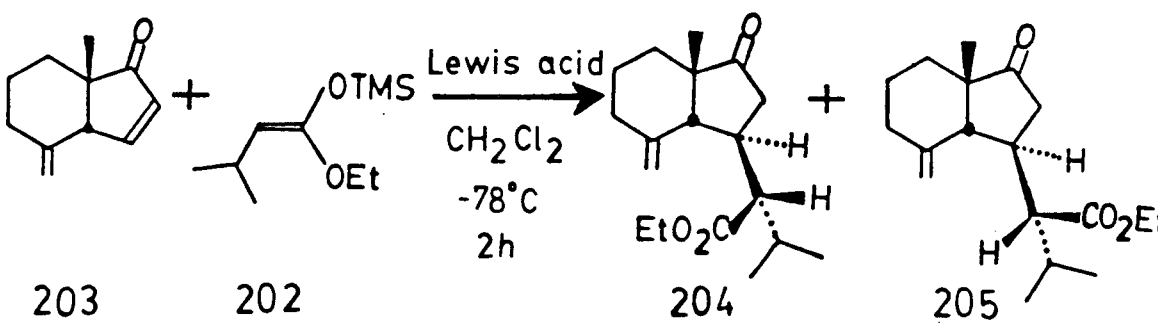


Treatment of the enone (203) with the trimethylsilyl ketene acetal (202) in refluxing acetonitrile[69b,c] or nitromethane[69d] provided none of the conjugate addition products (204) and/or (205). Only the enone (203) was recovered from the reaction mixtures. On the other hand, when a Lewis acid was present, the addition reaction proceeded smoothly.

---

* It is known that treatment of an ester with LDA in THF, followed by trapping of the resultant enolate anion with trimethylsilyl chloride, gives the corresponding (E)-trimethylsilyl ketene acetal predominantly. On the other hand, the geometrically isomeric (Z)-trimethylsilyl ketene acetal forms preferentially when the solvent is changed to 23% HMPA in THF (see reference 78). The stereochemistry of the trimethylsilyl ketene acetals was deduced from the ^{1}H nmr spectra. In general, the vinyl proton of the (E)-trimethylsilyl ketene acetal resonates at lower field than that of the (Z)-trimethylsilyl ketene acetal (see reference 79).

Thus, addition of the trimethylsilyl ketene acetal (202) to a mixture of the enone (203) and titanium tetrachloride in dichloromethane furnished a mixture (~1:1, glc analysis) of the conjugate addition products (204) and (205) in 88% yield (Scheme 24). When boron trifluoride-etherate was used as Lewis acid in the addition reaction, an approximately 1:1 mixture (glc analysis) of (204) and (205) was produced in 83% yield (Scheme 24). The use of stannic tetrachloride for the addition reaction provided, again, a mixture (~1:1, glc analysis) of (204) and (205) in 50% yield. In addition, 20% of the enone (203) was recovered (Scheme 24).



203 202 204 205

Lewis acid	Ratio*
$TiCl_4$	46:54
$SnCl_4$	46:54
$BF_3 \cdot Et_2O$	48:51

* Ratios of (204) to (205) were determined by glc analysis.

Scheme 24

Following Ireland's procedure,[78] a 43:57 mixture of the (E)- and (Z)-trimethylsilyl ketene acetals (202) and (221), respectively, (glc

analysis) was obtained (77%) by treatment of the ester (220) with LDA in 23% HMPA-THF, followed by the addition of trimethylsilyl chloride.* The ^1H nmr spectrum of the mixture (202) and (221) showed that the vinyl proton of (221) resonated at δ 3.33 (d, J = 8.5 Hz). This mixture of trimethylsilyl ketene acetals (202) and (221) was allowed to react with the enone (203) in the presence of titanium tetrachloride to give, in 86% yield, a mixture of (204) and (205) in a ratio of 68:32, respectively (glc analysis).

The experimental results summarized above indicated that Lewis acid-catalyzed addition of the trimethylsilyl ketene acetal (202) to the enone (203) did not show any stereoselectivity with respect to the newly formed chiral center in the side chain. However, the use of a 43:57 mixture of (202) and (221) did result in a slight preference for product (204) relative to (205).

The mixture of (204) and (205) was partially separated by using a combination of (slow) column chromatography on silica gel and multiple development preparative tlc (elution with 10:1 petroleum ether-ether). In this way, pure samples of (204) and (205) were obtained for characterization.

The keto ester (204) (mp 80-81°C, recrystallization from petroleum ether) exhibited a carbonyl absorption at 1730 cm^{-1} in its ir spectrum. The ^1H nmr spectrum of (204) (Figure 1) exhibited a pair of doublets at δ 0.94 and 0.95 (isopropyl methyl groups, J = 7 Hz in each case), a singlet at δ 1.01 (tertiary methyl group), a triplet at δ 1.23

---

* See footnote on p. 77.

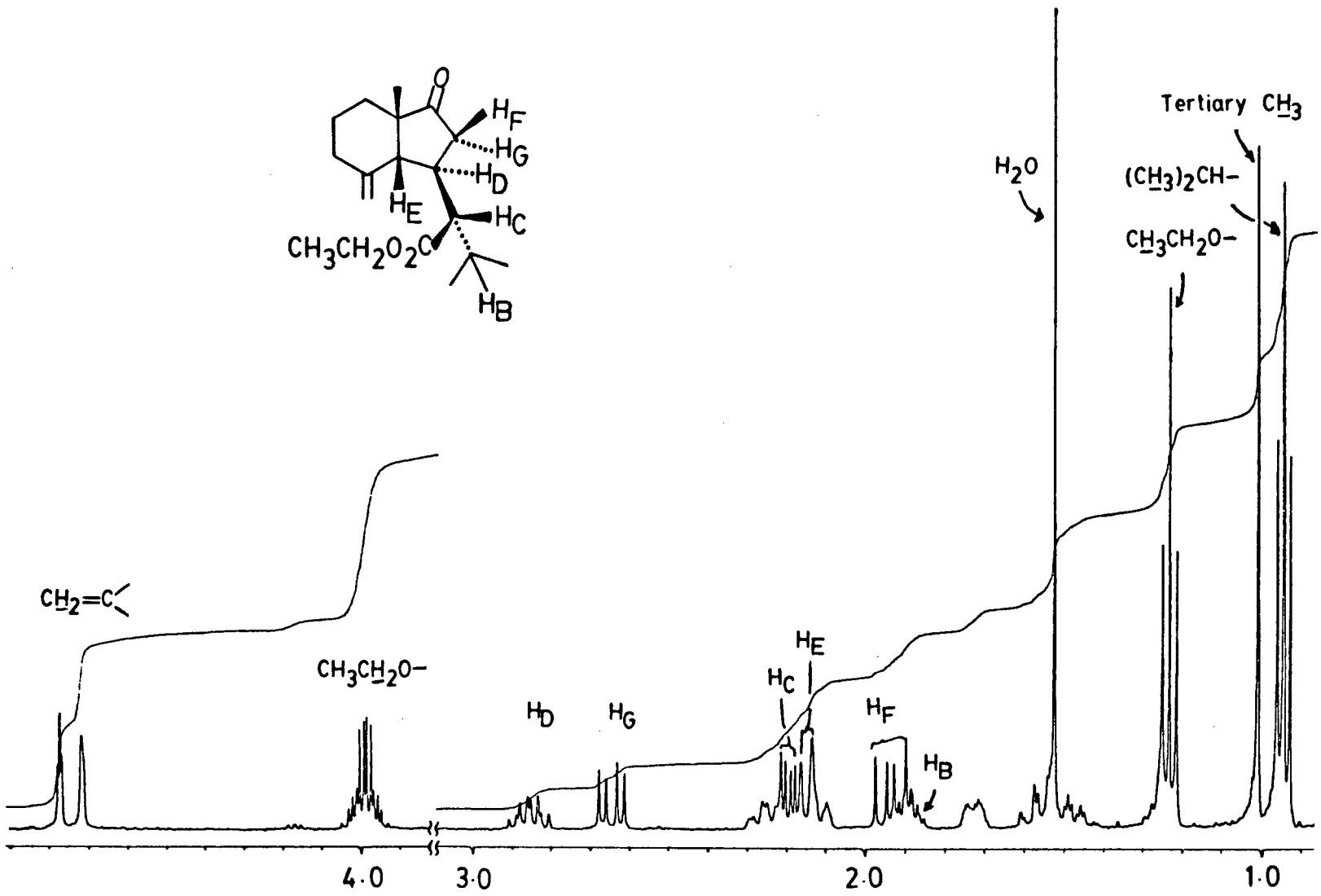
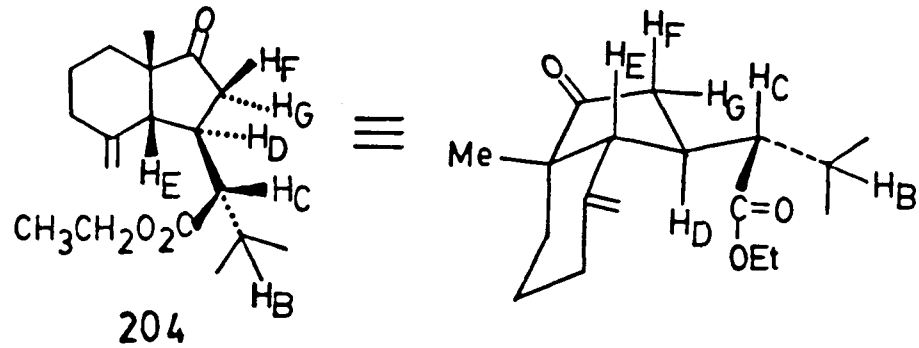


Fig. 1: The 400 MHz ^1H nmr spectrum of (204)



204

(-$OCH_2\underline{C}H_3$, $\underline{J}$ = 7 Hz), a partially obscured one-proton multiplet at δ 1.82-1.95 (H_B), a one-proton doublet of doublets at δ 1.94 (H_F, $\underline{J}$ = 18.5, 11.5 Hz), a partially obscured one-proton doublet at δ 2.15 (H_E, $\underline{J}$ = 11 Hz), a partially obscured one-proton doublet of doublets at δ 2.20 (H_C, $\underline{J}$ = 10, 4.5 Hz), a one-proton doublet of doublets at δ 2.65 (H_G, $\underline{J}$ = 18.5, 7.5 Hz), a one-proton multiplet at δ 2.79-2.93 (H_D), a two-proton multiplet at δ 3.92-4.06 (-$OC\underline{H}_2CH_3$), and a broad singlet and a triplet ($\underline{J}$ = 2 Hz) at δ 4.72 and 4.77, respectively (=$C\underline{H}_2$).

The assignment of the signals at δ 1.94 (d of d, $\underline{J}$ = 18.5, 11.5 Hz) and 2.65 (d of d, $\underline{J}$ = 18.5, 7.5 Hz) to the strongly coupled geminal protons H_F and H_G, respectively, were based partially on an examination of a molecular model, which showed that, in what appears to be the most stable conformation of (204), the H_F-H_D dihedral angle approximates 180° whereas the H_G-H_D dihedral angle is close to 30°. The mutual coupling between the protons H_F and H_G was confirmed by a decoupling experiment. Thus, irradiation at δ 2.65 (H_G) simplified the signal at δ 1.94 (H_F) to an "imperfect" doublet ($\underline{J}$ = 11.5 Hz)* (Figure 2). In the same

* In this decoupling experiment, the signal due to H_F should have collapsed to a doublet ($\underline{J}$ = 11.5 Hz). However, an "imperfect" doublet was obtained due to incomplete decoupling.

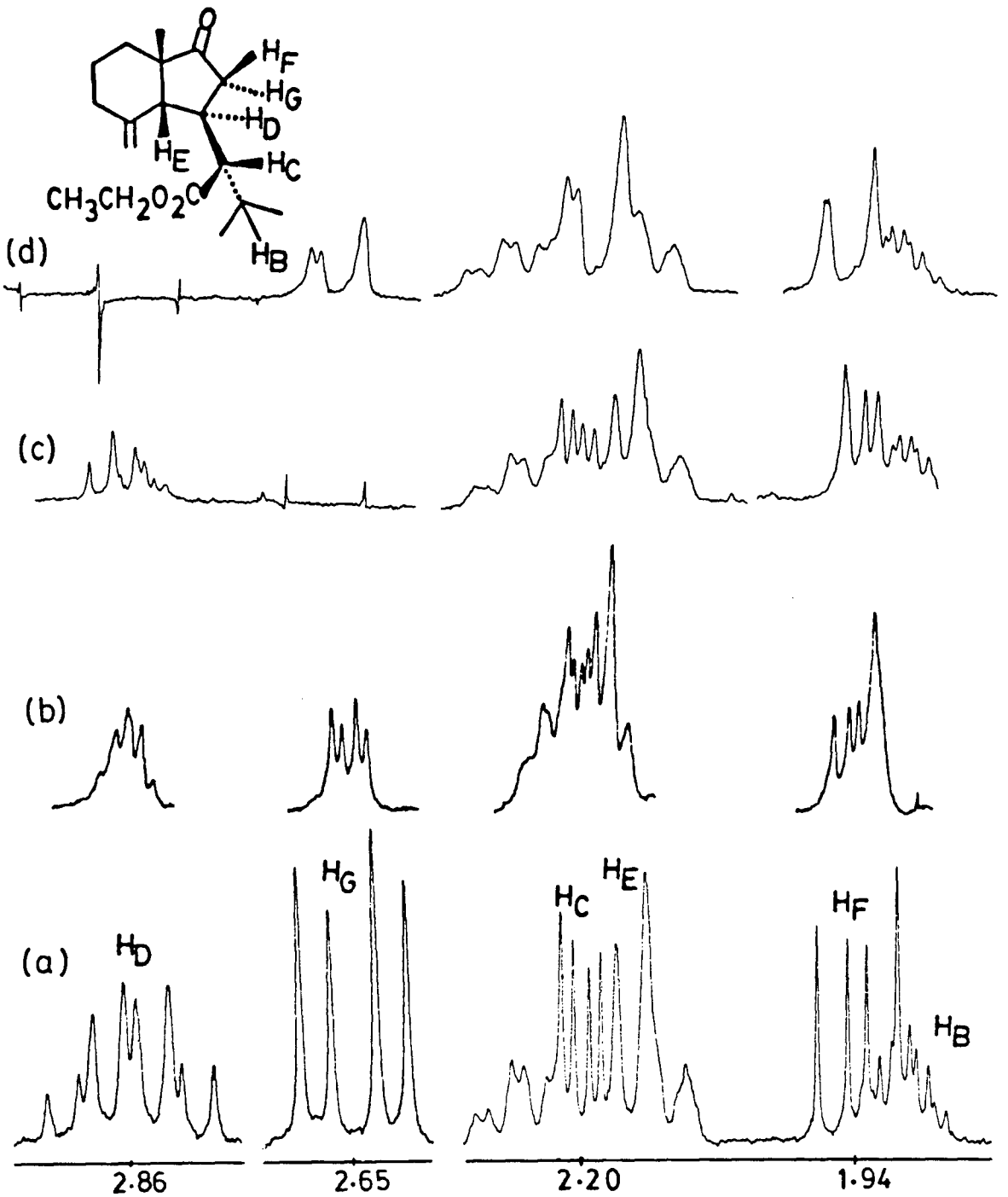


Fig. 2: The homonuclear spin decoupling experiments with (204): (a) the normal 400 MHz ^1H nmr spectrum expanded for the region δ 1.8-3.0, and the spectra with irradiations at (b) δ 0.95 (isopropyl methyl groups), (c) δ 2.65 (H_G), and (d) δ 2.86 (H_D).

decoupling experiment, the multiplet due to H_D (δ 2.79-2.93) also simplified. When H_D was decoupled, the signals due to H_F and H_G at δ 1.94 and 2.65 collapsed to doublets ($\underline{J}$ = 18.5 Hz in each case) (Figure 2). In the same decoupling experiment, the partially obscured doublet of doublets due to H_C at δ 2.20 collapsed to a doublet ($\underline{J}$ = 4.5 Hz) while the partially obscured doublet due to H_E at δ 2.15 collapsed to a singlet. In what appears to be the most stable conformation of (204), the dihedral angle between the trans-related protons H_E and H_D is close to 180° and, thus, the observed coupling constant ($\underline{J}_{ED}$ = 11 Hz) is consistent with the assigned stereochemistry. When the isopropyl methyl doublets at δ 0.95 and 0.94 were both decoupled, the partially hidden multiplet due to H_B at δ 1.82-1.95 collapsed to a very broad singlet* (Figure 2). Using a nOe difference experiment, in which the signal at δ 1.01 (bridgehead methyl singlet) was irradiated, enhancement of the signal at δ 2.15 (H_E) was observed (Figure 3). Therefore, the expectation that (204) possessed a cis ring fusion was verified.

The keto ester (205) (mp 69-70°C, recrystallization from petroleum ether) exhibited a carbonyl absorption at 1728 cm^{-1} in its ir spectrum. The ^1H nmr spectrum of (205) (Figure 4) exhibited a pair of doublets at δ 0.91 and 0.95 (isopropyl methyl groups, $\underline{J}$ = 7 Hz in each case), a singlet at δ 1.03 (tertiary methyl group), a triplet at δ 1.27

---

* Theoretically, the signal due to H_B should have collapsed to a doublet (coupling constant = $\underline{J}_{BC}$). However, because of the interference of the partially overlapping doublet of doublets (H_F), only a very broad singlet was observed.

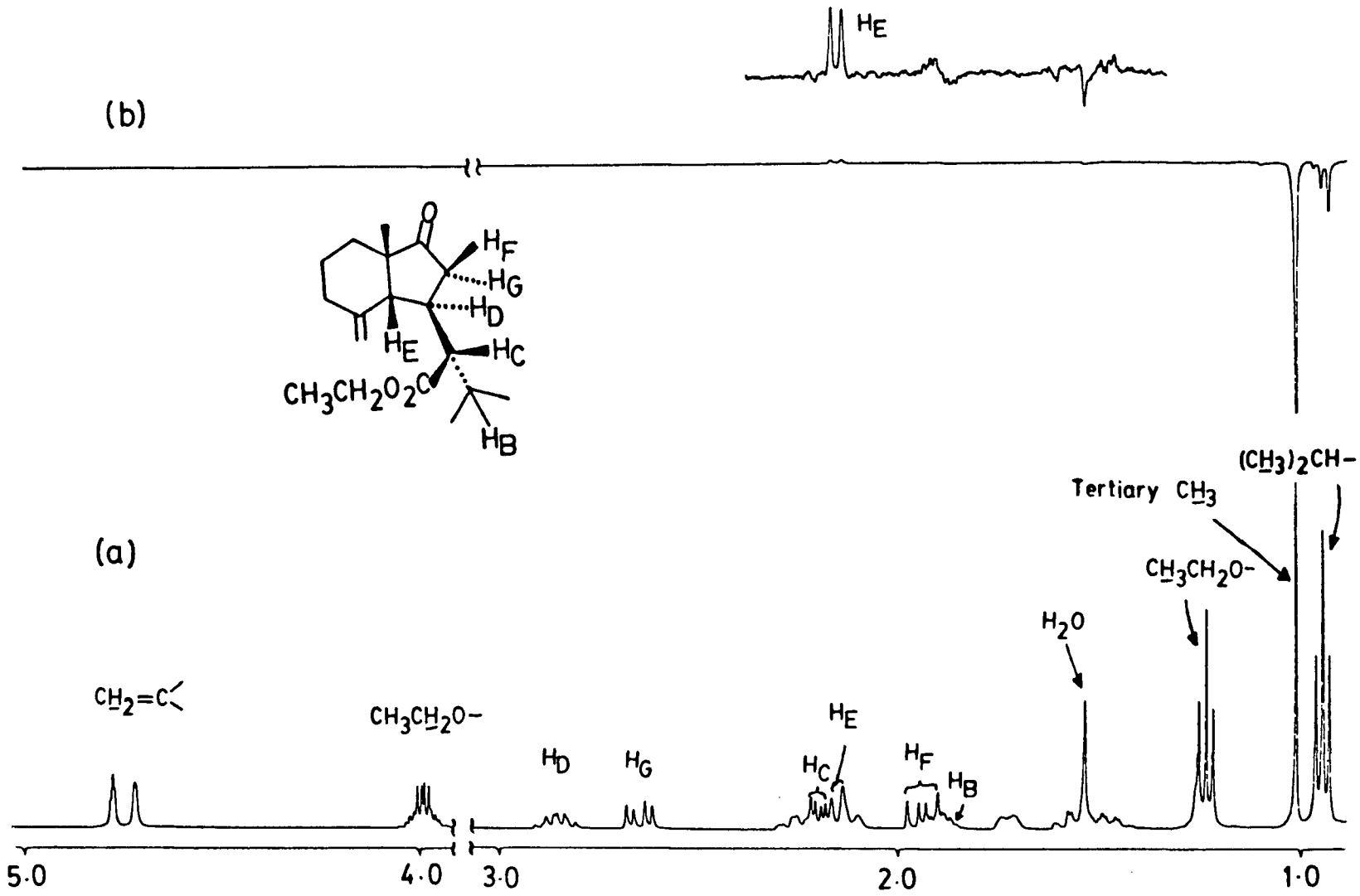


Fig. 3: The nOe difference experiment with (204):
(a) the normal 400 MHz ^1H spectrum, and (b) the nOe difference spectrum with irradiation at δ 1.01 (ring junction methyl group).

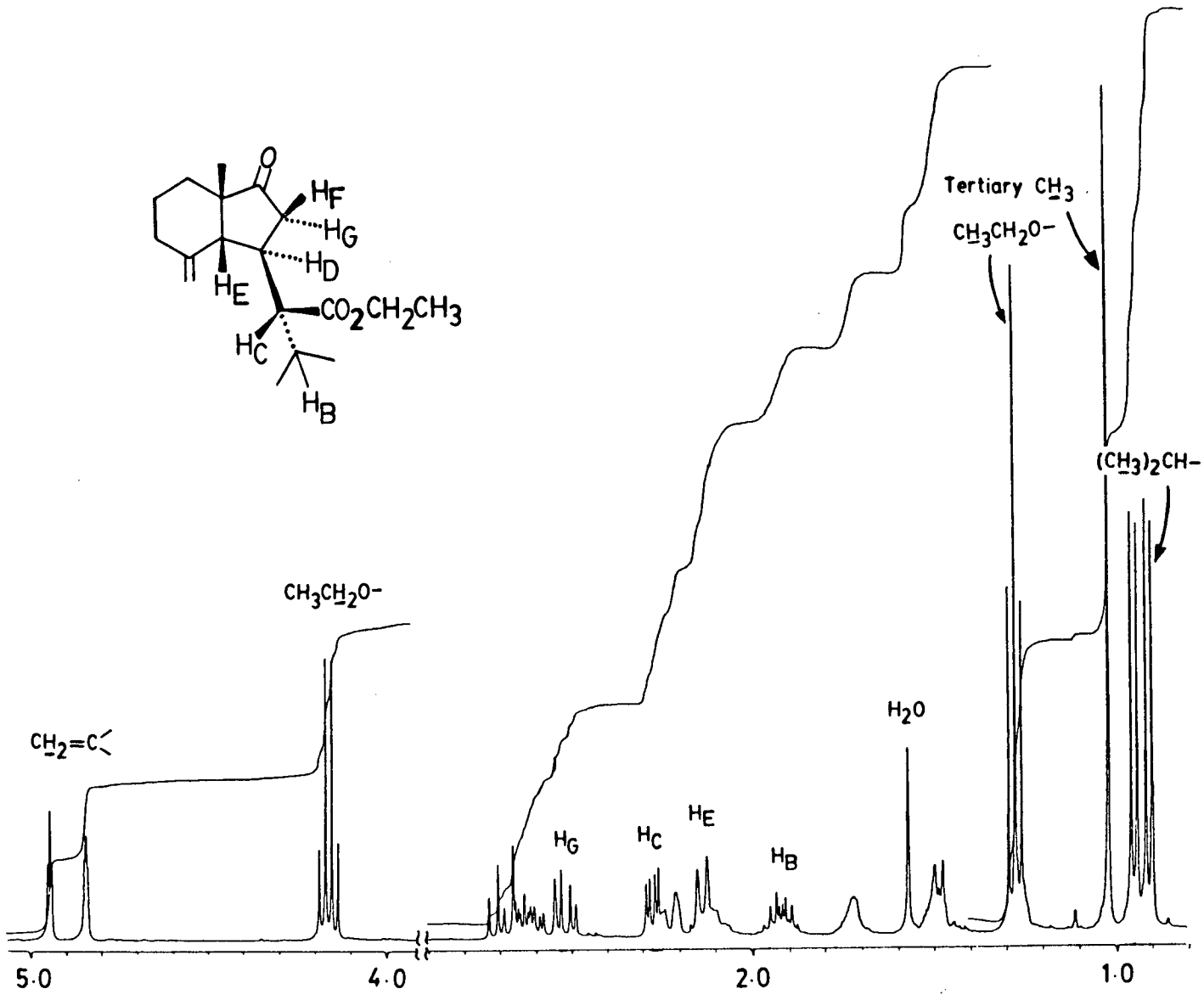
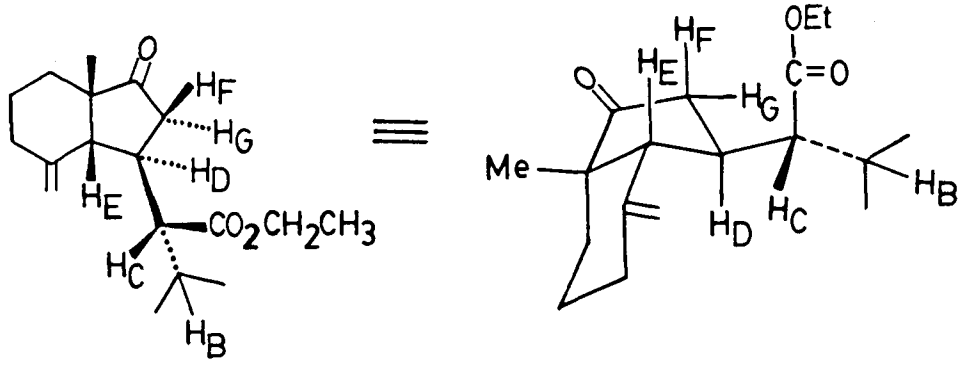


Fig 4: The 400 MHz ^{1}H nmr spectrum of (205)

(-$OCH_2\underline{C}H_3$, $\underline{J}$ = 7 Hz), a one-proton multiplet at δ 1.84-2.00 (H_B), a partially obscured one-proton doublet at δ 2.30 (H_E, $\underline{J}$ = 11 Hz), two one-proton doublet of doublets at δ 2.28 ($\underline{J}$ = 10, 4 Hz) and 2.52 ($\underline{J}$ = 17, 7 Hz) (H_C and H_G, respectively), a two-proton quartet at δ 4.16 (-$O\underline{C}H_2CH_3$, $\underline{J}$ = 7 Hz), and two one-proton triplets at δ 4.84 ($\underline{J}$ = 1.5 Hz) and 4.94 ($\underline{J}$ = 2 Hz) (=$C\underline{H}_2$).

Assignment of the signal at δ 2.52 (d of d, $\underline{J}$ = 17, 7 Hz) to H_G was based on the chemical shift and coupling constants associated with this resonance. In what appears to be the most stable conformation of (205), the H_G-H_D dihedral angle is about 30°, while the H_F-H_D dihedral angle is close to 180°. The observed coupling constants (17 Hz-geminal coupling; 7 Hz-vicinal coupling) are consistent with H_G having the configuration shown in (205). The other proton (H_F) adjacent to the ketone function was not clearly observed in the ^1H nmr spectrum of (205).



205

When the isopropyl methyl signals at δ 0.91 and 0.95 were both decoupled, the multiplet at δ 1.84-2.00 due to H_B collapsed to a doublet ($\underline{J}$ = 10 Hz) (Figure 5). Decoupling H_B caused the signals due to the isopropyl methyl groups at δ 0.91 and 0.95 to collapse to singlets

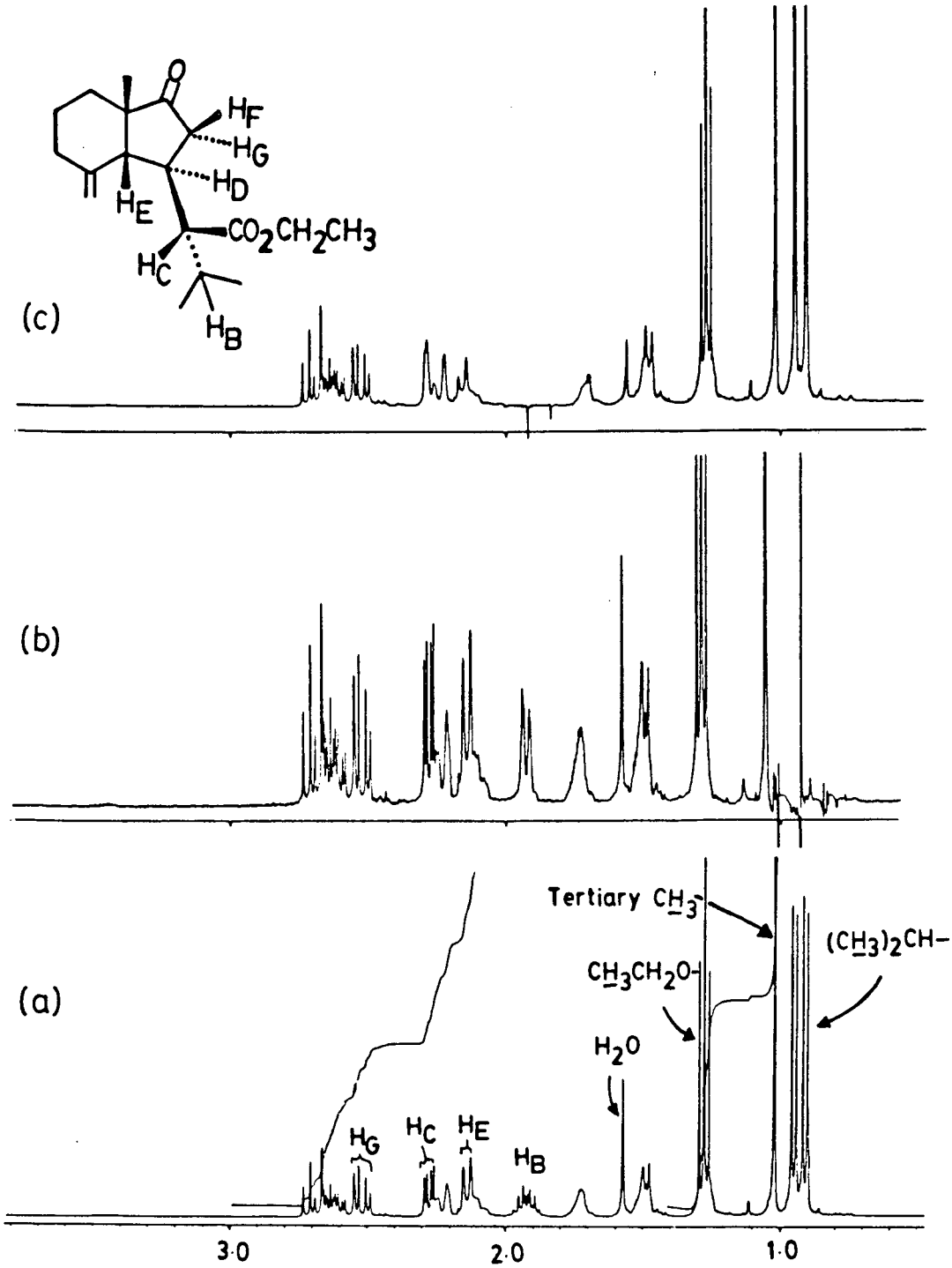


Fig. 5: The homonuclear spin decoupling experiments with (205): (a) the normal 400 MHz ^1H nmr spectrum for the region δ 0.8-3.0, and the spectra with irradiations at (b) δ 0.92 (isopropyl methyl groups), and (c) δ 1.91 (H_B).

(Figure 5). In the same experiment, the doublet of doublets due to H_C at δ 2.28 collapsed to a very broad singlet* (Figure 5). In a nOe difference experiment, in which the signal at δ 1.03 (bridgehead methyl singlet) was irradiated, enhancement of a signal at δ 2.30 (d, $\underline{J}$ = 11 Hz), which was partially obscured, was observed (Figure 6). On the basis of chemical shift and spin-spin coupling pattern, the latter resonance was assigned to H_E. Thus, the expectation that (205) possessed a <u>cis</u>-fused ring junction was confirmed. The <u>trans</u> relationhsip of protons H_E and H_D was indicated by the coupling constant, J_{ED} = 11 Hz. In what appears to be the most stable conformation of (205), the dihedral angle between the <u>trans</u>-related protons H_E and H_D is close to 180° and, thus, the observed coupling constant is consistent with the assigned stereochemistry.

Up to this point, assignment of the stereochemistry at C-10 for both compounds (204) and (205) was not possible. However, it was found later that compound (204) was related configurationally to (±)-axamide-1 (174) and (±)-axisonitrile-1 (173). Therefore, for the sake of clarity, structural formulas (204) and (205) show the correct relative stereochemistry of these two substances.

---

* Theoretically, the signal due to H_C should have collapsed to a doublet (J_{CD} = 4 Hz) when H_B was decoupled. However, a very broad singlet was obtained due to insufficient resolution in the spectrum and, probably, the interference of the other partially overlapping multiplet.

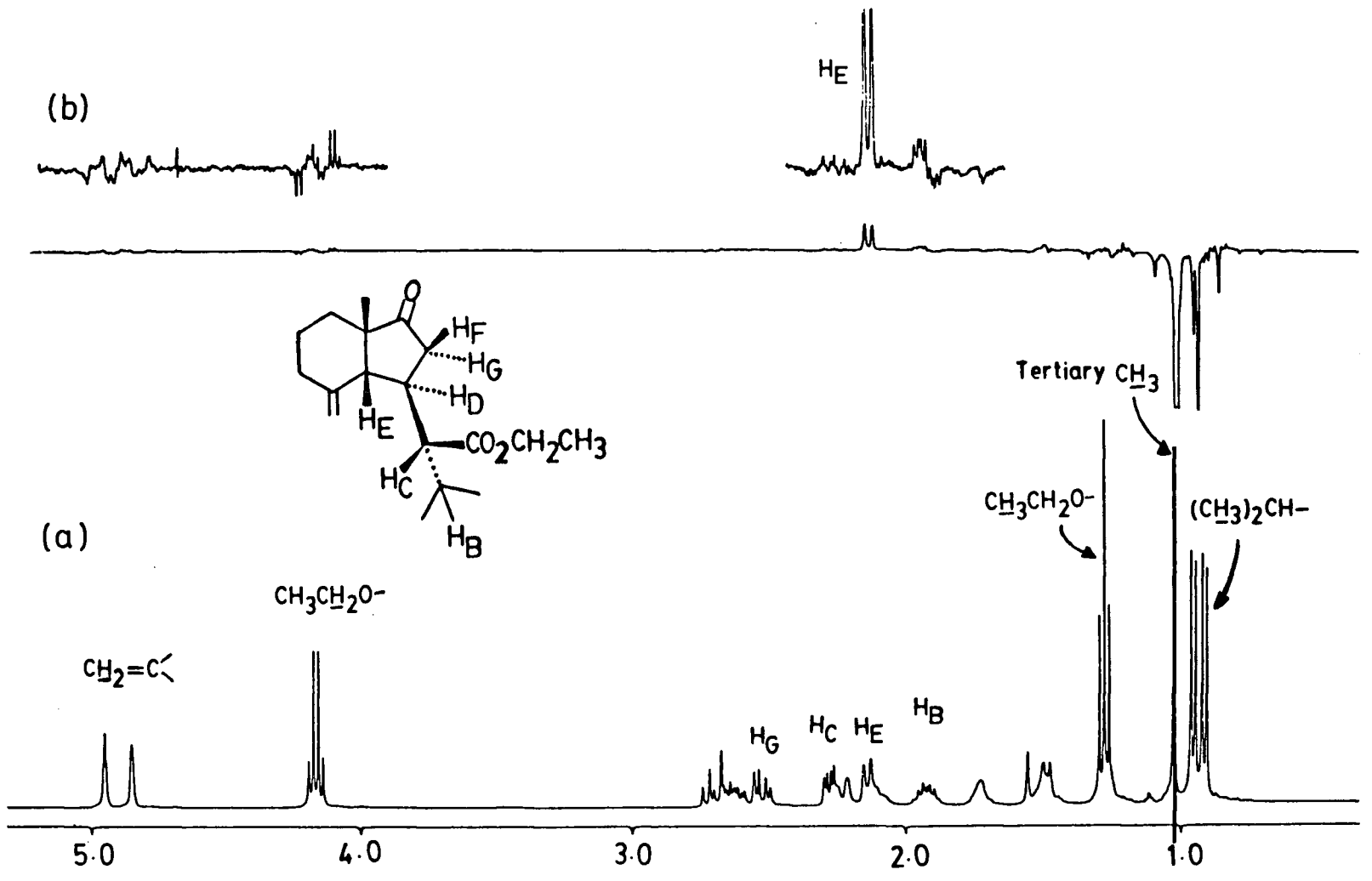
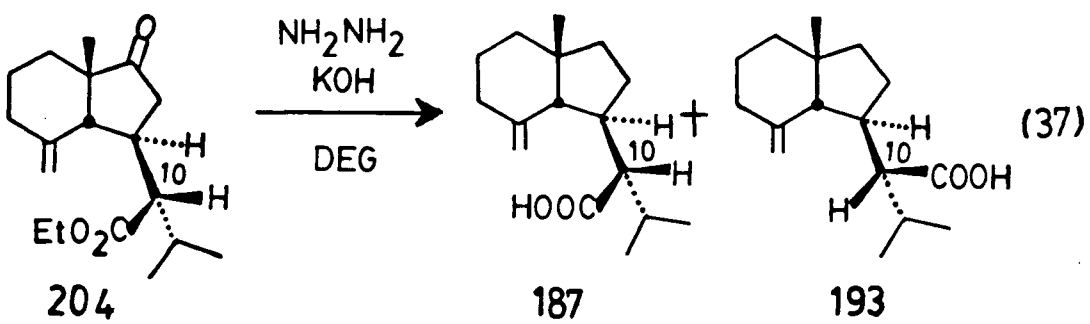


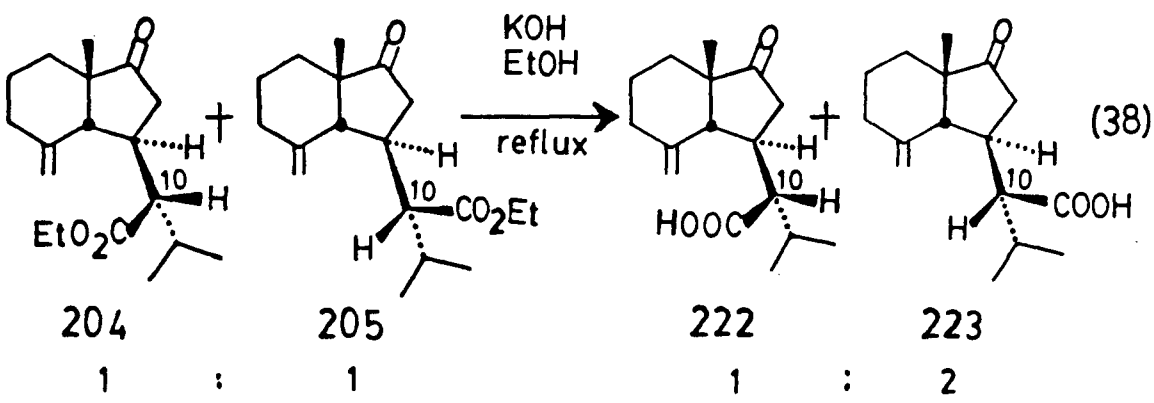
Fig. 6: The nOe difference experiment with (205):
(a) the normal 400 MHz ^1H nmr spectrum, and (b) the nOe difference spectrum with irradiation at δ 1.03 (ring junction methyl group).

It appeared that Wolff-Kishner reduction would be a suitable method for removal of the ketone function from (204). Presumably, the reaction conditions associated with this reaction would cause concommitant hydrolysis of the ester group. Reaction of the pure keto ester (204) with anhydrous hydrazine and potassium hydroxide in ethylene glycol[71] produced a mixture of acids in 61% yield [ir: ν_{max} 3500-2500 cm^{-1} (br), 1702 cm^{-1}]. In the ^1H nmr spectrum of this mixture, the olefinic protons gave rise to a broad singlet at δ 4.67, a broad singlet at δ 4.74, and a triplet at δ 4.80 ($\underline{J}$ = 2 Hz). The relative integrated areas of these signals were nearly equal. It was found later that the signal at δ 4.67 was related to the olefinic protons of the acid (187), while the signals at δ 4.74 and 4.80 were related to the olefinic protons of the acid (193). Therefore, a 1:2 mixture of the acids (187) and (193), respectively, was produced from the Wolff-Kishner reduction of (204) (equation 37). Clearly, partial epimerization at C-10 of (204) had occurred under the reaction conditions employed. The two products (187) and (193), could not be separated by column chromatography on silica gel.



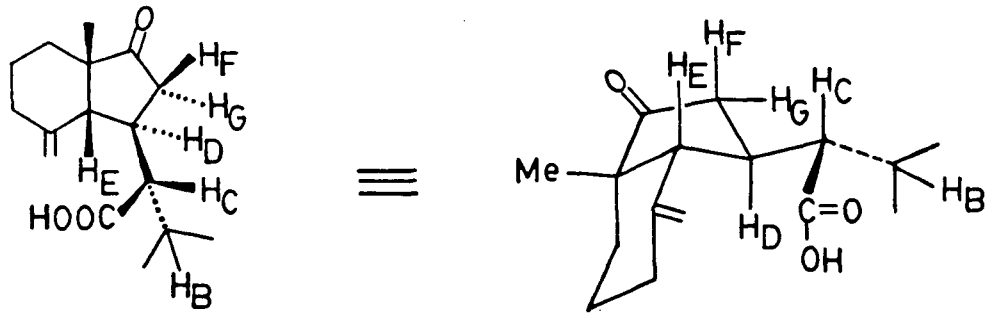
204 187 193 (37)

When a mixture of the ethyl esters (204) and (205) (ratio ~1:1) was subjected to base hydrolysis (KOH, EtOH, reflux, 2 days), a mixture of two compounds was obtained (equation 38). The ir spectrum of this mixture exhibited a broad absorption at 3400-2500 cm^{-1}, which was attributed to the O-H stretching vibration of a carboxylic acid. In the same ir spectrum, two carbonyl absorptions at 1735 cm^{-1} and 1703 cm^{-1} were observed. The former absorption was attributed to a cyclopentanone type carbonyl group, while the latter peak was attributed to a carboxylic acid type carbonyl group. In the ^1H nmr spectrum of the product mixture, the olefinic protons gave rise to a triplet at δ 4.76 ($\underline{J}$ = 1.5 Hz), a broad singlet at δ 4.80, a broad singlet at δ 4.88, and a triplet at δ 4.94 ($\underline{J}$ = 2 Hz). The relative integrated areas of these signals were 1:1:2:2, respectively. It was found later that the signals at δ 4.76 and 4.80 were related to the olefinic protons of the keto acid (222), while the signals at δ 4.88 and 4.94 were related to the olefinic protons of keto acid (223). Thus, a 1:2 mixture of the keto acids (222) and (223) was produced from the base hydrolysis of the 1:1 mixture of esters (204) and (205). Again, partial epimerization at C-10 of compound (204) had occurred.



Fortunately, the mixture of (222) and (223) could be separated by a combination of (repeated) column chromatography on silica gel (elution with 3:2 petroleum ether-ether) and fractional crystallization from ether, to give the pure keto acid (222) in 21% yield and the pure keto acid (223) in 50% yield. The remaining material (11%) consisted of a mixture of (222) and (223).

The ir spectrum of (222) (mp 172-173°C, recrystallization from ether) exhibited carbonyl absorptions at 1735 and 1703 cm^{-1} and a broad O-H stretching absorption at 3400-2500 cm^{-1}. The ^1H nmr spectrum of (222) (Figure 7) was very similar to that of the corresponding ethyl ester (204) (Figure 1). Thus, the following signals were observed in the ^1H nmr spectrum of (222): a pair of doublets at δ 0.93 and 1.05 (isopropyl methyl groups, J = 7 Hz in each case), a singlet at δ 1.00 (tertiary methyl group), an obscured one-proton multiplet at δ 1.86-2.00 (H_B), a partially obscured one-proton doublet of doublets at δ 1.94 (H_F, J = 18.5, 11.5 Hz), a partially obscured one-proton broad doublet at δ 2.16 (H_E, J = 10.5 Hz), a partially obscured one-proton doublet of doublets at δ 2.21 (H_C, J = 9.5, 4.5 Hz), a one-proton doublet of



222

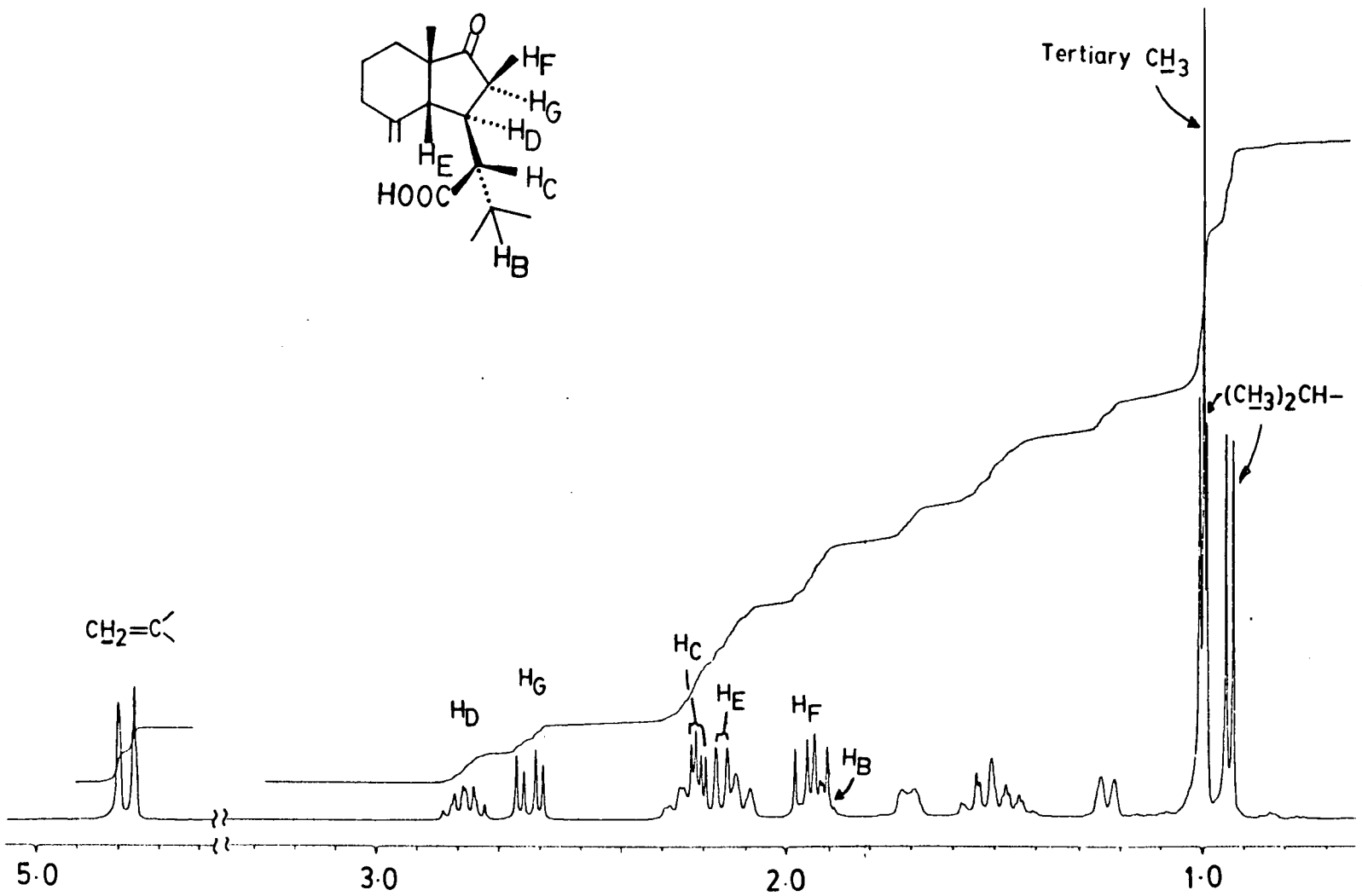


Fig. 7: The 400 MHz ^{1}H nmr spectrum of (222)

doublets at δ 2.62 (H_G, $\underline{J}$ = 18.5, 7.5 Hz), and a one-proton multiplet at δ 2.71-2.85 (H_D). Furthermore, the olefinic protons gave rise to a triplet at δ 4.76 ($\underline{J}$ = 1.5 Hz) and a broad singlet at δ 4.80.

The signals at δ 1.94 (d of d, $\underline{J}$ = 18.5, 11.5 Hz) and 2.62 (d of d, $\underline{J}$ = 18.5, 7.5 Hz) were assigned to the strongly coupled geminal protons H_F and H_G, respectively. These assignments were based partially on an examination of a molecular model, which showed that, in what appears to be the most stable conformation of (222), the H_F-H_D dihedral angle approximates 180° whereas the H_G-H_F dihedral angle is close to 30°. The coupling between H_F and H_G was confirmed by a decoupling experiment. Thus, irradiation at δ 2.62 (H_G) simplified the signal at δ 1.94 (H_F)* (Figure 8). In the same decoupling experiment, the signal due to H_D at δ 2.71-2.85 also simplified (Figure 8). When H_D was decoupled, the signals due to H_F and H_G at δ 1.94 and 2.62 collapsed to "imperfect" doublets** ($\underline{J}$ = 18.5 Hz in each case) (Figure 8). In the same decoupling experiment, the signals due to H_E and H_C collapsed to broad

---

* When H_G was decoupled, the signals due to H_F should have collapsed to a doublet ($\underline{J}_{DF}$ = 11.5 Hz). However, since the signal due to H_B overlapped with that of H_F, the collapsed doublet of H_F was not distinctly observed.

** When H_D was decoupled, the signals due to H_F and H_G should have collapsed to doublets with $\underline{J}_{FG}$ = 18.5 Hz in each case. However, the formation of "imperfect" doublets for H_F and H_G was due to incomplete decoupling in the decoupling experiment.

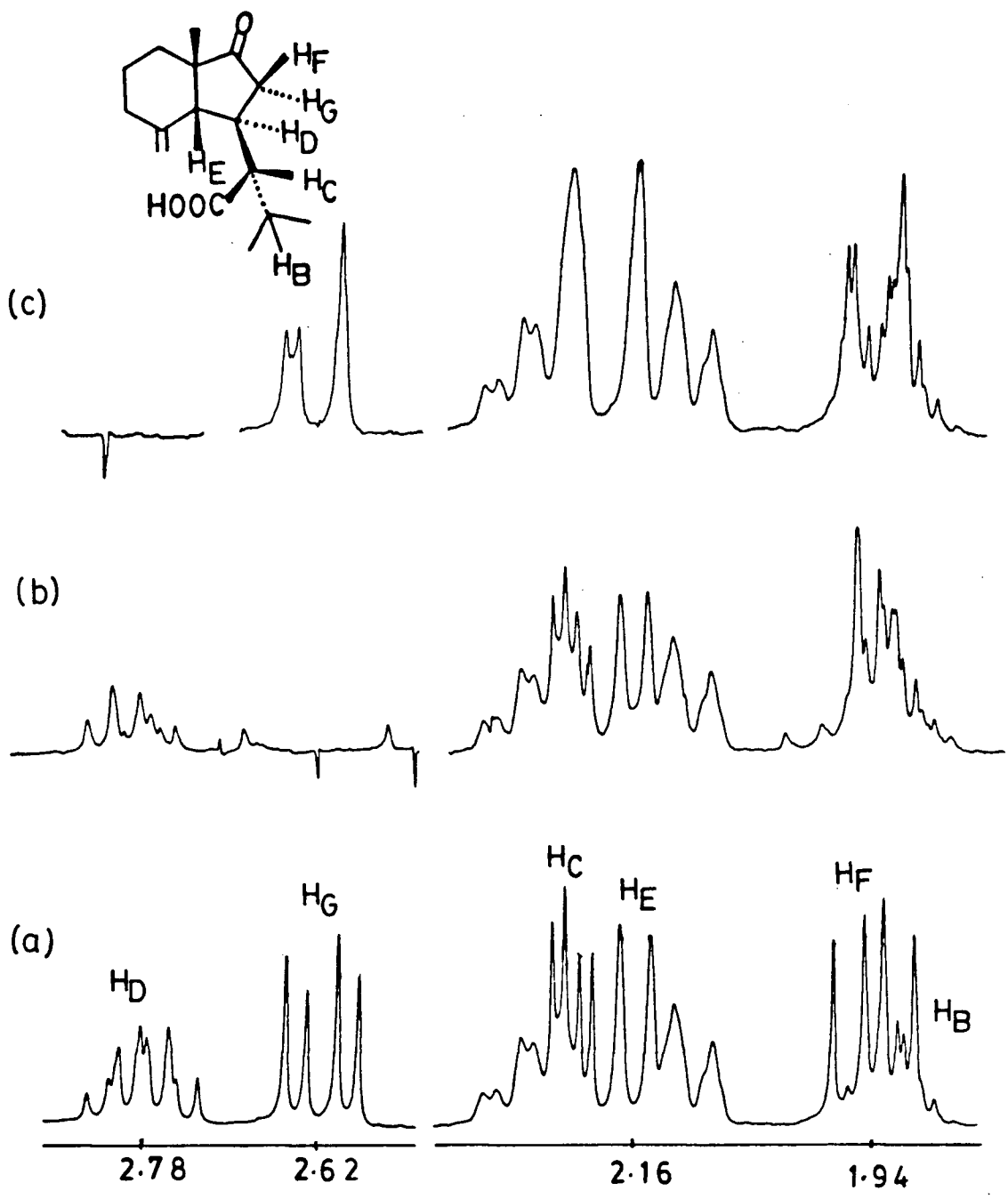
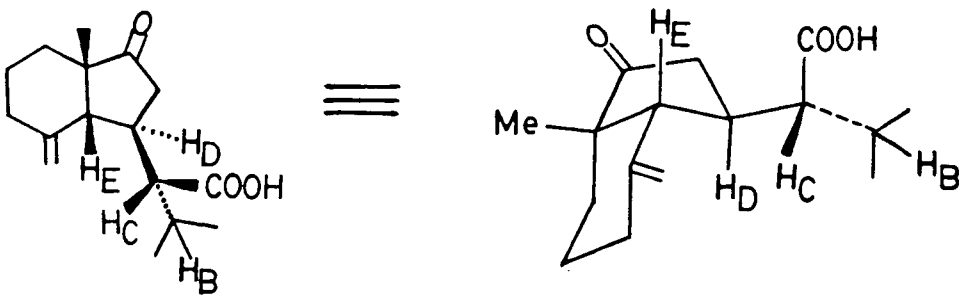


Fig. 8: The homonuclear spin decoupling experiments with (222): (a) the normal 400 MHz ^{1}H spectrum expanded for the region δ 1.8-2.9, and the spectra with irradiations at (b) δ 2.62 (H_G), and (c) δ 2.78 (H_D).

singlets* (Figure 8). The observed coupling constant between H_E and H_D (J_{ED} = 10.5 Hz) was consistent with the assigned stereochemistry since, in what appears to be the most stable conformation of (222), the dihedral angle between the trans-related protons H_E and H_D is close to 180°.

The keto acid (223) (mp 120-121°C, recrystallization from petroleum ether-ether) showed carbonyl absorptions at 1733 and 1703 cm^{-1} and a broad O-H stretching absorption at 3400-2500 cm^{-1} in its ir spectrum. The ^1H nmr spectrum of (223) (Figure 9) exhibited a pair of doublets at δ 0.95 and 0.96 (isopropyl methyl groups, J = 6.5 Hz in each case), a singlet at δ 1.03 (tertiary methyl group), a one-proton multiplet at δ 1.86-1.99 (H_B), a one-proton broad doublet at δ 2.22 (H_E, J = 10.5 Hz), a one-proton doublet of doublets at δ 2.32 (H_C, J = 9.5, 3.5 Hz) and a three-proton multiplet at δ 2.46-2.70. Furthermore, the olefinic



223

---

* When H_D was decoupled, the signal due to H_C should have collapsed to a doublet with J_{BC} = 4.5 Hz. However, because of the presence of a partially overlapping multiplet, the collapsed doublet of H_C was only seen as a very broad singlet.

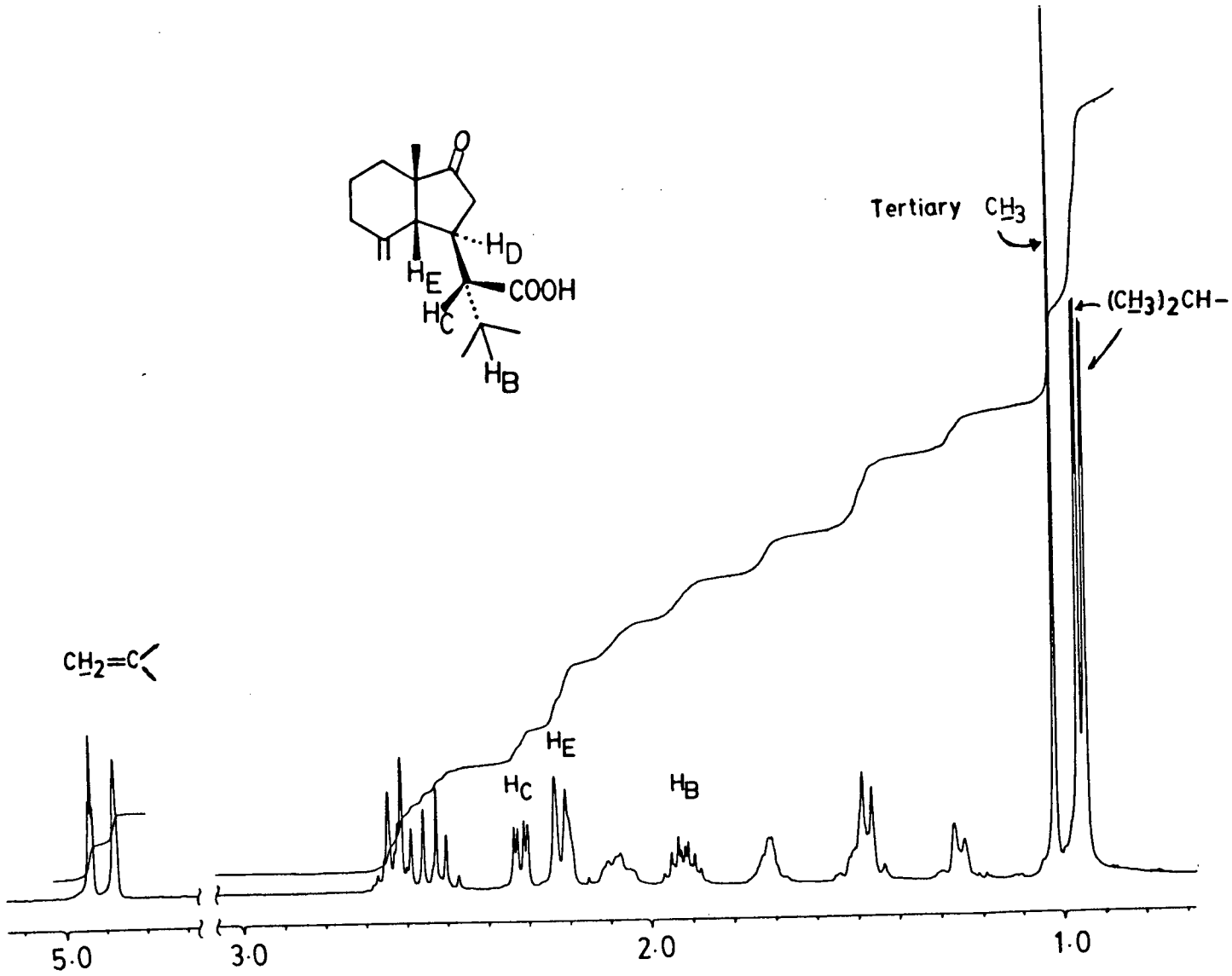


Fig. 9: The 400 MHz ^{1}H nmr spectrum of (223)

protons gave rise to a broad singlet at δ 4.88 and a triplet (J = 2 Hz) at δ 4.94. When the isopropyl methyl groups were both irradiated, the signal at δ 1.86-1.99 due to H_B collapsed to a doublet (J = 9.5 Hz) (Figure 10). When H_B was decoupled, the doublets due to the isopropyl methyl groups at δ 0.95 and 0.96 collapsed to singlets. In the same decoupling experiment, the signal due to H_C at δ 2.32 collapsed to a very broad singlet* (Figure 10). When H_C was decoupled, the signal due to H_B at δ 1.86-1.99 collapsed to a septet (J = 6.5 Hz), and the three-proton multiplet at δ 2.46-2.70, which presumably contained the proton H_D, simplified. The assignment of the signal at δ 2.22 to H_E was based on the chemical shift and spin-spin coupling pattern of this resonance and on a comparison of the ^1H nmr spectrum of (223) with that of the corresponding ethyl ester (205). Once more, the observed coupling constant between H_E and H_D (J_{ED} = 10.5 Hz) was consistent with the assigned stereochemistry since, in what appears to be the most stable conformation of (223), the dihedral angle between the *trans*-related protons H_E and H_D is close to 180°.

At this stage, there was still no information available concerning the stereochemistry at C-10 for (222) and (223). Thus, the assigned stereochemistries were based on the fact that (222) was eventually converted into (±)-axamide-1 (174) and (±)-axisonitrile-1 (173), while (223) was converted into the corresponding C-10-*epi* compounds (224) and (225), respectively.

---

* When H_B was decoupled, the signal due to H_C should have collapsed to a doublet (J_{CD} = 3.5 Hz).

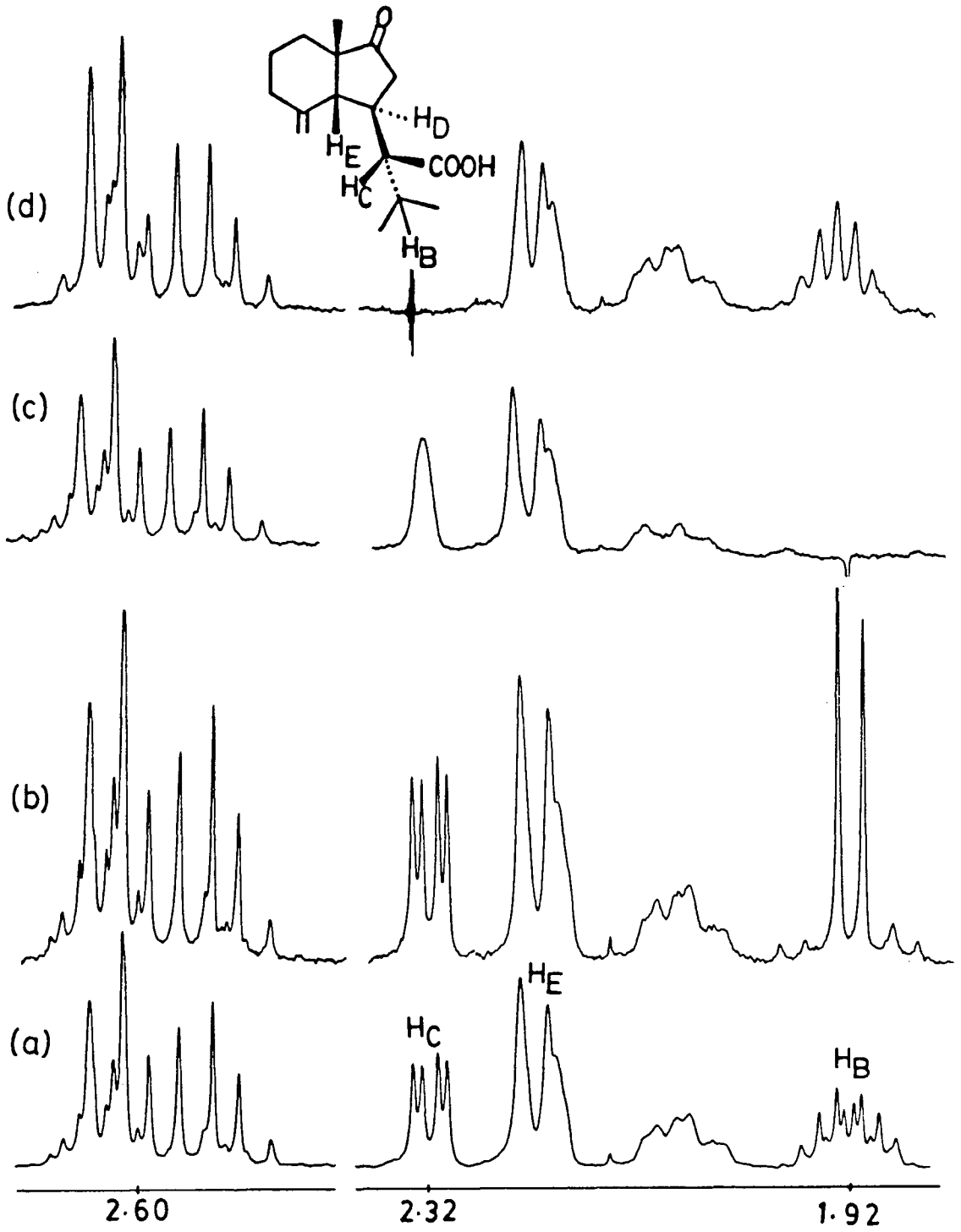
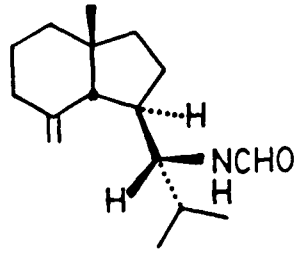
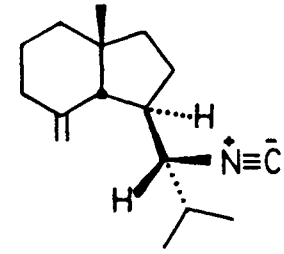


Fig. 10: The honomuclear spin decoupling experiments with (223): (a) the normal 400 MHz ^1H nmr spectrum expanded for the region δ 1.8-2.8, and the spectra with irradiations at (b) δ 0.95 (isopropyl methyl groups), (b) δ 1.92 (H_B), and (c) δ 2.32 (H_C).



224



225

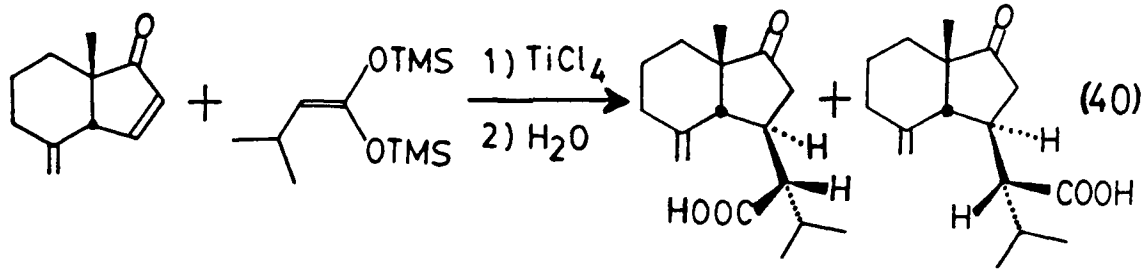
Presumably, under conditions of the Wolff-Kishner reduction, epimerization adjacent to a carboxylic acid function would be slower than that adjacent to the corresponding ester. Therefore, it would be desirable to generate the keto acids (222) and (223) directly from the enone (203). It was felt that this transformation could be done by reaction of the latter material with the bis(trimethylsilyl) ketene acetal (226). Although reactions of bis(trialkylsilyl) ketene acetals with aldehydes,[80,81] Schiff bases[81] and halides[82] in the presence of Lewis acid were known, conjugate additions of these reagents to enones were, to our knowledge, not carried out prior to our work. Recently, RajanBabu reported that 1,1-bis(trimethylsiloxy)-1-propene did not add to 2-cyclopenten-1-one in nitromethane at room temperature.[69d]

Reaction of 3-methylbutanoic acid (227) with 2.2 equivalents of LDA in THF, followed by successive addition of HMPA and trimethylsilyl chloride, gave 3-methyl-1,1-bis(trimethylsiloxy)-1-butene (226) in 86% yield (equation 39). The ^1H nmr spectrum of (226) exhibited two nine-proton singlets at δ 0.20 and 0.22 for the two trimethylsilyl ($-SiMe_3$) groups, while the vinyl proton gave rise to a doublet at δ 3.42 ($\underline{J}$ = 8 Hz).

Addition of the bis(trimethylsilyl) ketene acetal (226) to the

227 226 (39)

enone (203) in the presence of titanium tetrachloride gave a ~3:2 mixture of the keto acids (222) and (223) in 93% yield (equation 40). The ratio of the two products was deduced from the ^1H nmr spectrum of



(40)

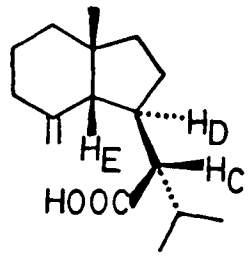
203 226 222 223

the mixture by careful integration of the resonance signals due to the olefinic protons. Thus, the spectrum exhibited four signals at δ 4.76 (t, $\underline{J}$ = 1.5), 4.80 (br s), 4.88 (br s), and 4.94 (t, $\underline{J}$ = 2 Hz). The relative integrated areas of these resonances were found to be 3:3:2:2, respectively. Since pure samples of compound (222) and (223) had been obtained previously (vide supra), it was known that the two signals at δ 4.76 and 4.80 were due to the olefinic protons of the keto acid (222), while the signals at δ 4.88 and 4.94 arose from the olefinic protons of the keto acid (223).

The mixture of (222) and (223) was separated by a combination of (repeated) column chromatography on silica gel (elution with 3:2 petro-

leum ether-ether) and fractional crystallization from ether. In this manner, the pure keto acid (222) was obtained in 44% yield, while the pure keto acid (223) was acquired in 32% yield. The remaining material (12%) consisted of a mixture of (222) and (223). The isolated pure keto acids (222) and (223) exhibited ^1H nmr spectra identical with those described before.

Wolff-Kishner reduction[71] of the pure keto acid (222) (NH_2NH_2, KOH, DEG) gave, in 90% yield, the pure acid (187) without any observable

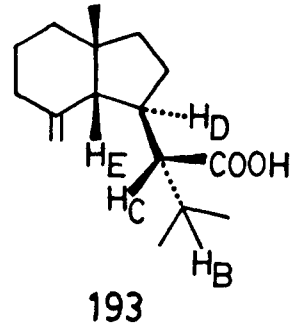


187

epimerization (^1H nmr spectroscopy). The acid (187) (mp 120-121°C, recrystallization from petroleum ether-ether) exhibited a broad O-H stretching absorption at 3500-2500 cm^{-1} and a carbonyl absorption at 1703 cm^{-1} in its ir spectrum. The ^1H nmr spectrum of (187) showed a pair of doublets at δ 0.96 and 0.97 (isopropyl methyl groups, $\underline{J}$ = 7 Hz in each case), a singlet at δ 0.94 (tertiary methyl group), a six-proton multiplet at δ 1.35-1.66, a one-proton broad doublet at δ 1.86 (H_E, $\underline{J}$ = 10.5 Hz), a three-proton multiplet at δ 1.90-2.07, a one-proton doublet of doublets at δ 2.10 (H_C, $\underline{J}$ = 9.5, 5 Hz), and a one-proton multiplet at δ 2.46-2.58 (H_D). Additionally, the olefinic protons gave rise to a broad singlet at δ 4.67. When H_D was decoupled, the signal due to H_E at δ 1.86 collapsed to a singlet while the signal due to H_C at δ 2.10

collapsed to a doublet (J = 5 Hz). In the same decoupling experiment, the multiplets at δ 1.35-1.66 and δ 1.90-2.07 simplified.

The keto acid (223) was converted into the acid (193) (an oil) (90%) *via* the same reaction conditions as those employed for the transformation of (222) into (187).[71] The ir spectrum of (193) showed a broad O-H stretching absorption at 3500-2500 cm^{-1} and a carbonyl absorption at 1702 cm^{-1}. The ^1H nmr spectrum of (193) exhibited a pair of doublets at δ 0.93 and 0.94 (isopropyl methyl groups, J = 7 Hz in each case), a singlet at δ 0.95 (tertiary methyl group), a partially obscured broad doublet at δ 1.91 (H_E, J = 11 Hz), a partially obscured multiplet at δ 1.96-2.08 (H_B), a doublet of doublets at δ 2.18 (H_C, J = 9, 5 Hz), and a one-proton multiplet at δ 2.40-2.50 (H_D). Furthermore, the olefinic protons gave rise to a broad singlet at δ 4.74 and a triplet (J = 2 Hz) at δ 4.80. When the isopropyl methyl groups were both decoupled, the signal due to H_B at δ 1.96-2.08 collapsed to a doublet (J = 9 Hz). When H_C was decoupled, the signals due to H_D and H_B at δ 2.40-2.50 and δ 1.96-2.08 simplified. When H_D was decoupled, the signal due to H_E at δ 1.91 collapsed to a broad singlet and the signal due to H_C at δ 2.18 collapsed to a doublet (J = 9 Hz).



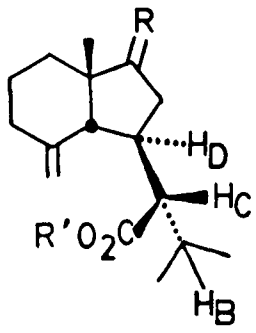
193

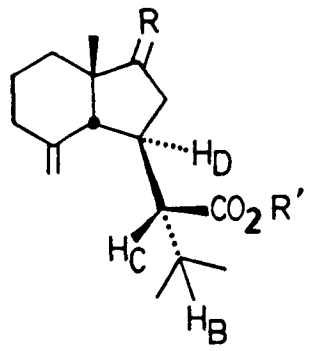
At this point, it is interesting to compare some of the ^1H nmr spectral data of compounds (204), (222) and (187), with those of the corresponding epimers (205), (223) and (193), respectively (Table IV). The signals due to H_B and H_C (δ 1.84-2.00 and 2.28, respectively) in compound (205) have chemical shifts very similar to those (δ 1.82-1.95 and 2.20, respectively) of H_B and H_C in the corresponding epimer (204). Similar observations could be made for the other two pairs of epimers (222)-(223) and (187)-(193) (see Table IV).

Of more interest, however, were the coupling constants J_{BC} and J_{CD} in the two series of epimeric compounds. Thus, for compounds (204), (222) and (187) the coupling constants J_{BC} and J_{CD} were found to be 4.5-5 Hz and 9.5-10 Hz respectively. On the other hand, for the series of epimeric compounds [(205), (223), (193), respectively], J_{BC} and J_{CD} were found to be 9-10 Hz and 3.5-5 Hz, respectively.

A careful examination of molecular models indicates that the observed coupling constants can be rationalized on the basis of conformational analysis. Furthermore, such an analysis, along with the ^1H data provides some evidence regarding the stereochemistry at C-10 of the two series of epimeric compounds. It is postulated that compounds (204), (222) and (187) exist largely in the conformation shown in (235), while the epimeric substances (205), (223) and (193) adopt primarily the conformation represented by (236). Thus, it is proposed that for both series of compounds, the preferred conformation is that in which the bulky isopropyl group is <u>anti</u> to C-8, with the methine proton (H_B) close to C-2 as shown in (235) and (236). In (235), the H_C-H_D dihedral angle approximates 180° while the H_B-H_C dihedral angle is close to 60°. On

Table IV: Partial ^1H nmr Spectral Data for Compounds (204), (205), (222), (223), (187) and (193).*



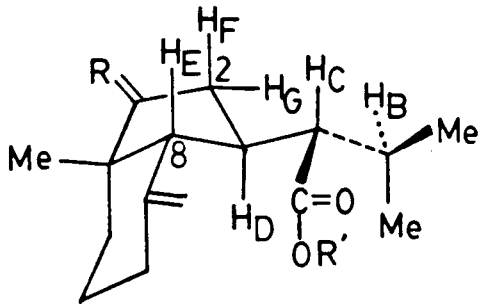


	(204) (R=O, R'=Et)	(205) (R=O, R'=Et)
δH_B	1.82-1.95 (m)	1.84-2.00 (m)
δH_C	2.20 (dd)	2.28 (dd)
δH_D	2.79-2.93 (m)	not clearly observed
J_{BC}	4.5	10
J_{CD}	10	4

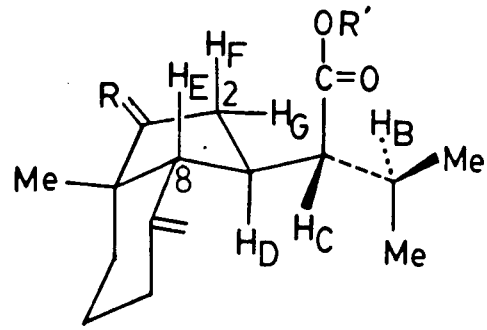
	(222) (R=O, R'=H)	(223) (R=O, R'=H)
δH_B	1.86-2.00 (m)	1.86-1.99 (m)
δH_C	2.21 (dd)	2.32 (dd)
δH_D	2.71-2.85 (m)	not clearly observed
J_{BC}	4.5	9.5
J_{CD}	9.5	3.5

	(187) (R=CH_2, R'=H)	(193) (R=CH_2, R'=H)
δH_B	not clearly observed	1.96-2.08 (m)
δH_C	2.10 (dd)	2.18 (dd)
δH_D	2.46-2.58 (m)	2.40-2.50 (m)
J_{BC}	5	9
J_{CD}	9.5	5

* All coupling constants were given in Hertz (Hz) and were determined by appropriate decoupling experiments (see text).



235

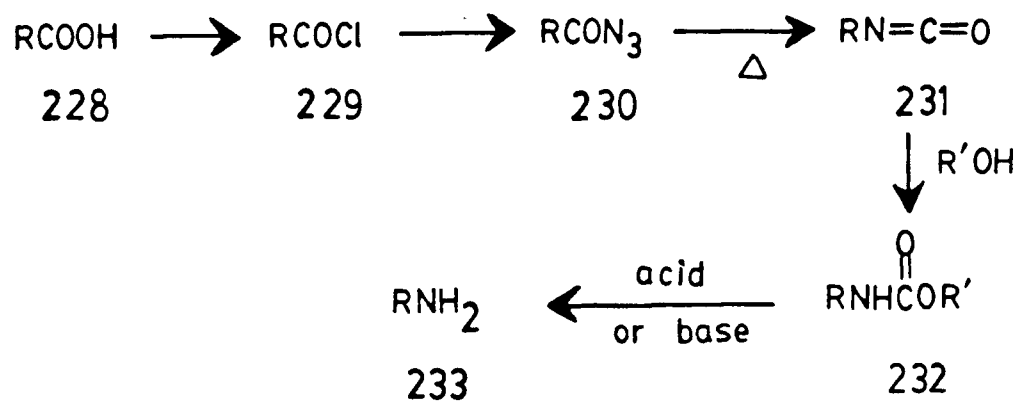


236

R = O, CH_2
R' = Et, H

the other hand, in (236), the H_C-H_D dihedral angle approximates 60°, while the H_B-H_C dihedral angle is close to 180°. Therefore, for one series of compounds, represented by conformation (235), one would expect a relatively large value for J_{CD} and a small value for J_{BC}. On the other hand, for the compounds possessing conformation (236), J_{CD} and J_{BC} would be expected to be quite small and relatively large, respectively. The fact that the magnitudes of the various coupling constants (see Table IV) were consistent with these expectations provides reasonable evidence for the stereochemical assignments.

Conversion of the carboxylic acids (187) and (193) into the corresponding amines would be achieved *via* a sequence of reactions outlined in Scheme 25.[64] Recently, Poulter[83] reported that an isocyanate generated by Curtius rearrangement of an acyl azide could be trapped efficiently with 2-trimethylsilylethanol. Treatment of the resultant carbamate with tetra-*n*-butylammonium fluoride affords the corresponding amine in good yield. This mild and essentially neutral method for cleavage of the carbamate avoids use of the strongly acidic or strongly basic conditions that are normally required for carbamate

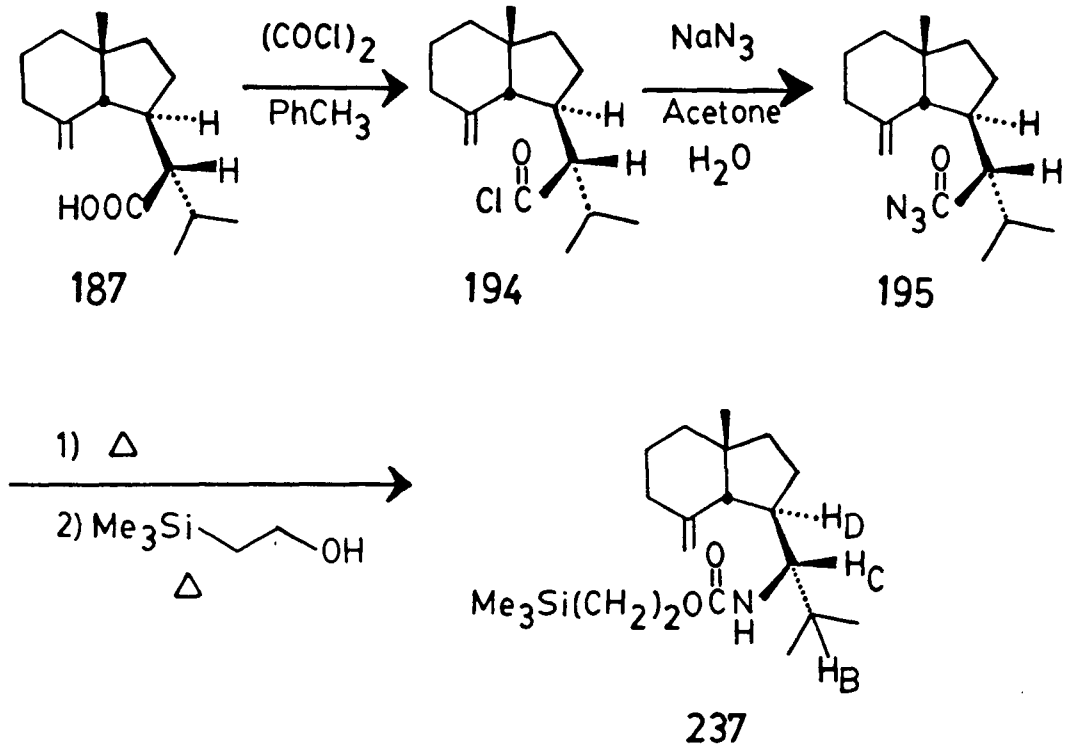


Scheme 25

hydrolysis.[64] Therefore, this method was adopted for the synthesis of the amines (186) and (234).

The carboxylic acid (187) was converted via the acid chloride (194) into the acyl azide (195). Curtius rearrangement of the latter substance, followed by treatment of the resultant isocyanate with 2-trimethylsilylethanol, afforded the crystalline carbamate (237) (mp 79.5-80.5°C, recrystallization from petroleum ether) in a yield of 89% from (187) (Scheme 26).

A carbonyl absorption at 1709 cm^{-1} and a N-H stretching absorption at 3446 cm^{-1} were observed in the ir spectrum of (237). The ^1H nmr spectrum of (237) exhibited a nine-proton singlet at δ 0.05 ($SiMe_3$ group), a pair of doublets at δ 0.73 and 0.87 (isopropyl methyl groups, J = 7 Hz in each case), a singlet at δ 0.91 (tertiary methyl group), and a triplet at δ 0.97 ($-CH_2\underline{CH_2}SiMe_3$, J = 8.5 Hz), a multiplet at δ 1.77-1.88 (H_B), a multiplet at δ 2.20-2.31 (H_D), a triplet of doublets

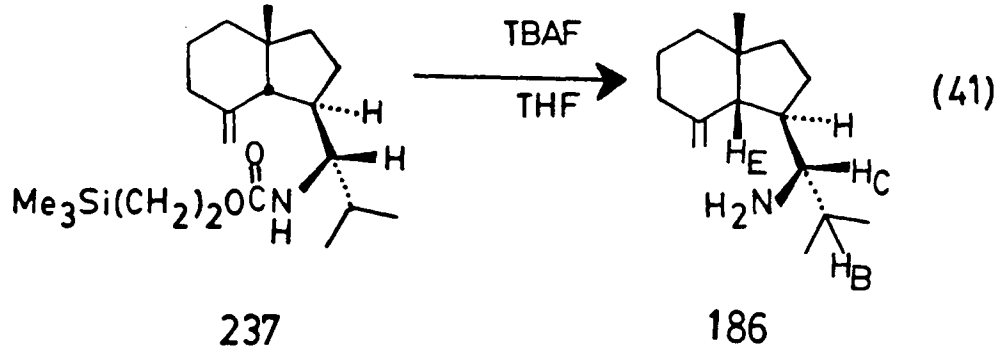


Scheme 26

at δ 3.47 (H_C, $\underline{J}$ = 10, 4 Hz), a multiplet at δ 4.06-4.20 (-C$\underline{H}_2$CH$_2$SiMe$_3$), and a broad doublet at δ 4.31 (-N$\underline{H}$-, $\underline{J}$ = 10 Hz). Additionally, the olefinic protons gave rise to broad singlets at δ 4.65 and 4.73. When the signal at δ 4.06-4.20 (-C$\underline{H}_2$CH$_2$SiMe$_3$) was decoupled, the signal at δ 0.97 due to -CH$_2$C$\underline{H}_2$SiMe$_3$ protons collapsed to a singlet. When one of the isopropyl methyl groups at δ 0.73 was decoupled, the signal due to H_B at δ 1.77-1.88 simplified. When H_B was decoupled, the signals due to the isopropyl methyl groups at δ 0.73 and 0.87 collapsed to singlets, and the signal due to H_C at δ 3.47 collapsed to a triplet ($\underline{J}$ = 10 Hz). When H_C was decoupled, the signal due to H_B collapsed to a septet ($\underline{J}$ = 7

Hz) and the signal due to H_D at δ 2.20-2.31 simplified. When the proton attached to nitrogen was decoupled, the signal due to H_C at δ 3.47 collapsed to a doublet of doublets (J = 10, 4 Hz).

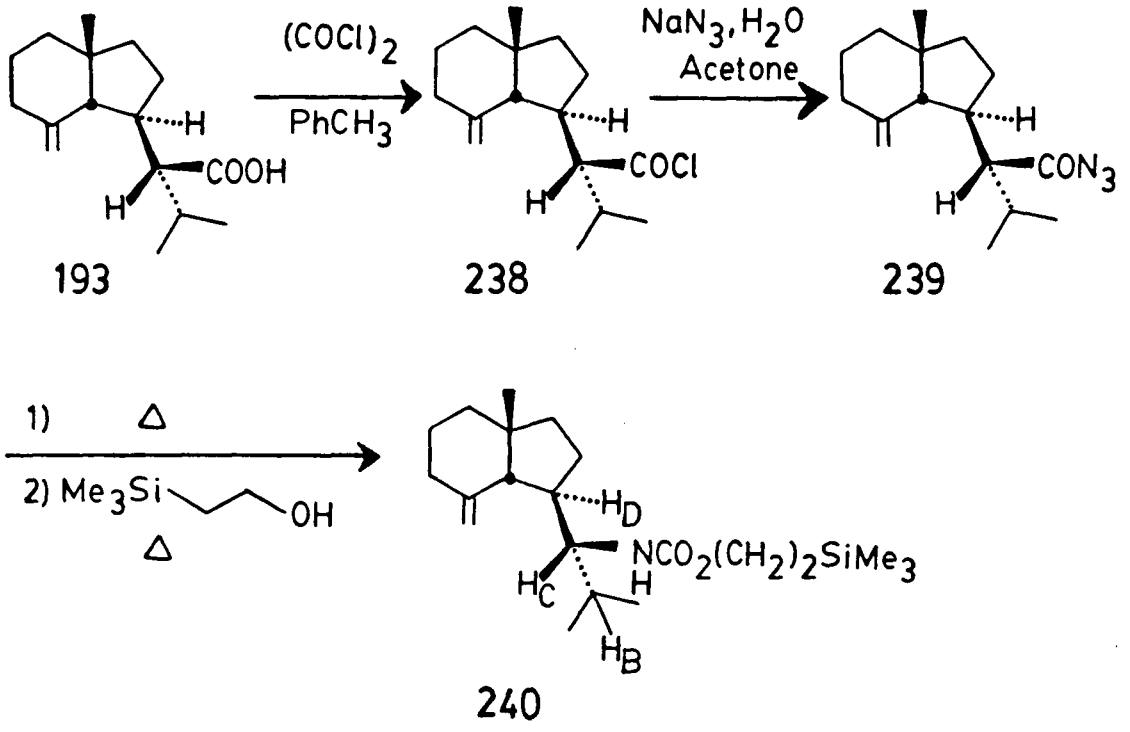
Reaction of (237) with tetra-n-butylammonium fluoride provided, in 72% yield, the amine (186) (equation 41). The ir spectrum of (186) exhibited two weak absorptions at 3397 and 3338 cm^{-1}, indicating the presence of an amino group. The ^1H nmr spectrum of (186) showed a pair of doublets at δ 0.82 and 0.92. (J = 6.5 Hz in each case) attributable to the isopropyl methyl groups, while the tertiary methyl group gave rise to a singlet at δ 0.94. A doublet of doublets due to H_C appeared at δ 2.51 (J = 8.5, 3.5 Hz), while a doublet due to H_E could be found at δ 1.97 (J = 10 Hz). Additionally, the olefinic protons gave rise to a broad singlet at δ 4.77, while a multiplet due to H_B appeared at δ 1.70-1.83. When one of the isopropyl methyl groups at δ 0.82 was decoupled, the signal due to H_B at δ 1.70-1.83 simplified. When H_C was decoupled, the signal due to H_B collapsed to a septet (J = 6.5 Hz) and a three-proton multiplet at δ 2.05-2.30, which presumably contained the proton H_D, simplified. The assignment of the signal at δ 1.97 to H_E was based on the chemical shift and coupling pattern of this resonance.



(41)

237 186

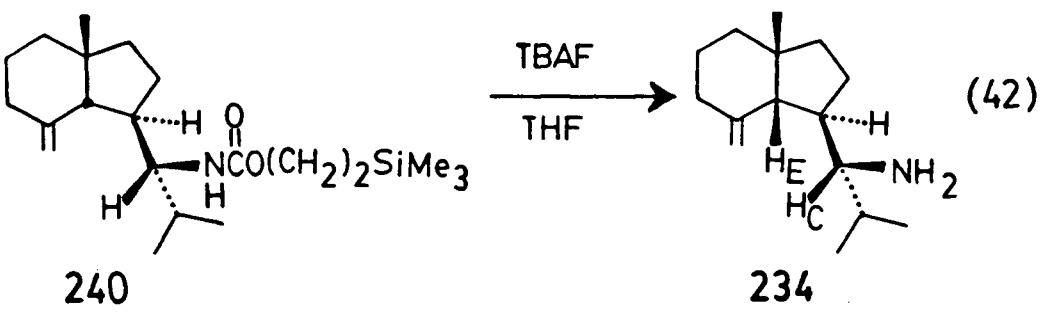
Subjection of the acid (193) to a sequence of reactions similar to that used for the conversion of (187) into (237) provided, in 82% yield, the crystalline carbamate (240), mp 86-87°C (recrystallization from petroleum ether) (Scheme 27). The ir spectrum of (240) showed a N-H stretching absorption at 3450 cm^{-1} and a carbonyl absorption at 1726 cm^{-1}. The ^1H nmr spectrum of (240) exhibited a nine-proton singlet at δ 0.05 ($-SiMe_3$), a pair of doublets at δ 0.85 and 0.88 (isopropyl methyl groups, $\underline{J}$ = 7 Hz in each case), a singlet at δ 0.95 (tertiary methyl group), a triplet at δ 0.99 ($-OCH_2C\underline{H}_2SiMe_3$, $\underline{J}$ = 8.5 Hz), a multiplet at δ 2.25-2.36 (H_D), a doublet of doublet of doublets at δ 3.41 (H_C, $\underline{J}$ = 10.5, 7, 4 Hz), a triplet at δ 4.16 ($-OC\underline{H}_2CH_2SiMe_3$, $\underline{J}$ = 8.5 Hz), a broad doublet at δ 4.43 ($-N\underline{H}-$, $\underline{J}$ = 10.5 Hz), and two broad singlets due to the



Scheme 27

olefinic protons at δ 4.77 and 4.81. When the signal at δ 4.16 ($-OC\underline{H}_2CH_2SiMe_3$) was decoupled, the signal due to $-OCH_2C\underline{H}_2SiMe_3$ protons at δ 0.99 collapsed to a singlet. When H_C was decoupled, the signals due to H_D and -N<u>H</u>- (δ 2.30 and 4.43, respectively) collapsed to a triplet of doublets ($\underline{J}$ = 11, 5.5 Hz) and a broad singlet, respectively. In the same decoupling experiment, a two-proton multiplet at δ 1.59-1.74, which presumably contained the proton H_B, simplified. When H_D was decoupled, the signal due to H_C at δ 3.41 collapsed to a doublet of doublets ($\underline{J}$ = 10.5, 7 Hz), and a two-proton multiplet at δ 1.76-1.95 simplified.

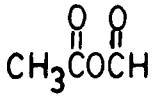
Treatment of the carbamate (240) with tetra-<u>n</u>-butylammonium fluoride gave the amine (234) in a yield of 72% (equation 42). The ir spectrum of (234) showed two weak absorption at 3387 and 3307 cm^{-1}, indicating the presence of a primary amine function. The ^1H nmr spectrum of (234) exhibited a pair of doublets at δ 0.86 and 0.89 (isopropyl methyl groups, $\underline{J}$ = 6.5 Hz, in each case), a singlet at δ 0.97 (tertiary methyl group), a broad doublet at δ1.95 (H_E, $\underline{J}$ = 11 Hz), and a doublet of doublets at δ 2.34 (H_C, $\underline{J}$ = 6.5, 3 Hz). Furthermore, the olefinic protons gave rise to broad singlets at δ 4.62 and 4.75. The assignment of the signals at δ 1.95 and 2.34 to H_E and H_C, respectively,



240 234 (42)

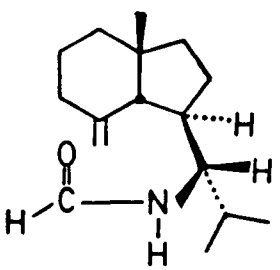
was based on the chemical shifts and/or the spin-spin coupling patterns of these resonances.

Formylation of the amine (186) was a straightforward process. Thus, the addition of freshly prepared acetic formic anhydride (241) to a solution of the amine (186) in ether at room temperature provided the (±)-axamide-1 (174) in 90% yield.[61] The ir spectrum of (174) exhibited an

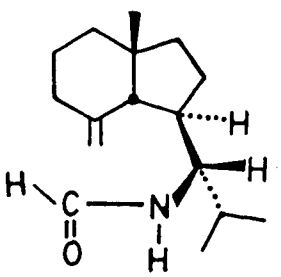


241

absorption at 3268 cm^{-1} for the N-H stretching vibration, a peak at 1660 cm^{-1} for the carbonyl absorption, and a peak at 890 cm^{-1} for the $C=CH_2$ group absorption. The ^1H nmr spectrum of (174) (Figure 11) was rather complicated. However, the appearance of two doublets due to formamide protons (H-C(=O)-) at δ 7.90 (J = 12 Hz) and 8.15 (J = 2 Hz) (integrated area ratio ~2:3, respectively) indicated that (174) consisted of a mixture of trans and cis rotamers in a ratio of ~2:3, respectively.[84]



cis 174



trans 174

Formylation of the amine (234) by treatment with acetic formic anhydride (241) provided (±)-10-epi-axamide-1 (224) in 88% yield.[61] The

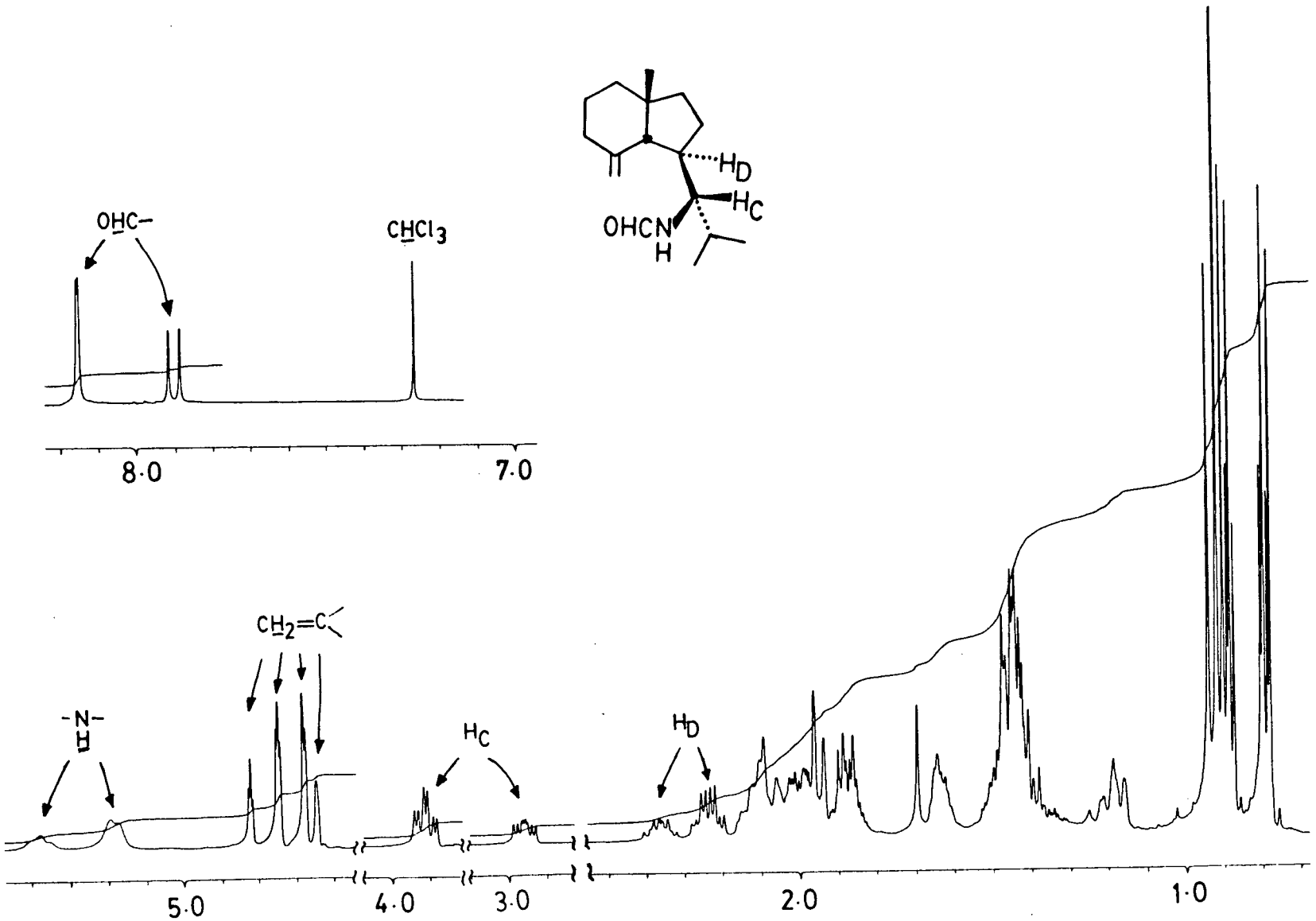
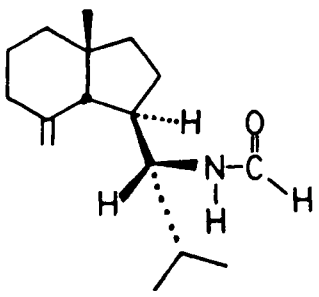


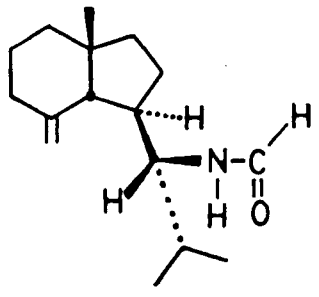
Fig. 11: The 400 MHz ^{1}H nmr spectrum of (±)-axamide-1 (174)

ir spectrum of (224) exhibited an absorption at 3288 cm^{-1} for the N-H stretching vibration, a peak at 1659 cm^{-1} for the carbonyl absorption, and a peak at 896 cm^{-1} for the $>C=CH_2$ group absorption. In the ^1H nmr spectrum of (224) (Figure 12), the formamide protons (H-C(=O)-) gave rise to a doublet at δ 7.97 (J = 12 Hz) and a broad singlet at δ 8.31 (integrated area ratio ~1:1, respectively). Therefore, compound (224) consisted of a mixture of trans and cis rotamers in a ratio of about 1:1.[84]

Comparison of the (limited) spectral data reported[56] for natural (+)-axamide-1 with those exhibited by compounds (174) and (224) did not lead to an unambiguous conclusion regarding compound identities.



cis 224



trans 224

Dehydration of (174) with p-toluenesulfonyl chloride in pyridine afforded, in 86% yield, the isonitrile (173),[85] which exhibited mp 45-46°C (recrystallization from petroleum ether). The ir spectrum of (173) showed an absorption at 2136 cm^{-1}, indicating the presence of an isonitrile function. Also observed in the ir spectrum of (173) was an absorption due to the $>C=CH_2$ group at 899 cm^{-1} and two peaks at 1376 and 1390 cm^{-1} due to the isopropyl methyl groups.

The 400 MHz ^1H nmr spectrum of (173) (Figure 13), as well as the

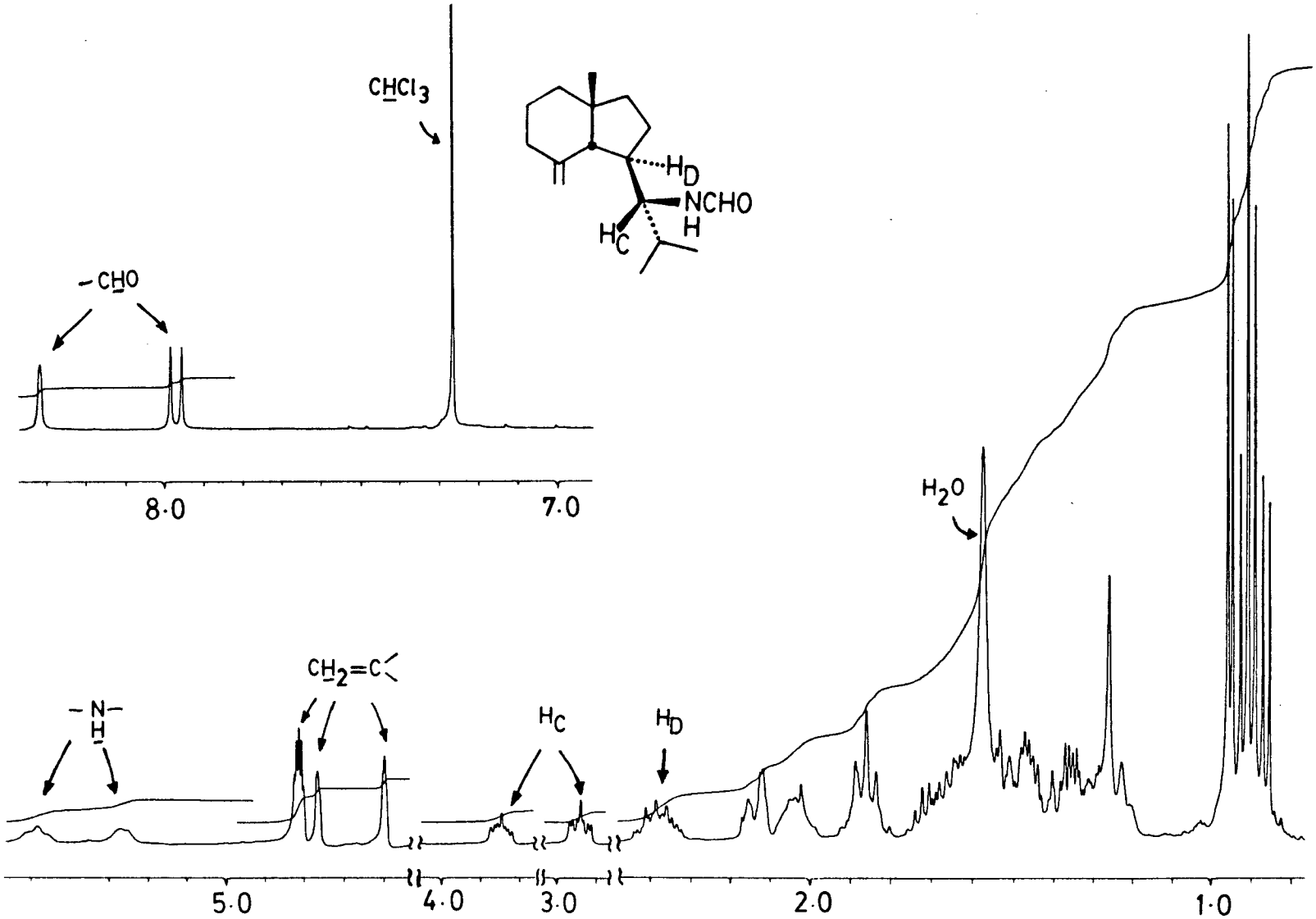


Fig. 12: The 400 MHz ^{1}H spectrum of (±)-10-epi-axamide-1 (224)

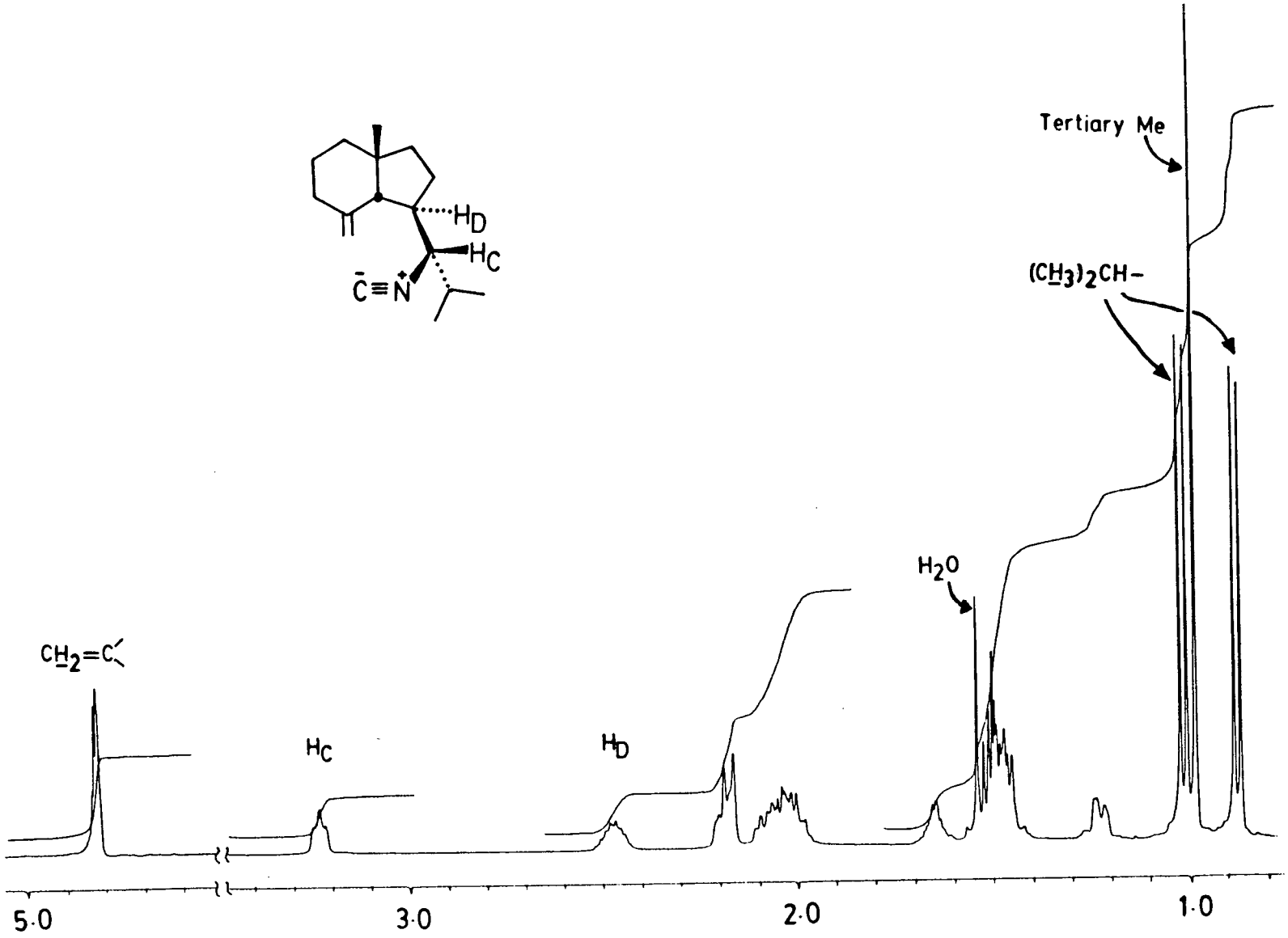
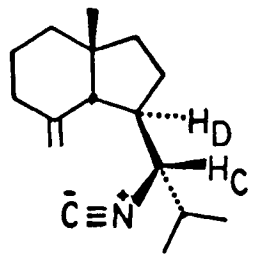


Fig. 13: The 400 MHz ^{1}H nmr spectrum of synthetic (±)-axisonitrile-1 (173)

chromatographic behavior (glc, tlc), were found to be identical with those of an authentic sample of (+)-axisonitrile-1* (Figure 14 for ^1H



173

nmr spectrum). This comparison also confirmed that (174) was (±)-axamide-1.

The 75 MHz ^{13}C nmr spectrum of (173) exhibited a 1:1:1 triplet at δ 155.535, 155.621, and 155.689 attributable to the isonitrile carbon.[86] Furthermore, a 1:1:1 triplet due to the α-carbon adjacent to the isonitrile function appeared at δ 67.691, 67.763, and 67.824.[86b]

Dehydration of (224) afforded (±)-10-epi-axisonitrile-1 (225) in 87% yield.[85] Compound (225) exhibited mp 53-54°C (recrystallization from petroleum ether) and its ir spectrum showed an absorption at 2135 cm^{-1} due to the isonitrile function, an absorption at 901 cm^{-1} due to the $>C=CH_2$ group, and two peaks at 1391 and 1377 cm^{-1} due to the isopropyl methyl groups. The 400 MHz ^1H nmr spectrum of (225) (Figure 15), as well as the chromatographic behavior (glc), were clearly different from those of natural (+)-axisonitrile-1.

---

* We are very grateful to Professor D. Sica for a sample of (+)-axisonitrile-1 and for a copy of its ^1H nmr spectrum.

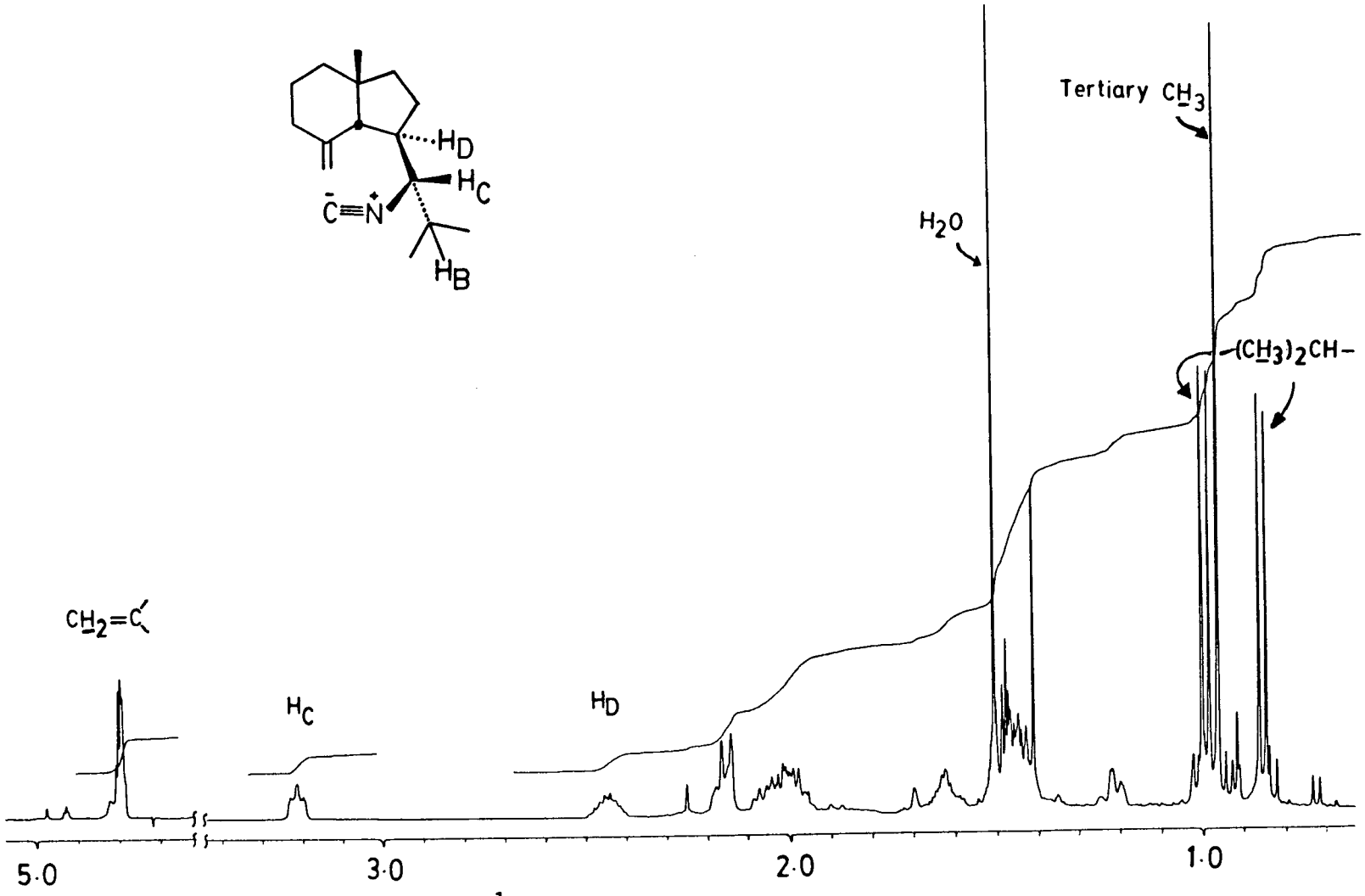


Fig. 14: The 400 MHz ^{1}H nmr spectrum of natural (+)-axisonitrile-1

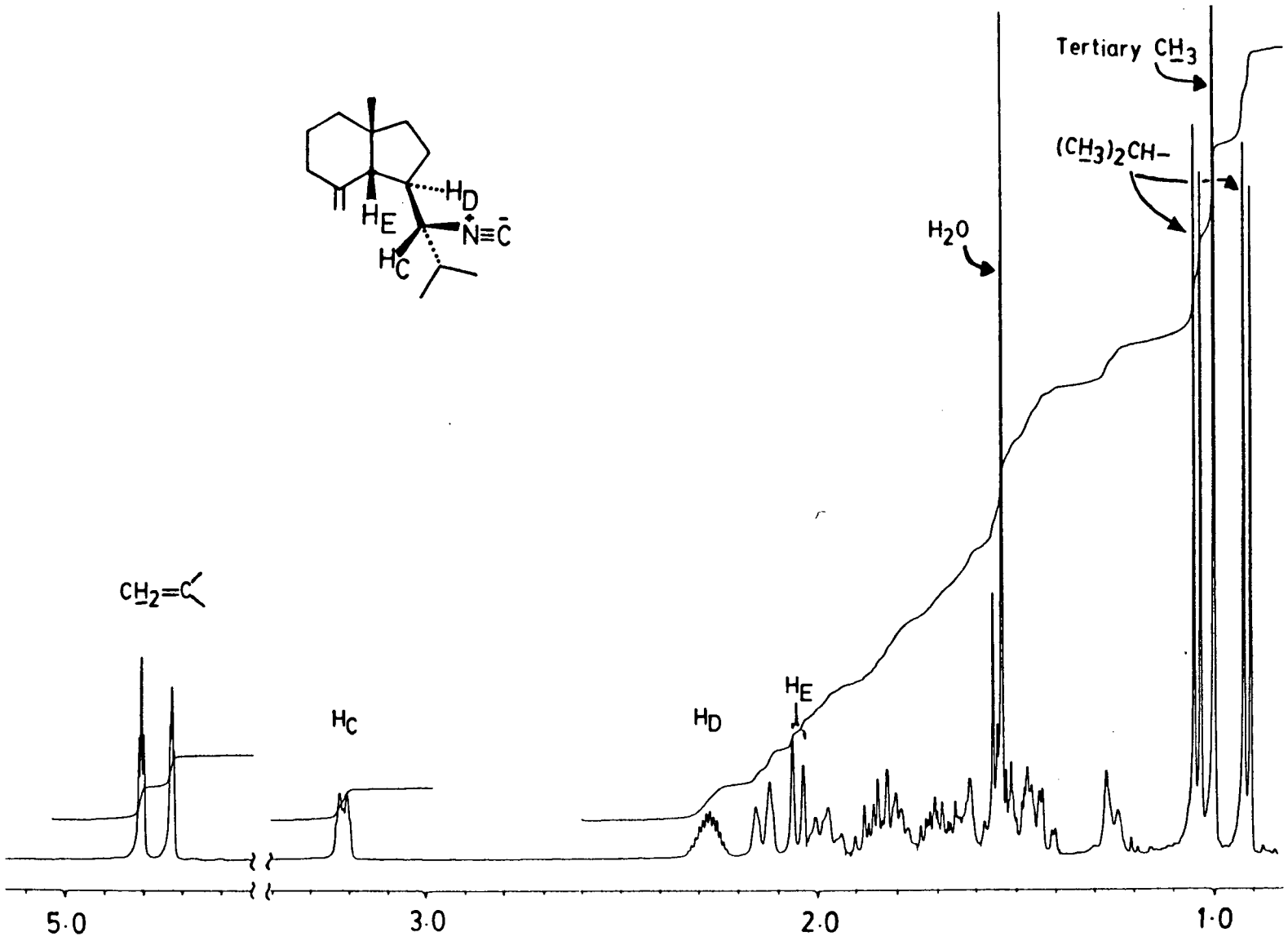
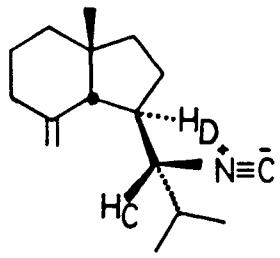


Fig. 15: The 400 MHz ^{1}H nmr spectrum of synthetic (±)-10-epi-axisonitrile-1 (225)



225

In summary, the total synthesis of (±)-axisonitrile-1 (173) was achieved in 13% overall yield from 2-methyl-2-cyclopenten-1-one (152). The overall yield of (±)-10-epi-axisonitrile-1 (225) was 9%. The synthetic sequences employed for these syntheses provided an example of the use of the newly developed methylenecyclohexane annulation method in natural product synthesis. Furthermore, the efficient titanium tetrachloride-catalyzed conjugate addition of 3-methyl-1,1-bis(trimethylsiloxy)-1-butene (226) to the enone (203) provided an interesting example of the use of this modified Mukaiyama reaction in a total synthesis.

EXPERIMENTAL

EXPERIMENTAL

General

Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are also uncorrected and those indicated as air-bath temperatures refer to short path (Kugelrohr) distillations. Infrared (ir) spectra were recorded either on a Perkin-Elmer model 710B infrared spectrophotometer using the 1601 cm^{-1} band of polystyrene film for calibration or on a Perkin-Elmer model 1710 Fourier Transform Infrared (FTIR) spectrometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C nmr) spectra were recorded in deutero-chloroform solutions. These spectra were recorded using a HXS-270 spectrometer, Varian XL-300 spectrometer, and/or Bruker models WP-80 or WH-400 spectrometers. Signal positions are given in parts per million (δ) relative to tetramethylsilane (TMS). In cases of compounds with trimethylstannyl and/or trimethylsilyl groups, the resonance positions were determined relative to the chloroform signal (δ 7.25).[51] The multiplicity, number of protons, coupling constants, and assignments (where possible) are indicated in parentheses. The tin-proton coupling constants (J_{Sn-H}) are given as $J_{^{117}Sn-H}/J_{^{119}Sn-H}$ where the coupling constants for the two isotopes are distinct and as an average of the two values where they are not distinct. Low resolution mass spectra were recorded with a Varian/MAT CH4B mass spectrometer while high resolution mass spectra were recorded with a Kratos/AEl MS 50 mass spectrometer.

Glc-mass spectrometric analyses were done using a Carlo ERBA GC series 4160 chromatograph coupled with a Kratos MS 80 RFA mass spectrometer. In cases of compounds with trimethylstannyl groups the molecular weight determinations (high resolution mass spectrometry) were based on ^{120}Sn and were made on the (M^+-15) peak.

Analytical gas-liquid chromatography (glc) was performed on a Hewlett-Packard model 5880 gas chromatograph equipped with a 12.5 m x 0.21 mm fused silica column coated with cross-linked SE-54 (column B) or a 12.5 m x 0.21 mm fused silica column coated with cross-linked OV-101 (column A) and a flame ionization detector. Glc was also performed on a Hewlett-Packard model 5990 gas chromatograph using a 12.5 m x 0.21 mm fused silica column coated with cross-linked SE-54 (column B) and a flame ionization detector.

Thin-layer chromatography (tlc) was carried out on commercial aluminum-backed silica gel plates (E. Merck, Type 5554). Preparative thin-layer chromatography was done on 20 cm x 20 cm plates coated with 2 mm of silica gel (E. Merck, Silica Gel 60). Conventional column chromatography was done on 70-230 mesh silica gel (E. Merck, Silica Gel 60) while flash chromatography[87] was done on 230-400 mesh silica gel (E. Merck, Silica Gel 60). Silica Gel impregnated with silver nitrate was prepared according to the following procedure.[52] A solution of 12.5 g of silver nitrate in 100 mL of deionized water was added to 50 g of 70-230 mesh silica gel (E. Merck, Silica Gel 60) with stirring until the slurry was homogeneous. Most of the water was removed under reduced pressure and the silica gel was dried under vacuum overnight at room temperature, with protection from light. The dried silica gel was

stored under argon in a brown bottle.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using carefully flame-dried glassware.

Cold temperatures were maintained by the use of the following baths:[88] aqueous calcium chloride/CO_2 (-20°C),[89] acetonitrile/CO_2 (-48°C), chloroform/CO_2 (-63°C), acetone/CO_2 (-78°C).

Solvents and Reagents

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl.

Dichloromethane was distilled from phosphorus pentoxide.

Diisopropylamine, N,N-dimethylformamide, hexamethylphosphoramide (HMPA) and pyridine were distilled from calcium hydride and stored over activated 4 Å molecular sieves.

Toluene was distilled from sodium and stored over activated 4 Å molecular sieves.

Methanol was distilled from magnesium methoxide and stored over activated 4 Å molecular sieves.

Acetic anhydride was distilled from calcium carbide.

Formic acid was refluxed with phthalic anhydride for 6 h and then was distilled.

Trimethylsilyl chloride was freshly distilled before use.

Acetone was distilled and stored over activated 4 Å molecular sieves.

The petroleum ether used was the fractions with a boiling point range of ca. 30-60°C.

Hexamethylditin was obtained from the Alfa Division of the Ventron Corporation or from Organometallics, Inc.

Solutions of methyllithium-lithium bromide complex in ether and n-butyllithium in hexane were obtained from Aldrich Chemical Co., Inc. and were standardized using the double-titration procedure of Gilman.[90]

Potassium hydride was obtained as a 35% suspension in mineral oil from the Aldrich Chemical Company, Inc. and was washed free of oil (with dry THF) before use.

Cuprous bromide-dimethyl sulfide complex was prepared by the method of House,[91] after washing commercial cuprous bromide with methanol.[92]

Lithium diisopropylamide was prepared by the addition of a solution of n-butyllithium (1.0 equiv) in hexane to a solution of diisopropylamine (1.0 equiv) in dry THF at -78°C. The resulting solution was then stirred at 0°C for 10 min before being used.[93]

Saturated basic aqueous ammonium chloride (pH 8) was prepared by the addition of ≈ 50 mL of aqueous ammonium hydroxide (58%) to 1 L of saturated aqueous ammonium chloride.

Tetra-n-butylammonium fluoride[94] was prepared by the titration of hydrofluoric acid with tetra-n-butylammonium hydroxide, with subsequent removal of water under vacuum at room temperature.

Boron trifluoride-etherate[95] was purified by distillation from calcium hydride (1 g per 250 mL of boron trifluoride-etherate) under reduced pressure (60°C/20 Torr).

p-Toluenesulfonyl chloride[96] was purified by recrystallization from

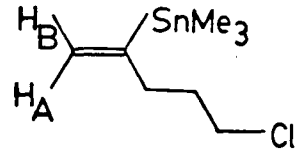
chloroform-petroleum ether.

N-Bromosuccinimide[97] was recrystallized from hot water.

Magnesium bromide-etherate was prepared by the reaction of 1,2-dibromoethane (freshly distilled) with magnesium metal in dry ether, with subsequent removal of ether under vacuum at room temperature.

All other reagents were commercially available and were utilized without further purification.

Preparation of 5-Chloro-2-trimethylstannyl-1-pentene (111)

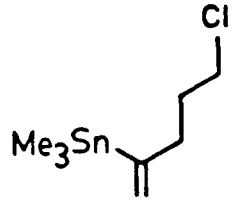


111

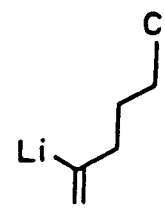
To a cold (-20°C), stirred solution of hexamethylditin (8.0 mL, 38.3 mmol) in 250 mL of dry THF was added methyllithium (40 mmol) as a solution in ether. The resulting pale yellow solution was stirred at -20°C for 15 min and then was cooled to -78°C. Solid cuprous bromide-dimethyl sulfide complex (7.9 g, 38.3 mmol) was added in one portion to the colorless solution at -78°C. The mixture was stirred at -78°C for 10 min, was warmed to -63°C, and then was stirred for an additional 15 min. The resulting reddish brown solution was recooled to -78°C. 5-Chloro-1-pentyne (3.2 mL, 30.2 mmol) was added and the reaction mixture was stirred at -78°C for 6 h. Acetic acid (3 mL),

methanol (3 mL), saturated aqueous ammonium chloride (pH 8) (200 mL) and ether (100 mL) were added successively. The mixture was allowed to warm to room temperature and was stirred vigorously with exposure to air. The blue aqueous layer was separated and extracted twice with ether. The combined ether extract was washed twice with saturated aquoeus ammonium chloride (pH 8), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residual material was subjected to column chromatography on silica gel (450 g, elution with petroleum ether). Distillation (air-bath temperature 80-85°C/25 Torr) of the oil obtained from the appropriate fractions provided 5.5 g (68%) of the chloride (111) as a colorless oil. This material exhibited ir (film): 1440, 920, 770 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 0.15 (s, 9H, $-SnMe_3$, J_{Sn-H} = 52/54 Hz), 1.85 (quintet, 2H, $-CH_2\underline{C}H_2CH_2Cl$, $\underline{J}$ = 7 Hz), 2.40 (br t, 2H, $-C\underline{H}_2CH_2CH_2Cl$, $\underline{J}$ = 7 Hz), 3.50 (t, 2H, $-C\underline{H}_2Cl$, $\underline{J}$ = 7 Hz), 5.20 (d of t, 1H, H_B, $\underline{J}$ = 2.5, 1 Hz, J_{Sn-H} = 70 Hz), 5.70 (d of t, 1H, H_A, $\underline{J}$ = 2.5, 1.5 Hz, J_{Sn-H} = 150 Hz). Exact Mass calcd. for $C_7H_{14}{}^{35}Cl^{120}Sn$ (M^+-CH_3): 252.9806; found: 252.9809.

Preparation of 5-Chloro-2-lithio-1-pentene (112) by the Transmetalation of 5-Chloro-2-trimethylstannyl-1-pentene (111)



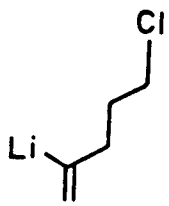
111



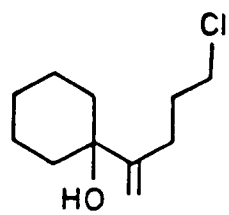
112

To a cold (-78°C), stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (111) (1.0 equiv) in dry THF [~1 mL per 0.1 mmol of (111)] was added methyllithium (~1.2 equiv) as a solution in ether. The resulting colorless solution was stirred at -78°C for an additional 15 min before being used.

General Procedure A: Reaction of 5-Chloro-2-lithio-1-pentene (112) with Cyclohexanone at Various Temperatures. Preparation of 5-Chloro-2-(1-hydroxycyclohexyl)-1-pentene (132)



112



132

A stirred solution of 5-chloro-2-lithio-1-pentene (112) (0.37 mmol) in dry THF (4 mL) at -78°C was allowed to warm up to an appropriate temperature and then was stirred for an additional 30 min. The solution was recooled to -78°C. Cyclohexanone (43 μL, 0.41 mmol) was added and the colorless reaction mixture was stirred at -78°C for 3 h. Saturated aqueous ammonium chloride (5 mL) and ether (10 mL) were added and the resulting mixture was allowed to warm to room temperature. The organic layer was washed with saturated aqueous ammonium chloride (2 x 5 mL), dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. Column chromatography of the residue on 5 g silica gel (elution with 3:2 petroleum ether-ether) followed by distillation of the material obtained from the appropriate fractions, provided the pure product (132).

(a) At -78°C

Following general procedure A described above, a solution of 5-chloro-2-lithio-1-pentene (112) (0.37 mmol) in dry THF (4 mL) was stirred at -78°C for a further 30 min before the addition of cyclohexanone (43 μL, 0.41 mmol). Normal workup, followed by column chromatography of the crude product and distillation (air-bath temperature 110-115°C/0.2 Torr) of the oil thus obtained, afforded 64 mg (84%) of the alcohol (132) as a colorless oil. This material exhibited ir (film): 3431, 3094, 1639, 902 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.12-1.30 (m, 2H), 1.50-1.70 (m, 9H), 1.98 (quintet, 2H, $-C\underline{H}_2CH_2Cl$, $\underline{J}$ = 7 Hz), 2.24 (t, 2H, $-C\underline{H}_2CH_2CH_2Cl$, $\underline{J}$ = 7 Hz), 3.36 (t, 2H, $-CH_2C\underline{H}_2Cl$, $\underline{J}$ = 7 Hz), 4.82, 5.14 (s, s, 1H each, olefinic protons). Exact Mass calcd. for $C_{11}H_{19}O^{35}Cl$: 202.1124; found: 202.1130.

(b) At -63°C

Following general procedure A, a solution of reagent (112) (0.37 mmol) in 4 mL of dry THF was stirred at -63°C for 30 min and then was

recooled to -78°C prior to addition of cyclohexanone (0.41 mmol). The alcohol (132) was obtained in 76% yield (57 mg). The ^{1}H nmr spectrum of this material was identical with that of the material described above.

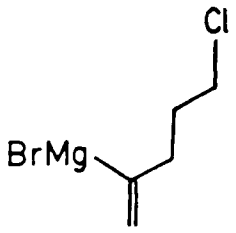
(c) At -48°C

Following general procedure A, a solution of reagent (112) (0.37 mmol) in 4 mL of dry THF was stirred at -48°C for 30 min and then was recooled to -78°C prior to addition of cyclohexanone (0.41 mmol). There was obtained 44 mg (58%) of the alcohol (132). This material exhibited a ^{1}H nmr spectrum identical with that given above.

(d) At -20°C

Following general procedure A, a solution of reagent (112) (0.37 mmol) in 4 mL of dry THF was stirred at -20°C for 30 min and then was recooled to -78°C prior to addition of cyclohexanone (0.41 mmol). Analysis of the crude product (40 mg) by glc and ^{1}H nmr spectroscopy showed that it contained none of the alcohol (132), but consisted nearly entirely of cyclohexanone.

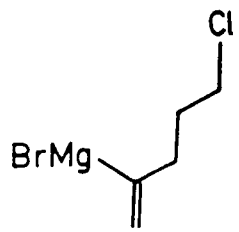
General Procedure B: Reaction of 2-Bromomagnesio-5-chloro-1-pentene (144) with Cyclic Enones, Catalyzed by Cuprous Bromide-Dimethyl Sulfide



144

To a cold (-78°C), stirred solution of 5-chloro-2-lithio-1-pentene (112) (1.0 equiv) in dry THF [~1.0 mL per 0.1 mmol of (112)] was added, in one portion, solid magnesium bromide-etherate (~1.2 equiv). The resulting milky solution was stirred at -78°C for 20 min. Solid cuprous bromide-dimethyl sulfide complex (~0.25 equiv) was added in one portion to this mixture at -78°C. To the slightly yellow mixture was added the cyclic enone (1.0 equiv) and the resulting bright yellow mixture was stirred at -78°C for 2-3 h. Saturated aqueous ammonium chloride (pH 8) (~5 mL) and ether (~10 mL) were added. The mixture was stirred rapidly and was allowed to warm to room temperature with exposure to air. The blue aqueous layer was separated and extracted twice with ether. The combined ether extract was washed twice with saturated aqueous ammonium chloride (pH 8), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (~ 5 g per 100 mg of crude product). Concentration of the appropriate fractions and distillation of the oil thus obtained, provided pure product.

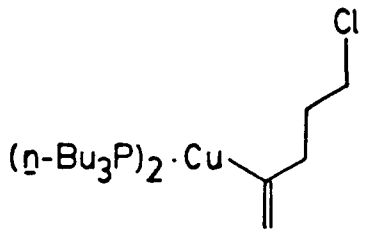
General Procedure C: Reaction of 2-Bromomagnesio-5-chloro-1-pentene (144) with Cyclic Enones, Catalyzed by Cuprous Bromide-Dimethyl Sulfide and Boron Trifluoride-Etherate



144

To a cold (-78°C), stirred solution of 5-chloro-2-lithio-1-pentene (112) (1.0 equiv) in dry THF [~1.0 mL per 0.1 mmol of (112)] was added, in one portion, solid magnesium bromide-etherate (~1.2 equiv) and the resulting milky solution was stirred at -78°C for 20 min. Solid cuprous bromide-dimethyl sulfide complex (~0.25 equiv) was added in one portion. To the slightly yellow mixture was added successively cyclic enone (1.0 equiv) and boron trifluoride-etherate (~ 1.2 equiv). The resulting bright yellow mixture was stirred at -78°C for 2-3 h. Saturated aqueous ammonium chloride (pH 8) (~5 mL) and ether (~10 mL) were added. The mixture was stirred rapidly and was allowed to warm to room temperature with exposure to air. The blue aqueous layer was separated and extracted twice with ether. The combined ether extract was washed twice with saturated aqueous ammonium chloride (pH 8), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (~ 5 g per 100 mg of crude material). Distillation of the material obtained from the appropriate fractions afforded pure product.

General Procedure D: Reaction of the Organocopper-phosphine Complex Reagent (145) with Cyclic Enones

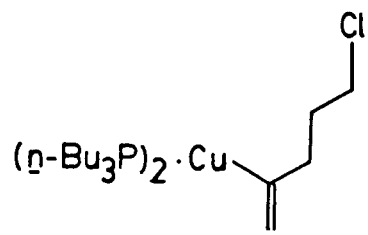


145

Solid cuprous bromide-dimethyl sulfide complex (1.1 equiv) was added to a stirred solution of tri-n-butylphosphine (2.0 equiv) in dry ether (~1.0 mL per 0.1 mmol of cuprous bromide-dimethyl sulfide complex). After the mixture had been stirred at room temperature for 10 min, all of the solid had dissolved. The solution was cooled to -78°C and then was transferred via a cannula to a cold (-78°C), stirred solution of 5-chloro-2-lithio-1-pentene (112) (1.0 equiv) in dry THF [~1.0 mL per 0.1 mmol of (112)]. The resulting light yellow solution was stirred at -78°C for 20 min. Enone (1.0 equiv) was added and the resulting bright yellow solution was stirred at -78°C for 1 h and then at -48°C for 2 h. Saturated aqueous ammonium chloride (pH 8) (5 mL) and ether (10 mL) were added. The mixture was stirred vigorously and was allowed to warm to room temperature with exposure to air. The blue aqueous layer was extracted twice with ether. The combined ether extract was washed twice with saturated aqueous ammonium chloride (pH 8), and then was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by column chromatography of the crude material on silica gel (~5 g per 100 mg of crude material, elution

with 20:1 to 7:1 petroleum ether-ether) and distillation of the oil obtained from the appropriate fractions, afforded pure product.

General Procedure E: Reaction of the Organocopper-phosphine Complex Reagent (145) with Cyclic Enones, Catalyzed by Boron Trifluoride-Etherate

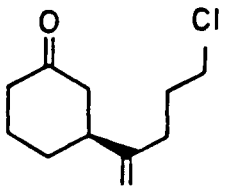


145

Solid cuprous bromide-dimethyl sulfide complex (1.1 equiv) was added to a stirred solution of tri-n-butylphosphine (2.0 equiv) in dry ether (~1.0 mL per 0.1 mmol of cuprous bromide-dimethyl sulfide complex) at room temperature. The mixture was stirred for 10 min to give a colorless solution. This solution was cooled to -78°C and then was transferred (cannula) to a cold (-78°C), stirred solution of 5-chloro-2-lithio-1-pentene (112) (1.0 equiv) in dry THF [~1.0 mL per 0.1 mmol of (112)]. The resulting pale yellow solution was stirred at -78°C for 20 min. Enone (1.0 equiv) and boron trifluoride-etherate (1.2 equiv) were added successively and the resulting bright yellow solution was stirred at -78°C for 1 h and then at -48°C for 2 h. Saturated aqueous ammonium chloride (pH 8) (5 mL) and ether (10 mL) were added. The mixture was stirred vigorously and was allowed to warm to room temperature with

exposure to air. The blue aqueous layer was extracted twice with ether. The combined ether extract was washed twice with saturated aqueous ammonium chloride (pH 8), and then was dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure, followed by column chromatography of the crude product on silica gel (~5 g per 100 mg of crude material, elution with 20:1 to 7:1 petroleum ether-ether) and distillation of the oil obtained from the appropriate fractions, afforded pure product.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-cyclohexanone (153)



153

(a) Using the Grignard Reagent (144)

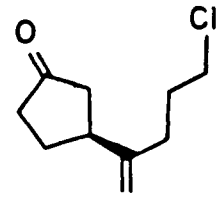
Following general procedure B, 2-cyclohexen-1-one (146) was converted into the conjugate addition product (153). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (112) (0.37 mmol) in 4 mL of dry THF; magnesium bromide-etherate (113 mg, 0.44 mmol); cuprous bromide-dimethyl sulfide complex (18.3 mg, 0.088 mmol) and 2-cyclohexen-1-one (146) (40 μL, 0.41 mmol). Workup, followed by

column chromatography of the crude product on silica gel (4 g, elution with 3:2 petroleum ether-ether) and distillation (air-bath temperature 82-85°C/0.2 Torr) of the oil obtained from the appropriate fractions, provided 60 mg (81%) of the chloro ketone (153) as a colorless oil. This material exhibited ir (film): 3050, 1700, 1630, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.52-1.74 (m, 2H), 1.85-2.0 (m, 3H), 2.02-2.14 (m, 1H), 2.15-2.24 (t, 2H, $-C\underline{H}_2CH_2CH_2Cl$, $\underline{J}$ = 7 Hz), 2.24-2.49 (m, 5H), 3.54 (t, 2H, $-C\underline{H}_2Cl$, $\underline{J}$ = 7 Hz), 4.85 (br s, 2H, olefinic protons). Exact Mass calcd. for $C_{11}H_{17}O^{35}Cl$: 200.0969; found: 200.0963.

(b) Using the Organocopper Reagent (145)

Following general procedure D, 2-cyclohexen-1-one (146) was converted into the conjugate addition product (153). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide complex (83.5 mg, 0.41 mmol) and tri-n-butylphosphine (0.18 mL, 0.73 mmol) in 4 mL of dry ether; 5-chloro-2-lithio-1-pentene (112) (0.36 mmol) in 3.6 mL of dry THF; 2-cyclohexen-1-one (146) (35 μL, 0.36 mmol). Workup, followed by column chromatography of the crude product on silica gel (6 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 82-85°C/0.2 Torr) of the oil obtained from the appropriate fractions, afforded 44 mg (61%) of the chloro ketone (153). The ^1H nmr spectrum of this material was identical with that of the material described above.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-cyclopentanone (157)



157

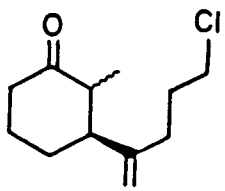
(a) Using the Grignard Reagent (144)

Following general procedure B, 2-cyclopenten-1-one (150) was converted into the conjugate addition product (157). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (112) (0.39 mmol) in 4 mL of dry THF; magnesium bromide-etherate (121 mg, 0.47 mmol); cuprous bromide-dimethyl sulfide complex (19 mg, 0.096 mmol); 2-cyclopenten-1-one (150) (38 μL, 0.39 mmol). Normal workup, followed by column chromatography of the crude product on silica gel (4 g, elution with 3:1 petroleum ether-ether) and distillation (air-bath temperature 90-95°C/0.2 Torr) of the oil obtained from the appropriate fractions, provided 38.7 mg (54%) of the chloro ketone (157). This material exhibited ir (film): 3050, 1735, 1630, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.72-1.86 (m, 1H), 1.93-2.01 (quintet, 2H, $-CH_2\underline{CH_2}CH_2Cl$, $\underline{J}$ = 7 Hz), 2.08-2.32 (m, 5H), 2.34-2.50 (m, 2H), 2.89 (m, 1H), 3.58 (t, 2H, $-\underline{CH_2}Cl$, $\underline{J}$ = 7 Hz), 4.86 (br s, 2H, olefinic protons). Exact Mass calcd. for $C_{10}H_{15}O^{35}Cl$: 186.0812; found: 186.0815.

(b) Using the Organocopper Reagent (145)

Following general procedure D, the conjugate addition product (157) was prepared from 2-cyclopenten-1-one (150). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide complex (75 mg, 0.36 mmol) and tri-n-butylphosphine (160 μL, 0.66 mmol) in 4 mL of dry ether; 5-chloro-2-lithio-1-pentene (112) (0.33 mmol) in 3.5 mL of dry THF; 2-cyclopenten-1-one (150) (28 μL, 0.33 mmol). Workup, followed by column chromatography of the crude material on silica gel (6 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 90-95°C/0.2 Torr) of the oil obtained from the appropriate fractions, afforded 39.9 mg (65%) of the chloro ketone (157). The ^{1}H nmr spectrum of this material was identical with that of the material described above.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-2-methylcyclohexanone (155)



155

(a) Using the Grignard Reagent (144)

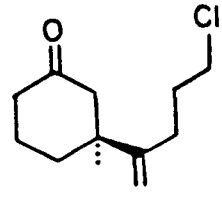
Following general procedure C, 2-methyl-2-cyclohexen-1-one (148)

was converted into the conjugate addition product (**155**). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (**112**) (0.18 mmol) in 2 mL of dry THF; magnesium bromide-etherate (56 mg, 0.22 mmol); cuprous bromide-dimethyl sulfide complex (14 mg, 0.067 mmol); 2-methyl-2-cyclohexen-1-one (**148**) (21 mg, 0.19 mmol); boron trifluoride-etherate (27 μL, 0.22 mmol). Workup, followed by column chromatography of the residual material on silica gel (3 g, elution with 3:1 petroleum ether-ether) and distillation (air-bath temperature 93-98°C/0.2 Torr) of the oil obtained from the appropriate fractions, afforded 21.8 mg (56%) of the chloro ketone (**155**) as a colorless oil. Analysis of this oil by glc (column B) showed that it consisted of two components in a ratio of ~12:1, while analysis by tlc (3:1 petroleum ether-ether) showed one spot. The ^{1}H nmr spectrum of this material also indicated an epimeric mixture (ratio ~12:1). This material exhibited ir (film): 3070, 1700, 1635, 900 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.95, 1.00 (d, d, 3H total, secondary methyl protons, ratio ~1:12, respectively, $\underline{J}$ = 7 Hz in each case), 1.65-1.80 (m, 2H), 1.80-1.97 (m, 3H), 1.97-2.21 (m, 3H), 2.21-2.32 (m, 1H), 2.44-2.60 (m, 2H), 2.60-2.70 (m, 1H, $>C\underline{H}CH_3$), 3.55 (t, 2H, $-C\underline{H}_2Cl$, $\underline{J}$ = 7 Hz), 4.75, 4.98 (br s, br s, ~0.9 H each, olefinic protons of major isomer), 4.86, 4.89 (br s, br s, ~0.1 each, olefinic protons of minor isomer). Irradiation at δ 1.00 caused the signal at δ 2.60-2.70 to collapse to a d ($\underline{J}$ = 7 Hz). Exact Mass calcd. for $C_{12}H_{19}O^{35}Cl$: 214.1126; found: 214.1124.

(b) Using the Organocopper Reagent (145)

Following general procedure D, chloro ketone (155) was obtained from 2-methyl-2-cyclohexen-1-one (148). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide complex (40 mg, 0.19 mmol) and tri-n-butylphosphine (91 μL, 0.36 mmol) in 2 mL of dry ether; 5-chloro-2-lithio-1-pentene (112) (0.18 mmol) in 2 mL of dry THF; 2-methyl-2-cyclohexen-1-one (148) (20 mg, 0.18 mmol). Workup, followed by column chromatography of the crude material on silica gel (5 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 93-98°C/0.2 Torr) of the oil obtained from the appropriate fractions, provided 22.5 mg (58%) of the chloro ketone (155). Analysis of this oil by glc (column B) and ^{1}H nmr spectroscopy showed that it consisted of an epimeric mixture in the ratio of ~6:1. The ^{1}H nmr spectrum of this mixture was very similar to that of the material described above.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-3-methylcyclohexanone (154)



154

(a) Using the Grignard Reagent (144)

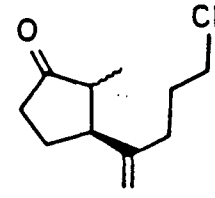
Following general procedure C, 3-methyl-2-cyclohexen-1-one (147) was converted into the conjugate addition product (154). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (112) (0.20 mmol) in 2 mL of dry THF; magnesium bromide-etherate (61.8 mg, 0.24 mmol); cuprous bromide-dimethyl sulfide complex (10 mg, 0.049 mmol); 3-methyl-2-cyclohexen-1-one (147) (23 μL, 0.20 mmol); boron trifluoride-etherate (27 μL, 0.22 mmol). Normal workup, followed by column chromatography of the crude product on silica gel (3 g, elution with 3:1 petroleum ether-ether) and distillation (air-bath temperature 85-90°C/0.2 Torr) of the oil obtained from the appropriate fractions, afforded 15.7 mg (37%) of the chloro ketone (154) as a colorless oil. This material exhibited ir (film): 3050, 1700, 1620, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.11 (s, 3H, tertiary methyl protons), 1.57-1.67 (m, 1H), 1.67-1.80 (m, 1H), 1.80-1.90 (m, 1H), 1.90-2.10 (m, 3H), 2.10-2.36 (m, 5H), 2.60 (br d, 1H, J = 14 Hz), 3.59 (t, 2H, -CH_2Cl, J = 7 Hz), 4.87, 4.93 (s, s, 1H each, olefinic protons). Exact Mass calcd. for $C_{12}H_{19}O^{35}Cl$: 214.1126; found: 214.1119.

(b) Using the Organocopper Reagent (145)

Following general procedure D, conjugate adduct (154) was obtained from 3-methyl-2-cyclohexen-1-one (147). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide

complex (131 mg, 0.63 mmol) and tri-n-butylphosphine (280 μL, 1.1 mmol) in 6.3 mL of dry ether; 5-chloro-2-lithio-1-pentene (112) (0.57 mmol) in 6.0 mL of dry THF; 3-methyl-2-cyclohexen-1-one (147) (65 μL, 0.57 mmol). Workup, followed by column chromatography of the crude material on silica gel (10 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 85-90°C/0.2 Torr) of the oil obtained from the appropriate fractions, yielded 62 mg (55%) of the chloro ketone (154). The ^{1}H nmr spectrum of this material was identical with that of the material given above.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-2-methylcyclopentanone (159)



159

(a) Using the Grignard Reagent (144)

Following general procedure C, 2-methyl-2-cyclopenten-1-one (152) was converted into the conjugate addition product (159). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (112) (0.18 mmol) in 2 mL of dry THF; magnesium bromide-etherate (55.7 mg, 0.22 mmol); cuprous bromide-dimethyl sulfide complex (13.2 mg, 0.064 mmol);

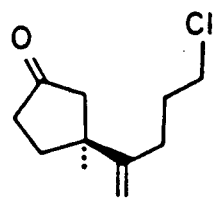
2-methyl-2-cyclopenten-1-one (152) (18 μL, 0.18 mmol); boron trifluoride-etherate (26 μL, 0.22 mmol). After normal workup, column chromatography of the crude material on silica gel (3 g, elution with 3:1 petroleum ether-ether) and distillation (air-bath temperature 90-95°C/0.2 Torr), afforded 12 mg (33%) of the chloro ketone (159) as a colorless oil. Analysis of this material by glc (column B) and ^{1}H nmr spectroscopy showed that it consisted of a mixture of epimers in the ratio of ~4:1. This material exhibited ir (film): 3060, 1730, 1635, 900 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.05, 0.88 (d, d, 3H total, secondary methyl protons, ratio ~4:1 respectively, J = 7 Hz in each case), 1.60-2.50 (m, ~9.25H), 2.78-2.88 (m, ~0.75H, signal related to the major isomer), 3.52-3.63 (m, 2H, -CH_2Cl), 4.78, 4.94 (s, s, ~0.75H each, olefinic protons of the major isomer), 4.89-4.92 (m, ~0.5H, olefinic protons of the minor isomer). Exact Mass calcd. for $C_{11}H_{17}O^{35}Cl$: 200.0969; found: 200.0975.

(b) Using the Organocopper Reagent (145)

Following general procedure D, chloro ketone (159) was obtained from 2-methyl-2-cyclopenten-1-one (152). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide complex (45.4 mg, 0.22 mmol) and tri-n-butylphosphine (98 μL, 0.39 mmol) in 2.2 mL of dry ether; 5-chloro-2-lithio-1-pentene (112) (0.19 mmol) in 2 mL of dry THF; 2-methyl-2-cyclopenten-1-one (152) (20 μL, 0.2 mmol). Workup, followed by column chromatography of the crude material on

silica gel (5 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 90-95°C/0.2 Torr) of the oil obtained from the appropriate fractions, provided 26.2 mg (67%) of the chloro ketone (159). Glc analysis (column B) of this material showed that it consisted of a ~2:1 mixture of epimers. The ^1H nmr spectrum of this material was very similar to that of the material described above.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-3-methylcyclopentanone (158)



158

(a) Using the Grignard Reagent (144)

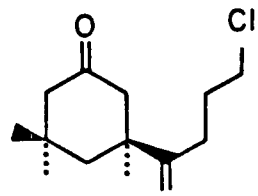
Following general procedure C, 3-methyl-2-cyclopenten-1-one (151) was converted into the conjugate addition product (158). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (112) (0.21 mmol) in 2 mL of dry THF; magnesium bromide-etherate (65.1 mg, 0.25 mmol); cuprous bromide-dimethyl sulfide complex (10.7 mg, 0.052 mmol), 3-methyl-2-cyclopenten-1-one (151) (21 μL, 0.21 mmol); boron trifluoride-etherate (30 μL, 0.25 mmol). Normal workup, followed by column chromatography of the crude material on silica gel (3 g, elution with 3:1 petroleum ether-ether) and distillation (air-bath temperature

76-85°C/0.2 Torr) of the oil obtained from the appropriate fractions, afforded 22.5 mg (54%) of the chloro ketone (**158**) as a colorless oil. This material exhibited ir (film): 3070, 1730, 1630, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.20 (s, 3H, tertiary methyl protons), 1.85-2.50 (m, 10H), 3.59 (t, 2H, $-C\underline{H}_2Cl$, $\underline{J}$ = 7 Hz), 4.82 (br s, 1H, olefinic proton), 4.88 (s, 1H, olefinic proton). Exact Mass calcd. for $C_{11}H_{17}O^{35}Cl$: 200.0969; found: 200.0969.

(b) Using the Organocopper Reagent (145)

Following general procedure E, chloro ketone (**158**) was obtained from 3-methyl-2-cyclopenten-1-one (**151**). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide complex (43 mg, 0.21 mmol) and tri-n-butylphosphine (95 μL, 0.38 mmol) in 2.1 mL of dry ether; 5-chloro-2-lithio-1-pentene (**112**) (0.19 mmol) in 2 mL of dry THF; 3-methyl-2-cyclopenten-1-one (**151**) (19 μL, 0.19 mmol); boron trifluoride-etherate (28 μL, 0.23 mmol). Workup, followed by column chromatography of the crude material on silica gel (5 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 76-85°C/0.2 Torr) of the oil obtained from the appropriate fractions, gave 14.3 mg (38%) of the chloro ketone (**158**). The ^1H nmr spectrum of this material was identical with that of the material given above.

Preparation of 3-[2-(5-Chloro-1-pentenyl)]-3,5,5-trimethylcyclohexanone (156)



156

(a) Using the Grignard Reagent (144)

Following general procedure C, 3,5,5-trimethyl-2-cyclohexen-1-one (149) was converted into the conjugate addition product (156). The following amounts of reagents were used: 5-chloro-2-lithio-1-pentene (112) (0.39 mmol) in 4 mL of dry THF; magnesium bromide-etherate (120.5 mg, 0.47 mmol); cuprous bromide-dimethyl sulfide complex (22.5 mg, 0.11 mmol), 3,5,5-trimethyl-2-cyclohexen-1-one (149) (58 μL, 0.39 mmol); boron trifluoride-etherate (58 μL, 0.47 mmol). The resultant mixture was stirred at -78°C for 4.5 h. Normal workup, followed by column chromatography of the crude material on silica gel (5 g, elution with 3:1 petroleum ether-ether) and distillation (air-bath temperature 82-86°C/0.2 Torr) of the oil obtained from the appropriate fractions, afforded 42.6 mg (45%) of the chloro ketone (156) as a colorless oil. This material exhibited ir (film): 3070, 1700, 1630, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.97, 1.04, 1.16 (s, s, s, 3H each, tertiary methyl protons), 1.58 (d, 1H, $\underline{J}$ = 14 Hz), 1.90-2.05 (m, 3H), 2.13-2.25 (m, 5H), 2.76 (d, 1H, $\underline{J}$ = 14 Hz), 3.59 (t, 2H, -$C\underline{H}_2$Cl, $\underline{J}$ = 7 Hz), 4.81, 5.04 (br

s, br s, 1H each, olefinic protons). Exact Mass calcd. for $C_{14}H_{23}O^{35}Cl$: 242.1437; found: 242.1436.

(b) Using the Organocopper Reagent (145)

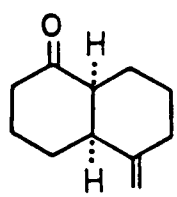
Following general procedure E, chloro ketone (156) was prepared from 3,5,5-trimethyl-2-cyclohexen-1-one (149). The following amounts of reagents were used: a solution of cuprous bromide-dimethyl sulfide complex (44 mg, 0.21 mmol) and tri-n-butylphosphine (97 μL, 0.39 mmol) in 2.1 mL of dry ether; 5-chloro-2-lithio-1-pentene (112) (0.19 mmol) in 2.0 mL of dry THF; 3,5,5-trimethyl-2-cyclohexen-1-one (149) (29 μL, 0.19 mmol); boron trifluoride-etherate (29 μL, 0.23 mmol). Workup, followed by column chromatography of the crude material on silica gel (5 g, elution with 20:1 to 7:1 petroleum ether-ether) and distillation (air-bath temperature 82-86°C/0.2 Torr) of the oil obtained from the appropriate fractions, provided 10 mg (21%) of the chloro ketone (156). This material exhibited a ^1H nmr spectrum identical with that of the material described above.

General Procedure F: Cyclization of the Chloro Ketones Derived from the Conjugate Addition of Reagents (144) and/or (145) to Cyclic Enones

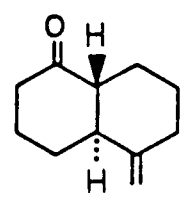
To a solution of the chloro ketone (1.0 equiv) in dry THF (~1 mL per 0.1 mmol of the chloro ketone) was added potassium hydride (~ 2.5

equiv) as a suspension in dry THF (~ 1 mL per mmol of potassium hydride) at room temperature. The resultant yellow mixture was stirred at room temperature for 2 h. Saturated aqueous ammonium chloride (5 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted twice with ether. The combined ether extract was washed once with brine and dried over anhydrous magnesium sulfate. Solvent removal under reduced pressure followed by distillation of the residual oil provided the product.

Preparation of cis-7-Methylenebicyclo[4.4.0]decan-2-one (160) and trans-7-Methylenebicyclo[4.4.0]decan-2-one (161)



160



161

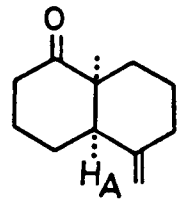
Following general procedure F, the chloro ketone (153) (44 mg, 0.22 mmol) in 2 mL of dry THF was allowed to react with potassium hydride (22 mg, 0.55 mmol) in 0.5 mL of dry THF. Workup, followed by distillation (air-bath temperature 100-120°C/33 Torr) of the crude material, afforded 31 mg (86%) of a colorless oil. This material showed one peak by glc analysis (column B) and two spots by tlc analysis (3:1 petroleum ether-ether). The ^{1}H nmr spectrum of this material showed that it consisted

of a mixture of cis and trans isomers in a ratio of 1:2, respectively. Column chromatography of this mixture on silica gel (10 g, elution with 12:1 petroleum ether-ether), followed by concentration of the appropriate fractions provided, in order of elution, 8 mg of the cis isomer (160) as a colorless oil (distillation temperature 95-100°C/33 Torr) and 17 mg of the trans isomer (161) as a white solid (mp 28-29°C, recrystallization from petroleum ether).

The cis ketone (160) exhibited ir (film): 3040, 1700, 1630, 895 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.31-1.45 (m, 1H), 1.45-1.64 (m, 2H), 1.64-1.79 (m, 1H), 1.79-1.94 (m, 2H), 2.00-2.19 (m, 3H), 2.19-2.30 (m, 2H), 2.36-2.55 (m, 2H), 2.63-2.72 (m, 1H), 4.66 (t, 1H, olefinic proton, J = 1.5 Hz), 4.69 (s, 1H, olefinic proton). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1202; found: 164.1205.

The trans ketone (161) exhibited ir ($CHCl_3$): 1700, 1635, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.20-1.36 (m, 1H), 1.36-1.52 (m, 1H), 1.60-1.78 (m, 2H), 1.83-2.09 (m, 6H), 2.09-2.21 (m, 1H), 2.23-2.45 (m, 3H), 4.69, 4.75 (s, s, 1H each, olefinic protons); ^{13}C nmr (20 MHz, $CDCl_3$) δ: 24.99, 25.30, 26.27, 27.61, 35.76, 41.26, 48.10, 55.53, 75.42, 77.02, 78.62, 105.74, 151.57, 212.45. Exact Mass calcd. for $C_{11}H_{16}O$: 164.1202; found: 164.1202.

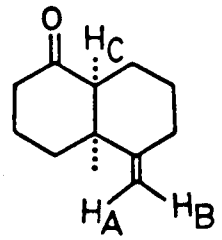
Preparation of cis-1-Methyl-7-methylenebicyclo[4.4.0]decan-2-one (164)



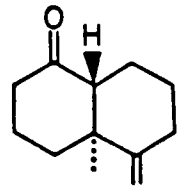
164

Following general procedure F, a solution of the mixture of chloro ketones (155) (21.7 mg, 0.1 mmol) in 1 mL of dry THF was allowed to react with potassium hydride (11 mg, 0.26 mmol) in 0.3 mL of dry THF. Workup, followed by distillation (air-bath temperature 85-92°C/22 Torr) of the crude material, afforded 14 mg (78%) of the bicyclic ketone (164) as a colorless oil. This material consisted of one component as shown by glc (column B) analysis and ^{1}H nmr spectroscopy. This material exhibited ir (film): 3050, 1695, 1635, 895 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.10 (s, 3H, tertiary methyl protons), 1.19-1.28 (m, 1H), 1.55-1.76 (m, 4H), 1.98-2.37 (m, 7H), 2.55-2.67 (m, 1H), 4.69 (t, 1H, olefinic proton, J = 1.5 Hz), 4.72 (t, 1H, olefinic proton, J = 2 Hz). In a nOe difference experiment, irradiation at δ 1.10 caused enhancement of a signal at δ 2.25 (d of d, J = 12, 6 Hz). Exact Mass calcd. for $C_{12}H_{18}O$: 178.1358; found: 178.1357.

Preparation of cis-6-Methyl-7-methylenebicyclo[4.4.0]decan-2-one (162) and trans-6-Methyl-7-methylenebicyclo[4.4.0]decan-2-one (163)



162



163

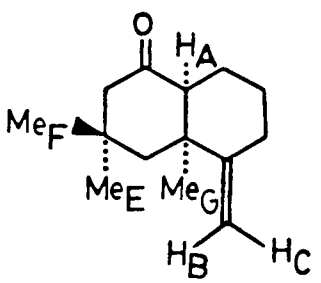
Following general procedure F, a solution of 22 mg (0.1 mmol) of the chloro ketone (154) in 1 mL of dry THF was allowed to react with potassium hydride (10 mg, 0.25 mmol) in 0.3 mL of dry THF. Normal workup, followed by distillation (air-bath temperature 100-113°C/33 Torr) of the crude material, afforded 15 mg (82%) of a colorless oil. Analysis of this oil by glc (column B) showed that it consisted of a mixture of cis and trans isomers in a ratio of 3.5:1, respectively. Column chromatography on silica gel impregnated with 25% silver nitrate (6 g, elution with 25:1 petroleum ether-ether), followed by concentration of the appropriate fractions and distillation afforded, in order of elution, 5 mg of the cis isomer (162) and 2 mg of the trans isomer (163), both as colorless oils. A mixture (5 mg) of (162) and (163) was also recovered.

The cis ketone (162) (distillation temperature 106-109°C/33 Torr) exhibited ir (film): 3060, 1700, 1630, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.17 (s, 3H, tertiary methyl protons), 1.28-1.47 (m, 2H), 1.61-1.70 (m, 1H), 1.75-2.05 (m, 4H), 2.15 (d of d, 1H, H_c, J = 10, 4 Hz),

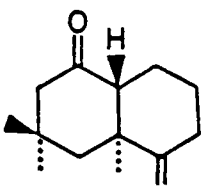
2.18-2.40 (m, 4H), 2.43-2.53 (m, 1H), 4.73 (s, 1H, olefinic proton, H_A), 4.76 (br s, 1H, olefinic proton, H_B). In a nOe difference experiment, irradiation at δ 1.17 caused enhancement of the signals at δ 4.73 (s) and δ 2.15 (d of d, $\underline{J}$ = 10, 4 Hz). Exact Mass calcd. for $C_{12}H_{18}O$: 178.1358; found: 178.1359.

The trans ketone (163) (distillation temperature 102-105°C/33 Torr) exhibited ir ($CHCl_3$): 3060, 1700, 1630, 895 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.95 (s, 3H, tertiary methyl protons), 1.20-1.35 (m, 1H), 1.50-1.75 (m, 2H), 1.84-2.40 (m, 10H), 4.70-4.76 (m, 2H, olefinic protons). Exact Mass calcd. for $C_{12}H_{18}O$: 178.1358; found: 178.1355.

Preparation of cis-7-Methylene-4,4,6-trimethylbicyclo[4.4.0]decan-2-one (165) and trans-7-Methylene-4,4,6-trimethylbicyclo[4.4.0]decan-2-one (166)



165



166

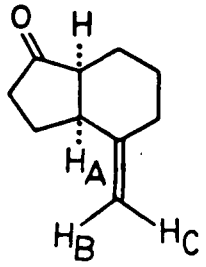
Following general procedure F, a solution of the chloro ketone (156) (76.7 mg, 0.32 mmol) in 3.2 mL of dry THF was allowed to react with potassium hydride (33 mg, 0.79 mmol) in 1 mL of dry THF. Workup, followed by distillation (air-bath temperature 70-86°C/24 Torr) of the crude material, afforded 58 mg (89%) of a colorless oil. Analysis of

this oil by glc (column B) showed that it consisted of a mixture of cis and trans isomers in a ratio of 8:1, respectively. Column chromatography of this material on silica gel impregnated with 25% silver nitrate (12 g, elution with 25:1 petroleum ether-ether), followed by concentration of the appropriate fractions, provided 5.7 mg of the cis isomer (**165**) as a white solid, mp 56-56.5°C (recrystallization from petroleum ether), and 46 mg of a mixture of (**165**) and (**166**). The trans isomer (**166**) was characterized after equilibration of the mixture as described later.

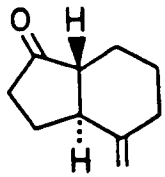
The cis ketone (**165**) exhibited ir ($CDCl_3$): 3070, 1690, 1620, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.05 (s, 3H, Me_F), 1.06 (s, 3H, Me_E), 1.26 (s, 3H, bridgehead methyl protons), 1.33 (d, 1H, J = 15 Hz), 1.43 (m, 1H), 1.63-1.76 (m, 2H), 1.92-2.03 (m, 1H), 2.08 (d of d of d, 1H, J = 14, 1.5, 1.5 Hz), 2.13 (d of d, 1H, H_A, J = 8, 4.5 Hz), 2.23-2.37 (m, 3H), 2.43 (d, 1H, J = 14 Hz), 4.77 (q, 1H, H_C, J = 1.5 Hz), 4.80 (br s, 1H, H_B). In a nOe difference experiment, irradiation at δ 1.26 caused enhancement of the signals at δ 1.06, 2.13 and 4.80. Exact Mass calcd. for $C_{14}H_{22}O$: 206.1672; found: 206.1680.

The trans ketone (**166**), a colorless oil (distillation temperature 72-75°C/24 Torr), exhibited ir (film): 3060, 1700, 1623, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.04, 1.10, 1.14 (s, s, s, 3H each, tertiary methyl protons), 1.19-1.34 (m, 1H), 1.49-1.72 (m, 2H), 1.76-1.91 (m, 2H), 2.01 (d, 1H, J = 13.5 Hz), 2.08-2.20 (m, 2H), 2.20-2.43 (m, 3H), 4.70, 4.73 (br s, br s, 1H each, olefinic protons). Exact Mass calcd. for $C_{14}H_{22}O$: 206.1671; found: 206.1675.

Preparation of cis-2-Methylenebicyclo[4.3.0]nonan-7-one (167) and trans-2-Methylenebicyclo[4.3.0]nonan-7-one (168)



167



168

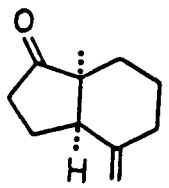
Following general procedure F, a solution of 36.8 mg (0.2 mmol) of the chloro ketone (157) in 2 mL of dry THF was allowed to react with potassium hydride (20 mg, 0.5 mmol) in 0.5 mL of dry THF. Workup, followed by distillation (air-bath temperature 70-85°C/23 Torr) of the crude material, afforded 24.8 mg (84%) of a colorless oil. Analysis of this oil by glc (column B) showed that it consisted of a mixture of the isomers (167) and (168) in a ratio of ~5:1, respectively. The ^1H nmr spectrum of this oil also indicated a mixture of epimers (~5:1). Column chromatography of the mixture on silica gel impregnated with 25% silver nitrate (6 g, elution with 20:1 petroleum ether-ether), followed by distillation (air-bath temperature 75-80°C/23 Torr) of the oil obtained from the appropriate fractions, provided 4 mg of the cis isomer (167) as a colorless oil. A mixture (11 mg) of (167) and (168) was also recovered.

The cis ketone (167) exhibited ir (film): 3050, 1730, 1635, 895 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.42-1.60 (m, 2H), 1.62-1.80 (m, 2H), 1.85-1.97 (m, 1H), 2.05-2.14 (m, 1H), 2.15-2.37 (m, 3H), 2.37-2.41 (m, 2H), 2.95(d of t, 1H, H_A, J = 7, 7 Hz), 4.79 (s, 1H, H_B), 4.80 (br s, 1H,

H_C). In a nOe difference experiment, irradiation at δ 2.95 caused enhancement of the signals at δ 4.79 (s) and 2.37-2.41 (m). Exact Mass calcd. for $C_{10}H_{14}O$: 150.1046; found: 150.1039.

The ^1H nmr spectrum of a mixture of the cis and trans ketones [(167) and (168)] showed that the alkene protons of the trans isomer (168) resonated at δ 4.66 (s) and 4.77 (br s). Exact Mass calcd. for $C_{10}H_{14}O$: 150.1046; found (glc-mass spectroscopy): 150.1066.

Preparation of cis-6-Methyl-2-methylenebicyclo[4.3.0]nonan-7-one (170)

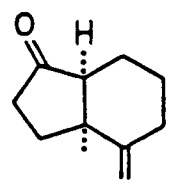


170

Following general procedure F, a solution of the mixture of chloro ketones (159) (37 mg, 0.18 mmol) in 1.8 mL of dry THF was allowed to react with potassium hydride (18 mg, 0.45 mmol) in 0.5 mL of dry THF. Workup, followed by distillation (air-bath temperature 68-73°C/23 Torr) of the crude oil afforded 27.4 mg (90%) of the bicyclic ketone (170) as a colorless oil. This oil consisted of one component as shown by glc (column B) and tlc (3:1 petroleum ether-ether) analysis and by ^1H nmr spectroscopy. This material exhibited ir (film): 3050, 1730, 1635, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.04 (s, 3H, tertiary methyl protons), 1.18-1.27 (m, 1H), 1.43-1.56 (m, 2H), 1.60-1.72 (m, 1H), 1.83-1.95 (m,

1H), 1.98-2.12 (m, 1H), 2.12-2.28 (m, 3H), 2.43-2.55 (m, 2H), 4.76-4.83 (m, 2H, olefinic protons). In a nOe difference experiment, irradiation at δ 1.04 caused enhancement of the signal at δ 2.49 (d of d, $\underline{J}$ = 12, 8 Hz). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1202; found: 164.1205.

Preparation of cis-1-Methyl-2-methylenebicyclo[4.3.0]nonan-7-one (169)



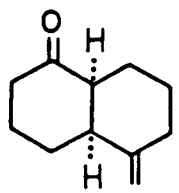
169

Following general procedure F, a solution of the chloro ketone (**158**) (32.7 mg, 0.16 mmol) in 1.6 mL of dry THF was allowed to react with potassium hydride (17 mg, 0.43 mmol) in 0.5 mL of dry THF. Workup, followed by distillation (air-bath temperature 72-76°C/23 Torr) of the crude material, afforded 21.7 mg (83%) of the bicyclic ketone (**169**) as a colorless oil. Analysis of this oil by glc (column B), tlc (3:1 petroleum ether-ether) and ^{1}H nmr spectroscopy indicated that it consisted of one component. This material exhibited ir (film): 3070, 1735, 1635, 900 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.15-1.30 (m, 1H), 1.34 (s, 3H, tertiary methyl protons), 1.50-1.61 (m, 3H), 1.97-2.10 (m, 2H), 2.10-2.33 (m, 4H), 2.45 (m, 1H), 4.77, 4.81 (s, s, 1H each, olefinic protons). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1202; found: 164.1208.

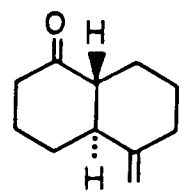
General Procedure G: Equilibration of Bicyclic Ketones Derived from the Cyclization of the Chloro Ketones

Sodium metal (10 mg, 0.43 mmol) was added to 0.5 mL of stirred, dry methanol at room temperature. After all of the sodium had reacted, a solution of appropriate bicyclic ketone in dry methanol (~0.5 mL per 0.1 mmol of bicyclic ketone) was added and the mixture was refluxed for 18 h. Saturated aqueous ammonium chloride (2 mL) and ether (4 mL) were added. The aqueous layer were separated and washed twice with ether. The combined ether extract was washed once with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure and distillation of the residual oil provided the product.

Equilibration of cis-7-Methylenebicyclo[4.4.0]decan-2-one (160) and trans-7-Methylenebicyclo[4.4.0]decan-2-one (161)



160



161

(a) Use of a Mixture of the Bicyclic Ketones (160) and (161)

Following general procedure G, a mixture of the cis and trans

bicyclic ketones (**160**) and (**161**) (ratio 1:2, respectively) (20 mg, 0.12 mmol) was equilibrated with sodium methoxide in refluxing dry methanol (1.1 mL). Workup, followed by distillation (air-bath temperature 110-120°C/33 Torr) of the crude material, provided 18 mg (90%) of a white solid. The ^{1}H nmr spectrum of this material was identical with that of the trans isomer (**161**).

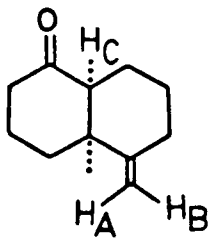
(b) Use of the Pure cis Ketone (**160**)

Following general procedure G, the pure cis ketone (**160**) (10 mg, 0.061 mmol) was treated with sodium methoxide in refluxing dry methanol (0.8 mL). Workup, followed by distillation (air-bath temperature 110-120°C/33 Torr) of the residue, afforded 7 mg (70%) of a white solid. This material exhibited ^{1}H nmr spectrum identical with that of the trans ketone (**161**).

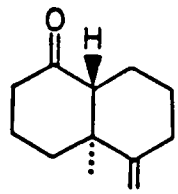
(c) Use of the Pure trans Isomer (**161**)

Following general procedure G, 13.4 mg (0.088 mmol) of the pure trans ketone (**161**) was treated with sodium methoxide in refluxing dry methanol (0.9 mL). Workup, followed by distillation (air-bath temperature 110-120°C/33 Torr) of the residue, afforded 10 mg (75%) of a white solid. This material exhibited ^{1}H nmr spectrum identical with that of the trans ketone (**161**).

Equilibration of cis-6-Methyl-7-methylenebicyclo[4.4.0]decan-2-one (162) and trans-6-Methyl-7-methylenebicyclo[4.4.0]decan-2-one (163)



162



163

(a) Use of the Pure cis Ketone (162)

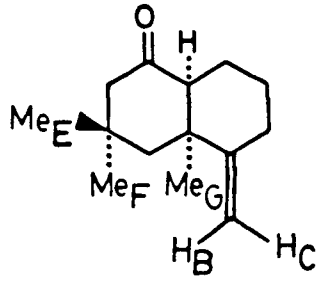
Following general procedure G, the pure cis ketone (162) (11 mg, 0.062 mg) was equilibrated with sodium methoxide in refluxing dry methanol (0.8 mL). Workup, followed by distillation (air-bath temperature 100-113°C/33 Torr) of the crude material, afforded 7 mg (64%) of a colorless oil. Analysis of this oil by glc (column B) showed that it consisted of the isomers (162) and (163) in a ratio of 1:2.8, respectively.

(b) Use of the Pure trans Ketone (163)

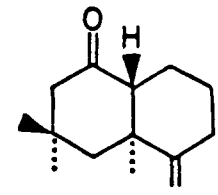
Following general procedure G, the pure trans ketone (163) (18 mg, 0.1 mmol) was equilibrated with sodium methoxide in refluxing dry methanol (1 mL). Workup and distillation (air-bath temperature 100-113°C/33 Torr) of the residue provided 14 mg (77%) of a colorless

oil. Analysis of this oil by glc (column B) indicated that it consisted of (162) and (163) in a ratio of 1:2.8, respectively.

Equilibration of cis-7-Methylene-4,4,6-trimethylcyclo[4.4.0]decan-2-one (165) and trans-7-Methylene-4,4,6-trimethylbicyclo[4.4.0]decan-2-one (166)



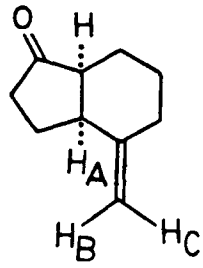
165



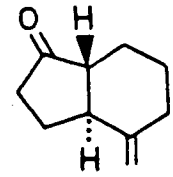
166

Following general procedure G, a mixture of the ketones (165) and (166) (ratio 8:1, respectively) (53.8 mg, 0.26 mmol) was equilibrated with sodium methoxide in refluxing dry methanol (2.5 mL). Workup afforded 50 mg (93%) of crude material. Analysis of this material by glc (column B) showed that it consisted of a mixture of (165) and (166) in a ratio of 1:2, respectively. Column chromatography of this mixture on silica gel impregnated with 25% silver nitrate (12 g, elution with 90:1 to 20:1 petroleum ether-ether), followed by concentration of the appropriate fractions, afforded, in order of elution, 10.9 mg of the cis ketone (165) as a white solid, 16 mg of a mixture of (165) and (166), and 16.8 mg of trans ketone (166) (distillation temperature 72-75°C/24 Torr) as a colorless oil.

Equilibration of cis-2-Methylenebicyclo[4.3.0]nonan-7-one (167) and trans-2-Methylenebicyclo[4.3.0]nonan-7-one (168)



167



168

(a) Use of a Mixture of (167) and (168)

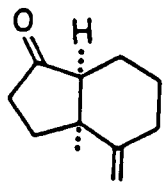
Following general procedure G, a mixture of ketones (167) and (168) (ratio 84:16, respectively) (15 mg, 0.091 mmol) was equilibrated with sodium methoxide in refluxing dry methanol (0.7 mL). Workup, followed by distillation (air-bath temperature 70-85°C/23 Torr) of the crude material, afforded 12 mg (80%) of a colorless oil. This oil consisted of a mixture of the ketones (167) and (168) in the ratio of 82:18, respectively, as determined by glc (column B) analysis.

(b) Use of the Pure cis Ketone (167)

Following general procedure G, the pure cis ketone (167) (15 mg, 0.091 mmol) was equilibrated with sodium methoxide in refluxing dry methanol (0.7 mL). Workup and distillation (air-bath temperature 70-85°C/23 Torr) of the crude product provided 10 mg (67%) of a colorless oil. This oil was shown by glc (column B) analysis to consist

of a mixture of ketones (167) and (168) in the ratio of 85:15, respectively.

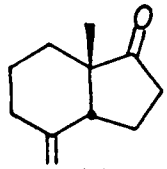
Equilibration of cis-1-Methyl-2-methylenebicyclo[4.3.0]nonan-7-one (169)



169

Following general procedure G, 11 mg (0.066 mmol) of the pure cis bicyclic ketone (169) was equilibrated with sodium methoxide in refluxing dry methanol (0.8 mL). Workup, followed by distillation (air-bath temperature 72-76°C/23 Torr) of the crude material, afforded 10 mg (91%) of a colorless oil. This material showed one peak by glc (column B) analysis and exhibited a ^{1}H nmr spectrum identical with that of the pure cis ketone (169).

Large Scale Preparation of 6-Methyl-2-methylenebicyclo[4.3.0]nonan-7-one (170)



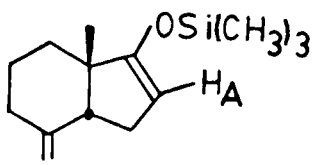
170

To a cold (-78°C), stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (111) (1.96 g, 7.3 mmol) in 30 mL of dry THF was added methyllithium (9.1 mmol) as a solution in ether and the colorless solution was stirred at -78°C for 15 min. Solid magnesium bromide-etherate (1.88 g, 7.3 mmol) was added in one portion and the milky mixture was stirred at -78°C for 20 min. Solid cuprous bromide-dimethyl sulfide complex (376 mg, 1.8 mmol) was added in one portion to this mixture at -78°C. To the pale yellow mixture was added successively a solution of 2-methyl-2-cyclopenten-1-one (152) (541 mg, 5.6 mmol) in 5 mL of dry THF and boron trifluoride-etherate (0.9 mL, 7.3 mmol). The resulting bright yellow mixture was stirred at -78°C for 3 h. Saturated aqueous ammonium chloride (pH 8) (25 mL) and ether (30 mL) were added and the mixture was allowed to warm to room temperature with vigorous stirring and exposure to air. The blue aqueous layer was separated and extracted twice with ether. The combined ether extract was washed twice with saturated aqueous ammonium chloride (pH 8), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (80 g, elution with 4:1 petroleum ether-ether). Distillation (air-bath temperature 90-95°C/0.2 Torr) of the oil obtained from the appropriate fractions afforded 996 mg (89%) of the mixture of chloro ketones (159) (ratio ~2:1).

Following general procedure F, a solution of the mixture of chloro ketones (159) (996 mg, 5.0 mmol) in 5 mL of dry THF was allowed to react with 498 mg (12.4 mmol) of potassium hydride in 5 mL of dry THF. Normal workup, followed by distillation (air-bath temperature 68-73°C/23 Torr)

of the crude material, afforded 789 mg (96%) of the bicyclic ketone (170) as a colorless oil.

Preparation of 6-Methyl-2-methylene-7-trimethylsiloxybicyclo[4.3.0]-non-7-ene (210)

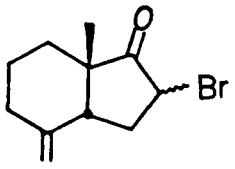


210

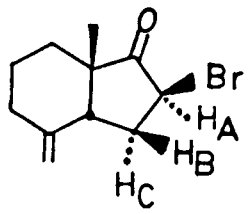
To a cold (-78°C), stirred solution of LDA (2.3 mmol) in 2.3 mL of dry THF was added a solution of 6-methyl-2-methylenebicyclo[4.3.0]nonan-7-one (170) (310 mg, 1.9 mmol) in 2 mL of dry THF. The solution was stirred at -78°C for 40 min, during which time a white solid was formed. Trimethylsilyl chloride (310 μL, 2.5 mmol) was added at -78°C and, after 5 min, the mixture was allowed to warm to room temperature and then was stirred for a further 1.5 h. During this time, the initially formed white precipitate dissolved and then, after a short time, was replaced by another precipitate. The mixture was diluted with 5 mL of dry ether and then was filtered. After the filtrate had been concentrated under reduced pressure, the residue was treated with 2 mL of dry ether and the resultant mixture was filtered again. Removal of solvent from the filtrate under reduced pressure, followed by distillation (air-bath temperature 82-88°C/25 Torr) of the residual material, afforded 446 mg

(99%) of the silyl enol ether (210) as a colorless oil. This material exhibited ir (film): 3050, 1630, 1252, 1235, 920, 895, 845 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.21 [s, 9H, $-Si(C\underline{H}_3)_3$], 0.97 (s, 3H, tertiary methyl protons), 1.24-1.65 (m, 4H), 2.09-2.26 (m, 4H), 2.42 (t, 1H, bridgehead proton, $\underline{J}$ = 9 Hz), 4.48 (t, 1H, H_A, $\underline{J}$ = 2 Hz), 4.70 (br s, 2H, $>C=C\underline{H}_2$). Exact Mass calcd. for $C_{14}H_{24}OSi$: 236.1597; found: 236.1599.

Preparation of 8-Bromo-6-methyl-2-methylenebicyclo[4.3.0]nonan-7-one (211)



211

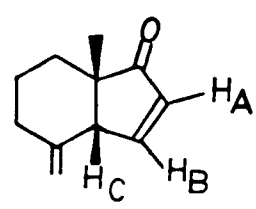


211a

A solution of N-bromosuccinimide (355 mg, 2.0 mmol) in 6 mL of dry THF was added dropwise to a solution of the silyl enol ether (210) (446 mg, 1.9 mmol) in 3 mL of dry THF at 0°C. After the mixture had been stirred for 15 min at 0°C, 15 mL of water and 15 mL of tetrachloromethane were added. The aqueous layer was separated and extracted twice with tetrachloromethane. The combined organic layer was washed once with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Distillation (air-bath temperature 48-52°C/0.2 Torr) of the residual oil afforded 425 mg (92%) of the bromo ketone (211)

as a colorless oil with very sweet smell. Analysis of this oil by glc (column B) showed that it consisted of a mixture of epimers in a ratio of 85:15. The major epimer (**211a**) exhibited ir (film): 3050, 1740, 1640, 1060, 900 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.24 (s, 3H, tertiary methyl protons), 1.29-1.78 (m, 4H), 2.05-2.18 (m, 1H), 2.14 (d of d of d, 1H, H_B, $\underline{J}$ = 15, 6.5, 1 Hz), 2.18-2.28 (m, 1H), 2.55 (d of d of d, 1H, H_C, $\underline{J}$ = 15, 11.5, 6.5 Hz), 2.96 (d of d, 1H, bridgehead proton, $\underline{J}$ = 11.5, 6.5 Hz), 4.42 (d of d, 1H, H_A, $\underline{J}$ = 6.5, 1 Hz), 4.87, 4.90 (br s, br s, 1H each, olefinic protons). Irradiation at δ 2.55 caused the signal at δ 4.42 to sharpen, and the signals at δ 2.96 and 2.14 to simplify; irradiation at δ 2.96 caused the resonance at δ 2.55 to collapse to a d of d ($\underline{J}$ = 15, 6.5 Hz) and the signal at δ 2.14 to simplify; irradiation at δ 4.42 caused the signals at δ 2.14 and 2.55 to collapse, in each case, to a d of d ($\underline{J}$ = 15, 6.5 and 15, 11.5 Hz, respectively). Exact Mass calcd. for $C_{11}H_{15}O^{79}Br$: 242.0306; found: 242.0303.

Preparation of 6-Methyl-2-methylenebicyclo[4.3.0]non-8-en-7-one (203)

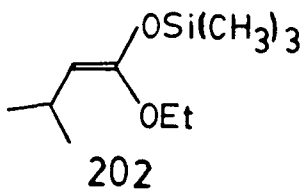


203

A solution of the bromo ketone (211) (425 mg, 1.76 mmol) in 5 mL of

dry DMF was added to a slurry of lithium bromide (315 mg, 3.6 mmol) and lithium carbonate (401 mg, 5.4 mmol) in 4 mL of dry DMF. The mixture was refluxed for 3 h and then was cooled and filtered. The collected salt was washed with 20 mL of ether. The combined filtrate was washed with water (3 x 15 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Distillation (air-bath temperature 90-100°C/25 Torr) of the residue provided 239 mg (84%) of the enone (203) as a colorless oil. This material exhibited ir (film): 3050, 3025, 1700, 1640, 900, 820 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 1.12 (s, 3H, tertiary methyl protons), 1.34-1.58 (m, 3H), 1.65 (m, 1H), 2.09 (m, 1H), 2.22 (m, 1H), 3.23 (br s, 1H, H_C), 4.92, 4.90 (br s, br s, 1H each, $\rangle C=CH_2$), 6.20 (d of d, 1H, H_A, J = 5.5, 2 Hz), 7.48 (d of d, 1H, H_B, J = 5.5, 2.5 Hz). In a nOe difference experiment, irradiation at δ 1.12 caused enhancement of the signal at δ 3.23. Exact Mass calcd. for $C_{11}H_{14}O$: 162.1045; found: 162.1046.

Preparation of (E)-1-Ethoxy-3-methyl-1-trimethylsiloxybut-1-ene (202)

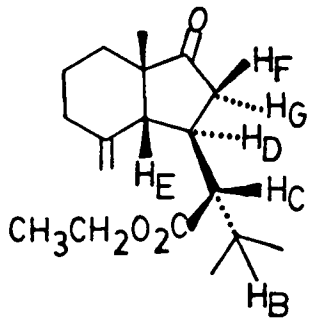


202

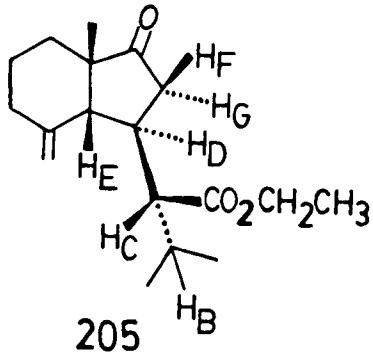
To a cold (-78°C), stirred solution of LDA (2.76 mmol) in 2.8 mL of

dry THF was added ethyl 3-methylbutanoate (299 mg, 2.3 mmol) in 2 mL of dry THF. The mixture was stirred at -78°C for 30 min. To this solution, trimethylsilyl chloride (410 μL, 3.2 mmol) was added. The solution was allowed to warm to room temperature and then was stirred for 1.5 h. The mixture was diluted with 5 mL of dry ether and then was filtered. After removal of the solvent from the filtrate (reduced pressure), the residue was treated with 2 mL of dry ether and the filtration was repeated. Removal of the solvent from the filtrate, followed by distillation (air-bath temperature 60-65°C/25 Torr) of the residual oil provided 419 mg (90%) of the silyl ketene acetal (**202**) as a colorless oil. Analysis of this material by glc (column B) indicated that it consisted of a mixture of (E) and (Z) isomers in a ratio of 95:5, respectively. This material was used immediately for the next reaction without further purification. This material exhibited ir (film): 1678, 1369, 1255, 1064, 891, 848 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 0.22 [s, 9H, $-Si(C\underline{H}_3)_3$], 0.95 [d, 6H, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz], 1.22 (t, 3H, $-OCH_2C\underline{H}_3$, $\underline{J}$ = 7 Hz), 2.25-2.80 [m, 1H, $-C\underline{H}(CH_3)_2$], 3.62 (d, 1H, vinyl proton, $\underline{J}$ = 9 Hz), 3.82 (q, 2H, $-OC\underline{H}_2CH_3$, $\underline{J}$ = 7 Hz).

Preparation of the Bicyclic Keto Esters (204) and (205)



204



205

To a cold (-78°C), stirred solution of the bicyclic enone (203) (198 mg, 1.23 mmol) in 2 mL of dry dichloromethane was added titanium tetrachloride (150 μL, 1.36 mmol) and the solution was stirred for a further 5 min. To the resultant orange red solution was added a solution of the silyl ketene acetal (202) (311 mg, 1.5 mmol) in 2 mL of dry dichloromethane. The color of the solution turned to dark red immediately. After the mixture had been stirred at -78°C for 2 h, it was treated with 8 mL of water and the resultant mixture was extracted with ether (3 x 15 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (80 g, elution with 3:1 petroleum ether-ether) provided, after concentration of the appropriate fractions, 322 mg (89%) of a white solid. Analysis of this material by glc (column B) and ^{1}H nmr spectroscopy showed that it consisted of a mixture of (204) and (205) in a ratio of ~1:1. By using a combination of careful column chromatography on silica gel (10 g of silica gel per 10 mg of mixture, elution with 10:1 petroleum ether-ether, slow dripping) and multiple development preparative tlc (11 times, 10:1 petroleum ether-ether), pure

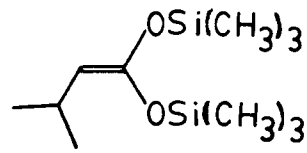
samples of (204) and (205) were obtained for characterization.

The keto ester (204), mp 80-81°C (recrystallization from petroleum ether), exhibited ir ($CHCl_3$): 3080, 3035, 1730, 1645, 1374, 1181, 902 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.94, 0.95 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 1.01 (s, 3H, tertiary methyl protons), 1.23 (t, 3H, $-OCH_2C\underline{H}_3$, $\underline{J}$ = 7 Hz), 1.20-1.30 (obscured m, 1H), 1.40-1.63 (m, 2H), 1.68-1.78 (m, 1H), 1.82-1.95 (partially obscured m, 1H, H_B), 1.94 (d of d, 1H, H_F, $\underline{J}$ = 18.5, 11.5 Hz), 2.07-2.15 (m, 1H), 2.15 (partially obscured d, 1H, H_E, $\underline{J}$ = 11 Hz), 2.20 (partially obscured d of d, 1H, H_C, $\underline{J}$ = 10, 4.5 Hz), 2.18-2.31 (m, 1H), 2.65 (d of d, 1H, H_G, $\underline{J}$ = 18.5, 7.5 Hz), 2.79-2.93 (m, 1H, H_D), 3.92-4.06 (m, 2H, $-OC\underline{H}_2CH_3$), 4.72 (br s, 1H, olefinic proton), 4.77 (t, 1H, olefinic proton, $\underline{J}$ = 2 Hz). Irradiation at δ 2.86 caused the signals at δ 1.94, 2.15, 2.20, and 2.65 to collapse to a d ($\underline{J}$ = 18.5 Hz), a s, a d ($\underline{J}$ = 4.5 Hz), and a d ($\underline{J}$ = 18.5 Hz), respectively; irradiation at δ 2.65 caused the resonance at δ 1.94 to collapse to an "imperfect" doublet ($\underline{J}$ = 11.5 Hz) and the signal at δ 2.86 to simplify; irradiation at δ 0.95 caused the multiplet at δ 1.83-1.94 to collapse to a broad singlet; in a nOe difference experiment, irradiation at δ 1.01 caused a weak enhancement of the signal at δ 2.15 (d, $\underline{J}$ = 11 Hz). Exact Mass calcd. for $C_{18}H_{28}O_3$: 292.2039; found: 292.2045.

The keto ester (205), mp 69-70°C (recrystallization from petroleum ether), exhibited ir ($CHCl_3$): 3070, 3028, 1728, 1645, 1377, 1188, 1152, 1029, 903 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.91, 0.95 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 1.03 (s, 3H, tertiary methyl protons), 1.27 (t, 3H, $-OCH_2C\underline{H}_3$, $\underline{J}$ = 7 Hz), 1.22-1.30 (obscured m, 1H),

1.45-1.55 (m, 2H), 1.67-1.77 (m, 1H), 1.84-2.00 (m, 1H, H_B), 2.03-2.17 (m, 1H), 2.30 (partially obscured d, 1H, H_E, $\underline{J}$ = 11 Hz), 2.18-2.28 (m, 1H), 2.28 (d of d, 1H, H_C, $\underline{J}$ = 10, 4 Hz), 2.52 (d of d, 1H, H_G, $\underline{J}$ = 17, 7 Hz), 2.56-2.74 (m, 2H), 4.16 (q, 2H, $-OC\underline{H}_2CH_3$, $\underline{J}$ = 7 Hz), 4.84 (t, 1H, olefinic proton, $\underline{J}$ = 1.5 Hz), 4.94 (t, 1H, olefinic proton, $\underline{J}$ = 2 Hz). Irradiation at δ 0.92 caused the multiplet at δ 1.84-2.00 to collapse to a d ($\underline{J}$ = 10 Hz); irradiation at δ 1.91 caused both of the doublets at δ 0.91 and 0.95 to collapse to singlets, and the d of d at δ 2.28 to collapse to a very broad singlet; in a nOe difference experiment, irradiation at δ 1.03 caused enhancement of the signal at δ 2.30 (d, $\underline{J}$ = 11 Hz). Exact Mass calcd. for $C_{18}H_{28}O_3$: 292.2039; found: 292.2041.

Preparation of 3-Methyl-1,1-bis(trimethylsiloxy)-1-butene (226)

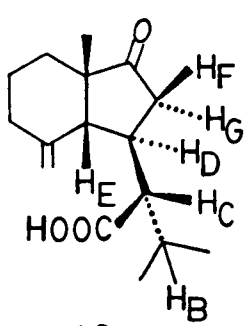


226

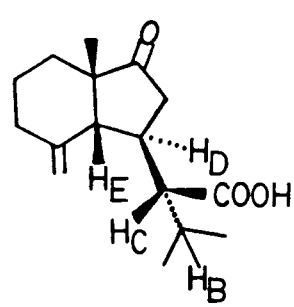
To a cold (-78°C), stirred solution of LDA (1.78 mmol) in 1.8 mL of dry THF was added 3-methylbutanoic acid (227) (82.8 mg, 0.81 mmol) in 2 mL of dry THF. After 5 min, the solution was warmed to 0°C and then was stirred at this temperature for 1.5 h. A white precipitate formed. HMPA (0.31 mL, 1.78 mmol) was added and the mixture was stirred for 15 min at 0°C. During this time, the white solid dissolved. To the clear, pale yellow solution was added 0.25 mL (1.97 mmol) of trimethylsilyl chlo-

ride. The solution was allowed to warm to room temperature and then was stirred for 1.5 h. Aqueous sodium bicarbonate (5%, 10 mL) and pentane (10 mL) were added. The organic layer was separated and washed with 5% aqueous sodium bicarbonate (4 x 10 mL), and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by distillation (air-bath temperature 80-90°C/25 Torr) of the residue, provided 172 mg (86%) of the bis(trimethylsilyl) ketene acetal (226) as a colorless oil. This material was used immediately for the next reaction without any further purification. This material exhibited ir (film): 1670, 1255, 1060, 890, 840, 760 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) δ: 0.20, 0.22 [s, s, 18H, $-Si(C\underline{H}_3)_3$ groups], 0.91 [d, 6H, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz], 2.41 [m, 1H, $-C\underline{H}(CH_3)_2$], 3.42 (d, 1H, vinyl proton, $\underline{J}$ = 8 Hz).

Preparation of the Bicyclic Keto Acids (222) and (223)



222



223

(a) Via Conjugate Addition of the Ketene Acetal (226) to Enone (203)

Titanium tetrachloride (69 μL, 0.63 mmol) was added to a stirred solution of the enone (203) (93 mg, 0.57 mmol) in 1 mL of dry dichloro-

methane at -78°C and the solution was stirred for 5 min. To this cold (-78°C), orange red solution was added slowly a solution of the ketene acetal (226) (168 mg, 0.68 mmol) in 1 mL of dry dichloromethane. The color of the solution turned to reddish brown immediately. The mixture was allowed to stir at -78°C for 2 h. Water (10 mL) was added and the mixture was allowed to warm to room temperature with stirring. After 5 min, the solution became colorless. The mixture was extracted with ether (3 x 15 mL). The combined ether extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford 150 mg of crude material. The ^1H nmr spectrum of this crude material indicated that it consisted of a mixture of (222) and (223) in the ratio of ~3:2, respectively. This mixture was subjected to a combination of (repeated) column chromatography on silica gel (20 g per 100 mg of sample, elution with 3:2 petroleum ether-ether) and fractional crystallization from ether. Eventually there was obtained 66 mg (44%) of the pure keto acid (222) and 48 mg (32%) of the pure keto acid (223), along with 18 mg (12%) of a mixture of (222) and (223).

Analytically pure sample of the keto acid (222) (recrystallization from ether) exhibited mp 172-173°C; ir ($CHCl_3$): 3400-2500 (br), 3030, 1735, 1703, 1646, 1375, 901 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.93, 1.05 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 1.00 (s, 3H, tertiary methyl protons), 1.23 (br d, 1H, $\underline{J}$ = 12 Hz), 1.38-1.59 (m, 2H), 1.66-1.75 (m, 1H), 1.86-2.00 (obscured m, 1H, H_B), 1.94 (d of d, 1H, H_F, $\underline{J}$ = 18.5, 11.5 Hz), 2.06-2.15 (m, 1H), 2.16 (partially obscured br d, 1H, H_E, $\underline{J}$ = 10.5 Hz), 2.21 (partially obscured d of d, 1H, H_C, $\underline{J}$ = 9.5, 4.5 Hz), 2.20-2.30 (m, 1H), 2.62 (d of d, 1H, H_G, $\underline{J}$ = 18.5, 7.5 Hz), 2.71-

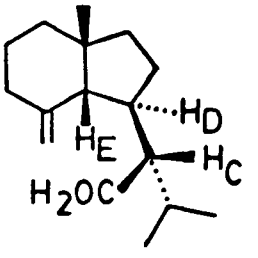
2.85 (m, 1H, H_D), 4.76 (t, 1H, olefinic proton, J = 1.5 Hz), 4.80 (br s, 1H, olefinic proton), 10.5-11.2 (br, 1H, -COOH). Irradiation at δ 2.62 caused the signals at δ 2.71-2.85 and 1.86-2.0 to simplify; irradiation at δ 2.78 caused the signals at δ 2.62, 2.16, 2.21 and 1.94 to collapse to a d (J = 18.5 Hz), a br s, a br s, and an "imperfect" doublet (J = 18.5 Hz), respectively; ^{13}C nmr (100 MHz, $CDCl_3$) δ: 17.12, 18.58, 21.48, 22.90, 28.50, 30.32, 34.51, 40.85, 51.18, 55.52, 58.84, 113.03, 144.97, 179.54, 218.00. Exact Mass calcd. for $C_{16}H_{24}O_3$: 264.1726; found: 264.1726.

Analytically pure sample of the keto acid (223) (recrystallization from petroleum ether-ether), exhibited mp 120-121°C; ir ($CHCl_3$): 3400-2500 (br), 3030, 1733, 1703, 1646, 1376, 907 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.95, 0.96 [d, d, 3H each, $-CH(CH_3)_2$, J = 6.5 Hz in each case], 1.03 (s, 3H, tertiary methyl protons), 1.21-1.30 (m, 1H), 1.42-1.57 (m, 2H), 1.66-1.77 (m, 1H), 1.86-1.99 (m, 1H, H_B), 2.01-2.04 (m, 1H), 2.17-2.23 (1 obscured H), 2.22 (br d, 1H, H_E, J = 10.5 Hz), 2.32 (d of d, 1H, H_C, J = 9.5, 3.5 Hz), 2.46-2.70 (m, 3H), 4.88 (br s, 1H, olefinic proton), 4.94 (t, 1H, olefinic proton, J = 2 Hz). Irradiation at δ 1.92 caused the doublets at δ 0.95 and 0.96 to sharpen and the signal at δ 2.32 to collapse to a br s; irradiation at δ 2.32 caused the signal at δ 1.86-1.99 to collapse to a septet (J = 6.5 Hz) and the signal at δ 2.46-2.70 to simplify; irradiation at δ 0.95 caused the signal at δ 1.86-1.99 to collapse to a d (J = 9.5 Hz). ^{13}C nmr (75 MHz, $CDCl_3$) δ: 18.83, 20.27, 21.37, 22.82, 28.69, 28.94, 30.65, 34.68, 37.57, 50.80, 52.25, 55.52, 113.76, 143.63, 178.93, 219.89. Exact Mass calcd. for $C_{16}H_{24}O_3$: 264.1726; found: 264.1727.

(b) Via Hydrolysis of the Keto Esters (204) and (205)

A mixture of the keto esters (204) and (205) (ratio ~1:1) (318 mg, 1.1 mmol) and potassium hydroxide (600 mg, 10.9 mmol) in 1.5 mL of ethanol and 0.5 mL of water was refluxed for 48 h. The solution was washed with ether (2 x 5 mL) and then was acidified with 1N hydrochloric acid. The resultant mixture was extracted with ether (3 x 10 mL). The combined ether extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to a combination of (repeated) column chromatography on silica gel (20 g per 100 mg of sample, elution with 3:2 petroleum ether-ether) and fractional crystallization from ether to afford 61.6 mg (21%) of the keto acid (222), 146 mg (50%) of the keto acid (223) and 32 mg (11%) of a mixture of (222) and (223). The isolated pure samples of (222) and (223) exhibited ^{1}H nmr spectra identical with those of the materials described above.

Preparation of the Bicyclic Acid (187)

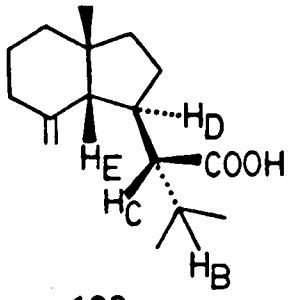


187

A stirred solution of the keto acid (222) (40 mg, 0.15 mmol) in anhydrous hydrazine (48 μL, 1.5 mmol) in 0.3 mL of diethylene glycol was

heated at 110°C for 3 h. The mixture was then heated at 190°C for 30 min, during which time excess hydrazine and water were allowed to distill from the solution. After the solution had been cooled to room temperature, 43 mg (0.75 mmol) of potassium hydroxide was added and the mixture was heated at 190°C for 6 h. Gas evolution was observed. The mixture was cooled to room temperature, was diluted with 5 mL of water, and then was acidified with 1N hydrochloric acid. Extraction of the resultant mixture with ether (3 x 5 mL), drying ($MgSO_4$) of the combined extract, and evaporation of the solvent under reduced pressure gave a white solid. This material was purified by column chromatography on silica gel (8 g, 4:1 petroleum ether-ether). Distillation (air-bath temperature 108-112°C/0.3 Torr) of the material obtained from the appropriate fractions afforded 34 mg (90%) of the acid (**187**) as a white solid. Recrystallization of this material from petroleum ether-ether afforded white needles, mp 120-121°C; ir ($CHCl_3$): 3500-2500 (br), 3071, 1703, 1644, 1390, 1374, 1219, 894 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.96, 0.97 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 0.94 (s, 3H, tertiary methyl protons), 1.16-1.24 (m, 1H), 1.35-1.66 (m, 6H), 1.86 (br d, 1H, H_E, $\underline{J}$ = 10.5 Hz), 1.90-2.07 (m, 3H), 2.10 (d of d, 1H, H_C, $\underline{J}$ = 9.5, 5 Hz), 2.13-2.24 (m, 1H), 2.46-2.58 (m, 1H, H_D), 4.67 (br s, 2H, olefinic protons). Irradiation at δ 2.50 caused the signal at δ 1.86 to collapse to a s, the signal at δ 2.10 to collapse to a d ($\underline{J}$ = 5 Hz) and the signals at δ 1.35-1.66 and 1.90-2.07 to simplify. Exact Mass calcd. for $C_{16}H_{26}O_2$: 250.1934; found: 250.1934.

Preparation of the Bicyclic Acid (193)

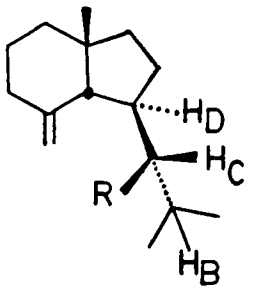


193

A stirred solution of the keto acid (223) (30 mg, 0.11 mmol) in anhydrous hydrazine (35 μL, 1.1 mmol) in 0.2 mL of diethylene glycol was heated at 110°C for 3 h. This mixture was then heated at 190°C for 30 min, during which time excess hydrazine and water were allowed to distill from the solution. The mixture was cooled and 31 mg (0.55 mmol) of potassium hydroxide was added. The mixture was heated at 190°C for 6 h. During this time, gas evolution was observed. The solution was cooled to room temperature, was diluted with 2 mL of water, and then was acidified with 1N hydrochloric acid. The resultant mixture was extracted with ether (3 x 6 mL). The combined ether extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (5 g, 4:1 petroleum ether-ether). Distillation (air-bath temperature 105-110°C/0.3 Torr) of the material obtained from the appropriate fractions afforded 25.6 mg (90%) of the bicyclic acid (193) as a colorless oil. This material exhibited ir (film): 3500-2500 (br), 3071, 1702, 1645, 1390, 1375, 1289, 1228, 1166, 895 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.93, 0.94 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case],

0.95 (s, 3H, tertiary methyl protons), 1.16-1.22 (m, 1H), 1.34-1.55 (m, 4H), 1.57-1.66 (m, 1H), 1.79-1.90 (m, 2H), 1.91 (partially obscured br d, 1H, H_E, $\underline{J}$ = 11 Hz), 1.96-2.08 (partially obscured m, 1H, H_B), 2.05-2.15 (m, 2H), 2.18 (d of d, 1H, H_C, $\underline{J}$ = 9, 5 Hz), 2.40-2.50 (m, 1H, H_D), 4.74 (br s, 1H, olefinic proton), 4.80 (t, 1H, olefinic proton, $\underline{J}$ = 2 Hz). Irradiation at δ 0.93 caused the signal at δ 1.96-2.08 to collapse to a d ($\underline{J}$ = 9 Hz); irradiation at δ 2.18 caused the signals at δ 2.40-2.50 and δ 1.96-2.08 to simplify; irradiation at δ 2.45 caused the signal at δ 1.91 to collapse to a s and the signal at δ 2.18 to collapse to a d ($\underline{J}$ = 9 Hz). Exact Mass calcd. for $C_{16}H_{26}O_2$: 250.1934; found: 250.1931.

Preparation of the Carbamate (237)



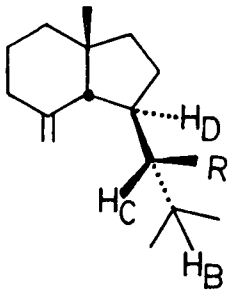
194 R= COCl
195 R= CON_3
237 R= $\underset{H}{NCO_2}(CH_2)_2SiMe_3$

To a stirred solution of the acid (187) (46 mg, 0.185 mmol) in 1.5 mL of dry toluene, under an atmosphere of argon, was added oxalyl chloride (64 μL, 0.74 mmol) and the mixture was stirred at room temperature. After 45 min, evolution of gas had ceased and the solvent was removed under reduced pressure. The residual pale yellow oil [the

acid chloride (194)] exhibited ir (film): 3072, 1794, 1646, 1393, 1375, 894 cm^{-1}. This material was dissolved in 1 mL of dry acetone and the solution was added to a rapidly stirred solution of sodium azide (50.5 mg, 0.74 mmol) in 0.2 mL of water at 0°C. After 15 min, 10 mL of hexanes and 5 mL of water were added. The organic layer was removed and the aqueous layer was extracted with 3 mL of hexanes. The combined organic extract was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure provided the acyl azide (195), which exhibited ir (film): 3070, 2271, 2130, 1714, 1644, 1373, 892 cm^{-1}. This material was dissolved in 0.2 mL of dry toluene and the solution was heated at 80°C with stirring. Evolution of nitrogen began immediately. After 2 h, 80 μL (0.55 mmol) of 2-trimethylsilylethanol was added and stirring at 80°C was continued for 20 h. Most of the solvent was removed under reduced pressure. The residue was dissolved in 6 mL of ether and the solution was washed with 5 mL of aqueous sodium hydroxide (1N). The ether layer was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by column chromatography of the residual material on silica gel (6 g, 6:1 petroleum ether-ether) and distillation (air-bath temperature 125-130°C/0.3 Torr) of the material obtained from the appropriate fractions, yielded 60 mg (89%) of carbamate (237) as a white solid. An analytically pure sample of (237), obtained by recrystallization from petroleum ether, exhibited mp 79.5-80.5°C; ir ($CHCl_3$): 3446, 3072, 1709, 1644, 1515, 1465, 896 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.05 (s, 9H, $-SiMe_3$), 0.73, 0.87 [s, s, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 0.91 (s, 3H, tertiary methyl protons), 0.97 (t, 2H, $-CH_2C\underline{H}_2SiMe_3$, $\underline{J}$ = 8.5 Hz),

1.13-1.23 (m, 1H), 1.36-1.51 (m, 5H), 1.59-1.68 (m, 1H), 1.77-1.88 (m, 1H, H_B), 1.90-2.00 (m, 2H), 2.00-2.16 (m, 2H), 2.20-2.31 (m, 1H, H_D), 3.47 (t of d, 1H, H_C, J = 10, 4 Hz), 4.06-4.20 (m, 2H, $-C\underline{H}_2CH_2SiMe_3$), 4.31 (br d, 1H, -NH-, J = 10 Hz), 4.65, 4.73 (br s, br s, 1H each, olefinic protons). Irradiation at δ 4.11 caused the t at δ 0.97 to collapse to a s; irradiation at δ 0.73 caused the m at δ 1.77-1.88 to simplify; irradiation at δ 1.80 caused the signal at δ 3.47 to collapse to a t (J = 7 Hz) and the signals at δ 0.73 and 0.87 to collapse to singlets; irradiation at δ 3.47 caused the multiplet at δ 1.77-1.88 to collapse to a septet (J = 7 Hz) and the m at δ 2.20-2.31 to simplify; irradiation at δ 4.31 caused the signal at δ 3.47 to collapse to a d of d (J = 10, 4 Hz). Exact Mass calcd. for $C_{21}H_{39}NOSi$: 365.2752; found: 365.2742.

Preparation of the Carbamate (240)



238 R= COCl

239 R= CON_3

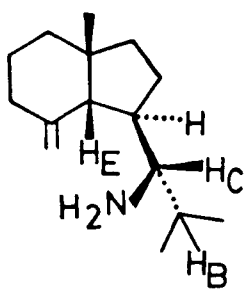
240 R= $\underset{H}{N}CO_2(CH_2)_2SiMe_3$

To a stirred solution of the acid (193) (25 mg, 0.1 mmol) in 1.0 mL of dry toluene, under an atmosphere of argon, was added oxalyl chloride (35 μL, 0.4 mmol) and the mixture was stirred for 45 min at room

temperature. After the evolution of gas had ceased, most of the solvent was removed under reduced pressure to give a pale yellow oil [the acid chloride (**238**)] which showed ir (film): 3072, 1795, 1645, 1464, 1392, 1335, 897 cm^{-1}. This oil was dissolved in 1 mL of dry acetone and the solution was added to a rapidly stirred solution of sodium azide (27 mg, 0.4 mmol) in 0.1 mL of water at 0°C. After 15 min, 5 mL of hexanes and 5 mL of water were added. The hexanes layer was separated and the aqueous layer was washed with hexanes (5 mL). The combined organic extract was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave the acyl azide (**239**) as a colorless oil which exhibited ir (film): 3070, 2267, 2129, 1712, 1644, 1389, 1376, 894 cm^{-1}. This oil was dissolved in 0.2 mL of dry toluene and the solution was heated with stirring at 80°C. Evolution of gas began immediately. After 2 h, 57 μL (0.4 mmol) of 2-trimethylsilylethanol was added and heating at 80°C was continued for 20 h. After removal of the solvent under reduced pressure, the residue was dissolved in 5 mL of ether and the solution was washed with 3 mL of aqueous sodium hydroxide (1N). The organic layer was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, provided a residue that was subjected to column chromatography on silica gel (6 g, 6:1 petroleum ether-ether). Concentration of the appropriate fractions and distillation (air-bath temperature 125-130°C/0.3 Torr) of the residual material yielded 30 mg (82%) of carbamate (**240**) as a white solid. Recrystallization of this material from petroleum ether gave an analytically pure sample, which exhibited mp 86-87°C; ir (CCl_4): 3450, 3073, 1726, 1643, 1464, 1375, 904 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.05 (s, 9H,

-$SiMe_3$), 0.85, 0.88 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 0.95 (s, 3H, tertiary methyl protons), 0.99 (t, 2H, $-CH_2C\underline{H}_2SiMe_3$, $\underline{J}$ = 8.5 Hz), 1.17-1.24 (m, 1H), 1.29-1.55 (series of multiplets, 5H), 1.59-1.74 (m, 2H), 1.76-1.95 (m, 2H), 1.99-2.16 (m, 2H), 2.25-2.36 (m, 1H, H_D), 3.41 (d of d of d, 1H, H_C, $\underline{J}$ = 10.5, 7, 4 Hz), 4.16 (t, 2H, $-OC\underline{H}_2CH_2SiMe_3$, $\underline{J}$ = 8.5 Hz), 4.43 (br d, 1H, -N<u>H</u>-, $\underline{J}$ = 10.5 Hz), 4.77, 4.81 (br s, br s, 1H each, olefinic protons). Irradiation at δ 2.30 caused the multiplet at δ 3.41 to collapse to a d of d ($\underline{J}$ = 10.5, 7 Hz) and the signal at δ 1.76-1.95 to simplify; irradiation at δ 4.16 caused the signal at δ 0.99 to collapse to a singlet; irradiation at δ 0.85 caused part of the multiplet at δ 1.59-1.74 to simplify; irradiation at δ 3.41 caused the signal at δ 4.43 to collapse to a broad singlet and the signal at δ 2.30 to collapse to a t of d ($\underline{J}$ = 11, 5.5 Hz) and the signal at δ 1.59-1.74 to simplify. <u>Exact Mass</u> calcd. for $C_{21}H_{39}NOSi$: 365.2752; found: 365.2754.

Preparation of the Amine (186)

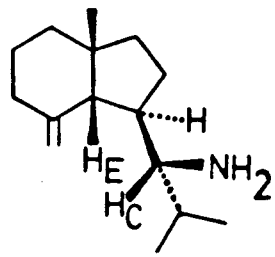


186

A solution of the carbamate (237) (43.9 mg, 0.12 mmol) in 1 mL of

dry THF was added to a stirred solution of tetra-n-butylammonium fluoride (136.5 mg, 0.5 mmol) in 0.5 mL of dry THF. The mixture was heated at 50°C for 35 min. After the mixture had been cooled to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in 5 mL of pentane. Water (4 mL) was added and the mixture was stirred vigorously for 10 min. The aqueous layer was separated and extracted twice with pentane. The combined pentane extract was washed once with aqueous ammonium chloride and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by distillation (air-bath temperature 70-75°C/0.3 Torr) of the residual material yielded 17.7 mg (72%) of the amine (**186**) as a colorless oil. This material exhibited ir (film): 3397, 3338, 3067, 1641, 1376, 1365, 889 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.82, 0.92 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 6.5 Hz in each case], 0.94 (s, 3H, tertiary methyl protons), 1.14-1.22 (br d, 1H), 1.20-1.35 (br s, 2H, $-N\underline{H}_2$), 1.32-1.60 (series of multiplets, 5H), 1.61-1.70 (m, 1H), 1.70-1.83 (m, 1H, H_B), 1.83-1.93 (m, 1H), 1.97 (d, 1H, H_E, $\underline{J}$ = 10 Hz), 2.05-2.30 (m, 3H), 2.51 (d of d, 1H, H_C, $\underline{J}$ = 8.5, 3.5 Hz), 4.77 (br s, 2H, olefinic protons). Irradiation at δ 2.51 caused the multiplet at δ 1.70-1.83 to collapse to a septet ($\underline{J}$ = 6.5 Hz) and the multiplet at δ 2.05-2.30 to simplify; irradiation at δ 0.82 caused the multiplet at δ 1.70-1.83 to simplify. Exact Mass calcd. for $C_{15}H_{27}N$: 221.2145; found: 221.2142.

Preparation of the Amine (234)

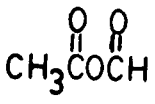


234

A solution of the carbamate (240) (26.9 mg, 0.074 mmol) in 0.6 mL of dry THF was added to a stirred solution of tetra-n-butylammonium fluoride (78.1 mg, 0.3 mmol) in 0.4 mL of dry THF. The mixture was heated at 50°C for 35 min. The solvent was removed under reduced pressure and the residue was dissolved in 3 mL of pentane. Water (3 mL) was added and the mixture was stirred vigorously for 10 min. The aqueous layer was separated and extracted twice with pentane. The combined pentane extract was washed with saturated ammonium chloride (3 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure and distillation (air-bath temperature 50-54°C/0.3 Torr) of the residual material afforded 12 mg (73%) of the amine (234) as a colorless oil. This material exhibited ir (film): 3387, 3307, 3067, 1643, 1375, 890 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.86, 0.89 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 6.5 Hz in each case], 0.97 (s, 3H, tertiary methyl protons), 1.17-1.24 (br d, 1H, $\underline{J}$ = 11 Hz), 1.30-1.80 (series of m, 10H), 1.95 (br d, 1H, H_E, $\underline{J}$ = 11 Hz), 2.02-2.15 (m, 2H), 2.23-2.34 (m, 1H), 2.34 (d of d, 1H, H_C, $\underline{J}$ = 6.5, 3 Hz), 4.62, 4.75 (br s, br s, 1H each, olefinic protons). Exact Mass calcd. for $C_{15}H_{27}N$:

221.2145; found: 221.2140.

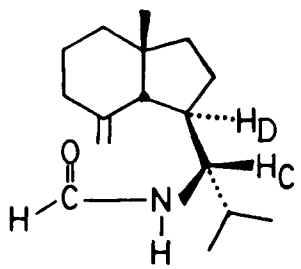
Preparation of Acetic Formic Anhydride (241)



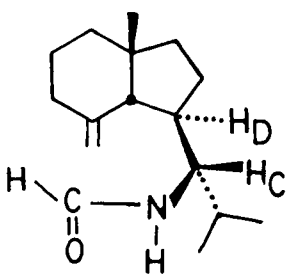
241

Formic acid (0.1 mL, 2.65 mmol) and acetic anhydride (0.25 mL, 2.65 mmol) were mixed together in a three-necked flask equipped with a condenser and a septum. The mixture was heated at 55°C for two hours. The required amount of the mixture was removed by syringe.

Preparation of (±)-Axamide-1 (174)



cis 174

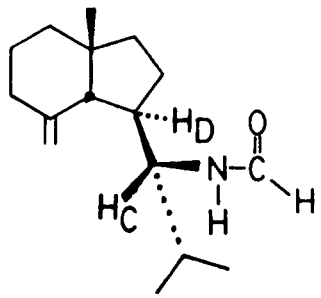


trans 174

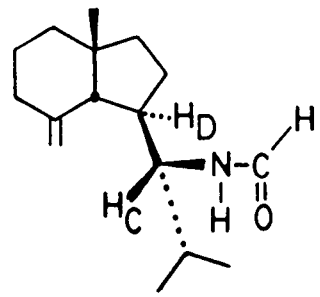
To a stirred solution of the amine (**186**) (17.7 mg, 0.08 mmol) in 0.6 mL of dry ether was added acetic formic anhydride (**241**) (24 μL, 0.16 mmol) and the mixture was stirred at room temperature for 10 h. Ether (5 mL) and water (2 mL) were added to the mixture and the layers were separated. The aqueous layer was washed twice with ether. The combined ether extract was dried over anhydruos magnesium sulfate. Removal of solvent under reduced pressure, followed by column chromatography of the residue on silica gel (5 g, elution with 6:1 petroleum ether-ether) and distillation (air-bath temperature 110-115°C/0.3 Torr) of the oil obtained from the appropriate fractions, provided 18 mg (90%) of (±)-axamide-1 (**174**) as a colorless, viscous oil. This material exhibited ir (film): 3268, 3067, 1660, 1383, 890 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.79, 0.89 [d, d, total 3.6 H, $-CH(C\underline{H}_3)_2$, *cis* rotamer, $\underline{J}$ = 7 Hz in each case], 0.80, 0.88 [d, d, total 2.4 H, $-CH(C\underline{H}_3)_2$, *trans* rotamer, $\underline{J}$ = 7 Hz in each case], 0.92 (s, 1.8 H, tertiary methyl protons, *cis* rotamer), 0.94 (s, 1.2 H, tertiary methyl protons, *trans* rotamer), 1.14-1.27 (m, 1H), 1.30-1.57 (m, 5H), 1.58-1.69 (m, 1H), 1.81-2.18 (m, 5H), 2.24 (q of d, 0.6 H, H_D, *cis* rotamer, $\underline{J}$ = 9.5, 5 Hz), 2.31-2.42 (m, 0.4H, H_D, *trans* rotamer), 2.96 (d of d of d, 0.4 H, H_C, *trans* rotamer, $\underline{J}$ = 13, 8.5, 4 Hz), 3.91 (t of d, 0.6 H, H_C, *cis* rotamer, $\underline{J}$ = 10, 4 Hz), 4.65, 4.82 (br s, t, 0.4 H each, olefinic protons, *trans* rotamer, $\underline{J}$ = 2 Hz), 4.68, 4.75 (t, t, 0.6 H each, olefinic protons, *cis* rotamer, $\underline{J}$ = 2.5 Hz and $\underline{J}$ = 2 Hz, respectively), 5.18 (br d, 0.6 H, $-N\underline{H}-$, *cis* rotamer, $\underline{J}$ = 10 Hz), 5.38 (br t, 0.4 H, $-N\underline{H}-$, *trans* rotamer, $\underline{J}$ = 13 Hz), 7.90 (d, 0.4 H, $-C\underline{H}O$, *trans* rotamer, $\underline{J}$ = 12 Hz), 8.15 (d, 0.6 H, $-C\underline{H}O$, *cis* rotamer, $\underline{J}$ = 2 Hz). Exact Mass calcd. for $C_{16}H_{27}NO$:

249.2094; found: 249.2091.

Preparation of (±)-10-epi-Axamide-1 (224)



cis 224

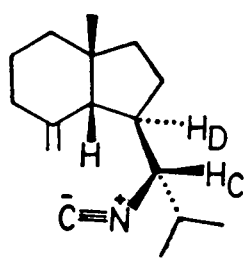


trans 224

To a stirred solution of the amine (234) (12 mg, 0.054 mmol) in 1 mL of dry ether was added acetic formic anhydride (241) (29 μL, 0.22 mmol) and the mixture was stirred at room temperature for 10 h. Ether (5 mL) and water (5 mL) were added. The aqueous layer was separated and washed twice with ether. The combined ether extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography of the residue on silica gel (5 g, elution with 6:1 petroleum ether-ether) and distillation (air-bath temperature 104-110°C/0.3 Torr) of the oil obtained from the appropriate fractions, provided 11.8 mg (88%) of (±)-10-epi-axamide-1 (224) as a colorless, viscous oil. This material exhibited ir (film): 3288, 3068, 1659, 1385, 896 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.84-0.98 [unresolved doublets and singlets due to two rotamers, 9H, $-CH(C\underline{H}_3)_2$ and tertiary methyl protons], 1.17-1.79 (m, 8H), 1.79-1.94 (m, 2H), 1.96-2.10 (m, 1H), 2.10-2.19 (m, 1H), 2.30-2.46 (m, 1H, H_D), 2.94 (d of d of d, 0.5H, H_C, J

= 11, 8, 3 Hz), 3.84 (d of d of d, 0.5H, H_C, J = 11, 7, 3 Hz), 4.59 (br s, 0.5H, olefinic proton), 4.76 (br s, 0.5H, olefinic proton), 4.79-4.84 (m, 1H, olefinic proton), 5.25 (br d, 0.5H, -NH-, J = 11 Hz), 5.42 (br t, 0.5H, -NH-, J = 11 Hz), 7.97 (d, 0.5H, -CHO, trans rotamer, 12 Hz), 8.31 (br s, 0.5H, cis rotamer, -CHO). Exact Mass calcd. for $C_{16}H_{27}NO$: 249.2094; found: 249.2092.

Preparation of (±)-Axisonitrile-1 (173)



173

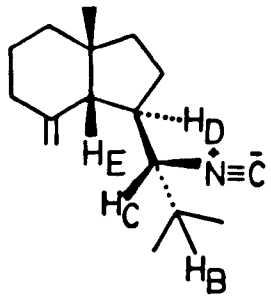
Solid p-toluenesulfonyl chloride (29.5 mg, 0.15 mmol) was added to a stirred solution of (±)-axamide-1 (174) (12.5 mg, 0.05 mmol) in 0.8 mL of dry pyridine and the mixture was stirred at room temperature for 3 h. A few chips of ice was added and the mixture was poured into ice water. The resultant mixture was extracted with pentane (2 x 5 mL). The combined pentane extract was washed twice with cold water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography of the residue on silica gel (3 g, 14:1 petroleum ether-ether) and distillation of the material obtained from the appropriate fractions afforded 10 mg (86%) of (±)-axisonitrile-1 (173) as a

white solid. Recrystallization of this material from petroleum ether provided an analytically pure sample, which exhibited mp 45-46°C; ir (CCl_4): 3072, 2136, 1645, 1390, 1375, 899 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.88, 1.02 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 6.5 Hz in each case], 0.99 (s, 3H, tertiary methyl protons), 1.19-1.29 (m, 1H), 1.40-1.59 (m, 5H), 1.59-1.71 (m, 1H), 1.94-2.13 (m, 3H), 2.14-2.23 (m, 2H), 2.47 (m, 1H, H_D), 3.23 (t of t, 1H, H_C, $\underline{J}$ = 7.5, 1.5 Hz), 4.79-4.85 (m, 2H, olefinic protons). Irradiation at δ 2.47 caused the signal at δ 3.23 to collapse to a br d ($\underline{J}$ = 7.5 Hz) and the multiplets at δ 2.14-2.23 and 1.94-2.14 to simplify. ^{13}C nmr (75 MHz, $CDCl_3$, proton decoupled) δ: 19.068, 19.779, 24.371, 24.442, 27.719, 29.727, 31.279, 33.301, 39.638, 40.092, 45.167, 57.137, (67.691, 67.763, 67.824, triplet), 111.633, 148.299, (155.535, 155.621, 155.689, triplet). Exact Mass calcd. for $C_{16}H_{25}N$: 231.1989; found: 231.1993. The spectral data derived from the synthetic material were identical with those of an authentic sample of (+)-axisonitrile-1.*

---

* We are very grateful to Professor D. Sica for a sample of (+)-axisonitrile-1 and for a copy of its ^1H nmr spectrum.

Preparation of (±)-10-epi-Axisonitrile-1 (225)



225

Solid p-toluenesulfonyl chloride (26.1 mg, 0.14 mmol) was added to a solution of (±)-10-epi-axamide-1 (224) (8.9 mg, 0.036 mmol) in 0.36 mL of dry pyridine at room temperature and the mixture was allowed to stir for 3.5 h. A few chips of ice was added and the mixture was poured into ice water. The resultant mixture was extracted with pentane (2 x 5 mL). The combined pentane extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (3 g, elution with 15:1 petroleum ether-ether) and distillation (air-bath temperature 63-68°C/0.3 Torr) of the material obtained from the appropriate fractions afforded 7.2 mg (87%) of (±)-10-epi-axisonitrile-1 (225) as a white solid. An analytically pure sample obtained by recrystallization of this material from petroleum ether, exhibited mp 53-54°C; ir (CCl_4): 3070, 2135, 1644, 1391, 1377, 901 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.92, 1.04 [d, d, 3H each, $-CH(C\underline{H}_3)_2$, $\underline{J}$ = 7 Hz in each case], 1.00 (s, 3H, tertiary methyl protons), 1.21-1.32 (m, 1H), 1.38-1.59 (m, 4H), 1.59-1.75 (m, 2H), 1.75-1.92 (m, 2H), 1.92-2.02 (m, 1H), 2.05 (d, 1H, H_E, $\underline{J}$ = 11 Hz), 2.14 (br d, $\underline{J}$ = 14 Hz), 2.22-2.34 (m, 1H, H_D), 3.18-3.25 (m, 1H, H_C), 4.72

(t, 1H, olefinic proton, J = 2.25 Hz), 4.80 (t, 1H, olefinic proton, J = 2 Hz). Irradiation at δ 2.28 caused the multiplet at δ 3.18-3.25 to collapse to a br d (J = 8 Hz), the d at δ 2.05 to collapse to a br s and the multiplet at δ 1.75-1.92 to simplify. ^{13}C nmr (75 MHz, $CDCl_3$, proton decoupled) δ: 19.423, 19.510, 22.941, 23.786, 24.621, 30.457, 31.406, 33.156, 39.995, 41.974, 43.175, 57.922, (63.912, 63.973, 64.046, triplet), 111.392, 146.862, (155.026, 155.097, 155.168, triplet). Exact Mass calcd. for $C_{16}H_{25}N$: 231.1988; found: 231.1981. The spectral data derived from this synthetic material were quite different from those of an authentic sample of (+)-axisonitrile-1.*

---

* We are very grateful to Professor D. Sica for a sample of (+)-axisonitrile-1 and for a copy of its ^1H nmr spectrum.

REFERENCES

REFERENCES

1. M.E. Jung, Tetrahedron, 32, 3 (1976).

2. (a) M.C. Kloetzel, Organic Reactions, 4, 1 (1948).

   (b) H.L. Holmes, Organic Reactions, 4, 60 (1948).

   (c) E. Ciganek, Organic Reactions, 32, 1 (1984).

   (d) Alex G. Fallis, Can. J. Chem., 62, 183 (1984).

3. (a) W.S. Johnson, Acc. Chem. Res., 1, 1 (1968).

   (b) M.F. Ansell and M.H. Palmer, Quart. Rev., 18, 211 (1964).

   (c) K. Sutherland, J. Chem. Soc., Chem. Commun., 526, 528 (1978).

   (d) K.-G. Gerling, H. Wolf, Tetrahedron Lett., 1293 (1985).

   (e) S.P. Tanis, P.M. Herrinton, L.A. Dixon, Tetrahedron Lett., 5347 (1985).

4. (a) M. Julia, Rec. Chem. Prog., 25, 3 (1964).

   (b) G.A. Molander, J.B. Etter, Tetrahedron Lett., 3281 (1984).

   (c) G. Stork, N.H. Baine, Tetrahedron Lett., 5927 (1985).

   (d) B. Giese, Angew. Chem. Int. Ed. Engl., 24, 553 (1985).

5. (a) W.L. Dilling, Chem. Rev., 66, 373 (1966); 69, 845 (1969).

   (b) P.E. Eaton, Acc. Chem. Res., 1, 50 (1968).

   (c) P. de Mayo, Acc. Chem. Res., 4, 41 (1971).

6. (a) J.M. Conia and P. Le Perchec, Syn., 1, (1975).

   (b) M. Karpf, J. Huguet, and A.S. Dreiding, Helv. Chim. Acta, 65, 13 (1982).

   (c) W. Oppolzer and R. Pitteloud, J. Am. Chem. Soc., 104, 6478, (1982).

7. (a) L.A. Paquette "Recent Synthetic Developments in Polyquinane Chemistry" in Topics in Current Chemistry, Vol. 119, Springer-Verlag, Berlin Heidelberg, 1984.

(b) M. Ramaiah, Syn., 529 (1984).

(c) B.M. Trost, Angew. Chem. Int. Ed. Engl., **25**, 1 (1986).

8. (a) R.E. Gawley, Syn., 777 (1976).

(b) B.P. Mundy, J. Chem. Ed., **50**, 110 (1973).

(c) B.P. Mundy, Concept of Organic Synthesis: Carbocyclic Chemistry, Marcel Dekker, New York, 1979, p. 40-50.

(d) H.O. House, Modern Synthetic Reactions, W.A. Benjamin, Phillipines, 1972, p. 595-623.

9. J.W. Comforth and R. Robinson, J. Chem. Soc., 1855 (1949).

10. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, J. Am. Chem. Soc., **85**, 207 (1963).

11. G. Stork and B. Ganem, J. Am. Chem. Soc., **95**, 6152 (1973).

12. B.M. Trost, Acc. Chem. Res., **11**, 453 (1978).

13. D. Seebach, Angew. Chem. Int. Ed. Engl., **18**, 239 (1979).

14. E.J. Corey, Pure Appl. Chem., **14**, 19 (1967).

15. (a) G.H. Posner, C.E. Whitten, J.J. Sterling, and D.J. Brunnelle, Tetrahedron Lett., 2591 (1974).

(b) G.H. Posner, J.J. Sterling, C.E. Whitten, C.M. Lentz, and D.J. Brunnelle, J. Am. Chem. Soc., **97**, 107 (1975).

16. F. Näf, R. Decorzant, and W. Thommen, Helv. Chem. Acta, **68**, 1808 (1975).

17. A. Itoh, S. Ozawa, K. Oshima, H. Nozaki, Tetrahedron Lett., 361 (1980).

18. M. Tada, Y. Sugimoto, and T. Takahashi, Bull. Chem. Soc. Japan, **53**, 2966 (1980).

19. J.A. Thomas, C.H. Heathcock, Tetrahedron Lett., 3235 (1980).

20. S.A. Bal, A. Marfat, and P. Helquist, J. Org. Chem., **47**, 5045 (1982).

21. R.A. Raphael, S.J. Telfer, Tetrahedron Lett., 489 (1985).

22. J. Ficini and A.M. Touzin, Tetrahedron Lett., 1081 (1977).

23. W.P. Jackson and S.V. Ley, J. Chem. Soc. Perkin Trans. I, 1516 (1981).

24. G. Büchi and H. Wuest, J. Org. Chem., 44, 546 (1979).

25. (a) G. Pattenden and G.M. Robertson, Tetrahedron, 42, 4001 (1985).

(b) G. Pattenden and G.M. Robertson, Tetrahedron Lett., 399 (1986).

26. (a) E. Piers and V. Karunaratne, J. Org. Chem., 48, 1774 (1983).

(b) E. Piers and V. Karunaratne, J. Chem. Soc., Chem. Commun., 935 (1983).

27. E. Piers and V. Karunaratne, Can. J. Chem., 62, 629 (1984).

28. E. Piers and V. Karunaratne, J. Chem. Soc., Chem. Commun., 959 (1984).

29. E. Piers and J.M. Chong, J. Chem. Soc., Chem. Commun., 934 (1983).

30. E.I. Negishi, Organometallics in Organic Synthesis, Vol. 1, John Wiley, New York, 1980, p. 410-412.

31. A.J. Lensink, H.A. Budding, and J.W. Marsman, J. Organomet. Chem., 9, 285 (1967).

32. H. Gilman, F.W. Moore, and R.G. Jones, J. Am. Chem. Soc., 63, 2482 (1941).

33. D. Seyferth and M.A. Weiner, Chem. Ind. (London), 402 (1959).

34. M. Gielen, "Recent developments in the Syntheses, Properties and Uses of Tetraorganotin Compounds", in Reviews on Silicon Germanium, Tin and Lead Compounds, Vol. V, No. 2, Freund Publishing House, Ltd. Tel-Aviv, 1981, p. 5.

35. G.J. McGarvey, J.S. Bajwa, J. Org. Chem., 49, 4091 (1984).

36. E. Piers and A.V. Gavai, personal communication.

37. W. Shand, Jr., V. Schomaker, and J.R. Fischer, J. Am. Chem. Soc., 66, 636 (1944).

38. G.H. Posner, An Introduction to Synthesis Using Organocopper Reagents, John Wiley and Sons, New York, 1980.

39. (a) G.H. Posner, "Conjugate Addition Reactions of Organocopper Reagents" in Organic Reactions, **19**, 1 (1972).

(b) R.J.K. Taylor, Synthesis, 364 (1985).

40. G.H. Posner, "Substitution Reactions Using Organocopper Reagents" in Organic Reactions, 22, 253 (1975).

41. S.H. Bertz, G. Dabbagh, and G.M. Villacorta, J. Am. Chem. Soc., **104**, 5824 (1982).

42. G.H. Posner, C.E. Whitten, and J.J. Sterling, J. Am. Chem. Soc., **95**, 7788 (1973).

43. W.H. Mandeville, G.M. Whitesides, J. Org. Chem., **39**, 400 (1974).

44. (a) S.H. Bertz and G. Dabbagh, J. Org. Chem., **49**, 1119 (1984).

(b) S.H. Bertz and G. Dabbagh, J. Chem. Soc., Chem. Commun., 1030 (1982).

45. (a) B.H. Lipshutz, R.S. Wilhelm, J.A. Kozlowski, Tetrahedron, 24, 5005 (1984).

(b) B.H. Lipshutz, J.A. Kozlowski, D.A. Parker, S.L. Nguyen, and K.E. McCarthy, J. Organometal. Chem., **285**, 437 (1985).

46. (a) D.B. Ledlie and G. Miller, J. Org. Chem., **44**, 1006 (1979).

(b) C.R. Johnson and D.S. Dhanoa, J. Chem. Soc., Chem. Commun., 358 (1982).

(c) T. Tsuda, T. Yazawa, K. Watanabe, T. Fujii, and T. Saegusa, J. Org. Chem., **46**, 192 (1981).

(d) Y. Yamamoto, S. Yamamoto, H. Yatagai, and K. Maruyama, J. Am. Chem. Soc., **102**, 2318 (1980).

(e) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, and K. Maruyama, J. Org. Chem., **47**, 119 (1982).

47. B.H. Lipshutz and R.S. Wilhelm, J. Am. Chem. Soc., **103**, 7672 (1981).

48. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, Tetrahedron Lett., 1247 (1980).

49. (a) A.B. Smith, III, P.J. Jerris, J. Org. Chem., **47**, 1845 (1982).

(b) B.H. Lipshutz, D.A. Parker, J.A. Kozlowski, and S.L. Nguyen, Tetrahedron Lett., 5959 (1984).

50. (a) J.M. Conia, F. Rouessac, Tetrahedron, **16**, 45 (1961).

(b) G.H. Posner, J.J. Sterling, C.E. Whitten, C.M. Lentz, D.J. Brunnelle, J. Am. Chem. Soc., **97**, 107 (1975).

51. D.H. Williams and I. Fleming, Spectroscopic Methods in Organic Chemistry, 3rd Ed., McGraw-Hill, London, 1980, p. 74-152.

52. J.G. Kirchner, "Thin-layer Chromatography" in Techniques of Chemistry, Editor: E.S. Perry, Vol. XIX, 2nd Ed., John Wiley and Sons, New York, 1978, p. 47, 80, 898-899.

53. I. Hagedorn and H. Tonjes, Pharmazie, **12**, 567 (2957); Chem. Abstr., **52**, 6362 (1958).

54. F. Cafieri, E. Fattorusso, S. Magno, C. Santacroce, and D. Sica, Tetrahedron, **29**, 4259 (1973).

55. (a) E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, and D. Sica, Tetrahedron, **30**, 3911 (1974).

(b) L. Minale, R. Riccio and G. Sodano, Tetrahedron, 30, 1341 (1974).

(c) B.J. Burreson, P.J. Scheuer, J. Finer, and J. Clardy, J. Am. Chem. Soc., **97**, 4763 (1975).

(d) B.J. Burreson and P.J. Scheuer, J. Chem. Soc., Chem. Commun., 1035 (1974).

(e) B.J. Burreson, C. Christophersen and P.J. Scheuer, J. Am. Chem. Soc., **97**, 201 (1975).

(f) B.J. Burreson, C. Christophersen and P.J. Scheuer, Tetrahedron, **31**, 2015 (1975).

(g) B. Di Blasio, E. Fattorusso, S. Magno, L. Mayol, C. Pedone, C. Santacroce, and D. Sica, Tetrahedron, **32**, 473 (1976).

(h) A. Iengo, L. Mayol, and C. Santacroce, Experientia, 33, 11 (1977).

(i) P. Ciminiello, E. Fattorusso, S. Magno, and L. Mayol, J. Org. Chem., **49**, 3949 (1984).

(j) P. Ciminiello, E. Fattorusso, S. Magno, and L. Mayol, J. Nat. Prod., **48**, 64 (1985).

(k) S.J. Wratten, D.J. Faulkner, K. Hirotsu, and J. Clardy, Tetrahedron Lett., 4345 (1978).

(l) R. Kazlauskas, P.T. Murphy, R.J. Wells, and J.F. Blount, Tetrahedron Lett., 315 (1980).

(m) H. Nakamura, J. Kobayashi, Y. Ohizumi, and Y. Hirata, Tetrahedron Lett., 5401 (1984).

(n) C.W.J. Chang, A. Patra, D.M. Roll, P.J. Scheuer, G.K. Matsumoto, and J. Clardy, J. Am. Chem. Soc., **106**, 4644 (1984).

(o) A. Patra, C.W.J. Chang, P.J. Scheuer, G.D. van Duyne, G.K. Matsumoto, and J. Clardy, J. Am. Chem. Soc., **106**, 7981 (1984).

56. E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, and D. Sica, Tetrahedron, **31**, 269 (1975).

57. S.S. Hall, D.J. Faulkner, J. Fayos, J. Clardy, J. Am. Chem. Soc., **95**, 7187 (1973).

58. M. Adinolfi, L. De Napoli, B. Di Blasio, A. Iengo, C. Pedone, and C. Santacroce, Tetrahedron Lett., 2815 (1977).

59. (a) J.E. Thompson, R.P.Walker, S.J. Wratten, and D.J. Faulkner, Tetrahedron, **38**, 1865 (1982).

(b) G. Cimino, S. De Rosa, S. De Stefano, and G. Sodano, Comp. Biochem. Physiol., **73B**, 471 (1982).

60. P. Hoffmann, G. Gokel, D. Marquarding, and I. Ugi, "Isonitrile Syntheses", in Isonitrile Chemistry, I. Ugi, ed., Academic Press, New York, 1971, p. 9.

61. C.W. Huffman, J. Org. Chem., **23**, 727 (1958).

62. D. Todd "The Wolff-Kishner Reduction", in Organic Reactions, Vol. IV, p. 379.

63. (a) M. Rathke, D. Sulllivan, Tetrahedron Lett., 4249 (1972).

(b) P.E. Pfeffer, L.S. Silbert, E. Kinsel, Tetrahedron Lett., 1163 (1973).

(c) J.-A. MacPhee and J.-E. Dubois, Tetrahedron, **36**, 775 (1980).

(d) A.P. Krapcho, E.A. Dundulis, J. Org. Chem., **45**, 3236 (1980).

(e) R.H. van der Veen and H. Cerfontain, J. Org. Chem., **50**, 342 (1985).

(f) A.P. Krapcho, D.S. Kashdan, and E.G.E. Jahngen, Jr., J. Org. Chem., 42, 1189 (1977).

(g) P.E. Pfeffer, L.S. Silbert, and J.M. Chirinko, Jr., J. Org. Chem., 37, 451 (1972).

64. P.A.S. Smith "The Curtius Reaction", in Organic Reactions, Vol. III, p. 337.

65. (a) G. Stork, R.L. Danheiser, J. Org. Chem., 38, 1775 (1973).

(b) M.L. Quesada, R.H. Schlessinger, and W.H. Parsons, J. Org. Chem., 43, 3968 (1978).

(c) M. Koreeda, Y. Liang, and H. Akagi, J. Chem. Soc., Chem. Commun., 449 (1979).

66. A.J. Barker and G. Pattenden, J. Chem. Soc. Perkin Trans. I, 1885 (1983).

67. B.H. Toder, S.J. Branca, R.K. Dieter, and A.B Smith, III, Syn. Commun., 435 (1975).

68. D.G. Morris, Chem. Soc. Rev., 397 (1982).

69. (a) K. Saigo, M. Osaki, and T. Mukaiyama, Chem. Lett., 163 (1976).

(b) Y. Kita, J. Segawa, J. Haruta, T. Fujii, and Y. Tamura, Tetrahedron Lett., 3779 (1980).

(c) Y. Kita, J. Segawa, J. Haruta, H. Yasuda, and Y. Tamura, J. Chem. Soc. Perkin Trans. I, 1099 (1982).

(d) T.V. RajanBabu, J. Org. Chem., 49, 2083 (1984).

(e) R.A. Bunce, M.F. Schlecht, W.G. Dauben, C.H. Heathcock, Tetrahedron Lett., 4943 (1983).

70. A.L. Gemal, and J.-L. Luche, J. Am. Chem. Soc., 103, 5454 (1981).

71. S. Binns, J.S.G. Cox, E.R.H. Jones, and B.G. Ketcheson, J. Org. Chem., 29, 1161 (1964).

72. (a) G.H. Posner, "Conjugate Addition Reactions of Organocopper Reagents", in Organic Reactions, Vol. 19, p. 1.

(b) G.H. Posner, C.E. Whitten, and J.J. Sterling, J. Am. Chem. Soc., 95, 7788 (1973).

73. (a) P.L. Stotter and R.A. Hill, J. Org. Chem., 38, 2576 (1973).

(b) E.J. Corey, and A.G. Hartmann, J. Am. Chem. Soc., **87**, 5736 (1965).

(c) R.H. Reuss and A. Hassner, J. Org. Chem., **39**, 1785 (1974).

(d) L. Blano, P. Amice, and J.M. Conia, Syn., 194 (1976).

(e) G. Vidari, S. Ferrino, and P.A. Grieco, J. Am. Chem. Soc., **106**, 3539 (1984).

74. (a) H.J. Reich, J.M. Renga, and I.L. Reich, J. Am. Chem. Soc., **97**, 5434 (1975).

(b) K.B. Sharpless, M.W. Young, and R.F. Lauer, Tetrahedron Lett., 1979 (1973).

(c) K.B. Sharpless, R. F. Lauer, and A.Y. Teranishi, J. Am. Chem. Soc., **95**, 6137 (1973).

75. Y. Ito, T. Hirao, and T. Saegusa, J. Org. Chem., **43**, 1011 (1978).

76. C. Ainsworth, F. Chen, and Y.-N. Kuo, J. Organomet. Chem., **46**, 59 (1972).

77. (a) C.H. Heathcock, M.H. Norman, and D.E. Uehling, J. Am. Chem. Soc., 2797 (1985).

(b) C.H. Heathcock and D.E. Uehling, J. Org. Chem., **51**, 280 (1986).

78. R.E. Ireland, R.H. Mueller, and A.K. Willard, J. Am. Chem. Soc., **98**, 2868 (1976).

79. (a) E. Nakamura, K. Hashimoto, and I. Kuwajima, Tetrahedron Lett., 2079 (1978).

(b) T.H. Chan, T. Aida, P.W.K. Lau, V. Gorys, and D.N. Harpp, Tetrahedron Lett., 4029 (1979).

80. J.-E. Dubois, G. Axiotis, and E. Bertounesque, Tetrahedron Lett., 4655 (1984).

81. J.-E. Dubois and G. Axiotis, Tetrahedron Lett., 2143 (1984).

82. H.A. Khan and I. Paterson, Tetrahedron Lett., 5083 (1982).

83. T.L. Capson and C.D. Poulter, Tetrahedron Lett., 3515 (1984).

84. (a) T. Drakenberg and S. Forsen, J. Phys. Chem., **74**, 1 (1970).

(b) B.H. Lipshutz, K.E. McCarthy, and R.W. Hungate, J. Org. Chem., 1218 (1984).

(c) P. Ciminiello, E. Fattorusso, S. Magno, and L. Mayol, J. Org. Chem., **49**, 3949 (1984).

(d) B.J. Burreson, C. Christophersen, and P.J. Scheuer, Tetrahedron, 2015 (1974).

85. W.R. Hertler and E.J. Corey, J. Org. Chem., **23**, 1221 (1958).

86. (a) G.C. Levy and G.L. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemisits, John Wiley and Sons, 1972, p. 129.

(b) I. Morishima, A. Mizuno, and T. Yonezawa, J. Chem. Soc., Chem. Commun., 1321 (1970).

87. W.C. Still, M. Kahn, and A. Mitra, J. Org. Chem., **43**, 2923 (1978).

88. A.J. Gordon and R.A. Ford, The Chemist's Companion, John Wiley and Sons, New York, 1972, p. 451.

89. Y.P. Bryan and R.H. Byrne, J. Chem. Ed., **47**, 361 (1970).

90. H. Gilman and F.K. Cartledge, J. Organomet. Chem., **2**, 447 (1964).

91. H.O. House, C.Y. Chu, J.M. Wilkens, and M.J. Umen, J. Org. Chem., **40**, 1460 (1975).

92. P.G.M. Wuts, Syn. Commun., **11**, 139 (1981).

93. R.J. Cregge, J.L. Herrmann, C.S. Lee, J.E. Richman, and R.H. Schlessinger, Tetrahedron Lett., 2435 (1973).

94. E.J. Corey, and A. Venkateswarlu, J. Am. Chem. Soc., **94**, 6190 (1972).

95. H.C. Brown, Organic Synthesis Via Boranes, John Wiley and Sons, New York, 1975, p. 259.

96. S.W. Pelletier, Chem. Ind., 1034 (1953).

97. H.J. Dauben, Jr., and L.L. McCoy, J. Am. Chem. Soc., **81**, 4863 (1959).