

SYNTHESIS AND THERMAL ELECTROCYCLIC REACTIONS OF  
SUBSTITUTED 7-(ETHOXYCARBONYL)BICYCLO[4.2.0]OCT-1(6)-ENES

by

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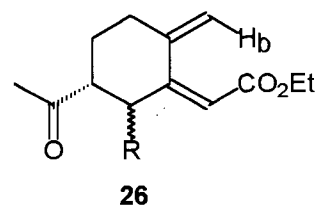
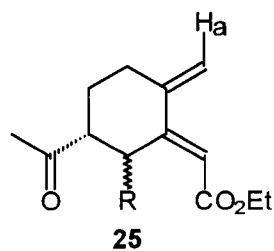
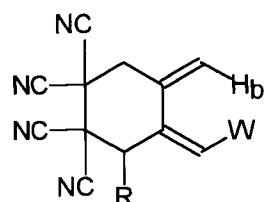
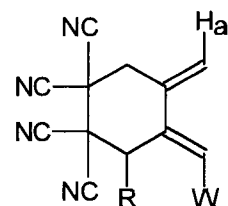
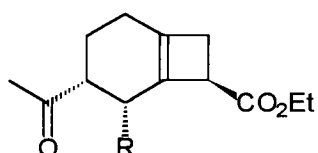
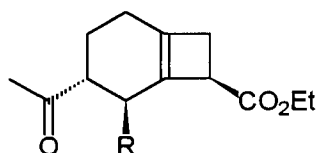
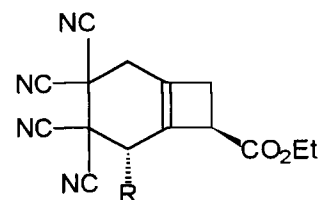
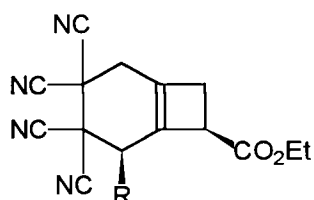
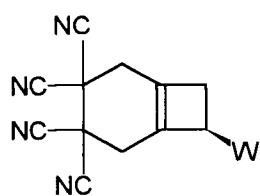
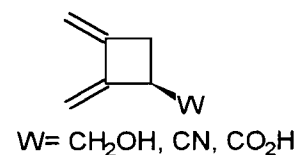
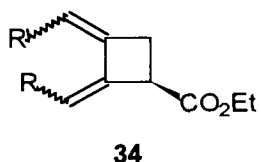
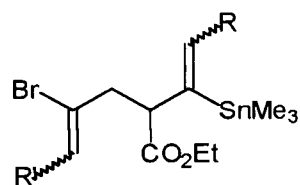
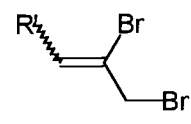
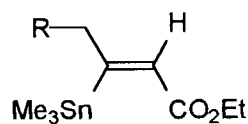
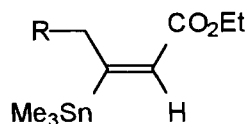
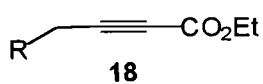
## ABSTRACT

The  $\alpha,\beta$ -acetylenic esters of general structure (18) were converted into the corresponding ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates of general structures (133) and (134), respectively. Deconjugation-alkylation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates (133) and (134) with alkylating agents of general structure (32) provided, stereoselectively, the functionalized esters of general structure (33).

Palladium(0)-catalyzed intramolecular cross-coupling reactions of esters (33) provided the ethyl 2,3-bis(alkylidene)cyclobutanecarboxylates of general structure (34) in good yields.

The Diels-Alder reactions of the 1-substituted 2,3-bis(methylene)cyclobutanes (243) and ethyl 2,3-bis(alkylidene)cyclobutanecarboxylates of general structure (34) ( $R' = H$ ) with the dienophiles TCNE and MVK were investigated. It was found that Diels-Alder reactions to prepare cycloaddition products (11), (14), (255-268) occurred with high face- and in some instances endo/exo- and regioselectivities. The conformations of some of these products (11), (14), (265-268) was determined by  $^1H$  NMR analysis and a series of decoupling and NOE difference experiments.

The torquoselectivity of the thermally-induced, conrotatory ring opening reaction of each of the bicyclic cyclobutenes (11), (14), (255-262), (264-268) to produce dienes of general structures (273) and (274) or (25) and (26) was investigated. Thermolysis of (262) produced only the product resulting from the outward rotation of the  $-CH_2OH$  group. Thermolysis of (255-262) and (264-268) produced mixtures of varying ratios of the outward (273) and inward (274) (or (25) and (26)) thermolysis products. The differing ratios of products was rationalized on the basis of electronic and / or steric factors.





## TABLE OF CONTENTS

ABSTRACT. ....	ii
TABLE OF CONTENTS. ....	iv
LIST OF TABLES. ....	viii
LIST OF FIGURES. ....	x
LIST OF ABBREVIATIONS. ....	xi
ACKNOWLEDGMENTS. ....	xiv
 I. INTRODUCTION. ....	 1
1. Overview of this Research Project. ....	1
2. Objectives of this Research Project. ....	7
3. Background information. ....	8
3.1 Previous work on the synthesis of alkyl 2,3-bis- alkylidenecyclobutanecarboxylates and related compounds. ....	8
3.2 Previous X-ray crystallographic studies on crystalline derivatives of 2,3-bis-alkylidenecyclobutanecarboxylates. ....	15
3.3 Diels-Alder reactions of the 2,3-bis-alkylidenecyclobutane- carboxylates. ....	17
3.4 Thermolysis of the cyclobutenes and related compounds. ....	19
 II. RESULTS AND DISCUSSION. ....	 36
1. Synthesis of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates. ....	36
1.1 Preparation of the $\alpha$ , $\beta$ -acetylenic esters. ....	37
1.2 Preparation of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates. ....	38

2.	Deconjugation-alkylation of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates. . . . .	50
2.1	Preparation of the ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-3-alkenoates. . . . .	50
2.2	Preparation of the alkylating agents. . . . .	58
2.2.1	Preparation of the 1,1-dibromo-1-alkenes. . . . .	59
2.2.2	Preparation of the 2-alkyn-1-ols. . . . .	60
2.2.3	Preparation of the alkyl ( <i>Z</i> )-2-bromo-2-alkene-1-ols. . . . .	61
2.2.4	Preparation of the alkyl ( <i>Z</i> )-1,2-dibromo-2-alkenes. . . . .	63
2.3	Deconjugation-alkylation of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates. . . . .	64
2.4	Deprotonation-alkylation of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-3-alkenoates. . . . .	65
3.	Synthesis of alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates and related derivatives. . . . .	70
3.1	Preparation of the alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates via palladium(0)-catalyzed coupling reactions. . . . .	70
3.2	Preparation and X-ray analysis of ( <i>Z,Z</i> )-2,3-bis(alkylidene)-cyclobutanecarboxamides. . . . .	80
3.3	Preparation of the 1-substituted-2,3-bis(methylene)cyclobutanes. . . . .	84
3.3.1	Preparation of 1-(hydroxymethyl)-2,3-bis(methylene)-cyclobutane. . . . .	85
3.3.2	Preparation of 1-formyl-2,3-bis(methylene)cyclobutane. . . . .	86
3.3.3	Preparation of 1-cyano-2,3-bis(methylene)cyclobutane. . . . .	87
3.3.4	Preparation of 2,3-bis(methylene)cyclobutanecarboxylic acid. . . . .	88

4.	Diels-Alder reactions of alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates and related compounds. . . . .	89
4.1	Diels-Alder reactions of dienes with tetracyanoethylene (TCNE). . .	90
4.2	Diels-Alder reactions of dienes with methyl vinyl ketone (MVK). . .	101
5.	Thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes. . . . .	111
5.1	Introduction. . . . .	111
5.2	Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes. . . . .	111
5.3	Small scale thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes. . . . .	123
III.	EXPERIMENTAL SECTION. . . . .	134
1.	General. . . . .	134
1.1	Data acquisition and presentation of results. . . . .	134
1.2	Reagents and solvents. . . . .	136
2.	Preparation of the 1,1-dibromo olefins. . . . .	137
3.	Preparation of the 1-alkynes. . . . .	141
4.	Preparation of the $\alpha,\beta$ -acetylenic Esters. . . . .	142
5.	Preparation of lithium (cyano)(trimethylstannyl)cuprate. . . . .	146
6.	Preparation of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates. . . . .	147
7.	Preparation of ethyl ( <i>E</i> )- and ( <i>Z</i> )-3-trimethylstannyl-3-alkenoates. . . . .	157
8.	Preparation of alkylating agents. . . . .	162
9.	Preparation of the diene esters. . . . .	170
10.	Preparation of the ethyl 2,3-bis(alkylidene)cyclobutanecarboxylates. . . . .	180
11.	Preparation of the cyclobutanecarboxamides. . . . .	192
12.	Preparation of the 1-substituted-2,3-bis(methylene)cyclobutanes. . . . .	197
13.	Diels-Alder reactions. . . . .	205
14.	Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes. . . . .	227

15.	Small scale thermal ring opening of the functionalized bicyclo [4.2.0]oct-1(6)-enes and direct determination of product ratios by $^1\text{H}$ NMR spectroscopy. ....	258
IV.	REFERENCES. ....	264
V.	APPENDIX. ....	269

## LIST OF TABLES

## Table

1.	Synthesis of the ethyl 2,3-bis-alkylidenecyclobutanecarboxylates <b>34</b> . . .	12
2.	Synthesis of the cyclopentanecarboxylates <b>69-72</b> and cyclohexanecarboxylates <b>73-75</b> . . . . .	14
3.	Products of the pyrolysis of 3,3-disubstituted cyclobutenes <b>75</b> . . . . .	21
4.	Calculated <i>Z:E</i> diene ratios based on steric effects . . . . .	22
5.	Substituent effects on the stereochemistry of cyclobutene electrocyclizations	24
6.	Predicted change in activation energy of cyclobutene opening ( $E_a=32$ kcal/mol) by C-3 substituents . . . . .	25
7.	Thermal electrocyclic ring opening of <i>cis</i> -3,4-disubstituted cyclobutenes . .	32
8.	Preparation of the $\alpha,\beta$ -acetylenic esters . . . . .	38
9.	Reaction of $\alpha,\beta$ -acetylenic esters with (trimethylstannyl)copper(I) reagents <b>135-140</b> . . . . .	42
10.	Preparation of alkyl ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates . . . . .	44
11.	Preparation of alkyl ( <i>E</i> )-3-trimethylstannyl-2-alkenoates . . . . .	46
12.	Partial $^1\text{H}$ NMR data for ( <i>E</i> )-3-trimethylstannyl-2-alkenoates <b>133</b> . . . . .	48
13.	Partial $^1\text{H}$ NMR data for ( <i>Z</i> )-3-trimethylstannyl-2-alkenoates <b>134</b> . . . . .	49
14.	Deprotonation-alkylation of ethyl ( <i>E</i> )-3-trimethylstannyl-3-alkenoates with 2,3-dibromopropene . . . . .	66
15.	Deprotonation-alkylation of ethyl ( <i>Z</i> )-3-trimethylstannyl-3-alkenoates with 2,3-dibromopropene . . . . .	67
16.	Partial $^1\text{H}$ NMR spectra data of the diene esters <b>164</b> and <b>211</b> . . . . .	68
17.	Stereocontrolled synthesis of alkyl 2,3-bis(alkylidene)- cyclobutanecarboxylates <b>221</b> . . . . .	75
18.	Diels-alder reactions of the cyclobutanecarboxylates <b>221</b> with tetracyanoethylene . . . . .	92
19.	Diels-alder reactions of the 1-substituted-2,3-bis(methylene)cyclobutanes with tetracyanoethylene . . . . .	94
20.	Diels-alder reactions of the cyclobutane carboxylates <b>221</b> with MVK . . . . .	104
21.	Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes <b>272</b> . . . . .	115
22.	Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes <b>23</b> . . . . .	118
23.	Partial $^1\text{H}$ NMR data for dienes <b>291</b> and <b>292</b> . . . . .	122

24.	Small scale thermolysis of the substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes of general structure <b>293</b> . . . . .	124
25.	Small scale thermolysis of the substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes of general structure <b>296</b> . . . . .	125
26.	Small scale thermolysis of the substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes of general structure <b>297</b> . . . . .	126
27.	Small scale thermolysis of the substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes of general structure <b>300</b> . . . . .	127
28.	Small scale thermolysis of the substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes of general structure <b>254</b> . . . . .	128

## LIST OF FIGURES

### Figure

1.	Diagrammatic view of the two possible directions that the dieneophile TCNE may approach the ethyl 2,3-bisalkylidenecyclobutanecarboxylates . . . . .	18
2.	HOMO and LUMO of the cyclobutene transition structure and the occupied $\rho$ orbital of a donor orbital . . . . .	23
3.	$^1\text{H}$ NMR spectrum of ester <b>233</b> . . . . .	78
4.	Stereoview of cyclobutane carboxamide <b>240</b> . . . . .	83
5.	Diagrammatic view of the two possible directions that the dieneophile TCNE may approach the ethyl 2,3-bisalkylidenecyclobutanecarboxylates . . . . .	91
6.	Stereoview of ester <b>256</b> . . . . .	97
7.	Favoured half-chair conformations of the Diels-Alder adducts ( <b>257-261</b> ) . . .	100
8.	The effect of a Lewis acid on the energies of the HOMO and LUMO of the dieneophile in the Diels-Alder reaction . . . . .	101
9.	Frontier orbitals showing the increased polarization of the LUMO of the double bond in the dieneophile in a Lewis acid catalyzed Diels-Alder reaction . . .	102
10.	Frontier orbitals showing the increased secondary orbital interaction in the Lewis acid catalyzed Diels-Alder reaction . . . . .	103
11.	Relative configuration and preferred conformation of ester <b>14</b> . . . . .	108
12.	Relative configuration and preferred conformation of ester <b>11</b> . . . . .	108
13.	Relative configuration and preferred conformation of ester <b>265</b> . . . . .	109
14.	Relative configuration and preferred conformation of ester <b>267</b> . . . . .	109
15.	Relative configuration and preferred conformation of ester <b>268</b> . . . . .	110
16.	Conformations of the thermolysis precursors . . . . .	129
17.	Product conformations of the thermolysis reactions . . . . .	132

## LIST OF ABBREVIATIONS

$\alpha$	- 1,2 relative position
Anal.	- elemental analysis
$\beta$	- 1,3 relative position
bp	- boiling point
br	- broad
<i>n</i> -Bu	- normal-butyl ( <i>n</i> - normal-)
<i>n</i> -BuLi	- <i>n</i> -butyllithium
c	- concentration in g/100 mL
$^{13}\text{C}$ NMR	- carbon-13 nuclear magnetic resonance
COSY	- ( $^1\text{H}$ - $^1\text{H}$ homonuclear) <u>c</u> orrelation <u>s</u> pectroscopy
CuBr•Me <sub>2</sub> S	- copper(I) bromide-dimethylsulfide
d	- doublet
$\delta$	- scale (nmr), dimensionless
Dibal	- diisobutyl aluminium hydride
DMF	- <i>N,N</i> -dimethylformamide
DMSO	- dimethylsulfoxide
D <sub>2</sub> O	- deuterium oxide
$\epsilon$	- molar absorptivity
e.g.	- exemplin gratia; for example
equiv.	- equivalent(s)
<i>et al.</i>	- et alia; and others
<i>E</i>	- entgegen (configuration)
$\gamma$	- 1,4 relative position
GLC	- gas-liquid chromatography
h	- hour(s)
HMPA	- hexamethylphosphoramide
$^1\text{H}$ nmr	- proton nuclear magnetic resonance
HOAc	- acetic acid
HOMO	- highest occupied molecular orbital
hplc	- high-performance liquid chromatography
<i>i</i> -	- iso-
ibid.	- ibidem; in the reference cited
i.e.	- idest; that is
IMID	- imidazole



IR	- infrared
$J$	- coupling constant (in Hz)
${}^nJ_{\text{Sn-H}}$	- $n$ bond(s) coupling for tin and proton nuclei (in Hz; $n = 2$ or $3$ )
$\text{KN}(\text{SiMe}_3)_2$	- potassium bis(trimethylsilyl)amide
LDA	- lithium diisopropylamide
$\text{LiAlH}_4$	- lithium aluminum hydride
lit.	- literature
LUMO	- lowest unoccupied molecular orbital
M	- molar ( $\text{mol dm}^{-3}$ ), or mega ( $10^6$ )
m	- multiplet
$(\text{Me}_3\text{Sn})_2$	- hexamethylditin
$[\text{Me}_3\text{SnCuCN}]\text{Li}$	- lithium (trimethylstannyl)(cyano)cuprate
$\text{Me}_3\text{SnCu}\cdot\text{Me}_2\text{S}$	- (trimethylstannyl)copper-dimethylsulfide
$[\text{Me}_3\text{SnCuSPh}]\text{Li}$	- lithium (trimethylstannyl)(phenylthio)cuprate
MHz	- megaHertz
min	- minute(s)
mp	- melting point
MVK	- methyl vinyl ketone
$n$ -	- normal-
NBS	- N-bromosuccinimide
NOE	- nuclear Overhauser effect
$o$ -	- ortho-
p	- page
$p$ -	- para-
$\text{Pd}(0)$	- palladium(0)
Ph	- phenyl
pH	- hydrogen ion concentration
$\text{Ph}_3\text{P}$	- triphenylphosphine
$\text{Ph}_3\text{P}=\text{CBr}_2$	- dibromomethylenetriphenylphosphorane
$(\text{Ph}_3\text{P})_4\text{Pd}$	- tetrakis(triphenylphosphine)palladium(0)
pp	- pages
$c$ -Pr	- cyclopropyl
$i$ -Pr	- isopropyl ( $i$ - - iso-)
$n$ -Pr	- normal-propyl ( $n$ - - normal-)
q	- quartet
$R$	- rectus (configuration)

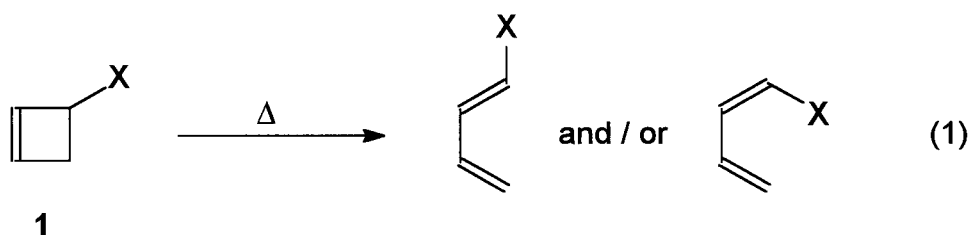
$R_f$	- retention factor (ratio of distance traveled by the center of a zone to the distance simultaneously traveled by the mobile phase); chromatographic term
<i>S</i>	- sinister (configuration)
<i>s</i>	- singlet, or second(s)
<i>t</i>	- triplet
<i>t</i> -	- tertiary
TCNE	- tetracyanoethylene
<i>tert</i> -	- tertiary-
THF	- tetrahydrofuran
TLC	- thin-layer chromatography
uv	- ultraviolet
Vol.	- volume
<i>Z</i>	- zusammen (configuration)
$ZnCl_2$	- zinc chloride
(+)	- rotation to the right
(-)	- rotation to the left
+ve	- positive
-ve	- negative

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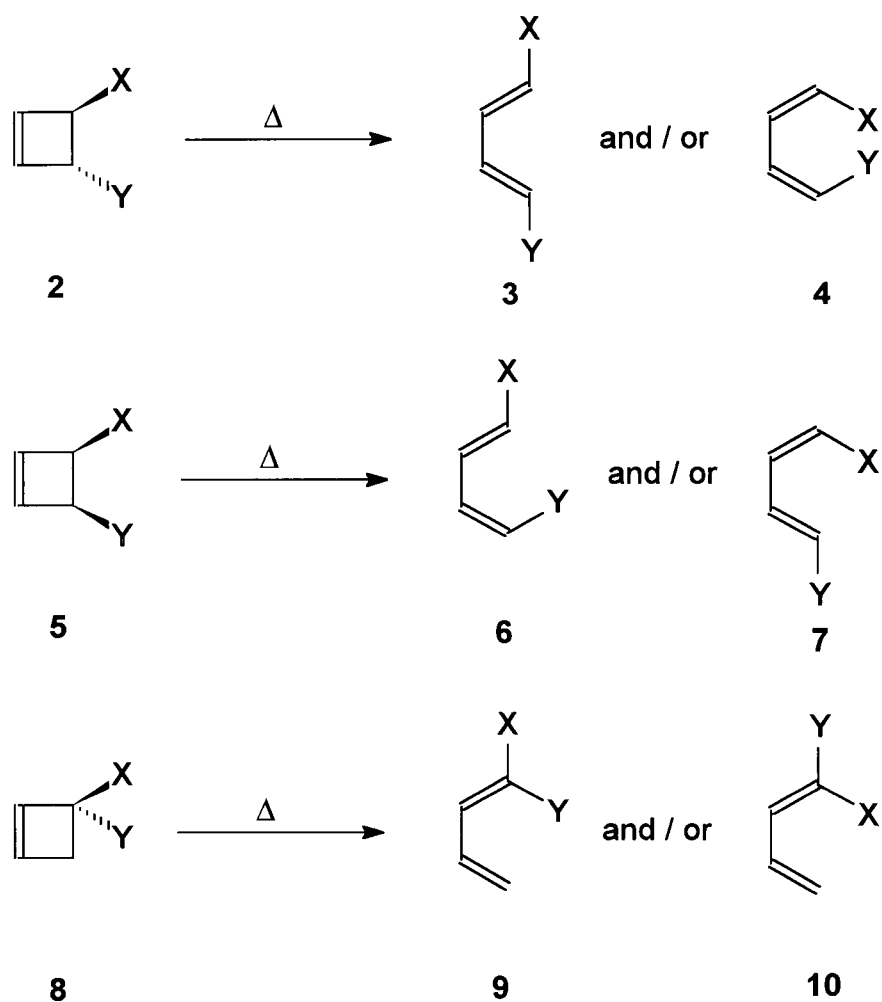
## I. INTRODUCTION

### 1. Overview of this research project



Thermolysis of cyclobutene results in an electrocyclic ring opening to produce 1,3-butadiene. This process proceeds *via* a thermally allowed conrotatory pathway.<sup>1</sup> The C<sub>3</sub>-monosubstituted cyclobutene (1) can open *via* one or both of two conrotatory pathways to give one or both of the "inward" or "outward" rotation products (Equation 1).

Similarly, C<sub>3</sub>,C<sub>4</sub> *trans*-disubstituted cyclobutenes (2) may open to give either one or both of the (*E,E*) or the (*Z,Z*) isomers (3) and (4) (Scheme 1). In contrast, the C<sub>3</sub>, C<sub>4</sub> *cis*-disubstituted cyclobutenes (5) or C<sub>3</sub>,C<sub>3</sub>-disubstituted cyclobutenes (8) must have one group rotating inward and one group rotating outward (Scheme 1).

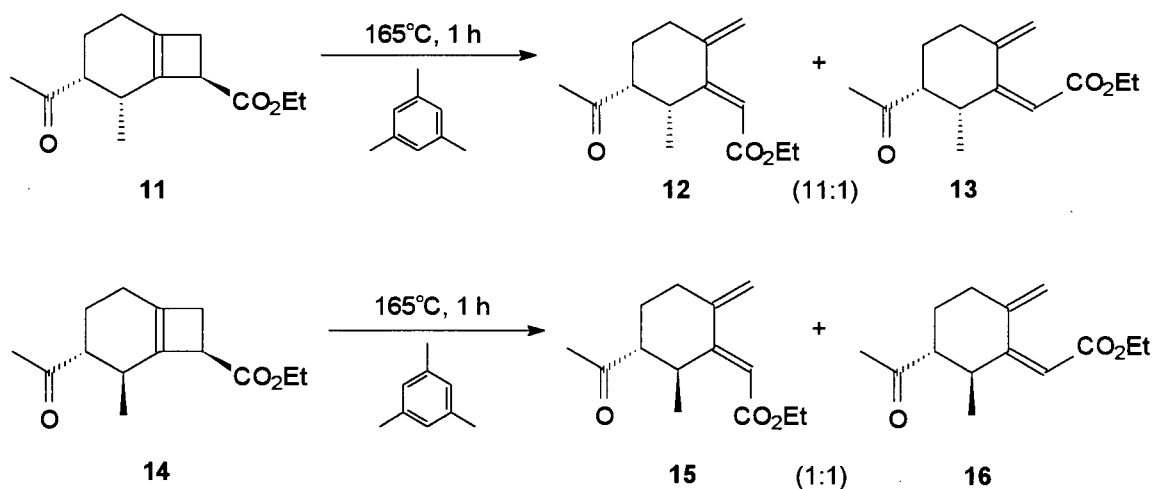


Scheme 1: Possible outcomes of the thermal ring opening of disubstituted cyclobutenes.

A number of studies by Frey,<sup>2-4</sup> Crigee,<sup>5</sup> Dolbier,<sup>6,7,8</sup> Stevens,<sup>9</sup> Houk,<sup>10</sup> and Piers<sup>11</sup> have shown that the nature of the substituents at C<sub>3</sub> affects the outcome of the thermal ring opening of substituted cyclobutenes of general structures (1) and (8). Studies by Frey<sup>2-4</sup> and Crigee<sup>5</sup> have shown that alkyl substituents tend to rotate preferentially outward due to the steric bulk of these substituents. On the basis of computational and experimental work, Houk proposed that it is the electronic nature of certain substituents that determines the direction of rotation (inward or outward) of the substituent.<sup>12</sup> Houk

predicted that groups that are good electron donors should prefer outward rotation while strongly electron withdrawing groups that are good electron acceptors should favour inward rotation.<sup>12</sup>

For example, Houk predicts on the basis of *ab initio*<sup>i</sup> calculations that the ester function should have a small (1.7-2.5 kcal/mol) preference for outward rotation.<sup>13,14,15</sup> Thus, the ratio of outward to inward rotation products is expected to fall between 7:1-18:1 at 165°C. Piers and Lu have provided some evidence supporting this prediction.<sup>11</sup> For example, ester (11) was thermolyzed in refluxing mesitylene (165°C for 1 h) to produce an 11:1 mixture of the outward (12) and the inward (13) rotation products (Scheme 2).



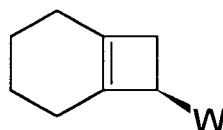
Scheme 2

Interestingly, the diastereomer of (11), compound (14), was thermolyzed under the same conditions to produce a 1:1 mixture of outward (15) and inward (16) rotation products (Scheme 2). An inspection of molecular models indicates that the ester group

<sup>i</sup> *Ab initio* calculations are quantum mechanical calculations where the Schrodinger equation is approximated.

would have to slide past the pseudoequatorial Me group of (14) in the transition state leading to outward rotation product (15). This destabilizing steric interaction would be expected to increase the transition state energy for outward rotation, making inward rotation more competitive.

One of the objectives of this research program was to test the predictions of Houk regarding the effect of the nature of the substituent on the ratio of outward to inward rotation products.



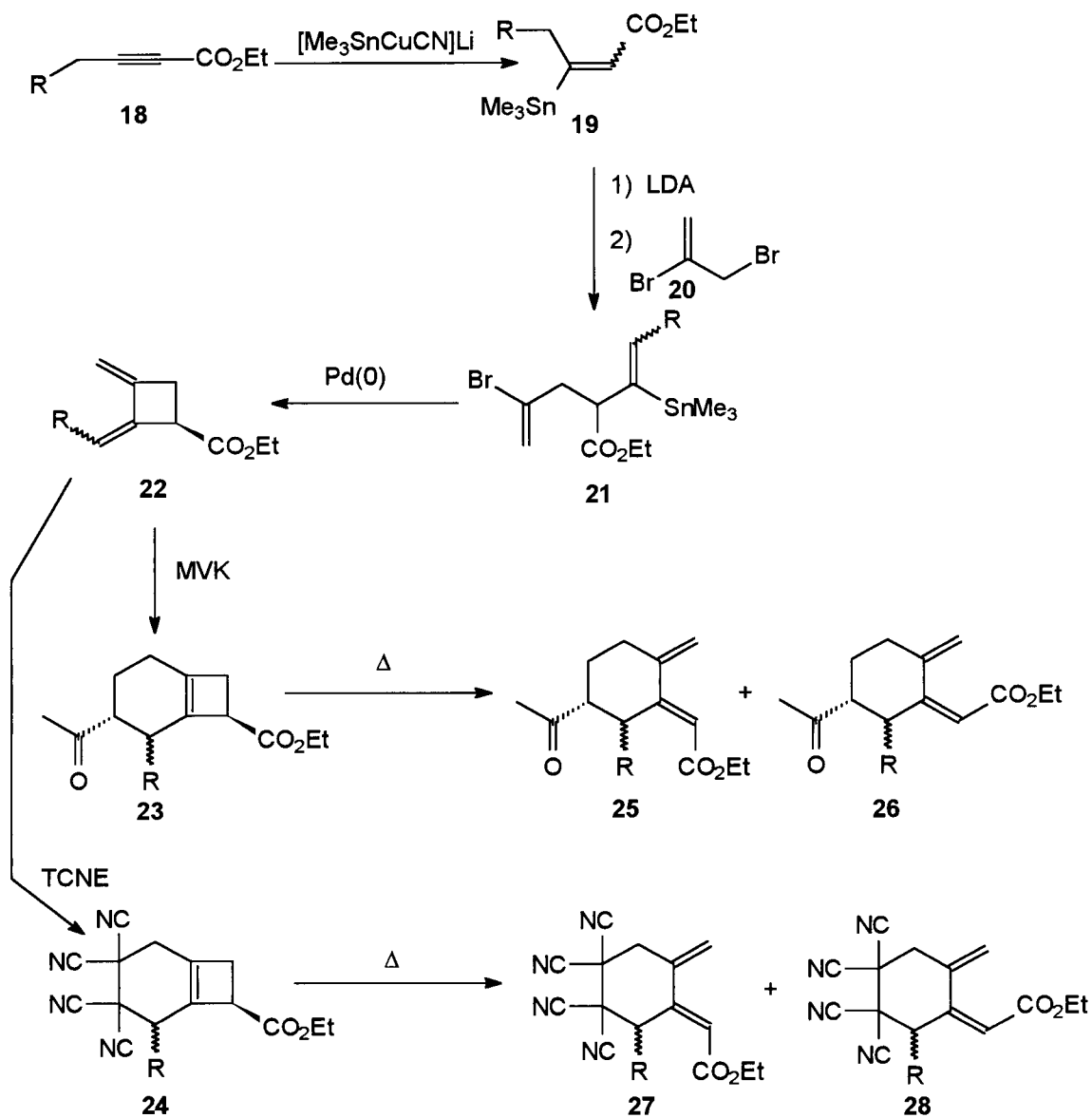
17

Efforts were to be made to develop new synthetic sequences to compounds of general structure (17) where W= -CO<sub>2</sub>Et, -CN, -CO<sub>2</sub>H, -CO<sub>2</sub><sup>-</sup>, -CH<sub>2</sub>OH. These compounds were then to be thermolyzed and the results of these experiments were to be compared with the predictions of Houk.<sup>13,14,15</sup>

The second objective of this research endeavor was to study the effect of increasing the steric bulk of the C-5 alkyl substituent (R) on various 5-substituted 7-(ethoxycarbonyl)- bicyclo[4.2.0]oct-1(6)-enes (23) or (24) on the ratios of outward (25 and 27) to inward (26 and 28) rotation thermolysis products (Scheme 3).

Using methodology that had been previously developed in our laboratories,<sup>16,17</sup> it appeared that compounds of general structure (23) and (24) (where R=H, Me, *i*-Pr, *c*-Hex) could readily be prepared (Scheme 3). A conformational study on all of the 5-substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes synthesized would allow one to determine if the R groups on the six membered rings are in pseudoaxial or pseudoequatorial orientations. This should provide insight of the effects of non-bonding interactions involving these groups on the torquoselectivity<sup>ii</sup> of the reaction.

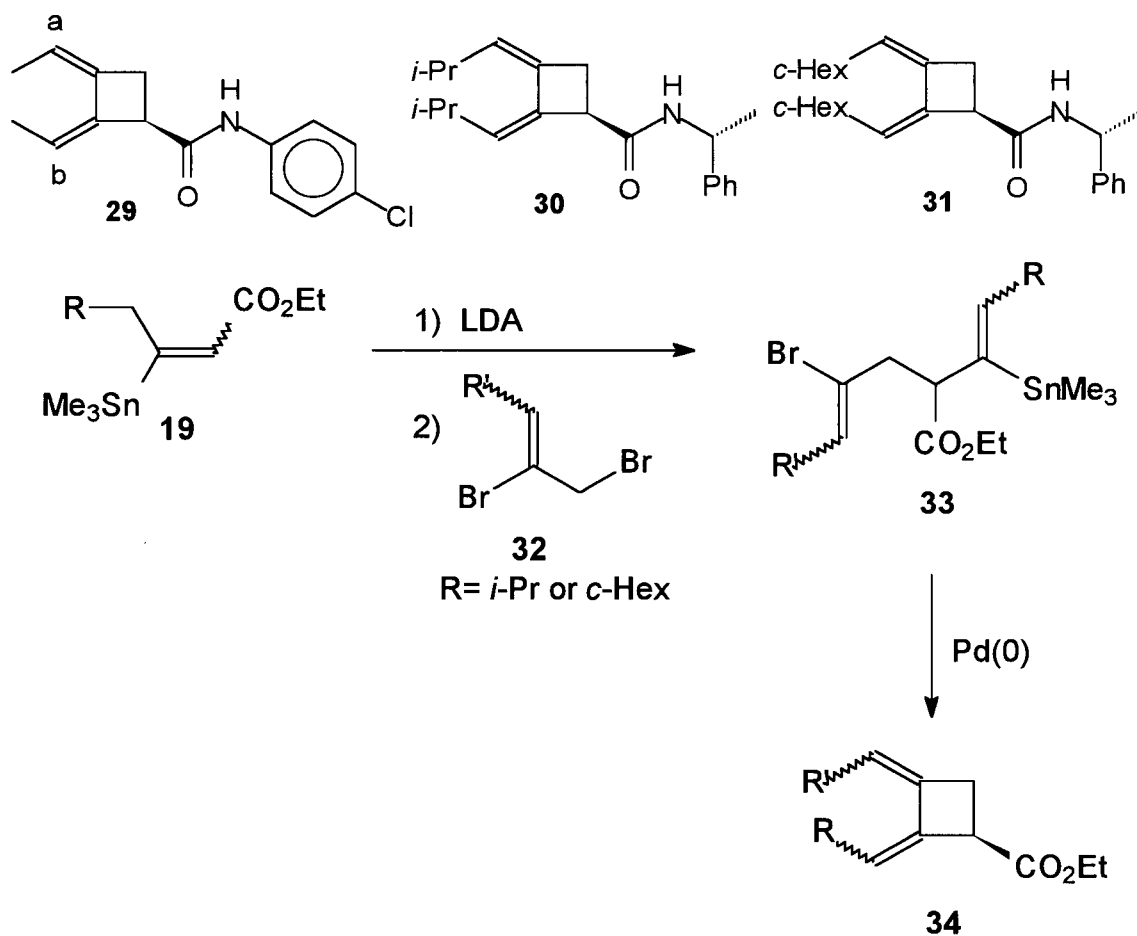
<sup>ii</sup> Torquoselectivity is referred to as the selectivity for outward or inward twisting of the breaking C-C cyclobutene bond.<sup>34</sup>



Scheme 3

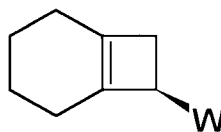


The strained compound (**29**), which, in the solid state, has a torsion angle of  $23^\circ$  between carbons a and b of the *cisoid* diene unit, has been prepared.<sup>16</sup> By using the methodology outlined in Scheme 3 where (**20**) is replaced by reagents of general structure (**32**), highly strained dienes (**30**) and (**31**) could be synthesized and the torsion angles determined from X-ray analysis (Scheme 4). The transformation of (**33**) to (**34**) can be accomplished using a Pd(0)-catalyzed cross coupling between the vinyltrimethylstannyl and the vinyl bromide moieties. Thus, a third objective of this research project was the synthesis and study of the reactivity of these highly strained molecules while determining the scope and limitations of the intramolecular Pd(0)-catalyzed cross-coupling procedure.



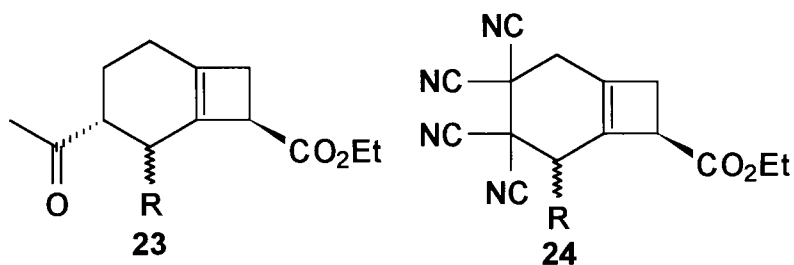
Scheme 4

## 2. Objectives of this research project

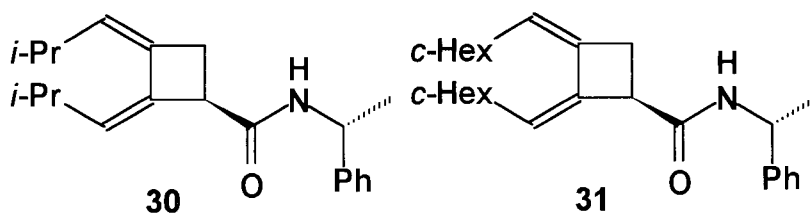


17

1. The first objective of this research project was to develop new synthetic sequences to compounds of general structure (17) where  $W = -CO_2Et$ ,  $-CN$ ,  $-CO_2H$ ,  $-CO_2^-$ ,  $-CH_2OH$ . These compounds were then to be thermolyzed and the results of these experiments were to be compared with the predictions of Houk.<sup>13,14,15</sup>



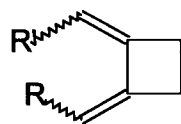
2. The second objective of this research endeavor was to study the effect of increasing the steric bulk of the C-5 alkyl substituent ( $R$ ) on various 5-substituted 7-(ethoxycarbonyl)- bicyclo[4.2.0]oct-1(6)-enes (23) or (24) on the ratios of outward (25 and 27) to inward (26 and 28) rotation thermolysis products (Scheme 3, page 5)



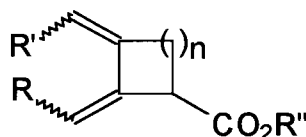
3. The third objective of this research project was the synthesis and study of the reactivity of the highly strained dienes (30 and 31) and determining the scope and limitations of the intramolecular  $Pd(0)$ -catalyzed cross-coupling procedure used to prepare them.

### 3. Background information

#### 3.1 Previous work on the synthesis of alkyl 2,3-bis-alkylidenecyclobutanecarboxylates (36) and related compounds (37) and (38)



35



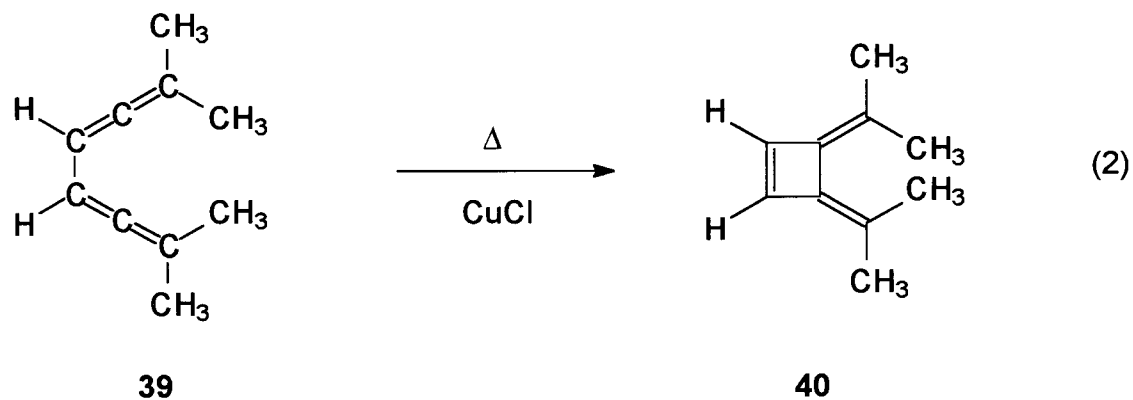
36 n=1

37 n=2

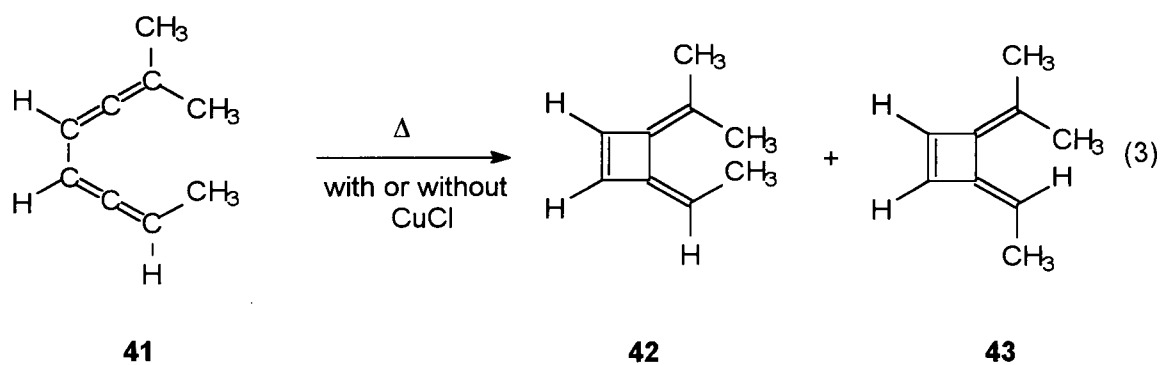
38 n=3

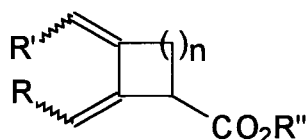
Traditional methods for the syntheses of substituted 1,2-*bis*-alkylidenecyclobutanes of general structure (35) are inefficient, stereochemically ambiguous, and difficult to carry out in the laboratory.<sup>18,19,20,21</sup> For example, the preparation of (35) ( $R=R'=H$ ), which proceeds *via* a thermal  $[\pi^2_s + \pi^2_s]$  cycloaddition or dimerization of allene, requires passing allene through a tube packed with glass balls and heated to 500°C.<sup>18</sup> The pyrolysate was collected in a flask cooled with dry ice, was fractionally distilled to remove unreacted allene, and the allene recycled 10 times to afford 25% of 1,2-*bis*-methylidenecyclobutane (35,  $R=R'=H$ ).

Recently, Pasto and co-workers have developed a low temperature method of converting substituted *bis*-allenes into substituted 3,4-*bis*-alkylidenecyclobutenes.<sup>22</sup> For example, the *bis*-allene (39) was heated at 65°C in deuteriochloroform in the presence of cuprous chloride to produce quantitatively the trialkene (40) (Equation 2). Interestingly, a strictly thermally-induced ring closure of tetraene (39) to (40) could not be accomplished.



However, when the starting *bis*-allene does not have four identical substituents at C<sub>1</sub> and C<sub>6</sub>, there is only modest stereoselectivity favouring the less strained product. Thus, heating of the bisallene (41) at 65°C in deuteriochloroform in the presence of cuprous chloride provided a 1:2 mixture of (42) and (43), while heating of the bisallene (41) in the gas phase at 322°C produced about a 1:1 mixture of these two products (Equation 3).<sup>22</sup>



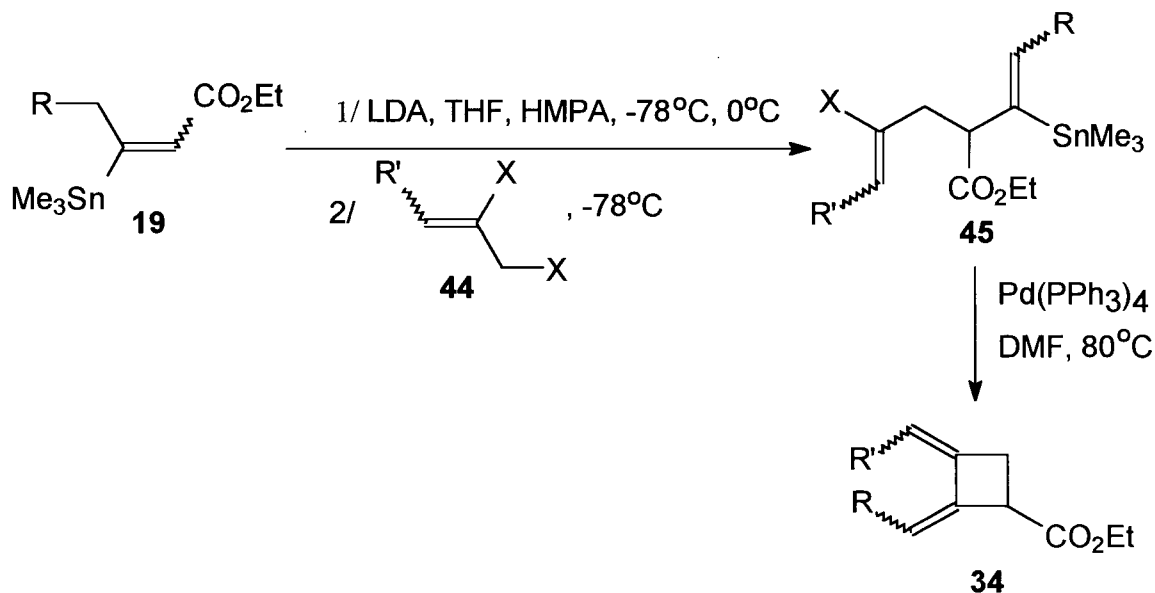


**36**  $n=1$

**37**  $n=2$

**38**  $n=3$

Piers and Lu have developed an efficient and stereoselective method for the synthesis of various alkyl 2,3-*bis*-alkylidenecyclobutanecarboxylates (**36**) and higher ring homologs (**37**) and (**38**).<sup>16,23</sup> The first step in a synthetic route to the cyclobutanecarboxylates involves preparing a suitable ethyl (*E*) or (*Z*)-3-trimethylstannyl-2-alkenoate (**19**) via Morton and Chong's methodology developed in our laboratories.<sup>17</sup> Treatment of alkenoates of general structure (**19**) with LDA in a THF-HMPA solvent under conditions previously reported,<sup>23</sup> followed by alkylation with the appropriate (*E*) or (*Z*)-1,2-dihalo-2-alkene (**44**) afforded the corresponding diene esters (**45**) (Scheme 5). Palladium (0)-catalyzed intramolecular cross coupling of the diene esters (**45**) results in formation of the stereochemically defined cyclobutanecarboxylates (**34**) (Scheme 5).



Scheme 5

Several ethyl 2,3-*bis*-alkylenecyclobutanecarboxylates (**34**) were prepared via this general method and the results are summarized in Table 1. It is important to note that in all cases the conversions of the diene esters (**45**) into their corresponding cyclobutanecarboxylates (**34**) were completely stereoselective and proceeded in good to excellent yields. A slightly modified procedure for entries 4 and 5 was required because standard reaction conditions gave none of the desired cyclobutanecarboxylate.<sup>16</sup> When Et<sub>3</sub>N (1 equiv.) was added to the reaction mixture, the reaction proceeded to give the desired products in the indicated yields.

Table 1: Synthesis of the ethyl 2,3-*bis*-alkylenecyclobutanecarboxylates **34**.<sup>16</sup>

Reaction scheme showing the conversion of substrate **45** to product **34** under conditions **a**.

Entry	Substrate	Product	Yield(%) <sup>b</sup>
1	<p><b>46</b></p>	<p><b>53</b></p>	82
2	<p><b>47</b></p>	<p><b>54</b></p>	89
3	<p><b>48</b></p>	<p><b>55</b></p>	96
4 <sup>c</sup>	<p><b>49</b></p>	<p><b>56</b></p>	68
5 <sup>c</sup>	<p><b>50</b></p>	<p><b>57</b></p>	70
6	<p><b>51</b></p>	<p><b>58</b></p>	97
7	<p><b>52</b></p>	<p><b>59</b></p>	93

<sup>a</sup>Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 equiv.), DMF, 80 °C, 1 h unless otherwise noted.<sup>b</sup>Yield of purified, distilled product.<sup>c</sup>Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 equiv.), Et<sub>3</sub>N (1 equiv.), DMF, 80 °C, 1 h.

Ethyl 2,3-*bis*-alkylidenecyclopentane- (37) and cyclohexanecarboxylates (38) were synthesized by carrying out synthetic sequences similar to those outlined above.<sup>16</sup> Thus, by alkylation of the vinylstannane esters of general structure (19) with alkylating agents (60) or (61), Lu was able to prepare selectively the diene esters (62) through (68) (Table 2). Treatment of these substrates with Pd(Ph<sub>3</sub>P)<sub>4</sub>/DMF/LiCl/80°C for 1 h gave the corresponding cyclopentanecarboxylates (69-72) and cyclohexanecarboxylates (73-75) in good yields. However, in the absence of LiCl, the palladium(0)-catalyzed coupling reactions of diene esters (62) and (65) leading to cyclopentanecarboxylates (69) and (72) were not as efficient. Compounds (76) and (77) were produced as side products in entries 1 and 4, respectively. LiCl (2 equiv.) was required to effect efficient transformation of (62) and (65) into (69) and (72), respectively. In the absence of LiCl, a mixture of products was obtained.<sup>16</sup>

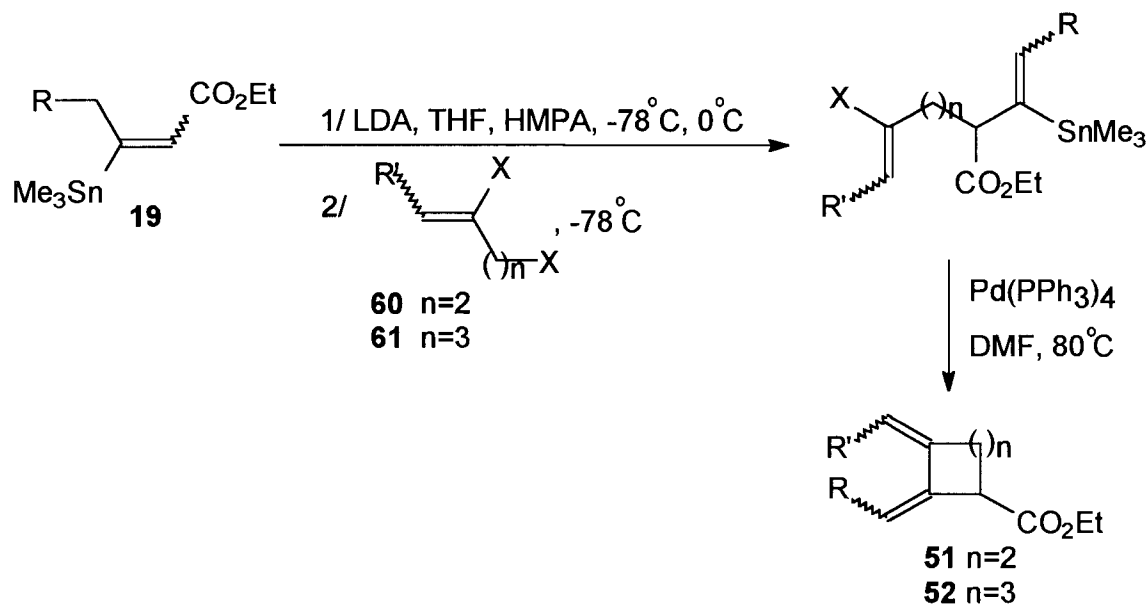
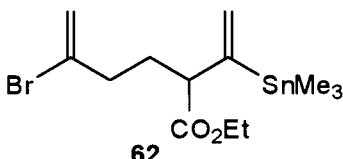
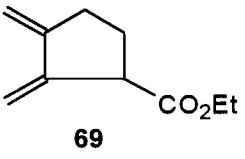
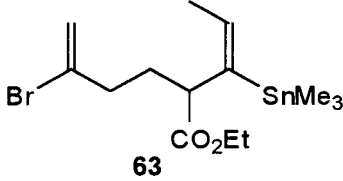
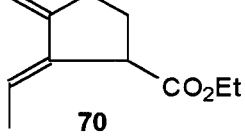
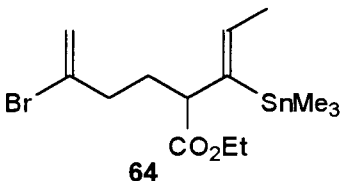
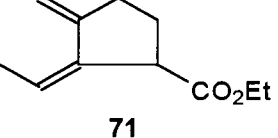
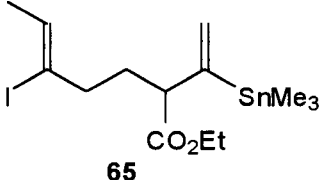
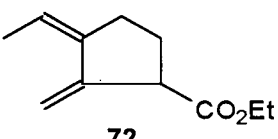
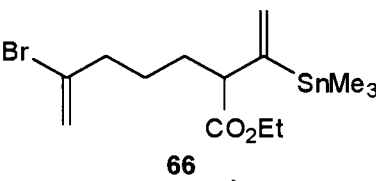
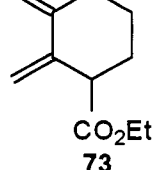
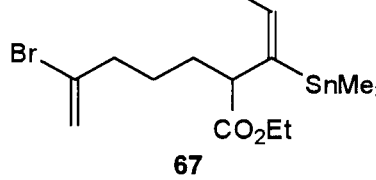
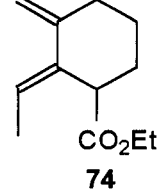
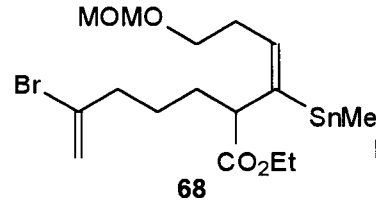
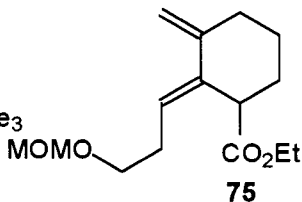
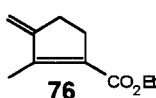


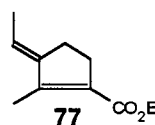


Table 2: Synthesis of the cyclopentanecarboxylates **69-72** and cyclohexanecarboxylates **73-75**.<sup>16</sup>

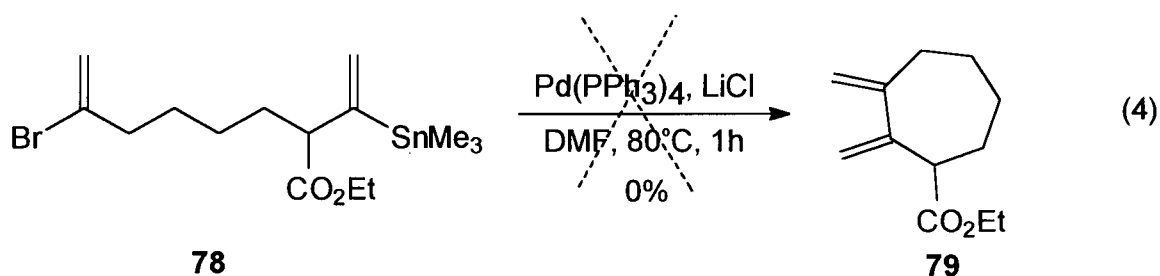
Entry	Substrate	Product	Yield(%) <sup>b</sup>
1a	 <b>62</b>	 <b>69</b>	85 <sup>c</sup>
2	 <b>63</b>	 <b>70</b>	84
3	 <b>64</b>	 <b>71</b>	79
4a	 <b>65</b>	 <b>72</b>	83 <sup>d</sup>
5	 <b>66</b>	 <b>73</b>	74
6	 <b>67</b>	 <b>74</b>	68
7	 <b>68</b>	 <b>75</b>	54

<sup>a</sup> Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 equiv.), LiCl (2 equiv.), DMF, 80°C, 1h.<sup>b</sup> Yield of purified, distilled product.

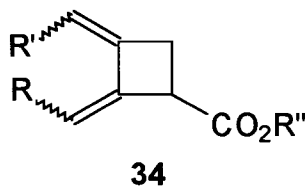
<sup>c</sup>  **76** was produced in the absence of LiCl

<sup>d</sup>  **77** was produced in the absence of LiCl

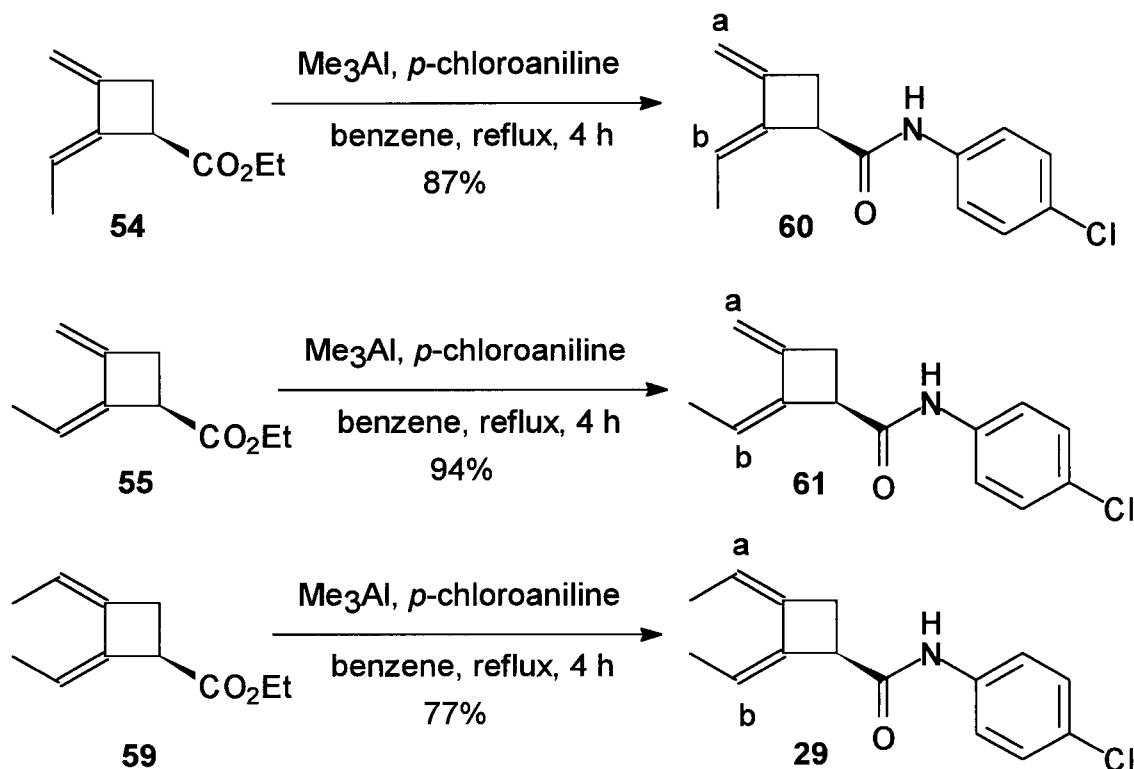
Though the above methodology proved to be effective for the synthesis of the 4-, 5- and 6-membered ring carboxylates, all attempts to synthesize the 7-membered ring homolog (**79**) were unsuccessful. Indeed, treatment of (**78**) under the conditions shown gave no coupled product (**79**) (Equation 4).



### 3.2 Previous X- ray crystallographic studies on crystalline derivatives of 2,3-bis-alkylenecyclobutanecarboxylates



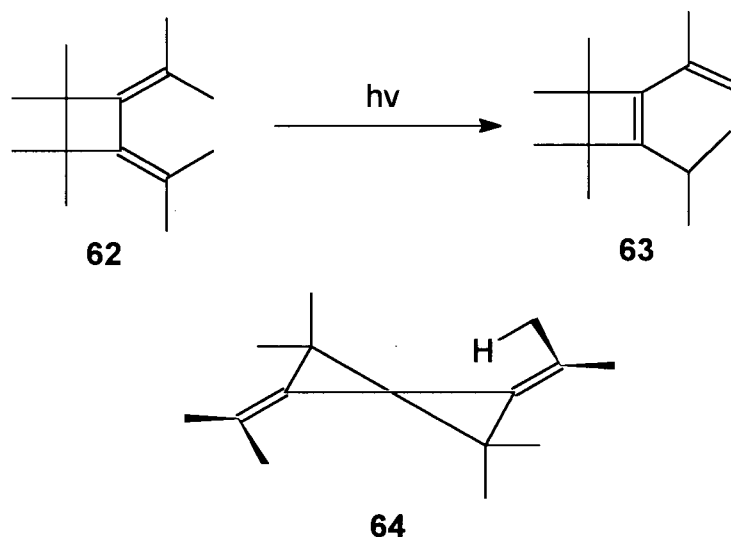
Following his initial synthetic work on the cyclobutanecarboxylates (**34**), Lu noted that the cyclobutanecarboxylates (**54**), (**55**) and (**59**) should be quite strained. In particular compound (**59**) will be very strained due to the steric repulsion between the two vinylic methyl groups. To determine the effect of this repulsion on the geometry of the cisoid diene unit, Lu prepared crystalline derivatives of compounds (**54**), (**55**) and (**59**) via a procedure previously reported by Weinreb<sup>24</sup> (Scheme 6).



Scheme 6

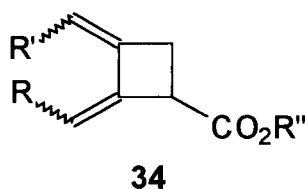
X-ray analyses of the crystalline derivatives (**60**), (**61**) and (**29**) showed that the torsional angle between carbons a and b of the cisoid diene units were  $3.9^\circ$ ,  $4.8^\circ$ , and  $25.4^\circ$ , respectively.<sup>16</sup> The latter result provides a rationale why (**59**) does not undergo Diels-Alder cycloaddition reactions, since the four carbons of the *cisoid* diene unit must be in a planer or nearly planer conformation in order for the Diels-Alder reaction to proceed.

Other researchers have found results similar to those observed by Lu. Kiefer and Fukunaga have shown that the diene (**62**) readily undergoes an antarafacial 1,5 hydrogen shift to afford compound (**63**) (Scheme 7).<sup>25</sup> Kiefer concluded that "serious Van der Waal repulsion between the 'endo' allylic methyl groups in the planer configuration of (**64**) is most efficiently relieved by a combination of ring puckering and conrotatory torsion of the isopropylidene groups".<sup>25</sup>



Scheme 7

### 3.3 Diels-Alder Reactions of the 2,3-bisalkylenecyclobutanecarboxylates (**34**)



Since the initial publication by Kurt Alder and Otto Diels on [4+2]-cycloadditions (the Diels-Alder Reaction),<sup>26</sup> there have been numerous papers published on the synthetic application and mechanistic aspects of this reaction due to its importance in organic chemistry.<sup>27,28,29</sup>

Studies were performed in our laboratories on Diels-Alder reactions of alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates with tetracyanoethylene (TCNE) and methyl vinyl ketone (MVK).<sup>16</sup> In the case of TCNE the dieneophile approaches the diene unit from the side opposite to the carboxylate group (Figure 1) to minimize steric repulsion. Thus, reaction of (**65**) and (**66**) with TCNE produced the cycloadducts (**67**) and (**68**), respectively (Scheme 7).

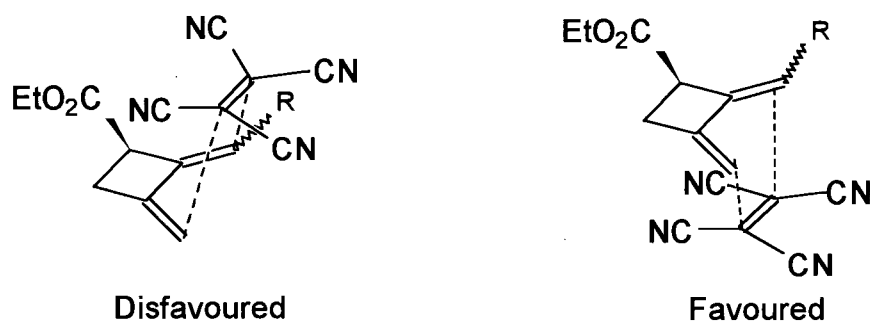
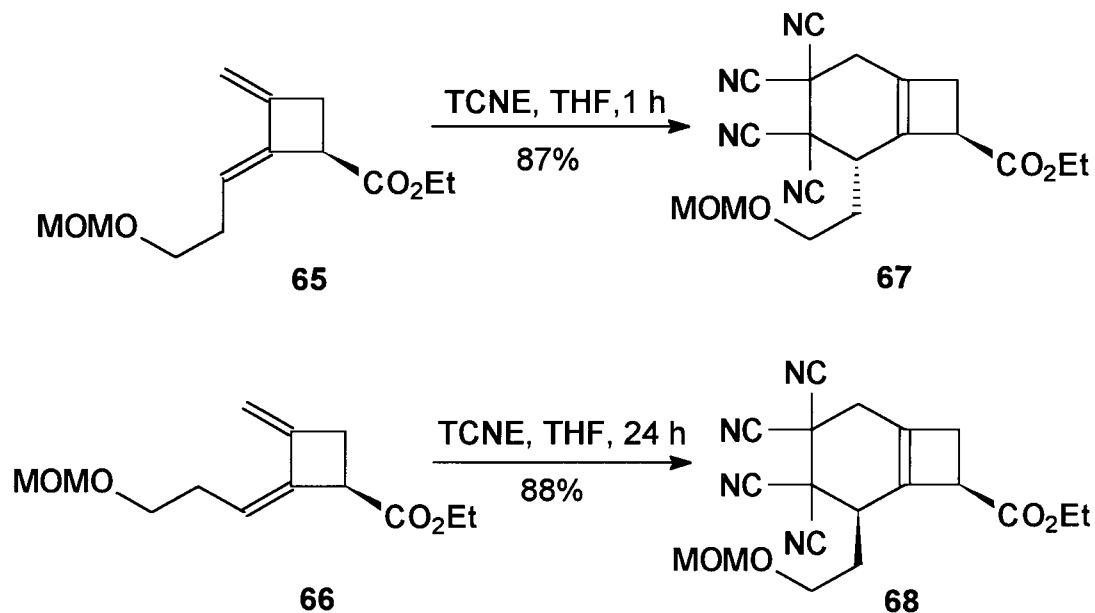


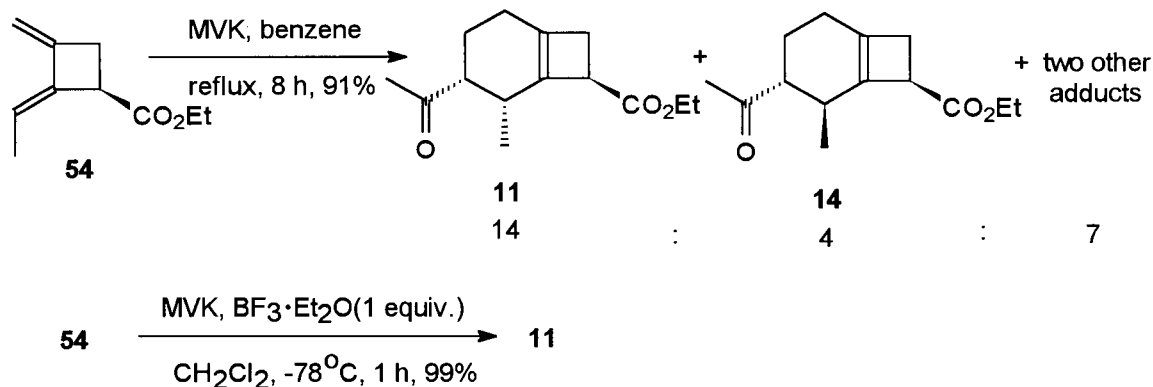
Figure 1: Diagrammatic view of the two possible directions that the dieneophile TCNE may approach the ethyl 2,3-bis(alkylidene)cyclobutane carboxylates.



Scheme 8

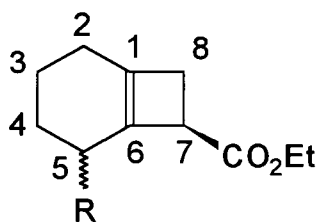
It was also found that reaction of the diene (**54**) with methyl vinyl ketone in refluxing benzene for 8 h resulted in a mixture of (**11**), (**14**) and two other adducts in a ratio of 14:4:4:3 (Scheme 9).<sup>16</sup> The stereoselectivity for the process was improved by treatment of the diene (**54**) with the dieneophile in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , a Lewis

acid, at  $-78^{\circ}\text{C}$  for 1 h in methylene chloride. Under these conditions the cycloadduct (**11**) was produced exclusively in 99% yield.



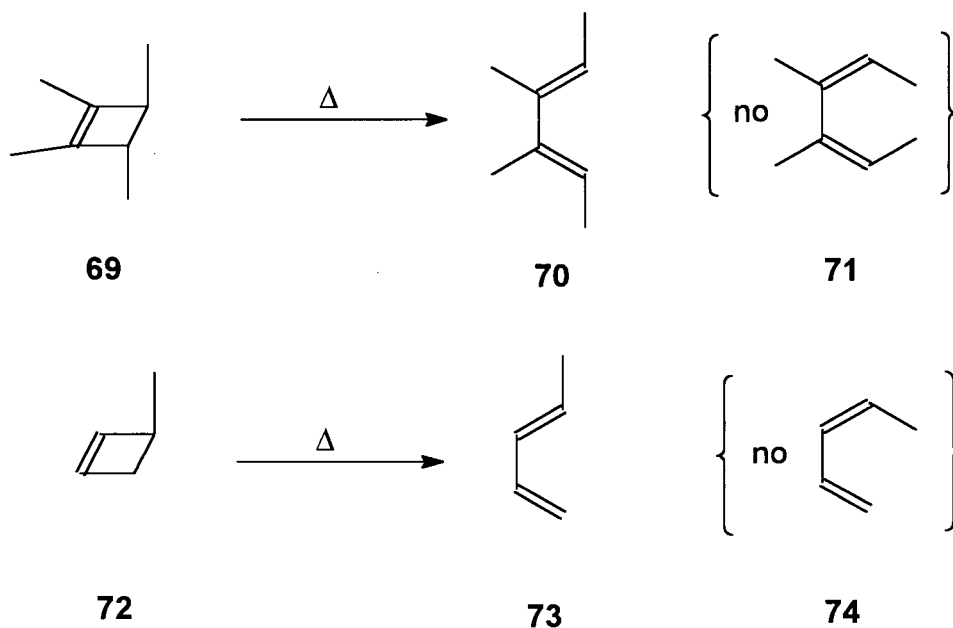
Scheme 9

A complete discussion of the rationale behind these observations will be presented in the discussion section of this thesis. Nevertheless, by using the above methodology, it appeared that a general synthetic route to the 5-substituted 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes, with defined stereochemistry at C-5, was available.



### 3.4 Thermolysis of the cyclobutenes and related compounds

Studies undertaken by Frey,<sup>2,3,4</sup> Crigee<sup>5</sup> and co-workers on the thermolysis of cyclobutenes with alkyl substituents at C-3 or at C-3 and C-4 (Scheme 10) showed that alkyl groups preferentially rotate outward. Thus, thermolysis of the *trans*-1,2,3,4-tetramethylcyclobutene (**69**) produces exclusively the (*E,E*)-isomer (**70**)<sup>5</sup> (Scheme 10) while thermolysis of 3-methylcyclobutene (**72**) gives only *trans*-piperylene (**73**)<sup>3</sup> (Scheme 9).



Scheme 10

The exclusive formation of (70) and (73) was attributed to the destabilizing steric interactions in the transition states leading to the more strained inward rotation products (71) and (74). Later studies by Dolbier<sup>6,7,8</sup> and Stevens<sup>9</sup> contradict this argument. These workers found that in the thermolysis of certain substituted cyclobutenes, steric effects contribute little to the overall direction of conrotatory ring opening.

Curry and Stevens synthesized a number of 3-alkyl-3-methyl cyclobutenes (75) and heated them under thermolysis conditions (180°C) to produce the *Z* isomers (76) (resulting from outward rotation of the methyl group and inward rotation of the R group) and the *E* isomers (77) (Me in, R out) (Equation 5).<sup>9</sup> The results of this study are summarized in Table 3.<sup>9</sup>

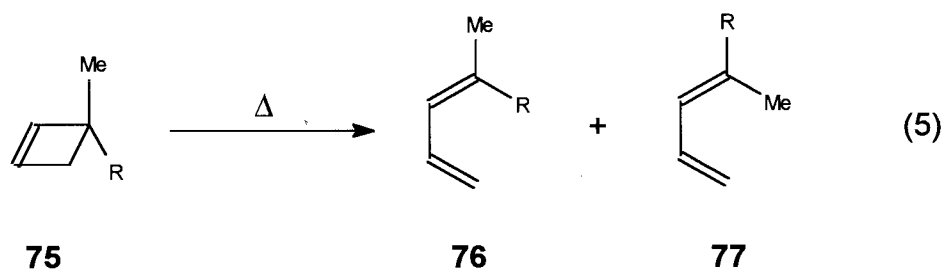


Table 3: Products of the pyrolysis of 3,3-disubstituted cyclobutenes (75).<sup>9</sup>

R in (75)	Z-isomer (76)	E-isomer (77)
<i>t</i> -Butyl	32	68
<i>i</i> -Propyl	65.5	34.5
<i>n</i> -Propyl	62	38
Cyclopropyl	43	57
Ethyl	68	32
C <sub>2</sub> D <sub>5</sub>	61	39
Phenyl	30	70
4-Methoxyphenyl	52	48
3-Methoxyphenyl	32	68
4-Cyanophenyl	45	55

*A-priori*, based upon steric arguments, one would expect that the larger R is relative to methyl, the greater the ratio of (77) to (76) should be. Clearly this is not the case as the ratio of (77):(76) (inward R:outward R) is  $\approx 2:1$  when R=isopropyl, *n*-propyl, or ethyl and  $\approx 1:1$  for R=cyclopropyl and 4-methoxyphenyl (Table 3). Furthermore, if one calculates the Z:E ratios expected based upon the A-values of the substituents, the observed ratios are clearly less than those expected (Table 4).<sup>9</sup>



Table 4: Calculated *Z:E* diene ratios based on steric effects.<sup>9</sup>

R in (76) and (77)	Et	Pr <sup>n</sup>	Pr <sup>i</sup>	cyclopropyl	Bu <sup>t</sup>	Ph
(A <sub>R</sub> -A <sub>Me</sub> )/kcal mol <sup>-1</sup>	0.11	0.41	0.41	-	3.41	1.23
Calc. <i>Z:E</i>	42:58	25:75	25:75	50:50	2:98	1:5
Obs. <i>Z:E</i>	68:32	62:38	66:34	43:57	32:68	30:70

In 1984 Houk proposed an elegant theory, based upon extensive computational calculations, which provides insight into rotational preference of certain substituents. Houk proposed that it was the electronic nature of certain substituents that determines the direction of rotation (inward or outward) of the substituent.<sup>12</sup> Based upon these calculations, Houk predicted that groups that are good electron donors should prefer outward rotation while strongly electron withdrawing groups that are good electron acceptors should favour inward rotation.

Calculations by Houk on the transition state for cyclobutane conrotatory electrocyclic opening show that the HOMO is primarily a stretched and twisted  $\sigma$  bond orbital while the LUMO is primarily a stretched and twisted  $\sigma^*$  orbital.<sup>13</sup> The filled p orbital of a donor(D) substituent and the  $\sigma$  and  $\sigma^*$  orbitals are sketched in Figure 2.

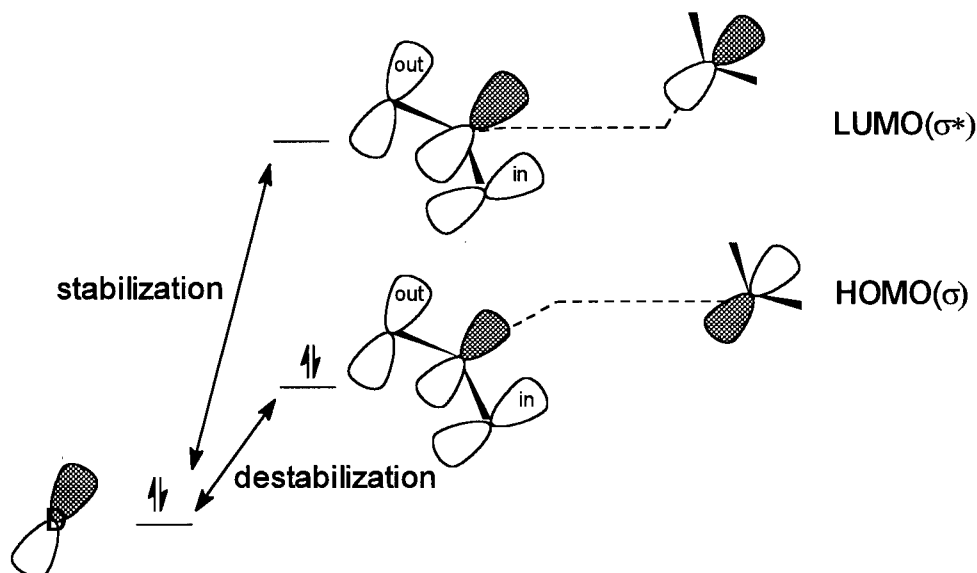


Figure 2: HOMO and LUMO of the cyclobutene transition structure and the occupied p orbital of a donor orbital.

In Houk's words,<sup>13</sup>

"Upon outward rotation of a donor substituent, the donor orbital can mix with the LUMO, resulting in stabilization and lowering of the activation energy. This is only partially counteracted by the destabilizing antiaromatic four-electron interaction of the donor orbital with the distorted cyclobutene HOMO. Because of the location of the donor orbital upon outward rotation (shown by the dashed lines labeled "out"), the donor orbital overlaps primarily with the atomic orbital at C<sub>3</sub>. Upon inward rotation, the donor orbital will move into the location marked by the dashed orbital labeled "in". In this location the donor orbital overlaps with the atomic orbitals at both C<sub>3</sub> and C<sub>4</sub>. The interaction of an inwardly rotating donor orbital with the distorted cyclobutene LUMO is less than that of an outwardly rotating donor orbital, because the signs of the neighboring lobes of the atomic orbitals at C<sub>3</sub> and C<sub>4</sub> are opposite. Consequently, stabilization upon inward rotation of the donor is less than upon outward rotation. At the same time, the donor orbital overlaps more with the distorted cyclobutene HOMO upon inward rotation than upon outward rotation, due to overlap at both C<sub>3</sub> and C<sub>4</sub>. This destabilizing interaction is larger for inward rotation than outward rotation. Thus, both interactions favor outward rotation, and the extent of this preference depends upon the donor ability of the substituent. With  $\pi$ -acceptor substituents, orbital

interactions also occur between the HOMO of cyclobutene and the empty orbital of the acceptor. This two-electron stabilizing interaction is maximized when the acceptor rotates inward and may cause acceptors to preferentially rotate inward."<sup>13</sup>

Houk has made extensive *ab initio* molecular orbital calculations on hypothetical molecules in the gas phase using the Gaussian 82-90 programs with the STO-36 and 6-3116\*\* basis sets developed by Pople and co-workers.<sup>30</sup> Some of Houk's predictions are outlined in Tables 5<sup>13</sup> and 6.<sup>13,14,15</sup> The substituents are listed in order of increasing  $\sigma_{\text{R}}^{\circ}$  values) in Table 5.

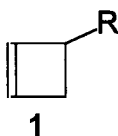


Table 5: Substituent effects on the stereochemistry of cyclobutene electrocyclizations<sup>13</sup>

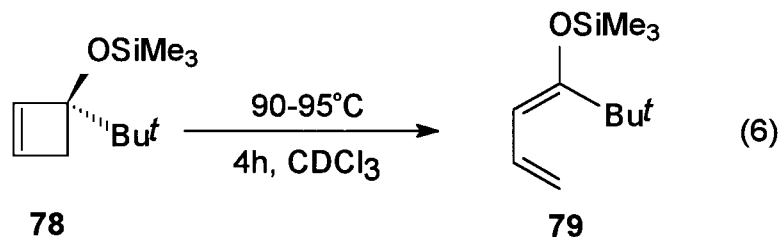
R	$\sigma_{\text{R}}^{\circ}$	$E_{\text{a}}(\text{in-out}) \text{ kcal mol}^{-1}$ (6-31G**/3-21G)
NH <sub>2</sub>	-0.48	17.5
OH	-0.43	17.2
F	-0.34	16.9
CH <sub>3</sub>	-0.11	6.8
H	0.0	0.0
CN	0.13	4.3
NO <sub>2</sub>	0.15	7.4
CHO	0.24	-4.6
NO	0.32	-2.6
BH <sub>2</sub>	-	-18.2

Table 6: Predicted change in activation energy of cyclobutene opening ( $E_a=32 \text{ kcal mol}^{-1}$ ) by C-3 substituents. Calculations are 6-31G\*\*/3-21G.

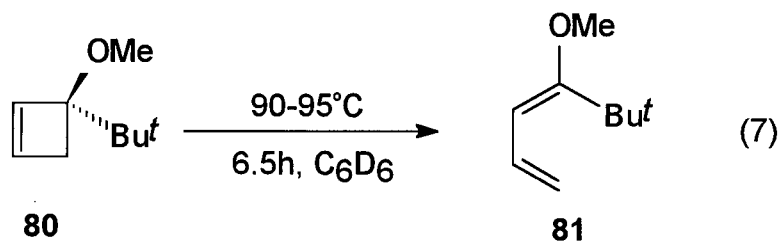
Substituent	$\Delta E_a(\text{out})$ $\text{kcal mol}^{-1}$	$\Delta E_a(\text{in})$ $\text{kcal mol}^{-1}$	$\Delta\Delta E_a(\text{in-out})$ $\text{kcal mol}^{-1}$
$-\text{CO}_2^-$	-6.4	+0.9	+7.3 <sup>13</sup>
$-\text{CN}$	-2.3	+2.3	+4.6 <sup>13</sup>
$-\text{CO}_2\text{Me}$	-4.2	-1.7	+2.5 <sup>13</sup>
$-\text{CO}_2\text{Me}$	-3.0	-1.3	+1.7 <sup>14</sup>
$-\text{CO}_2\text{H}$	-4.3	-2.0	+2.3 <sup>13,15</sup>
$-\text{CO}_2\text{H}$	-3.1	-1.6	+1.5 <sup>14</sup>
$-\text{CHO}$	-2.3	-6.9	-4.6 <sup>13</sup>
$-\text{CO}_2\text{H}_2^+$	-10.2	-15.8	-5.6 <sup>13</sup>
$-\text{CO}_2\text{H}_2^+$	-11.0	-15.8	-4.8 <sup>15</sup>
$-\text{Me}$	-1	+3	+4 <sup>12</sup>
$-\text{Cl}$	-3	+6	+9 <sup>12</sup>
$-\text{OR}$	-9	+5	+14 <sup>12</sup>

As can be seen in Table 5, groups such as  $\text{NH}_2$ ,  $\text{OH}$  and  $\text{F}$  strongly prefer outward rotation ( $E_a(\text{in-out}) = 17.5, 17.2, 16.9 \text{ kcal/mol}$ , respectively) while  $-\text{CHO}$ ,  $\text{NO}$ , and  $\text{BH}_2$  (good  $\pi$  electron acceptors) prefer inward rotation ( $E_a(\text{in-out}) = -4.6, -2.6$ , and  $-18.2 \text{ kcal/mol}$ , respectively).<sup>13</sup> In Table 6, we see that the mild electron withdrawing nature of the carboxylic acid group (which prefers outward rotation by  $1.5 \text{ kcal/mol}$ )<sup>14</sup> can be changed by deprotonation to the carboxylate or protonation to the protonated acid. The carboxylate group has donor character and prefers outward rotation by  $7.3 \text{ kcal/mol}$ <sup>13</sup> while the protonated acid is a strong electron-withdrawing group and prefers

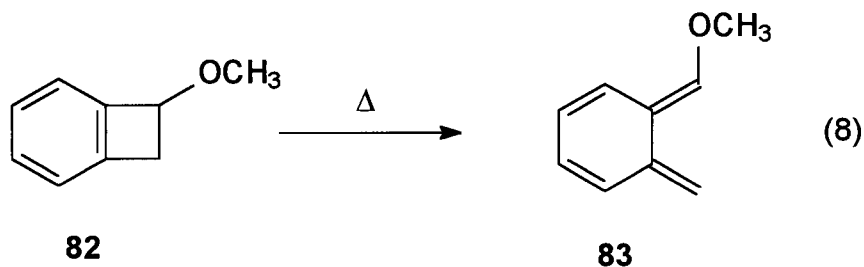
inward rotation by 11.0 kcal/mol.<sup>13</sup> Experimental results by Houk,<sup>14,31,32,33,34</sup> Piers,<sup>11</sup> Trost,<sup>35</sup> Wallace,<sup>36,37,38</sup> Rickborn,<sup>39</sup> Rimbault and co-workers<sup>40</sup> support some of these predictions. For example, when 3-*tert*-butyl-3-(trimethylsiloxy) cyclobutene (**78**) is heated in CDCl<sub>3</sub> at 90-95°C for 4 hr only the product (**79**) resulting from inward rotation of the *tert*-butyl group and outward rotation of the TMSO group is observed (Equation 6).<sup>33</sup>



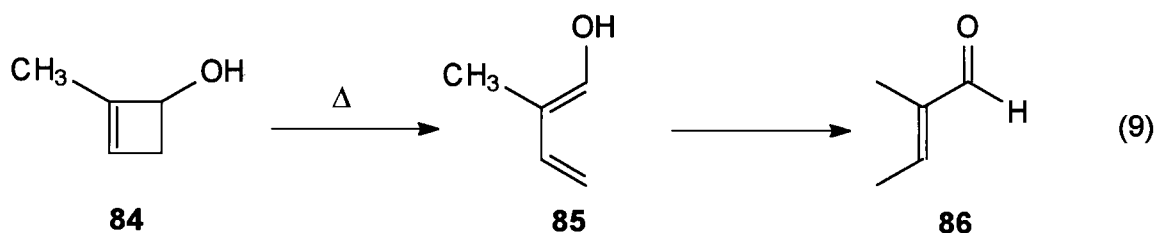
To determine if there was any steric effect by the large trimethylsilyl group, Houk and co-workers prepared and thermolyzed 3-methoxy-3-*tert*-butylcyclobutene (**80**). Again, only the product (**81**) resulting from outward rotation of the methoxy group and inward rotation of the "bulky" *tert*-butyl group was produced (Equation 7).<sup>33</sup>



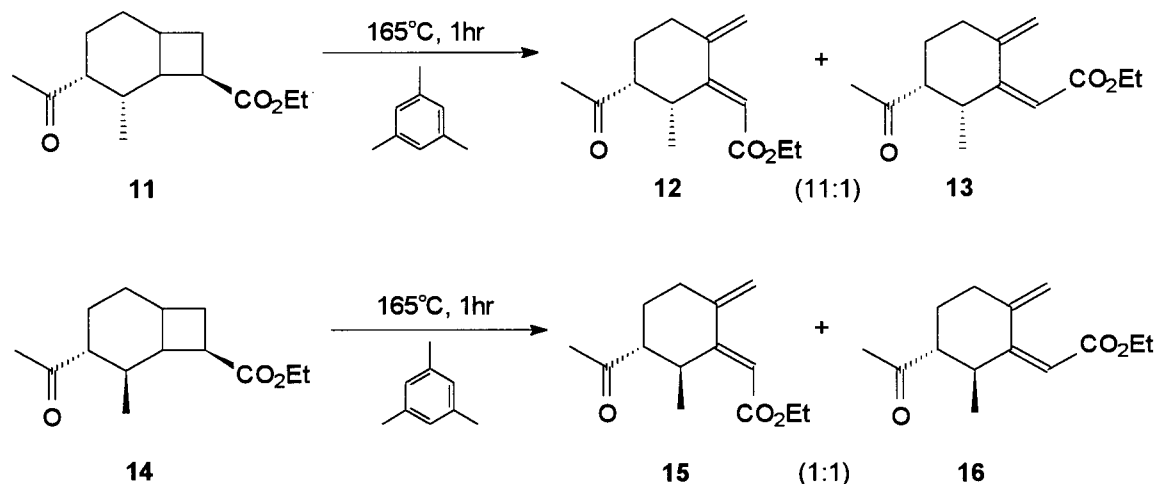
Sammes and co-workers found that thermolysis of  $\alpha$ -methoxybenzocyclobutene (**82**) to  $\alpha$ -methoxy-o-xylene (**83**) occurs with exclusive formation of the *E* (outward rotation) product and that the methoxy substituent lowers the activation energy for this ring opening by 9 kcal/mol as compared to the unsubstituted case (Equation 8).<sup>41</sup>



Rimbault and co-workers<sup>40</sup> found that 2-methyl-3-hydroxybutene (**84**) undergoes thermolysis to give only the product resulting from outward rotation of the alcohol group to afford (**85**), which rearranges to give (**86**) (Equation 9).



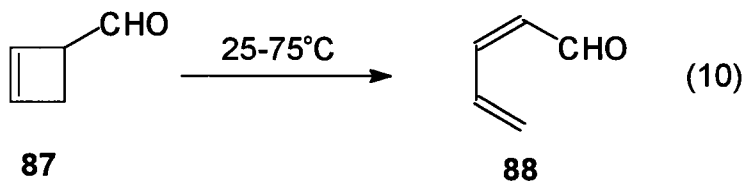
As mentioned previously in this introduction, Houk predicts that the ester function should have a slight (1.7-2.5 kcal/mol) preference for outward rotation.<sup>13,14</sup> Thus, the ratio of outward to inward rotation products is expected to fall between 7:1-18:1 at 165°C. Piers and Lu have provided evidence supporting this prediction.<sup>11</sup> Ester (**11**) was thermolyzed in refluxing mesitylene (165°C for 1 hr) to obtain an 11:1 mixture of the outward (**12**) to the inward (**13**) rotation products (Scheme 11).



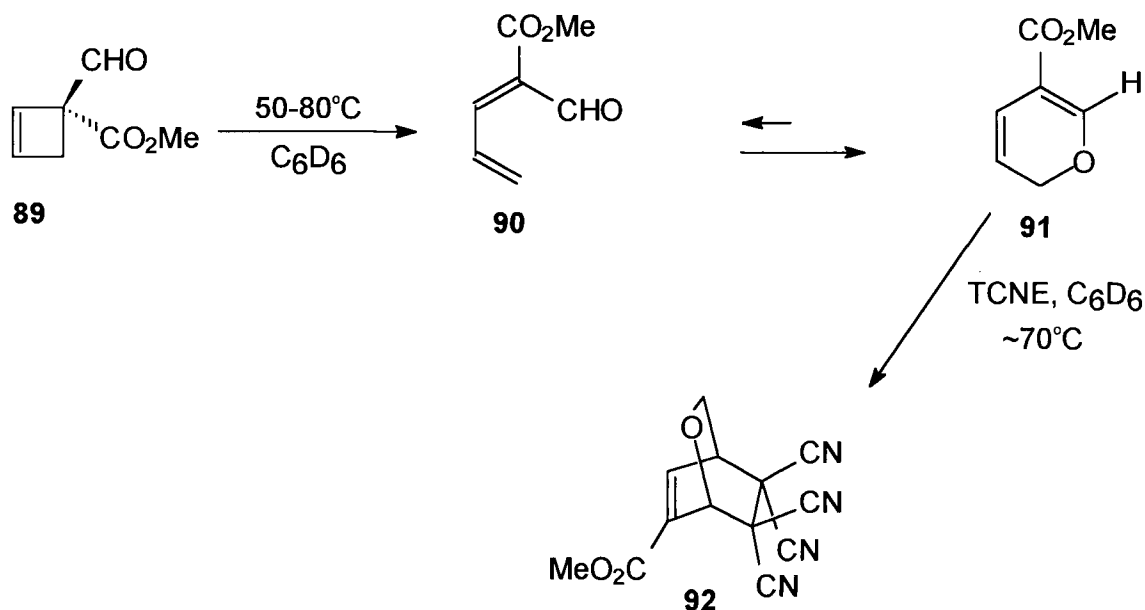
Scheme 11

Interestingly, the  $\beta$  isomer of (11), compound (14), was thermolyzed under the same conditions to produce a 1:1 mixture of outward (15) and inward (16) rotation products (Scheme 11). An inspection of molecular models indicated that the ester group would have to slide past the pseudoequatorial Me group of (14) in the transition state leading to outward rotation product (15). This destabilizing interaction may increase the transition state energy for outward rotation, making inward rotation more competitive.

A good  $\pi$  acceptor substituent such as the formyl group is predicted to prefer inward rotation over outward rotation by 4.6 kcal/mol (Table 6). Houk and co-workers<sup>42</sup> thermolyzed 3-formyl butene (87) and found that only the product (88) resulting from inward rotation of the formyl group was produced (Equation 10).



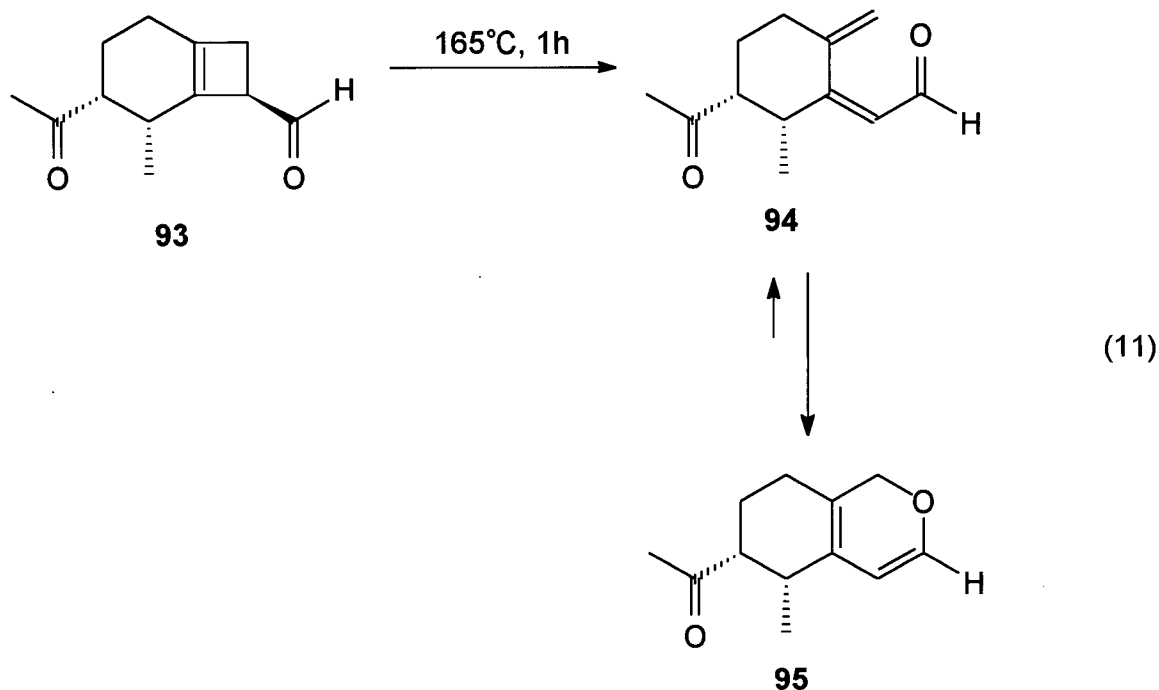
Houk and co-workers thermolyzed the 3,3-disubstituted cyclobutene (**89**) and found, not surprisingly, that only the product (**90**) resulting from outward rotation of the ester and inward rotation of the aldehyde group was produced (Scheme 2).<sup>14</sup> This compound, once formed, reversibly isomerizes to the (2H)-pyrane (**91**), which could not be isolated in pure form. Its structure was confirmed by trapping with one equivalent of tetracyanoethylene at 70°C to form the Diels-Alder adduct (**92**).



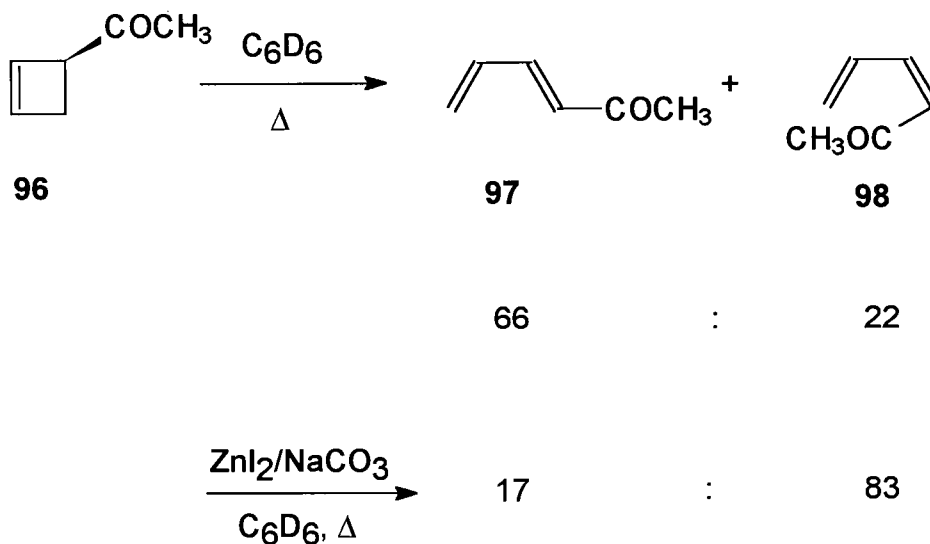
Scheme 12

Piers and Lu observed a similar result when aldehyde (**93**) was thermolyzed (Equation 11).<sup>11</sup> Thermolysis of (**93**) produced the inward rotation products (**94**) and (**95**) in a ratio of 1:2, respectively. Compound (**95**) is formed by reversible electrocyclic ring closure of dienal (**94**). These compounds slowly interconvert at room temperature and thus could not be obtained pure.



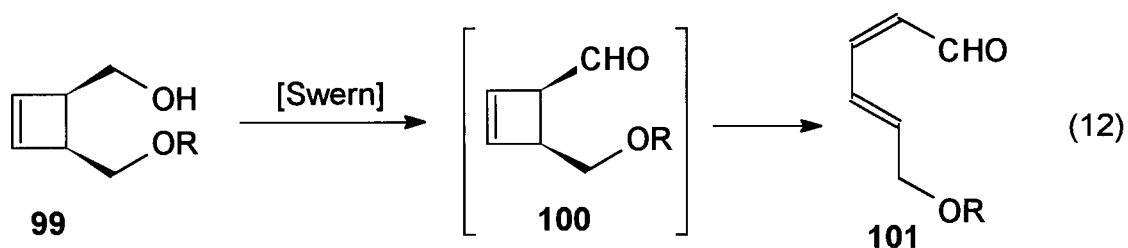


Recently, Houk and co-workers have predicted the acetyl group should favour outward rotation by 1.2 kcal/mol.<sup>32</sup> However, if a Lewis acid such as  $\text{ZnI}_2$  is added, it was calculated that inward rotation would then be favoured over outward rotation by  $\approx$  1.5 kcal/mol. Houk proceeded to thermolyze 3-acetylcyclobutene (**96**) in deuteriobenzene at  $80^\circ\text{C}$  to give initially a 2:1 mixture of outward (**97**) to inward (**98**) rotation products (Scheme 13). The study was complicated by the fact that inward rotation isomer (**98**) is unstable and isomerizes to (**97**) overnight. In contrast, treatment of (**96**) with  $\text{ZnI}_2/\text{Na}_2\text{CO}_3$  in benzene at  $80^\circ\text{C}$  produced a 17:83 mixture of outward (**97**) to inward (**98**) rotation products where the major product results from inward rotation of the acetyl group. Thus, Houk has given evidence suggesting that the "torquoselectivity" can be reversed by addition of a Lewis acid catalyst.

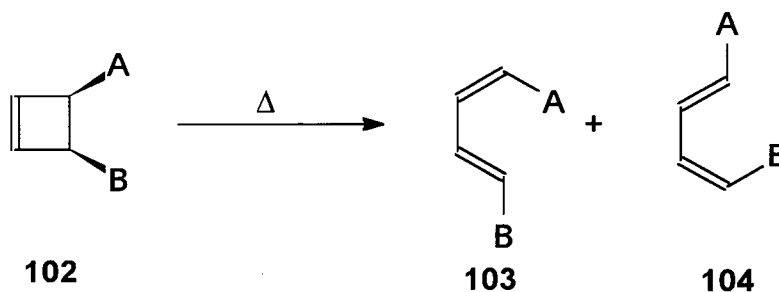


Scheme 13

For 3,4 disubstituted cyclobutenes the effects of the substituents are thought to be additive.<sup>12</sup> Wallace and co-workers<sup>36</sup> oxidized the alcohol (99) by Swern conditions and were unable to isolate the aldehyde (100) as it spontaneously opened to give the product (107) resulting from rotation of the aldehyde group in and rotation of the alkoxyethyl group out (Equation 12).



Wallace has synthesized a number of other *cis*-3,4-hetero-disubstituted cyclobutenes (102) and compared the relative torquoselectivities of the two functional groups (Table 7).<sup>37,38</sup>

Table 7: Thermal electrocyclic ring opening of *cis*-3,4-disubstituted-cyclobutenes.<sup>38</sup>

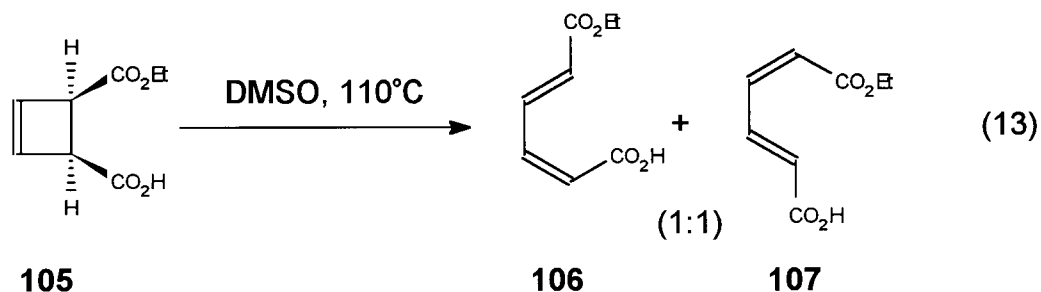
<u>Entry</u>	<u>A</u>	<u>B</u>	<u>Solvent</u>	<u>Temp(°C)</u>	<u>Time(hr)</u>	<u>Ratio(103:104)</u>
1	-CHO	-CO <sub>2</sub> Me	PhMe	110	1	2:1
2	-CO <sub>2</sub> H	-CO <sub>2</sub> R <sup>a</sup>	ClCH <sub>2</sub> CH <sub>2</sub> Cl	83	10	1:1
3	-CO <sub>2</sub> R <sup>a</sup>	-CO <sub>2</sub> Me	PhMe	110	1	1.4:1
4	-COCl	-CO <sub>2</sub> Me	PhMe	110	1	4:1
5	-CHO	-OPMB <sup>b</sup>	CH <sub>2</sub> Cl <sub>2</sub>	<20	<0.5	>20:1
6	-CHO	-OPMB <sup>b</sup>	THF	<20	<0.5	>20:1
7	-CHO	-Et	CH <sub>2</sub> Cl <sub>2</sub>	<20	<0.5	>20:1

<sup>a</sup>R=2-naphthyl

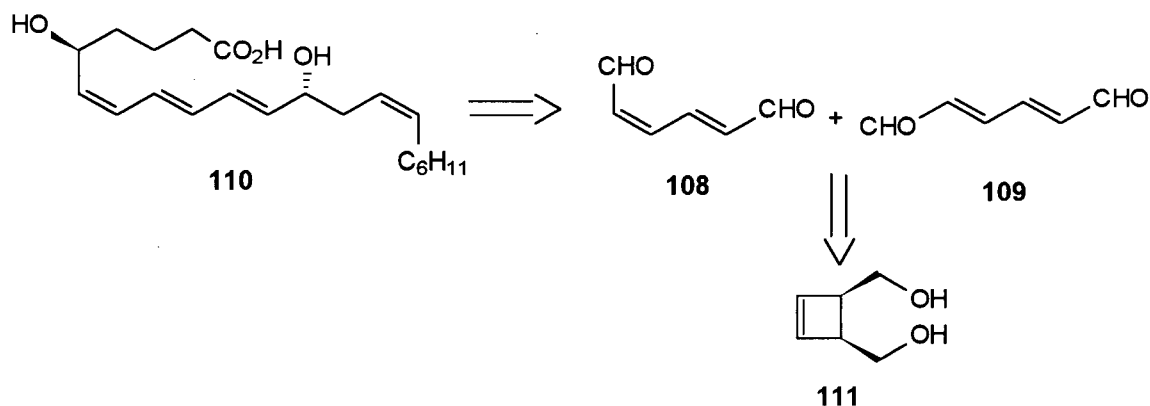
<sup>b</sup>PMB=*p*-methoxybenzyl

The results in this table indicate that the tendency towards inward rotation of the acyl functional group decreases along the order COCl > CO<sub>2</sub>H > CO<sub>2</sub>(2-naphthyl) > CO<sub>2</sub>Me. This is in good accord with the theoretical predictions of Houk.

Apparently the solvent may play some role in the ratio of outward to inward rotation product produced. Trost and co-workers<sup>35</sup> synthesized the cyclobutene (105) and thermolyzed it in dimethyl sulfoxide at 110°C and found a 1:1 ratio of products (106) and (107) (Equation 13). When the same starting material was heated in dichlorethane there was a significant increase in the amount of (106) relative to (107).

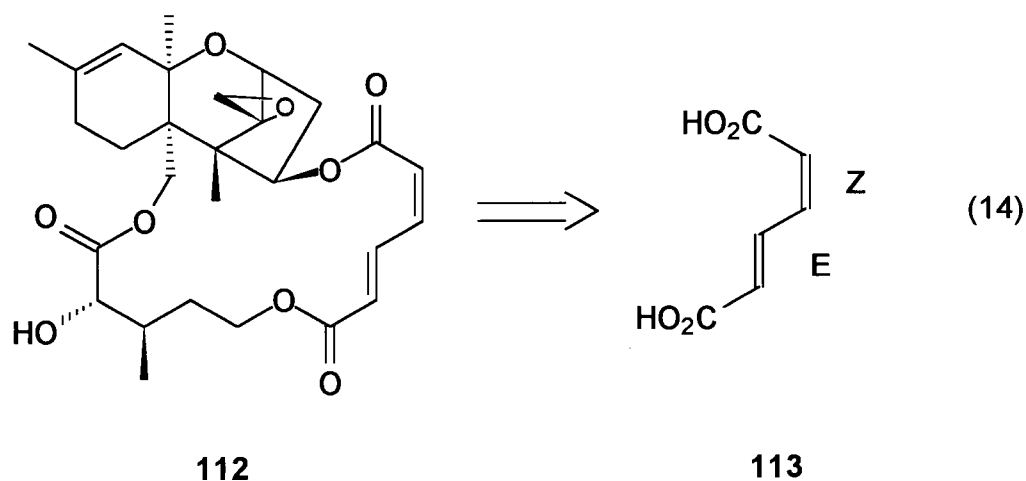


So far there have been few reports in the literature concerning the use of cyclobutene conrotatory ring openings in a total synthesis. Wallace<sup>37</sup> envisioned that the two conjugated dienes (**108**) and (**109**), generated by ring opening of a derivative of (**110**), would be structural components towards a total synthesis of leukotriene B<sub>4</sub> (**111**) (Scheme 15). Though Wallace has met with some success with model studies directed towards the synthesis of diene units (**108**) and (**109**), a complete synthesis of (**110**) using this chemistry has not yet been reported.

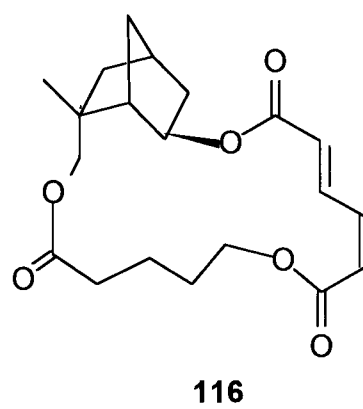
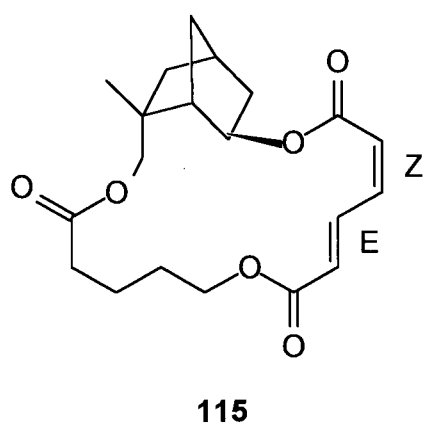
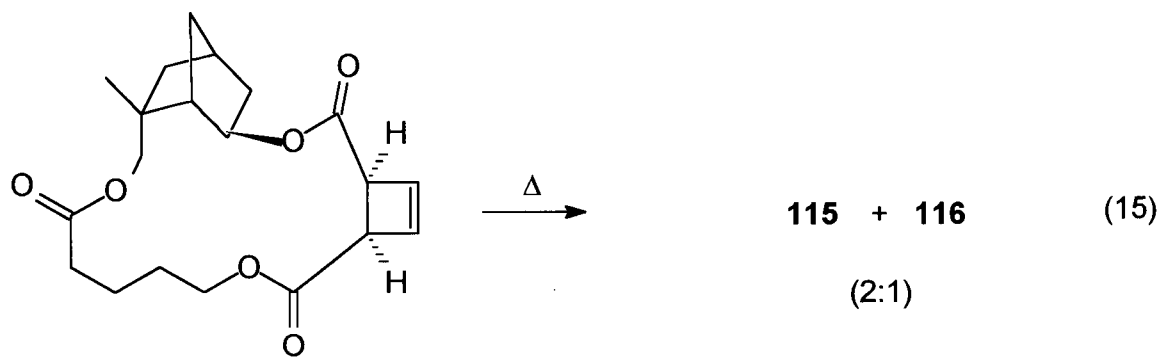


Scheme 14

Trost and co-workers have carried out a number of model studies directed towards the synthesis of verrucarin A (**112**).<sup>35</sup> One of the three fragments required was the (*Z,E*) di-acid (**113**), which was thought to be accessible from the thermal ring opening of a cyclobutene (Equation 14).



Trost and co-workers prepared the verrucarin A model macrocycle (**114**). Thermal ring opening of cyclobutene (**114**) afforded a 2:1 mixture of (**115**) and the corresponding (*E,Z*) isomer (**116**) (Equation 15).

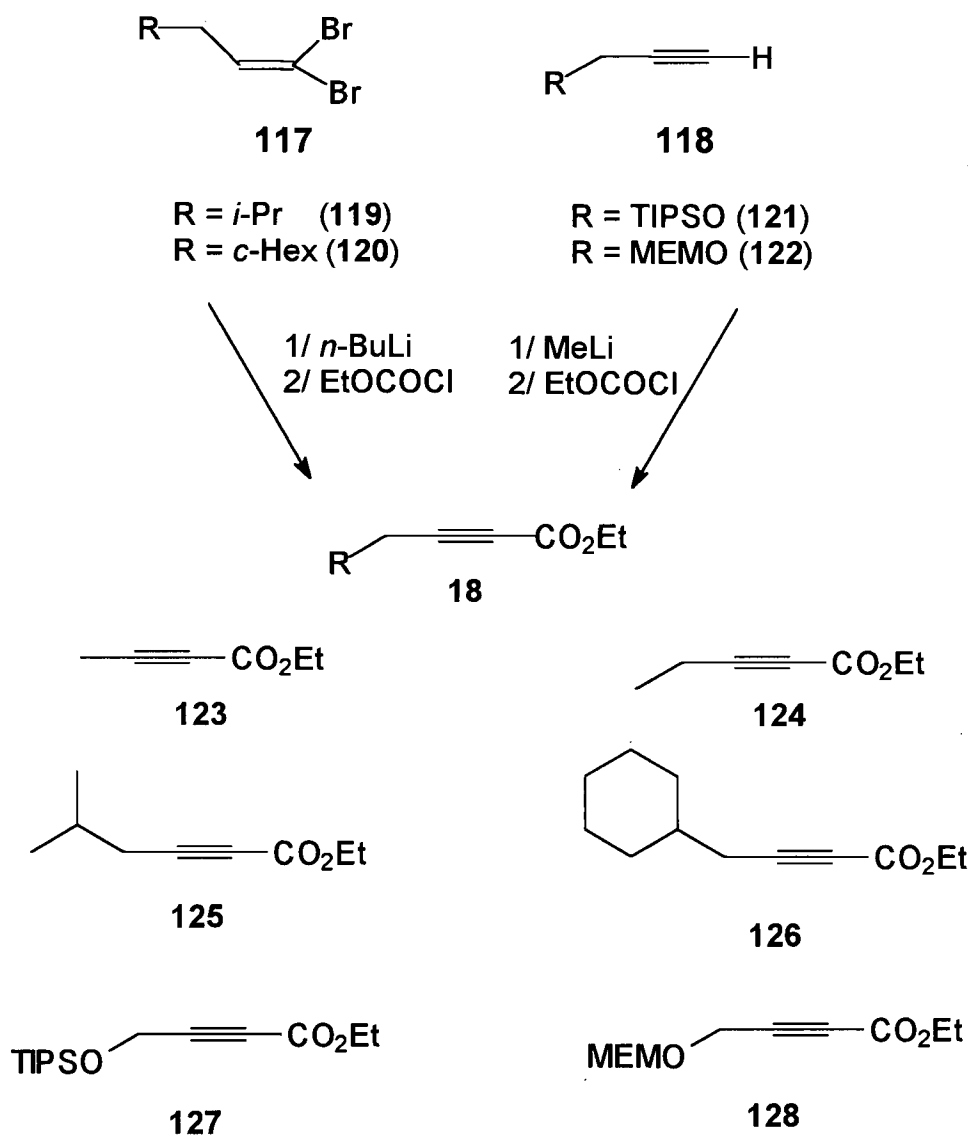


## II. RESULTS AND DISCUSSION

### 1. Synthesis of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates

#### 1.1 Preparation of the $\alpha$ , $\beta$ -acetylenic esters

Several  $\alpha$ ,  $\beta$ -acetylenic esters of general structure **18** (*i.e.* **123-128**) were required for this study. Ethyl 2-butyrate (**123**) and ethyl 2-pentynoate (**124**) are available commercially. The remaining  $\alpha$ ,  $\beta$ -acetylenic esters (**125-128**) were prepared from either the corresponding 1,1-dibromo-1-alkene of general structure **117** or the corresponding 1-alkyne of general structure **118** via the procedures outlined in Table 8.

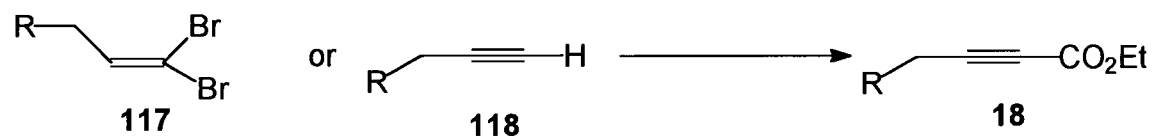


Addition of *n*-butyllithium (2.5 equiv.) to a THF solution of 1,1-dibromo-3-cyclohexylpropene (120) (-78°C, 1 h; room temperature, 1 h) afforded the corresponding lithium acetylide which, upon reaction with ethyl chloroformate (1.1 equiv., -20°C, 1 h; room temperature, 1 h), yielded ethyl 4-cyclohexyl-2-butynoate (126) (90%, Table 8, Entry 2). In a similar manner, ethyl 5-methyl-2-hexynoate (125) was prepared from 1,1-dibromo-4-methyl-1-pentene (119) (82%, Table 8, Entry 1).<sup>43</sup>

Addition of methyllithium (1 equiv.) to a THF solution of 3-(triisopropylsiloxy)propyne (121) (-78°C, 15 min; -20°C, 1 h) afforded the corresponding lithium acetylide which, upon reaction with ethyl chloroformate (1 equiv., -20°C, 1 h; room temperature, 1 h) yielded ethyl 4-(triisopropylsiloxy)-2-butynoate (127) (76%, Table 8, Entry 3). In a similar manner, ethyl 4-[(2-methoxyethoxy)methoxy]-2-butynoate (128) was prepared from 3-[(2-methoxyethoxy)methoxy]propyne (122) (79%, Table 8, Entry 4).

The spectral data derived from the  $\alpha$ ,  $\beta$ -acetylenic esters (125-128) were consistent with the assigned structures. For example, each of the  $\alpha$ ,  $\beta$ -acetylenic esters (125-128) exhibited a C $\equiv$ C stretch in the IR spectrum in the region 2232 - 2241 cm<sup>-1</sup> (Table 8).



Table 8: Preparation of the  $\alpha$ ,  $\beta$ -acetylenic esters

Entry	Substrate	Procedure <sup>a</sup>	R	Product	Yield (%) <sup>b</sup>	IR C $\equiv$ C stretching absorption (cm <sup>-1</sup> )
1	119	A	<i>i</i> -Pr	125	82	2232
2	120	A	<i>c</i> -Hex	126	90	2234
3	121	B	$((\text{CH}_3)_2\text{CH})_3\text{SiO}$	127	76	2241
4	122	B	$\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{O}$	128	79	2240

<sup>a</sup>A. (Starting material of general structure 117)

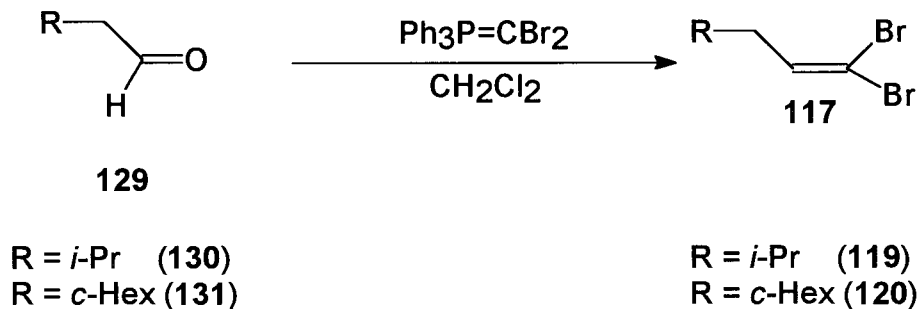
1. *n*-BuLi (2.5 equiv.), THF, -78°C, 1 h; room temperature, 1 h.
2. Ethyl chloroformate (1.1 equiv.), -20°C, 1 h; room temperature, 1 h.

<sup>a</sup>B. (Starting material of general structure 118)

1. MeLi (1 equiv.), THF, -78°C, 15 min; -20°C, 1 h.
2. Ethyl chloroformate (1 equiv.), -20°C, 1 h; room temperature, 1 h.

<sup>b</sup>Yield of purified, distilled product.

The 1,1-dibromo-1-alkenes of general structure 117 (119 and 120) were prepared from the corresponding commercially available aldehydes of general structure 129 (Scheme 15).

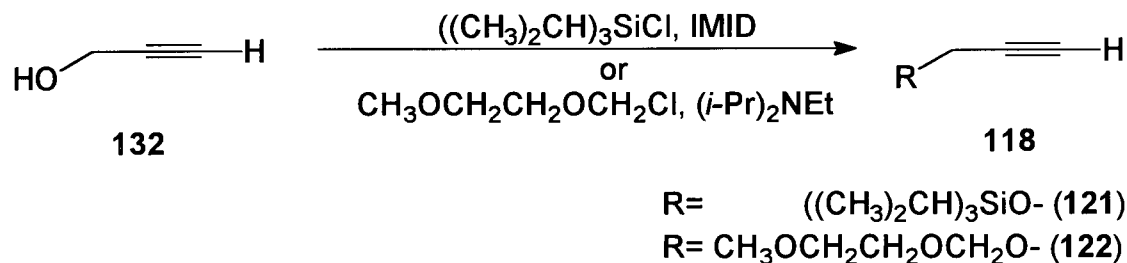


Scheme 15

For example, treatment of cyclohexylethanal (131) with 2 equiv. of dibromomethylenetriphenylphosphorane<sup>43</sup> in dichloromethane (room temperature, 30 min) afforded 1,1-dibromo-3-cyclohexylpropene (120) in a 89% yield. In a similar manner 1,1-dibromo-4-methyl-1-pentene (119) was prepared in a 81% yield from 3-methylbutanal (130). It should be noted that it is important to cool the reaction mixture below 50°C when synthesizing the dibromomethylenetriphenylphosphorane reagent (from triphenylphosphine and carbon tetrabromide) as the reaction is extremely exothermic.

The spectral data derived from the 1,1-dibromo-1-alkenes (119 and 120) were consistent with the assigned structures. For example, the <sup>1</sup>H NMR spectrum of alkene (120) displayed the expected signals for the trisubstituted alkene moiety (a one proton triplet at δ 6.42, *J* = 7 Hz) and two allylic protons (a two proton doublet of doublets at δ 2.05, *J* = 7, 7 Hz). The IR spectrum of alkene (120) displayed a C=C stretching absorption at 1621 cm<sup>-1</sup>.

The 1-alkynes of general structure 118 (121 and 122) were prepared by reaction of 2-propyn-1-ol (132) with the appropriate reagent (Scheme 16).



Scheme 16

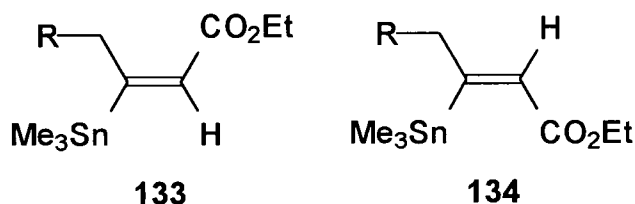
For example, treatment of 2-propyn-1-ol (132) in dry dichloromethane with 1.5 equiv. of imidazole and 0.95 equiv. of triisopropylsilyl chloride (room temperature, 2 h) afforded 3-(triisopropylsiloxy)propyne (121) in a 75% yield. In a similar manner, 2-propyn-1-ol was treated with diisopropylethylamine ((*i*-Pr)<sub>2</sub>NEt) and (2-methoxyethoxy)methyl chloride to afford 3-[(2-methoxyethoxy)methoxy]propyne (122) in a 79% yield.

The spectral data for the 1-alkynes (121 and 122) were consistent with the assigned structures. For example, 3-(triisopropylsiloxy)propyne (121) displayed the expected signal for a triisopropylsiloxy moiety (an 18 proton doublet at  $\delta$  1.06,  $J$  = 6 Hz, and a three proton multiplet at  $\delta$  1.08-1.14), a terminal alkyne proton (a one proton triplet at  $\delta$  2.46,  $J$  = 2 Hz) and a two proton doublet at  $\delta$  4.37,  $J$  = 2 Hz, -OCH<sub>2</sub>SiR<sub>3</sub>.

## 1.2 Preparation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates

Several ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates of general structure 133 and 134 were required for this study. Morton and Chong, in our laboratories, have studied the reaction of (trialkylstannyl)copper(I) reagents with  $\alpha,\beta$ -acetylenic esters.<sup>44</sup> By a proper choice of the appropriate (trialkylstannyl)copper(I) reagent and the reaction

conditions, either the (*E*)-(133) or (*Z*)-3-trimethylstannyl-2-alkenoate (134) can be produced stereoselectively.

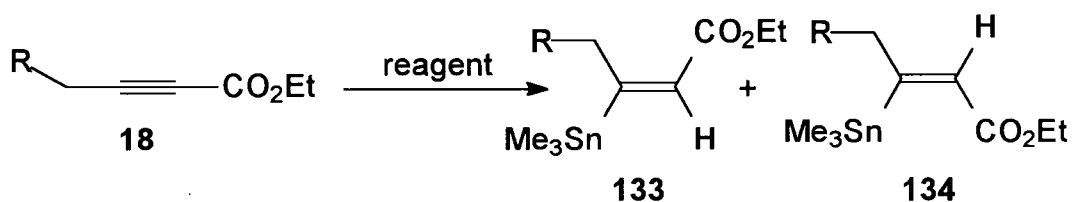


For example, addition of ethyl 2-pentynoate (124) to a solution of lithium (phenylthio-trimethylstannyl)cuprate (135) (THF, -100°C, 15 min; -78°C, 3 h) in the presence of 1.7 equiv. of methanol produced, upon workup, the (*E*) isomer in >99% isomeric purity (Table 9, Entry 1).<sup>44</sup> In contrast, reaction of (135) with (124) (THF, -78°C, 15 min, -48°C, 4 h), followed by quenching with MeOH, afforded the (*Z*) isomer in ~98% isomeric purity (Table 9, Entry 2).

The nature of the stannylcopper(I) reagent also affects the stereochemical outcome of the reaction (Table 9, Entries 3, 4, and 5). Treatment of ethyl 2-butyrate (123) with (135) (THF, -78°C, 15 min, -48°C, 4 h), followed by protonolysis with MeOH, afforded the (*Z*) isomer in ~98% isomeric purity (Table 9, Entry 3). In contrast, treatment of (123) with (trimethylstannyl)copper(I)-dimethyl sulphide (136) or lithium(trimethylstannyl)-(cyano)cuprate (137) under similar reaction conditions produced the (*E*) isomer in >99% and 96% isomeric purities, respectively (Table 9, Entries 4 and 5).<sup>44</sup>

While high stereoselectivities were obtained from the reaction of reagent (135) with  $\alpha,\beta$ -acetylenic esters with an alkyl function on the  $\gamma$  carbon as outlined above, anomalous results were obtained when the substrate contained an ether function on the  $\gamma$  carbon (Table 9, Entry 6). For example, reaction between (135) and (138) under the conditions described gave the desired (*Z*) isomer in only 29% yield, while the product (139) resulting from transfer of the phenylthio group predominated (35% yield).<sup>44</sup>

**Table 9: Reaction of  $\alpha,\beta$ -acetylenic esters with (trimethylstannyl)copper (I) reagents (135-140)**



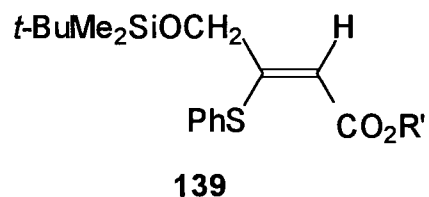
Entry	Starting Material	R	Reagent, Conditions <sup>a</sup>	Product Ratio (E/Z)	Yield (%)
1	124	Me	135 [Me <sub>3</sub> SnCuSPh]Li, A	>99:1	79
2	124	Me	135 [Me <sub>3</sub> SnCuSPh]Li, B	2:98	76
3	123	H	135 [Me <sub>3</sub> SnCuSPh]Li, B	2:98	76
4	123	H	136 Me <sub>3</sub> SnCu•Me <sub>2</sub> S, B	>99:1	68
5	123	H	137 [Me <sub>3</sub> SnCuCN]Li, C	96:4	86
6	138	<i>t</i> -BuMe <sub>2</sub> SiO-	135 [Me <sub>3</sub> SnCuSPh]Li, B	≤7:≥93 <sup>b</sup>	29
7	138	<i>t</i> -BuMe <sub>2</sub> SiO-	140[Me <sub>3</sub> SnCu(2-Th)(CN)]Li <sub>2</sub> , C	≤5:≥95	65

<sup>a</sup>A: THF, 2.0 equiv. **135**, 1.7 equiv. MeOH, -100°C, 15 min, -78°C, 3 h.

<sup>a</sup>B: THF, 1.3 equiv. reagent, -78°C, 15 min, -48°C, 4 h, then quench with MeOH.

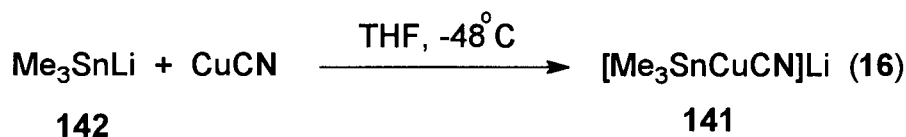
<sup>a</sup>C: THF, 1.3 equiv. reagent, -78°C, 3 h, then quench with NH<sub>4</sub>Cl.

<sup>b</sup>Compound **139** was the major product.



Tillyer, in our laboratories, has prepared the higher order cuprate, dilithium(trimethylstannyl)(2-thienyl)(cyano)cuprate (**140**), which has been useful in overcoming these difficulties.<sup>45</sup> Treatment of substrate (**138**) with (**140**) (THF, -78°C, 3 h) afforded the (*Z*) isomer in ~95% isomeric purity and in a 65% yield (Table 9, Entry 7).

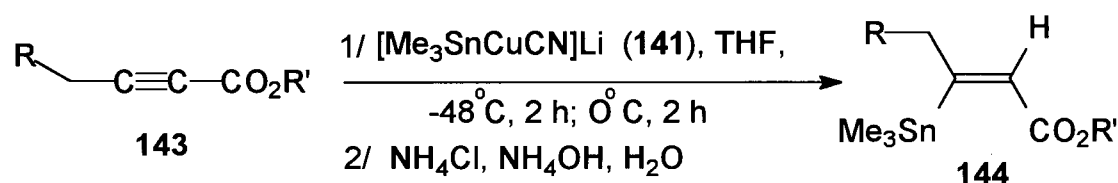
Thus, it can be seen that by a proper choice of the appropriate lower or higher order cuprate reagent and reaction conditions, the  $\alpha,\beta$ -acetylenic esters can be stereoselectively converted into the corresponding (*E*)- or (*Z*)-3-trimethylstannyl-2-alkenoates. There are, however, some drawbacks to using reagent (**135**) for the synthesis of (**133**) and (**134**). The required starting material, phenylthiocopper(I) (PhSCu), for the preparation of (**135**) is tedious to make.<sup>46</sup> To prepare phenylthiocopper(I) one must use thiophenol, a chemical with a notably offensive odour. More importantly PhSCu, like many copper(I) salts, is not very stable and thus storage for a prolonged period makes the PhSCu unsuitable for the synthesis of reagent (**135**). In contrast, copper(I) cyanide (CuCN) is readily available, reasonably stable,<sup>47</sup> and has been used extensively for the generation of organocuprates. Therefore, we carried out a brief study to determine whether or not lithium (trimethylstannyl)(cyano)cuprate [Me<sub>3</sub>SnCuCN]Li (**141**), which is prepared by reaction of trimethylstannyl lithium (Me<sub>3</sub>SnLi) (**142**) with CuCN in THF (Equation 16), could be used as a substitute for reagent (**135**) in the transformation of (**18**) into (**133**).



This project was carried out in collaboration with a Mr. Timothy Wong from our laboratories.<sup>48</sup> Reaction of (**143**) with approximately 1.05 equiv. of the cuprate (**141**) in THF at -48°C for 2 h and then at 0°C for 2 h, followed by workup, gave a crude product

consisting almost entirely of the desired *Z*-alkenoate (**144**) (Table 10). Very little of the corresponding *E*-alkenoate (**145**) was produced. Purification of the crude product by flash chromatography<sup>49</sup> on silica gel, followed by distillation, provided the pure *Z*-alkenoate. For example, treatment of ethyl 4-cyclohexyl-2-butynoate (**126**) with 1.04 equiv. of cyanocuprate (**141**) under the reaction conditions outlined above provided ethyl (*Z*)-4-cyclohexyl-3-trimethylstannyl-2-butenate (**152**) in a 81% yield (Table 10, Entry 4).

Table 10: Preparation of alkyl (*Z*)-3-trimethylstannyl-2-alkenoates<sup>50</sup>



Entry	Acetylenic ester	R	R'	Equiv. of cuprate	Product <sup>a</sup>	Yield (%) <sup>b</sup>
1	<b>124</b>	Me	Et	1.09	<b>149</b>	72
2	<b>127</b>	( <i>i</i> -Pr) <sub>3</sub> SiO-	Et	1.06	<b>150</b>	76
3	<b>128</b>	MEMO-	Et	1.06	<b>151</b>	72
4	<b>126</b>	<i>c</i> -Hex-	Et	1.04	<b>152</b>	81
5	<b>146<sup>c</sup></b>	<i>t</i> -BuMe <sub>2</sub> SiO(CH <sub>2</sub> ) <sub>2</sub>	Me	1.05	<b>153<sup>c</sup></b>	78
6	<b>147<sup>c</sup></b>	Cl(CH <sub>2</sub> ) <sub>2</sub>	Me	1.05	<b>154<sup>c</sup></b>	79
7	<b>148<sup>c</sup></b>	HC≡C-(CH <sub>2</sub> ) <sub>2</sub>	Me	1.01	<b>155<sup>c</sup></b>	78

<sup>a</sup>The isolated crude products contained small amounts (~1-4% and 1-2%, respectively) of the corresponding alkyl (*E*)-trimethylstannyl-2-alkenoates and alkyl (*E*)-2,3-bis-trimethylstannyl-2-alkenoates. These minor products could, in each case, be removed by a combination of flash chromatography and distillation.

<sup>b</sup>Yields refer to purified, distilled products.

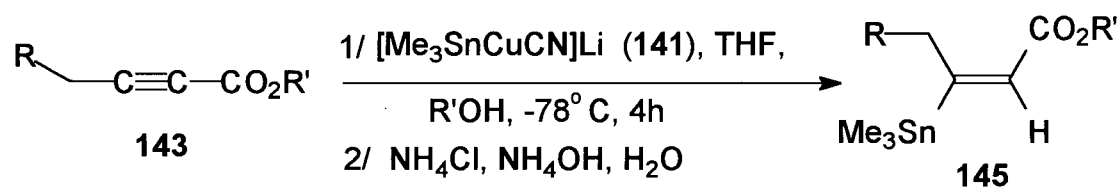
<sup>c</sup>Compounds **146-148** and **153-155** were prepared by Mr. Timothy Wong.

It was determined that cyanocuprate (141) was also suitable for transformation of the acetylenic esters (143) into the (*E*)-enoates (156-162) listed in Table 11. For example, reaction of ethyl-2-pentynoate (124) with 1.30 equiv. of cyanocuprate (141) at -78°C in THF for 4 h in the presence of 1.3 equiv. of ethanol provided a crude product that consisted of a mixture of the (*E*)- and (*Z*)-2-pentenoates (156) and (149) in a ratio of 97:3, respectively. Purification of this crude product by flash chromatography and distillation provided pure (156) in 69% yield (Table 11, Entry 1).

Treatment of acetylenic esters (126-128) and (146-148) under similar conditions produced the corresponding alkyl (*E*)-3-trimethylstannyl-2-alkenoates (157-162) in good yields (Table 11).

The structural assignments for the (*E*)- (133) and (*Z*)-3-trimethylstannyl-2-alkenoates (134) were supported by the  $^1\text{H}$  NMR spectral data obtained for these compounds. The two isomers could be distinguished from each other by three methods, including the chemical shifts of the allylic protons, the chemical shifts of the vinyl protons, and, most importantly, the tin-proton coupling values ( $^3J_{\text{Sn-H}}$ ) between the olefinic proton and the tin atoms ( $^{117}\text{Sn}$ ,  $^{119}\text{Sn}$ ) (Tables 12 and 13). Tin-proton coupling values ( $^3J_{\text{Sn-H}}$ ) for the (*E*)-trimethylstannyl esters (133), in which the olefinic proton is *cis* to the trimethylstannyl moiety, are typically 70-90 Hz, while for the (*Z*) counterparts, in which the olefinic proton is *trans* to the trimethylstannyl moiety, they are typically 115-130 Hz.<sup>51</sup>



Table 11: Preparation of alkyl (*E*)-3-trimethylstannyl-2-alkenoates<sup>50</sup>

Entry	Acetylenic ester	R	R'	Equiv. of cuprate	Product <sup>a</sup>	Yield (%) <sup>b</sup>
1	124	Me	Et	1.30	156	69
2	127	( <i>i</i> -Pr) <sub>3</sub> SiO-	Et	1.31	157	74
3	128	MEMO-	Et	1.30	158	70
4	126	<i>c</i> -Hex-	Et	1.50	159	81 <sup>d</sup>
5	146 <sup>c</sup>	<i>t</i> -BuMe <sub>2</sub> SiO(CH <sub>2</sub> ) <sub>2</sub>	Me	1.30	160	77
6	147 <sup>c</sup>	Cl(CH <sub>2</sub> ) <sub>2</sub>	Me	1.30	161	80
7	148 <sup>c</sup>	HC≡C-(CH <sub>2</sub> ) <sub>2</sub>	Me	1.30	162	72

<sup>a</sup>The isolated crude products contained small amounts (~1-5%) of the corresponding alkyl (*Z*)-trimethylstannyl-2-alkenoates. This minor product could, in each case, be removed by a combination of flash chromatography and distillation.

<sup>b</sup>Yields refer to purified, distilled products.

<sup>c</sup>Compounds 146-148 and 160-162 were prepared by Mr. Timothy Wong.

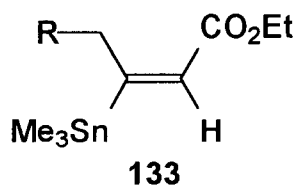
<sup>d</sup>The reaction time in this experiment was 7 h rather than 4 h.

For example, in the  $^1\text{H}$  NMR spectrum of ethyl (*E*)-4-[(2-methoxyethoxy)methoxy]-3-trimethylstannyl-2-butenolate (**158**), the  $^3J_{\text{Sn-H}}$  value is 73 Hz (Table 12, Entry 3) while in the spectrum of the (*Z*)-isomer (**151**), the  $^3J_{\text{Sn-H}}$  value is 112 Hz (Table 13, Entry 3).

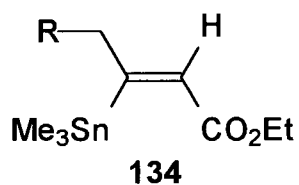
In Table 12 it can be seen that the chemical shift of the allylic methylene protons of the (*E*)-alkenoates (**133**) are downfield in each case as compared to the corresponding chemical shifts of the (*Z*)-alkenoates (**134**) (Table 13). This is caused by the fact that the deshielding ester moiety for each of the (*E*)-alkenoates (**133**) is *cis* to the allylic methylene protons.

Furthermore, it can be seen that the chemical shifts of the olefinic protons of the (*E*)-alkenoates (**133**) (Table 12) are upfield as compared to the corresponding resonances of the (*Z*)-alkenoates (Table 13). This is expected as it is known that the electron rich trimethylstannyl moiety shields olefinic protons that are *cis* to itself as is the case with the (*E*)-alkenoates (**133**).

**Table 12: Partial  $^1\text{H}$  NMR Data for (*E*)-3-trimethylstannyl-2-alkenoates (133)**



Entry	2-Alkenoate	R	$^3J_{\text{Sn-H}}$ of the olefinic proton	$\delta$ of the allylic methylene protons	$\delta$ of the olefinic protons
1	<b>156</b>	Me	74	2.89	5.94
2	<b>157</b>	( <i>i</i> -Pr) $_3$ SiO	78	4.95	5.89
3	<b>158</b>	MEMO	73	4.79	5.92
4	<b>159</b>	<i>c</i> -Hex	82	2.83	6.03
5	<b>163</b>	<i>i</i> -Pr	76	2.82	6.03

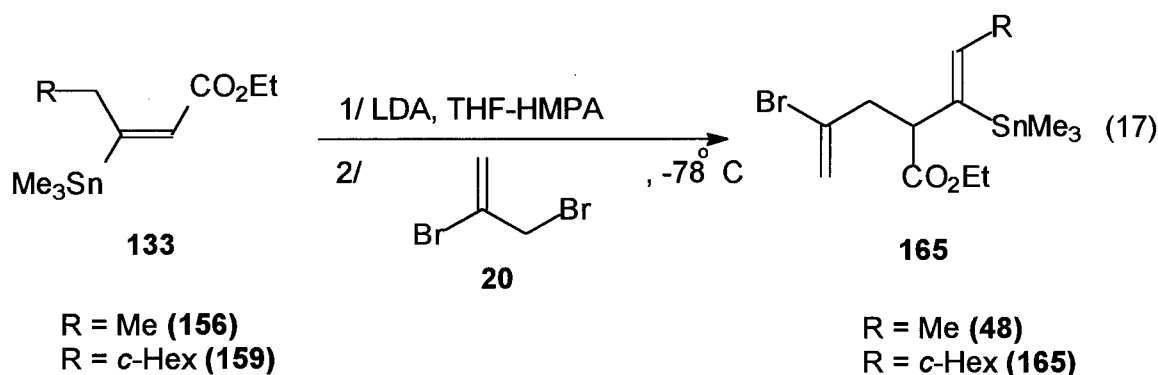
Table 13: Partial  $^1\text{H}$  NMR Data for (Z)-3-trimethylstannyl-2-alkenoates (**134**)

Entry	2-Alkenoate	R	$^3J_{\text{Sn-H}}$ of the olefinic proton	$\delta$ of the allylic methylene protons	$\delta$ of the olefinic protons
1	<b>149</b>	Me	120	2.45	6.36
2	<b>150</b>	( <i>i</i> -Pr) $_3$ SiO	114	4.52	6.72
3	<b>151</b>	MEMO	112	4.38	6.63
4	<b>152</b>	<i>c</i> -Hex	124	2.28	6.29
5	<b>164</b>	<i>i</i> -Pr	120	2.28	6.26

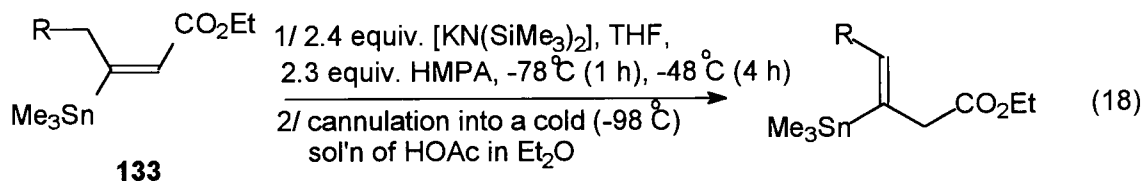
## 2. Deconjugation-alkylation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates

### 2.1 Preparation of the Ethyl (*E*)- and (*Z*)-3-trimethylstannyl-3-alkenoates

The next stage of the research project involved deconjugation-alkylation of various ethyl (*E*)-3-trimethylstannyl-2-alkenoates of general structure (133) with 2,3-dibromopropene (20) to afford trimethyl stannyl alkenoates of the general structure (165) (Equation 17).



Deprotonation of (156) with lithium diisopropylamide (LDA) in THF followed by alkylation with 2,3-dibromopropene (20) to give (48) had been previously reported<sup>16, 23</sup> and was stated to proceed in satisfactory yield (72%). Unfortunately, the same procedure when applied to vinylstannane (159) was not satisfactory. The expected product (165) was produced in only 12% yield and was accompanied by numerous, unidentified side products. Numerous attempts were made to improve this reaction using a variety of experimental conditions. Eventually, it was discovered that hindered vinylstannanes such as (159) and (166) could be deconjugated to the corresponding ethyl (*Z*)-3-trimethylstannyl-3-alkenoates (*i.e.* 167 and 168) using potassium bis(trimethylsilyl)amide [ $\text{KN}(\text{SiMe}_3)_2$ ] as the base (Equation 18).



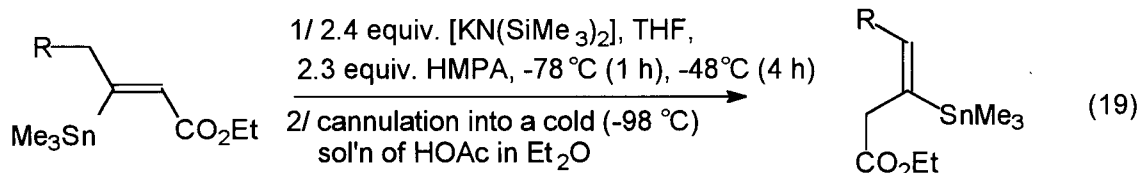
R = *c*-Hex (**159**)  
 R = *i*-Pr (**166**)

R = *c*-Hex (**167**)      Yield 85%  
 R = *i*-Pr (**168**)      Yield 90%

It should be noted that freshly prepared and distilled starting materials (**159**) and (**166**) must be used for this procedure. Substrates that were not freshly purified gave inferior, anomolous results.

The configurations of the esters (**167**) and (**168**) (Equation 18) were readily assigned on the basis of  $^1\text{H}$  NMR spectroscopic data, in particular the magnitude of the coupling constant ( $^3J_{\text{Sn-H}}$ ) between the olefinic proton and the tin atom. For example in (**167**) and (**168**), where the olefinic proton is in a *trans* relationship to the  $\text{Me}_3\text{Sn}$  moiety, the  $^3J_{\text{Sn-H}}$  values are  $\sim 131$  Hz, as expected.<sup>51</sup> As anticipated, the IR spectra of the (*Z*)-esters (**167**) and (**168**) showed strong C=O stretching frequencies at  $\sim 1734\text{ cm}^{-1}$ , which is at a higher frequency than their (*E*)-conjugated counterparts (**159**) and (**166**) at  $\sim 1704\text{ cm}^{-1}$ .

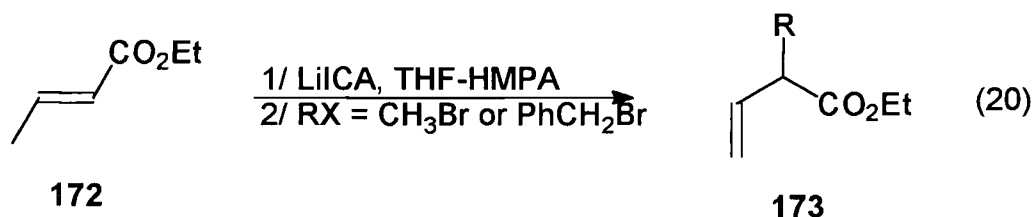
The synthesis of the ethyl (*E*)-3-trimethylstannyl-3-pentenoates (**169**) and (**170**) involved deconjugation of the corresponding ethyl (*Z*)-3-trimethylstannyl-2-alkenoates (**152**) and (**171**) (Equation 19).



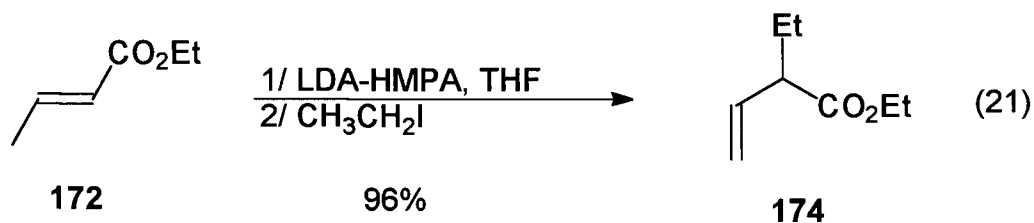
R = *c*-Hex (**152**)  
 R = *i*-Pr (**171**)

R = *c*-Hex (**169**)      Yield 91%  
 R = *i*-Pr (**170**)      Yield 87%

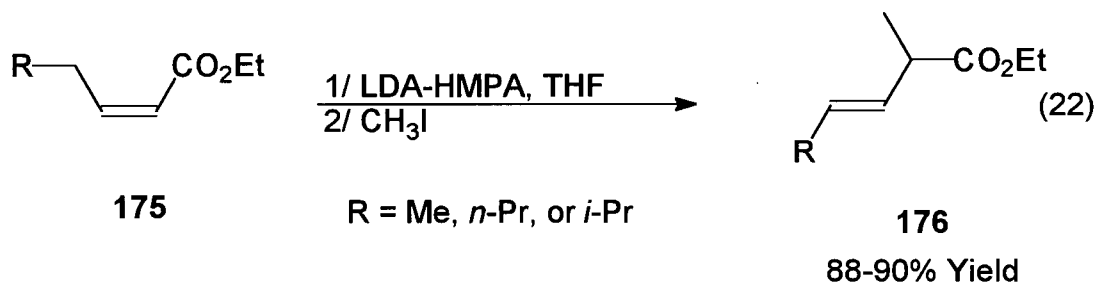
Reports on deconjugation and deconjugation-alkylation reactions of  $\alpha,\beta$ -unsaturated esters have been numerous in the past two decades because of the synthetic potential of these methods. A paper by Rathke and Sullivan in 1972<sup>52</sup> reported that deprotonation of ethyl (*E*)-2-butenate (172) with lithium *N*-isopropylcyclohexylamide (LiICA) in THF-HMPA at  $-78^{\circ}\text{C}$ , followed by quenching the resultant dieneolate anion with various electrophiles, afforded the corresponding unconjugated esters (173) in good yields (Equation 20).



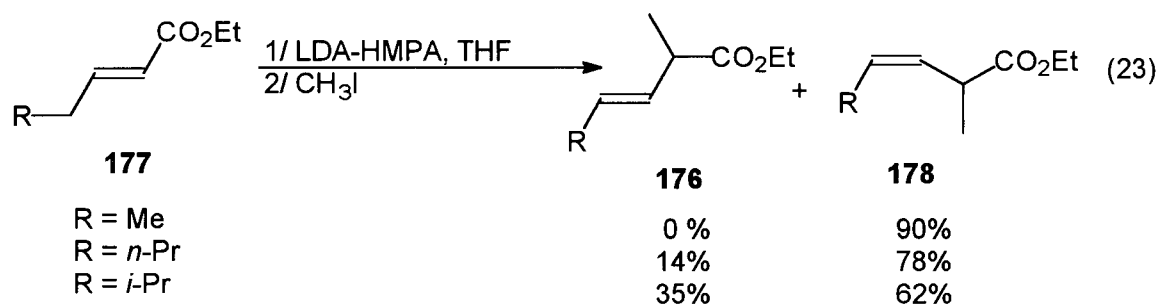
Similar results indicating the preference for alkylation at the  $\alpha$ -carbon after formation of the dienolate anions from  $\alpha,\beta$ -unsaturated esters was observed by Schlessinger et al.<sup>53</sup> In their study, a 1:1 complex of HMPA and LDA was formed by addition of HMPA (1.1 equiv.) to a THF solution of LDA (1 equiv.) (30 min,  $-78^{\circ}\text{C}$ ). Sequential addition of ethyl (*E*)-2-butenate (172) (1 equiv.) (10 min,  $-78^{\circ}\text{C}$ ) and iodoethane to this solution afforded the  $\alpha$ -alkylated adduct (174) in a 96% yield (Equation 21). According to their simple molecular orbital calculations on the dienolate anion of (172), alkylation occurred at the position of maximum negative charge (the  $\alpha$ -carbon atom).



Studies examining the stereochemical outcome of the deconjugation-alkylation of a series of  $\alpha,\beta$ -unsaturated esters have been carried out by Kende and Toder.<sup>54</sup> It was found, for example, that the deconjugation-methylation of the ethyl (*Z*)-2-alkenoates (**175**) proceeds to give exclusively the corresponding alkylated (*E*)-3-alkenoates (**176**) in good yields (88-90%) (Equation 22).



In contrast, it was found that the deconjugation-methylation of the ethyl (*E*)-2-alkenoates (**177**) to provide the corresponding alkylated (*Z*)-3-alkenoate (**178**) was less selective (Equation 23), with the stereoselectivity decreasing as the size of the R group increased.

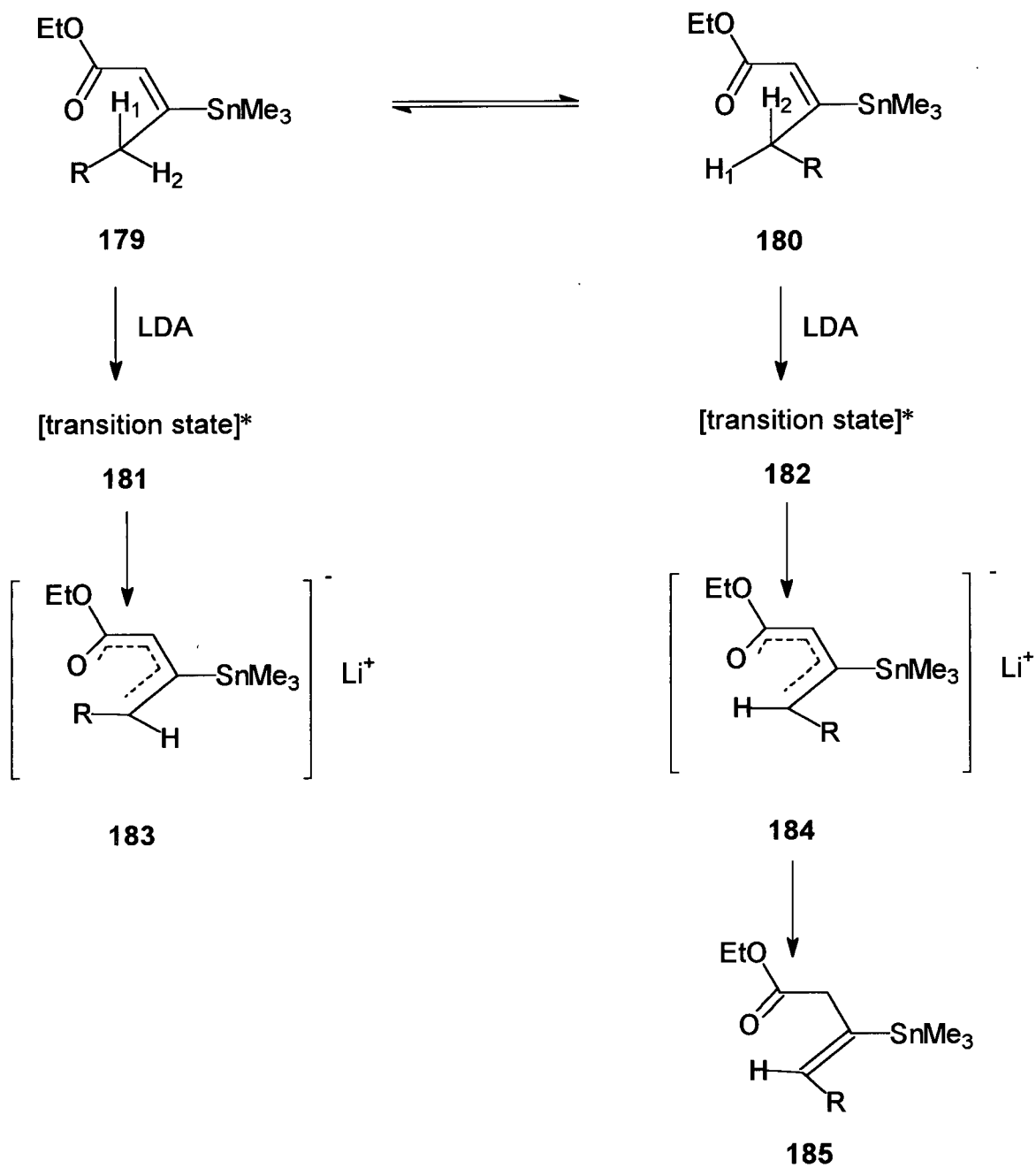


The stereoselectivity of these transformations (Equations 22 and 23) is suggested to arise in the deprotonation step<sup>54</sup> and a modified version of Kende and Toder's



formulations (Schemes 17 and 18) is believed to provide a reasonable rationale for the transformations given on page 50 (Equations 18 and 19).

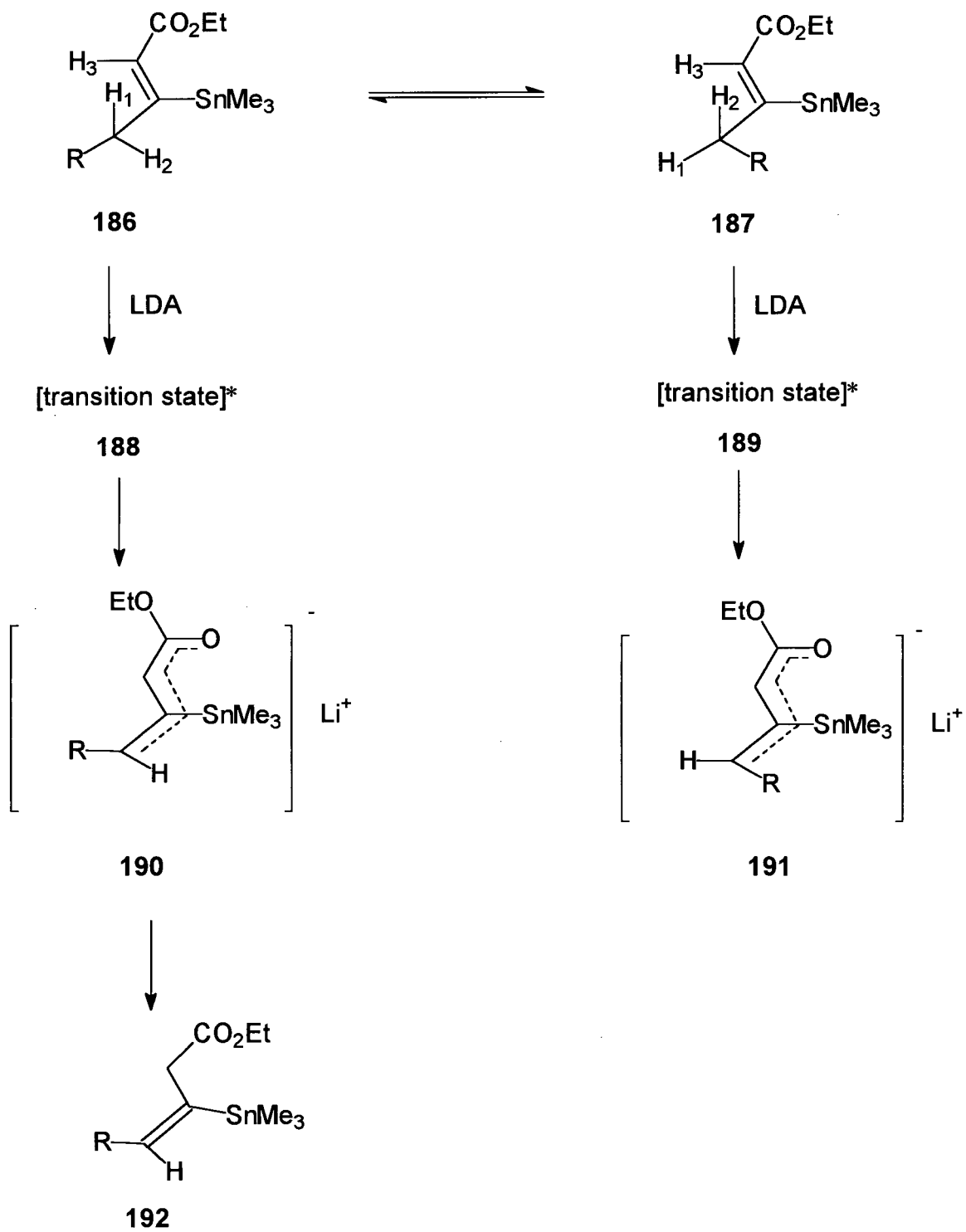
For the kinetically-controlled deprotonation of the (*E*)-3-trimethylstannyl-2-alkenoates (Scheme 17), two possible ground state conformations (179) and (180) can be envisioned where a C-H bond is aligned perpendicular to the plane of the conjugated  $\pi$  system. Removal of H<sub>2</sub> from (180) leads to an extended enolate (184) via a transition state (182) which would be destabilized by the A<sup>1,2</sup> strain<sup>55</sup> between the R and Me<sub>3</sub>Sn groups. In contrast, the transition state (181) generated by removal of H<sub>1</sub> from (179) would have severe A<sup>1,3</sup> strain<sup>55</sup> between the R and CO<sub>2</sub>Et groups. The A<sup>1,3</sup> strain in (181) would be expected to be greater than the A<sup>1,2</sup> strain in (182) due to the length of the Sn-C bond (~2Å). Thus, the pathway (180)→(182)→(184)→(185) would be favoured leading to the formation of the (*Z*)-3-trimethylstannyl-2-alkenoates.



Scheme 17

Similarly, for the kinetically-controlled deprotonation of the (Z)-3-trimethylstannyl-2-alkenoates (Scheme 18), two possible ground state conformations (186) and (187) can be envisioned where a C-H bond is aligned perpendicular to the plane of the conjugated  $\pi$  system. Removal of H<sub>2</sub> from (187) leads to a transition state (189) which is destabilized by the A<sup>1,2</sup> strain<sup>55</sup> between the R and Me<sub>3</sub>Sn groups. This destabilization would be expected to be greater than the relatively small destabilizations in the transition state (188) from the A<sup>1,3</sup> strain<sup>55</sup> between the R group and olefinic proton (H<sub>3</sub>) and the A<sup>1,2</sup> strain between the SnMe<sub>3</sub> group and the allylic proton H<sub>2</sub>. Thus the deconjugation of the (Z)-3-trimethylstannyl-2-alkenoates should proceed via the pathway (186)→(188)→(190)→(192) to provide the (Z)-3-trimethylstannyl-3-alkenoates exclusively.

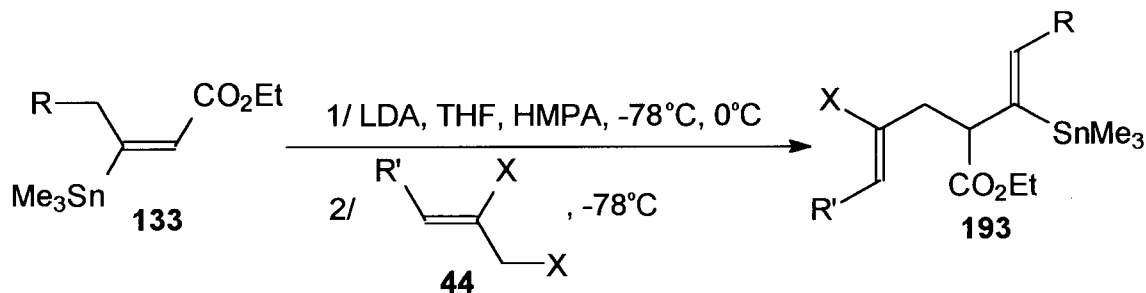
In summary, it was found that the deconjugation-alkylation of the ethyl (*E*)-3-trimethylstannyl-2-alkenoates (133) with 2,3-dibromopropene (20) to afford the 3-trimethylstannyl-3-alkenoates (165) did not proceed satisfactorily (Equation 17, page 49). On the other hand, deconjugation of the ethyl (*E*)- and (*Z*)-3-trimethyl stannyl-2-alkenoates could be accomplished satisfactorily using potassium bis(trimethylsilyl)amide as the base (Equation 18, page 50).



Scheme 18

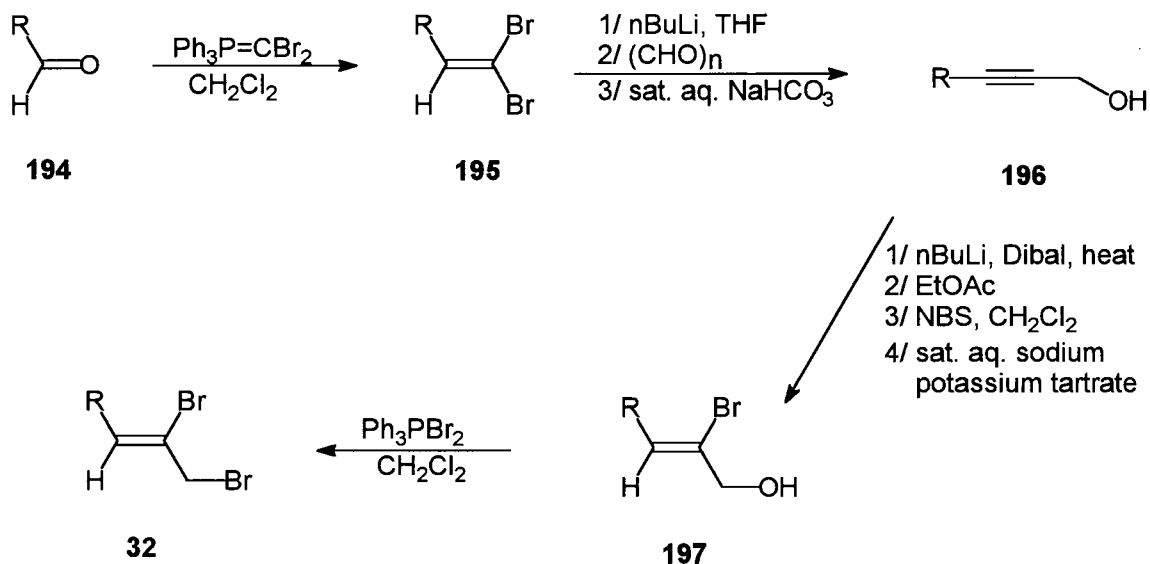
## 2.2 Preparation of the alkylating agents

At this stage of the project it became necessary to produce (Z)-1,2-dihalo-2-alkenes of the general structure (44) for use as alkylating agents to lead to the diene esters (193) (Scheme 19).



Scheme 19

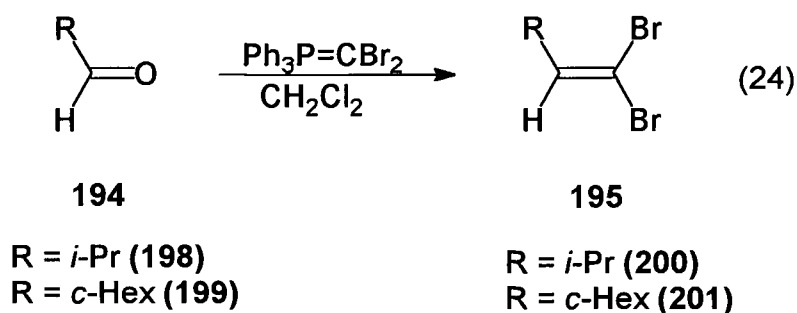
The sequence employed utilized several steps and is outlined in Scheme 20.



Scheme 20

### 2.2.1 Preparation of the 1,1-dibromo-1-alkenes

The 1,1-dibromo-1-alkenes of general structure (195) (200 and 201) were prepared from the corresponding commercially available aldehydes of general structure (194) (Equation 24).

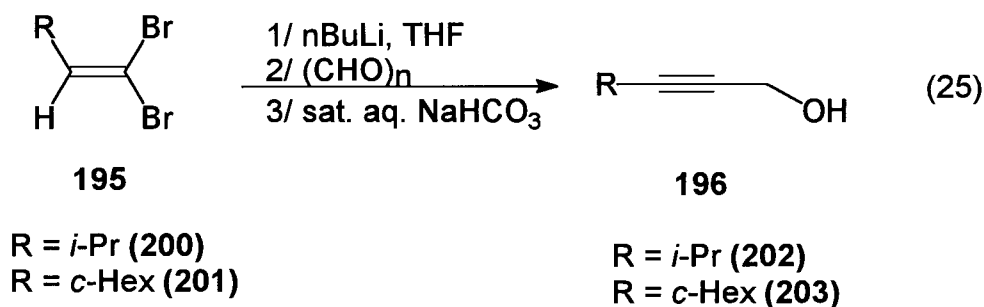


Following the procedure given on page 38 of the Discussion provided 1,1-dibromo-3-methyl-1-butene (200) in 82% yield from 2-methylpropanal (198) and 1,1-dibromo-2-cyclohexylethene (201) in 89% yield from cyclohexanecarboxaldehyde (199).<sup>43</sup>

The spectral data derived from the 1,1-dibromo-1-alkenes (200 and 201) were consistent with the assigned structures. For example, the <sup>1</sup>H NMR spectrum of alkene (200) displayed the expected signals for the trisubstituted alkene moiety (a 1-proton doublet at  $\delta$  6.22,  $J$  = 9 Hz) and one allylic proton (a 1-proton multiplet at  $\delta$  2.57). The IR spectrum of alkene (200) displayed a C=C stretching absorption at 1609 cm<sup>-1</sup>.

### 2.2.2 Preparation of the 2-alkyn-1-ols

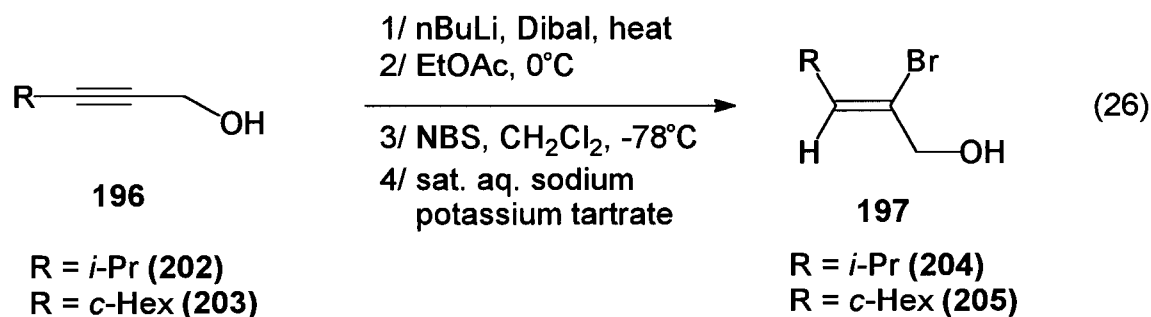
The 2-alkyn-1-ols of general structure (196) (202 and 203) were prepared from the corresponding 1,1-dibromo-1-alkenes of general structure (195) (200 and 201) (Equation 25).<sup>43</sup>



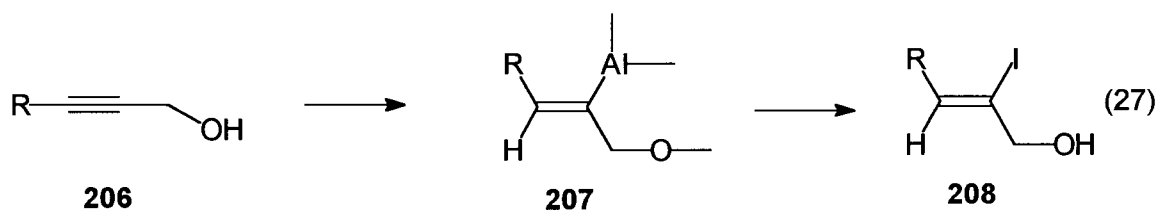
Addition<sup>43</sup> of *n*-butyllithium (2.5 equiv.) to a THF solution of 1,1-dibromo-3-methyl-1-butene (200) (-78°C, 1 h; room temperature, 1 h) afforded the corresponding lithium acetylide which, upon reaction with paraformaldehyde (3.0 equiv., -20°C, 1 h; room temperature, 1 h), produced 4-methyl-2-pentyn-1-ol (202) in 79% yield. In a similar manner, 3-cyclohexyl-2-propyn-1-ol (203) was prepared from 1,1-dibromo-2-cyclohexylethene (201) in 81% yield. The spectral data for the 2-alkyn-1-ols (202 and 203) were consistent with the assigned structures. For example, the <sup>1</sup>H NMR spectrum of alkyne (202) displayed the expected signal for a CH<sub>2</sub> group next to an alkyne and hydroxy group (a two proton doublet at  $\delta$  4.22,  $J$  = 3 Hz) and an OH group (a one proton triplet at  $\delta$  1.60,  $J$  = 3 Hz). The IR spectrum of the alkyne (202) displayed a C $\equiv$ C stretching absorption at 2256 cm<sup>-1</sup> and an O-H stretching absorption at 3400 cm<sup>-1</sup>.

### 2.2.3 Preparation of the (Z)-2-bromo-2-alken-1-ols

The (Z)-2-bromo-2-alken-1-ols of general structure (197) (204 and 205) were prepared from the corresponding 2-alkyn-1-ols of general structure (196) (202 and 203) (Equation 26).

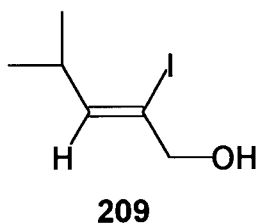


The procedure used was a modification of that developed by Corey *et al.*<sup>56</sup> to transform propargylic alcohols (206) into (Z)-2-iodo-2-alken-1-ols (208) via a vinyl aluminum derivative (207) (Equation 27).



Corey's procedure, which utilizes iodine to convert the vinylaluminum derivatives (207) into the alcohols (208), was initially successfully used to synthesize (Z)-2-iodo-4-methyl-2-pentene-1-ol (209).





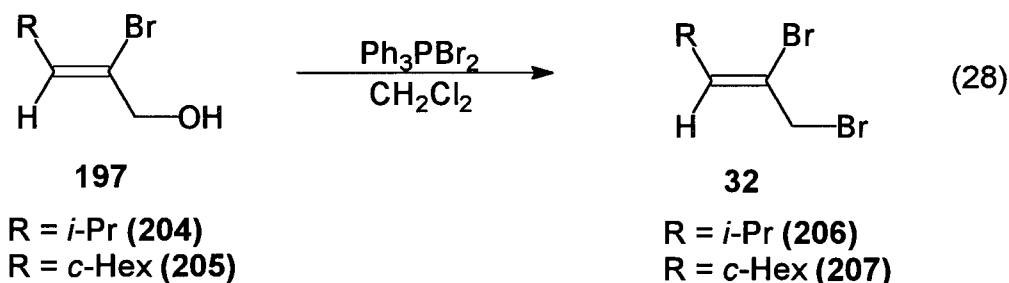
Unfortunately, the alkylating agent derived from (209), (*Z*)-1-bromo-2-iodo-4-methyl-2-pentene, was unsuitable in later steps and efforts were made to modify Corey's method to produce the bromo equivalent of (209), compound (204). (*Z*)-1,2-Dibromo-4-methyl-2-pentene, derived from (204), was later found to be of synthetic utility.

Sequential addition of *n*-butyllithium (1.0 equiv.) and Dibal (3 equiv.) to a cold (-20°C) Et<sub>2</sub>O solution of 4-methyl-2-pentyn-1-ol (202) followed by heating at 35°C for 64 h and recooling to 0°C afforded a solution of the corresponding vinylaluminum derivative, to which was added ethyl acetate (2 equiv.). The resulting mixture was stirred at 0°C for 10 min, cooled to -78°C, and cannulated into a cold (-78°C) solution of NBS (5 equiv.). Work-up and purification of the crude product produced (*Z*)-2-bromo-4-methyl-2-pentene-1-ol (204) in 63% yield. In a similar manner, 3-cyclohexyl-2-propyn-1-ol (203) was converted into (*Z*)-2-bromo-3-cyclohexyl-2-propen-1-ol (205) in 52% yield.

The spectral data for the (*Z*)-2-bromo-2-alken-1-ols (204 and 205) were consistent with the assigned structures. For example, the <sup>1</sup>H NMR spectrum of the alkene (204) displayed the expected signal for an allylic CH<sub>2</sub> group containing a hydroxyl group (a 2-proton doublet at δ 4.20, *J* = 8 Hz), an OH group (a 1-proton triplet at δ 1.87, *J* = 8 Hz), and a vinyl proton (a 1-proton doublet at δ 5.80, *J* = 8 Hz). A <sup>1</sup>H NMR NOE difference experiment supported the assignment of the stereochemistry of the double bond as the irradiation of the allylic protons at δ 4.20 led to enhancement of the olefinic proton at δ 5.80. The IR spectrum of the alkene (204) displayed C=C and O-H stretching absorptions at 1657 and 3348 cm<sup>-1</sup>, respectively. High resolution mass spectrometry showed that the molecular formula for (204) was C<sub>6</sub>H<sub>11</sub>BrO.

#### 2.2.4 Preparation of the (Z)-1,2-dibromo-2-alkenes

The (Z)-dibromoalkenes of general structure (32) (206 and 207) were prepared from the corresponding (Z)-2-bromo-2-alkene-1-ols of general structure (197) (204 and 205) (Equation 28).

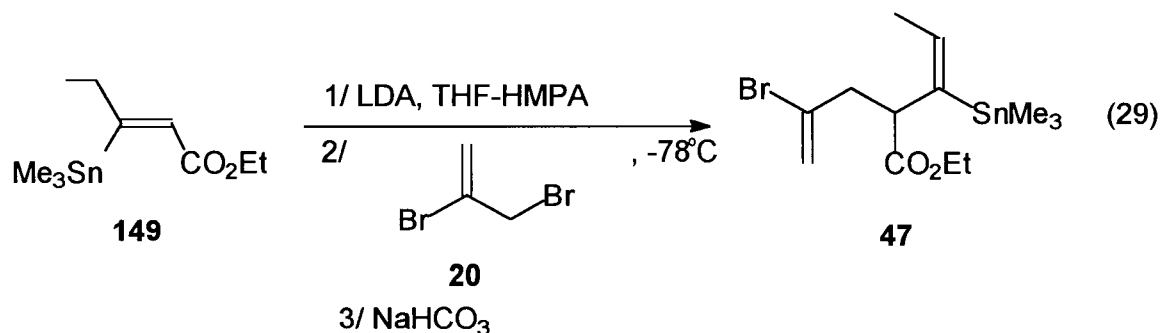


To a stirred solution of triphenylphosphine (1.1 equiv.) and bromine (1.1 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  was added (Z)-2-bromo-4-methyl-2-penten-1-ol (204). After the mixture had been stirred for 3.5 hours, pentane was added. Work-up produced (Z)-1,2-dibromo-4-methyl-2-pentene (206) in 76% yield. In a similar manner (Z)-2-bromo-3-cyclohexyl-2-propen-1-ol (205) was converted into (Z)-2,3-dibromo-1-cyclohexylpropene (207) in 73% yield.

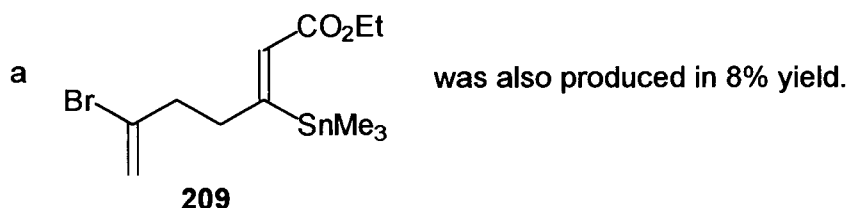
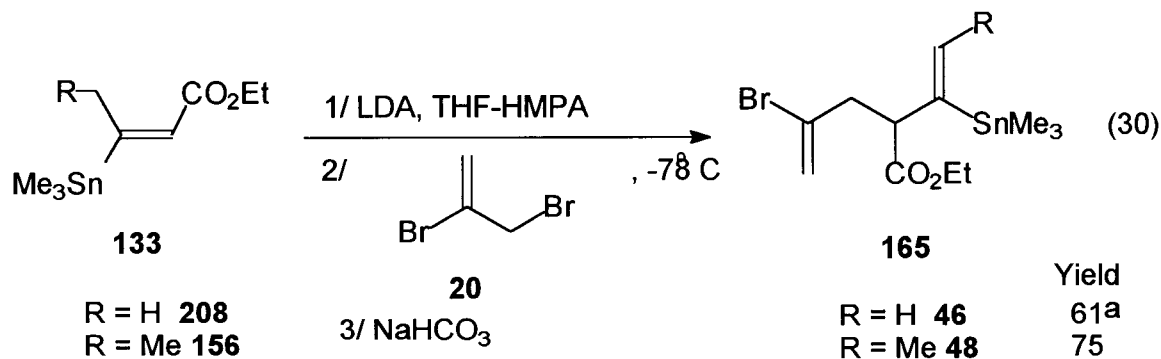
The spectral data derived from the (Z)-dibromoalkenes (206 and 207) were consistent with the assigned structures. For example, the  $^1\text{H}$  NMR spectrum of the alkene (206) displayed the expected signals from the allylic  $\text{CH}_2\text{Br}$  (a 2-proton singlet at  $\delta$  4.21) and the olefinic proton (a 1-proton doublet at  $\delta$  5.91,  $J = 9$  Hz). A  $^1\text{H}$  NMR NOE difference experiment supported the assignment of the stereochemistry of the double bond. Thus, irradiation of the allylic protons at  $\delta$  4.21 led to enhancement of the olefinic proton at  $\delta$  5.91. The IR spectrum of alkene (206) displayed a  $\text{C}=\text{C}$  stretching absorption at  $1643\text{ cm}^{-1}$ . High resolution mass spectrometry showed that the molecular formula for (206) was  $\text{C}_6\text{H}_{10}\text{Br}_2$ .

### 2.3 Deconjugation-alkylation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates

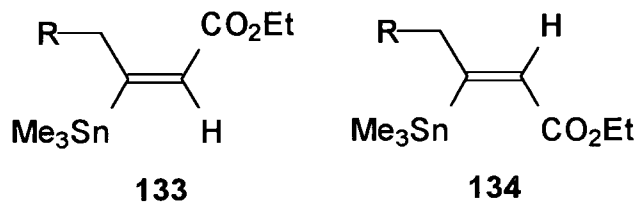
Deconjugation-alkylation of certain ethyl (*E*)- and (*Z*)-trimethylstannyl-2-alkenoates (Equations 29 and 30) with 2,3-dibromopropene (**20**) was accomplished readily.<sup>11, 16</sup> For example, addition of a THF solution of ethyl (*Z*)-3-trimethylstannyl-2-pentenoate (**149**) to a stirred solution of LDA/HMPA (2.3 equiv.) in THF (-78°C, 0.5 h; 0°C, 0.5 h) afforded a yellow solution of the corresponding lithium dienolate (Equation 29). Cooling of the solution to -78°C followed by addition of 2,3-dibromopropene (**20**) (1.5 equiv.) and stirring of the reaction mixture at -78°C for 1 h, provided, after work-up and purification of the crude product by distillation, ethyl (*E*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**47**) in 72% yield.



Using a similar procedure, ethyl (*E*)-3-trimethylstannyl-2-pentenoate (**156**) and ethyl (*E*)-3-trimethylstannyl-2-butenolate (**208**) were converted into ethyl (*Z*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**48**) and ethyl 4-bromo-2-[1-(trimethylstannyl) ethenyl]-4-pentenoate (**46**) in 75% and 61% yields, respectively (Equation 30). Also produced as a side product from the deconjugation-alkylation of (**208**) was the  $\gamma$ -alkylated product (**209**) in 8% yield.



#### 2.4 Deprotonation-alkylation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-3-alkenoates

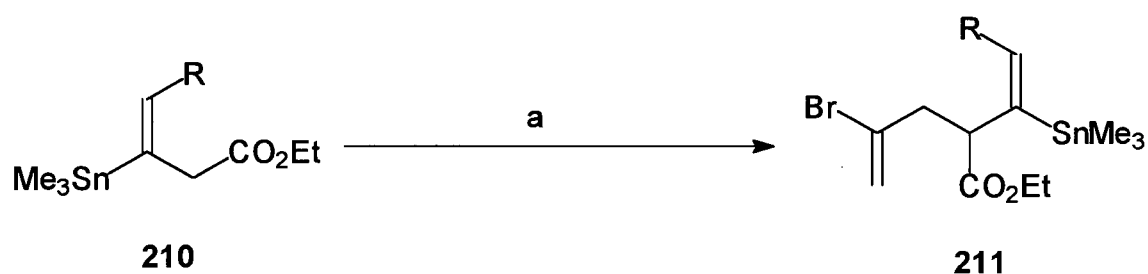


A procedure similar to that employed to deconjugate-alkylate the ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates (**133**) and (**134**), respectively, was used to deprotonate-alkylate the ethyl (*E*)- and (*Z*)-3-trimethylstannyl-3-alkenoates (**210**) and (**214**) (Tables 14 and 15). For example, ethyl (*E*)-5-methyl-3-trimethylstannyl-3-hexenoate (**170**) was converted into ethyl (*E*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**212**) in 87% yield (Table 14, Entry 1). In a similar fashion, the ester (**169**) was transformed efficiently into (**213**), (Table 14, Entry 2).

Similar results were obtained for the (*Z*)-alkenoates (Table 15). For example, ethyl (*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (**168**) was converted into ethyl (*Z*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**216**) in 84% yield

(Table 15, Entry 1). While the conversion of ester (167) into (217) proceeded in high yield (Table 15, Entry 2) this was not the case for the conversion of esters (168) and (167) into dienes (218) and (219) which proceeded in lower yields. Analysis of the crude product by TLC and GLC analysis indicated a significant amount of starting material remained for the later two reactions.

Table 14: Deprotonation-alkylation of ethyl (*E*)-3-trimethylstannyl-3-alkenoates with 2,3-dibromopropene



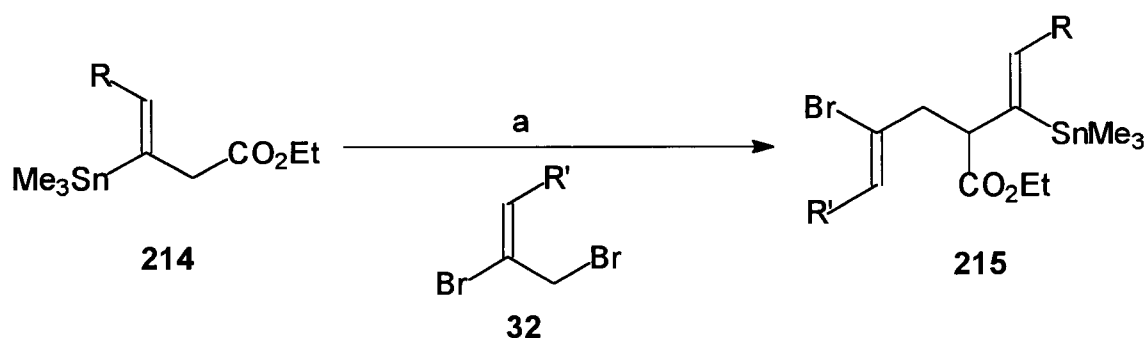
Entry	Substrate	R	Product	Yield <sup>b</sup>
1	170	<i>i</i> -Pr	212	87%
2	169	<i>c</i> -Hex	213	91%

<sup>a</sup>1. LDA/HMPA (2.3 equiv.), THF, -78°C, 0.5 h; 0°C, 0.5 h.

2. 2,3-Dibromopropene (20) (1.5 equiv.), -78°C, 1 h.

<sup>b</sup>Yield of purified, distilled product

**Table 15: Deprotonation-alkylation of ethyl (*Z*)-3-trimethylstannyl-3-alkenoates with various alkylating agents**



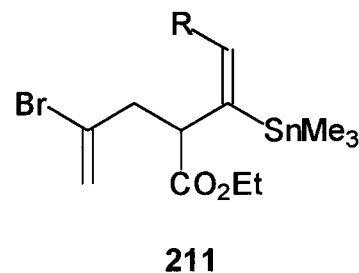
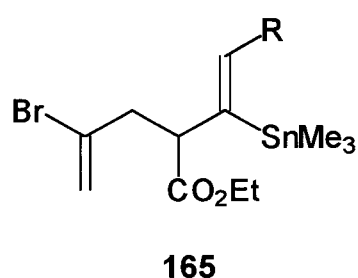
Entry	Substrate	R	R'	Product	Yield <sup>b</sup>
1	<b>168</b>	<i>i</i> -Pr	H	<b>216</b>	84%
2	<b>167</b>	<i>c</i> -Hex	H	<b>217</b>	93%
3	<b>168</b>	<i>i</i> -Pr	<i>i</i> -Pr	<b>218</b>	72%
4	<b>167</b>	<i>c</i> -Hex	<i>c</i> -Hex	<b>219</b>	60%

<sup>a</sup>1. LDA/HMPA (2.3 equiv.), THF, -78°C, 0.5 h; 0°C, 0.5 h.

2. Reagent (**32**) (1.5 equiv.), -78°C, 1 h.

<sup>b</sup>Yield of purified, distilled product

The <sup>1</sup>H NMR spectral data for the diene esters of general structure (**165**) and (**211**) were consistent with their structural assignments. When the spectra of the (*Z*)-diene esters (**165**) and (*E*)-diene esters (**211**) were compared, three consistent differences in the <sup>1</sup>H NMR spectra were evident, including the chemical shifts of the methine proton vicinal to the ethyl ester group, the chemical shift of the olefinic proton vicinal to the trimethylstannyl moiety, and the tin-proton coupling constant (<sup>3</sup>*J*<sub>Sn-H</sub>) associated with the olefinic proton vicinal to the trimethylstannyl moiety and the <sup>117</sup>Sn and <sup>119</sup>Sn isotopes (Table 16).

Table 16: Partial  $^1\text{H}$  NMR spectra data of the diene esters (164) and (211)

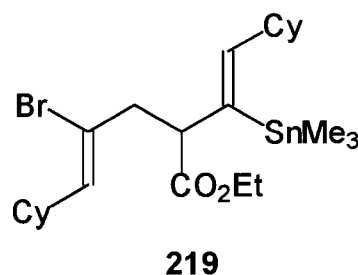
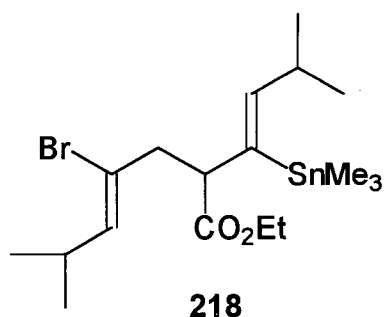
Entry	Cmpd. <b>165</b>	Cmpd. <b>211</b>	R	$\delta$ of methine proton next to $-\text{CO}_2\text{Et}$	$\delta$ of olefinic proton vicinal to $\text{SnMe}_3$	$^3J_{\text{Sn-H}}$ of the olefinic proton (Hz) vicinal to $\text{SnMe}_3$
1	<b>48</b>		Me	3.56	6.18	128
2	<b>216</b>		<i>i</i> -Pr	3.43	5.86	126
3	<b>217</b>		<i>c</i> -Hex	3.43	5.89	128
4		<b>47</b>	Me	4.06-4.20	5.86	73
5		<b>212</b>	<i>i</i> -Pr	4.03	5.48	72
6		<b>213</b>	<i>c</i> -Hex	4.03	5.50	76

For example, the  $^1\text{H}$  NMR spectrum of ethyl (*Z*)-2-(2-bromo-2-propenyl)-5-trimethyl-3-trimethylstannyl-3-hexenoate (**216**) displayed the expected signal for a trimethylstannyl group (a 9-proton singlet at  $\delta$  0.18 with  $^2J_{\text{Sn-H}} = 52$  Hz), an isopropyl group (two 3-proton doublets at  $\delta$  0.92 and  $\delta$  0.95,  $J = 6$  Hz and a 1-proton multiplet at  $\delta$  2.13-2.21), an ethyl ester moiety (a 3-proton triplet at  $\delta$  1.22,  $J = 7$  Hz and a 2-proton multiplet at  $\delta$  4.06-4.15), a 2-bromopropenyl moiety (two 1-proton doublet of doublets at  $\delta$  2.54 and  $\delta$  2.93,  $J = 15, 8$  and  $15, 6$  Hz, respectively, and two 1-proton broad singlets at

$\delta$  5.39 and 5.50) and a methine proton adjacent to the  $\text{CO}_2\text{Et}$  function at  $\delta$  3.43 (a 1-proton doublet of doublets,  $J = 8, 6$  Hz,  $^3J_{\text{Sn-H}} = 56$  Hz). A one proton doublet at  $\delta$  5.86,  $J = 10$  Hz with a tin proton coupling  $^3J_{\text{Sn-H}} = 126$  Hz<sup>51</sup> accounted for an olefinic proton *trans* to the trimethylstannyl group.

The  $^1\text{H}$  NMR spectrum of the corresponding (*E*)-diene ester (**212**) was very similar to that of (**216**) except for three notable differences. Firstly, the position of the methine proton next to the ethyl ester moiety was now upfield at  $\delta$  4.03 as the R group is now in a *cis* relationship with respect to this methine proton. Secondly, the position of the olefinic proton vicinal to the  $\text{SnMe}_3$  function was upfield at  $\delta$  5.48 as it is *cis* to the electron rich  $\text{SnMe}_3$  group and the tin-proton coupling value  $^3J_{\text{Sn-H}} = 72$  Hz corresponds to an olefinic proton *cis* to the trimethylstannyl group.<sup>51</sup> These three consistent differences between dienes (**48**) and (**47**) and between dienes (**217**) and (**213**) can be seen in Table 16.

These three trends noted above were also observed with the  $^1\text{H}$  NMR spectral data for diene esters (**218**) and (**219**).



For example, the methine proton attached to the ethyl ester group of (**218**) displayed a chemical shift of  $\delta$  3.50, consistent with the (*Z*)-diene esters (**165**, Table 16). The olefinic proton displayed a chemical shift of  $\delta$  5.85 and a tin-proton coupling constant  $^3J_{\text{Sn-H}} = 126$  Hz consistent with the olefinic proton being *trans* to the trimethylstannyl

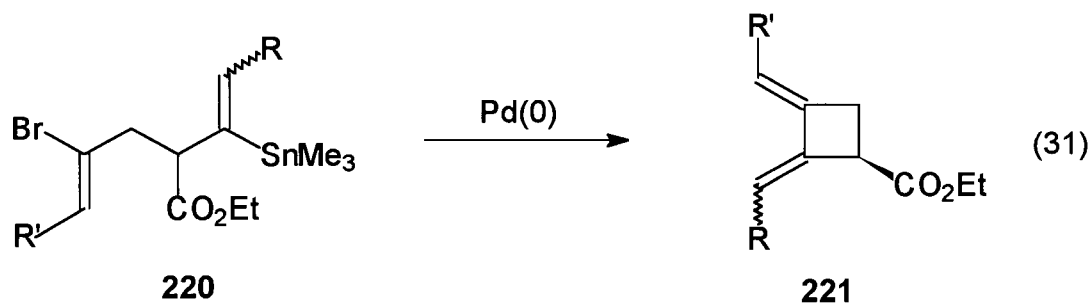


group in (218).<sup>51</sup> Diene ester (219) displayed similar <sup>1</sup>H NMR spectral data with respect to the methine and olefinic protons.

### 3. Synthesis of alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates and related derivatives

#### 3.1 Preparation of the alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates via palladium (0)-catalyzed coupling reactions

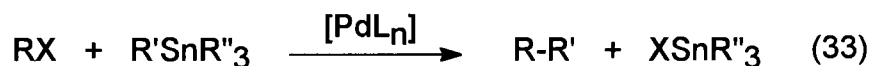
With the diene esters of general structure (220) in hand, the 2,3-bis(alkylidene)-cyclobutanecarboxylates (221) were accessible via a palladium (0)-catalyzed intramolecular coupling of the vinylstannane and the vinyl halide functions (Equation 31).



Carbon-carbon bond formation is one of the most important operations that a synthetic chemist must consider when designing a synthesis and chemists have increasingly been making use of various "cross-coupling" reactions. In general, the term "cross-coupling" refers to "the process of single bond C-C formation between two hydrocarbon groups on the basis of the reaction of an organometal compound with an organic halide or similar electrophilic derivative (Equation 32)."<sup>57</sup>



Of the many organometallic reagents available, organostannanes have found wide applications as they can be prepared via a number of methods, are not particularly air or moisture sensitive, and can be purified and stored. Furthermore, cross-coupling reactions involving organostannanes and a palladium (0) catalyst are mild, tolerant of a wide variety of functional groups, are stereospecific and regioselective, and often give high yields of product.<sup>58,59</sup> The reaction is of the general type (Equation 33) where the "leaving group" X is generally a halide or triflate and the palladium catalysts employed depend upon the nature of the particular groups being coupled, though tetrakis(triphenylphosphine)palladium (0) is the most widely used.

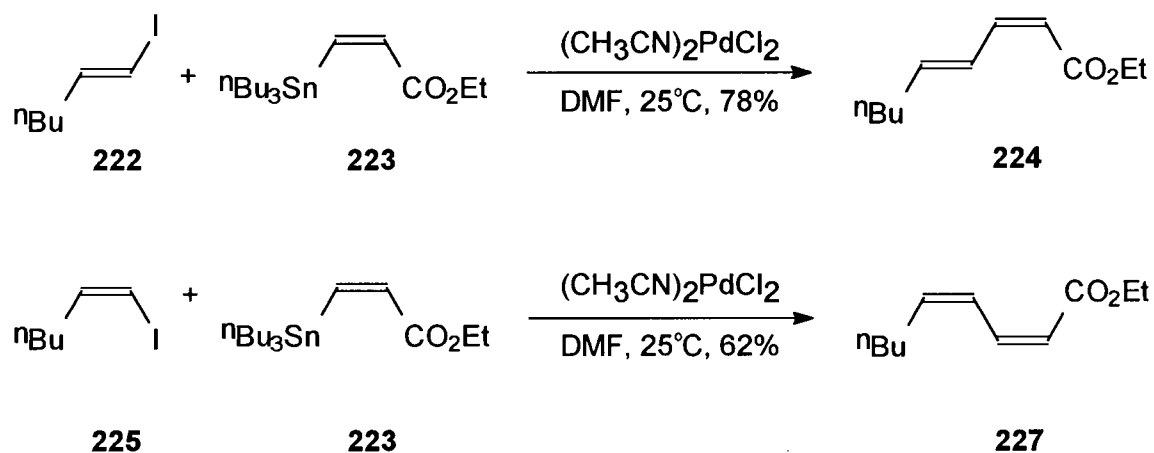


The driving force for the reaction is the formation of triorganotin halide.<sup>58</sup> As can be seen in Equation 33, only one of the groups (R') on tin participates in the coupling reaction as a second group (R'') leaves the Sn atom  $\approx 100 \times$  slower than the first.<sup>58</sup> If the four groups are not identical it is the nature of the R group which determines which group is to be transferred from the tin.<sup>60</sup> Preference for transfer follows the order  $RC\equiv C > RC=CH > Aryl > RCH=CH-CH_2 \cong ArylCH_2 > H_3COCH_2 > C_nH_{2n-1}$ .<sup>58</sup> A simple alkyl group transfers the slowest and, therefore, when an organostannane contains three methyl groups and one alkenyl or aryl group, the latter group will transfer exclusively. The use of trimethylorganostannanes is often preferred over other trialkylorganostannanes (*e.g.* tri(*n*-butyl)organostannanes). This is because the by-product of the coupling reaction, trimethylstannyl chloride, is water soluble and thus can be easily removed from the desired product while tri(*n*-butyl)stannyl chloride is not water soluble and therefore not easily removed.

J.K. Stille, a pioneer in this field, had extensively studied the palladium (0)-catalyzed intermolecular cross couplings of alkyl and aryl stannanes with acyl halides,<sup>61</sup> benzyl halides,<sup>62</sup> allyl halides,<sup>63</sup> vinyl halides,<sup>64, 68</sup> vinyl triflates,<sup>65</sup> aryl halides,<sup>66</sup> and aryl triflates.<sup>67</sup> Of these studies, those in which a vinyl group on the organotin substrate moiety is transferred, are of special interest as conjugated dienes are produced with a suitable substrate.<sup>59</sup> Both vinyl halides and vinyl triflates have been shown to be useful substrates in this regard.

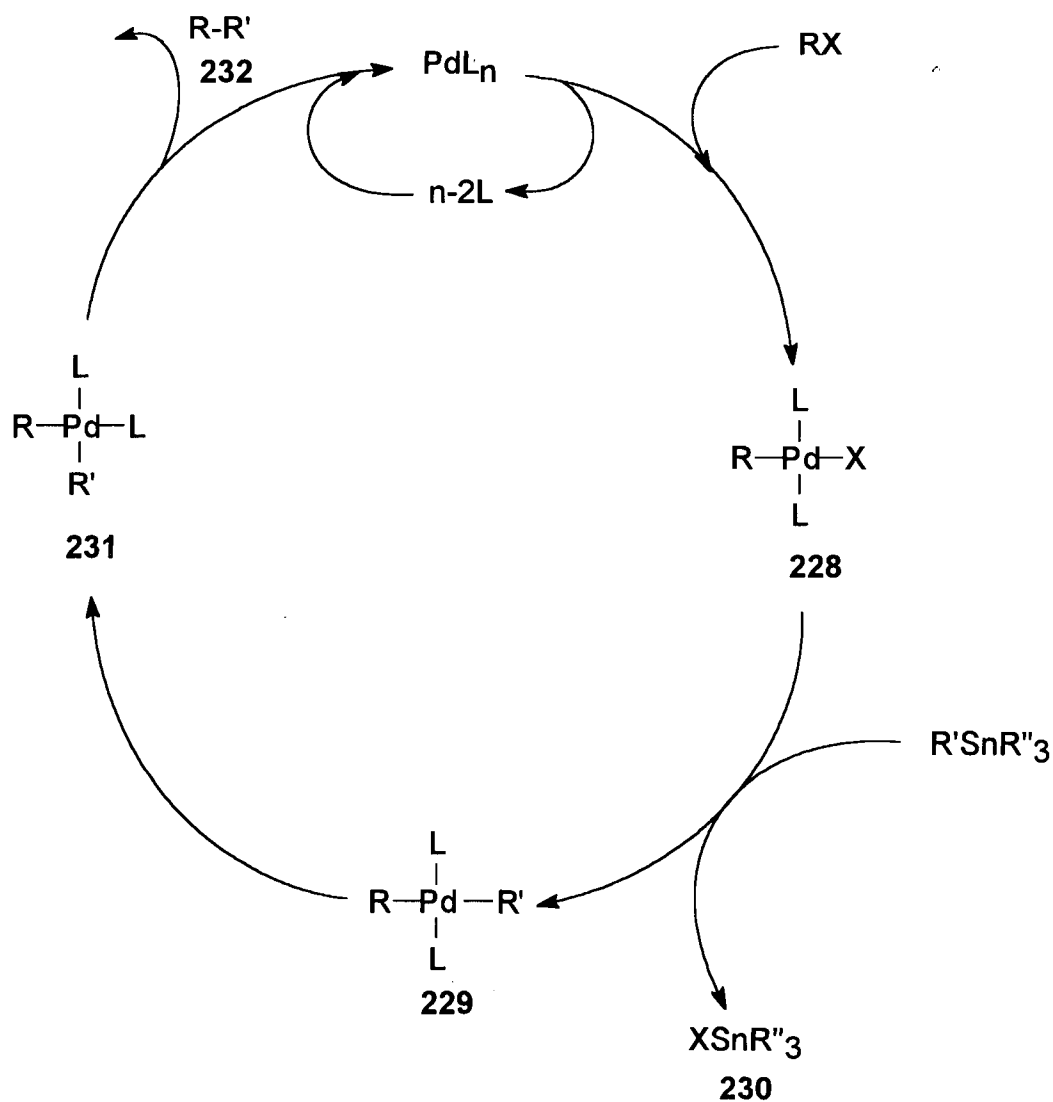
(*E*)- or (*Z*)- Substituted vinyl halides couple with (*E*)- or (*Z*)- vinylstannanes to give good yields of unsymmetrical dienes in which retention of double bond configuration has occurred.<sup>68</sup> Thus, treatment of (*E*)-1-iodo-1-hexene (**222**) with ethyl (*Z*)-3-tri-*n*-butylstannyl-2-propenoate (**223**) under the reported conditions provided the (*E*-*Z*) product (**224**), while treatment of (*Z*)-1-iodo-1-hexene (**225**) with (**223**) provided the (*Z*-*Z*) isomer (**227**) (Scheme 21).<sup>68</sup>

Both vinyl iodides and vinyl bromides can be used in the coupling reaction though vinyl bromides require longer reaction times and higher temperatures (e.g. 100°C vs. 25°C) than their iodo counterparts.<sup>58</sup>



Scheme 21

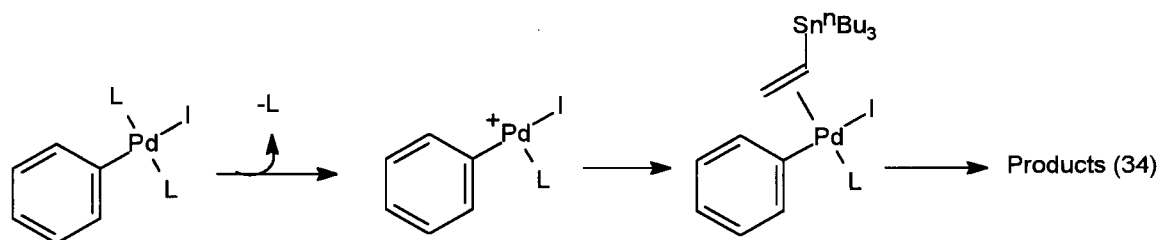
Many studies have been published regarding the mechanism for palladium (0) cross coupling of vinylstannanes with vinyl halides or vinyl triflates.<sup>63,65</sup> The catalytic cycle proposed by Stille for the direct coupling reaction of a vinylstannane and vinyl halide is shown in Scheme 22.<sup>58</sup>



Scheme 22

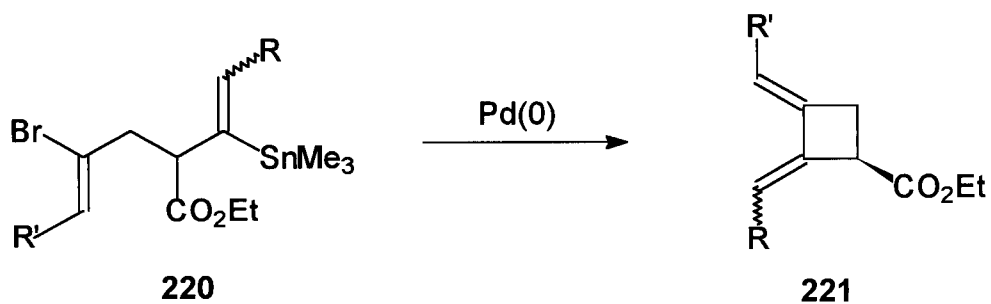
Oxidative addition of the palladium (0) catalysts into the RX bond yields the palladium(II) intermediate (228). Transmetalation between (228) and a vinyltrialkylstannane then occurs to give intermediate (229) and a trialkylstannyl halide (230). The intermediate (229) then undergoes *trans-cis* isomerization to give (231), followed by rapid reductive elimination, to release the coupled product (232). The coupling of a vinyl triflate and organostannane was proposed by Stille to proceed via an analogous pathway.<sup>65,69</sup>

Recently, Farina has performed  $^{31}\text{P}$  NMR and kinetic studies which suggest that ligand dissociation is a key step in the transmetalation step outlined above and that a  $\pi$  complex between the Pd(II) intermediate and the olefinic stannane is formed in one of the steps in the mechanism (Equation 34).<sup>70</sup>



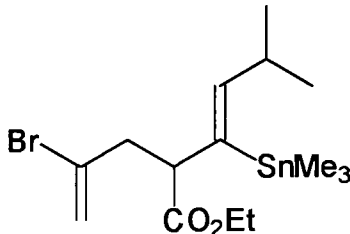
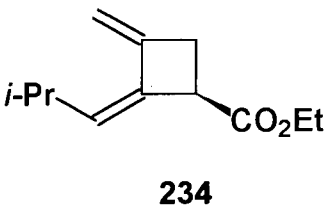
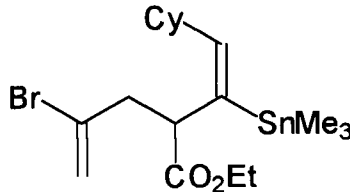
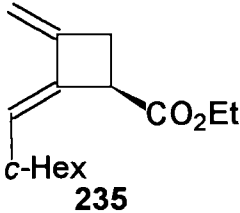
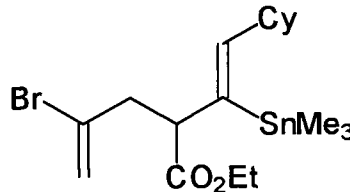
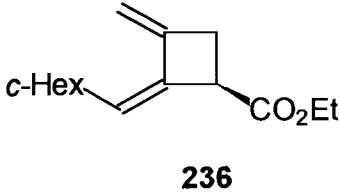
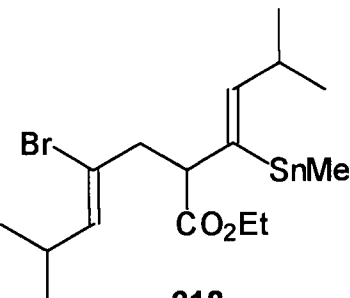
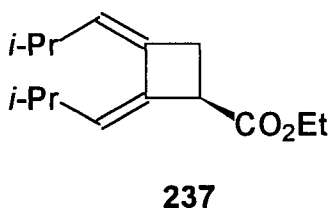
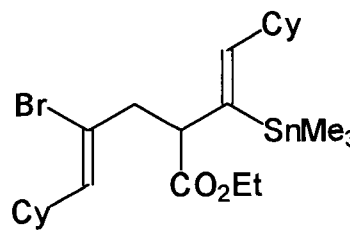
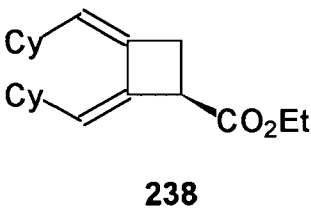
Treatment of diene esters (220), which contain vinyl bromide and vinyl trimethylstannane functions, with  $(\text{Ph}_3\text{P})_4\text{Pd}$  (5 mol %) in dry DMF at  $80^\circ\text{C}$  for 1 h provided a synthetic pathway to the alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates (221) (Table 17).

Table 17: Stereocontrolled synthesis of alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates

221<sup>a</sup>

Entry	Substrate 220	Product 221	% Yield <sup>b</sup>
1	<p style="text-align: center;"><b>46</b></p>	<p style="text-align: center;"><b>53</b></p>	82
2	<p style="text-align: center;"><b>47</b></p>	<p style="text-align: center;"><b>54</b></p>	80
3	<p style="text-align: center;"><b>48</b></p>	<p style="text-align: center;"><b>55</b></p>	85
4	<p style="text-align: center;"><b>212</b></p>	<p style="text-align: center;"><b>233</b></p>	79

Table 17 (cont)

5	 <p><b>216</b></p>	 <p><b>234</b></p>	90
6	 <p><b>213</b></p>	 <p><b>235</b></p>	83
7	 <p><b>217</b></p>	 <p><b>236</b></p>	79
8	 <p><b>218</b></p>	 <p><b>237</b></p>	83 <sup>c</sup>
9	 <p><b>219</b></p>	 <p><b>238</b></p>	21 <sup>d</sup> , 84 <sup>e</sup>

<sup>a</sup>All reactions were carried out under the following conditions (unless otherwise noted):

(Ph<sub>3</sub>P)<sub>4</sub>Pd (5 mol %) in dry DMF at 80°C for 1 h.

Table 17 (cont.)

<sup>b</sup>Yield of purified distilled product.

<sup>c</sup>Experimental Conditions: (Ph<sub>3</sub>P)<sub>4</sub>Pd (10 mol %) in dry DMF at 80°C for 2.5 h.

<sup>d</sup>Experimental Conditions: (Ph<sub>3</sub>P)<sub>4</sub>Pd (10 mol %) in dry DMF at 80°C for 48 h.

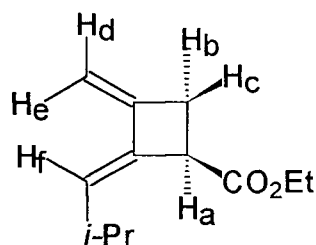
<sup>e</sup>Experimental Conditions: CuCl (2.8 equiv.) in dry DMF at 60°C for 10 min.

For example, addition of (Ph<sub>3</sub>P)<sub>4</sub>Pd (5 mol %) to a 0.07 M solution of ethyl (*E*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**212**) in DMF gave a pale yellow solution. Upon heating at 80°C for 1 h the solution turned dark brown. GLC analysis of a solution of the crude product indicated that only one product had formed. Flash chromatography of the crude product and distillation of the acquired oil afforded 79% of ethyl (*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**) as a colourless oil.

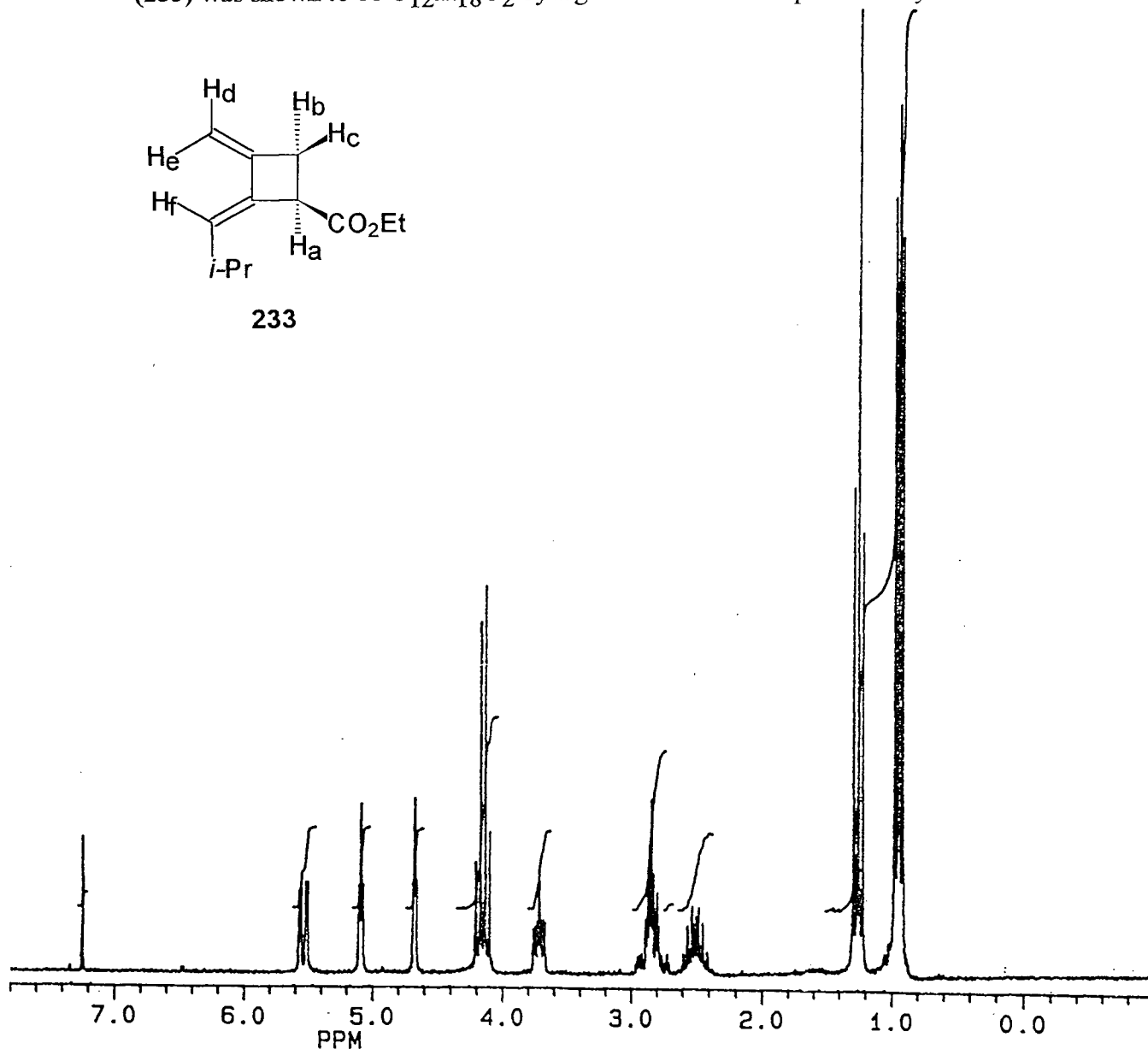
The assigned structure of (**233**) was confirmed in the following manner. The <sup>1</sup>H NMR spectrum of (**233**) (Figure 3) showed the expected signals for an ethyl ester moiety (a 3-proton triplet at  $\delta$  1.25,  $J = 7$  Hz, and a 2-proton multiplet at  $\delta$  4.13-4.18), a methylene group (H<sub>b</sub>, a 1-proton doublet of doublets of doublets of doublets at  $\delta$  2.79,  $J_{bc} = 15$  Hz,  $J_{ba} = 9$  Hz,  $J_{be} = 2.5$  Hz,  $J_{bd} = 2$  Hz; and H<sub>c</sub>, a 1 proton multiplet at  $\delta$  2.84-2.91), a methine proton (H<sub>a</sub>, a 1-proton multiplet at  $\delta$  3.68-3.73), and an isopropyl group (two 3-proton doublets at  $\delta$  0.93 and  $\delta$  0.96,  $J = 7$  Hz each and a 1-proton multiplet at  $\delta$  2.45-2.55). It should be noted that the signal for the methylene group of the ethyl ester moiety is a multiplet because the geminal protons are diastereotopic. There were also the expected signals for three olefinic protons (H<sub>d</sub>, a 1-proton doublet of doublets at  $\delta$  4.66,  $J_{db} = J_{dc} = 2$  Hz; H<sub>e</sub>, a 1-proton doublet of doublets at  $\delta$  5.09,  $J_{eb} = J_{ec} = 2.5$  Hz; and H<sub>f</sub>, a 1-proton doublet of doublets at  $\delta$  5.54,  $J_{fa} = 3$  Hz,  $J_{(CH_3)_2CH-f} = 10$  Hz). In a series of NOE difference experiments irradiation at  $\delta$  2.50 (-CH(CH<sub>3</sub>)<sub>2</sub>) caused enhancement of the signals at  $\delta$  0.93 (one of -CH(CH<sub>3</sub>)<sub>2</sub>),  $\delta$  0.96 (one of -CH(CH<sub>3</sub>)<sub>2</sub>),



and  $\delta$  3.68-3.73 ( $H_a$ ) while irradiation at  $\delta$  3.70 ( $H_a$ ) caused enhancement of the signals at  $\delta$  0.93 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  0.96 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  2.50 ( $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  2.79 ( $H_b$ ). Irradiation at  $\delta$  5.54 ( $H_f$ ) caused enhancement of the signals at  $\delta$  0.93 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  0.96 (one of  $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  5.09 ( $H_e$ ). The IR spectrum of (233) showed a strong C=O stretching frequency at  $1736\text{ cm}^{-1}$  and the molecular formula of (233) was shown to be  $\text{C}_{12}\text{H}_{18}\text{O}_2$  by high resolution mass spectrometry.



233

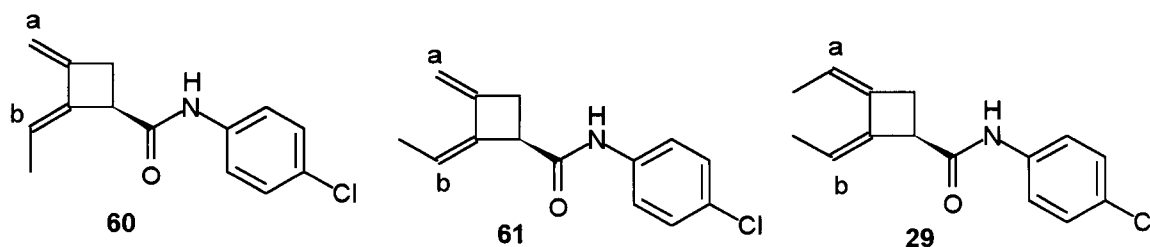
Figure 3:  $^1\text{H}$  NMR of ester 233

In a similar fashion, the diene esters (46-48) (213) and (216-219) were converted into the corresponding alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates (53-55) and (234-238) in good yields (Table 17). Of noteworthy mention are the longer reaction times and the greater amount of catalyst required to transform the diene esters (218) and (219) into the esters (237) and (238). The transformation of (219) into (238) also produced the product (238) in low (21%) yield (Table 17, Entry 9). Fortunately, a new method of coupling vinylstannanes and vinyl halides using CuCl had been developed in our laboratories.<sup>48, 71</sup> Thus, treatment of (219) with CuCl (2.8 equiv.) in dry DMF at 60°C for 10 min provided, upon workup and distillation of the acquired oil, a 84% yield of ester (238).

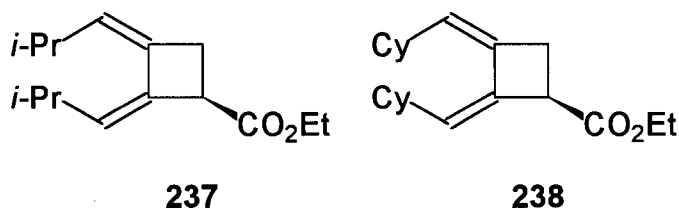
<sup>1</sup>H NMR analyses, including NOE difference and decoupling experiments, were performed on all of the cyclobutanecarboxylates (221) (Table 17) to confirm their structures. All of the cyclobutanecarboxylates exhibited absorption bands at 1735-1740 cm<sup>-1</sup> for C=O stretching vibration of the ethyl ester moiety in their IR spectra. High resolution mass spectrometry confirmed the molecular formula in each case.

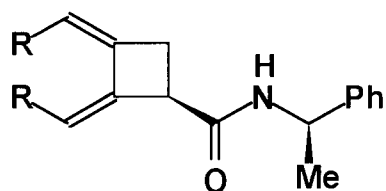
### 3.2 Preparation and X-ray analysis of the (Z,Z)-2,3-bis(alkylidene)cyclobutane-carboxamides (239-242)

The cisoid diene units of the crystalline compounds (60), (61) and (29) have been found by X-ray analysis to be non-planar.<sup>16</sup> The torsion angles between carbons a and b of the cisoid diene units were found to be 3.9°, 4.8°, and 25.4°, respectively.<sup>16</sup>

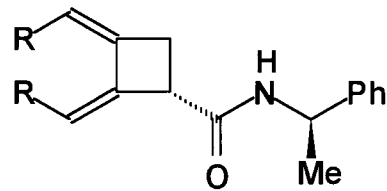


The cyclobutanecarboxylates (237) and (238) should be highly strained compounds due to the severe steric repulsion between the two vinylic isopropyl groups in (237) and two vinylic cyclohexyl groups in (238) particularly if the diene systems are planar. Indeed, it would be expected that the cisoid diene units of (237) and (238) would be non-planar and that the torsion angle between carbons a and b of the cisoid diene units of (237) and (238) would be larger than that of (29). Esters (237) and (238) are oils, so it was necessary to prepare suitable amide derivatives to provide crystals appropriate for X-ray analysis.



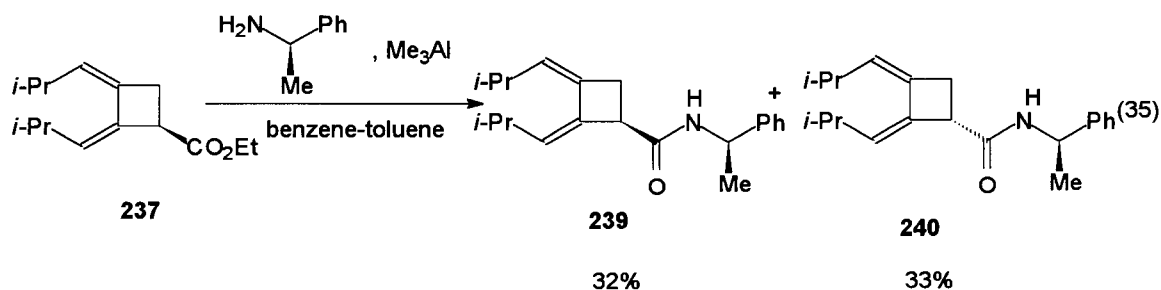


R = *i* - Pr (239)  
R = *c* - Hex (241)



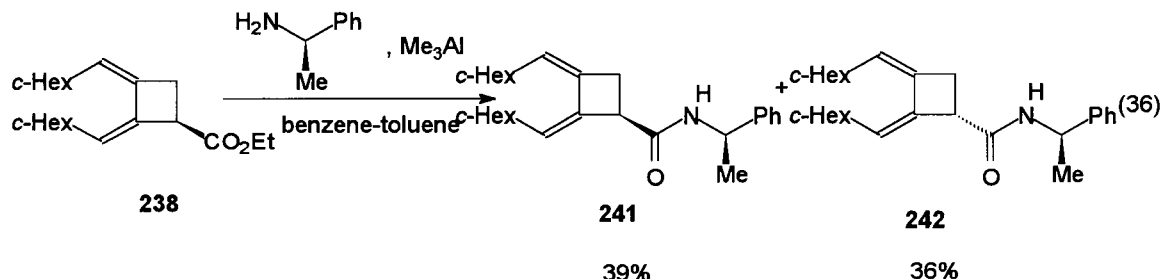
R = *i* - Pr (240)  
R = *c* - Hex (242)

To that end, the crystalline amide derivatives (239-242) were prepared from cyclobutanecarboxylates (237) and (238) (Equations 35 and 36) employing a procedure developed by Weinreb *et al.*<sup>72</sup> Only derivative (240) was found to be suitable for X-ray analysis.



For example, to a stirred solution of (R)-(+)-1-phenylethylamine (2.24 equiv.) in dry benzene (16 mL) was added, dropwise, a solution of trimethylaluminum (2.24 equiv.) in toluene (room temperature, 20 min) to produce a yellowish solution. Addition of the cyclobutanecarboxylate (237) (1 equiv.) in 2 mL dry benzene, followed by refluxing (4 h), provided, after acidic work-up, radial chromatography, and recrystallization from a petroleum ether - Et<sub>2</sub>O mixture, 32% and 33% yields of the cyclobutanecarboxamides (239) and (240), respectively. The cyclobutanecarboxamide (240) exhibited colourless, needle-like crystals of melting point, 110-111°C, while the diastereomer (239) consisted of colourless, needle-like crystals of melting point, 103-104°C.

In a similar fashion, the cyclobutanecarboxamides (**241**) and (**242**) were prepared from (**238**) in 39% and 36% yields, respectively (Equation 36).



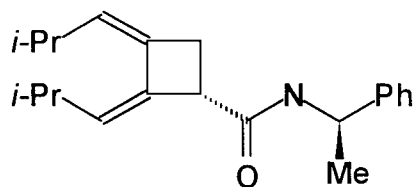
The cyclobutanecarboxamide (**241**) was recrystallized as colourless needle-like crystals (melting point, 163-165°C dec.) and (**242**) as colourless needle-like crystals (melting point, 169-170°C dec.).

Compounds (**241**) and (**242**) were thermally stable on a short-term basis (less than 1 day) and complete spectral data were obtained. However, it was impossible to obtain suitable crystals for analysis by single crystal X-ray crystallography before both of these compounds decomposed. Thus, only single crystal X-ray analysis on (**240**) was obtained.

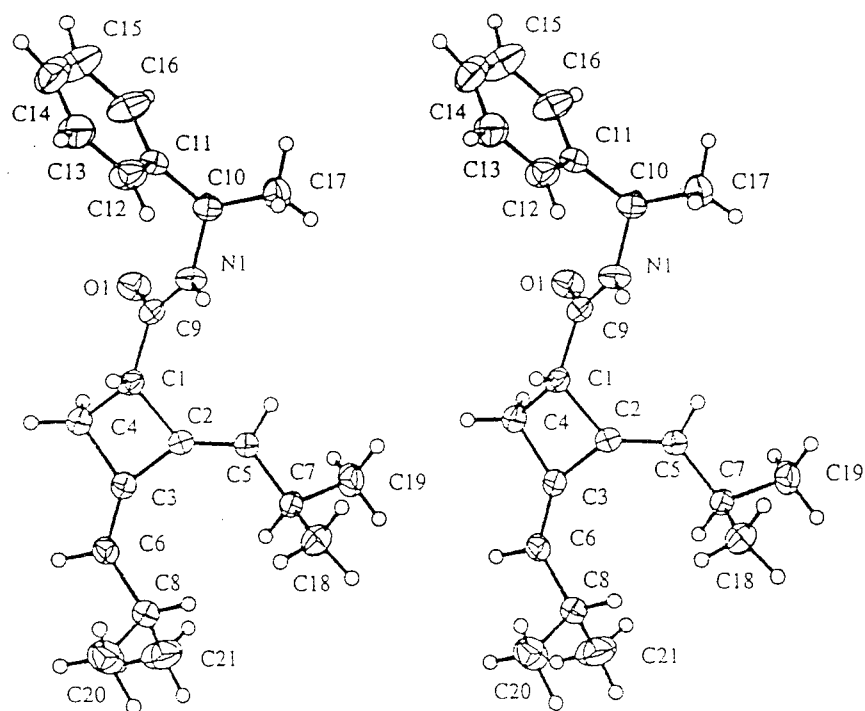
Single crystal X-ray analysis of (**240**) (Appendix 1) indicated that the torsional angle between the C-5-C-2 (for the purpose of this discussion, the numbering system used for compound (**240**) is that in Figure 4) and C-3-C-6 bonds is 38.7° (Figure 2). The bond lengths between the carbon atoms in the four-membered ring are as follows: C-1-C-2, 1.537(3)Å; C-2-C-3, 1.490(3)Å; C-3-C-4, 1.519(3)Å; and C-4-C-1, 1.546(3)Å (Figure 4).

The x-ray analysis clearly shows that the four-membered ring of (**240**) is not a perfect square. The C-2-C-3 bond is somewhat shorter than the rest of the cyclobutane C-C bonds. The *cisoid* diene unit of (**240**) was found to have its planarity severely disrupted, with the torsional angle being 38.7°. This distortion from planarity is due to the severe steric repulsion between the two isopropyl groups should the *cisoid* diene unit adopt a planar conformation. It is noteworthy to mention that the torsional angle of (**240**)

(38.7°) is greater than that of compound (29) (25.4°), which differs in having two vinylic methyl groups instead of two vinylic isopropyl groups.



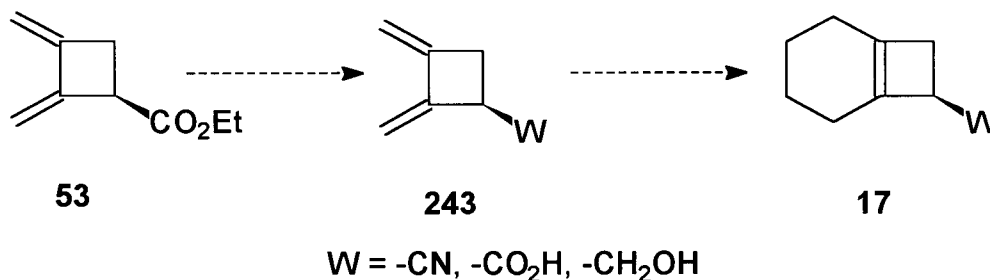
**240**



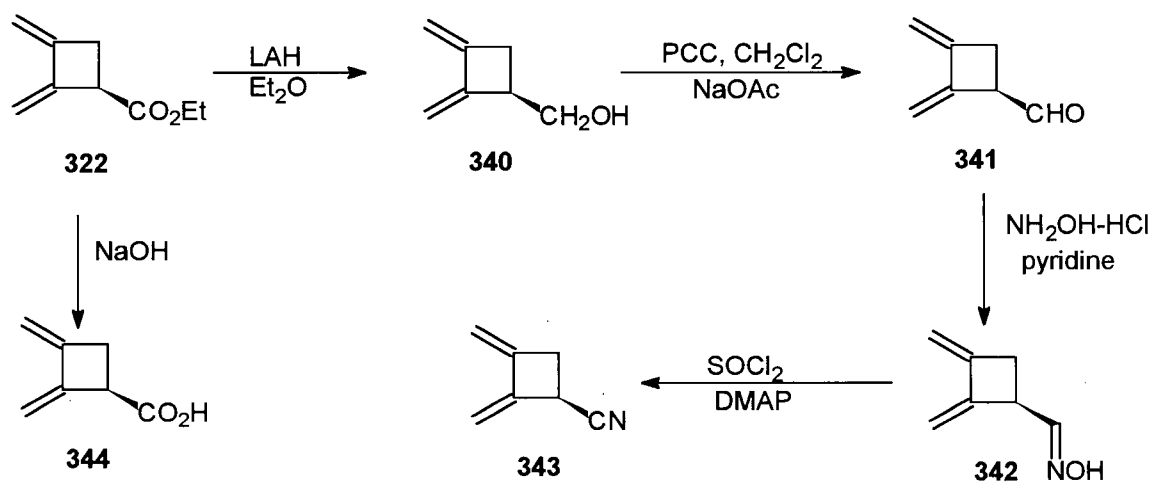
**Figure 4: Stereoview of the cyclobutanecarboxamide 240**

### 3.3 Preparation of the 1-substituted-2,3-bis (methylene) cyclobutanes

Compounds of general structure (17) where  $W = -\text{CN}$ ,  $-\text{CO}_2\text{H}$ , and  $-\text{CH}_2\text{OH}$  were also required as thermolysis precursors.

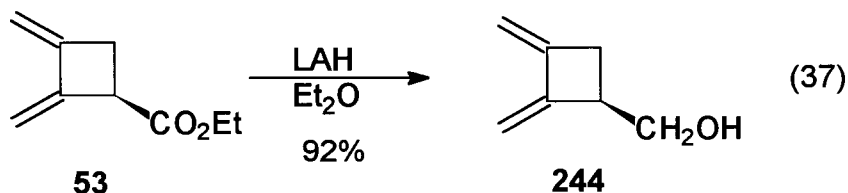


After some experimentation, it was found that the most expedient route to compounds of general structure (17) was via conversion of the ethyl ester group of (53) into the desired functional group of (243) followed by a  $4\pi + 2\pi$  cycloaddition of the 1-substituted 2,3-bis(methylene)cyclobutane (243) with a suitable dienophile. To this end, several 1-substituted-2,3-bis(methylene)cyclobutanes of general structure (243) were prepared as shown in Scheme 23.



Scheme 23

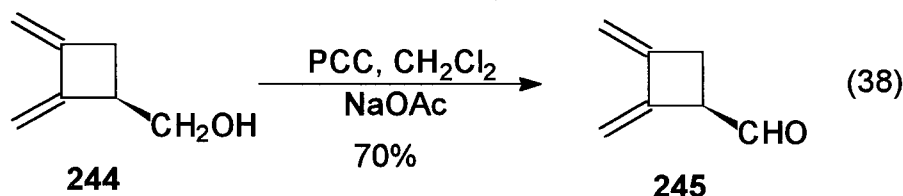
### 3.3.1 Preparation of 1-(hydroxymethyl)-2,3-bis(methylene)cyclobutane (244)



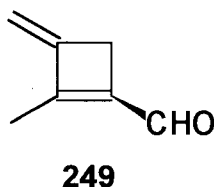
The alcohol (**244**) was readily obtained from the cyclobutanecarboxylate (**53**). Treatment of the cyclobutanecarboxylate (**53**) with lithium aluminum hydride (1.0 equiv.) (0°C, 10 min; room temperature, 10 min) afforded, after work-up, radial chromatography, and distillation of the crude reaction product, a 92% yield of the alcohol (**244**) (Equation 37). The  $^1\text{H}$  NMR spectrum of (**244**) showed signals similar to those found in the  $^1\text{H}$  NMR spectrum of (**53**) with the exception that the signals for the ethyl ester moiety were replaced by those of a  $-\text{CH}_2\text{OH}$  group (a 1-proton broad singlet at  $\delta$  1.53 and a two proton multiplet at  $\delta$  3.65-3.77). The IR spectrum of (**244**) showed a strong broad absorption at  $3351\text{ cm}^{-1}$  indicating the presence of an OH moiety. The high resolution mass spectrum of alcohol (**244**) indicated that it had a molecular formula of  $\text{C}_7\text{H}_{10}\text{O}$ .



### 3.3.2 Preparation of 1-formyl-2,3-bis(methylene)cyclobutane (245)

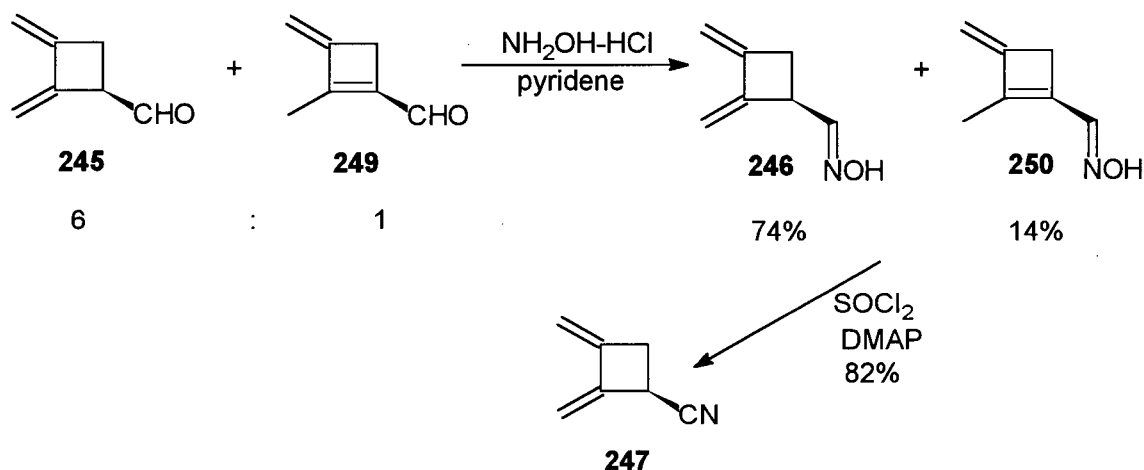


The aldehyde (**245**) was readily obtained from the alcohol (**244**) via the following procedure. Addition of (**244**) to a stirred solution of pyridinium chlorochromate (2.0 equiv.) and sodium acetate (3.5 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  (room temperature, 2 h) afforded, after filtration of the crude reaction mixture (through a column of Florisil), and distillation of the acquired oil, a 70% yield of the aldehyde (**245**) (Equation 38). Compound (**245**) proved to be extremely unstable (polymerizing rapidly after distillation) and thus had to be used immediately in subsequent synthetic sequences. Furthermore, during the filtration step of the work-up, (**245**) partially isomerized to the aldehyde (**249**) if the elution rate of the crude reaction mixture through the Florisil was slow.



The  $^1\text{H}$  NMR spectrum of (**245**) was similar to that of the alcohol (**244**) with the exception that the  $-\text{CH}_2\text{OH}$  signals were replaced with the resonances of an aldehyde group (a 1-proton doublet at  $\delta$  9.68,  $J = 2$  Hz). The IR spectrum of (**245**) exhibited a strong absorption at  $1719\text{ cm}^{-1}$  indicating the presence of the  $-\text{CHO}$  moiety. The high resolution mass spectrum of the aldehyde (**245**) indicated that it had a molecular formula of  $\text{C}_7\text{H}_8\text{O}$ .

### 3.3.3 Preparation of 1-cyano-2,3-bis(methylene)cyclobutane (**247**)



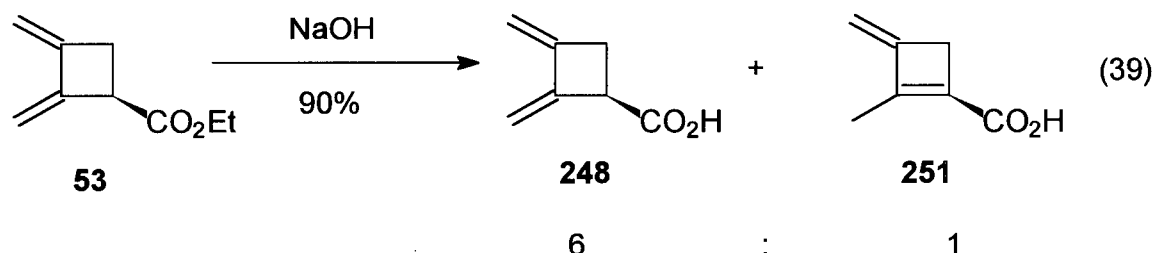
Scheme 24

To a stirred solution of the aldehydes (**245**) and (**249**) (6:1 mixture as determined by  $^1\text{H}$  NMR spectroscopy) in dry DMF was added hydroxylamine hydrochloride (5.1 equiv.) and dry pyridine (5.1 equiv.) and the resultant mixture was stirred for 1 h. Workup, radial chromatography, and recrystallization (1:1 hexanes -  $\text{Et}_2\text{O}$ ) of the crude product, afforded the oxime (**246**) in a 74% yield and the oxime (**250**) in a 14% yield (Scheme 24). Compound (**246**) consisted of a 3:2 mixture of geometric isomers with respect to the oxime function. The high resolution mass spectrum of (**246**) indicated that it had a molecular formula of  $\text{C}_7\text{H}_9\text{NO}$ .

The oxime (**246**) was added to a cold ( $-10^\circ\text{C}$ ) stirred solution of thionyl chloride (1.1 equiv.) and DMAP (1.25 equiv.) in  $\text{CH}_2\text{Cl}_2$  ( $-10^\circ\text{C}$ , 2 min) to produce a yellow solution. More DMAP (1.25 equiv.) was added, the solution warmed (room temperature, 30 min) and upon work-up, chromatography, and distillation of the crude product there was obtained 82% of the nitrile (**247**) as a volatile oil (Scheme 24). The  $^1\text{H}$  NMR spectrum of (**247**) was similar to that of aldehyde (**245**). The IR spectrum of (**247**) displayed a strong absorption at  $2240\text{ cm}^{-1}$  which indicated the presence of a nitrile

moiety. The high resolution mass spectrum of (247) indicated that it had a molecular formula of  $C_7H_7N$ .

### 3.3.4 Preparation of 2,3-bis(methylene)cyclobutanecarboxylic acid (248)

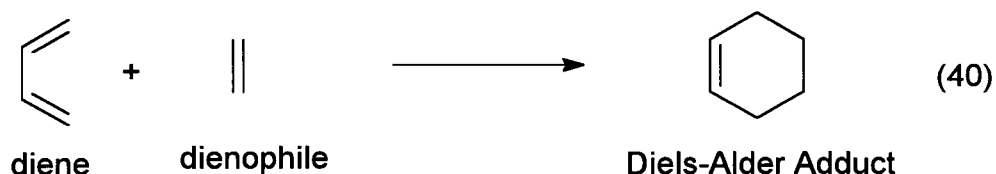


Treatment of a solution of the cyclobutanecarboxylate (53) in an ethanol-water mixture with NaOH (1.25 equiv.) (room temperature, 2 h) afforded, after work-up, a 90% yield of a 6:1 mixture of the acids (248) and (251) (Equation 39). Attempts to separate these products by radial and flash chromatography on silica gel were unsuccessful and this mixture was used without further purification in later synthetic steps.

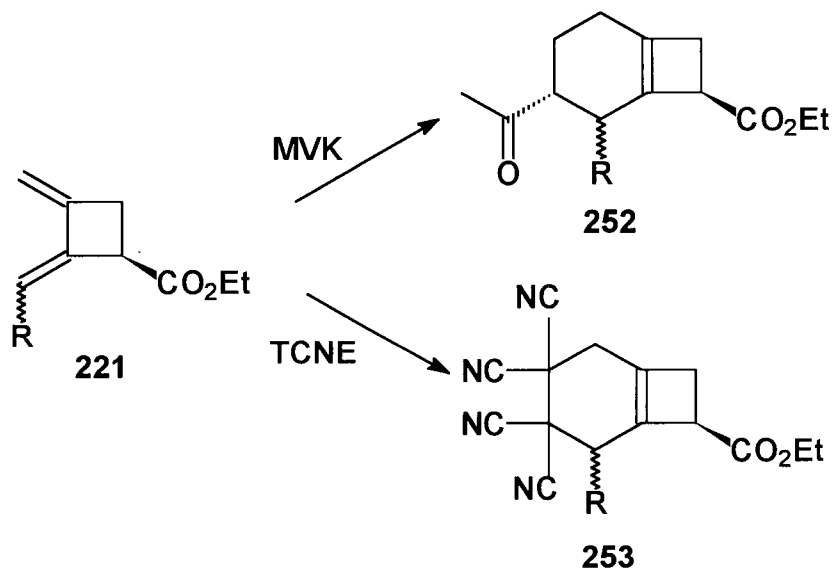
The IR spectrum of the mixture displayed the absorptions expected for a carboxylic acid moiety (a strong, broad absorption at  $3390\text{--}2670\text{ cm}^{-1}$  and a strong absorption at  $1705\text{ cm}^{-1}$ ). The high resolution mass spectrum of the mixture indicated that it had a molecular formula of  $C_7H_8O_2$ .

4. Diels-Alder reactions of alkyl 2,3-bis(alkylidene)cyclobutanecarboxylates and related substances

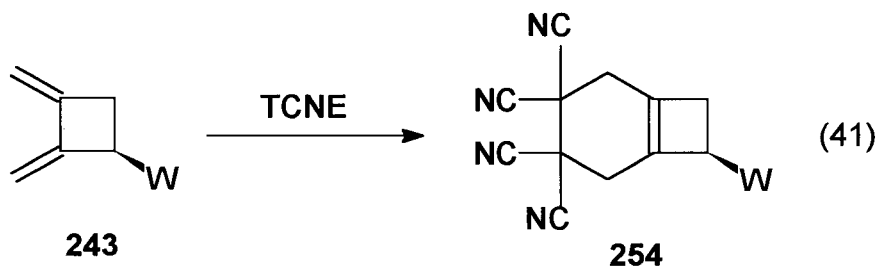
The Diels-Alder reaction involves a  $[4\pi + 2\pi]$  cycloaddition of a conjugated diene and dienophile to form a 6-membered ring (Equation 40).



With the availability of several alkyl 2-alkylidene-3-methylenecyclobutanecarboxylates (**221**) (Scheme 25) and 1-substituted 2,3-bis(methylene)cyclobutanes (**243**) (Equation 41), the Diels-Alder reactions of these compounds with a variety of dienophiles was investigated. The products of these Diels-Alder reactions, the bicyclo[4.2.0]oct-1(6)-enes (**252-254**), are the substrates of the thermolysis studies which will be discussed in detail in the final chapter of this Discussion.



Scheme 25



#### 4.1 Diels-Alder reactions of dienes with tetracyanoethylene (TCNE)

The greater the number of electron-attracting substituents on a double bond, the more reactive is the dienophile due to a lowering of the energy of the lowest unoccupied molecular orbital (LUMO).<sup>73</sup> Tetracyanoethylene (TCNE) is a highly reactive dienophile because it possesses four conjugated nitrile groups.<sup>74</sup> It was important to use a highly reactive dienophile like TCNE because of the instability of two of the dienes (243) (W = CHO, CN). As tetracyanoethylene (TCNE) is symmetrical, it can also be used to show the face selectivity of the Diels-Alder reactions for dienes with at least one

substituent on the diene. The Diels-Alder adduct produced is typically the one resulting from  $\alpha$ -face approach of the TCNE (Figure 5). This is because there is relatively little steric hindrance in the transition state resulting from  $\alpha$ -face approach as compared to the transition state resulting from  $\beta$ -face approach where there is an ester group present.

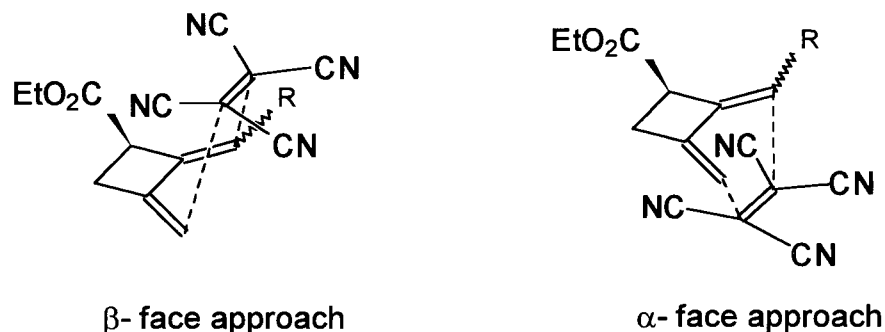
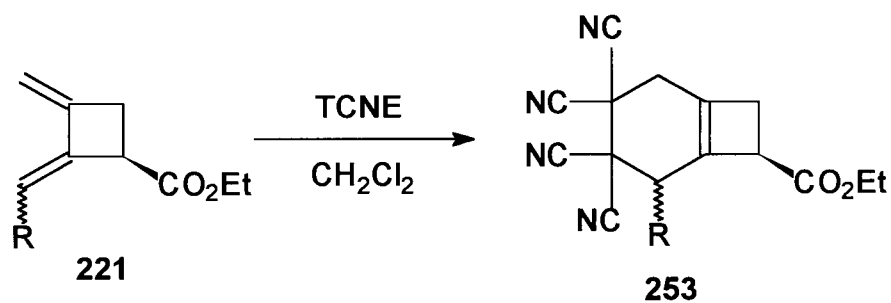


Figure 5: Diagrammatic view of the two possible directions that the dienophile TCNE may approach the 2,3-bis(alkylidene)cyclobutanecarboxylates

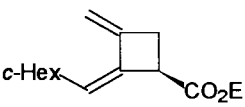
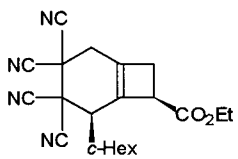
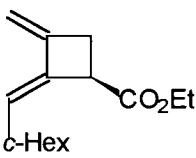
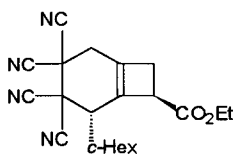
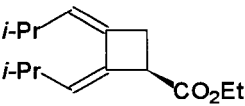
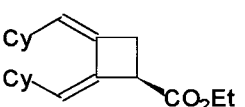
The general procedure for the preparation of the TCNE adducts of dienes (221) and (243) is as follows. To a stirred solution of the appropriate ethyl cyclobutanecarboxylate (221) or the 1-substituted-2,3-bis(methylene)cyclobutane (243) (1 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  (8-12 mL/mmol of substrate) was added tetracyanoethylene (1 equiv., unless noted otherwise). The reaction mixture was stirred for 0.5 hours at room temperature (unless noted otherwise) and the solvent was removed under reduced pressure. Radial chromatography of the crude product followed by recrystallization (1:1 hexanes- $\text{Et}_2\text{O}$ ) of the acquired solids afforded the corresponding products (253) and (254) respectively, as crystalline solids. The results from these Diels-Alder reactions are summarized in Tables 18 and 19.

Table 18: Diels-Alder reactions of the cyclobutanecarboxylates **221** with tetracyanoethylene



Entry	Substrate	Equiv. TCNE	Reaction Time	Product	Yield (%) <sup>a</sup>
1	<p style="text-align: center;"><b>53</b></p>	1.0	0.5 h	<p style="text-align: center;"><b>255</b></p>	68
2	<p style="text-align: center;"><b>55</b></p>	1.0	0.5 h	<p style="text-align: center;"><b>256</b></p>	77
3	<p style="text-align: center;"><b>54</b></p>	1.0	0.5 h	<p style="text-align: center;"><b>257</b></p>	78
4	<p style="text-align: center;"><b>234</b></p>	1.5	4 days	<p style="text-align: center;"><b>258</b></p>	65
5	<p style="text-align: center;"><b>233</b></p>	1.1	0.5 h	<p style="text-align: center;"><b>259</b></p>	66

Table 18 (cont.)

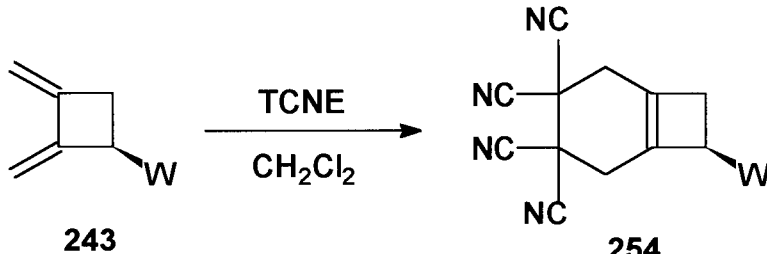
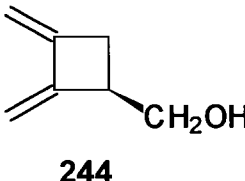
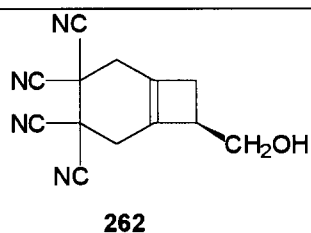
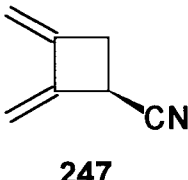
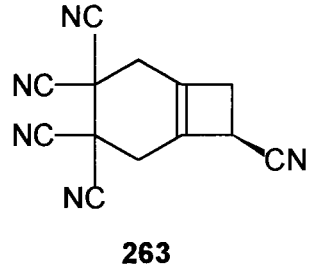
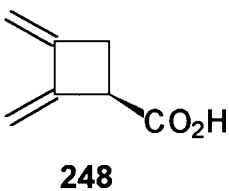
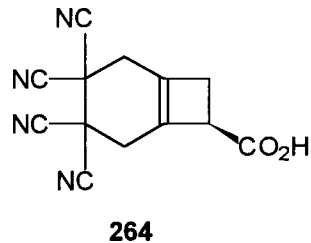
6	 <b>236</b>	1.5	4 days	 <b>260</b>	73
7	 <b>235</b>	1.0	0.5 h	 <b>261</b>	70
8	 <b>237</b>	2.0	4 days	no reaction	
9	 <b>238</b>	2.0	4 days	no reaction	

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<sup>a</sup>Yield of purified, recrystallized product.



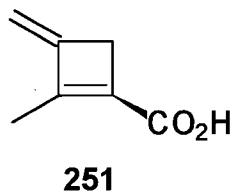
Table 19: Diels-Alder reactions of the 1-substituted-2,3-bis(methylene)cyclobutanes with tetracyanoethylene<sup>a</sup>

<div style="text-align: center;">  </div>			
Entry	Substrate	Product	Yield (%) <sup>b</sup>
1	 244	 262	73
2	 247	 263	69
3 <sup>c</sup>	 248	 264	44

<sup>a</sup>TCNE (1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 0.5 h.

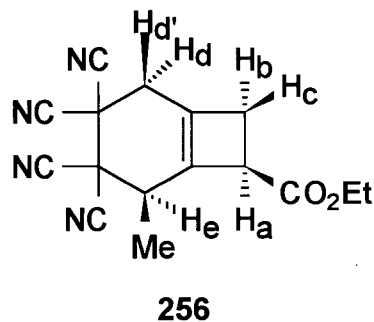
<sup>b</sup>Yield of purified, recrystallized product.

<sup>c</sup>Substrate was a 6:1 mixture of 248 and 251.



For example, the diene (**53**) was treated with TCNE (1 equiv.) in  $\text{CH}_2\text{Cl}_2$  at room temperature for 30 min. GLC analysis of the reaction mixture showed that no starting material was left. Radial chromatography and recrystallization (1:1 hexanes -  $\text{Et}_2\text{O}$ ) of the acquired solid afforded a 68% yield of the ester (**255**) as fine white crystals (melting point  $128\text{--}129^\circ\text{C}$ ).

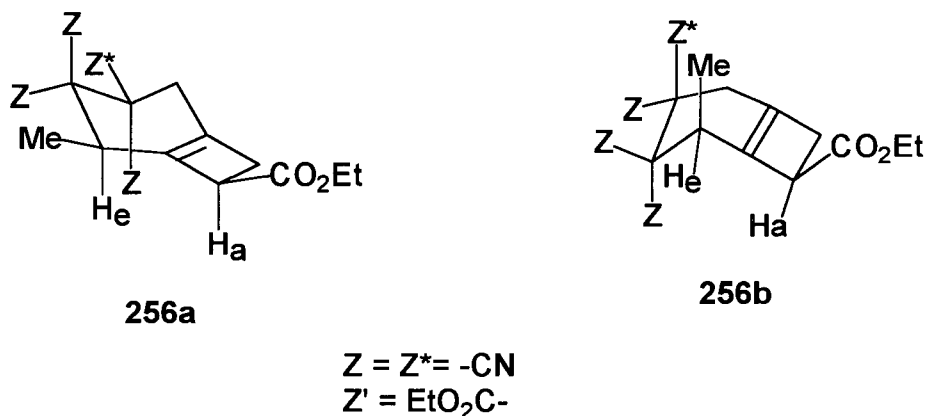
The procedures and yields were similar for the other dienes listed on Tables 18 and 19, the most notable differences being the extended reaction times required for the dienes (**234**) and (**236**) and the fact that the dienes (**237**) and (**238**) failed to react at all. This can be attributed to the number and geometry of the substituents on the diene moiety. The presence of one *cis*-substituent increases the required reaction time from 0.5 h to 4 days, presumably due to steric hindrance by the *cis*-substituent towards the approaching dienophile and the non planarity of the cisoid diene unit. In the case of dienes (**237**) and (**238**), two *cis*-substituents on the diene moiety causes the diene to be severely distorted from planarity and thus the Diels-Alder reaction cannot proceed.



The spectral data were consistent with the assigned structures and where the diene has a substituent the structure resulting from  $\alpha$ -face approach of the dienophile TCNE. For example, the IR spectrum of (**256**) displayed absorptions at  $2258\text{ cm}^{-1}$  and  $1731\text{ cm}^{-1}$ , corresponding to  $\text{C}\equiv\text{N}$  and  $\text{C}=\text{O}$  stretching frequencies, respectively. The  $^1\text{H}$  NMR spectrum of (**256**) exhibited the signals for an ethyl ester moiety (a 3-proton triplet at  $\delta$  1.27,  $J = 7\text{ Hz}$  and a 2-proton multiplet at  $\delta$  4.12-4.22), a methyl group (a 3-proton

doublet at  $\delta$  1.50,  $J = 7$  Hz), and six allylic protons. Ester (**256**) was shown to have a molecular formula of  $C_{15}H_{12}O_2N_4$  by high resolution mass spectrometry.

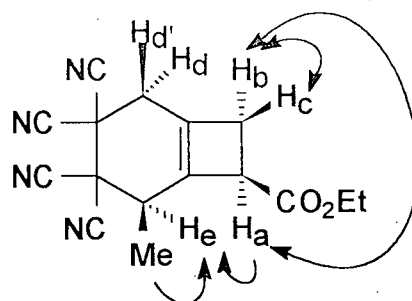
The relative configuration of each of the products (Tables 18 and 19) was considered by conformational analysis and  $^1H$  NMR data, including a series of decoupling and NOE difference experiments. For example, ester (**256**) would be expected to have two "reasonable" conformations, (**256a**) and (**256b**) where the cyclohexane ring adopts a half-chair conformation.



Of the two conformations, (**256b**) would be expected to be less stable because of the 1,3-diaxial interaction between the Me and  $Z^*$  group. Conformation (**256a**), which has the methyl group in a pseudoequatorial orientation, has no such interaction and thus would be expected to be the favoured conformation.

The proposed conformation was supported by a series of NOE difference experiments and by single crystal X-ray analysis (Figure 6). For example in a series of NOE experiments, irradiation of the methyl group at  $\delta$  1.50 led to enhancement of the signal at  $\delta$  3.27-3.32 leading one to conclude that this signal is due to proton  $H_e$ . Irradiation at  $\delta$  3.73 ( $H_a$ , which is always the more deshielded of the methine protons) led to enhancement of the signals at  $\delta$  3.27-3.32 ( $H_e$ ) and  $\delta$  2.90 ( $H_b$ ). This experiment

suggests that ester (256) has adopted conformation (256a) as a strong NOE enhancement would be expected to be observed for the axial protons  $H_e$  and  $H_a$  in (256a).



352

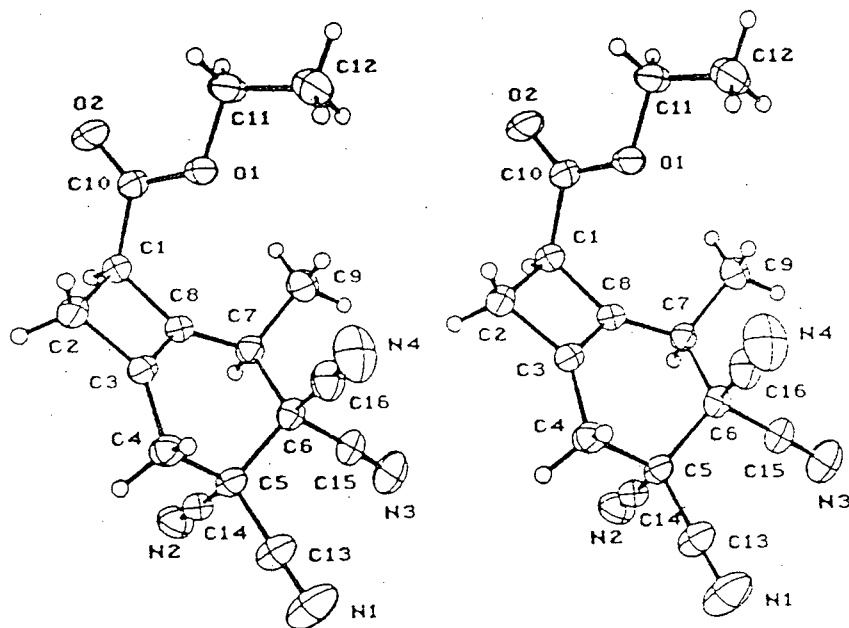
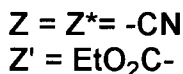
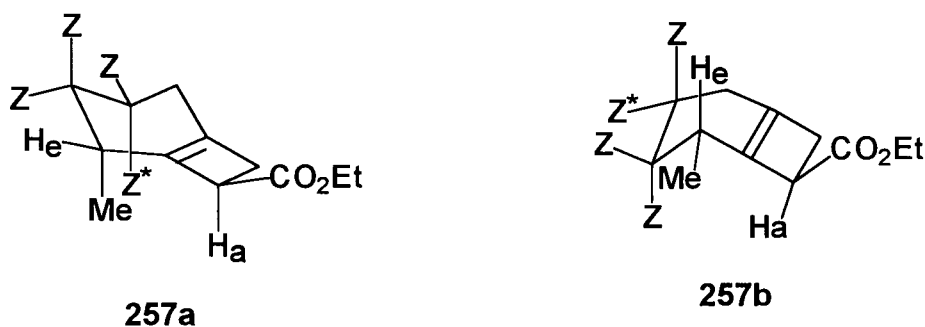


Figure 6: Stereoview of ester (256)

In a similar fashion Diels-Alder adducts (257-261) were prepared, and conformations analyzed on the basis of  $^1\text{H}$  NMR data and a series of decoupling and NOE difference experiments. Unlike compound (256) where single crystal X-ray analysis could support the assigned conformation in the solid state, irrefutable evidence supporting one product conformation for adducts (257-261) was not obtained. For example, ester (257) would be expected to have two "reasonable" conformations, (257a) and (257b) where the cyclohexane ring adopts a half-chair conformation.



Of the two conformations, (257a) would be expected to be less stable because of the 1,3-diaxial interaction between the Me and  $Z^*$  group. Conformation (257b), which has the methyl group in a pseudoequatorial orientation, has no such interaction and thus would be expected to be the favoured conformation. Ester (257), as do all of compounds (256-261), exhibit a  $^1\text{H}$  NMR spectrum complicated by the fact that almost all of the signals are multiplets i.e. ( $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.28 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.57 (d, 3H,  $J = 7$  Hz,  $-\text{CHCH}_3$ ), 2.82-2.88 (m, 1H,  $\text{H}_c$ ), 2.93-3.00 (m, 1H,  $\text{H}_b$ ), 3.09-3.20 (m, 2H,  $\text{H}_d$ ), 3.31-3.40 (m, 1H,  $\text{H}_e$ ), 3.74-3.78 (m, 1H,  $\text{H}_a$ ), 4.18 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ )). A series of decoupling experiments were performed and proved useful in determining which protons were coupled together, however, most of the original multiplets were only sharpened rather than being resolved. In a series of NOE difference

experiments irradiation of the signal at  $\delta$  1.57 ( $-\text{CHCH}_3$ ) led to enhancement of the signals at  $\delta$  3.31-3.40 ( $\text{H}_e$ ) and  $\delta$  3.74-3.78 ( $\text{H}_a$ ) while irradiation of the signal at  $\delta$  3.36 ( $\text{H}_e$ ) led to the enhancement of the signal at  $\delta$  1.57 ( $-\text{CHCH}_3$ ). Irradiation of the signal at  $\delta$  3.76 ( $\text{H}_a$ ) led to the enhancement of the signals at  $\delta$  1.57 ( $-\text{CHCH}_3$ ) and  $\delta$  2.93-3.00 ( $\text{H}_b$ ). These NOE difference experiments might suggest that ester (257) adopts the conformation (257a) where the methyl group and  $\text{H}_a$  are in a pseudoaxial orientation and a strong NOE enhancement should be observed. Closer inspection of a molecular model of (257b), however, reveals that the methyl group and  $\text{H}_a$  are still relatively close together in proximity and an NOE enhancement between these groups would be expected.

Thus without any conclusive evidence, it was assumed that in each case, the half chair conformation in which the alkyl group adopts a pseudoequatorial orientation was preferred due to steric factors (Figure 7).

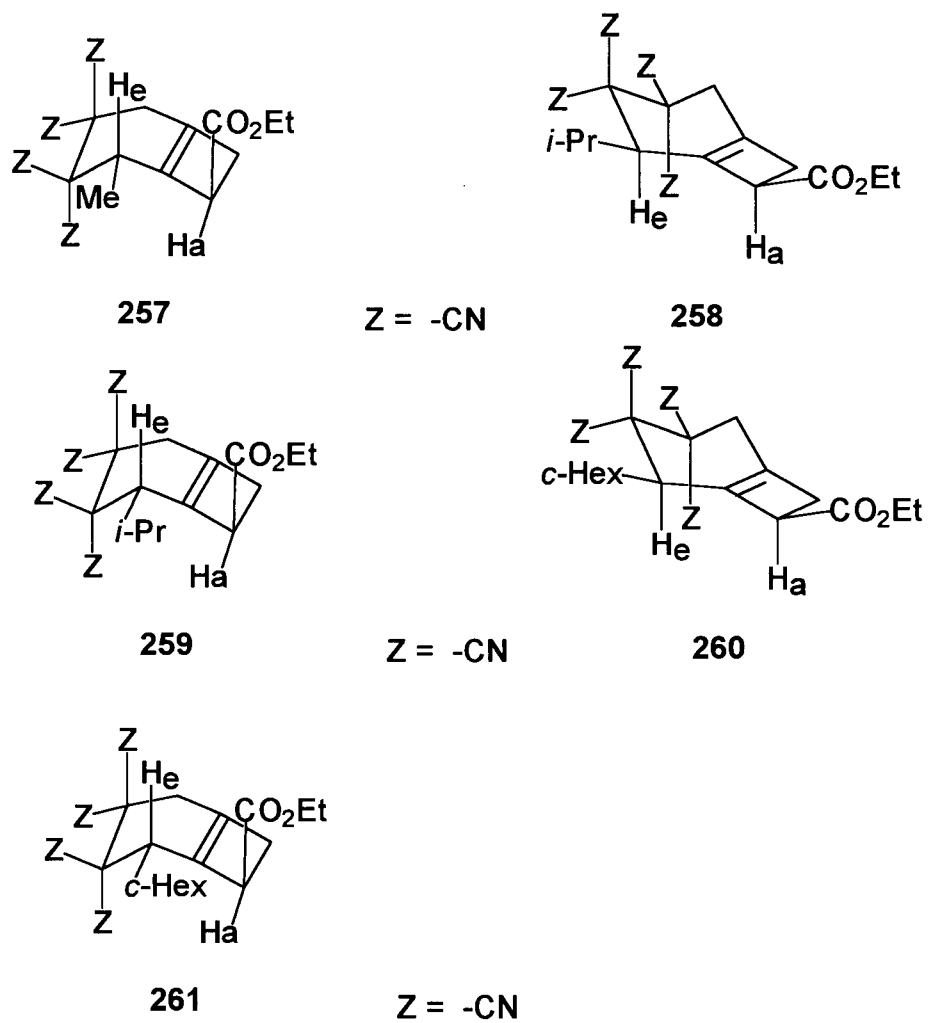


Figure 7: Favoured half-chair conformations of the Diels-Alder adducts (257-261).

#### 4.2 Diels-Alder reactions of dienes with methyl vinyl ketone (MVK)

It has been reported previously in this laboratory that, under thermal conditions, Diels-Alder reactions of some 1,2-bis-exocyclic dienes with dienophiles is neither stereo- nor regioselective.<sup>16</sup> Previous experimentation has shown that addition of a Lewis acid, such as  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , to the Diels-Alder reaction improves the stereo- and regioselectivity of the Diels-Alder reaction as well as the rate of reaction.<sup>16,73</sup> This effect of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  on these Diels-Alder reactions can be rationalized using frontier molecular orbital theory.<sup>73, 75-77</sup> In the Diels-Alder reaction, the principle interaction is between the HOMO of the diene and the LUMO of the dienophile (Figure 8). The energy difference between these two orbitals governs the overall rate of the Diels-Alder reaction. Addition of a Lewis acid such as  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , which co-ordinates with the carbonyl group of the dienophile, lowers the energy of the HOMO and LUMO orbitals of the dienophile. This makes the HOMO (diene)  $\rightarrow$  LUMO (dienophile) transition less energetic and thus increases the rate of the reaction.

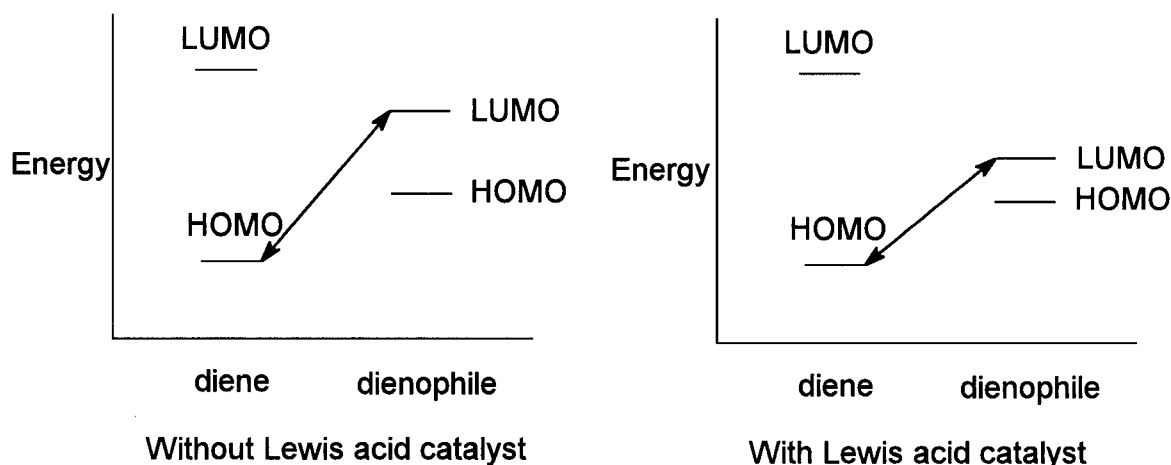


Figure 8: The effect of a Lewis acid on the energies of the HOMO and LUMO of the dienophile in the Diels-Alder reaction.



Addition of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to MVK also causes the LUMO of the MVK to have greater polarization, with the  $\alpha$ -carbon and the  $\beta$ -carbon having orbitals with larger and smaller co-efficients as compared to those of uncoordinated MVK (Figure 9). This increased polarization in MVK increases the regioselectivity of the reaction.

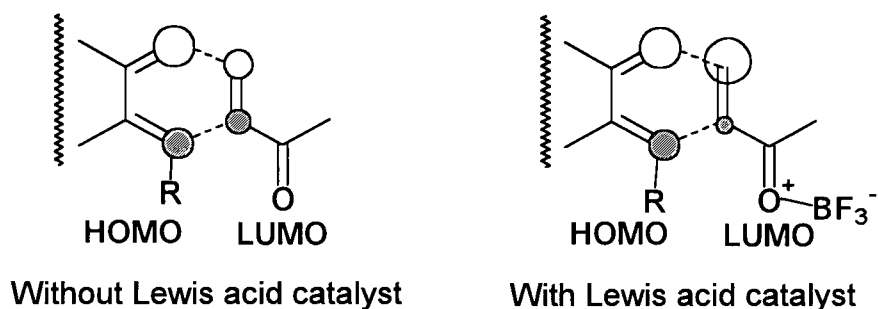


Figure 9: Orbitals showing the increased polarization of the LUMO of the double bond in the dienophile in the Lewis acid catalyzed Diels-Alder reaction

Finally, the endo selectivity of the Diels-Alder reactions (from secondary orbital interactions) is greatly enhanced because of an increase in the LUMO coefficient of the carbonyl carbon atom (Figure 10).

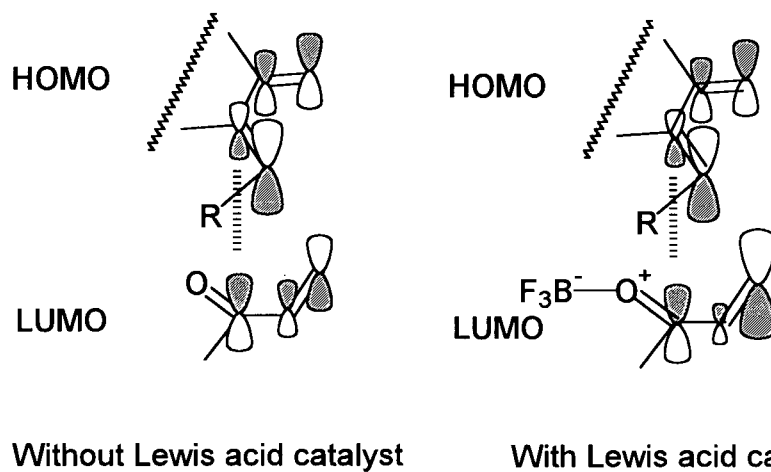
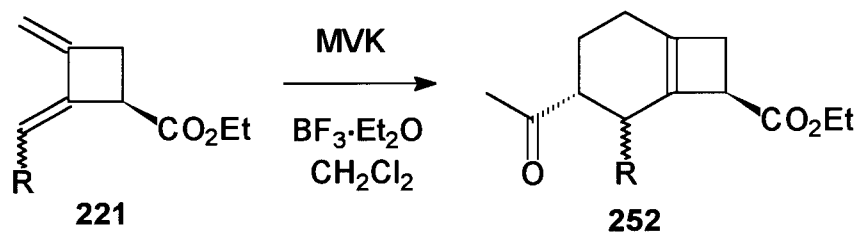


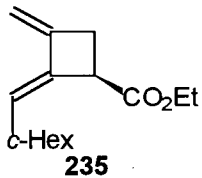
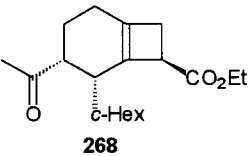
Figure 10: Frontier orbitals showing the increased secondary orbital interaction in the Lewis-acid catalyzed Diels-Alder reaction

Therefore  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was chosen as a Lewis acid catalyst for the Diels-Alder reactions of the cyclobutanecarboxylates (**221**) with MVK. The results of the reactions are summarized in Table 20. The stereochemistry of each of the products was assigned on the basis of  $^1\text{H}$  NMR data and a series of decoupling and NOE experiments.

Table 20: Diels-Alder reactions of the cyclobutanecarboxylates **221** with MVK<sup>a</sup>

Entry	Substrate	Reaction Time	Product	Yield (%) <sup>b</sup>
1	<p style="text-align: center;"><b>55</b></p>	3 h	<p style="text-align: center;"><b>14</b></p>	58%
2	<p style="text-align: center;"><b>54</b></p>	1.5 h	<p style="text-align: center;"><b>11</b></p>	88%
3	<p style="text-align: center;"><b>234</b></p>	8 h <sup>c</sup>	<p style="text-align: center;"><b>265</b></p>	50%
4	<p style="text-align: center;"><b>233</b></p>	2 h	<p style="text-align: center;"><b>266</b></p>	84%
5	<p style="text-align: center;"><b>236</b></p>	8 h <sup>c</sup>	<p style="text-align: center;"><b>267</b></p>	75%

Table 20 (cont.)

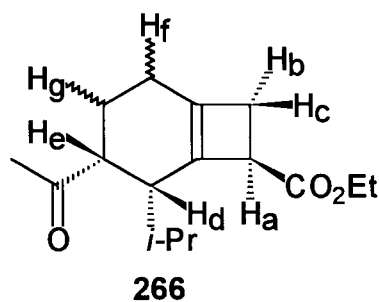
6	 235	3.5 h	 268	87%
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<sup>a</sup>MVK (5 equiv.),  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv.),  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$

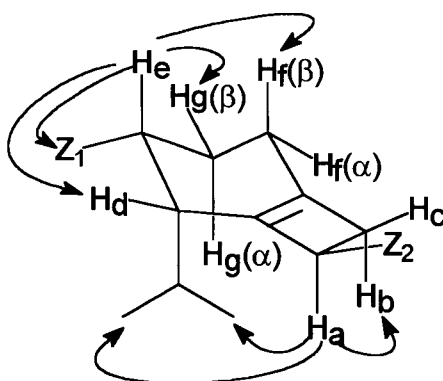
<sup>b</sup>Yield of purified product that had been kept under reduced pressure (vacuum pump) for 2 h.

<sup>c</sup>The reaction temperature was  $-48^\circ\text{C}$  for this reaction.

For example, addition of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv.) to a mixture of (233) and MVK (5 equiv.) in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ , followed by a reaction time of 2 h, work-up and radial chromatography, gave an 84% yield of (266) (Table 20, Entry 4). The  $^1\text{H}$  NMR spectrum of (266) displayed the expected signals for an isopropyl group (two 3-proton doublets at  $\delta$  0.82 and  $\delta$  0.92,  $J = 7$  Hz and a 1-proton multiplet at  $\delta$  1.57-1.65), an ethyl ester moiety (a 3-proton triplet at  $\delta$  1.26,  $J = 7$  Hz and a 2-proton multiplet at  $\delta$  4.15) and a methyl ketone moiety (a 3-proton singlet at  $\delta$  2.15).



Other assigned protons included:  $H_a$ , a 1-proton multiplet at  $\delta$  3.62-3.67;  $H_b$ , a 1-proton multiplet at  $\delta$  2.72-2.78;  $2 \times H_f$ , a 2-proton multiplet at  $\delta$  1.95-2.01; one of  $H_g$ , a 1-proton multiplet at  $\delta$  1.75-1.85; one of  $H_g$ , a 1-proton multiplet at  $\delta$  1.85-1.94; and  $H_c$  and  $H_d$ , a 2-proton multiplet at  $\delta$  2.50-2.59. These spectral assignments were confirmed by a series of decoupling and NOE experiments. Only the key data required to determine the orientation of the isopropyl group will be reported here. Complete decoupling and NOE data can be found on page 221 of the experimental. In the decoupling experiments, irradiation at  $\delta$  1.60 ( $-\underline{CH}(\underline{CH}_3)_2$ ) converted the doublets at  $\delta$  0.82 (one of  $-\underline{CH}(\underline{CH}_3)_2$ ) and  $\delta$  0.92 (one of  $-\underline{CH}(\underline{CH}_3)_2$ ) into singlets; irradiation at  $\delta$  2.55 ( $H_c$ ,  $H_d$ ) simplified the multiplet at  $\delta$  2.80-2.87 ( $H_e$ ) into a doublet of doublets,  $J = 9, 3$  Hz [thus,  $J_{HeHg(\alpha)} = 9$  Hz and  $J_{HeHg(\beta)} = 3$  Hz]. Irradiation at  $\delta$  1.80 (one of  $H_g$ ) converted the multiplet at  $\delta$  2.80-2.87 ( $H_e$ ) into a doublet of doublets ( $J = 9, 6$  Hz) [thus,  $J_{HeHd} = 6$  Hz].



266

$Z_1 = \text{CH}_3\text{CO}$

$Z_2 = \text{EtO}_2\text{C}-$

In a series of NOE difference experiments, irradiation at  $\delta$  3.65 ( $H_a$ ) caused enhancement of the signals at  $\delta$  0.82 (one of  $-\underline{CH}(\underline{CH}_3)_2$ ),  $\delta$  0.92 (one of  $-\underline{CH}(\underline{CH}_3)_2$ ),  $\delta$  1.26 ( $-\text{OCH}_2\underline{\text{CH}}_3$ ) and  $\delta$  2.72-2.78 ( $H_b$ ) as depicted in the diagram above. Thus, the isopropyl group is *cis* to the proton  $H_a$  and adopts a pseudoaxial orientation. If this is

true, then proton  $H_e$  should assume a pseudoaxial orientation. This is supported by the NOE experiments. Saturation of the signal at  $\delta$  2.82 ( $H_e$ ) caused enhancement of the signals at  $\delta$  1.75-1.85 ( $H_g(\beta)$ ),  $\delta$  1.95-2.01 ( $H_f(\beta)$ ),  $\delta$  2.15 ( $CH_3CO-$ ), and  $\delta$  2.54-2.59 ( $H_d$ ). There is also confirmation of the proposed conformation of (266) from the coupling constant between protons  $H_e$  and  $H_g(\alpha)$  ( $J = 9$  Hz). Thus, in summary, it is demonstrated that the isopropyl group is *cis* to the proton  $H_a$  and that the cyclohexene ring of (266) adopts a half-chair conformation with both the proton  $H_e$  and the isopropyl group in pseudoaxial orientations.

The IR spectrum of (266) showed absorptions at 1731 and 1709  $cm^{-1}$  for the stretching frequencies of the two different carbonyl groups. High resolution mass spectrometry confirmed that compound 266 has a molecular formula of  $C_{16}H_{24}O_3$ .

Similar conformational analyses were performed on the other cycloaddition products (11, 14, 265, 267, 268, Table 26) to determine the relative stereochemistry and orientation of the alkyl group of these compounds. The results are summarized in Figures 11-15 showing key data from decoupling and NOE experiments and the conformation of each compound. In each case except for (14) the alkyl substituent on C-5 adopts a pseudoaxial orientation. For esters (265) and (267) this is due presumably to minimize the steric repulsion between the alkyl substituent and the neighbouring acetyl group. For compound (14) the conformation where both the acetyl and methyl group adopt a pseudoequatorial orientation is favoured. Presumably the steric repulsion between the acetyl and methyl group is of less consequence than the 1,3-diaxial interactions which would occur between  $H_f$  and the Me group on (14) if the Me group adopted a pseudoaxial orientation. Support for these conformational assignments has appeared in a paper by Houk<sup>78</sup> where MM2 calculations were performed to determine the most stable reactant conformations and orientation (pseudoaxial or pseudoequatorial) of the R group on esters (255-259), (11), (14) and (265-266). The computational results were in agreement with the experimental results for all compounds except for (265). For ester (265), Houk

predicted that the pseudoequatorial orientation of the  $\beta$ -*i*-Pr group would be preferred over the pseudoaxial orientation.<sup>78</sup> Houk doesn't have a clear explanation for why experimentally the  $\beta$ -*i*-Pr group is in a pseudoaxial orientation, but he suggests that steric repulsion between the *i*-Pr group and neighbouring acetyl group (when both substituents are in a pseudoequatorial orientation) promotes the pseudoaxial orientation of the  $\beta$ -*i*-Pr group.

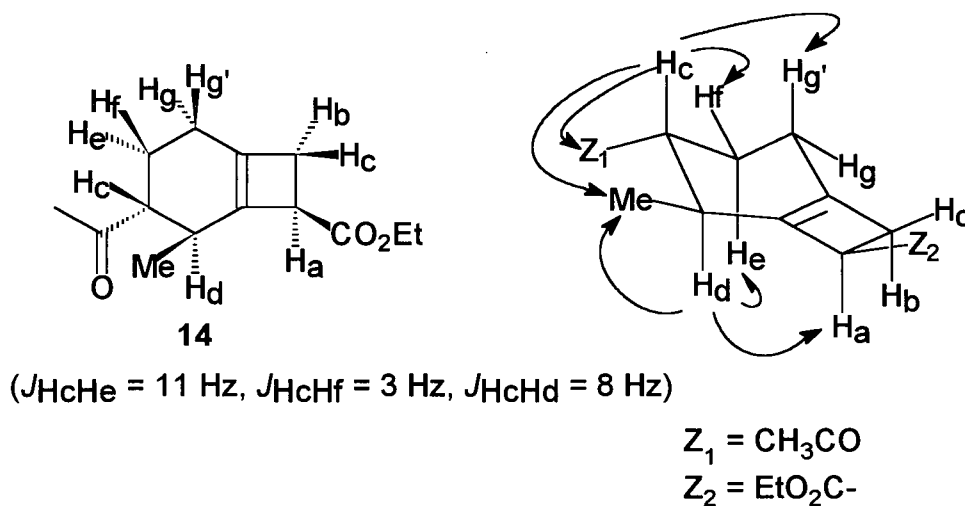


Figure 11: Relative configuration and preferred conformation of ester (14).

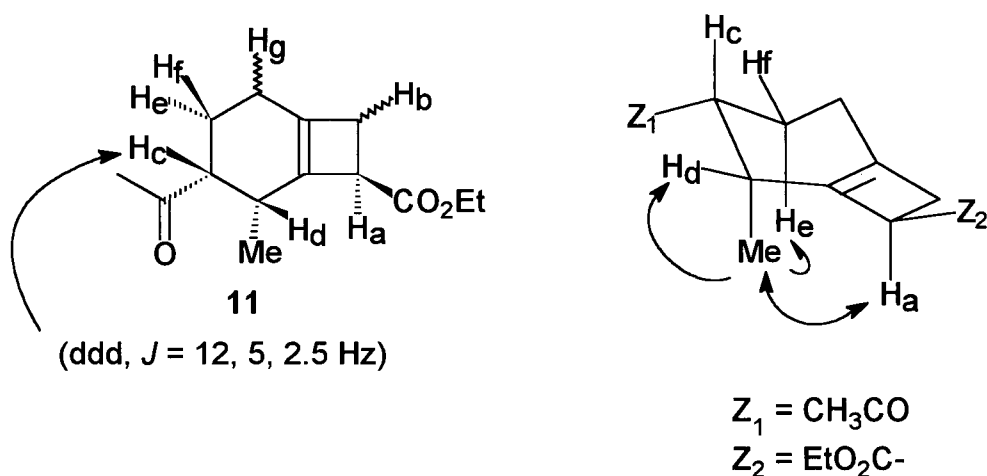


Figure 12: Relative configuration and preferred conformation of ester (11).

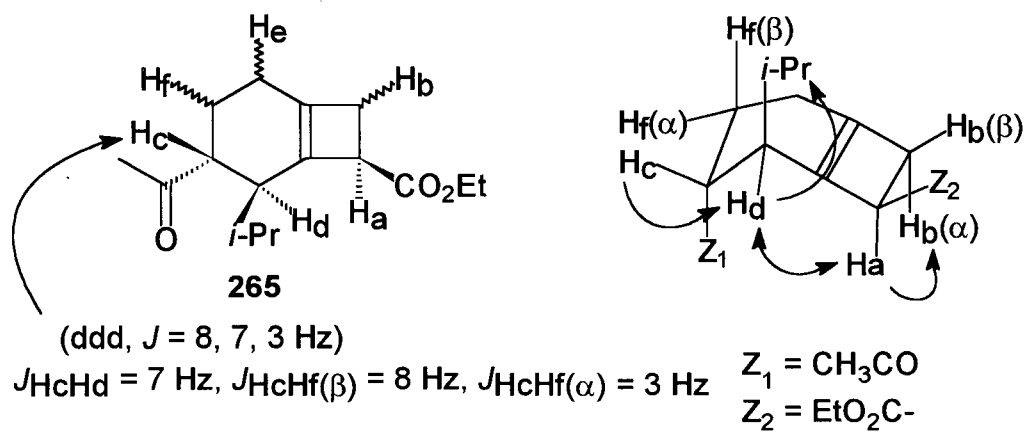


Figure 13: Relative configuration and preferred conformation of ester (265).

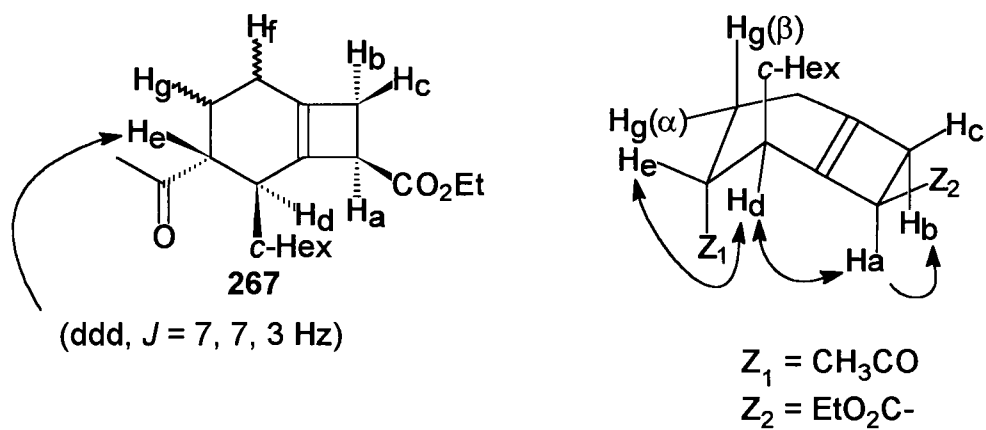


Figure 14: Relative configuration and preferred conformation of ester (267).



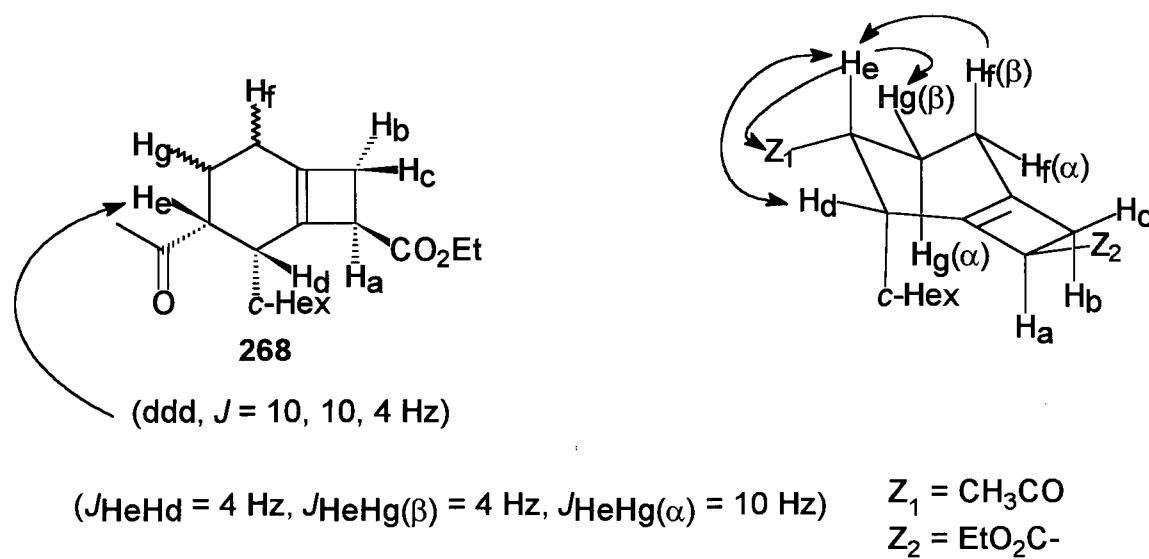
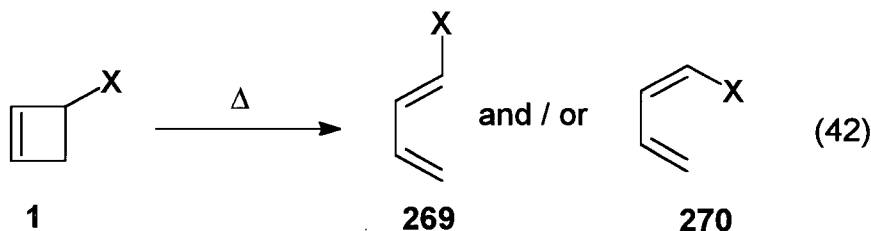


Figure 15: Relative configuration and preferred conformation of ester (268).

## 5. Thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes

### 5.1 Introduction

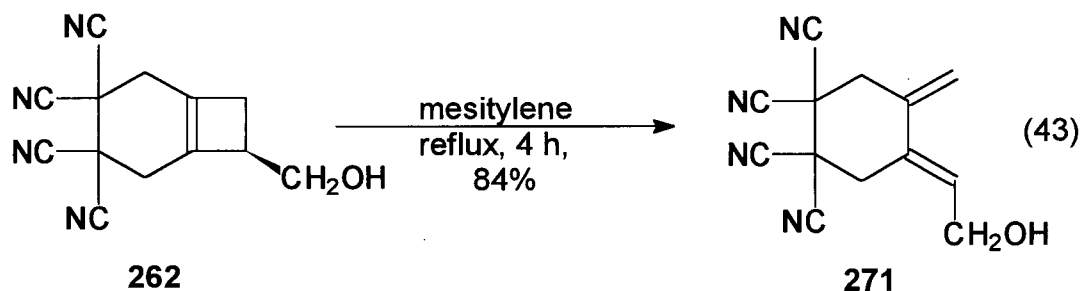


Thermolysis of cyclobutene results in an electrocyclic ring opening to produce 1,3-butadiene. This process proceeds *via* a thermally-allowed conrotatory pathway.<sup>1</sup> The C-3 substituted cyclobutene (**1**) can open *via* one or both of two conrotatory pathways to give one or both of the "inward" (**270**) or "outward" (**269**) rotation products (Equation 42). Houk proposed that it was the electronic nature of certain substituents that determines the direction of rotation (inward or outward) of the substituent.<sup>12-15</sup> Based upon *ab initio* calculations, Houk predicted that groups that are good electron donors should prefer outward rotation while strongly electron withdrawing groups that are good electron acceptors should favour inward rotation.<sup>13</sup> From the work described above, a variety of bicyclo[4.2.0]oct-1(6)-enes with different C-7 substituents ( $-\text{CH}_2\text{OH}$ ,  $\text{CO}_2\text{Et}$ ,  $\text{CO}_2\text{H}$ ,  $\text{CN}$ ) were available and thus the thermal ring opening reaction of the substrates could be investigated.

### 5.2 Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes

It is well known that cyclobutenes (**1**) in which **X** is a methyl or substituted methyl afforded exclusively the outward rotation product (**269**). Computations by Houk have predicted that, when  $\text{W} = \text{CH}_3$  outward rotation should be favoured by 5.3 kcal/mol.<sup>79</sup> Houk interprets this as a steric effect which, in part, involves repulsion between the filled

orbital of the methyl and  $\delta$  orbital of the breaking bond.<sup>79</sup> Thus, we would expect substrate (262), which has a  $\text{CH}_2\text{OH}$  substituent, to undergo ring opening to give exclusively the product resulting from outward rotation (Equation 43).

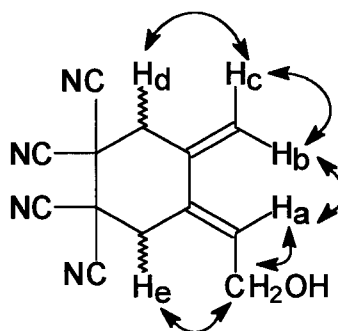


A solution of (262) in dry mesitylene was refluxed at 165°C for 4 h under an argon atmosphere. Analysis of the crude reaction mixture by GLC and TLC indicated that only one product had been formed. The reaction mixture was cooled to room temperature and the mesitylene was removed by radial chromatography on silica gel. The  $^1\text{H}$  NMR spectrum of the crude product confirmed that only diene (271) had been produced. Recrystallization (1:1 pet. ether:ether) afforded an 84% yield of (271) as colourless crystals (m.p. 118-119°C).

The spectral data for (271) was in accord with the assigned structure. The  $^1\text{H}$  NMR spectrum of (271) displayed the expected signals for a  $-\text{CH}_2\text{OH}$  group (a 1-proton broad singlet at  $\delta$  1.55 and a 2-proton doublet at  $\delta$  4.32,  $J = 7$  Hz), two allylic methylene groups (two 2-proton singlets at  $\delta$  3.15 and  $\delta$  3.34, respectively), and three olefinic protons ( $\text{H}_\text{c}$  and  $\text{H}_\text{b}$ , two 1-proton singlets at  $\delta$  5.20 and 5.42, respectively, and  $\text{H}_\text{a}$ , a 1-proton triplet at  $\delta$  6.13,  $J = 7$  Hz). The geometry of (271) was assigned on the basis of NOE difference experiments. Thus, irradiation at  $\delta$  3.15 ( $\text{H}_\text{d}$ ) caused enhancement of the signal at  $\delta$  5.20 ( $\text{H}_\text{c}$ ) while irradiation at  $\delta$  3.34 ( $\text{H}_\text{e}$ ) caused enhancement of the signal at  $\delta$  4.32 ( $-\text{CH}_2\text{OH}$ ). Irradiation at  $\delta$  4.32 ( $-\text{CH}_2\text{OH}$ ) caused enhancement of the signals at  $\delta$  3.34 ( $\text{H}_\text{e}$ ) and  $\delta$  6.13 ( $\text{H}_\text{a}$ ) while irradiation at  $\delta$  5.20 ( $\text{H}_\text{c}$ )

caused enhancement of the signals at  $\delta$  3.15 ( $H_d$ ) and  $\delta$  5.42 ( $H_b$ ). Irradiation at  $\delta$  5.42 ( $H_b$ ) caused enhancement of the signals at  $\delta$  5.20 ( $H_c$ ) and  $\delta$  6.13 ( $H_a$ ) while irradiation at  $\delta$  6.13 ( $H_a$ ) caused enhancement of the signals at  $\delta$  4.32 ( $-\underline{C}H_2OH$ ) and  $\delta$  5.42 ( $H_b$ ).

These experiments are summarized in the formula (271) given below.



271

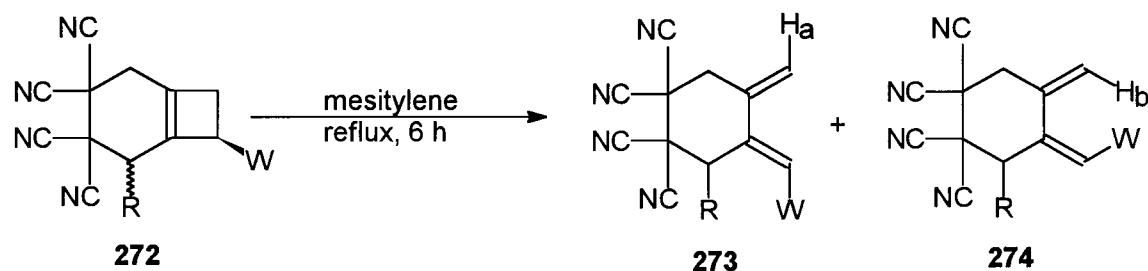
Using a procedure similar to that reported above, the bicyclo[4.2.0]oct-1(6)-enes (255-262) (Table 21) and (11, 14, 265-268) (Table 22) were thermolyzed. The ratio of the products was determined by  $^1H$  NMR analysis on the crude product by integration of the signals  $H_a$  on the outward rotation (273 or 25) and  $H_b$  on the inward rotation (274 or 26) isomers (Tables 21 and 22). The signals  $H_a$  and  $H_b$  on (273, 274, 25 and 26) were chosen as they were well resolved from other signals in the  $^1H$  NMR spectrum of the mixture, often appeared as broad singlets, and had chemical shifts close enough to each other such that the integration ratios were more accurate. To confirm that these integration ratios were accurate, spectra were often replotted and reintegrated and the ratios of other distinct signals belonging to the inward and rotation isomers in the  $^1H$  NMR of the crude mixture were determined and compared with the ratio of  $H_a$  to  $H_b$ . To confirm that the thermolysis products were stable under the reaction conditions employed, a small sample of each of the purified products (273 or 25) and (274 or 26) were heated separately as a  $C_6D_6$  solution in a sealed glass tube. After being subjected

to thermolysis conditions the  $^1\text{H}$ -NMR spectrum of each product was examined. There was no indication of product rearrangement and thus each of the thermolysis products was found to be stable under the conditions employed.

For example, in one experiment, the ester (258) (Table 21, Entry 4) was thermolyzed and the solvent was removed to give a crude product. Integration of the signals due to  $\text{H}_a$  (a 1-proton broad singlet at  $\delta$  5.35) in (279) and  $\text{H}_b$  (a 1-proton broad singlet at  $\delta$  5.30) in (280) in the  $^1\text{H}$  NMR spectrum of this material showed that the outward (279) to inward (280) rotation isomers had been produced in a ratio of 1:1.5. The crude product was subjected to radial chromatography on silica gel to give the separated outward and inward rotation products in yields of 32 percent and 44 percent, respectively.

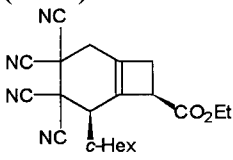
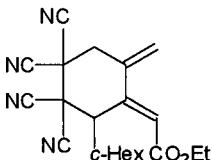
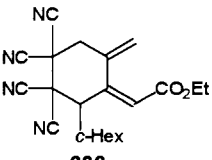
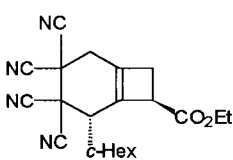
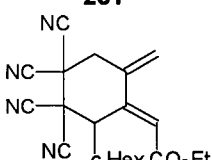
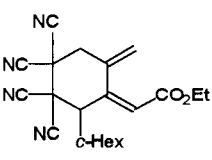
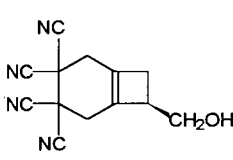
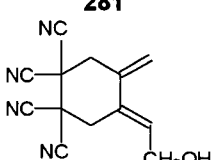
The experimental procedure and overall yields of both isomers were similar of the other experiments summarized in table 21. For example, the ester (259) (Table 21, Entry 4) was thermolyzed and the solvent was removed to give a crude product. Integration of the signals due to  $\text{H}_a$  (a 1-proton broad singlet at  $\delta$  5.35) in (279) and  $\text{H}_b$  (a 1-proton broad singlet at  $\delta$  5.30) in (280) in the  $^1\text{H}$  NMR spectrum of this material showed that the outward (279) to inward (280) rotation isomers had been produced in a ratio of 1:1.6. The crude product was subjected to radial chromatography on silica gel to give the separated outward and inward rotation products in yields of 27 percent and 41 percent, respectively.

Table 21: Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes (**272**)



Entry	Substrate	Outward Rotation Product <b>273</b>	Inward Rotation Product <b>274</b>	<sup>1</sup> H NMR ratio <sup>a</sup> <b>273:274</b>	Yield (%) <sup>b, c</sup>	
					<b>273</b>	<b>274</b>
1 <sup>d</sup>				18:1	80	5
	<b>255</b>	<b>275</b>	<b>276</b>			
2 <sup>e</sup>				2.6:1	53	21
	<b>256</b>	<b>277</b>	<b>278</b>			
3 <sup>e</sup>				4.3:1	56	14
	<b>257</b>	<b>277</b>	<b>278</b>			
4				1:1.5	32	44
	<b>258</b>	<b>279</b>	<b>280</b>			
5				1:1.6	27	41
	<b>259</b>	<b>279</b>	<b>280</b>			

Table 21 (cont.)

6	 <b>260</b>	 <b>281</b>	 <b>282</b>	1:1.2	32	39
7	 <b>261</b>	 <b>281</b>	 <b>282</b>	1:1.3	36	51
8	 <b>262</b>	 <b>271</b>		>99:1	84	0

<sup>a</sup>The ratio of the products was determined directly by the integration of the signals due to H<sub>A</sub> and H<sub>B</sub> (formulas 273 and 274).

<sup>b</sup>Yield of purified, recrystallized product.

<sup>c</sup>Each of the products was found to be stable under the thermolysis conditions employed.

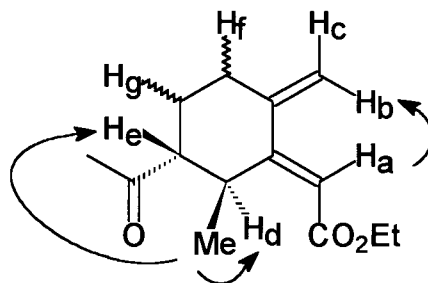
<sup>d</sup>A modified procedure where a reaction temperature of 145°C and a time of 3.5 h was used.

<sup>e</sup>A modified procedure where the reaction time was 4 hours was used.

Each of the experiments in Table 22 was carried out in a fashion similar to that in Table 22. For example, a solution of compound (14) in dry mesitylene was heated to 165°C and refluxed for 4 h under argon atmosphere (Table 22, Entry 1). The mesitylene was removed by radial chromatography and the  $^1\text{H}$  NMR spectrum of the crude product showed a ratio of outward rotation diene (15) to inward rotation diene (16) of 1:1. The mixture was again subjected to radial chromatography and trace amounts of solvent removed (vacuum pump) from the acquired liquids to give dienes (15) and (16) in 37% and 38% yields, respectively.

Other experiments in Table 22 gave similar overall yields ranging from 67 percent (Entry 2) to 87 percent (Entry 5). In each case, all of the products were fully characterized. Stereochemical assignments were made by  $^1\text{H}$  NMR spectroscopy, primarily NOE difference experiments.

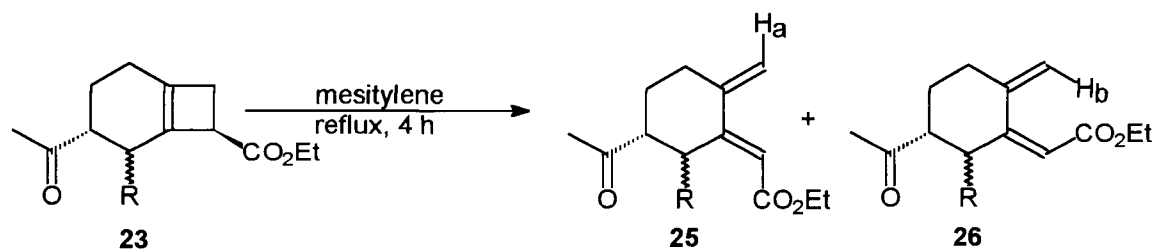
For example, the spectral data for (15) and (16) were in accord with the assigned structures.



15

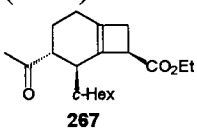
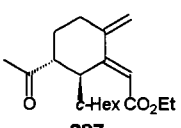
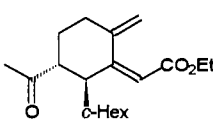
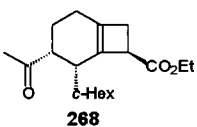
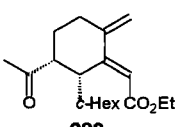
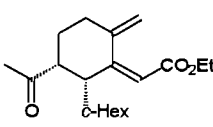


**Table 22: Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)-enes (23)**



Entry	Substrate (23)	Outward Rotation Product (25)	Inward Rotation Product (26)	<sup>1</sup> H NMR Ratio <sup>a</sup> 25:26	Yield (%) <sup>b, c</sup>	
					25	26
1				1:1	37	38
2				11.5:1	61	6
3				1:2.2	25	60
4				3.9:1	68:18	

Table 22 (cont.)

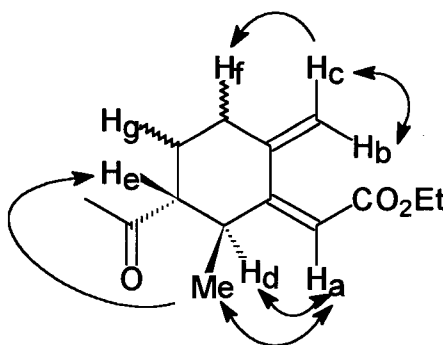
5	 267	 287	 288	1:2.6	25	62
6	 268	 289	 290	4:1	67	17

<sup>a</sup>The ratio of products was determined directly by the integration of the signals due to H<sub>A</sub> and H<sub>B</sub> (formulas 25 and 26).

<sup>b</sup>Yield of purified product that had been kept under a vacuum pump for 2 h.

<sup>c</sup>Each of the products was found to be stable under the thermolysis conditions employed.

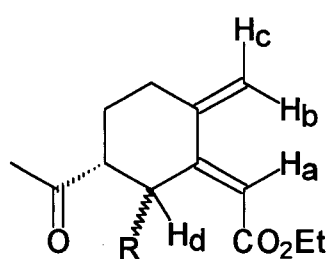
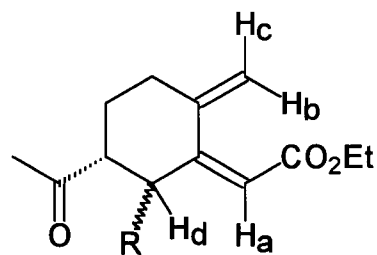
The  $^1\text{H}$  NMR spectrum of (15) exhibited the signals for three olefinic protons ( $\text{H}_a$ , a 1-proton singlet at  $\delta$  5.80;  $\text{H}_b$ , a 1-proton doublet of doublets at  $\delta$  5.00,  $J = 2, 2$  Hz; and  $\text{H}_c$ , a 1-proton doublet at  $\delta$  4.83,  $J = 2$  Hz). The signal due to  $\text{H}_d$  (a 1-proton broad quartet,  $J = 7$  Hz) was observed at  $\delta$  4.52, suggesting that it is in the deshielding cone of the carbonyl group of the ester moiety and that the double bond must have an (*E*)-geometry. The assigned stereochemistry of (15) was consistent with  $^1\text{H}$  NMR NOE difference experiments. Thus, irradiation at  $\delta$  1.15 ( $-\text{CHCH}_3$ ) caused enhancement of the signals at  $\delta$  2.50-2.55 ( $\text{H}_e$ ) and  $\delta$  4.52 ( $\text{H}_d$ ) and irradiation at  $\delta$  5.80 ( $\text{H}_a$ ) caused enhancement of the signal at  $\delta$  5.00 ( $\text{H}_b$ ).



16

The  $^1\text{H}$  NMR spectrum of (16) was similar to, but slightly different from, that of (15). Most notably, the chemical shift of  $\text{H}_d$  (a 1-proton multiplet) appeared at  $\delta$  2.60-2.65, which suggests the double bond had a (*Z*)-geometry. The order of the chemical shifts of the three olefinic protons in (16) was slightly different from those of (15). In (16), the chemical shifts of  $\text{H}_a$  (a 1-proton doublet,  $J = 2$  Hz),  $\text{H}_b$  (a 1-proton broad singlet) and  $\text{H}_c$  (a 1-proton broad singlet) were  $\delta$  5.59,  $\delta$  4.80, and  $\delta$  4.91 ppm respectively. Thus we see that though  $\text{H}_a$  remains as the most downfield proton,  $\text{H}_b$  is

now upfield of  $H_C$  as compared to outward rotation diene (15). The two differences in the  $^1H$  NMR spectra of the outward rotation (15) and inward rotation (16) isomers were also observed with other pairs of thermolyses products and the results are summarized in Table 15. The assigned stereochemistry of (16) was consistent with  $^1H$  NMR NOE difference experiments. Thus, irradiation at  $\delta$  1.0 ( $-CHCH_3$ ) caused enhancement of the signals at  $\delta$  2.45 ( $H_E$ ),  $\delta$  2.60-2.65 ( $H_D$ ), and  $\delta$  5.59 ( $H_A$ ) while irradiation at  $\delta$  2.60 ( $H_D$ ) caused enhancement of the signals at  $\delta$  1.60-1.70 (one of  $H_G$ ),  $\delta$  1.00 ( $-CHCH_3$ ) and  $\delta$  5.59 ( $H_A$ ). Irradiation at  $\delta$  4.78 ( $H_B$ ) caused enhancement of the signal at  $\delta$  4.91 ( $H_C$ ) while irradiation at  $\delta$  4.91 ( $H_C$ ) caused enhancement of the signals at  $\delta$  4.80 ( $H_B$ ) and  $\delta$  2.49 (one of  $H_F$ ). Irradiation of  $\delta$  5.59 ( $H_A$ ) caused enhancement of the signals at  $\delta$  2.60-2.65 ( $H_D$ ) and  $\delta$  1.00 ( $-CHCH_3$ ).

Table 23: Partial  $^1\text{H}$  NMR Data for dienes (291) and (292)**291****292**

Entry	Outward Rotation Diene (291)	Inward Rotation Diene (292)	R	$\delta$ of $\text{H}_d$	$\delta$ of $\text{H}_a$	$\delta$ of $\text{H}_b$	$\delta$ of $\text{H}_c$
1	15		$\beta$ -Me	4.52	5.80	5.00	4.83
2		16	$\beta$ -Me	2.60- 2.65	5.59	4.80	4.91
3	12		$\alpha$ -Me	4.54- 4.63	5.79	5.00	4.87
4		13	$\alpha$ -Me	2.90- 2.98	5.72	4.86	5.05
5	283		$\beta$ - <i>i</i> -Pr	4.08- 4.17	5.83	4.91	4.76
6		284	$\beta$ - <i>i</i> -Pr	2.26- 2.33	5.59	4.80	4.96
7	285		$\alpha$ - <i>i</i> -Pr	4.43	5.81	4.95	4.82
8		286	$\alpha$ - <i>i</i> -Pr	2.49- 2.55	5.68	4.87	5.02

Table 23 (cont.)

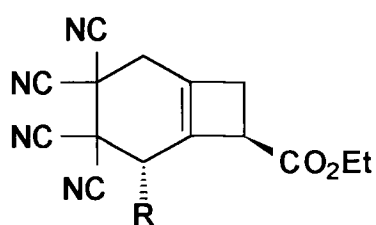
9	287	$\beta$ -c-Hex	4.18	5.83	4.88	4.75
10	288	$\beta$ -c-Hex	2.38	5.53	4.77	4.94
11	289	$\alpha$ -c-Hex	4.48	5.82	4.93	4.83
12	290	$\alpha$ -c-Hex	2.48-	5.66	4.85	5.03
			2.62			

### 5.3 Small Scale Thermal Ring Opening of the Functionalized Bicyclo[4.2.0]oct-1(6)-enes

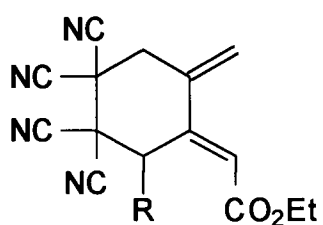
With one exception, each of the thermolyses were carried out by heating a solution of the appropriate bicyclo[4.2.0]oct-1(6)-ene (**272**) or (**23**) in either dry deuteriobenzene or deuteriomethylene chloride in a sealed tube at 160-165°C (4-6 h). For substrate (**255**), the reaction was carried out at 143-145°C (3.5 h) to avoid partial product isomerization to the corresponding  $\beta$ - $\gamma$  unsaturated ester.

There were several advantages to this procedure. Firstly, the product ratios can be determined directly by integration of the appropriate olefinic protons in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture. Secondly, since very little of the starting material is required for the reaction, the experiments can be carried out in duplicate and triplicate, thus allowing a more statistically accurate ratio of the thermolysis products to be determined. A summary of the results can be seen in Tables 24 through 28.

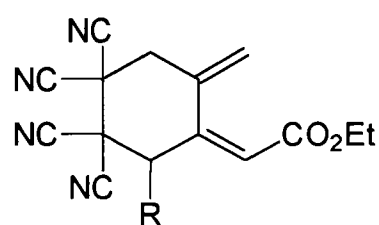
Table 24: Small scale thermolysis of the substituted 7-(ethoxycarbonyl) bicyclo[4.2.0]oct-1(6)-enes of general structure (293)



293



294



295

255 R = H

257 R = Me

259 R = *i* - Pr261 R = *c* - Hex

275 R = H

277 R = Me

279 R = *i* - Pr281 R = *c* - Hex

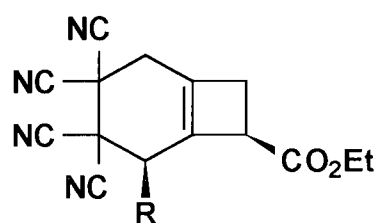
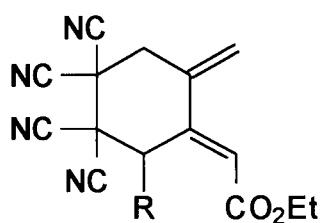
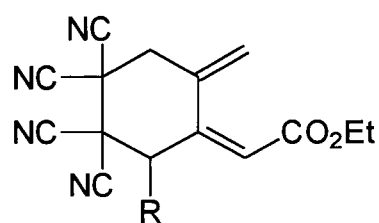
276 R = H

278 R = Me

280 R = *i* - Pr282 R = *c* - Hex

Expt	Substrate	Solvent	Time	Temp.	Ratio of Products	
1	255	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	16	1
2	255	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	18	1
3	257	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.3	1
4	257	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.1	1
5	257	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.3	1
6	259	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
7	259	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4
8	259	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
9	261	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4
10	261	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.3
11	261	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4

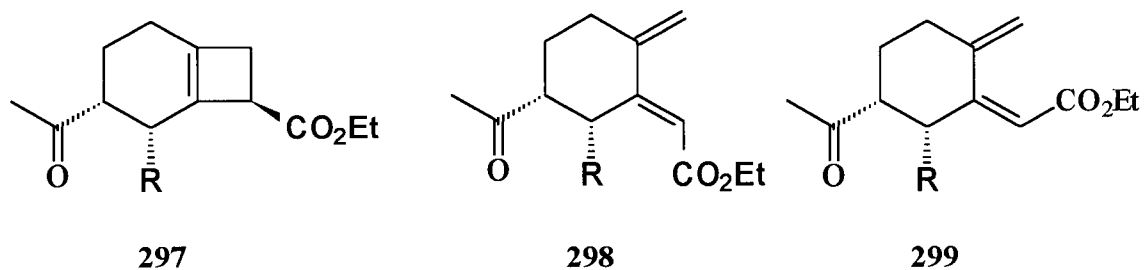
**Table 25: Small scale thermolysis of the substituted 7-(ethoxycarbonyl) bicyclo[4.2.0]oct-1(6)-enes of general structure (296)**

**296****294****205****256** R = Me**258** R = *i* - Pr**260** R = *c* - Hex**277** R = Me**279** R = *i* - Pr**281** R = *c* - Hex**278** R = Me**280** R = *i* - Pr**282** R = *c* - Hex

Expt	Substrate	Solvent	Time	Temp.	Ratio of Products	
12	<b>256</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	2.5	1
13	<b>256</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	2.6	1
14	<b>256</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	2.7	1
15	<b>258</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
16	<b>258</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4
17	<b>260</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
18	<b>260</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4



**Table 26: Small scale thermolysis of the substituted 7-(ethoxycarbonyl) bicyclo[4.2.0]oct-1(6)-enes of general structure (297)**



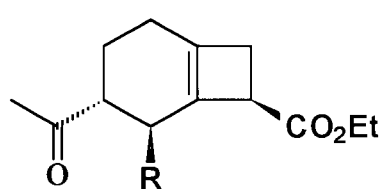
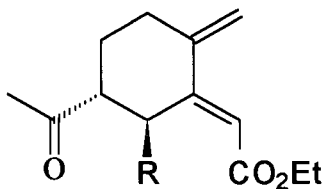
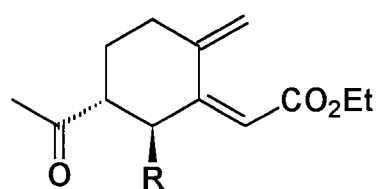
**11** R = Me  
**266** R = *i* - Pr  
**268** R = *c* - Hex

**12** R = Me  
**285** R = *i* - Pr  
**289** R = *c* - Hex

**13** R = Me  
**286** R = *i* - Pr  
**290** R = *c* - Hex

Expt	Substrate	Solvent	Time	Temp.	Ratio of Products	
19	<b>11</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	10	1
20	<b>11</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	11	1
21	<b>266</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.0	1
22	<b>266</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	3.6	1
23	<b>266</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	4.3	1
24	<b>268</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	3.8	1
25	<b>268</b>	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	3.7	1

**Table 27: Small Scale thermolysis of the substituted 7-(ethoxycarbonyl) bicyclo[4.2.0]oct-1(6)-enes of general structure (300)**

**300****301****302**

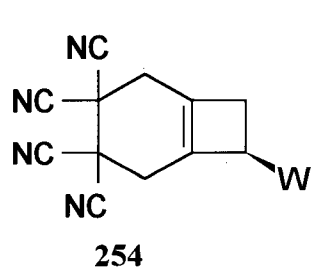
**14** R = Me  
**265** R = *i* - Pr  
**267** R = *c* - Hex

**15** R = Me  
**283** R = *i* - Pr  
**287** R = *c* - Hex

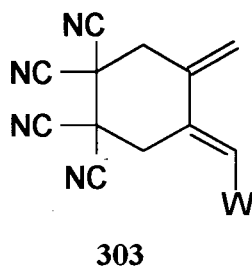
**16** R = Me  
**284** R = *i* - Pr  
**288** R = *c* - Hex

Expt	Substrate	Solvent	Time	Temp.	Ratio of Products	
26	<b>14</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1.0	1
27	<b>14</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1.0	1
28	<b>265</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.4
29	<b>265</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.2
30	<b>265</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.4
31	<b>267</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.6
32	<b>267</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.5
33	<b>267</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.8

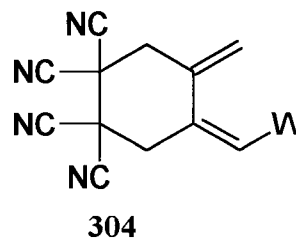
**Table 28: Small scale thermolysis of several substituted bicyclo[4.2.0]oct-1(6)-enes of general structure (254)**



**255** W = - CO<sub>2</sub>Et  
**262** W = - CH<sub>2</sub>OH  
**264** W = - CO<sub>2</sub>H



**275** W = - CO<sub>2</sub>Et  
**271** W = - CH<sub>2</sub>OH  
**305** W = - CO<sub>2</sub>H



**276** W = - CO<sub>2</sub>Et  
**271b** W = - CH<sub>2</sub>OH  
**306** W = - CO<sub>2</sub>H

Expt	Substrate	Solvent	Time	Temp.	Ratio of Products	
1	<b>255</b>	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	16	1
2	<b>255</b>	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	18	1
34	<b>255</b>	CD <sub>2</sub> Cl <sub>2</sub>	3.5 h	145°C	17	1
35	<b>262</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	>99	1
36	<b>262</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	>99	1
37	<b>264</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	7.3	1
38	<b>264</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	7.4	1
39	<b>264</b>	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	7.0	1

Having the results from several series of thermolysis reactions (Tables 21, 22, and 24-28) in hand, it is necessary to interpret these results with respect to both the functional group at C-7 of the bicyclo[4.2.0]oct-1(6)-ene and the alkyl group on C-5. To aid in interpretation of the results, the orientations of the alkyl group on the half chair conformations of the thermolysis precursors are summarized in Figure 16.

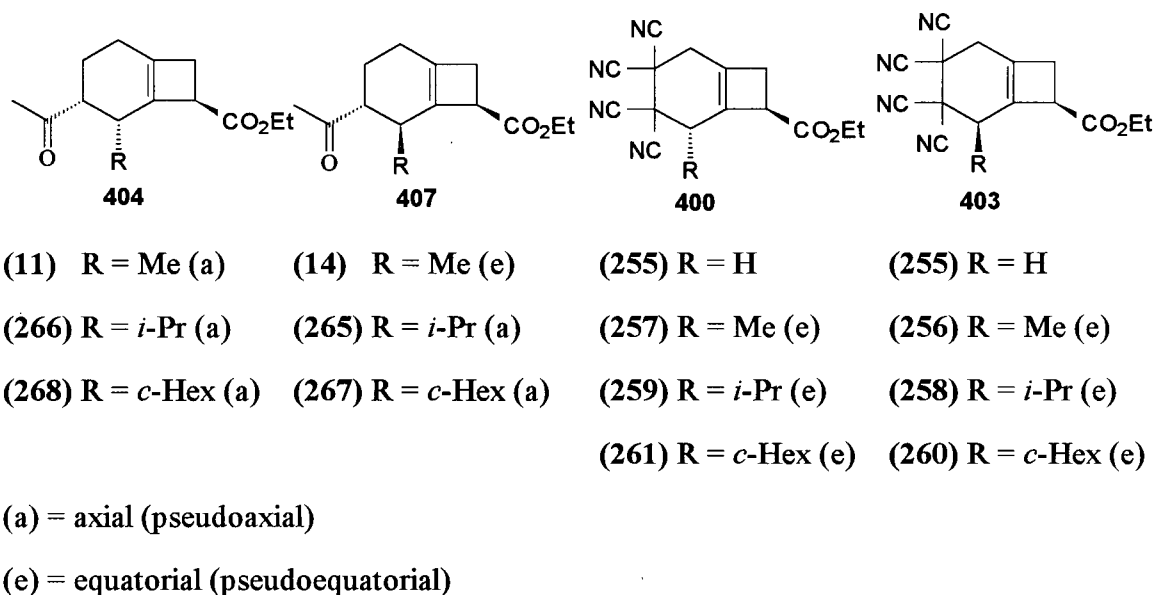


Figure 16: Conformational data for the thermolysis precursors (11), (14), (255-261) and (265-268)

Compound (255) where R = H structurally is the closest compound to the 3-methoxycarbonylcyclobutene for which Houk performed his calculations.<sup>13</sup> We would expect the steric effects on the outward rotation of the ester group to be minimal as R = H for (255) and thus (255) should represent the "parent" compound from which the tendency of an ester group to rotate outward can be determined. Thermolysis of (255) provided the outward and inward rotation products (275) and (276) in an average ratio of 17:1 (Expts 1 and 2, Table 24). The calculated energy of activation difference between the two transition states based upon this ratio is ~2.4 kcal/mol. This is compared to a value of

1.7 kcal/mol calculated by Houk and co-workers.<sup>13</sup> Although Houk performed his calculations on 3-methoxycarbonyl cyclobutene, this result still suggests the tendency of an ester group to rotate outward may be more than predicted.

Thermolysis of (11) where R is an  $\alpha$ -Me group gave an 11:1 ratio of outward rotation and inward rotation products (12) and (13) (Expts 19 and 20, Table 26). The decrease in the ratio of outward and inward rotation products presumably results from a weak steric interaction between the  $\alpha$ -Me group and the ester moiety in the transition state leading towards the outward rotation product. As the size of the  $\alpha$ -R group increases from R = Me to R = *i*-Pr to R = *c*-hex, this steric effect becomes more pronounced and the ratio of outward to inward rotation products drops further (Expts 21-25, Table 26).

The steric interaction between a  $\beta$ -R group and an ester group is apparently more severe than a steric interaction between an  $\alpha$ -R group and an ester group as seen by a comparison of the data in Tables 27 and Table 26. When R is a pseudoequatorial  $\beta$ -Me group, the ratio of outward rotation to inward rotation products drops to 1:1 (Expts 26 and 27, Table 27) as compared to 11:1 for an  $\alpha$ -Me group (Expts 19 and 20, Table 26). Similarly, pseudoaxial  $\beta$ -*i*-Pr and  $\beta$ -*c*-Hex groups hinders outward rotation more than their  $\alpha$  counterparts (Expts 28-33, Table 27). In fact, for these substrates, the major product was the inward rotation product, which is contrary to the electronic tendency of the ester function to rotate outwards. There seems to be only a slight increase in inward rotation product for a pseudoaxial  $\beta$ -*c*-Hex group (1:2.6 outward:inward, Expts 31-33, Table 27) as compared to a pseudoaxial  $\beta$ -*i*-Pr (1:2.3 outward:inward, Expts 28-30, Table 27).

When examining the data on Tables 24 and 25 for substrates which have either a  $\beta$ -R group or an  $\alpha$ -R group, we see that the tendency for the ester group to rotate outwards is less than that of the parent compound (255) (Expts 1-18, Table 24 and 25). The amount of the outward rotation product decreases as the R group increases in size

from methyl to isopropyl or cyclohexyl (compare Expts 3-5 with Expts 6-11, Table 24) or (compare Expts 12-14 with Expts 15-18, Table 25).

Surprisingly, unlike the data from Tables 26 and 27, the ratios of products obtained from pseudoequatorial  $\beta$ -R groups was similar to that obtained from pseudoequatorial  $\alpha$ -R groups (compare Expts 3-11, Table 24 with Expts 12-18, Table 25). Thus, in terms of steric inhibition towards the outward rotation of the ester group, pseudoequatorial  $\alpha$ -R and pseudoequatorial  $\beta$ -R groups are similar.

The results of the thermolysis reactions (Tables 24-28) were published in a paper by Piers and Ellis in 1993.<sup>80</sup> "Inspired" by this publication, Houk and Nakamura undertook a study designed to predict the experimental results using extensive quantum mechanical calculations and a transition state force field model for the compounds (255-259), (11), (14) and (265-266).<sup>78</sup>

Houk first performed MM2 calculations to determine the most stable reactant conformations and orientation (pseudoaxial or pseudoequatorial) of the R group on reactants (255-259), (11), (14) and (265-266). The computational results were in agreement with the experimental results for all compounds except for (265). For ester (265), Houk predicted that the pseudoequatorial orientation of the  $\beta$ -*i*-Pr group would be preferred over the pseudoaxial orientation.<sup>78</sup> Houk doesn't have a clear explanation for why the experimental results differ from his predictions, experimentally the  $\beta$ -*i*-Pr group is in a pseudoaxial orientation, but he suggests that steric repulsion between the *i*-Pr group and neighbouring acetyl group (when both substituents are in a pseudoequatorial orientation) promotes the pseudoaxial orientation of the  $\beta$ -*i*-Pr group.

Houk determined that there are two possible conformations, chair and twist boat, for each of the thermolysis products (Figure 17).<sup>78</sup>

MM2 computations were performed to determine the energies of these product conformations (*i.e.* inward-twist boat, outward chair, inward chair, and outward-twist

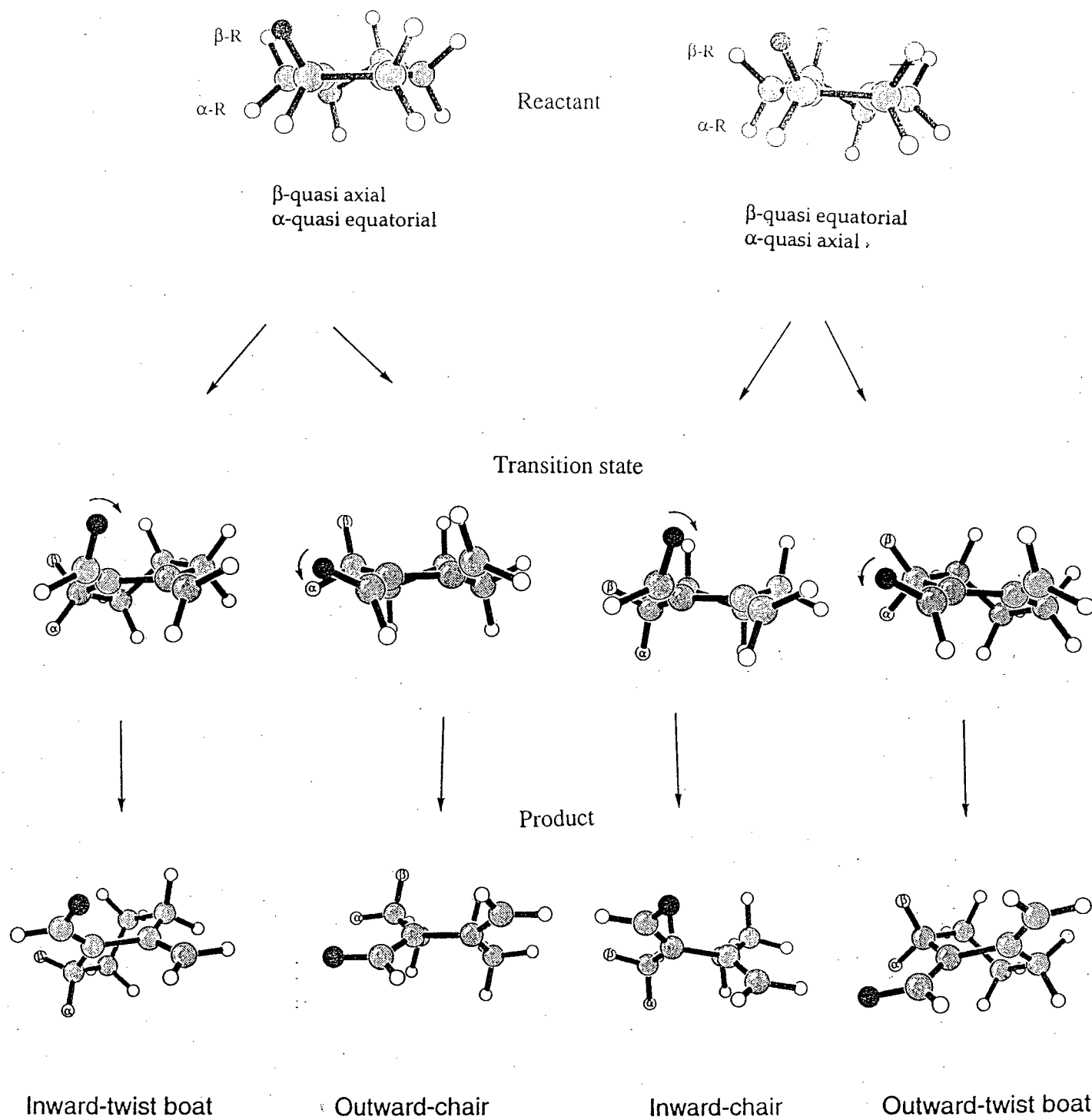


Figure 17: Product conformations of the thermolysis reactions.<sup>78</sup>

boat) for substrates (255-259), (11), (14) and (265-266). The energy difference between these products' conformations was compared with the experimental ratios of products.

Houk found no correlation between the experimental ratios of outward and inward pathways and the product stabilities.<sup>78</sup> However, when a transition state modeling analysis using *ab initio* orbital calculations was used to calculate the energies of the various transition state structures, a good correlation between the calculated energy difference of the outward transition state and inward transition state, and the experimental ratio of products was found.<sup>78</sup>

Thermolysis of (264) where W is a carboxylic acid group provided the outward rotation (305) and inward rotation (306) products in an average ratio of 7.2:1 (Expts 37-39, Table 28). This compares to an average value of 17:1 (outward to inward) for the ester (255) (Expts 1, 2, and 34, Table 28). Calculations by Houk have shown that the CO<sub>2</sub>H group prefers outward rotation by 1.5 kcal mol<sup>-1</sup> as compared to the ester function which prefers outward rotation by 1.7 kcal mol<sup>-1</sup>.<sup>14</sup> It is not surprising, therefore, to find that the ratio of outward to inward rotation products for (264) where W is a carboxylic acid group is somewhat less than for (255) where R is an ester group.

In summary, the substituted bicyclo[4.2.0]oct-1(6)-enes (255-268), (11) and (14) were thermolyzed and the ratio of outward and inward rotation products compared to the predictions by Houk and co-workers.<sup>12, 13, 14</sup> For simple systems (255), (262), and (264) where steric effects were minimized the results are in good agreement with Houk's calculations.<sup>14</sup> For more complicated systems, those which contain β-R groups on C-5, the electronically induced tendency for the ester function to prefer rotate outward was changed such that the inward rotation product was preferred for substrates (265) and (267). This result can be rationalized on the basis of a steric effect between the alkyl group and the ester function in the transition states leading towards the outward and inward rotation products. Finally, Houk has shown that the results of these thermolysis reactions can be rationalized on the basis of *ab initio* and MM2 calculations.<sup>78</sup>



## IV. EXPERIMENTAL SECTION

### 1. GENERAL

#### 1.1 Data Acquisition and Presentation of Results

Infrared (IR) spectra were recorded on liquid films between sodium chloride plates or on potassium bromide pellets using a Perkin-Elmer model 1710 Fourier Transform Infrared (FTIR) Spectrophotometer with internal calibration.

Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on a Bruker model WH-400 spectrometer using deuteriochloroform ( $\text{CDCl}_3$ ) as the solvent unless otherwise noted. Signal positions are given in  $\delta$  units in parts per million from tetramethylsilane and are measured relative to the chloroform signal at  $\delta$  7.24 or the benzene signal at  $\delta$  7.15. The multiplicity, number of protons, coupling constants, and assignments (when known) are given in parentheses. Coupling constants ( $J$  values) are given in Hertz (Hz). Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. When a hydrogen was observed to be coupled with the same coupling constant to two, three, or four protons which are chemically and magnetically non-equivalent, the designation dd, ddd, dddd, and dddt are used instead of using t, q, quintet and hextet, respectively. For compounds exhibiting AB and ABX type spin systems, the quoted values for chemical shifts and coupling constants are measured as if they were first order systems, although these values only approximate the real values. Decoupling experiments refer to  $^1\text{H}$ - $^1\text{H}$  spin decoupling experiments. The nuclear Overhauser enhancement (NOE) difference experiments were recorded on a Bruker WH-400 NMR spectrometer.  $^1\text{H}$ - $^1\text{H}$  Homonuclear correlation (COSY) experiments were recorded on a Bruker AC-200 spectrometer. The tin-proton coupling constants ( $J_{\text{Sn-H}}$ ) are given as an average of the  $^{117}\text{Sn}$  and  $^{119}\text{Sn}$  values (unless otherwise stated).

Carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were recorded on a Varian model XL-300 spectrometer at 75.3 MHz, or on Bruker AM-200 (50.3 MHz), AM-400 (100.4 MHz) or AMX-500 (125.8 MHz) spectrometers, using deuteriochloroform as the solvent unless

otherwise noted. Signal positions are given in  $\delta$  units in parts per million and are measured relative to the chloroform signal at  $\delta$  77.0.<sup>81</sup>

Low resolution electron impact mass spectra were recorded on an AEI MS9/DS55SM or on a KRATOS MS50/DS55SM mass spectrometer. High resolution electron impact mass spectra were recorded on a KRATOS MS50/DS55SM mass spectrometer. For compounds containing the  $\text{Me}_3\text{Sn}$  moiety, high resolution mass spectrometric measurements are based on  $^{120}\text{Sn}$  and were made on the  $(\text{M}^+-\text{Me})$  signal.

Elemental analyses were performed on a Carlo erba CHN elemental analyzer, model 1106, at University of British Columbia Microanalytical Laboratory.

Gas-liquid chromatography (GLC) analyses were performed on a Hewlett-Packard model 5880A or 5890 capillary chromatograph, both using flame ionization detectors and a 25 m x 0.32 mm fused silica column coated with cross-linked 5% phenylmethyl silicone.

Thin layer chromatography (TLC) was carried out on commercially available aluminum backed silica gel plates (E. Merck, type 5554, 0.2 mm). Visualization was accomplished with ultraviolet light (254 nm), and/or a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v). Flash chromatography was performed using 230-400 mesh silica gel (E. Merck, Silica Gel 60). Radial chromatography<sup>82</sup> was done on a Chromatotron Model 7924 using 1, 2, or 4 mm thick radial plates (silica gel 60, PF 254, with calcium sulfate, E. Merck #7749).

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures refer to air-bath temperatures of bulb-to-bulb (Kugelrohr) distillations and are uncorrected.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame and/or oven ( $\sim 150^\circ\text{C}$ ) dried.

Concentration, evaporation or removal of the solvent under reduced pressure (water aspirator) refer to solvent removal via a Buchi rotary evaporator at  $\sim 15$  Torr.

Cold temperatures were maintained by use of the following baths:  $0^\circ\text{C}$ , ice/water;  $-20^\circ\text{C}$ , aqueous calcium chloride/ $\text{CO}_2$  (27g  $\text{CaCl}_2$ /100 mL  $\text{H}_2\text{O}$ );  $-48^\circ\text{C}$ , cyclohexane/ $\text{CO}_2$ ;

-78°C, acetone/CO<sub>2</sub>; -98°C, MeOH/liquid nitrogen.

## 1.2 Reagents and Solvents

Solvents and reagents were purified and dried using established procedures.<sup>83</sup>

Petroleum ether refers to a hydrocarbon mixture with bp 35-60°C. Ether refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl. Benzene, dichloromethane, diisopropylamine, DMF, DMSO, HMPA, acetonitrile, mesitylene, and pyridine were refluxed over and then distilled from calcium hydride. DMF, HMPA, and pyridine were stored over 4A molecular sieves. Sodium was added to EtOH and EtOH was distilled from the resulting solution of sodium ethoxide.

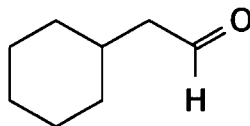
Solutions of methyllithium (LiBr complex in ether) and butyllithium (in hexane) were obtained from Aldrich Chemical Co., Inc. and were standardized using the procedure of Kofron and Baclawski.<sup>84</sup>

Lithium diisopropylamide (*i*-Pr<sub>2</sub>NLi) solution was prepared by the addition of a solution of butyllithium (1.0 equiv.) in hexane to a solution of diisopropylamine (1.1 equiv.) in THF at -78°C. The resulting colourless or faintly yellow solution was stirred at 0°C for ten minutes prior to use.

Aqueous NH<sub>4</sub>Cl-NH<sub>4</sub>OH solution (pH 8) was prepared by the addition of 50 mL of aqueous ammonia (58%) to 950 mL of saturated aqueous ammonium chloride.

Boron trifluoride-etherate was purified by distillation from calcium hydride (1 g per 250 mL of BF<sub>3</sub>·Et<sub>2</sub>O) under reduced pressure (60 °C/20 Torr).<sup>85</sup>

Preparation of cyclohexylethanal (131)

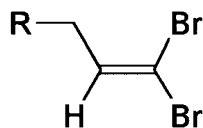


**131**

To a stirred mixture of pyridinium chlorochromate (33.7g, 156 mmol) and sodium acetate (3.2g, 39 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (200 mL) was added a solution of commercially available 2-cyclohexylethanol (**308**) (10.0 g, 78.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (300 mL). The mixture was stirred at room temperature for 2 hours. Diethyl ether (400 mL) was added and the resultant mixture was filtered through a column of Florisil (6 cm diameter, 7.5 cm depth). The column was eluted with 1 L of  $\text{Et}_2\text{O}$ . Concentration of the combined eluate, followed by distillation

(50-56 °C/15 Torr) of the remaining liquid, gave 9.03 g (92%) of cyclohexylethanal (**4**), a colourless oil that exhibited IR (neat): 1725, 1441  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.95-1.10 (m, 2H), 1.10-1.23 (m, 1H), 1.25-1.37 (m, 2H), 1.65-1.80 (m, 5H), 1.85-1.95 (m, 1H,  $-\text{CHR}_2$ ), 2.29 (dd, 2H,  $J = 6, 2$  Hz,  $-\text{CH}_2\text{CHO}$ ), 9.75 (t, 1H,  $J = 2$  Hz,  $-\text{CHO}$ ); Exact Mass calcd. for  $\text{C}_8\text{H}_{14}\text{O}$  ( $\text{M}^+ - 1$ ): 125.0966; found: 125.0960.

2. General Procedure 1: Preparation of the 1,1-dibromoolefins (**117**)<sup>43</sup>

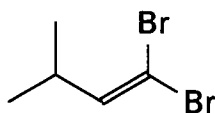


**117**

To a solution of  $\text{CBr}_4$  (2 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  (~5.3 mL/mmol of aldehyde substrate) was added slowly (at a rate such that the temperature of the reaction mixture remained below

50°C) a solution of triphenylphosphine (4 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (~5.3 mL/mmol of aldehyde substrate). After the resultant mixture had been stirred for 5 min., a solution of the appropriate aldehyde (1 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (~10.6 mL/mmol of aldehyde) was added over a period of 10 min. and the mixture was then stirred at room temperature for an additional 30 min. Pentane (three-quarters the volume of the total volume of the reaction mixture) was added and the resultant mixture was filtered through a column of Florisil (6 cm diameter, 1.65 g Florisil/mmol aldehyde). The column was eluted with pentane (1.5 times the volume of the total volume of the reaction mixture). The combined eluate was concentrated and the remaining oil was distilled via bulb-to-bulb distillation to afford the corresponding dibromoolefin.

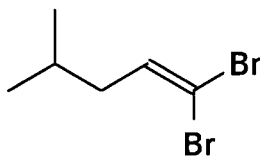
Preparation of 1,1-dibromo-3-methyl-1-butene (200)<sup>86,43</sup>



**200**

Following general procedure 1 outlined above, commercially available 2-methylpropanal (**198**) was converted into the dibromoolefin (**200**). The following amounts of reagents and solvents were used: CBr<sub>4</sub> (36.8 g, 111 mmol) in 300 mL dry CH<sub>2</sub>Cl<sub>2</sub>, triphenylphosphine (58.2 g, 222 mmol) in 300 mL dry CH<sub>2</sub>Cl<sub>2</sub>, 2-methylpropanal (**198**) (4.00 g, 55.5 mmol) in 600 mL dry CH<sub>2</sub>Cl<sub>2</sub>. Normal workup, followed by distillation (45-47°C/10 Torr) of the material thus obtained, afforded 10.41 g (82%) of 1,1-dibromo-3-methyl-1-butene (**6**) as a colourless oil which exhibited IR (neat): 1609, 1465, 1276, 777 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.03 (d, 6H, *J*= 7 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 2.57 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 6.22 (d, 1H, *J*= 9 Hz, =CH); <sup>13</sup>C NMR (75.3 MHz) δ: 21.2, 33.1, 86.8, 145.1. Anal. calcd. for C<sub>5</sub>H<sub>8</sub>Br<sub>2</sub>: C 26.35, H 3.54; found: C 26.47, H 3.54. Exact Mass calcd. for C<sub>5</sub>H<sub>8</sub><sup>79</sup>Br<sup>81</sup>Br: 227.8974; found: 227.8972.

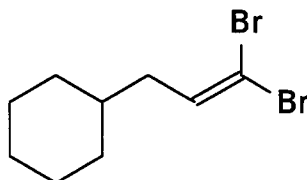
Preparation of 1,1-dibromo-4-methyl-1-pentene (119)<sup>43</sup>



**119**

Following general procedure 1 outlined above, commercially available 3-methylbutanal (**130**) was converted into the dibromoolefin (**119**). The following amounts of reagents and solvents were used:  $\text{CBr}_4$  (15.4 g, 46.4 mmol) in 125 mL dry  $\text{CH}_2\text{Cl}_2$ , triphenylphosphine (24.3 g, 92.7 mmol) in 125 mL dry  $\text{CH}_2\text{Cl}_2$ , 3-methylbutanal (**130**) (2.00 g, 23.2 mmol) in 250 mL dry  $\text{CH}_2\text{Cl}_2$ . Normal workup, followed by distillation (60-63 °C/15 Torr) of the material thus obtained, afforded 4.54 g (81 %) of 1,1-dibromo-4-methyl-1-pentene (**119**) as a colourless oil which exhibited IR (neat): 1619, 1466, 1386, 1369, 854, 781  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.92 (d, 6H,  $J = 7$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 1.68-1.80 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 1.98 (dd, 2H,  $J = 7, 7$  Hz,  $=\text{C}-\text{CH}_2-$ ), 6.38 (t, 1H,  $J = 7$  Hz, olefinic proton);  $^{13}\text{C}$  NMR (50.3 MHz)  $\delta$ : 22.2, 27.7, 41.8, 88.8, 137.8. Anal. calcd. for  $\text{C}_6\text{H}_{10}\text{Br}_2$ : C 29.78, H 4.17; found: C 29.84, H 4.14. Exact Mass calcd. for  $\text{C}_6\text{H}_{10}^{79}\text{Br}^{81}\text{Br}$ : 241.9129; found: 241.9123.

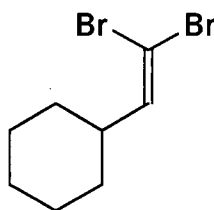
Preparation of 1,1-dibromo-3-cyclohexylpropene (120)<sup>43</sup>



**120**

Following general procedure 1 outlined above, commercially available cyclohexylethanal (**131**) was converted into the dibromoolefin (**120**). The following amounts of reagents and solvents were used:  $\text{CBr}_4$  (18.71 g, 56.4 mmol) in 150 mL dry  $\text{CH}_2\text{Cl}_2$ , triphenylphosphine (29.59 g, 112.8 mmol) in 150 mL dry  $\text{CH}_2\text{Cl}_2$ , cyclohexylethanal (**131**) (3.55 g, 28.1 mmol) in 300 mL dry  $\text{CH}_2\text{Cl}_2$ . Normal workup, followed by distillation (125-130°C/15 Torr) of the material thus obtained, afforded 6.56 g (83%) of 1,1-dibromo-3-cyclohexylpropene (**120**) as a colourless oil which exhibited IR (neat): 1621, 1448, 785  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.90-1.05 (m, 2H), 1.10-1.30 (m, 3H), 1.35-1.50 (m, 1H), 1.55-1.90 (m, 5H), 2.05 (dd, 2H,  $J=7, 7$  Hz,  $=\text{C}-\text{CH}_2-$ ), 6.42 (t, 1H,  $J=7$  Hz, olefinic proton);  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 26.2, 26.3, 32.9, 37.2, 40.6, 88.7, 137.8. Anal. calcd. for  $\text{C}_9\text{H}_{14}\text{Br}_2$ : C 38.33, H 5.01; found: C 38.60, H 5.13. Exact Mass calcd. for  $\text{C}_9\text{H}_{14}^{79}\text{Br}^{81}\text{Br}$ : 281.9443; found: 281.9440.

#### Preparation of 1,1-dibromo-2-cyclohexylethene (**201**)

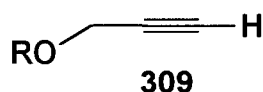


**201**

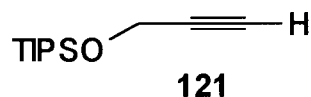
Following general procedure 1 outlined above, commercially available cyclohexanecarboxaldehyde (**199**) was converted into the dibromoolefin (**201**). The following amounts of reagents and solvents were used:  $\text{CBr}_4$  (36.8 g, 111 mmol) in 300 mL dry  $\text{CH}_2\text{Cl}_2$ , triphenylphosphine (58.2 g, 222 mmol) in 300 mL dry  $\text{CH}_2\text{Cl}_2$ , cyclohexanecarboxaldehyde (**199**) (6.23 g, 55.5 mmol) in 600 mL dry  $\text{CH}_2\text{Cl}_2$ . Normal workup, followed by distillation (85-88 °C/ 15 Torr) of the material thus obtained, afforded 13.29 g (89 %) of 1,1-dibromo-2-cyclohexylethene (**201**) as a colourless oil which exhibited IR (neat): 1611, 1448

$\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.03-1.34 (m, 5H), 1.60-1.81 (m, 5H), 2.20-2.31 (m, 1H, allylic proton), 6.22 (d, 1H,  $J = 9$  Hz, olefinic proton);  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 25.5, 25.7, 31.2, 42.4, 87.0, 143.7. Anal. calcd. for  $\text{C}_8\text{H}_{12}\text{Br}_2$ : C 35.85, H 4.52; found: C 35.74, H 4.42. Exact Mass calcd. for  $\text{C}_8\text{H}_{12}^{79}\text{Br}^{81}\text{Br}$ : 267.9287; found: 267.9284.

### 3. Preparation of the 1-alkynes of general structure (309)<sup>50</sup>



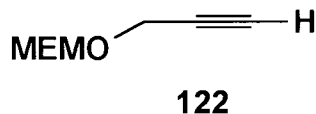
### Preparation of 3-(triisopropylsiloxy)propyne (121)<sup>50</sup>



To a stirred solution of 2-propyn-1-ol (1.02 g, 18.2 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) was added sequentially imidazole (1.86 g, 27.3 mmol) and triisopropylsilyl chloride (3.33 g, 17.3 mmol) and the resultant mixture was stirred at room temperature for 2 h. Aqueous  $\text{NH}_4\text{Cl}$ - $\text{NH}_4\text{OH}$  (pH 8) (25 mL) was added and the mixture was extracted thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography (35 g silica gel, hexanes) of the crude oil obtained and distillation (45-47°C/0.15 Torr) gave 2.75 g (75%, based on  $(i\text{-Pr})_3\text{SiCl}$ ) of 3-(triisopropylsiloxy)propyne (**121**), as a colourless oil that displayed IR (neat): 3313, 2123, 1465, 1107  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.06 (d, 18H,  $J = 6$  Hz,  $((\text{CH}_3)_2\text{-CH})_3\text{Si-}$ ), 1.10 (m, 3H,  $((\text{CH}_3)_2\text{-CH})_3\text{Si-}$ ), 2.46 (t, 1H,  $J = 2$  Hz,  $\equiv\text{CH}$ ), 4.37 (d, 2H,  $J = 2$  Hz,  $-\text{OCH}_2\text{SiR}_3$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 11.9, 17.8, 51.7, 72.5, 82.4. Anal. calcd. for  $\text{C}_{12}\text{H}_{24}\text{OSi}$ : C 67.86, H 11.39; found: C 67.86, H 11.43. Exact Mass calcd. for  $\text{C}_{12}\text{H}_{24}\text{OSi}$ : 212.1598; found: 212.1604.



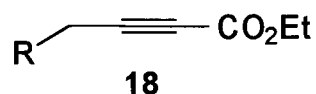
Preparation of 3-[(2-methoxyethoxy)methoxy]propyne (122)<sup>50</sup>



To a cold (0°C), stirred solution of 2-propyn-1-ol (1.02 g, 18.2 mmol) and (*i*-Pr)<sub>2</sub>NEt (3.53 g, 27.3 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added, over a period of 1 minute, 2.16 g (17.3 mmol) of MeOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>Cl and the resulting mixture was stirred at 0°C for 3.5 h. Hydrochloric acid (2 N, 15 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (50 g silica gel, 4:1 hexanes-Et<sub>2</sub>O) of the remaining crude oil and distillation (65-68°C/10 Torr) of the liquid thus obtained gave 1.98 g (79%) of 3-[(2-methoxyethoxy)methoxy]propyne (**122**), as a colourless oil that showed IR (neat): 3262, 2118, 1454, 1110 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 2.40 (t, 1H, *J*= 2 Hz, -C≡C-H), 3.38 (s, 3H, -OCH<sub>3</sub>), 3.52-3.56 (m, 2H), 3.68-3.72 (m, 2H), 4.22 (d, 2H, *J*= 2 Hz, -OCH<sub>2</sub>C≡CH), 4.78 (s, 2H, -OCH<sub>2</sub>O-); <sup>13</sup>C NMR (100.4 MHz) δ: 54.1, 58.9, 67.1, 71.6, 74.2, 79.3, 93.8. Anal. calcd. for C<sub>7</sub>H<sub>12</sub>O<sub>3</sub>: C 58.32, H 8.39; found: C 58.56, H 8.49. Exact Mass calcd. for C<sub>7</sub>H<sub>11</sub>O<sub>3</sub> (M<sup>+</sup>-1): 143.0704; found: 143.0700.

4 Preparation of the α,β-acetylenic esters

4.1 General Procedure 2: Preparation of the α,β-acetylenic esters (18) from 1,1-dibromo-1-alkenes<sup>43</sup>



To a cold (-78 °C), stirred solution of the appropriate 1,1-dibromo-1-alkene (117) (1 equiv.) in dry THF (12-13 mL/mmol) was added, dropwise, a solution of *n*-butyllithium (2.5 equiv.) in hexanes. The mixture was stirred at -78°C for 1 hour, at room temperature for 1 hour and was then recooled to -20°C. Ethyl chloroformate (1.1 equiv.) was added and the mixture was stirred at -20°C for 1 hour and at room temperature for 1 hour. Saturated aqueous NaHCO<sub>3</sub> solution (three-quarter the volume of the total volume of the reaction mixture) was added and the mixture thoroughly extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography of the crude product followed by bulb-to-bulb distillation of the acquired oil afforded the corresponding  $\alpha,\beta$ -acetylenic ester.

Preparation of ethyl 4-cyclohexyl-2-butynoate (126)

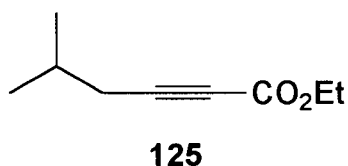


126

Following general procedure 2 outlined above, 1,1-dibromo-3-cyclohexylpropene (120) was converted into the  $\alpha,\beta$ -acetylenic ester (126). The following amounts of reagents and solvents were used: substrate (120) (2.50 g, 8.86 mmol) in 115 mL dry THF, *n*-butyllithium (22.2 mmol) in hexanes, and ethyl chloroformate (1.06 g, 9.76 mmol). Normal workup, followed by flash chromatography (75 g silica gel, 95:5 petroleum ether - Et<sub>2</sub>O) of the crude product and distillation (90-96°C/12 Torr) of the acquired liquid provided 1.55 g (90%) of ethyl 4-cyclohexyl-2-butynoate (126) as a colourless oil which exhibited IR (neat): 2232, 1713, 1249, 1076 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.97-1.08 (m, 2H), 1.12-1.30 (m, 2H), 1.32 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.50-1.60 (m, 2H), 1.65-1.87 (m, 5H), 2.25 (d, 2H, *J* = 7 Hz,  $\equiv\text{C}-\text{CH}_2-$ ),

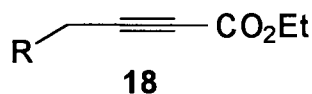
4.24 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 14.1, 25.8, 25.9, 26.4, 32.7, 36.7, 61.8, 74.0, 88.6, 153.8. Anal. calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : C 74.20, H 9.35; found: C 74.40, H 9.41. Exact Mass calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : 194.1307; found: 194.1309.

#### Preparation of ethyl 5-methyl-2-hexynoate (125)



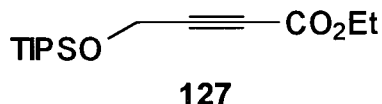
Following general procedure 2 outlined above, 1,1-dibromo-4-methyl-1-pentene (**119**) was converted into the  $\alpha,\beta$ -acetylenic ester (**125**). The following amounts of reagents and solvents were used: substrate (**119**) (4.00 g, 16.5 mmol) in 200 mL dry THF, *n*-butyllithium (41 mmol) in hexanes, and ethyl chloroformate (1.97 g, 18.1 mmol). Normal workup, followed by flash chromatography (75 g silica gel, 95:5 petroleum ether -  $\text{Et}_2\text{O}$ ) of the crude product and distillation (90-100°C/20 Torr) of the acquired liquid provided 2.08 g (82%) of ethyl 5-methyl-2-hexynoate (**125**) as a colourless oil which exhibited IR (neat): 2234, 1713, 1389, 1251  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.02 (d, 6H,  $J = 7$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 1.32 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.88-1.99 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.24 (d, 2H,  $J = 6$  Hz,  $-\text{CH}_2\text{C}\equiv\text{C}-$ ), 4.22 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (50.3 MHz)  $\delta$ : 14.0, 22.0, 27.5, 27.7, 61.7, 74.0, 88.4, 153.9. Anal. calcd. for  $\text{C}_9\text{H}_{14}\text{O}_2$ : C 70.10, H 9.15; found: C 69.90, H 9.12. Exact Mass calcd. for  $\text{C}_9\text{H}_{14}\text{O}_2$ : 154.0994; found: 154.0997.

#### 4.2 General Procedure 3: Preparation of the $\alpha,\beta$ -acetylenic esters (**18**) from 1-alkynes



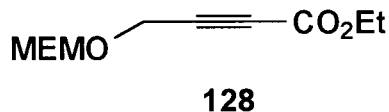
To a cold (-78°C), stirred solution of the appropriate 1-alkyne (1 equiv.) in dry THF (4.5-6.5 mL/mmol) was added, dropwise, a solution of methyllithium (1 equiv.) in Et<sub>2</sub>O. After the solution had been stirred at -78°C for 15 minutes and at -20°C for 1 hour, ethyl chloroformate (1 equiv.) was added. The resulting mixture was stirred at -20°C for 1 hour and at room temperature for 1 hour. Saturated aqueous NaHCO<sub>3</sub> solution (equal volume as the total volume of the reaction mixture) was added and the mixture was extracted thoroughly with Et<sub>2</sub>O. The combined extracts were washed twice with brine and then were dried (MgSO<sub>4</sub>) and concentrated. Distillation of the remaining oil afforded the corresponding α,β-acetylenic ester.

Preparation of ethyl 4-(Triisopropylsiloxy)-2-butyrate (127)<sup>50</sup>



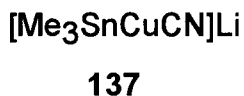
Following general procedure 3 outlined above, 3-(triisopropylsiloxy)propyne (121) was converted into the α,β-acetylenic ester (127). The following amounts of reagents and solvents were used: substrate (121) (500 mg, 2.36 mmol) in 15 mL dry THF, methyllithium (2.36 mmol), and ethyl chloroformate (256 mg, 2.36 mmol). Normal workup, followed by distillation (98-99°C/0.11 Torr) of the remaining oil yielded 512 mg (76%) of ethyl 4-(triisopropylsiloxy)-2-butyrate (127) as a colourless oil that exhibited IR (neat): 2241, 1718, 1465, 1258 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.04 (d, 18H, *J* = 6.0 Hz, ((CH<sub>3</sub>)<sub>2</sub>-CH)<sub>3</sub>Si-), 1.07-1.14 (m, 3H, ((CH<sub>3</sub>)<sub>2</sub>-CH)<sub>3</sub>Si-), 1.29 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.20 (q, 2H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.49 (s, 2H, -OCH<sub>2</sub>C≡C-); <sup>13</sup>C NMR (100.4 MHz) δ: 11.9, 13.9, 17.7, 51.4, 61.9, 76.4, 85.7, 155.5. Anal. calcd. for C<sub>15</sub>H<sub>28</sub>O<sub>3</sub>Si: C 63.33, H 9.92; found: C 63.34, H 9.84. Exact Mass calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>3</sub>Si (M<sup>+</sup> - *i*-Pr): 241.1260; found: 241.1261.

Preparation of ethyl 4-[(2-methoxyethoxy)methoxy]-2-butynoate (128)<sup>50</sup>



Following general procedure 3 outlined above, 3-[(2-methoxyethoxy)methoxy]propyne (122) was converted into the  $\alpha,\beta$ -acetylenic ester (128). The following amounts of reagents and solvents were used: substrate (122) (500 mg, 3.47 mmol) in 15 mL dry THF, methyllithium (3.47 mmol), and ethyl chloroformate (377 mg, 3.47 mmol). Normal workup, followed by distillation (85-87°C/0.11 Torr) of the remaining oil yielded 595 mg (79%) of ethyl 4-[(2-methoxyethoxy)methoxy]-2-butynoate (128) as a colourless oil that exhibited IR (neat): 2240, 1718, 1450, 1254, 1045  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.30 (t, 3H,  $J = 7.5$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 3.39 (s, 3H,  $-\text{OCH}_3$ ), 3.51-3.55 (m, 2H), 3.69-3.73 (m, 2H), 4.20 (q, 2H,  $J = 7.5$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.34 (s, 2H,  $-\text{OCH}_2\text{C}\equiv$ ), 4.77 (s, 2H,  $-\text{OCH}_2\text{O}-$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 14.0, 54.0, 59.0, 62.1, 67.4, 71.6, 77.8, 83.0, 94.3, 153.1. Anal. calcd. for  $\text{C}_{10}\text{H}_{16}\text{O}_5$ : C 55.55, H 7.46; found: C 55.51, H 7.47. Exact Mass calcd. for  $\text{C}_{10}\text{H}_{15}\text{O}_5$  ( $\text{M}^+ - 1$ ): 215.0920; found: 215.0918.

5 Preparation of lithium (cyano)(trimethylstannyl)cuprate (137)<sup>44</sup>

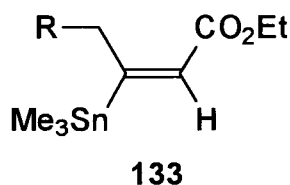


To a cold (-20°C), stirred solution of hexamethylditin in dry THF (~5 mL per mmol of  $\text{Me}_3\text{SnSnMe}_3$ ), under an argon atmosphere, was added a solution of methyllithium in diethyl ether (1 equiv.). The resulting pale yellow-green solution was stirred at -20°C for 20 min and was recooled to -48°C and copper(I) cyanide (1 equiv.) was added. The resulting mixture

was stirred at  $-48^{\circ}\text{C}$  for 20 min, producing a pale yellow solution of lithium (cyano)(trimethylstannyl)cuprate (137).

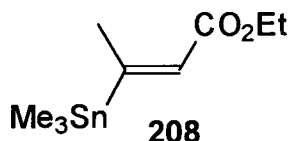
## 6 Preparation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates<sup>50</sup>

### 6.1 General Procedure 4: Preparation of ethyl (*E*)-3-trimethylstannyl-2-alkenoates (133)



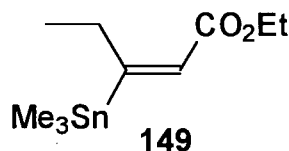
To a cold ( $-78^{\circ}\text{C}$ ), stirred solution of  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137) (1.09-1.50 equiv.) in dry THF was added dry ethanol (1.09-1.50 equiv.). After 5 min, a solution of the appropriate  $\alpha,\beta$ -acetylenic ester (1.0 equiv.) in dry THF was added dropwise and the mixture was stirred at  $-78^{\circ}\text{C}$  for 4 h. Aqueous  $\text{NH}_4\text{Cl}$ - $\text{NH}_4\text{OH}$  (pH 8) (one-half the volume of the total volume of the reaction mixture) was added, the mixture was opened to the atmosphere, was allowed to warm to room temperature, and was stirred vigorously until the aqueous phase became deep blue. The phases were separated and the aqueous phase was extracted thoroughly with  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. The crude product was purified by flash or radial chromatography followed by distillation to afford the corresponding ethyl (*E*)-3-trimethylstannyl-2-alkenoate (133).

Preparation of ethyl (*E*)-3-trimethylstannyl-2-butenolate (208)<sup>44</sup>



Following general procedure 4 outlined above, commercially available ethyl 2-butyrate (123) was converted into the ester (208). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137) (77.9 mmol) in 350 mL of dry THF, EtOH (4.57 mL, 77.9 mmol) and ethyl 2-butyrate (123) (8.00 g, 71.3 mmol) in 35 mL of dry THF. Flash chromatography (350 g silica gel, 200:3 hexanes-Et<sub>2</sub>O) of the crude product and distillation (55-60°C/0.12 Torr) of the acquired liquid afforded 13.9 g (71%) of ethyl (*E*)-3-trimethylstannyl-2-butenolate (208) as a colourless oil that exhibited IR (neat): 1714, 1604, 1177, 771  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.17 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub> = 54 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.27 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.37 (d, 3H, *J* = 2 Hz, <sup>3</sup>J<sub>Sn-H</sub> = 50 Hz, =CCH<sub>3</sub>), 4.14 (q, 2H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.96 (q, 1H, *J* = 2 Hz, <sup>3</sup>J<sub>Sn-H</sub> = 72 Hz, =CH); <sup>13</sup>C NMR (50.3 MHz)  $\delta$ : -10.1, 14.3, 21.4, 59.5, 127.9, 164.4, 168.0. Anal. calcd. for C<sub>9</sub>H<sub>18</sub>O<sub>2</sub>Sn: C 39.04, H 6.55; found: C 38.88, H 6.59. Exact Mass calcd. for C<sub>8</sub>H<sub>15</sub>O<sub>2</sub>Sn (M<sup>+</sup>-CH<sub>3</sub>): 263.0094; found: 263.0090.

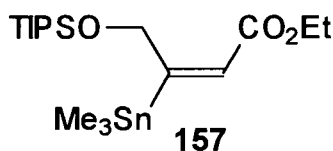
Preparation of ethyl (*E*)-3-trimethylstannyl-2-pentenoate (149)<sup>50</sup>



Following general procedure 4 outlined above, commercially available ethyl 2-pentynoate (124) was converted into the ester (149). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137) (1.03 mmol) in 5 mL of dry THF, EtOH (0.060

mL, 1.0 mmol) and ethyl 2-pentynoate (**124**) (100 mg, 0.792 mmol) in 0.5 mL of dry THF. Radial chromatography (4 mm plate, 98:2 hexanes-Et<sub>2</sub>O) of the crude product and distillation (48-61°C/0.12 Torr) of the acquired liquid afforded 159 mg (69%) of ethyl (*E*)-3-trimethylstannyl-2-pentenoate (**149**), a colourless oil that exhibited IR (neat): 1718, 1598, 1179, 774 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.21 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=54 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.05 (t, 3H, *J*= 8 Hz, =CCH<sub>2</sub>CH<sub>3</sub>), 1.29 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.89 (qd, 2H, *J*= 8, 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=64 Hz, =CCH<sub>2</sub>CH<sub>3</sub>), 4.16 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.94 (t, 1H, *J*= 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=74 Hz, =CHR); <sup>13</sup>C NMR (50.3 MHz) δ: -9.1, 14.1, 14.3, 27.9, 59.6, 126.9, 164.3, 174.5. Anal. calcd. for C<sub>10</sub>H<sub>20</sub>O<sub>2</sub>Sn: C 41.28, H 6.93; found: C 41.08, H 6.87. Exact Mass calcd. for C<sub>9</sub>H<sub>17</sub>O<sub>2</sub>Sn (M<sup>+</sup>-CH<sub>3</sub>): 277.0250; found: 277.0250.

Preparation of ethyl (*E*)-4-(triisopropylsiloxy)-3-trimethylstannyl-2-butenolate (**157**)<sup>50</sup>

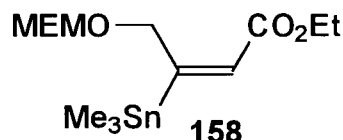


Following general procedure 4 outlined above, ethyl 4-(triisopropylsiloxy)-2-butyrate (**127**) was converted into the ester (**157**). The following amounts of reagents and solvents were used: [Me<sub>3</sub>SnCuCN]Li (**137**) (0.46 mmol) in 3 mL of dry THF, EtOH (0.027 mL, 0.46 mmol) and ethyl 4-(triisopropylsiloxy)-2-butyrate (**127**) (100 mg, 0.352 mmol) in 0.5 mL of dry THF. Flash chromatography (10 g silica gel, 97:3 hexanes-Et<sub>2</sub>O) of the crude product and distillation (115-120°C/0.11 Torr) of the acquired liquid afforded 117 mg (74%) of ethyl (*E*)-4-(triisopropylsiloxy)-3-trimethylstannyl-2-butenolate (**157**), a colourless oil that exhibited IR (neat): 1712, 1603, 1184, 1047 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.21 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>= 57 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.05 (d, 18H, *J*= 6 Hz, ((CH<sub>3</sub>)<sub>2</sub>CH)<sub>3</sub>Si-), 1.09-1.15 (m, 3H, ((CH<sub>3</sub>)<sub>2</sub>CH)<sub>3</sub>Si-), 1.27 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.12 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.95 (d, 2H, *J*= 2.5



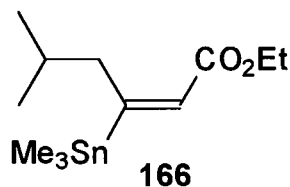
Hz,  $^3J_{\text{Sn-H}}=30$  Hz,  $=\text{CCH}_2\text{O}$ ), 5.89 (t, 1H,  $J=2.5$  Hz,  $^3J_{\text{Sn-H}}=78$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -7.9, 11.9, 14.3, 18.0, 59.8, 67.2, 123.4, 161.8, 178.5. Anal. calcd. for  $\text{C}_{18}\text{H}_{38}\text{O}_3\text{SiSn}$ : C 48.12, H 8.52; found: C 48.23, H 8.58. Exact Mass calcd. for  $\text{C}_{17}\text{H}_{35}\text{O}_3\text{SiSn}$  ( $\text{M}^+-\text{CH}_3$ ): 435.1376; found: 435.1374.

Preparation of ethyl (*E*)-4-[(2-methoxyethoxy)methoxy]-3-trimethylstannyl-2-butenolate (158)<sup>49</sup>



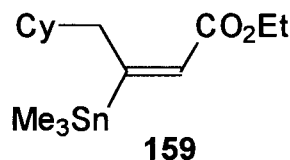
Following general procedure 4 outlined above, ethyl 4-[(2-methoxyethoxy)methoxy]-2-butyrate (128) was converted into the ester (158). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137), 0.60 mmol, in 4 mL of dry THF, EtOH (0.035 mL, 0.60 mmol) and ethyl 4-[(2-methoxyethoxy)methoxy]-2-butyrate (128), (100 mg, 0.462 mmol), in 0.5 mL of dry THF. Flash chromatography (10 g silica gel, 3:1 hexanes-Et<sub>2</sub>O) of the crude product and distillation (85-93°C/0.11 Torr) of the acquired liquid afforded 122 mg (70%) of ethyl (*E*)-4-[(2-methoxyethoxy)methoxy]-3-trimethylstannyl-2-butenolate (158), a colourless oil that exhibited IR (neat): 1709, 1608, 1370, 1186  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.19 (s, 9H,  $^2J_{\text{Sn-H}}=56$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.26 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 3.37 (s, 3H,  $-\text{OCH}_3$ ), 3.51-3.56 (m, 2H), 3.63-3.68 (m, 2H), 4.13 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.72 (s, 2H,  $-\text{OCH}_2\text{O}-$ ), 4.79 (d, 2H,  $J=2.5$  Hz,  $^3J_{\text{Sn-H}}=30$  Hz,  $=\text{CCH}_2$ ), 5.92 (t, 1H,  $J=2.5$  Hz,  $^3J_{\text{Sn-H}}=73$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -8.1, 14.2, 59.0, 59.9, 66.9, 71.7, 72.1, 95.2, 124.5, 164.3, 173.6. Anal. calcd. for  $\text{C}_{13}\text{H}_{26}\text{O}_5\text{Sn}$ : C 40.98, H 6.88; found: C 41.23, H 7.01. Exact Mass calcd. for  $\text{C}_{12}\text{H}_{23}\text{O}_5\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 367.0567; found: 367.0564.

Preparation of ethyl (*E*)-5-methyl-3-trimethylstannyl-2-hexenoate (166)



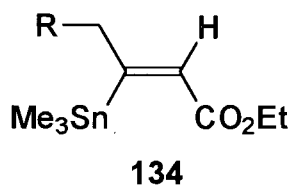
Following general procedure 4 outlined above, ethyl 5-methyl-2-hexynoate (**125**) was converted into the ester (**166**). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (**137**), 39.9 mmol, in 400 mL of dry THF, EtOH (2.30 mL, 39.9 mmol), and ethyl 5-methyl-2-hexynoate (**125**) (4.10 g, 26.6 mmol) in 25 mL of dry THF. Flash chromatography (100 g silica gel, 98:2 hexanes-Et<sub>2</sub>O) of the crude product and distillation (70-85°C/0.12 Torr) of the acquired liquid afforded 8.11 g (95%) of ethyl (*E*)-5-methyl-3-trimethylstannyl-2-hexenoate (**166**), a colourless oil that exhibited IR (neat): 1718, 1598, 1385, 1367, 1176, 771  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.21 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=54 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 0.93 (d, 6H, *J*= 7 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.29 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.66-1.70 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 2.82 (dd, 2H, *J*= 7, 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=62 Hz, -CH<sub>2</sub>C=), 4.17 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 6.03 (t, 1H, *J*= 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=76 Hz, =CH); <sup>13</sup>C NMR (50.3 MHz)  $\delta$ : -9.0, 14.3, 22.5, 29.1, 43.2, 59.6, 128.4, 164.5, 172.5. Anal. calcd. for C<sub>12</sub>H<sub>24</sub>O<sub>2</sub>Sn: C 45.18, H 7.58; found: C 44.99, H 7.57. Exact Mass calcd. for C<sub>11</sub>H<sub>21</sub>O<sub>2</sub>Sn (M<sup>+</sup>-CH<sub>3</sub>): 305.0564; found: 305.0557.

Preparation of ethyl (*E*)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**159**)<sup>50</sup>



Following general procedure 4 outlined above, ethyl 4-cyclohexyl-2-butynoate (**126**) was converted into the ester (**159**). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (**137**), 30.9 mmol, in 320 mL of dry THF, EtOH (1.78 mL, 30.9 mmol), and ethyl 4-cyclohexyl-2-butynoate (**126**) (4.00 g, 20.6 mmol) in 10 mL of dry THF. Flash chromatography (50 g silica gel, 98:2 hexanes-Et<sub>2</sub>O) of the crude product and distillation (120-130°C/0.12 Torr) of the acquired liquid afforded 5.98 g (81%) of ethyl (*E*)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**159**), a colourless oil that exhibited IR (neat): 1718, 1598, 1177, 770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.19 (s, 9H,  $^2J_{\text{Sn-H}}=56$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.95-1.05 (m, 2H), 1.13-1.23 (m, 3H), 1.29 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.32-1.40 (m, 1H), 1.60-1.75 (m, 5H), 2.83 (d, 2H,  $J=8$  Hz,  $^3J_{\text{Sn-H}}=61$  Hz,  $=\text{CCH}_2$ ), 4.16 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 6.03 (s, 1H,  $^3J_{\text{Sn-H}}=82$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (50.3 MHz)  $\delta$ : -9.0, 14.3, 26.39, 26.44, 33.2, 38.7, 41.9, 59.6, 128.4, 164.5, 172.4. Anal. calcd. for  $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Sn}$ : C 50.17, H 7.86; found: C 50.40, H 7.88. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{25}\text{O}_2\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 345.0877; found: 345.0881.

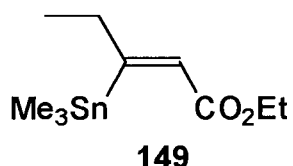
## 6.2 General Procedure 5: Preparation of ethyl (*Z*)-trimethylstannyl-2-alkenoates (**134**)<sup>50</sup>



To a cold (-48°C), stirred solution of  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (**137**) (1.01-1.09 equiv.) in dry THF was added, dropwise, a solution of the appropriate  $\alpha,\beta$ -acetylenic ester (1.0 equiv.) in dry THF and the mixture was stirred at -48°C for 2 hours and at 0°C for 2 hours. Aqueous  $\text{NH}_4\text{Cl-NH}_4\text{OH}$  (pH 8) (one-half the volume of the total volume of the reaction mixture) was added, the mixture was opened to the atmosphere, was allowed to warm to room temperature, and was stirred vigorously until the aqueous phase became deep blue. The phases were

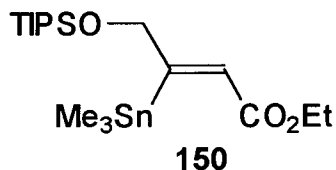
separated and the aqueous phase was extracted thoroughly with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. The crude product was separated by flash or radial chromatography and purified by distillation to afford the corresponding ethyl (*Z*)-3-trimethylstannyl-2-alkenoate (**134**).

Preparation of ethyl (*Z*)-3-trimethylstannyl-2-pentenoate (**149**)<sup>50</sup>



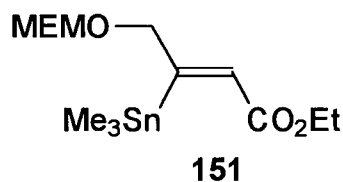
Following general procedure 5 outlined above, commercially available ethyl 2-pentynoate (**124**) was converted into the ester (**149**). The following amounts of reagents and solvents were used: [Me<sub>3</sub>SnCuCN]Li (**137**) (0.86 mmol) in 4 mL of dry THF and ethyl 2-pentynoate (**124**) (100 mg, 0.792 mmol) in 0.5 mL of dry THF. Radial chromatography (4 mm plate, 98:2 hexanes-Et<sub>2</sub>O) of the crude product and distillation (52-60°C/0.12 Torr) of the acquired liquid afforded 163 mg (70%) of ethyl (*Z*)-3-trimethylstannyl-2-pentenoate (**149**), a colourless oil that exhibited IR (neat): 1703, 1601, 1201, 772 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.18 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=55 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.04 (t, 3H, *J*= 8 Hz, =CCH<sub>2</sub>CH<sub>3</sub>), 1.29 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.45 (qd, 2H, *J*= 7, 1.5 Hz, <sup>3</sup>J<sub>Sn-H</sub>=43 Hz, =CCH<sub>2</sub>CH<sub>3</sub>), 4.18 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 6.36 (t, 1H, *J*= 1.5 Hz, <sup>3</sup>J<sub>Sn-H</sub>=120 Hz, =CH); <sup>13</sup>C NMR (50.3 MHz) δ: -7.5, 13.6, 14.3, 32.9, 60.2, 126.9, 168.1, 177.1. Anal. calcd. for C<sub>10</sub>H<sub>20</sub>O<sub>2</sub>Sn: C 41.28, H 6.93; found: C 41.47, H 7.09. Exact Mass calcd. for C<sub>9</sub>H<sub>17</sub>O<sub>2</sub>Sn (M<sup>+</sup>-CH<sub>3</sub>): 277.0250; found: 277.0244.

Preparation of ethyl (Z)-4-(triisopropylsiloxy)-3-trimethylstannyl-2-butenolate (150)<sup>50</sup>



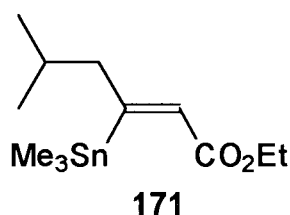
Following general procedure 5 outlined above, ethyl 4-(triisopropylsiloxy)-2-butyrate (127) was converted into the ester (150). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137), 0.37 mmol, in 3 mL of dry THF and ethyl 4-(triisopropylsiloxy)-2-butyrate (127) (100 mg, 0.35 mmol) in 0.5 mL of dry THF. Flash chromatography (10 g silica gel, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (100-104°C/0.11 Torr) of the acquired liquid afforded 120 mg (76%) of ethyl (Z)-4-(triisopropylsiloxy)-3-trimethylstannyl-2-butenolate (150), a colourless oil that exhibited IR (neat): 1702, 1609, 1465, 1299, 1191, 1044  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.18 (s, 9H,  $^2J_{\text{Sn-H}} = 56$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.05 (d, 18H,  $J = 6$  Hz,  $((\text{CH}_3)_2\text{CH})_3\text{Si-}$ ), 1.08-1.15 (m, 3H,  $((\text{CH}_3)_2\text{-CH})_3\text{Si-}$ ), 1.27 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.15 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.52 (d, 3H,  $J = 2.5$  Hz,  $^3J_{\text{Sn-H}} = 19$  Hz,  $=\text{CCH}_2\text{O}$ ), 6.72 (t, 1H,  $J = 2$  Hz,  $^3J_{\text{Sn-H}} = 114$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -7.9, 11.9, 14.2, 17.9, 60.3, 68.6, 124.6, 168.3, 171.6. Anal. calcd. for  $\text{C}_{18}\text{H}_{38}\text{O}_3\text{SiSn}$ : C 48.12, H 8.52; found: C 48.14, H 8.60. Exact Mass calcd. for  $\text{C}_{17}\text{H}_{35}\text{O}_3\text{SiSn}$  ( $\text{M}^+ - \text{CH}_3$ ): 435.1376; found: 435.1360.

Preparation of ethyl (Z)-4-[(2-methoxyethoxy)methoxy]-3-trimethylstannyl-2-butenolate (151)<sup>49</sup>



Following general procedure 5 outlined above, ethyl 4-[(2-methoxyethoxy)methoxy]-2-butyrate (128) was converted into the ester (151). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137), 0.49 mmol, in 4 mL of dry THF and ethyl 4-[(2-methoxyethoxy)methoxy]-2-butyrate (128) (100 mg, 0.46 mmol) in 0.5 mL of dry THF. Flash chromatography (10 g silica gel, 85:15 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (95-98°C/0.11 Torr) of the acquired liquid afforded 127 mg (72%) of ethyl (Z)-4-[(2-methoxyethoxy)methoxy]-3-trimethylstannyl-2-butenate (151), a colourless oil that exhibited IR (neat): 1702, 1608, 1368, 1198  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.18 (s, 9H,  $^2J_{\text{Sn-H}} = 56$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.28 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 3.37 (s, 3H,  $-\text{OCH}_3$ ), 3.52 (m, 2H), 3.71 (m, 2H), 4.17 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.38 (d, 2H,  $J = 2$  Hz,  $^3J_{\text{Sn-H}} = 20$  Hz,  $=\text{CCH}_2$ ), 4.75 (s, 2H,  $-\text{OCH}_2\text{O}-$ ), 6.63 (t, 1H,  $J = 2$  Hz,  $^3J_{\text{Sn-H}} = 112$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -7.7, 14.2, 58.9, 60.4, 66.9, 71.7, 72.4, 95.0, 125.8, 167.5, 168.7. Anal. calcd. for  $\text{C}_{13}\text{H}_{26}\text{O}_5\text{Sn}$ : C 40.98, H 6.88; found: C 41.20, H 7.01. Exact Mass calcd. for  $\text{C}_{12}\text{H}_{23}\text{O}_5\text{Sn}$  ( $\text{M}^+ - \text{CH}_3$ ): 367.0567; found: 367.0575.

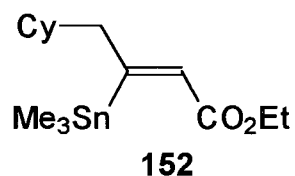
#### Preparation of ethyl (Z)-5-methyl-3-trimethylstannyl-2-hexenoate (171)



Following general procedure 5 outlined above, ethyl 5-methyl-2-hexynoate (125) was converted into the ester (171). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (137), 1.09 mmol, in 5 mL of dry THF and ethyl 5-methyl-2-hexynoate (125), (154 mg, 1.00 mmol), in 0.5 mL of dry THF. Flash chromatography (20 g silica gel, 98:2 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (82-90°C/0.12 Torr) of the acquired liquid

afforded 268 mg (84%) of ethyl (Z)-5-methyl-3-trimethylstannyl-2-hexenoate (**171**), a colourless oil that exhibited IR (neat): 1704, 1598, 1385, 1365, 1176, 769  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.15 (s, 9H,  $^2J_{\text{Sn-H}}=56$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.86 (d, 6H,  $J=7$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 1.28 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.61-1.68 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.28 (dd, 2H,  $J=7, 1$  Hz,  $^3J_{\text{Sn-H}}=54$  Hz,  $-\text{CH}_2\text{C}=\text{CH}$ ), 4.17 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 6.29 (t, 1H,  $J=1$  Hz,  $^3J_{\text{Sn-H}}=120$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : -7.3, 14.3, 22.4, 27.9, 49.4, 60.3, 129.1, 129.2, 174.7. Anal. calcd. for  $\text{C}_{12}\text{H}_{24}\text{O}_2\text{Sn}$ : C 45.18, H 7.58; found: C 45.45, H 7.49. Exact Mass calcd. for  $\text{C}_{11}\text{H}_{21}\text{O}_2\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 305.0564; found: 305.0558.

Preparation of ethyl (Z)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**152**)<sup>50</sup>

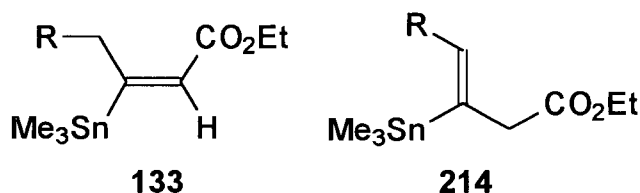


Following general procedure 5 outlined above, ethyl 4-cyclohexyl-2-butynoate (**126**) was converted into the ester (**152**). The following amounts of reagents and solvents were used:  $[\text{Me}_3\text{SnCuCN}]\text{Li}$  (**137**), 0.54 mmol, in 4.5 mL of dry THF and ethyl 4-cyclohexyl-2-butynoate (**126**) (100 mg, 0.515 mmol) in 1 mL of dry THF. Flash chromatography (12 g silica gel, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (104-107°C/0.12 Torr) of the acquired liquid afforded 149 mg (81%) of ethyl (Z)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**152**), a colourless oil that exhibited IR (neat): 1703, 1599, 1064  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.15 (s, 9H,  $^2J_{\text{Sn-H}}=55$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.80-0.92 (m, 2H), 1.10-1.21 (m, 4H), 1.26 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.30-1.36 (m, 1H), 1.56-1.71 (m, 4H), 2.28 (d, 2H,  $J=7$  Hz,  $^3J_{\text{Sn-H}}=56$  Hz,  $=\text{CCH}_2\text{R}$ ), 4.15 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 6.26 (s, 1H,  $^3J_{\text{Sn-H}}=124$  Hz,  $=\text{CH}$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -7.3, 14.3, 26.4, 26.5, 33.2, 37.5, 47.9, 60.3, 129.1, 167.8, 174.6. Anal. calcd.

for  $C_{15}H_{28}O_2Sn$ : C 50.17, H 7.86; found: C 50.10, H 7.82. Exact Mass calcd. for  $C_{14}H_{25}O_2Sn$  ( $M^+-CH_3$ ): 345.0877; found: 345.0871.

## 7 Preparation of ethyl (*E*)- and (*Z*)-3-trimethylstannyl-3-alkenoates

### 7.1 General Procedure 6: Preparation of ethyl (*Z*)-3-trimethylstannyl-3-alkenoates (214)

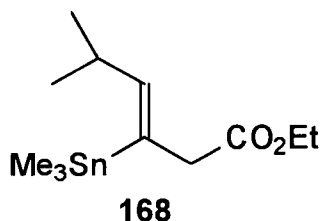


To a cold ( $-78^\circ C$ ), stirred solution of commercially available potassium hexamethyldisilazide (2.4 equiv.) in dry THF ( $\sim 10$  mL/mmol of ester) was added, dropwise, HMPA (2.3 equiv.). After the resultant mixture had been stirred for 5 minutes, a solution of the appropriate ethyl (*E*)-3-trimethylstannyl-2-alkenoate (**133**) (1 equiv.) in dry THF ( $\sim 1$  mL/mmol of ester) was added dropwise, over a period of 10 minutes. The mixture was stirred at  $-78^\circ C$  for 1 hour, at  $-48^\circ C$  for 4 hours, recooled to  $-78^\circ C$ , and cannulated into a cold ( $-98^\circ C$ ), stirred solution of glacial acetic acid ( $\sim 0.33$  mL/mmol of ester) in dry  $Et_2O$  ( $\sim 3$  mL/mmol of ester). The solution was allowed to warm to room temperature and saturated aqueous  $NaHCO_3$  solution (one-half the volume of the total volume of the reaction mixture) was added and the mixture was thoroughly extracted with  $Et_2O$ . The combined extracts were washed with brine, dried ( $MgSO_4$ ), and concentrated. Flash chromatography of the crude product, followed by bulb-to-bulb distillation of the acquired oil, afforded the corresponding alkyl (*Z*)-3-trimethylstannyl-3-alkenoate (**214**). It is important to note that the alkyl (*E*)-3-trimethylstannyl-2-alkenoate (**133**) must be of high purity and freshly distilled prior to use.



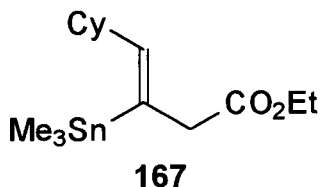
or the product resulting from the above reaction will be the corresponding alkyl  
(*E*)-3-trimethylstannyl-3-alkenoate (210).

Preparation of ethyl (*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (168)



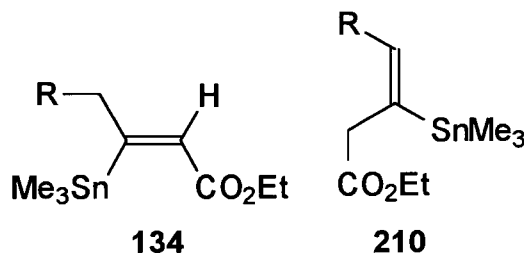
Following general procedure 6 outlined above, ethyl  
(*E*)-5-methyl-3-trimethylstannyl-2-hexenoate (166) was converted into the ester (168). The  
following amounts of reagents and solvents were used: potassium hexamethyldisilazide (0.60 g,  
3.0 mmol) in 13 mL dry THF, HMPA (0.516 g, 2.88 mmol), and ethyl  
(*E*)-5-methyl-3-trimethylstannyl-2-hexenoate (166) (400 mg, 1.25 mmol) in 1 mL of dry THF.  
Flash chromatography (50 g silica gel, 98:2 hexanes-Et<sub>2</sub>O) of the crude product and distillation  
(70-85°C/0.12 Torr) of the acquired liquid afforded 359 mg (90%) of ethyl  
(*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (168), a colourless oil that exhibited IR (neat):  
1734, 1369, 1179, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.18 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=56 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>),  
0.97 (d, 6H, *J*= 7 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.26 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.16-2.26 (m, 1H,  
-CH(CH<sub>3</sub>)<sub>2</sub>), 3.15 (d, 2H, *J*= 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=53 Hz, =C-CH<sub>2</sub>-), 4.12 (q, 2H, *J*= 7 Hz,  
-OCH<sub>2</sub>CH<sub>3</sub>), 5.82 (dt, 1H, *J*= 10, 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=131 Hz, =CH); <sup>13</sup>C NMR (50.3 MHz) δ:  
-7.9, 14.2, 23.1, 34.3, 44.9, 60.4, 133.1, 151.6, 173.0. Anal. calcd. for C<sub>12</sub>H<sub>24</sub>O<sub>2</sub>Sn: C 45.18,  
H 7.58; found: C 45.39, H 7.58. Exact Mass calcd. for C<sub>11</sub>H<sub>21</sub>O<sub>2</sub>Sn (M<sup>+</sup>-CH<sub>3</sub>): 305.0564;  
found: 305.0560.

Preparation of ethyl (*Z*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**167**)



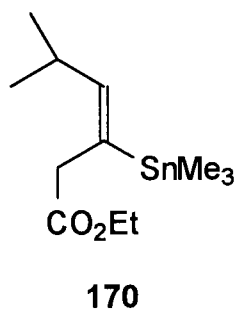
Following general procedure 6 outlined above, ethyl (*E*)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**159**) was converted into the ester (**167**). The following amounts of reagents and solvents were used: potassium hexamethyldisilazide (0.348 g, 1.74 mmol) in 7 mL dry THF, HMPA (0.300 g, 1.67 mmol), and ethyl (*E*)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**159**) (260 mg, 0.724 mmol) in 1 mL of dry THF. Flash chromatography (25 g silica gel, 97:3 hexanes-Et<sub>2</sub>O) of the crude product and distillation (115-120°C/0.12 Torr) of the acquired liquid afforded 221 mg (85%) of ethyl (*Z*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**167**), a colourless oil that exhibited IR (neat): 1734, 1622, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.18 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=54 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.05-1.20 (m, 4H), 1.24 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.55-1.75 (m, 6H), 1.80-1.90 (m, 1H), 3.18 (s, 2H, <sup>3</sup>J<sub>Sn-H</sub>=56 Hz, =C-CH<sub>2</sub>-), 4.11 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.86 (d, 1H, *J*= 9 Hz, <sup>3</sup>J<sub>Sn-H</sub>=132 Hz, =CH); <sup>13</sup>C NMR (100.4 MHz) δ: -8.0, 14.2, 25.9, 26.0, 33.3, 44.4, 44.8, 60.4, 134.0, 150.3, 173.0. Anal. calcd. for C<sub>15</sub>H<sub>28</sub>O<sub>2</sub>: C 50.17, H 7.86; found: C 50.47, H 7.89. Exact Mass calcd. for C<sub>14</sub>H<sub>25</sub>O<sub>2</sub> (M<sup>+</sup>-CH<sub>3</sub>): 345.0877; found: 345.0878.

## 7.2 General Procedure 7: Preparation of ethyl (*E*)-3-trimethylstannyl-3-alkenoates (210)



To a cold ( $-78^\circ\text{C}$ ), stirred solution of potassium hexamethyldisilide (2.4 equiv.) in dry THF ( $\sim 10$  mL/mmol of ester) was added, dropwise, HMPA (2.3 equiv.). After the resultant mixture had been stirred for 5 minutes, a solution of the appropriate ethyl (*Z*)-3-trimethylstannyl-2-alkenoate (**134**) (1 equiv.) in dry THF ( $\sim 1$  mL/mmol of ester) was added dropwise over a period of 10 minutes. The mixture was stirred at  $-78^\circ\text{C}$  for 1 hour, at  $-48^\circ\text{C}$  for 4 hours, recooled to  $-78^\circ\text{C}$ , and cannulated into a cold ( $-98^\circ\text{C}$ ), stirred solution of glacial acetic acid ( $\sim 0.33$  mL/mmol of ester) in dry  $\text{Et}_2\text{O}$  ( $\sim 3$  mL/mmol of ester). The solution was allowed to warm to room temperature and saturated aqueous  $\text{NaHCO}_3$  (one half the volume of the total volume of the reaction mixture) was added and the mixture was thoroughly extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Flash chromatography of the crude product followed by bulb-to-bulb distillation of the acquired oil afforded the corresponding ethyl (*E*)-3-trimethylstannyl-3-alkenoate (**210**).

### Preparation of ethyl (*E*)-5-methyl-3-trimethylstannyl-3-hexenoate (170)



Following general procedure 7 outlined above, ethyl

(*Z*)-5-methyl-3-trimethylstannyl-2-hexenoate (**171**) was converted into the ester (**170**). The following amounts of reagents and solvents were used: potassium hexamethyldisilazide (0.24 g, 1.2 mmol) in 5 mL dry THF, HMPA (0.21 g, 1.2 mmol), and ethyl

(*Z*)-5-methyl-3-trimethylstannyl-2-hexenoate (**171**), (159 mg, 0.499 mmol), in 0.5 mL of dry THF. Flash chromatography (10 g silica gel, 98:2 hexanes-Et<sub>2</sub>O) of the crude product and distillation (70–73°C/0.10 Torr) of the acquired liquid afforded 139 mg (87%) of ethyl

(*E*)-5-methyl-3-trimethylstannyl-3-hexenoate (**170**), a colourless oil that exhibited IR (neat):

1733, 1611, 1465, 1298, 1181 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.10 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=54 Hz,

-Sn(CH<sub>3</sub>)<sub>3</sub>), 0.93 (d, 6H, *J*= 7 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.22 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>),

2.64–2.72 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 3.26 (d, 2H, *J*= 1.5 Hz, <sup>3</sup>J<sub>Sn-H</sub>=55 Hz, =C-CH<sub>2</sub>-), 4.09 (q,

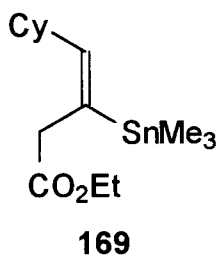
2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.50 (dt, 1H, *J*= 6, 1.5 Hz, <sup>3</sup>J<sub>Sn-H</sub>=75 Hz, =CH); <sup>13</sup>C NMR

(100.4 MHz) δ: -8.8, 14.2, 22.9, 27.7, 37.7, 60.5, 132.9, 151.1, 172.7. Anal. calcd. for

C<sub>12</sub>H<sub>24</sub>O<sub>2</sub>Sn: C 45.18, H 7.58; found: C 45.21, H 7.52. Exact Mass calcd. for C<sub>11</sub>H<sub>21</sub>O<sub>2</sub>Sn

(M<sup>+</sup>-CH<sub>3</sub>): 305.0564; found: 305.0560.

#### Preparation of ethyl (*E*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**169**)



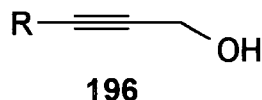
Following general procedure 7 outlined above, ethyl

(*Z*)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**152**) was converted into the ester (**169**). The following amounts of reagents and solvents were used: potassium hexamethyldisilazide (0.200

g, 1.00 mmol) in 5 mL dry THF, HMPA (0.17 g, 0.95 mmol), and ethyl (Z)-4-cyclohexyl-3-trimethylstannyl-2-butenolate (**152**) (150 mg, 0.418 mmol) in 0.5 mL of dry THF. Flash chromatography (10 g silica gel, 97:3 hexanes-Et<sub>2</sub>O) of the crude product and distillation (84-85°C/0.11 Torr) of the acquired liquid afforded 137 mg (91%) of ethyl (E)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**169**), a colourless oil that exhibited IR (neat): 1733, 1610, 1180 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.09 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=54 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.00-1.12 (m, 2H), 1.13-1.20 (m, 2H), 1.23 (t, 3H, J= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.54-1.73 (m, 6H), 2.30-2.40 (m, 1H), 3.26 (d, 2H, J= 1.5 Hz, <sup>3</sup>J<sub>Sn-H</sub>=56 Hz, =C-CH<sub>2</sub>-), 4.10 (q, 2H, J= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.51 (dt, 1H, J= 9, 1.5 Hz, <sup>3</sup>J<sub>Sn-H</sub>=76 Hz, =CH); <sup>13</sup>C NMR (50.2 MHz) δ: -8.7, 14.2, 25.9, 26.0, 32.9, 37.6, 37.7, 60.6, 133.6, 149.7, 204.1. Anal. calcd. for C<sub>15</sub>H<sub>28</sub>O<sub>2</sub>Sn: C 50.17, H 7.86; found: C 50.55, H 7.86. Exact Mass calcd. for C<sub>14</sub>H<sub>25</sub>O<sub>2</sub>Sn (M<sup>+</sup>-CH<sub>3</sub>): 345.0877; found: 345.0874.

## 8 Preparation of alkylating agents

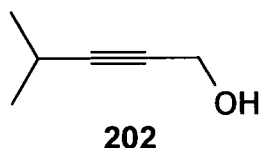
### 8.1 General Procedure 8: Preparation of 2-alkyn-1-ols (**196**) from 1,1-dibromo-1-alkenes (**195**)<sup>43</sup>



To a cold (-78 °C), stirred solution of the appropriate 1,1-dibromo-1-alkene (**196**) (1 equiv.) in dry THF ( ~10 mL/mmol of the substrate) was added, dropwise, a solution of *n*-butyllithium (2.5 equiv.) in hexanes. The mixture was stirred at -78°C for 1 hour, at room temperature for 1 hour, and was then recooled to -20°C. Paraformaldehyde (3 equiv.) was added and the mixture was stirred at -20°C for 1 hour and at room temperature for 1 hour. Saturated aqueous NaHCO<sub>3</sub> solution (three-quarter the volume of the total volume of the

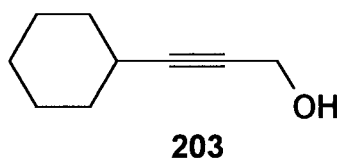
reaction mixture) was added and the mixture was thoroughly extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Distillation of the acquired oil afforded the corresponding 2-alkyn-1-ol (196).

#### Preparation of 4-methyl-2-pentyn-1-ol (202)



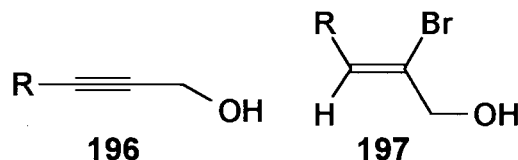
Following general procedure 8 outlined above, 1,1-dibromo-3-methyl-1-butene (200) was converted into the alcohol (202). The following amounts of reagents and solvents were used: substrate (200) (10.0 g, 43.9 mmol) in 450 mL dry THF, *n*-butyllithium (110 mmol) in hexanes, and paraformaldehyde (3.95 g, 132 mmol). Normal workup, followed by distillation (63-64°C/12 Torr) of the crude product provided 3.42 g (79%) of 4-methyl-2-pentyn-1-ol (10) as a colourless oil which exhibited IR (neat): 3400 (br), 2256, 1465, 1320, 1055 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz) δ: 1.14 (d, 6H, *J*= 7.5 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.60 (t, 1H, *J*= 3 Hz, -OH), 2.51-2.61 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 4.22 (br d, 2H, *J*= 3 Hz, ≡C-CH<sub>2</sub>OH); <sup>13</sup>C NMR (125 MHz) δ: 20.5, 22.9, 51.3, 88.0, 91.9. Exact Mass calcd. for C<sub>6</sub>H<sub>10</sub>O: 98.0732; found: 98.0732.

#### Preparation of 3-cyclohexyl-2-propyn-1-ol (203)



Following general procedure 8 outlined above, 1,1-dibromo-2-cyclohexylethene (**201**) was converted into the alcohol (**203**). The following amounts of reagents and solvents were used: substrate (**201**) (13.1 g, 48.9 mmol) in 500 mL dry THF, *n*-butyllithium (122 mmol) in hexanes, and paraformaldehyde (4.40 g, 147 mmol). Normal workup, followed by distillation (91°C /12 Torr) of the crude product, provided 5.87 g (87%) of 3-cyclohexyl-2-propyn-1-ol (**11**) as a colourless oil which exhibited IR (neat): 3360 (br), 2229, 1449, 1018 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 1.20-1.71 (m, 11H), 2.31-2.41 (m, 1H, -C $\equiv$ CCH), 4.23 (dd, 2H,  $J$ = 6, 1 Hz, -CH<sub>2</sub>OH); <sup>13</sup>C NMR (100.4 MHz)  $\delta$ : 24.8, 25.7, 29.0, 32.5, 51.4, 78.1, 90.6. Anal. calcd. for C<sub>9</sub>H<sub>14</sub>O: C 78.21, H 10.21; found: C 78.24, H 10.30. Exact Mass calcd. for C<sub>9</sub>H<sub>14</sub>O: 138.1045; found: 138.1043.

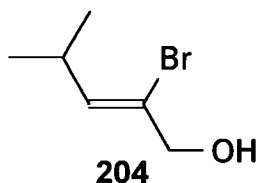
## 8.2 General Procedure 9: Preparation of the (Z)-2-bromo-2-alken-1-ols (**197**)<sup>56</sup>



To a cold (-20°C), stirred solution of the appropriate 2-alkyne-1-ol (**196**) in dry Et<sub>2</sub>O (~1 mL/mmol of the alcohol) were added sequentially, dropwise, solutions of *n*-butyllithium (1 equiv.) in hexanes and Dibal (3 equiv.) in hexanes. The mixture was heated at 35°C for 64 hours, and was then recooled to 0°C. Ethyl acetate (2 equiv.) was added and the mixture was stirred at 0°C for 10 min., cooled to -78°C, and cannulated into a cold (-78°C) solution of NBS (5 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (~20 mL/mmol of the substrate alcohol). The resultant mixture was stirred at -78°C for 15 minutes. Saturated aqueous sodium potassium tartrate (one half the volume of the total volume of the reaction mixture) was added and the mixture was thoroughly extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and

concentrated. Flash or radial chromatography of the crude product followed by bulb-to-bulb distillation of the acquired oil afforded the corresponding (Z)-2-bromo-2-alken-1-ol (197).

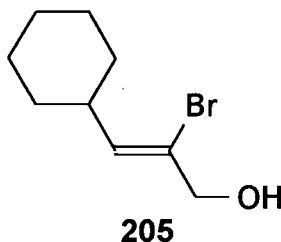
Preparation of (Z)-2-bromo-4-methyl-2-penten-1-ol (204)



Following general procedure 9 outlined above, 4-methyl-2-pentyn-1-ol (**202**) was converted into the alcohol (**204**). The following amounts of reagents and solvents were used: substrate (**202**) (0.250 g, 2.55 mmol) in 3 mL dry Et<sub>2</sub>O, *n*-butyllithium (2.55 mmol) in hexanes, Dibal (7.65 mmol) in hexanes, EtOAc (0.49 mL, 5.1 mmol), and NBS (2.27 g, 12.8 mmol) in 50 mL dry CH<sub>2</sub>Cl<sub>2</sub>. Normal workup, followed by flash chromatography (25g silica gel, 3:1 hexanes-Et<sub>2</sub>O) of the crude product and then distillation (45-50°C/12 Torr) of the acquired liquid provided 286 mg (63%) of (Z)-2-bromo-4-methyl-2-penten-1-ol (**204**) as a colourless oil which exhibited IR (neat): 3348 (br), 1657, 1466, 1083 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.00 (d, 6H, *J*= 7 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.87 (t, 1H, *J*= 8 Hz, -OH), 2.65-2.75 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 4.20 (d, 2H, *J*= 8 Hz, =C-CH<sub>2</sub>OH), 5.80 (d, 1H, *J*= 8 Hz, =CH); NOE difference experiment: irradiation at δ 4.20 led to enhancement of the signal at δ 5.80; <sup>13</sup>C NMR (75.3 MHz) δ: 21.6, 30.6, 68.5, 124.3, 137.1. Exact Mass calcd. for C<sub>6</sub>H<sub>11</sub><sup>79</sup>BrO: 177.9992; found: 177.9980.

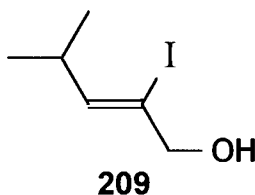


Preparation of (Z)-2-bromo-3-cyclohexyl-2-propen-1-ol (205)



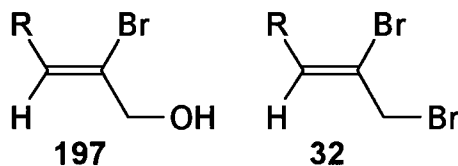
Following general procedure 9 outlined above, 3-cyclohexyl-2-propyn-1-ol (**203**) was converted into the alcohol (**205**). The following amounts of reagents and solvents were used: substrate (**203**) (1.20 g, 8.68 mmol) in 8.5 mL dry Et<sub>2</sub>O, *n*-butyllithium (8.68 mmol) in hexanes, Dibal (26 mmol) in hexanes, EtOAc (1.67 mL, 17.4 mmol), and NBS (7.75 g, 43.4 mmol) in 160 mL dry CH<sub>2</sub>Cl<sub>2</sub>. Normal workup, followed by radial chromatography (4 mm plate, 3:1 hexanes-Et<sub>2</sub>O) of the crude product and distillation (60-65°C/0.12 Torr) of the acquired liquid provided 985 mg (52%) of (Z)-2-bromo-3-cyclohexyl-2-propen-1-ol (**205**) as a colourless oil which exhibited IR (neat): 3343 (br), 1449, 1082 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.03-1.42 (m, 5H), 1.61-1.75 (m, 5H), 1.85 (t, 1H, *J* = 7 Hz, -OH), 2.41 (m, 1H, =C-CH), 4.20 (d, 2H, *J* = 7 Hz, =C-CH<sub>2</sub>OH), 5.80 (d, 1H, *J* = 9 Hz, =CH); <sup>13</sup>C NMR (100.4 MHz) δ: 25.5, 25.8, 31.6, 39.9, 68.5, 124.4, 135.5. Anal. calcd. for C<sub>9</sub>H<sub>15</sub>OBr: C 49.33, H 6.90; found: C 49.60, H 6.90. Exact Mass calcd. for C<sub>9</sub>H<sub>15</sub><sup>81</sup>BrO: 220.0287; found: 220.0289.

Preparation of (Z)-2-iodo-4-methyl-2-penten-1-ol (209)



To a cold ( $-20^{\circ}\text{C}$ ), stirred solution of 4-methyl-2-pentyn-1-ol (**202**) (100 mg, 1.02 mmol) in dry  $\text{Et}_2\text{O}$  (1 mL) were added sequentially, dropwise, solutions of *n*-butyllithium (1.02 mmol) in hexanes and Dibal (3 mmol) in hexanes. The mixture was heated at  $35^{\circ}\text{C}$  for 48 hours, and was then recooled to  $0^{\circ}\text{C}$ . Ethyl acetate (0.200 g, 2.08 mmol) was added and the mixture was stirred at  $0^{\circ}\text{C}$  for 10 min., cooled to  $-78^{\circ}\text{C}$ , and was cannulated into a cold ( $-78^{\circ}\text{C}$ ) solution of iodine (2.4 g, 9.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20 mL). The resultant mixture was stirred at  $-78^{\circ}\text{C}$  for 15 minutes. Saturated aqueous sodium thiosulphate (13 mL) was added and the mixture was thoroughly extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Flash chromatography (10 g silica gel, 4:1 petroleum ether- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation ( $80\text{--}90^{\circ}\text{C}/15$  Torr) of the acquired oil afforded 105 mg (46%) of (*Z*)-2-iodo-4-methyl-2-penten-1-ol (**209**) as a colourless oil which exhibited IR (neat): 3347 (br), 1641, 1465,  $1270\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.02 (d, 6H,  $J=7$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 1.82 (br s, 1H,  $-\text{OH}$ ), 2.52-2.62 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 4.21 (s, 2H,  $=\text{C}-\text{CH}_2\text{OH}$ ), 5.68 (d, 1H,  $J=9$  Hz,  $=\text{CH}$ ); NOE difference experiment: irradiation at  $\delta$  5.68 led to enhancement of the signal at 4.21;  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 21.4, 35.4, 71.6, 128.3, 142.8. Exact Mass calcd. for  $\text{C}_6\text{H}_{11}\text{IO}$ : 225.9855; found: 225.9855.

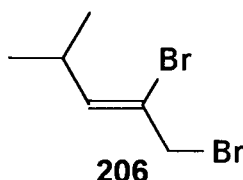
### 8.3 General Procedure 10: Preparation of the (*Z*)-1,2-dibromo-2-alkenes (**32**)



To a stirred solution of triphenylphosphine (1.1 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  ( $\sim 4$  mL/mmol of the alcohol substrate) was added, dropwise, bromine (1.1 equiv.) until a faint yellow colour persisted and then a few crystals of triphenylphosphine were added until the solution became colourless. The mixture was stirred for 10 minutes at room temperature and a solution of the

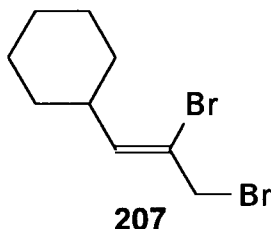
appropriate alcohol (197) (1 equiv.) in dry  $\text{CH}_2\text{Cl}_2$  ( $\sim 2.7$  mL/mmol of alcohol) was added. The resultant mixture was stirred at room temperature for 3.5 hours. *n*-Pentane (equal volume to the total volume of the reaction mixture) was added and the resultant slurry was poured onto a short column of Florisil (1 g Florisil/mmol of alcohol substrate). The column was eluted with 5 volumes of pentane (each of equal volume to the total volume of the reaction mixture) and the combined eluate was concentrated. Radial chromatography of the crude product, followed by bulb-to-bulb distillation of the acquired oil, gave the corresponding (*Z*)-1,2-dibromo-2-alkene (32).

Preparation of (*Z*)-1,2-dibromo-4-methyl-2-pentene (206)



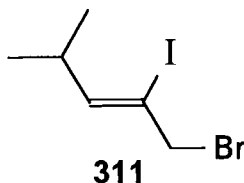
Following general procedure 10 outlined above, (*Z*)-2-bromo-4-methyl-2-penten-1-ol (204) was converted into the dibromide (206). The following amounts of reagents and solvents were used: triphenylphosphine (1.29 g, 4.91 mmol) in 18 mL of dry  $\text{CH}_2\text{Cl}_2$ , bromine (0.78 g, 4.9 mmol), and alcohol (204) (0.800 g, 4.47 mmol) in 12 mL dry  $\text{CH}_2\text{Cl}_2$ . Normal workup, followed by radial chromatography (4 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) and distillation ( $35\text{--}40^\circ\text{C}/12$  Torr) afforded 0.81g (76%) of (*Z*)-1,2-dibromo-4-methyl-2-pentene (206) as a colourless oil that exhibited IR (neat):  $1643, 1213\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.02 (d, 6H,  $J = 7$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 2.62-2.71 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 4.21 (s, 2H,  $=\text{CCH}_2\text{Br}$ ), 5.91 (d, 1H,  $J = 9$  Hz,  $=\text{CH}$ ); NOE difference experiment: irradiation at  $\delta$  4.21 led to enhancement of the signal at 5.91;  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 21.3, 39.1, 31.35, 120.1, 141.2. Exact Mass calcd. for  $\text{C}_6\text{H}_{10}^{81}\text{Br}^{79}\text{Br}$ : 241.9131; found: 241.9133.

Preparation of (Z)-2,3-dibromo-1-cyclohexyl-1-propene (207)



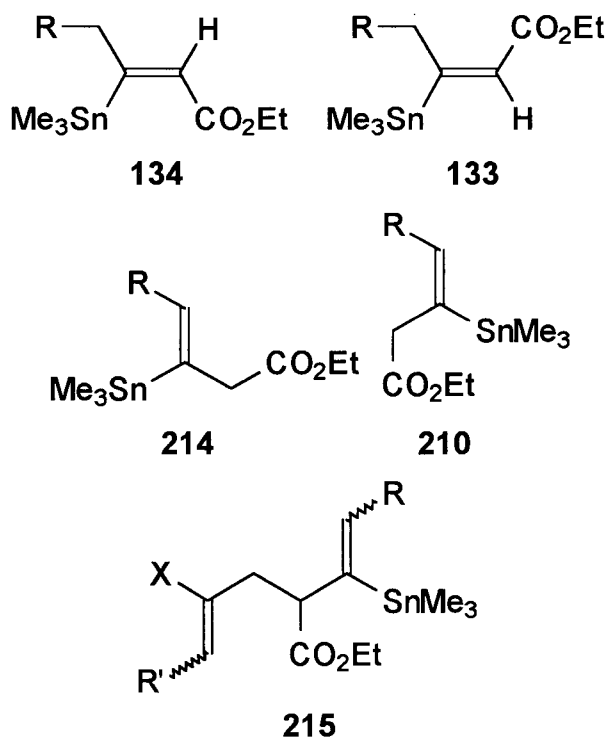
Following general procedure 10 outlined above, (Z)-2-bromo-3-cyclohexyl-2-propen-1-ol (**205**) was converted into the dibromide (**207**). The following amounts of reagents and solvents were used: triphenylphosphine (1.05 g, 4.00 mmol) in 16 mL dry  $\text{CH}_2\text{Cl}_2$ , bromine (0.64 g, 4.0 mmol), and alcohol (**205**) (0.800 g, 3.65 mmol) in 10 mL dry  $\text{CH}_2\text{Cl}_2$ . Normal workup, followed by radial chromatography (4 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) and distillation (58-63°C/0.12 Torr) afforded 0.756 g (73%) of (Z)-2,3-dibromo-1-cyclohexyl-1-propene (**207**) as a colourless oil that exhibited IR (neat): 1641, 1241  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.03-1.37 (m, 6H), 1.60-1.78 (m, 4H), 2.32-2.43 (m, 1H), 4.21 (s, 2H,  $=\text{C}-\text{CH}_2\text{Br}$ ), 5.92 (d, 1H,  $J = 9$  Hz,  $=\text{CH}$ ); NOE difference experiment: irradiation at  $\delta$  4.21 led to enhancement of the signal at 5.92;  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 25.4, 25.8, 31.3, 39.2, 40.7, 120.4, 139.8. Anal. calcd. for  $\text{C}_9\text{H}_{14}\text{Br}_2$ : C 38.33, H 5.00; found: C 38.60, H 5.00. Exact Mass calcd. for  $\text{C}_9\text{H}_{14}^{81}\text{Br}^{79}\text{Br}$ : 281.9444; found: 281.9445.

Preparation of (Z)-1-Bromo-2-iodo-4-methyl-2-pentene (311)



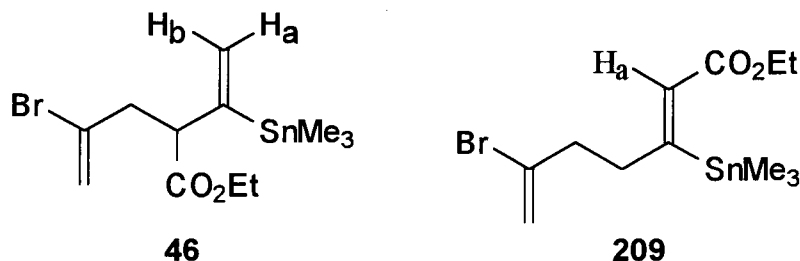
Following general procedure 10 outlined above, (*Z*)-2-iodo-4-methyl-2-penten-1-ol (**209**) was converted into (*Z*)-1-bromo-2-iodo-4-methyl-2-pentene (**311**). The following amounts of reagents and solvents were used: triphenylphosphine (0.320 g, 1.22 mmol) in 5 mL dry CH<sub>2</sub>Cl<sub>2</sub>, bromine (0.19 g, 1.2 mmol), and alcohol (**209**) (0.250 g, 1.11 mmol) in 5 mL dry CH<sub>2</sub>Cl<sub>2</sub>. Normal workup, followed by distillation (45-50°C/12 Torr) afforded 0.17 g (53%) of (*Z*)-1-bromo-2-iodo-4-methyl-2-pentene (**311**) as a colourless oil that exhibited IR (neat): 1631, 1464, 1209 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.04 (d, 6H, *J* = 7 Hz, -CH(CH<sub>3</sub>)<sub>2</sub>), 2.48-2.56 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 4.32 (s, 2H, =CCH<sub>2</sub>Br), 5.74 (d, 1H, *J* = 9 Hz, =CH); <sup>13</sup>C NMR (75.3 MHz) δ: 21.2, 36.1, 43.5, 128.4, 147.2. Exact Mass calcd. for C<sub>6</sub>H<sub>10</sub><sup>81</sup>BrI: 289.8994; found: 289.8996.

9. General Procedure 11: Preparation of the diene esters (**215**)



To a cold ( $-78^{\circ}\text{C}$ ), stirred solution of lithium diisopropylamide (1.1-2.4 equiv.) in dry THF (6.4 - 14.5 mL/mmol of ester substrate) was added, dropwise, HMPA (1.1-2.4 equiv.). After the resultant mixture had been stirred for 15 minutes, a solution of the appropriate ethyl 3-trimethylstannyl-2-alkenoate (**133** or **134**) or ethyl 3-trimethylstannyl-3-alkenoate (**210** or **214**) in dry THF (0.95-1.8 mL/mmol of ester substrate) was added dropwise. The mixture was stirred at  $-78^{\circ}\text{C}$  for 30 minutes, at  $0^{\circ}\text{C}$  for 30 minutes, and recooled to  $-78^{\circ}\text{C}$ . The appropriate allylic halide (1.3-1.5 equiv.) was added rapidly and the reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 hour. Saturated aqueous  $\text{NaHCO}_3$  solution (one half the volume of the total volume of the reaction mixture) was added and the mixture thoroughly extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Flash, radial, or liquid chromatography of the crude product, followed by bulb-to-bulb distillation of the acquired oil, afforded the corresponding diene ester (**215**).

Preparation of ethyl 4-bromo-2-[1-(trimethylstannyl)ethenyl]-4-pentenoate (**46**)<sup>16</sup>

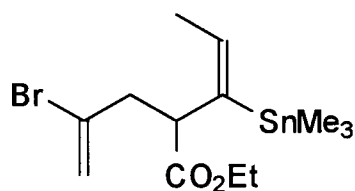


Following general procedure 11 outlined above, ethyl (*E*)-3-trimethylstannyl-2-butenate (**208**) was converted into the diene ester (**46**). The following amounts of reagents and solvents were used: LDA (9.3 mmol) in 55 mL of dry THF, HMPA (1.7 g, 9.3 mmol), ethyl (*E*)-3-trimethylstannyl-2-butenate (**208**) (2.33 g, 8.41 mmol) in 8 mL of dry THF, and 2,3-dibromopropene (**20**) (2.52 g, 12.6 mmol). Radial chromatography (4 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation

(78-84°C/0.12 Torr) of the acquired oils afforded 2.03 g (61%) of the more polar diene ester (46) as a colourless oil and 0.25 g (8%) of the less polar diene ester (209) also as a colourless oil. Diene ester (46) exhibited IR (neat): 1728, 1631, 1277, 771  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.18 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.24 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.53 (dd, 1H,  $J=15, 8$  Hz, one of  $=\text{C}(\text{Br})-\text{CH}_2$ ), 2.92 (dd, 1H,  $J=15, 8$  Hz, one of  $=\text{C}(\text{Br})-\text{CH}_2$ ), 3.58 (br t, 1H,  $J=8$  Hz,  $^3J_{\text{Sn-H}}=62$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.08-4.16 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 5.34 (d, 1H,  $J=2$  Hz,  $^3J_{\text{Sn-H}}=66$  Hz,  $\text{H}_a$ ), 5.41 (d, 1H,  $J=2$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.54 (d, 1H,  $J=2$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.82 (dd, 1H,  $J=2, 1$  Hz,  $^3J_{\text{Sn-H}}=137$  Hz,  $\text{H}_b$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -8.2, 14.2, 44.2, 54.3, 60.9, 118.9, 128.7, 130.9, 151.4, 173.3. Anal. calcd. for  $\text{C}_{12}\text{H}_{21}\text{BrO}_2\text{Sn}$ : C 36.43, H 5.35; found: C 36.23, H 5.28. Exact Mass calcd. for  $\text{C}_{11}\text{H}_{18}^{79}\text{BrO}_2\text{Sn}(\text{M}^+-\text{CH}_3)$ : 380.9511; found: 380.9508.

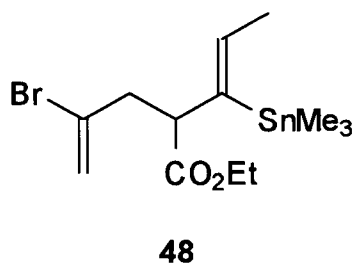
Diene ester (209) exhibited IR (neat): 1703, 1630, 1209, 772  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.21 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.29 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.50 (br t, 2H,  $J=8$  Hz,  $=\text{CCH}_2$ ), 2.70 (br t, 2H,  $J=8$  Hz,  $=\text{CCH}_2$ ), 4.18 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 5.40 (br d, 1H,  $J=2$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.55 (br d, 1H,  $J=2$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 6.40 (dd, 1H,  $J=2, 1$  Hz,  $^3J_{\text{Sn-H}}=118$  Hz,  $\text{H}_a$ ). Anal. calcd. for  $\text{C}_{12}\text{H}_{21}\text{BrO}_2\text{Sn}$ : C 36.43, H 5.35; found: C 36.19, H 5.27. Exact Mass calcd. for  $\text{C}_{11}\text{H}_{18}^{79}\text{BrO}_2\text{Sn}(\text{M}^+-\text{CH}_3)$ : 380.9511; found: 380.9511.

Preparation of ethyl (*E*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (47)<sup>16</sup>



Following general procedure 11 outlined above, ethyl (Z)-3-trimethylstannyl-2-pentenoate (**149**) was converted into the diene ester (**47**). The following amounts of reagents and solvents were used: LDA (0.79 mmol) in 5 mL of dry THF, HMPA (142 mg, 0.792 mmol), ethyl (Z)-3-trimethylstannyl-2-pentenoate (**149**) (100 mg, 0.344 mmol) in 0.5 mL of dry THF, and 2,3-dibromopropene (**20**) (103 mg, 0.516 mmol). Flash chromatography (10 g of silica gel, 19:1 hexanes-Et<sub>2</sub>O) of the crude product followed by distillation (85-90°C/0.12 Torr) of the acquired oil afforded 101 mg (72%) of ethyl (E)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**47**) as a colourless oil that exhibited IR (neat): 1728, 1631, 1180, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.13 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=54 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.24 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.81 (d, 3H, *J*= 6.5 Hz, =CHCH<sub>3</sub>), 2.44 (ddd, 1H, *J*= 14, 6.5, 1 Hz, one of =C-CH<sub>2</sub>R), 2.94 (ddd, 1H, *J*= 14, 8, 1 Hz, one of =C-CH<sub>2</sub>R), 4.06-4.20 (m, 3H, -OCH<sub>2</sub>CH<sub>3</sub> and -CHCO<sub>2</sub>Et), 5.42 (d, 1H, *J*= 2 Hz, one of -(Br)C=CH<sub>2</sub>), 5.56 (br d, 1H, *J*= 2 Hz, one of -(Br)C=CH<sub>2</sub>), 5.86 (qd, 1H, *J*= 6.5, 1 Hz, <sup>3</sup>J<sub>Sn-H</sub>=73 Hz, =CHCH<sub>3</sub>). Exact Mass calcd. for C<sub>12</sub>H<sub>20</sub><sup>79</sup>BrO<sub>2</sub>Sn(M<sup>+</sup>-CH<sub>3</sub>): 394.9667; found: 394.9662.

Preparation of ethyl (Z)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**48**)<sup>16</sup>

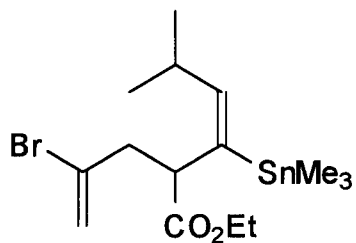


Following general procedure 11 outlined above, ethyl (E)-3-trimethylstannyl-2-pentenoate (**156**) was converted into the diene ester (**48**). The following amounts of reagents and solvents were used: LDA (0.79 mmol) in 5 mL of dry THF,



HMPA (142 mg, 0.79 mmol), ethyl (*E*)-3-trimethylstannyl-2-pentenoate (**156**) (100 mg, 0.344 mmol) in 0.5 mL of dry THF, and 2,3-dibromopropene (**20**) (103 mg, 0.516 mmol). Flash chromatography (10 g of silica gel, 19:1 hexanes-Et<sub>2</sub>O) of the crude product followed by distillation (85-90°C/0.12 Torr) of the acquired oil afforded 106 mg (75%) of ethyl (*Z*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**47**) as a colourless oil that exhibited IR (neat): 1729, 1631, 1178, 777 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.20 (s, 9H, <sup>2</sup>J<sub>Sn-H</sub>=52 Hz, -Sn(CH<sub>3</sub>)<sub>3</sub>), 1.23 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.79 (d, 3H, *J*= 7 Hz, =CHCH<sub>3</sub>), 2.53 (dd, 1H, *J*= 15, 7 Hz, one of =C-CH<sub>2</sub>R), 2.94 (dd, 1H, *J*= 15, 7 Hz, one of =C-CH<sub>2</sub>R), 3.50 (br t, 1H, *J*= 7 Hz, <sup>3</sup>J<sub>Sn-H</sub>=68 Hz, -CHCO<sub>2</sub>Et), 4.11 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.39 (d, 1H, *J*= 1.5 Hz, one of -(Br)C=CH<sub>2</sub>), 5.51 (br s, 1H, one of -(Br)C=CH<sub>2</sub>), 6.18 (q, 1H, *J*= 7 Hz, <sup>3</sup>J<sub>Sn-H</sub>=128 Hz, =CHCH<sub>3</sub>). Exact Mass calcd. for C<sub>12</sub>H<sub>20</sub><sup>79</sup>BrO<sub>2</sub>Sn(M<sup>+</sup>-CH<sub>3</sub>): 394.9667; found: 394.9674.

Preparation of ethyl (*E*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**212**)

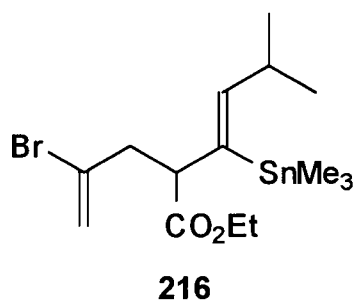


**212**

Following general procedure 11 outlined above, ethyl (*E*)-5-methyl-3-trimethylstannyl-3-hexenoate (**170**) was converted into the diene ester (**212**). The following amounts of reagents and solvents were used: LDA (9.38 mmol) in 26 mL of dry THF, HMPA (1.69 g, 9.43 mmol), ethyl (*E*)-5-methyl-3-trimethylstannyl-3-hexenoate (**170**) (1.30 g, 4.08 mmol) in 5 mL of dry THF, and 2,3-dibromopropene (**20**) (1.21 g, 6.06 mmol). Flash chromatography (100 g of silica gel, 97:3 hexanes-Et<sub>2</sub>O) of the crude product followed

by distillation (90-92°C/0.12 Torr) of the acquired oil afforded 1.55 g (87%) of ethyl (*E*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**212**) as a colourless oil that exhibited IR (neat): 1733, 1611, 1465, 1298, 1181  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.12 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.96 (d, 6H,  $J=6$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 1.22 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.42 (dd, 1H,  $J=15, 7$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 2.78-2.87 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.93 (dd, 1H,  $J=15, 7$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 4.03 (t, 1H,  $J=7$  Hz,  $^3J_{\text{Sn-H}}=62$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.09 (q, 2H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 5.40 (d, 1H,  $J=1$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.48 (d, 1H,  $J=9$  Hz,  $^3J_{\text{Sn-H}}=72$  Hz,  $=\text{CHiPr}$ ), 5.53 (br s, 1H, one of  $-(\text{Br})\text{C}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -7.5, 14.1, 23.0, 28.0, 45.0, 47.4, 60.7, 118.6, 131.0, 137.4, 152.0, 173.9. Anal. calcd. for  $\text{C}_{15}\text{H}_{27}\text{BrO}_2\text{Sn}$ : C 41.13, H 6.22; found: C 41.35, H 6.19. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{24}^{79}\text{BrO}_2\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 422.9982; found: 422.9976.

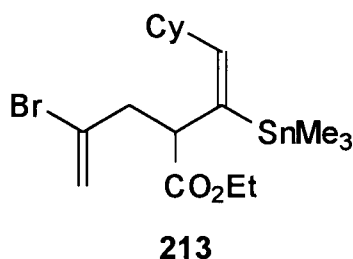
Preparation of ethyl (*Z*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**216**)



Following general procedure 11 outlined above, ethyl (*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (**168**) was converted into the diene ester (**216**). The following amounts of reagents and solvents were used: LDA (0.72 mmol) in 2.5 mL of dry THF, HMPA (0.13 g, 0.73 mmol), ethyl (*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (**168**) (100 mg, 0.313 mmol) in 0.5 mL of dry THF, and 2,3-dibromopropene (**20**) (94 mg, 0.47 mmol). Flash chromatography (10 g of silica gel, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation (95-102°C/0.12 Torr) of the acquired oil afforded 115 mg (84%) of

ethyl (*Z*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**216**) as a colourless oil that exhibited IR (neat): 1729, 1631, 1276, 1179  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.18 (s, 9H,  $^2J_{\text{Sn-H}}=52$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.92 (d, 3H,  $J=6$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.95 (d, 3H,  $J=6$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.22 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.13-2.21 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.54 (dd, 1H,  $J=15, 8$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2$ ), 2.93 (dd, 1H,  $J=15, 6$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2$ ), 3.43 (dd, 1H,  $J=8, 6$  Hz,  $^3J_{\text{Sn-H}}=56$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.06-4.15 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 5.39 (br s, 1H, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.50 (br s, 1H, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.86 (d, 1H,  $J=10$  Hz,  $^3J_{\text{Sn-H}}=126$  Hz,  $=\text{CH}(\text{iPr})$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : -7.0, 14.2, 23.0, 23.2, 34.3, 43.7, 52.3, 60.7, 118.7, 131.7, 136.2, 151.6, 173.7. Anal. calcd. for  $\text{C}_{15}\text{H}_{27}\text{BrO}_2\text{Sn}$ : C 41.13, H 6.22; found: C 41.51, H 6.19. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{24}^{81}\text{BrO}_2\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 424.9962; found: 424.9954.

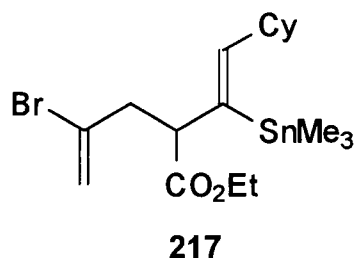
Preparation of ethyl (*E*)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**213**)



Following general procedure 11 outlined above, ethyl (*E*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**169**) was converted into the diene ester (**213**). The following amounts of reagents and solvents were used: LDA (8.32 mmol) in 26 mL of dry THF, HMPA (1.50 g, 8.37 mmol), (*E*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**169**) (1.30 g, 3.62 mmol) in 5 mL of dry THF, and 2,3-dibromopropene (**20**) (1.09 g, 5.46 mmol). Radial chromatography (4 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation (122-125°C/0.12 Torr) of the acquired oil afforded 1.57 g (91%) of ethyl

(*E*)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**213**) as a colourless oil that exhibited IR (neat): 1728, 1621, 1179, 769  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.10 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.99-1.11 (m, 2H), 1.12-1.20 (m, 1H), 1.23 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.24-1.36 (m, 2H), 1.55-1.73 (m, 5H), 2.40 (dd, 1H,  $J=14, 7$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 2.45-2.55 (m, 1H), 2.93 (dd, 1H,  $J=14, 7$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 4.03 (br t, 1H,  $J=7$  Hz,  $^3J_{\text{Sn-H}}=82$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.03-4.16 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 5.40 (d, 1H,  $J=1.5$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ ), 5.50 (d, 1H,  $J=8$  Hz,  $^3J_{\text{Sn-H}}=76$  Hz,  $=\text{CHCy}$ ), 5.52 (d, 1H,  $J=1.5$  Hz, one of  $-(\text{Br})\text{C}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : -7.1, 14.1, 25.6, 25.7, 25.8, 33.0, 33.3, 43.6, 44.3, 52.2, 60.6, 118.7, 131.6, 136.9, 150.2, 173.7. Anal. calcd. for  $\text{C}_{18}\text{H}_{31}\text{BrO}_2\text{Sn}$ : C 45.22, H 6.54; found: C 45.47, H 6.48. Exact Mass calcd. for  $\text{C}_{17}\text{H}_{28}^{79}\text{BrO}_2\text{Sn} (\text{M}^+-\text{CH}_3)$ : 463.0295; found: 463.0295.

Preparation of ethyl (*Z*)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**217**)

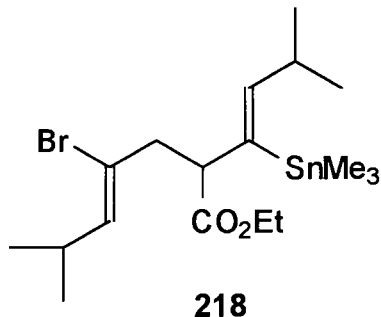


Following general procedure 11 outlined above, ethyl (*Z*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**167**) was converted into the diene ester (**217**). The following amounts of reagents and solvents were used: LDA (9.98 mmol) in 30 mL of dry THF, HMPA (1.80 g, 9.99 mmol), ethyl (*Z*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**167**) (1.56 g, 4.34 mmol) in 5 mL of dry THF, and 2,3-dibromopropene (**20**) (1.3 g, 6.5 mmol). Radial chromatography (4 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation (125-129°C/0.12 Torr) of the acquired oil afforded 1.92 g (93%) of ethyl

(*Z*)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**217**) as a colourless oil that exhibited IR (neat): 1730, 1631, 1449, 1179  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.17 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.03-1.17 (m, 6H), 1.22 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.48-1.72 (m, 4H), 1.80-1.90 (m, 1H,  $-\text{CHR}_2$ ), 2.53 (dd, 1H,  $J=14, 8$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 2.92 (dd, 1H,  $J=14, 6$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 3.43 (dd, 1H,  $J=8, 6$  Hz,  $^3J_{\text{Sn-H}}=60$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.05-4.15 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 5.37 (d, 1H,  $J=1$  Hz, one of  $-\text{BrC}=\text{CH}_2$ ), 5.50 (br s, 1H, one of  $-\text{BrC}=\text{CH}_2$ ), 5.89 (d, 1H,  $J=10$  Hz,  $^3J_{\text{Sn-H}}=128$  Hz,  $=\text{CHCy}$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : -7.0, 14.2, 25.69, 25.74, 25.8, 33.1, 33.3, 43.7, 44.4, 52.3, 60.6, 118.7, 131.7, 137.0, 150.2, 173.7. Anal. calcd. for  $\text{C}_{18}\text{H}_{31}\text{BrO}_2\text{Sn}$ : C 45.22, H 6.54; found: C 45.53, H 6.43. Exact Mass calcd. for  $\text{C}_{17}\text{H}_{28}^{79}\text{BrO}_2\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 463.0295; found: 463.0289.

#### Preparation of ethyl

#### (*Z*)-4-bromo-6-methyl-2-((*Z*)-3-methyl-1-trimethylstannyl-1-butenyl)-4-heptenoate (**218**)



Following general procedure 11 outlined above, ethyl

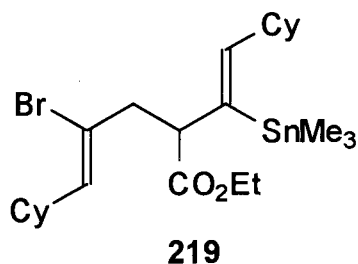
(*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (**168**) was converted into the diene ester (**218**).

The following amounts of reagents and solvents were used: LDA (4.32 mmol) in 16 mL of dry THF, HMPA (0.78 g, 4.3 mmol), ethyl (*Z*)-5-methyl-3-trimethylstannyl-3-hexenoate (**168**) (600 mg, 1.88 mmol) in 2 mL of dry THF, and (*Z*)-1,2-dibromo-4-methyl-2-pentene (**206**) (600 mg, 2.48 mmol). Radial chromatography (4 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by removal of traces of solvent under reduced pressure (vacuum pump) from the acquired material afforded 650 mg (72%) of ethyl

(*Z*)-4-bromo-6-methyl-2-((*Z*)-3-methyl-1-trimethylstannyl-1-butenyl)-4-heptenoate (**218**) as a colourless oil that exhibited IR (neat): 1729, 1617, 1181, 771  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz)  $\delta$ : 0.20 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 0.90-0.99 (m, 12H, 2 x  $-\text{CH}(\text{CH}_3)_2$ ), 1.23 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.13-2.23 (m, 1H, one of  $-\text{CH}(\text{CH}_3)_2$ ), 2.51 (dd, 1H,  $J=14, 9$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 2.60-2.70 (m, 1H, one of  $-\text{CH}(\text{CH}_3)_2$ ), 2.93 (dd, 1H,  $J=14, 6$  Hz,  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 3.50 (dd, 1H,  $J=9, 6$  Hz,  $^3J_{\text{Sn-H}}=71$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.03-4.16 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 5.39 (d, 1H,  $J=9$  Hz,  $-\text{BrC}=\text{CHR}$ ), 5.85 (d, 1H,  $J=10$  Hz,  $^3J_{\text{Sn-H}}=126$  Hz,  $-\text{SnC}=\text{CHR}$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : -6.9, 14.2, 21.8, 22.0, 23.09, 23.13, 31.0, 34.3, 43.7, 52.9, 60.6, 122.9, 136.4, 138.0, 151.4, 174.0. Anal. calcd. for  $\text{C}_{18}\text{H}_{33}\text{BrO}_2\text{Sn}$ : C 45.03, H 6.93; found: C 45.31, H 6.96. Exact Mass calcd. for  $\text{C}_{17}\text{H}_{30}^{81}\text{BrO}_2\text{Sn}$  ( $\text{M}^+-\text{CH}_3$ ): 465.0452; found: 465.0443.

#### Preparation of ethyl

(*Z*)-4-bromo-5-cyclohexyl-2-((*Z*)-2-cyclohexyl-1-trimethylstannylethenyl)-4-pentenoate (**219**)



Following general procedure 11 outlined above, ethyl

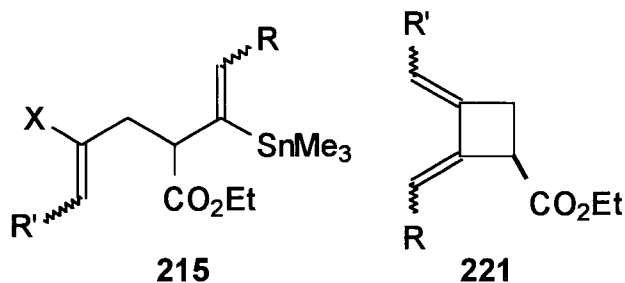
(*Z*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**167**) was converted into the diene ester (**219**).

The following amounts of reagents and solvents were used: LDA (0.64 mmol) in 2 mL of dry THF, HMPA (0.12 g, 0.67 mmol), ethyl (*Z*)-4-cyclohexyl-3-trimethylstannyl-3-butenolate (**167**) (100 mg, 0.279 mmol) in 0.5 mL of dry THF, and (*Z*)-2,3-dibromo-1-cyclohexylpropene (**207**) (110 mg, 0.390 mmol). Radial chromatography (2 mm plate, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation (135-140°C/0.12 Torr) of the acquired liquid afforded 93 mg

(60%) of ethyl

(*Z*)-4-bromo-5-cyclohexyl-2-((*Z*)-2-cyclohexyl-1-trimethylstannylethenyl)-4-pentenoate (**219**) as a colourless oil that exhibited IR (neat): 1729, 1449, 1185  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.15 (s, 9H,  $^2J_{\text{Sn-H}}=54$  Hz,  $-\text{Sn}(\text{CH}_3)_3$ ), 1.01-1.30 (m, 12H), 1.22 (t, 3H,  $J=7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.55-1.71 (m, 8H), 1.80-1.88 (m, 1H, one of  $=\text{CHCH}_2\text{R}_2$ ), 2.27-2.35 (m, 1H, one of  $=\text{CHCH}_2\text{R}_2$ ), 2.51 (dd, 1H,  $J=14, 9$  Hz, one of  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 2.88 (ddd, 1H,  $J=14, 6, 1$  Hz,  $=\text{C}(\text{Br})\text{CH}_2\text{R}$ ), 3.46 (dd, 1H,  $J=9, 6$  Hz,  $^3J_{\text{Sn-H}}=72$  Hz,  $-\text{CHCO}_2\text{Et}$ ), 4.02-4.13 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 5.40 (br d, 1H,  $J=9$  Hz,  $-\text{BrC}=\text{CHR}$ ), 5.87 (d, 1H,  $J=10$  Hz,  $^3J_{\text{Sn-H}}=136$  Hz,  $-\text{SnC}=\text{CHR}$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : -6.9, 14.1, 14.2, 25.7, 25.8, 25.9, 31.6, 33.2, 40.5, 43.8, 44.3, 53.1, 60.5, 123.1, 136.4, 137.4, 150.0, 174.0. Anal. calcd. for  $\text{C}_{24}\text{H}_{41}\text{BrO}_2\text{Sn}$ : C 51.45, H 7.38; found: C 51.08, H 7.57. Exact Mass calcd. for  $\text{C}_{23}\text{H}_{38}^{81}\text{BrO}_2\text{Sn} (\text{M}^+-\text{CH}_3)$ : 545.1078; found: 545.1076.

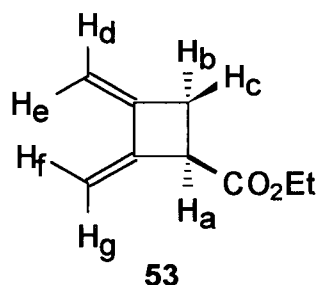
10. General Procedure 12: Preparation of the ethyl 2,3-bis(alkylidene)cyclobutane-carboxylates (**221**)<sup>16</sup>



A stirred solution of tetrakis(triphenylphosphine)palladium (0) (~0.05 equiv., unless noted otherwise) and the appropriate diene ester (**215**) (1.00 eq.) in dry DMF (8.2-24 mL/mmol ester) was heated at 80°C for 1.5 hours, unless noted otherwise. The reaction mixture was cooled to room temperature, water (equal volume to the total volume of the reaction mixture) was added and the mixture was thoroughly extracted with *n*-pentane. The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Flash or radial chromatography, unless noted

otherwise, of the crude product followed by bulb-to-bulb distillation of the acquired oil afforded the corresponding ethyl 2,3-bis(alkylidene)cyclobutanecarboxylate (**221**).

Preparation of ethyl 2,3-bis(methylene)cyclobutanecarboxylate (**53**)<sup>16</sup>

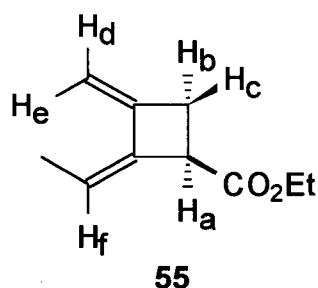


Following general procedure 12 outlined above, ethyl 4-bromo-2-[(1-trimethylstannyl)ethenyl]-4-pentenoate (**46**) was converted into the cyclobutanecarboxylate (**53**). The following amounts of reagents and solvents were used: Pd(PPh<sub>3</sub>)<sub>4</sub> (168 mg, 0.145 mmol) and ethyl 4-bromo-2-[(1-trimethylstannyl)ethenyl]-4-pentenoate (**46**) (1.40 g, 3.54 mmol) in 40 mL of dry DMF. Normal workup followed by distillation (60-70°C/15 Torr) of the crude product afforded 439 mg (82%) of ethyl 2,3-bis(methylene)cyclobutanecarboxylate (**53**) as a colourless oil which exhibited IR (neat): 1736, 1682, 1181, 1041, 888 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.29 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.81 (dddd, 1H, *J* = 15, 9, 2.5, 2 Hz, H<sub>b</sub>), 3.06 (dddd, 1H, *J* = 15, 6, 2.5, 2 Hz, H<sub>c</sub>), 3.68-3.78 (m, 1H, H<sub>a</sub>), 4.10-4.24 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.81 (br s, 1H, H<sub>d</sub>), 5.01 (br d, 1H, *J* = 2 Hz, H<sub>g</sub>), 5.23 (dd, 1H, *J* = 2.5, 2.5 Hz, H<sub>e</sub>), 5.26 (d, 1H, *J* = 3 Hz, H<sub>f</sub>); in a series of decoupling experiments, irradiation at δ 2.81 (H<sub>b</sub>) converted the signal at δ 3.06 (H<sub>c</sub>) to a multiplet, the multiplet at δ 3.68-3.78 (H<sub>a</sub>) was sharpened, and the doublet of doublets at δ 5.23 (H<sub>e</sub>) was converted to a doublet (*J* = 2.5 Hz); irradiation of the signal at δ 3.06 (H<sub>c</sub>) converted the signal at δ 2.81 (H<sub>b</sub>) into a multiplet, simplified the multiplet at δ 3.68-3.78 (H<sub>a</sub>), and the doublet of doublets at δ 5.23 (H<sub>e</sub>) into a doublet (*J* = 2.5 Hz); irradiation at δ 3.73 (H<sub>a</sub>) converted the signal at δ 2.81 (H<sub>b</sub>) into a ddd (*J* = 15, 2.5, 2 Hz), the signal at δ 3.06 (H<sub>c</sub>) into



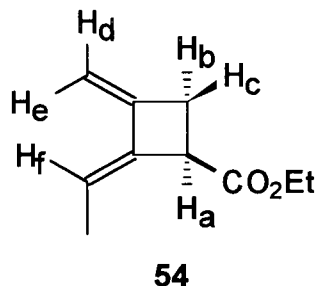
a ddd ( $J = 15, 2.5, 2$  Hz), and the signals at  $\delta$  5.01 ( $H_g$ ) and  $\delta$  5.26 ( $H_f$ ) were converted into singlets; irradiation at  $\delta$  5.23 ( $H_e$ ) converted the signal at  $\delta$  2.81 ( $H_b$ ) into a ddd ( $J = 15, 9, 2$  Hz) and the signal at  $\delta$  3.06 ( $H_c$ ) into a ddd ( $J = 15, 6, 2$  Hz); irradiation at  $\delta$  5.26 ( $H_f$ ) simplified the multiplet at  $\delta$  3.68-3.78 ( $H_a$ ). NOE difference experiments: irradiation at  $\delta$  5.26 ( $H_f$ ) caused enhancement of the signal at  $\delta$  5.01 ( $H_g$ ); irradiation at  $\delta$  3.73 ( $H_a$ ) caused enhancement of the signal at  $\delta$  2.81 ( $H_b$ ).  $^{13}\text{C}$  NMR (50.3 MHz)  $\delta$ : 14.2, 31.1, 43.8, 60.8, 105.1, 145.7, 146.4, 163.2, 174.5. Exact Mass calcd. for  $\text{C}_9\text{H}_{12}\text{O}_2$ : 152.0837; found: 152.0843.

Preparation of ethyl (*Z*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**)<sup>16</sup>



Following general procedure 12 outlined above, ethyl (*Z*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**48**) was converted into the cyclobutanecarboxylate (**55**). The following amounts of reagents and solvents were used:  $\text{Pd}(\text{PPh}_3)_4$  (230 mg, 0.199 mmol), and ethyl (*Z*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**48**) (1.60 g, 3.90 mmol) in 40 mL of dry DMF. Normal workup followed by distillation (82-94°C/15 Torr) of the crude product afforded 550 mg (85%) of ethyl (*Z*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**) as a colourless oil which exhibited spectral characteristics identical to those previously reported.<sup>16</sup>

Preparation of ethyl (*E*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**54**)<sup>16</sup>



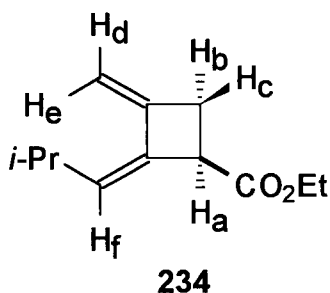
Following general procedure 12 outlined above, ethyl

(*E*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**47**) was converted into the cyclobutanecarboxylate (**54**). The following amounts of reagents and solvents were used:

$\text{Pd}(\text{PPh}_3)_4$  (145 mg, 0.125 mmol) and ethyl

(*E*)-2-(2-bromo-2-propenyl)-3-trimethylstannyl-3-pentenoate (**47**) (1.00 g, 2.44 mmol) in 20 mL of dry DMF. Normal workup followed by distillation (80-90°C/15 Torr) of the crude product afforded 326 mg (80%) of ethyl (*E*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**) as a colourless oil which exhibited exhibited spectral characteristics identical to those previously reported.<sup>16</sup>

Preparation of ethyl (*Z*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**234**)



Following general procedure 12 outlined above, ethyl

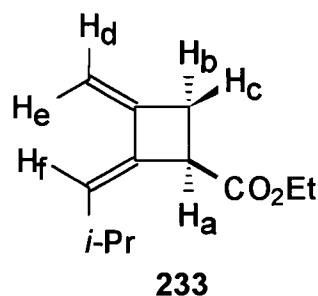
(*Z*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**216**) was converted into the cyclobutanecarboxylate (**234**). The following amounts of reagents and solvents were used:

$\text{Pd}(\text{PPh}_3)_4$  (14 mg, 12  $\mu\text{mol}$ ), and ethyl

(*Z*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**216**) (100 mg, 0.228 mmol) in 3 mL of dry DMF. Normal workup followed by flash chromatography (10 g silica gel, 95:5 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (46-48°C/0.12 Torr) of the acquired oil afforded 40 mg (90%) of ethyl

(*Z*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**234**) as a colourless oil which exhibited IR (neat): 1737, 1179, 873  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.97 (d, 3H,  $J = 6.5$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.00 (d, 3H,  $J = 6.5$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.25 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.64-2.76 (m, 2H,  $-\text{CH}(\text{CH}_3)_2$ ,  $\text{H}_b$ ), 2.90-2.99 (m, 1H,  $\text{H}_c$ ), 3.54-3.60 (m, 1H,  $\text{H}_a$ ), 4.08-4.22 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 4.87 (d, 1H,  $J = 1$  Hz,  $\text{H}_d$ ), 5.09 (dd, 1H,  $J = 2.5, 2.5$  Hz,  $\text{H}_e$ ), 5.29 (d, 1H,  $J = 9.5$  Hz,  $\text{H}_f$ ); NOE difference experiments: irradiation at  $\delta$  0.97 caused enhancement of the signals at  $\delta$  2.64-2.76 ( $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  5.29 ( $\text{H}_f$ ); irradiation at  $\delta$  3.57 ( $\text{H}_a$ ) caused enhancement of the signals at  $\delta$  2.68-2.72 ( $\text{H}_b$ ) and  $\delta$  5.29 ( $\text{H}_f$ ); irradiation at  $\delta$  5.09 ( $\text{H}_e$ ) caused enhancement of the signals at  $\delta$  2.64-2.76 ( $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  4.87 ( $\text{H}_d$ ).  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 14.3, 22.4 (2 carbons), 28.0, 30.9, 42.6, 60.6, 107.5, 134.1, 135.5, 145.8, 153.8. Anal. calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : C 74.19, H 9.34; found: C 74.00, H 9.40. Exact Mass calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : 194.1306; found: 194.1312.

Preparation of ethyl (*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**)



Following general procedure 12 outlined above, ethyl

(*E*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**212**) was converted into the cyclobutanecarboxylate (**233**). The following amounts of reagents and solvents were used:

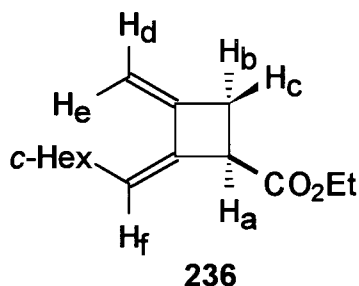
$\text{Pd}(\text{PPh}_3)_4$  (14 mg, 12  $\mu\text{mol}$ ), and ethyl

(*E*)-2-(2-bromo-2-propenyl)-5-methyl-3-trimethylstannyl-3-hexenoate (**212**) (100 mg,

0.228 mmol) in 3 mL of dry DMF. Normal workup followed by flash chromatography (10 g silica gel, 95:5 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (36-38°C/0.12 Torr) of the acquired oil afforded 35 mg (79%) of ethyl

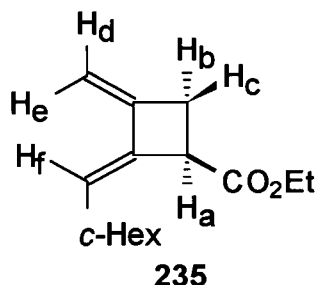
(*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**) as a colourless oil which exhibited IR (neat): 1736, 1650, 1178, 865  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.93 (d, 3H,  $J$  = 7 Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.96 (d, 3H,  $J$  = 7 Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.25 (t, 3H,  $J$  = 7 Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.45-2.55 (m, 1H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.79 (dddd, 1H,  $J$  = 15, 9, 2.5, 2.0 Hz,  $\text{H}_b$ ), 2.84-2.91 (m, 1H,  $\text{H}_c$ ), 3.68-3.73 (m, 1H,  $\text{H}_a$ ), 4.13-4.18 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 4.66 (dd, 1H,  $J$  = 2, 2 Hz,  $\text{H}_d$ ), 5.09 (dd, 1H,  $J$  = 2.5, 2.5 Hz,  $\text{H}_e$ ), 5.54 (dd, 1H,  $J$  = 10, 3 Hz,  $\text{H}_f$ ); NOE difference experiments: irradiation at  $\delta$  2.50 ( $-\text{CH}(\text{CH}_3)_2$ ) caused enhancement of the signals at  $\delta$  0.93 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  0.96 (one of  $-\text{CH}(\text{CH}_3)_2$ ), and  $\delta$  3.68-3.73 ( $\text{H}_a$ ); irradiation at  $\delta$  3.70 ( $\text{H}_a$ ) caused enhancement of the signals at  $\delta$  0.93 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  0.96 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  2.50 ( $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  2.79 ( $\text{H}_b$ ); irradiation at  $\delta$  5.54 ( $\text{H}_f$ ) caused enhancement of the signals at  $\delta$  0.93 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  0.96 (one of  $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  5.09 ( $\text{H}_e$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.2, 22.5, 22.6, 27.6, 31.9, 42.6, 60.8, 102.5, 130.0, 135.7, 146.2, 173.4. Anal. calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : C 74.19, H 9.34; found: C 73.98, H 9.36. Exact Mass calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_2$ : 194.1306; found: 194.1307.

Preparation of ethyl (Z)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (236)



Following general procedure 12 outlined above, ethyl (Z)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**217**) was converted into the cyclobutanecarboxylate (**236**). The following amounts of reagents and solvents were used: Pd(PPh<sub>3</sub>)<sub>4</sub> (7 mg, 6 μmol), and ethyl (Z)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**217**) (50 mg, 0.10 mmol) in 2 mL of dry DMF. Normal workup followed by flash chromatography (5 g silica gel, 97:3 hexanes-Et<sub>2</sub>O) of the crude product and distillation (52-54°C/0.12 Torr) of the acquired oil afforded 18.5 mg (79%) of ethyl (Z)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**236**) as a colourless oil which exhibited IR (neat): 1737, 1645, 1178 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.00-1.30 (m, 6H), 1.24 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.55-1.74 (m, 4H), 2.32-2.43 (m, 1H, =CCH<sub>2</sub>R<sub>2</sub>), 2.69 (dddd, 1H, *J* = 16, 8, 2.5, 2.0 Hz, H<sub>b</sub>), 2.90-2.98 (m, 1H, H<sub>c</sub>), 3.54-3.60 (m, 1H, H<sub>a</sub>), 4.09-4.21 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.86 (br d, 1H, *J* = 2 Hz, H<sub>d</sub>), 5.07 (dd, 1H, *J* = 2.5, 2.5 Hz, H<sub>e</sub>), 5.32 (d, 1H, *J* = 9.5 Hz, H<sub>f</sub>); NOE difference experiments: irradiation at δ 2.38 (=CCH<sub>2</sub>R<sub>2</sub>) caused enhancement of the signals at δ 1.55-1.74, δ 5.07 (H<sub>e</sub>) and δ 5.32 (H<sub>f</sub>); irradiation at δ 3.57 (H<sub>a</sub>) caused enhancement of the signals at δ 2.69 (H<sub>b</sub>) and δ 5.32 (H<sub>f</sub>); irradiation at δ 5.07 (H<sub>e</sub>) caused enhancement of the signals at δ 2.32-2.43 (=CCH<sub>2</sub>R<sub>2</sub>) and δ 4.86 (H<sub>d</sub>); irradiation at δ 5.32 (H<sub>f</sub>) caused enhancement of the signals at δ 1.00-1.30, δ 2.32-2.43 (=CCH<sub>2</sub>R<sub>2</sub>), and δ 3.54-3.60 (H<sub>a</sub>). <sup>13</sup>C NMR (100.4 MHz) δ: 14.3, 25.8, 25.9, 26.0, 30.9, 32.39, 32.44, 37.7, 42.7, 60.5, 107.3, 132.6, 135.9, 145.9, 172.8. Anal. calcd. for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>: C 76.88, H 9.47; found: C 76.79, H 9.39. Exact Mass calcd. for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>: 234.1619; found: 234.1624.

Preparation of ethyl (*E*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (235)



Following general procedure 12 outlined above, ethyl (*E*)

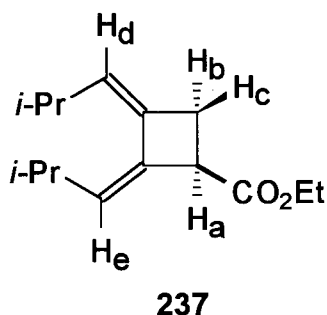
2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**213**) was converted into the cyclobutanecarboxylate (**235**). The following amounts of reagents and solvents were used:

$\text{Pd}(\text{PPh}_3)_4$  (7 mg, 6  $\mu\text{mol}$ ), and ethyl (*E*)-2-(2-cyclohexyl-1-trimethylstannylethenyl)-4-bromo-4-pentenoate (**213**) (50 mg, 0.10 mmol) in 2 mL of dry DMF. Normal workup followed by flash chromatography (5 g silica gel, 97:3 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and distillation (48-49°C/0.12 Torr) of the acquired oil afforded 19.5 mg (83%) of ethyl

(*E*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**235**) as a colourless oil which exhibited IR (neat): 1735, 1650, 1154  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.00-1.11 (m, 2H), 1.11-1.22 (m, 2H), 1.26 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.55-1.74 (m, 6H), 2.13-2.24 (m, 1H,  $=\text{C}-\text{CH}_2$ ), 2.78 (dddd, 1H,  $J = 16, 9, 2.5, 2.0$  Hz,  $\text{H}_b$ ), 2.85-2.93 (m, 1H,  $\text{H}_c$ ), 3.68-3.74 (m, 1H,  $\text{H}_a$ ), 4.15 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.66 (dd, 1H,  $J = 2, 2$  Hz,  $\text{H}_d$ ), 5.08 (dd, 1H,  $J = 2.5, 2.5$  Hz,  $\text{H}_e$ ), 5.56 (dd, 1H,  $J = 9.5, 2.5$  Hz,  $\text{H}_f$ ); NOE difference experiments: irradiation at  $\delta$  2.19 ( $=\text{C}-\text{CH}_2$ ) caused enhancement of the signals at  $\delta$  1.55-1.74,  $\delta$  3.68-3.74 ( $\text{H}_a$ ) and  $\delta$  5.56 ( $\text{H}_f$ ); irradiation at  $\delta$  3.71 ( $\text{H}_a$ ) caused enhancement of the signals at  $\delta$  2.13-2.24 ( $=\text{C}-\text{CH}_2$ ) and  $\delta$  2.78 ( $\text{H}_b$ ); irradiation at  $\delta$  5.56 ( $\text{H}_f$ ) caused enhancement of the signals at  $\delta$  1.11-1.22,  $\delta$  2.13-2.24 ( $=\text{C}-\text{CH}_2$ ), and  $\delta$  5.08 ( $\text{H}_e$ ).  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 14.3, 25.8, 26.0, 31.9, 32.6, 37.1, 42.7, 60.8, 102.5, 128.6, 136.3, 146.4, 173.5. Anal. calcd. for

$C_{15}H_{22}O_2$ : C 76.88, H 9.47; found: C 76.74, H 9.51. Exact Mass calcd. for  $C_{15}H_{22}O_2$ : 234.1619; found: 234.1617.

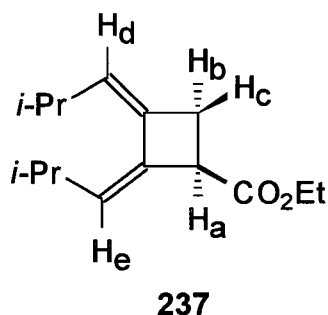
Preparation of ethyl (Z,Z)-2,3-bis(2-methylpropylidene)cyclobutanecarboxylate (237)



Following a modified version of general procedure 12 outlined above in which the reaction time was 2.5 hours and the amount of the catalyst was 0.1 eq., ethyl (Z)-4-bromo-6-methyl-2-((Z)-3-methyl-1-trimethylstannyl-1-butenyl)-4-heptenoate (**218**) was converted into the cyclobutanecarboxylate (**237**). The following amounts of reagents and solvents were used:  $Pd(PPh_3)_4$  (50 mg, 43  $\mu$ mol), and ethyl (Z)-4-bromo-6-methyl-2-((Z)-3-methyl-1-trimethylstannyl-1-butenyl)-4-heptenoate (**218**) (200 mg, 0.417 mmol) in 10 mL of dry DMF. Normal workup followed by flash chromatography (10 g silica gel, 95:5 hexanes-Et<sub>2</sub>O) of the crude product and distillation (47-50°C/0.12 Torr) of the acquired oil afforded 82 mg (83%) of ethyl (Z,Z)-2,3-bis(2-methylpropylidene)cyclobutanecarboxylate (**237**) as a colourless oil which exhibited IR (neat): 1737, 1466, 1176  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 0.95-1.01 (m, 12H, 2 x -CH(CH<sub>3</sub>)<sub>2</sub>), 1.25 (t, 3H,  $J$ = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.50-2.61 (m, 3H, 2 x -CH(CH<sub>3</sub>)<sub>2</sub>, H<sub>b</sub>), 2.82 (ddd, 1H,  $J$ = 14, 6.5, 2 Hz, H<sub>c</sub>), 3.48 (ddd, 1H,  $J$ = 8, 6.5, 2 Hz, H<sub>a</sub>), 4.11-4.22 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.92 (br d, 1H,  $J$ = 10 Hz, H<sub>d</sub>), 5.08 (br d, 1H,  $J$ = 10 Hz, H<sub>e</sub>); NOE difference experiments: irradiation at  $\delta$  3.48 (H<sub>a</sub>) caused enhancement of the signals at  $\delta$  2.50-2.57 (H<sub>b</sub>) and  $\delta$  5.08 (H<sub>e</sub>); irradiation at  $\delta$  4.92 (H<sub>d</sub>) caused enhancement of the signals at  $\delta$  0.95-0.99 (-CH(CH<sub>3</sub>)<sub>2</sub>),  $\delta$  2.50-2.60 (-CH(CH<sub>3</sub>)<sub>2</sub>, H<sub>b</sub>), and  $\delta$  2.82 (H<sub>c</sub>); irradiation at  $\delta$  5.08 (H<sub>e</sub>) caused

enhancement of the signals at  $\delta$  0.97-1.01 ( $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  2.53-2.61 ( $-\text{CH}(\text{CH}_3)_2$ ), and  $\delta$  3.48 ( $\text{H}_a$ ).  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 14.3, 22.77, 23.13, 23.27, 23.34, 29.3, 29.5, 31.0, 43.2, 60.4, 131.2, 131.3, 133.5, 135.1, 172.9. Anal. calcd. for  $\text{C}_{15}\text{H}_{24}\text{O}_2$ : C 76.22, H 10.24; found: C 75.98, H 10.30. Exact Mass calcd. for  $\text{C}_{15}\text{H}_{24}\text{O}_2$ : 236.1777; found: 236.1777.

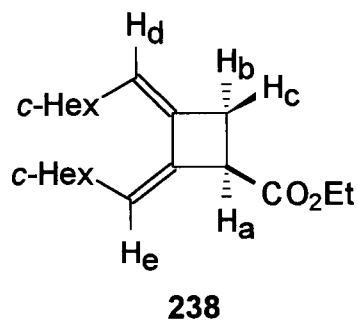
Preparation of ethyl (Z,Z)-2,3-bis(2-methylpropylidene)cyclobutanecarboxylate (237) by CuCl methodology<sup>48, 84</sup>



To a hot (60°C), stirred solution of cuprous chloride (318 mg, 3.21 mmol, 2.8 equiv.) in 20 mL DMF was added a solution of ethyl (Z)-4-bromo-6-methyl-2-((Z)-3-methyl-1-trimethylstannyl-1-butenyl)-4-heptenoate (**52**) (550 mg, 1.15 mmol) in 20 mL of dry DMF. The reaction mixture was stirred for 10 minutes at 60°C and was then cooled to room temperature. Aqueous  $\text{NH}_4\text{Cl}$ - $\text{NH}_4\text{OH}$  (pH 8, 50 mL) was added and the mixture was thoroughly extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Radial chromatography (2 mm plate, 19:1 hexanes- $\text{Et}_2\text{O}$ ) of the crude product, followed by removal of traces of solvent (vacuum pump) from the acquired liquid afforded 221 mg (81%) of ethyl (Z,Z)-2,3-bis(2-methylpropylidene)cyclobutanecarboxylate (**60**), a colourless oil that exhibited spectra identical with those reported in the last experiment.



Preparation of ethyl (Z,Z)-2,3-bis(cyclohexylmethylene)cyclobutanecarboxylate (238)



Following a modified version of general procedure 12 outlined above in which the reaction time was 48 hours and the amount of the catalyst was 0.1 eq., ethyl

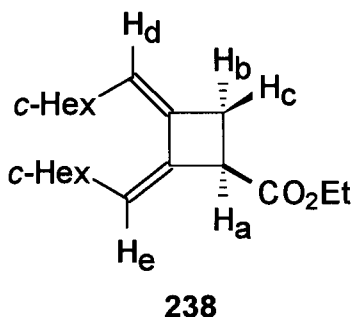
(Z)-4-bromo-5-cyclohexyl-2-((Z)-2-cyclohexyl-1-trimethylstannylethenyl)-4-pentenoate (219) was converted into the cyclobutanecarboxylate (238). The following amounts of reagents and solvents were used: Pd(PPh<sub>3</sub>)<sub>4</sub> (11 mg, 9 μmol), and ethyl

(Z)-4-bromo-5-cyclohexyl-2-((Z)-2-cyclohexyl-1-trimethylstannylethenyl)-4-pentenoate (219) (50 mg, 0.089 mmol) in 2.5 mL of dry DMF. Normal workup followed by flash chromatography (10 g silica gel, 95:5 hexanes-Et<sub>2</sub>O) of the crude product and distillation (47-50°C/0.12 Torr) of the acquired oil afforded 6 mg (21%) of ethyl

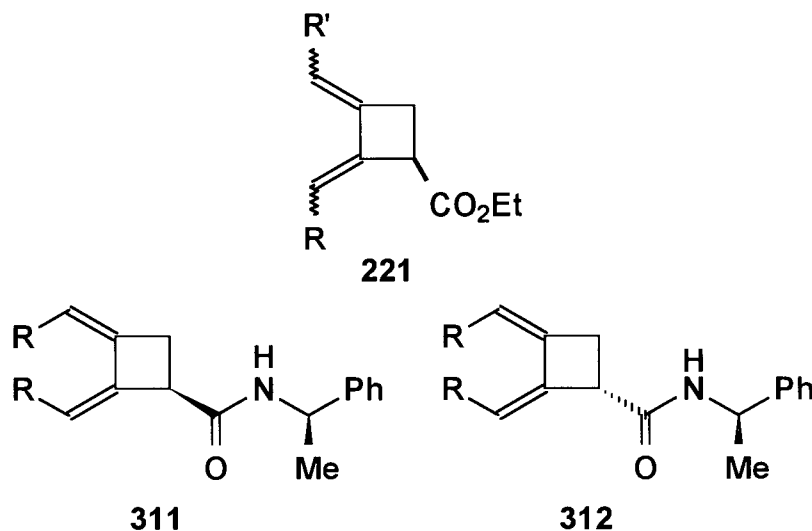
(Z,Z)-2,3-bis(cyclohexylmethylene)cyclobutanecarboxylate (238), a colourless oil that exhibited IR (neat): 1740, 1692, 1449, 1173 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.01-1.32 (m, 13H including at δ 1.25 a triplet, 3H, J= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.61-1.77 (m, 10H), 2.15-2.27 (m, 2H, =C-CH<sub>2</sub>R<sub>2</sub>), 2.53 (ddd, 1H, J= 16, 9, 2 Hz, H<sub>b</sub>), 2.82 (ddd, 1H, J= 16, 6, 2 Hz, H<sub>c</sub>), 3.49 (ddd, 1H, J= 9, 6, 2.5 Hz, H<sub>a</sub>), 4.10-4.20 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.93 (br d, 1H, J= 10 Hz, H<sub>d</sub>), 5.11 (br d, 1H, J= 10 Hz, H<sub>e</sub>); NOE difference experiments: irradiation at δ 2.53 (H<sub>b</sub>) caused enhancement of the signals at δ 2.82 (H<sub>c</sub>), δ 4.93 (H<sub>d</sub>) and δ 3.49 (H<sub>a</sub>); irradiation at δ 2.82 (H<sub>c</sub>) caused enhancement of the signal at δ 2.53 (H<sub>b</sub>); irradiation at δ 3.49 (H<sub>a</sub>) caused enhancement of the signals at δ 2.53 (H<sub>b</sub>) and δ 5.11 (H<sub>e</sub>); irradiation at δ 5.11 (H<sub>e</sub>) caused enhancement of the signals at δ 1.01-1.20 and δ 3.49 (H<sub>a</sub>). <sup>13</sup>C NMR (75.3 MHz) δ: 14.4,

25.88, 25.97, 26.01, 30.9, 33.4, 33.5, 33.6, 39.0, 39.2, 43.3, 60.4, 129.4, 129.7, 134.0, 135.7, 173.0. Anal. calcd. for  $C_{21}H_{32}O_2$ : C 79.69, H 10.20; found: C 79.42, H 10.31. Exact Mass calcd. for  $C_{21}H_{32}O_2$ : 316.2402; found: 316.2408.

Preparation of ethyl (Z,Z)-2,3-bis(cyclohexylmethylene)cyclobutanecarboxylate (238) by CuCl methodology<sup>48, 84</sup>

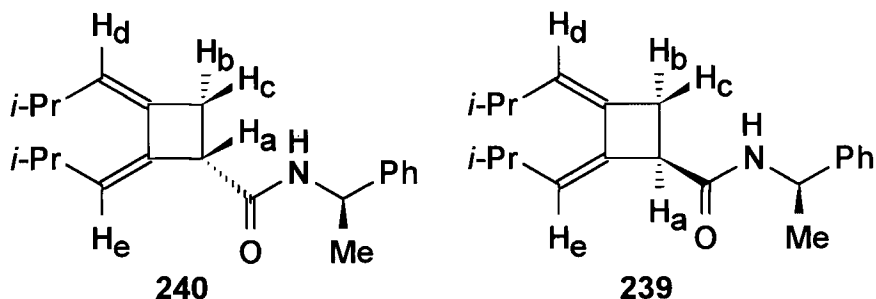


To a hot (60°C), stirred solution of cuprous chloride (25 mg, 0.25 mmol, 2.8 equiv.) in 2 mL of dry DMF was added a solution of ethyl (Z)-4-bromo-5-cyclohexyl-2-((Z)-2-cyclohexyl-1-trimethylstannylethenyl)-4-pentenoate (219) (50 mg, 0.089 mmol) in 2 mL of dry DMF. The reaction mixture was stirred for 10 minutes at 60°C and was then cooled to room temperature. Aqueous  $NH_4Cl-NH_4OH$  (pH 8, 4 mL) was added and the mixture was thoroughly extracted with  $Et_2O$ . The combined extracts were washed with brine, dried  $MgSO_4$ , and concentrated. Radial chromatography (1 mm plate, 2:1  $CCl_4-C_6H_6$ ) of the crude product followed by removal of traces of solvent (vacuum pump) from the acquired liquid afforded 24 mg (84%) of ethyl (Z,Z)-2,3-bis(cyclohexylmethylene)cyclobutanecarboxylate (239), a colourless oil that exhibited spectra identical with those reported in the last experiment.

11. General Procedure 13: Preparation of cyclobutanecarboxamides (311 and 312)<sup>71</sup>

To a stirred solution of (*R*)-(+)-1-phenylethylamine (~2.24 equiv.) in dry benzene (15-19 mL/mmol of ester) at room temperature was added, dropwise, a solution of trimethylaluminum in toluene (2.24 equiv.). After the resultant mixture had been stirred for 20 minutes, a solution of the appropriate cyclobutanecarboxylate (**221**) (1 equiv.) in dry benzene (2.4-5.0 mL/mmol of ester) was added and the resulting mixture was refluxed for 4 hours. Hydrochloric acid (2 M, equal volume to the total volume of the reaction mixture) was added and the mixture was thoroughly extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Radial chromatography of the crude product followed by recrystallization of the acquired solids afforded the diastereoisomers (**311**) and (**312**).

Preparation of the cyclobutanecarboxamides (239) and (240)



Following general procedure 13 outlined above, ethyl

(*Z,Z*)-2,3-bis(2-methylpropylidene)cyclobutanecarboxylate (**237**) was converted into the cyclobutanecarboxamides (**239**) and (**240**). The following amounts of reagents and solvents were used: (*R*)-(+)-1-phenylethylamine (231 mg, 1.91 mmol) in 16 mL of dry benzene, trimethylaluminum (1.90 mmol), and ethyl

(*Z,Z*)-2,3-bis(2-methylpropylidene)cyclobutanecarboxylate (**237**) (200 mg, 0.846 mmol) in 2 mL of dry benzene. Normal workup, followed by radial chromatography (2 mm plate, 2:1 hexanes-Et<sub>2</sub>O) and recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solids afforded 85 mg (32%) of cyclobutanecarboxamide (**240**) as a colourless solid (melting point, 110-111°C) and 88 mg (33%) of cyclobutanecarboxamide (**239**) as a colourless solid (melting point, 103-104°C).

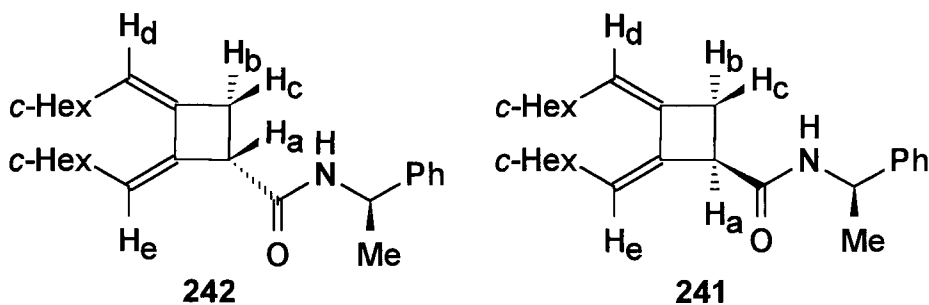
Cyclobutanecarboxamide (**240**) exhibited IR (KBr): 3337, 1724, 1654, 1524, 1234 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.92-1.02 (m, 12H, 2 x -CH(CH<sub>3</sub>)<sub>2</sub>), 1.47 (d, 3H, *J*= 7 Hz, -NCHCH<sub>3</sub>), 2.50-2.63 (m, 3H, 2 x -CH(CH<sub>3</sub>)<sub>2</sub>, H<sub>b</sub>), 2.75 (ddd, 1H, *J*= 14, 8, 2 Hz, H<sub>c</sub>), 3.39 (ddd, 1H, *J*= 8, 6, 2.5 Hz, H<sub>a</sub>), 4.96 (br d, 1H, *J*= 9 Hz, H<sub>d</sub>), 4.98 (br d, 1H, *J*= 9 Hz, H<sub>e</sub>), 5.12 (quintet, 1H, *J*= 7 Hz, -NCHCH<sub>3</sub>), 6.02 (br d, 1H, *J*= 7 Hz, -NH), 7.23-7.33 (m, 5H, aromatic); in a series of decoupling experiments, irradiation at δ 2.75 (H<sub>c</sub>) simplified the multiplet at δ 2.55-2.63 (H<sub>b</sub>) and converted the signal at δ 3.39 (H<sub>a</sub>) to a doublet of doublets (*J*= 6, 2.5 Hz); irradiation at δ 3.39 (H<sub>a</sub>) simplified the multiplet at δ 2.55-2.63 (H<sub>b</sub>), converted the signal at δ 2.75 (H<sub>c</sub>) to a (dd, *J*= 14, 2 Hz), and sharpened the doublet at δ 4.98 (H<sub>e</sub>);

irradiation at  $\delta$  4.97 ( $H_d$ ,  $H_e$ ) simplified the multiplet at  $\delta$  2.50-2.63 ( $2 \times -CH(CH_3)_2$ ,  $H_b$ ), changed the signal at  $\delta$  2.75 ( $H_c$ ) to a (dd,  $J=14, 8$  Hz), and altered the signal at  $\delta$  3.39 ( $H_a$ ) to a (dd,  $J=8, 6$  Hz); irradiation at  $\delta$  5.12 ( $-NCHCH_3$ ) simplified the doublet at  $\delta$  1.47 ( $-NCHCH_3$ ) to a singlet and sharpened the broad doublet at  $\delta$  6.02 ( $-NH$ ) to a broad singlet; irradiation at  $\delta$  6.02 ( $-NH$ ) simplified the quintet at  $\delta$  5.12 ( $-NCHCH_3$ ) to a quartet ( $J=7$  Hz); NOE difference experiments: irradiation of the signal at  $\delta$  2.75 ( $H_c$ ) led to enhancement of the signals at  $\delta$  2.55-2.63 ( $H_b$ ) and  $\delta$  3.39 ( $H_a$ ); irradiation of the signal at  $\delta$  3.39 ( $H_a$ ) led to the enhancement of the signals at  $\delta$  2.75 ( $H_c$ ),  $\delta$  4.98 ( $H_e$ ), and  $\delta$  6.02 ( $-NH$ ); irradiation of the signal at  $\delta$  4.97 ( $H_d$ ,  $H_e$ ) led to the enhancement of the signals at  $\delta$  0.92-1.02 ( $2 \times -CH(CH_3)_2$ ), 2.50-2.63 ( $2 \times -CH(CH_3)_2$ ,  $H_b$ ),  $\delta$  2.75 ( $H_c$ ),  $\delta$  3.39 ( $H_a$ ), and  $\delta$  6.02 ( $-NH$ ); irradiation of the signal at  $\delta$  5.12 ( $-NCHCH_3$ ) led to the enhancement of the signals at  $\delta$  1.47 ( $NCHCH_3$ ) and  $\delta$  7.23-7.33; irradiation of the signal at  $\delta$  6.02 ( $-NH$ ) led to the enhancement of the signals at  $\delta$  3.39 ( $H_a$ ),  $\delta$  4.98 ( $H_e$ ),  $\delta$  5.12 ( $-NCHCH_3$ ) and  $\delta$  7.23-7.33;  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 21.9, 23.0, 23.2, 23.3, 29.6, 33.2, 45.5, 48.4, 126.0, 127.3, 128.7, 132.0, 132.1, 133.5, 136.3, 143.2, 171.9. Anal. calcd. for  $C_{21}H_{29}NO$ : C 80.98, H 9.39, N 4.50; found: C 80.30, H 9.35, N 4.36. Exact Mass calcd. for  $C_{21}H_{29}NO$ : 311.2249; found: 311.2251. X-Ray crystallographic data for compound (240) can be seen in appendix V.

Cyclobutanecarboxamide (239) exhibited IR (KBr): 3318, 1726, 1654  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 0.92-1.02 (m, 12H,  $2 \times -CH(CH_3)_2$ ), 1.47 (d, 3H,  $J=7$  Hz,  $NCHCH_3$ ), 2.49-2.61 (m, 3H,  $2 \times -CH(CH_3)_2$ ,  $H_c$ ), 2.73 (ddd, 1H,  $J=14, 9, 2$  Hz,  $H_b$ ), 3.39 (ddd, 1H,  $J=9, 6, 2$  Hz,  $H_a$ ), 4.94 (br d, 1H,  $J=10$  Hz,  $H_d$ ), 5.01 (br d, 1H,  $J=10$  Hz,  $H_e$ ), 5.12 (quintet, 1H,  $J=7$  Hz,  $-NCHCH_3$ ), 6.01 (br d, 1H,  $J=7$  Hz,  $-NH$ ), 7.23-7.33 (m, 5H, aromatic); in a series of decoupling experiments, irradiation at  $\delta$  2.73 ( $H_b$ ) simplified the multiplet at  $\delta$  2.55-2.61 ( $H_c$ ) and the changed signal at  $\delta$  3.39 ( $H_a$ ) to a doublet of doublets ( $J=6, 2$  Hz); irradiation at  $\delta$  3.39 ( $H_a$ ) simplified the multiplet at  $\delta$  2.55-2.61 ( $H_c$ ) and sharpened the signal at  $\delta$  2.73 ( $H_b$ ) to a (dd,  $J=14, 2$  Hz); irradiation at  $\delta$  4.94 ( $H_d$ ) simplified the multiplet at  $\delta$  2.49-2.61

(-CH(CH<sub>3</sub>)<sub>2</sub>, H<sub>c</sub>), and converted the signal at  $\delta$  2.73 (H<sub>b</sub>) to a doublet of doublets ( $J$ = 14, 9 Hz); irradiation at  $\delta$  5.01 (H<sub>e</sub>) simplified the signal at  $\delta$  3.39 (H<sub>a</sub>) to a doublet of doublets ( $J$ = 9, 6 Hz); irradiation at  $\delta$  5.12 (-NCHCH<sub>3</sub>) simplified the doublet at  $\delta$  1.47 (-NCHCH<sub>3</sub>) to a singlet and changed the broad doublet at  $\delta$  6.01 (-NH) to a broad singlet; irradiation at  $\delta$  6.01 (-NH) simplified the quintet at  $\delta$  5.12 (-NCHCH<sub>3</sub>) to a quartet ( $J$ = 7 Hz); NOE difference experiments: irradiation of the signal at  $\delta$  2.73 (H<sub>b</sub>) led to enhancement of the signals at  $\delta$  2.55-2.61 (H<sub>c</sub>) and  $\delta$  3.39 (H<sub>a</sub>); irradiation of the signal at  $\delta$  3.39 (H<sub>a</sub>) led to the enhancement of the signals at  $\delta$  2.73 (H<sub>b</sub>); irradiation of the signal at  $\delta$  5.01 (H<sub>e</sub>) led to the enhancement of the signals at  $\delta$  0.92-1.02 (-CH(CH<sub>3</sub>)<sub>2</sub>); irradiation of the signal at  $\delta$  5.12 (-NCHCH<sub>3</sub>) led to the enhancement of the signals at  $\delta$  1.47 (-NCHCH<sub>3</sub>); irradiation of the signal at  $\delta$  6.01 (-NH) led to the enhancement of the signals at  $\delta$  3.39 (H<sub>a</sub>) and  $\delta$  5.01 (H<sub>e</sub>); <sup>13</sup>C NMR (100.4 MHz)  $\delta$ : 21.9, 23.0, 23.2, 23.3, 29.5, 29.6, 45.5, 48.4, 125.9, 127.3, 128.6, 132.0, 132.1, 133.7, 136.0, 142.4, 171.9. Anal. calcd. for C<sub>21</sub>H<sub>29</sub>NO: C 80.98, H 9.39, N 4.50; found: C 80.90, H 9.22, N 4.36. Exact Mass calcd. for C<sub>21</sub>H<sub>29</sub>NO: 311.2249; found: 311.2254.

#### Preparation of the cyclobutanecarboxamides (241) and (242)



Following general procedure 13 outlined above, ethyl (Z,Z)-2,3-bis(cyclohexylmethylene)cyclobutanecarboxylate (238) was converted into the cyclobutanecarboxamides (241) and (242). The following amounts of reagents and solvents were used: (*R*)-(+)-1-phenylethylamine (110 mg, 0.908 mmol) in 6 mL of dry benzene,

trimethylaluminum (0.91 mmol), and ethyl

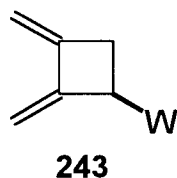
(*Z,Z*)-2,3-bis(cyclohexylmethylene)cyclobutanecarboxylate (**238**) (130 mg, 0.411 mmol) in 2 mL of dry benzene. Normal workup, followed by radial chromatography (2 mm plate, 1:1 hexanes-Et<sub>2</sub>O) and recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solids afforded 62 mg (39%) of cyclobutanecarboxamide (**242**) as a colourless solid (melting point, 163-165°C, dec.) and 58 mg (36%) of cyclobutanecarboxamide (**241**) as a colourless solid (melting point, 169-170°C dec.).

Cyclobutanecarboxamide (**242**) exhibited IR (KBr): 3397, 1733, 1637, 1178 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.98-1.33 (m, 8H), 1.45 (d, 3H, *J* = 7 Hz, NCHCH<sub>3</sub>), 1.60-1.76 (m, 12H), 2.14-2.29 (m, 2H, =C-CHR<sub>2</sub>), 2.60 (ddd, 1H, *J* = 14, 6, 2 Hz, H<sub>b</sub>), 2.76 (ddd, 1H, *J* = 14, 9, 2 Hz, H<sub>c</sub>), 3.35-3.41 (m, 1H, H<sub>a</sub>), 4.94 (br d, 1H, *J* = 10 Hz, H<sub>d</sub>), 5.01 (br d, 1H, *J* = 10 Hz, H<sub>e</sub>), 5.10 (quintet, 1H, *J* = 7 Hz, -NCHCH<sub>3</sub>), 6.02 (br d, 1H, *J* = 7 Hz, -NH), 7.25-7.34 (m, 5H, aromatic); NOE difference experiments: irradiation of the signal at δ 2.60 (H<sub>b</sub>) led to enhancement of the signals at δ 2.76 (H<sub>c</sub>) and δ 4.94 (H<sub>d</sub>); irradiation of the signal at δ 2.76 (H<sub>c</sub>) led to the enhancement of the signals at δ 2.60 (H<sub>b</sub>) and 3.35-3.41 (H<sub>a</sub>); irradiation of the signal at δ 3.37 (H<sub>a</sub>) led to the enhancement of the signals at δ 2.76 (H<sub>c</sub>), δ 5.01 (H<sub>e</sub>), and δ 6.02 (-NH); irradiation of the signals at δ 4.94-5.05 (H<sub>d</sub>, H<sub>e</sub>) led to the enhancement of the signals at δ 1.09-1.20, δ 2.20-2.29 (=C-CHR<sub>2</sub>), δ 2.60 (H<sub>b</sub>), δ 2.76 (H<sub>c</sub>), δ 3.35-3.41 (H<sub>a</sub>), and δ 6.02 (-NH); irradiation of the signal at δ 5.10 (-NCHCH<sub>3</sub>) led to the enhancement of the signals at δ 1.45 (-NCHCH<sub>3</sub>), δ 6.02 (-NH), and δ 7.25-7.34; irradiation of the signal at δ 6.02 (-NH) led to the enhancement of the signals at δ 2.76 (H<sub>c</sub>), δ 3.35-3.41 (H<sub>a</sub>), δ 5.01 (H<sub>e</sub>), δ 5.10 (-NCHCH<sub>3</sub>), and δ 7.25-7.34; <sup>13</sup>C NMR (100.4 MHz) δ: 21.9, 25.8, 25.9, 26.0, 33.1, 33.3, 33.40, 33.44, 33.5, 39.1, 39.3, 45.5, 48.4, 126.0, 127.3, 128.6, 130.6, 130.7, 134.0, 136.9, 143.2, 172.4. Exact Mass calcd. for C<sub>27</sub>H<sub>37</sub>ON: 391.2875; found: 391.2874.

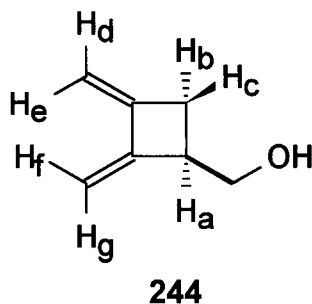
Cyclobutanecarboxamide (**241**) exhibited IR (KBr): 3301, 1708, 1651, 1242 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.01-1.14 (m, 4H), 1.15-1.31 (m, 4H), 1.46 (d, 3H, *J* = 7 Hz, NCHCH<sub>3</sub>), 1.60-1.76 (m, 12H), 2.13-2.28 (m, 2H, =C-CHR<sub>2</sub>), 2.57 (ddd, 1H, *J* = 14, 6, 2 Hz,

$H_C$ ), 2.74 (ddd, 1H,  $J = 14, 10, 2$  Hz,  $H_B$ ), 3.35-3.41 (m, 1H,  $H_A$ ), 4.95 (br d, 1H,  $J = 10$  Hz,  $H_D$ ), 5.04 (br d, 1H,  $J = 10$  Hz,  $H_E$ ), 5.10 (quintet, 1H,  $J = 7$  Hz,  $-NCHCH_3$ ), 6.05 (br d, 1H,  $J = 7$  Hz,  $-NH$ ), 7.25-7.33 (m, 5H, aromatic); NOE difference experiments: irradiation of the signal at  $\delta$  2.57 ( $H_C$ ) led to enhancement of the signal at  $\delta$  2.74 ( $H_B$ ); irradiation of the signal at  $\delta$  2.74 ( $H_B$ ) led to the enhancement of the signals at  $\delta$  2.57 ( $H_C$ ) and  $\delta$  3.35-3.41 ( $H_A$ ); irradiation of the signal at  $\delta$  3.38 ( $H_A$ ) led to the enhancement of the signals at  $\delta$  2.74 ( $H_B$ ) and  $\delta$  5.04 ( $H_E$ ); irradiation of the signal at  $\delta$  5.04 ( $H_E$ ) led to the enhancement of the signals at  $\delta$  1.20-1.31,  $\delta$  1.60-1.71,  $\delta$  3.35-3.41 ( $H_A$ ); irradiation of the signal at  $\delta$  5.10 ( $-NCHCH_3$ ) led to the enhancement of the signals at  $\delta$  1.46 ( $-NCHCH_3$ ) and  $\delta$  7.25-7.33; irradiation of the signal at  $\delta$  6.05 ( $-NH$ ) led to the enhancement of the signals at  $\delta$  3.35-3.41 ( $H_A$ ),  $\delta$  5.04 ( $H_E$ ),  $\delta$  5.10 ( $-NCHCH_3$ ), and  $\delta$  7.25-7.33. Exact Mass calcd. for  $C_{27}H_{37}ON$ : 391.2875; found: 391.2880.

12. Preparation of the 1-substituted-2,3-bis(methylene)cyclobutanes (243)



Preparation of 1-(hydroxymethyl)-2,3-bis(methylene)cyclobutane (244)

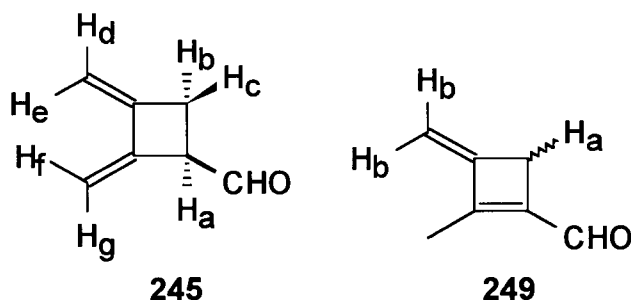




To a cold (0°C), stirred solution of lithium aluminum hydride (125 mg, 3.29 mmol) in 12 mL of dry Et<sub>2</sub>O was added dropwise a solution of ethyl 2,3-bis(methylene)cyclobutanecarboxylate (**53**) (500 mg, 3.29 mmol) in 4 mL of dry Et<sub>2</sub>O. The reaction mixture was stirred at 0°C for 10 minutes, warmed to room temperature, and then was stirred for a further 10 minutes. A saturated aqueous solution of sodium-potassium tartrate (Rochelles salt) (10 mL) was added dropwise (caution-exothermic) and the mixture was thoroughly extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Radial chromatography (4 mm plate, Et<sub>2</sub>O) of the crude product, followed by distillation (90-93°C/15 Torr) of the acquired oil, gave 332 mg (92%) of 1-(hydroxymethyl)-2,3-bis(methylene)cyclobutane (**244**) as a colourless oil which exhibited IR (neat): 3351 (br), 1653, 1028, 883 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.53 (br s, 1H, -OH), 2.38-2.46 (m, 1H, H<sub>b</sub>), 2.74 (dddd, 1H, *J*= 15, 9, 2.5, 2.5 Hz, H<sub>c</sub>), 3.05-3.13 (m, 1H, H<sub>a</sub>), 3.65-3.77 (m, 2H, -CH<sub>2</sub>OH), 4.75 (dd, 1H, *J*= 2.5, 2.5 Hz, H<sub>d</sub>), 4.82 (d, 1H, *J*= 1.5 Hz, H<sub>g</sub>), 5.19 (dd, 1H, *J*= 2.5, 2.5 Hz, H<sub>e</sub>), 5.21 (d, 1H, *J*= 2.5 Hz, H<sub>f</sub>). In a series of decoupling experiments, irradiation at δ 2.41 (H<sub>b</sub>) converted the signal at δ 2.74 (H<sub>c</sub>) to a doublet of doublets (*J*= 9, 2.5, 2.5 Hz), converted the doublet of doublets at δ 4.75 (H<sub>d</sub>) to a doublet (*J*= 2.5 Hz), converted the doublet of doublets at δ 5.19 (H<sub>e</sub>) to a doublet (*J*= 2.5 Hz) and simplified the multiplet at δ 3.05-3.13 (H<sub>a</sub>); irradiation at δ 2.74 (H<sub>c</sub>) simplified the multiplets at δ 2.38-2.46 (H<sub>b</sub>) and δ 3.05-3.13 (H<sub>a</sub>) and converted the doublet of doublets at 4.75 (H<sub>d</sub>) and δ 5.19 (H<sub>e</sub>) to doublets (*J*= 2.5 Hz in each case); irradiation at δ 3.10 (H<sub>a</sub>) simplified the multiplet at δ 2.38-2.46 (H<sub>b</sub>) to a doublet of doublet of doublets (*J*= 15, 2.5, 2.5 Hz), simplified the signal at δ 2.74 (H<sub>c</sub>) to a doublet of doublet of doublets (*J*= 15, 2.5, 2.5 Hz), simplified the multiplet at δ 3.65-3.77 (-CH<sub>2</sub>OH), and converted the doublets at δ 4.82 (H<sub>g</sub>) and δ 5.21 (H<sub>f</sub>) to singlets; irradiation at δ 5.19 (H<sub>e</sub>) converted the signal at δ 2.38-2.46 (H<sub>b</sub>) to a doublet of doublet of doublets (*J*= 15, 6, 2.5 Hz), and converted the signal at δ 2.74 (H<sub>c</sub>) to a doublet of doublet of doublets (*J*= 15, 9, 2.5 Hz). NOE difference experiments; irradiation at δ 2.41 (H<sub>b</sub>) caused

enhancement of the signals at  $\delta$  2.74 ( $H_C$ ) and  $\delta$  3.05-3.13 ( $H_A$ ); irradiation at  $\delta$  2.74 ( $H_C$ ) caused enhancement of the signal at  $\delta$  2.38-2.46 ( $H_B$ ); irradiation at  $\delta$  3.05 ( $H_A$ ) caused enhancement of the signals at  $\delta$  2.38-2.46 ( $H_B$ ),  $\delta$  3.65-3.77 ( $-\underline{CH}_2OH$ ) and  $\delta$  4.82 ( $H_G$ ); irradiation at  $\delta$  4.75 ( $H_D$ ) caused enhancement of the signals at  $\delta$  5.19 ( $H_E$ ) and  $\delta$  2.38-2.46 ( $H_B$ ).  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 31.3, 42.4, 65.1, 103.6, 104.6, 146.6, 150.1. Anal. calcd. for  $C_7H_{10}O$ : C 76.32, H 9.16; found: C 76.31, H 9.33. Exact Mass calcd. for  $C_7H_{10}O$ : 110.0731; found: 110.0730.

Preparation of 1-formyl-2,3-bis(methylene)cyclobutane (245)

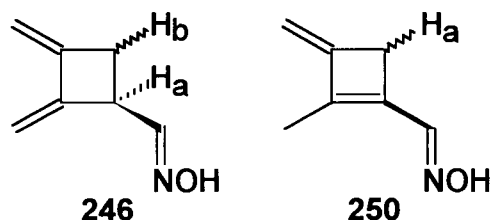


To a stirred mixture of pyridinium chlorochromate (391 mg, 1.81 mmol) and sodium acetate (264 mg, 3.22 mmol) in dry  $CH_2Cl_2$  (250 mL) was added a solution of 1-(hydroxymethyl)-2,3-bis(methylene)cyclobutane (244) (100 mg, 0.908 mmol) in dry  $CH_2Cl_2$  (5 mL). The mixture was stirred at room temperature for 2 hours. Diethyl ether (200 mL) was added and the resultant mixture was filtered through a column of Florisil (6 cm diameter, 2 cm depth). The column was eluted quickly with 200 mL of  $Et_2O$ . Concentration of the combined eluate (100 Torr), followed by distillation (40-45  $^{\circ}C$ /45 Torr) of the remaining liquid, gave 69 mg (70%) of 1-formyl-2,3-bis(methylene)cyclobutane (245). This compound was found to be extremely unstable at room temperature, polymerizing within 15 minutes of distillation. It should be noted that the aldehyde (245) isomerizes to the conjugated diene (249) upon exposure to silica gel. Thus one must filter the crude reaction mixture quickly (pressurized) through a *short and wide* plug of Florisil. Flash or radial chromatography cannot be used to purify this

compound after filtration. If one does obtain a mixture of aldehyde products one can use this mixture without further purification in the next step (conversion to the oxime) and separate the oxime isomers by radial chromatography. Compound (245), a colourless oil, exhibits IR (neat): 2715, 1719, 1655, 1407, 888  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 2.82 (dddd, 1H,  $J = 15, 9, 2.5, 2.5$  Hz,  $\text{H}_b$ ), 2.94-3.01 (m, 1H,  $\text{H}_c$ ), 3.66-3.74 (m, 1H,  $\text{H}_a$ ), 4.82 (dd, 1H,  $J = 2.5, 2.5$  Hz,  $\text{H}_d$ ), 4.92 (br d, 1H,  $J = 2$  Hz,  $\text{H}_g$ ), 5.23 (dd, 1H,  $J = 2.5, 2.5$  Hz,  $\text{H}_e$ ), 5.34 (d, 1H,  $J = 3$  Hz,  $\text{H}_f$ ), 9.68 (d, 1H,  $J = 2$  Hz,  $-\text{CHO}$ ); in a series of decoupling experiments, irradiation at  $\delta$  2.82 ( $\text{H}_b$ ) sharpened the multiplets at  $\delta$  2.94-3.01 ( $\text{H}_c$ ) and  $\delta$  3.66-3.74 ( $\text{H}_a$ ), and converted the doublet of doublets at  $\delta$  4.82 ( $\text{H}_d$ ) and  $\delta$  5.23 ( $\text{H}_e$ ) each to doublets ( $J = 2.5$  Hz); irradiation at  $\delta$  2.98 ( $\text{H}_c$ ) sharpened the multiplet at  $\delta$  3.66-3.74 ( $\text{H}_a$ ), converted the signal at  $\delta$  2.82 ( $\text{H}_b$ ) to a doublet of doublet of doublets ( $J = 9, 2.5, 2.5$  Hz) and converted the doublet of doublets at  $\delta$  4.82 ( $\text{H}_d$ ) and  $\delta$  5.23 ( $\text{H}_e$ ) each to doublets ( $J = 2.5$  Hz); irradiation at  $\delta$  3.70 ( $\text{H}_a$ ) simplified the signal at  $\delta$  2.82 ( $\text{H}_b$ ) to a doublet of doublet of doublets ( $J = 15, 2.5, 2.5$  Hz), converted the signal at  $\delta$  2.94-3.01 ( $\text{H}_c$ ) to a doublet of doublet of doublets ( $J = 15, 2.5, 2.5$  Hz), and converted the signals at  $\delta$  4.92 ( $\text{H}_g$ ),  $\delta$  5.34 ( $\text{H}_f$ ) and  $\delta$  9.68 ( $-\text{CHO}$ ) to singlets; irradiation at  $\delta$  5.23 ( $\text{H}_e$ ) converted the signal at  $\delta$  2.82 ( $\text{H}_b$ ) to a doublet of doublet of doublets ( $J = 15, 9, 2.5$  Hz) and the signal at  $\delta$  2.94-3.01 ( $\text{H}_c$ ) to a doublet of doublet of doublets ( $J = 15, 6, 2.5$  Hz); irradiation at  $\delta$  5.34 ( $\text{H}_f$ ) simplified the multiplet at  $\delta$  3.66-3.74 ( $\text{H}_a$ ). NOE difference experiments; irradiation at  $\delta$  2.82 ( $\text{H}_b$ ) caused enhancement of the signals at  $\delta$  2.94-3.01 ( $\text{H}_c$ ) and  $\delta$  3.66-3.74 ( $\text{H}_a$ ); irradiation at  $\delta$  2.98 ( $\text{H}_c$ ) caused enhancement of the signals at  $\delta$  2.82 ( $\text{H}_b$ ) and  $\delta$  4.82 ( $\text{H}_d$ ); irradiation at  $\delta$  3.70 ( $\text{H}_a$ ) caused enhancement of the signals at  $\delta$  2.82 ( $\text{H}_b$ ) and  $\delta$  9.68 ( $-\text{CHO}$ ); irradiation at  $\delta$  4.82 ( $\text{H}_d$ ) caused enhancement of the signal at  $\delta$  5.23 ( $\text{H}_e$ ); irradiation at  $\delta$  5.23 ( $\text{H}_e$ ) caused enhancement of the signal at  $\delta$  4.82 ( $\text{H}_d$ ); irradiation at  $\delta$  5.34 ( $\text{H}_f$ ) caused enhancement of the signal at  $\delta$  4.92 ( $\text{H}_g$ ).  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 28.6, 51.8, 105.8, 106.6, 144.6, 145.3, 199.0. Exact Mass calcd. for  $\text{C}_7\text{H}_8\text{O}$ : 108.0575; found: 108.0578.

The  $^1\text{H}$  NMR signals that are assigned to aldehyde (249) (when produced as a mixture with (245)) were the following:  $\delta$  2.11 (t, 3H,  $J = 2$  Hz,  $=\text{CCH}_3$ ), 3.03 (br s, 2H,  $\text{H}_a$ ), 5.01 (br s, 1H, one of  $\text{H}_b$ ), 5.27 (br s, 1H, one of  $\text{H}_b$ ), 9.92 (s, 1H,  $-\text{CHO}$ ).

Preparation of 1-(formyl)-2,3-bis(methylene)cyclobutane oxime (246)

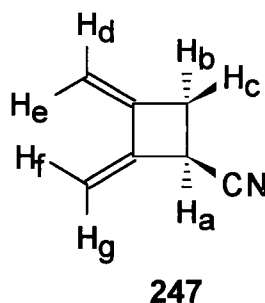


To a stirred solution of the aldehydes (245) and (249) (6:1 mixture as determined by  $^1\text{H}$  NMR spectroscopy, 125 mg, 1.16 mmol, 1.00 equiv.) in dry DMF (10 mL) was added hydroxylamine hydrochloride (410 mg, 5.9 mmol, 5.1 equiv.) and dry pyridine (0.47 mL, 5.1 equiv.). The resultant solution was heated to  $70^\circ\text{C}$  and stirred for 1 hour. The solution was cooled to room temperature, water (10 mL) was added, and the mixture was thoroughly extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Radial chromatography (1 mm plate, 3:1 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by removal of traces of solvent (vacuum pump) from the acquired materials gave 105 mg (74%) of (246) as a viscous oil and 20 mg (14%) of (250) as a colourless solid (melting point,  $120\text{--}121^\circ\text{C}$  after recrystallization from 1:1 hexanes- $\text{Et}_2\text{O}$ ).  $^1\text{H}$  NMR (400 MHz) analysis of oxime (246) indicated that it consisted of a 3:2 mixture of geometric isomers with respect to the oxime function. All attempts to separate these two isomers proved unsuccessful. The following  $^1\text{H}$  NMR signals (400 MHz) could be assigned to the major isomer of oxime (246):  $\delta$  2.62-2.72 (m,  $\sim 0.6\text{H}$ , one of  $\text{H}_b$ ),  $\delta$  2.93-3.06 (m,  $\sim 0.6\text{H}$ , one of  $\text{H}_b$ ),  $\delta$  3.67-3.75 (m,  $\sim 0.6\text{H}$ ,  $\text{H}_a$ ), 7.48 (d,  $\sim 0.6\text{H}$ ,  $J = 7$  Hz,  $-\text{CH}=\text{NOH}$ ). The following  $^1\text{H}$  NMR signals (400 MHz) could be assigned to the minor isomer of oxime (246):  $\delta$  2.52-2.62 (m,  $\sim 0.4\text{H}$ , one of  $\text{H}_b$ ),  $\delta$  2.85-2.92 (m,  $\sim 0.4\text{H}$ , one of  $\text{H}_b$ ),  $\delta$  4.29-4.35 (m,  $\sim 0.4\text{H}$ ,  $\text{H}_a$ ), 6.82 (d,  $\sim 0.4\text{H}$ ,  $J = 7$  Hz,

-CH=NOH). The following  $^1\text{H}$  NMR signals (400 MHz) could not be specifically assigned to either of the two isomers of (246):  $\delta$  4.80-4.92 (m, 2H, olefinic),  $\delta$  5.21-5.31 (m, 2H, olefinic). Mixture (246) also exhibited IR (neat): 3398 (br), 1673, 1279, 974  $\text{cm}^{-1}$ . Anal. calcd. for  $\text{C}_7\text{H}_9\text{NO}$ : C 68.27, H 7.37, N 11.35; found: C 68.20, H 7.29, N 11.70. Exact Mass calcd. for  $\text{C}_7\text{H}_9\text{NO}$ : 123.0684; found: 123.0684.

$^1\text{H}$  NMR (400 MHz) analysis of oxime (250) indicated that it consisted of a 12:1 mixture of geometric isomers. Attempts to separate these two isomers were unsuccessful. The  $^1\text{H}$  NMR signals (400 MHz) assigned to the major isomer were:  $\delta$ : 1.85 (t, 3H,  $J=2$  Hz,  $=\text{CRCH}_3$ ), 3.01 (br s, 2H,  $\text{H}_a$ ), 4.65 (s, 1H, one of  $=\text{CH}_2$ ), 4.83 (br s, 1H, one of  $=\text{CH}_2$ ), 7.95 (s, 1H,  $=\text{CHNOH}$ ). The  $^1\text{H}$  NMR signals (400 MHz) assigned to the minor isomer were:  $\delta$ : 2.09 (t,  $J=2$  Hz,  $=\text{CRCH}_3$ ), 3.30 (br s, one of  $\text{H}_a$ ), 4.72 (br s,  $=\text{CH}_2$ ), 4.91 (br s,  $=\text{CHNOH}$ ). The mixture exhibited IR (neat): 3195 (br), 1673, 975  $\text{cm}^{-1}$ . Anal. calcd. for  $\text{C}_7\text{H}_9\text{NO}$ : C 68.27, H 7.37, N 11.35; found: C 68.26, H 7.17, N 11.05. Exact Mass calcd. for  $\text{C}_7\text{H}_9\text{NO}$ : 123.0684; found: 123.0685.

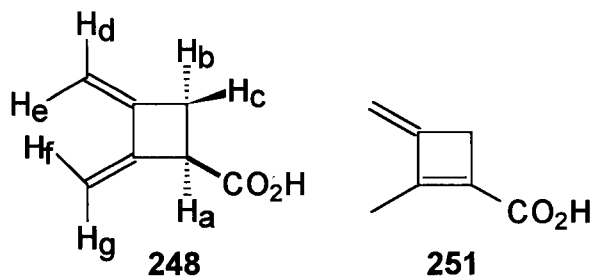
#### Preparation of 1-cyano-2,3-bis(methylene)cyclobutane (247)



To a cold ( $-10^\circ\text{C}$ ), stirred solution of thionyl chloride (1.1 equiv., 47  $\mu\text{L}$ ) in dry  $\text{CH}_2\text{Cl}_2$  (4 mL) was added DMAP (1.25 equiv., 89 mg) and the resultant mixture was stirred at  $-10^\circ\text{C}$  for 5 minutes. Oxime (246) (70 mg, 0.58 mmol) was added, the mixture was stirred for 2 minutes, and DMAP (1.25 equiv., 89 mg) was added. The mixture was warmed to room temperature and stirred for an additional 30 minutes. Water (4 mL) was added and the mixture

was thoroughly extracted with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. Radial chromatography (1 mm plate, 1:1 hexanes- $\text{Et}_2\text{O}$ ) of the crude product followed by distillation ( $45\text{--}50^\circ\text{C}/45\text{ mm Hg}$ ) of the acquired oil gave 49 mg (82%) of 1-cyano-2,3-bis(methylene)cyclobutane (**247**) as a colourless oil (Caution: stench, unstable, volatile), which exhibited IR (neat):  $2240, 1656, 894\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 2.97-3.03 (m, 2H,  $\text{H}_b, \text{H}_c$ ), 3.65-3.73 (m, 1H,  $\text{H}_a$ ), 4.88 (dd, 1H,  $J=2.5, 2.5\text{ Hz}$ ,  $\text{H}_d$ ), 5.09 (br s, 1H,  $\text{H}_g$ ), 5.27 (dd, 1H,  $J=2.5, 2.5\text{ Hz}$ ,  $\text{H}_e$ ), 5.37 (d, 1H,  $J=2.5\text{ Hz}$ ,  $\text{H}_f$ ); NOE difference experiments: irradiation of the signal at  $\delta$  5.37 ( $\text{H}_f$ ) led to enhancement of the signal at  $\delta$  5.09 ( $\text{H}_g$ ); irradiation of the signal at  $\delta$  5.09 ( $\text{H}_g$ ) led to enhancement of the signal at  $\delta$  5.37 ( $\text{H}_f$ ); irradiation of the signal at  $\delta$  4.88 ( $\text{H}_d$ ) led to enhancement of the signal at  $\delta$  2.97-3.01 ( $\text{H}_c$ ) and  $\delta$  5.27 ( $\text{H}_e$ ); irradiation of the signal at  $\delta$  3.70 ( $\text{H}_a$ ) led to enhancement of the signal at  $\delta$  2.99-3.03 ( $\text{H}_b$ ) and  $\delta$  5.09 ( $\text{H}_g$ ); irradiation of the signal at  $\delta$  3.00 ( $\text{H}_b, \text{H}_c$ ) led to enhancement of the signals at  $\delta$  4.88 ( $\text{H}_d$ ) and  $\delta$  3.65-3.73 ( $\text{H}_a$ ). In a series of decoupling experiments, irradiation at  $\delta$  3.70 ( $\text{H}_a$ ) simplified the multiplet at  $\delta$  2.97-3.03 ( $\text{H}_b, \text{H}_c$ ) and converted the signals at  $\delta$  5.09 ( $\text{H}_g$ ) and  $\delta$  5.37 ( $\text{H}_f$ ) into sharp singlets; irradiation at  $\delta$  3.00 ( $\text{H}_b, \text{H}_c$ ) simplified the multiplet at  $\delta$  3.65-3.73 ( $\text{H}_a$ ), and converted the signals at  $\delta$  4.88 ( $\text{H}_d$ ) and  $\delta$  5.27 ( $\text{H}_e$ ) to singlets. Exact Mass calcd. for  $\text{C}_7\text{H}_7\text{N}$ : 105.0578; found: 105.0575.

Preparation of 2,3-bis(methylene)cyclobutanecarboxylic acid (**248**)

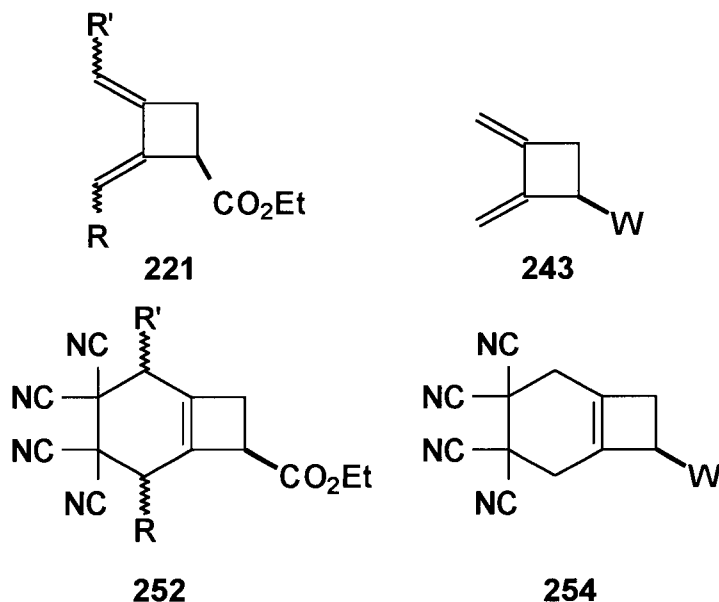


To a stirred solution of ethyl 2,3-bis(methylene)cyclobutanecarboxylate (**53**) (150 mg, 0.990 mmol) in 4 mL of 1:1  $\text{EtOH-H}_2\text{O}$  was added NaOH (1.25 equiv., 59 mg). The resultant

mixture was stirred at room temperature for 2 hours. The solution was extracted with Et<sub>2</sub>O (2 x 4 mL) to remove residual amounts of starting material and the aqueous layer was acidified until pH 2 with 3M hydrochloric acid. The acidified aqueous layer was extracted with Et<sub>2</sub>O (3 x 4 mL). The extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Removal of trace amounts of solvent (vacuum pump) from the acquired liquid gave 110 mg (90%) of a 6:1 mixture (<sup>1</sup>H NMR spectroscopy) of acids (**248**) and (**251**), as a viscous oil. Attempts to separate compounds (**248**) and (**251**) were unsuccessful and this material was used without further purification. The <sup>1</sup>H NMR (400 MHz) signals assigned to acid (**248**) were: δ: 2.83 (dddd, 1H, *J*= 16, 10, 2.5, 2.0 Hz, H<sub>b</sub>), 3.00-3.07 (m, 1H, H<sub>c</sub>), 3.72-3.79 (m, 1H, H<sub>a</sub>), 4.81 (dd, 1H, *J*= 2,2 Hz, H<sub>d</sub>), 5.03 (d, 1H, *J*= 2 Hz, H<sub>g</sub>), 5.22 (dd, 1H, *J*= 2.5, 2.5 Hz, H<sub>e</sub>), 5.30 (d, 1H, *J*= 3 Hz, H<sub>f</sub>). In a series of decoupling experiments, irradiation at δ 5.30 (H<sub>f</sub>) converted the multiplet at δ 3.72-3.79 to a doublet of doublets of doublets (*J*= 10, 7, 2 Hz); irradiation at δ 5.22 (H<sub>e</sub>) converted the multiplet at δ 3.00-3.07 (H<sub>c</sub>) to a doublet of doublet of doublets (*J*= 16, 7, 2 Hz) and the signal at δ 2.83 (H<sub>b</sub>) to a doublet of doublet of doublets (*J*= 16, 10, 2 Hz); irradiation at δ 3.75 (H<sub>a</sub>) converted the doublets at δ 5.03 (H<sub>g</sub>) and δ 5.30 (H<sub>f</sub>) to singlets, converted the multiplet at δ 3.00-3.07 (H<sub>c</sub>) to a doublet of doublet of doublets (*J*= 16, 2.5, 2.0 Hz) and converted the signal at δ 2.83 (H<sub>b</sub>) to a doublet of doublet of doublets (*J*= 16, 2.5, 2.0 Hz); irradiation at δ 3.05 (H<sub>c</sub>) simplified the signals at δ 4.81 (H<sub>d</sub>) and δ 5.22 (H<sub>e</sub>) to doublets (*J*= 2.0, 2.5 Hz, respectively), sharpened the multiplet at δ 3.72- 3.79 (H<sub>a</sub>) and converted the signal at δ 2.83 (H<sub>b</sub>) to a doublet of doublet of doublets (*J*= 10, 2.5, 2.0 Hz); irradiation at δ 2.83 (H<sub>b</sub>) converted the signals at δ 4.81 and δ 5.22 (H<sub>e</sub>) to doublets (*J*= 2.0, 2.5 Hz, respectively) and simplified the multiplets at δ 3.72-3.79 (H<sub>a</sub>) and δ 3.00-3.07 (H<sub>c</sub>). The <sup>1</sup>H NMR (400 MHz) signals assigned to acid (**59a**) were: δ: 2.01 (dd, 3H, *J*= 2, 2 Hz, -CH<sub>3</sub>), 3.02-3.08 (m, 2H, -CH<sub>2</sub>-), 4.89 (br s, 1H, one of =CH<sub>2</sub>), 5.12 (br s, 1H, one of =CH<sub>2</sub>). The mixture exhibited IR (neat): 2970 (br), 1705, 1440, 1250 cm<sup>-1</sup>. Exact mass calcd. for C<sub>7</sub>H<sub>8</sub>O<sub>2</sub>: 125.0424; found: 125.0420.

### 13. Diels-Alder reactions

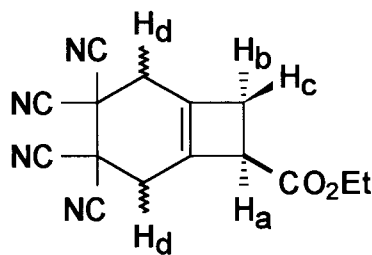
#### 13.1 General Procedure 14: Preparation of the functionalized bicyclo[4.2.0]oct-1(6)-enes (252) and (254)



To a stirred solution of the appropriate ethyl cyclobutanecarboxylate (**221**) or the 1-substituted-2,3-bis(methylene)cyclobutane (**243**) (1 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (8-12 mL/mmol of substrate) was added tetracyanoethylene (1 equiv., unless noted otherwise). The reaction mixture was stirred for 0.5 hours at room temperature (unless noted otherwise) and the solvent was removed under reduced pressure. Radial chromatography of the crude product followed by recrystallization (1:1 hexanes-Et<sub>2</sub>O) of the acquired solids afforded the corresponding products (**252**) and (**254**), respectively, as crystalline solids.



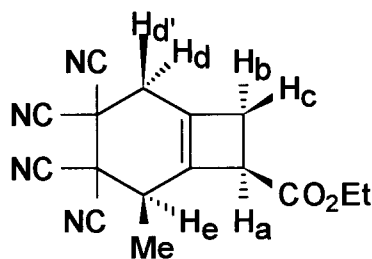
Preparation of the ester (255)



**255**

Following general procedure 14 outlined above, ethyl 2,3-bis(methylene)cyclobutanecarboxylate (**53**) was converted into the ester (**255**). The following amounts of reagents and solvents were used: ethyl 2,3-bis(methylene)cyclobutanecarboxylate (**53**) (500 mg, 3.29 mmol) in 36 mL of dry  $\text{CH}_2\text{Cl}_2$  and tetracyanoethylene (427 mg, 3.29 mmol). Normal workup, followed by radial chromatography (4 mm plate,  $\text{CH}_2\text{Cl}_2$ ) of the crude product and recrystallization (1:1 hexanes- $\text{Et}_2\text{O}$ ) of the acquired solid afforded 630 mg (68%) of ester (**255**) as fine colourless crystals (melting point 128-129°C). This material exhibited IR (KBr): 2255, 1729, 1264, 1199  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.27 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.85 (dm, 1H,  $J = 14$  Hz,  $\text{H}_c$ ), 3.05 (dm, 1H,  $J = 14$  Hz,  $\text{H}_b$ ), 3.09-3.34 (m, 4H,  $\text{H}_d$ ), 3.76-3.81 (m, 1H,  $\text{H}_a$ ), 4.15-4.23 (m, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ); NOE difference experiments: irradiation of the signals at  $\delta$  3.20 ( $\text{H}_d$ ) led to the enhancement of the signal at  $\delta$  3.76-3.81 ( $\text{H}_a$ ); irradiation of the signal at  $\delta$  3.77 ( $\text{H}_a$ ) led to the enhancement of the signal at  $\delta$  3.05 ( $\text{H}_b$ );  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.2, 32.5, 33.4, 35.4, 38.06, 38.13, 45.6, 61.4, 110.39, 110.40, 110.43, 110.45, 135.1, 137.9, 170.2. Anal. calcd. for  $\text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_4$ : C 64.31, H 4.28, N 19.99; found: C 64.16, H 4.38, N 20.13. Exact Mass calcd. for  $\text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_4$ : 280.0970; found: 280.0964.

Preparation of the ester (256)

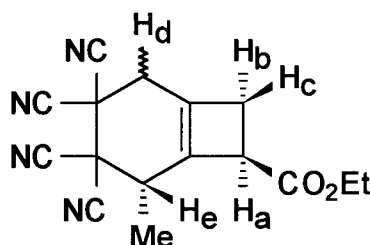


**256**

Following general procedure 14 outlined above, ethyl (Z)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**) was converted into the ester (**256**). The following amounts of reagents and solvents were used: ethyl (Z)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**) (250 mg, 1.51 mmol) in 13 mL of dry  $\text{CH}_2\text{Cl}_2$  and tetracyanoethylene (198 mg, 1.51 mmol). Normal workup, followed by radial chromatography (4 mm plate,  $\text{CH}_2\text{Cl}_2$ ) of the crude product and recrystallization (1:1 hexanes- $\text{Et}_2\text{O}$ ) of the acquired solid afforded 340 mg (77%) of ester (**256**) as colourless crystals (mp 110-111°C). This material exhibited IR (KBr): 2258, 1731, 1256, 1034  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.27 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.50 (d, 3H,  $J = 7$  Hz,  $-\text{CHCH}_3$ ), 2.81 (dm, 1H,  $J = 14$  Hz,  $\text{H}_c$ ), 2.90 (dm, 1H,  $J = 14$  Hz,  $\text{H}_b$ ), 3.09 (dm, 1H,  $J = 16$  Hz,  $\text{H}_d$ ), 3.22 (br d, 1H,  $J = 16$  Hz,  $\text{H}_{d'}$ ), 3.27-3.32 (m, 1H,  $\text{H}_e$ ), 3.70-3.75 (m, 1H,  $\text{H}_a$ ), 4.12-4.22 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ); in a series of decoupling experiments, irradiation at  $\delta$  2.81 ( $\text{H}_c$ ) converted the doublet of multiplets at  $\delta$  2.90 ( $\text{H}_b$ ) to a multiplet and sharpened the signals at  $\delta$  3.09 ( $\text{H}_d$ ),  $\delta$  3.22 ( $\text{H}_{d'}$ ), and  $\delta$  3.70-3.75 ( $\text{H}_a$ ); irradiation at  $\delta$  2.90 ( $\text{H}_b$ ) converted the doublet of multiplets at  $\delta$  2.81 ( $\text{H}_c$ ) to a multiplet and sharpened the signals at  $\delta$  3.22 ( $\text{H}_{d'}$ ) and  $\delta$  3.70-3.75 ( $\text{H}_a$ ); irradiation at  $\delta$  3.09 ( $\text{H}_d$ ) converted the doublet at  $\delta$  3.22 ( $\text{H}_{d'}$ ) to a broad singlet, sharpened the doublet of multiplets at  $\delta$  2.81 ( $\text{H}_c$ ), and converted the signal at  $\delta$  2.90 ( $\text{H}_b$ ) to a doublet of doublet of doublets ( $J = 14, 3, 3$  Hz); irradiation at  $\delta$  3.22 ( $\text{H}_{d'}$ ) sharpened the signals at  $\delta$  2.81 ( $\text{H}_c$ ) and  $\delta$  2.90 ( $\text{H}_b$ ), and converted the broad doublet at  $\delta$  3.09 ( $\text{H}_d$ ) to a broad

singlet; irradiation at  $\delta$  3.73 ( $H_a$ ) sharpened the signals at  $\delta$  2.81 ( $H_c$ ),  $\delta$  2.90 ( $H_b$ ) and  $\delta$  3.27-3.32 ( $H_e$ ). NOE difference experiments: irradiation of the signal at  $\delta$  1.50 ( $-\text{CHCH}_3$ ) led to enhancement of the signal at  $\delta$  3.22 ( $H_d'$ ) and  $\delta$  3.27-3.32 ( $H_e$ ); irradiation of the signal at  $\delta$  2.81 ( $H_c$ ) led to the enhancement of the signal at  $\delta$  2.90 ( $H_b$ ); irradiation of the signal at  $\delta$  2.90 ( $H_b$ ) led to the enhancement of the signals at  $\delta$  2.81 ( $H_c$ ) and  $\delta$  3.70-3.75 ( $H_a$ ); irradiation of the signal at  $\delta$  3.73 ( $H_a$ ) led to the enhancement of the signal at  $\delta$  2.90 ( $H_b$ ) and  $\delta$  3.27-3.32 ( $H_e$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 13.1, 14.1, 33.4, 34.5, 37.7, 38.6, 44.6, 45.3, 61.4, 108.5, 110.4, 110.7, 110.8, 138.0, 139.0, 170.7. Anal. calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_4$ : C 65.29, H 4.80, N 19.04; found: C 65.28, H 4.82, N 19.00. Exact Mass calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_4$ : 294.1118; found: 294.1123. X-Ray crystallographic data for compound (256) can be seen in Appendix V.

#### Preparation of the ester (257)

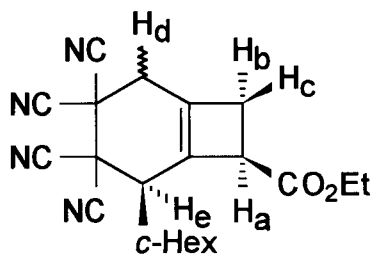


**257**

Following general procedure 14 outlined above, ethyl (*E*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**54**) was converted into the ester (**257**). The following amounts of reagents and solvents were used: ethyl (*E*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**54**) (150 mg, 0.903 mmol) in 10 mL of dry  $\text{CH}_2\text{Cl}_2$  and tetracyanoethylene (116 mg, 0.906 mmol). Normal workup, followed by radial chromatography (4 mm plate,  $\text{CH}_2\text{Cl}_2$ ) of the crude product, and recrystallization (1:1 hexanes- $\text{Et}_2\text{O}$ ) of the acquired solid afforded 185 mg (70%) of ester (**257**) as fine colourless crystals (mp 152-153°C). This material exhibited IR (KBr): 2255, 1737, 1190, 1028  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.28 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.57 (d, 3H,  $J = 7$  Hz,  $-\text{CHCH}_3$ ), 2.82-2.88 (m, 1H,  $\text{H}_c$ ), 2.93-3.00 (m, 1H,  $\text{H}_b$ ), 3.09-3.20 (m, 2H,  $\text{H}_d$ ), 3.31-3.40 (m, 1H,  $\text{H}_e$ ), 3.74-3.78 (m, 1H,  $\text{H}_a$ ), 4.18 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.57 ( $-\text{CHCH}_3$ ) sharpened the signal at  $\delta$  3.31-3.40 ( $\text{H}_e$ ); irradiation at  $\delta$  2.85 ( $\text{H}_c$ ) sharpened the multiplets at  $\delta$  2.93-3.00 ( $\text{H}_b$ ),  $\delta$  3.09-3.20 ( $\text{H}_d$ ) and  $\delta$  3.74-3.78 ( $\text{H}_a$ ); irradiation at  $\delta$  2.97 ( $\text{H}_b$ ) sharpened the multiplets at  $\delta$  2.82-2.88 ( $\text{H}_c$ ),  $\delta$  3.09-3.20 ( $\text{H}_d$ ) and  $\delta$  3.74-3.78 ( $\text{H}_a$ ); irradiation at  $\delta$  3.36 ( $\text{H}_e$ ) converted the doublet at  $\delta$  1.57 ( $-\text{CHCH}_3$ ) to a singlet and sharpened the multiplet at  $\delta$  3.74-3.78 ( $\text{H}_a$ ); irradiation at  $\delta$  3.77 ( $\text{H}_a$ ) converted the multiplet at  $\delta$  2.82-2.88 ( $\text{H}_c$ ) to a doublet of doublets ( $J = 14, 3$  Hz) and the multiplet at  $\delta$  2.93-3.00 ( $\text{H}_b$ ) to a broad doublet of doublets ( $J = 14, 2.5$  Hz), and sharpened the multiplet at  $\delta$  3.31-3.40 ( $\text{H}_e$ ). NOE difference experiments: irradiation of the signal at  $\delta$  1.57 ( $-\text{CHCH}_3$ ) led to enhancement of the signals at  $\delta$  3.31-3.40 ( $\text{H}_e$ ) and  $\delta$  3.74-3.78 ( $\text{H}_a$ ); irradiation of the signal at  $\delta$  3.36 ( $\text{H}_e$ ) led to the enhancement of the signal at  $\delta$  1.57 ( $-\text{CHCH}_3$ ); irradiation of the signal at  $\delta$  3.76 ( $\text{H}_a$ ) led to the enhancement of the signals at  $\delta$  1.57 ( $-\text{CHCH}_3$ ) and  $\delta$  2.93-3.00 ( $\text{H}_b$ );  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 13.2, 14.2, 33.4, 34.4, 37.7, 39.1, 44.6, 45.1, 61.5, 108.9, 110.1, 110.7, 110.9, 136.7, 139.8, 170.1. Anal. calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_4$ : C 65.29, H 4.80, N 19.04; found: C 65.10, H 4.85, N 19.00. Exact Mass calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_4$ : 294.1118; found: 294.1117.

#### Preparation of the ester (260)



260

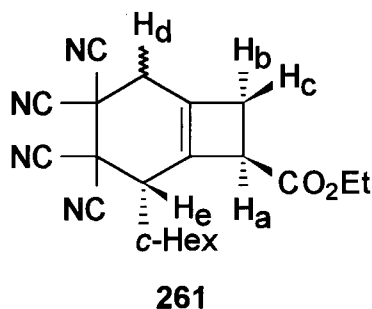
Following a modified version of general procedure 14 outlined above, in which the reaction mixture was allowed to stir at room temperature for 4 days instead of 0.5 hours and 1.5 equiv. tetracyanoethylene was used, ethyl

(*Z*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**236**) was converted into the ester (**260**). The following amounts of reagents and solvents were used: ethyl

(*Z*)-2-cyclohexylmethylene-3-methylenecyclobutane-carboxylate (**236**) (200 mg, 0.854 mmol) in 9 mL of dry CH<sub>2</sub>Cl<sub>2</sub> and tetracyanoethylene (167 mg, 1.30 mmol). Normal workup, followed by radial chromatography (4 mm plate, CH<sub>2</sub>Cl<sub>2</sub>) of the crude product, and recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solid afforded 224 mg (73%) of ester (**260**) as fine colourless crystals (mp 138-139°C). This material exhibited IR (KBr): 2252, 1725, 1329, 1166 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.04-1.46 (m, 9H, includes triplet at δ 1.28, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.66-2.05 (m, 5H), 2.68 (dm, 1H, *J*= 14 Hz, H<sub>C</sub>), 2.80-2.89 (m, 2H, H<sub>b</sub>, H<sub>e</sub>), 3.07 (br d, 1H, *J*= 18 Hz, one of H<sub>d</sub>), 3.22 (br d, 1H, *J*= 18 Hz, one of H<sub>d</sub>), 3.74-3.78 (m, 1H, H<sub>a</sub>), 4.10-4.23 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>); in a series of decoupling experiments, irradiation at δ 2.68 (H<sub>C</sub>) sharpened the multiplets at δ 2.80-2.89 (H<sub>b</sub>) and δ 3.74-3.78 (H<sub>a</sub>); irradiation at δ 2.85 (H<sub>b</sub>, H<sub>e</sub>) converted the doublet of multiplets at δ 2.68 (H<sub>C</sub>) to a multiplet and sharpened the multiplet at δ 3.74-3.78 (H<sub>a</sub>); irradiation at δ 3.07 (one of H<sub>d</sub>) converted the broad doublet at δ 3.22 (one of H<sub>d</sub>) to a broad singlet and sharpened the doublet of multiplets at δ 2.68 (H<sub>C</sub>); irradiation at δ 3.22 (one of H<sub>d</sub>) converted the broad doublet at δ 3.07 (one of H<sub>d</sub>) to a broad singlet and sharpened the multiplet at δ 2.80-2.89 (H<sub>e</sub>); irradiation at δ 3.76 (H<sub>a</sub>) simplified the broad doublet at δ 2.68 (H<sub>C</sub>) and the multiplet at δ 2.85 (H<sub>b</sub>, H<sub>e</sub>). NOE difference experiments: irradiation of the signal at δ 2.68 (H<sub>C</sub>) led to enhancement of the signal at δ 2.85 (H<sub>b</sub>); irradiation of the signal at δ 2.85 (H<sub>b</sub>, H<sub>e</sub>) led to the enhancement of the signals at δ 2.68 (H<sub>C</sub>) and δ 3.74-3.78 (H<sub>a</sub>); irradiation of the signal at δ 3.07 (one of H<sub>d</sub>) led to the enhancement of the signal at δ 3.22 (one of H<sub>d</sub>); irradiation of the signal at δ 3.22 (one of H<sub>d</sub>) led to the enhancement of the signal at δ 3.07 (one of H<sub>d</sub>); irradiation of the signal at δ 3.76 (H<sub>a</sub>) led to the enhancement of the signals at δ 1.79-1.93 and δ 2.80-2.89 (H<sub>b</sub>, H<sub>e</sub>); <sup>13</sup>C NMR (100.4 MHz) δ: 14.8, 25.6, 26.0, 26.4, 30.5, 32.86, 32.93, 35.1, 39.7, 40.6, 42.6, 47.0, 47.5, 61.5,

109.7, 110.2, 111.0, 111.7, 137.5, 139.4, 170.8. Anal. calcd. for  $C_{21}H_{22}O_2N_4$ : C 69.59, H 6.12, N 15.46; found: C 69.69, H 6.16, N 15.48. Exact Mass calcd. for  $C_{21}H_{22}O_2N_4$ : 362.1743; found: 362.1734.

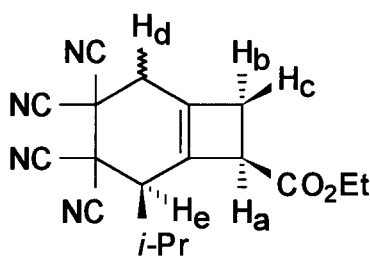
#### Preparation of the ester (261)



Following general procedure 14 outlined above, ethyl (*E*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**235**) was converted into the ester (**261**). The following amounts of reagents and solvents were used: ethyl (*E*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**235**) (125 mg, 0.533 mmol) in 5 mL of dry  $CH_2Cl_2$ , and tetracyanoethylene (70 mg, 0.54 mmol). Normal workup, followed by radial chromatography (4 mm plate,  $CH_2Cl_2$ ) of the crude product, and recrystallization (1:1 petroleum ether- $Et_2O$ ) of the acquired solid afforded 136 mg (70%) of ester (**261**) as fine colourless crystals (mp 147-148°C). This material exhibited IR (KBr): 2271, 1727, 1326, 1186  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 1.10-1.45 (m, 9H, includes triplet at  $\delta$  1.25, 3H,  $J$  = 7 Hz,  $-OCH_2CH_3$ ), 1.68-2.04 (m, 5H), 2.62-2.69 (dm, 1H,  $J$  = 14 Hz,  $H_C$ ), 2.97-3.06 (m, 2H,  $H_b$ ,  $H_e$ ), 3.07 (d, 1H,  $J$  = 14 Hz, one of  $H_d$ ), 3.14 (br d, 1H,  $J$  = 14 Hz, one of  $H_d$ ), 3.79-3.83 (m, 1H,  $H_a$ ), 4.18 (q, 2H,  $J$  = 7 Hz,  $-OCH_2CH_3$ ); in a series of decoupling experiments, irradiation at  $\delta$  2.65 ( $H_C$ ) simplified the multiplets at  $\delta$  3.00-3.06 ( $H_b$ ) and  $\delta$  3.79-3.83 ( $H_a$ ), and sharpened the broad doublet at  $\delta$  3.14 (one of  $H_d$ ); irradiation at  $\delta$  3.03 ( $H_b$ ,  $H_e$ ) converted the doublet of multiplets at  $\delta$  2.62-2.69 ( $H_C$ ) to a multiplet, sharpened the broad doublet at  $\delta$  3.14 (one of  $H_d$ )

and sharpened the multiplet at  $\delta$  3.79-3.83 ( $H_a$ ); irradiation at  $\delta$  3.14 (one of  $H_d$ ) converted the doublet of multiplets at  $\delta$  2.62-2.69 ( $H_c$ ) to a broad doublet of doublets ( $J = 14, 2.5$  Hz) and converted the broad doublet at  $\delta$  3.07 (one of  $H_d$ ) to a broad singlet; irradiation at  $\delta$  3.82 ( $H_a$ ) converted the multiplet at  $\delta$  2.62-2.69 ( $H_c$ ) to a doublet of doublets ( $J = 14, 3$  Hz) and simplified the multiplet at  $\delta$  2.97-3.06 ( $H_b, H_e$ ). NOE difference experiments: irradiation of the signal at  $\delta$  2.65 ( $H_c$ ) led to enhancement of the signal at  $\delta$  3.00-3.06 ( $H_b$ ); irradiation of the signal at  $\delta$  3.03 ( $H_b, H_e$ ) led to the enhancement of the signals at  $\delta$  1.85-2.00,  $\delta$  2.62-2.69 ( $H_c$ ), and  $\delta$  3.79-3.83 ( $H_a$ ); irradiation of the signal at  $\delta$  3.82 ( $H_a$ ) led to the enhancement of the signals at  $\delta$  1.95-2.04 and  $\delta$  3.00-3.06 ( $H_b$ );  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 14.1, 25.3, 25.6, 26.4, 31.4, 32.6, 33.1, 34.8, 38.0, 41.0, 41.8, 46.6, 48.0, 61.2, 108.7, 110.7, 111.0, 112.1, 138.2, 139.4, 171.3. Anal. calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_4$ : C 69.59, H 6.12, N 15.46; found: C 69.60, H 6.03, N 15.63. Exact Mass calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_4$ : 362.1743; found: 362.1738.

#### Preparation of the ester (258)

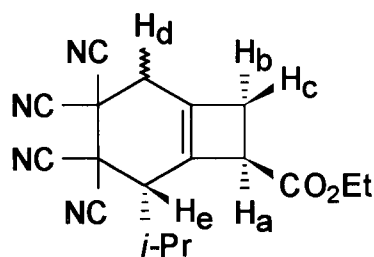


**258**

Following a modified version of general procedure 14 outlined above in which the reaction mixture was allowed to stir at room temperature for 4 days instead of 0.5 hours and 1.5 equiv. tetracyanoethylene was used, ethyl (Z)-2-(2-methylpropylidene)-3-methylenecyclobutane-carboxylate (**234**) was converted into the ester (**79**). The following amounts of reagents and solvents were used: ethyl (Z)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**69**) (100 mg, 0.515 mmol) in 6 mL of dry  $\text{CH}_2\text{Cl}_2$ , and tetracyanoethylene (100 mg, 0.779 mmol). Normal workup, followed by radial chromatography (4 mm plate, 3:1 hexanes- $\text{Et}_2\text{O}$ ) of the crude product, and

recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solid afforded 107 mg (65%) of ester (**258**) as fine colourless crystals (mp 80-81°C). This material exhibited IR (KBr): 2253, 1729, 1474, 1262, 1198 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.09 (d, 3H, *J* = 6.5 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.27 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.30 (d, 3H, *J* = 6.5 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 2.18-2.28 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 2.69 (dm, 1H, *J* = 12 Hz, H<sub>c</sub>), 2.78-2.83 (m, 1H, H<sub>e</sub>), 2.83-2.88 (dm, *J* = 12 Hz, 1H, H<sub>b</sub>), 3.07 (br d, 1H, *J* = 18 Hz, one of H<sub>d</sub>), 3.24 (br d, 1H, *J* = 18 Hz, one of H<sub>d</sub>), 3.76-3.81 (m, 1H, H<sub>a</sub>), 4.17 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>); NOE difference experiments: irradiation of the signal at δ 2.22 (-CH(CH<sub>3</sub>)<sub>2</sub>) led to enhancement of the signals at δ 1.09 (one of -CH(CH<sub>3</sub>)<sub>2</sub>), δ 1.30 (one of -CH(CH<sub>3</sub>)<sub>2</sub>), and δ 2.78-2.83 (H<sub>e</sub>); irradiation of the signal at δ 3.24 (one of H<sub>d</sub>) led to the enhancement of the signals at δ 3.07 (one of H<sub>d</sub>) and δ 1.09 (one of -CH(CH<sub>3</sub>)<sub>2</sub>); irradiation of the signal at δ 3.79 (H<sub>a</sub>) led to the enhancement of the signals at δ 2.78-2.83 (H<sub>e</sub>) and δ 2.83-2.88 (H<sub>b</sub>); <sup>13</sup>C NMR (100.4 MHz) δ: 14.0, 21.3, 21.7, 28.6, 33.0, 34.7, 41.0, 42.4, 46.8, 48.7, 61.3, 108.7, 110.6, 110.9, 112.0, 138.1, 138.8, 171.2. Anal. calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>N<sub>4</sub>: C 67.06, H 5.63, N 17.38; found: C 66.81, H 5.68, N 17.31. Exact Mass calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>N<sub>4</sub>: 322.1430; found: 322.1432.

#### Preparation of the ester (**259**)



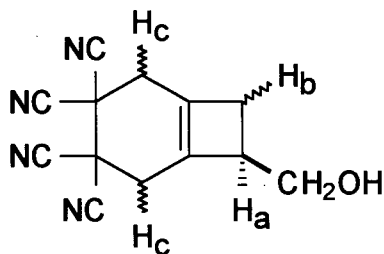
**259**

Following a modified version of general procedure 14 outlined above, in which 1.1 equiv. tetracyanoethylene was used, ethyl (*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**) was converted into the ester (**259**). The following amounts of reagents and solvents were used: ethyl



(*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**) (150 mg, 0.773 mmol) in 9 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, and tetracyanoethylene (110 mg, 0.852 mmol). Normal workup, followed by radial chromatography (4 mm plate, CH<sub>2</sub>Cl<sub>2</sub>) of the crude product, and recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solid afforded 162 mg (66%) of ester (**259**) as fine colourless crystals (mp 87-88°C). This material exhibited IR (KBr): 2253, 1729, 1467, 1263, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.20 (d, 3H, *J*= 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.22 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.26 (d, 3H, *J*= 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 2.18-2.26 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 2.65-2.72 (dm, 1H, *J*= 14 Hz, H<sub>C</sub>), 3.03-3.07 (m, 2H, H<sub>b</sub>, H<sub>e</sub>), 3.10-3.19 (m, 2H, H<sub>d</sub>), 3.79-3.83 (m, 1H, H<sub>a</sub>), 4.13-4.22 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>); NOE difference experiments: irradiation of the signal at δ 2.20 (-CH(CH<sub>3</sub>)<sub>2</sub>) led to enhancement of the signals at δ 1.20 (one of -CH(CH<sub>3</sub>)<sub>2</sub>), δ 1.26 (one of -CH(CH<sub>3</sub>)<sub>2</sub>), and δ 3.04-3.07 (H<sub>e</sub>); irradiation of the signal at δ 2.68 (H<sub>C</sub>) led to the enhancement of the signals at δ 3.04-3.07 (H<sub>b</sub>); irradiation of the signal at δ 3.81 (H<sub>a</sub>) led to the enhancement of the signals at δ 1.20 (one of -CH(CH<sub>3</sub>)<sub>2</sub>) and δ 3.04-3.07 (H<sub>b</sub>); <sup>13</sup>C NMR (100.4 MHz) δ: 14.2, 19.9, 22.8, 29.8, 32.9, 35.2, 41.2, 42.9, 46.8, 47.9, 61.5, 109.5, 110.1, 111.0, 111.6, 137.8, 139.2, 170.7. Anal. calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>N<sub>4</sub>: C 67.06, H 5.63, N 17.38; found: C 66.86, H 5.72, N 17.17. Exact Mass calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>N<sub>4</sub>: 322.1430; found: 322.1427.

#### Preparation of the alcohol (**262**)



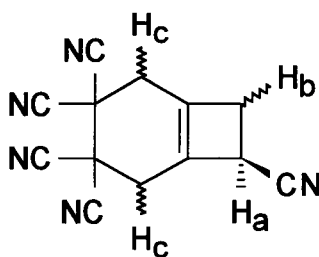
**262**

Following general procedure 14 outlined above, 1-(hydroxymethyl)-2,3-bis(methylene)cyclobutane (**244**) was converted into the alcohol (**262**).

The following amounts of reagents and solvents were used:

1-(hydroxymethyl)-2,3-bis(methylene)cyclobutane (**244**) (275 mg, 2.50 mmol) in 30 mL of dry  $\text{CH}_2\text{Cl}_2$ , and tetracyanoethylene (326 mg, 2.50 mmol). Normal workup, followed by radial chromatography (4 mm plate,  $\text{CH}_2\text{Cl}_2$ ) of the crude product and recrystallization (1:1 petroleum ether- $\text{Et}_2\text{O}$ ) of the acquired solid, afforded 433 mg (73%) of alcohol (**262**) as fine colourless crystals (mp 94-95°C). This material exhibited IR (KBr): 3345 (br), 2257, 1659, 1437, 1029  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.63 (br s, 1H, -OH), 2.36 (dm, 1H,  $J = 15$  Hz, one of  $\text{H}_b$ ), 2.78 (dm, 1H,  $J = 15$  Hz, one of  $\text{H}_b$ ), 3.05-3.31 (m, 5H,  $\text{H}_a$ ,  $\text{H}_c$ ), 3.67 (dd, 1H,  $J = 12, 8$  Hz, one of  $-\text{CH}_2\text{OH}$ ), 3.90 (dd, 1H,  $J = 12, 6$  Hz, one of  $-\text{CH}_2\text{OH}$ );  $^{13}\text{C}$  NMR (acetone- $d_6$ , 100.4 MHz)  $\delta$ : 33.2, 33.6, 34.2, 39.7, 40.0, 46.7, 64.4, 112.36, 112.41, 112.47, 112.52, 136.8, 139.8. Anal. calcd. for  $\text{C}_{13}\text{H}_{10}\text{ON}_4$ : C 65.54, H 4.23, N 23.52; found: C 65.53, H 4.37, N 23.28. Exact Mass calcd. for  $\text{C}_{13}\text{H}_{10}\text{ON}_4$ : 238.0854; found: 238.0849.

#### Preparation of the nitrile (**263**)



**263**

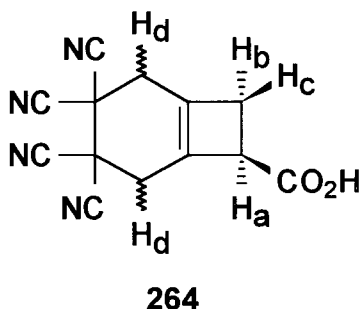
Following general procedure 14 outlined above,

1-(cyano)-2,3-bis(methylene)cyclobutane (**247**) was converted into the nitrile (**263**). The following amounts of reagents and solvents were used:

1-(cyano)-2,3-bis(methylene)cyclobutane (**247**) (40 mg, 0.38 mmol) in 4 mL of dry  $\text{CH}_2\text{Cl}_2$ , and tetracyanoethylene (50 mg, 0.39 mmol). Normal workup, followed by radial chromatography (1 mm plate,  $\text{CH}_2\text{Cl}_2$ ) of the crude product and recrystallization (1:1 petroleum ether- $\text{Et}_2\text{O}$ ) of the acquired solid, afforded 61 mg (69%) of nitrile (**263**) as fine

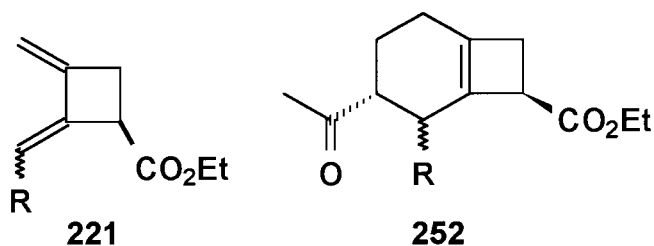
colourless crystals (mp 163-165°C). This material exhibited IR (KBr): 2245, 1663, 1436, 912  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 3.06-3.33 (m, 6H,  $\text{H}_b$ ,  $\text{H}_c$ ), 3.81 (dd, 1H,  $J = 2, 2$  Hz,  $\text{H}_a$ ); Anal. calcd. for  $\text{C}_{13}\text{H}_7\text{N}_5$ : C 66.95, H 3.03, N 30.03; found: C 67.15, H 2.98, N 29.90. Exact Mass calcd. for  $\text{C}_{13}\text{H}_7\text{N}_5$ : 233.0701; found: 233.0702.

#### Preparation of the acid (264)



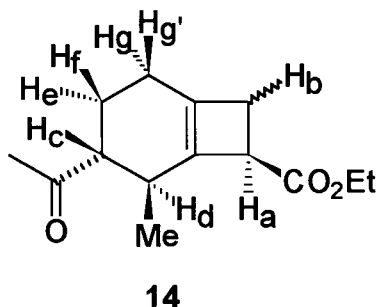
Following general procedure 14 outlined above, a 2.5:1 mixture of acids (248) and (251) were used to synthesize the acid (264). The following amounts of reagents and solvents were used: 1-(carboxy)-2,3-bis(methylene)cyclobutane (248) and 1-carboxy-3-methylene-2-methylcyclobut-1-ene (251) (2.5:1 mixture) (125 mg, 1.01 mmol) in 12 mL of dry  $\text{CH}_2\text{Cl}_2$ , and tetracyanoethylene (132 mg, 1.02 mmol). Normal workup, followed by radial chromatography (1 mm plate,  $\text{Et}_2\text{O}$ ) of the crude product and recrystallization (1:1 hexanes- $\text{Et}_2\text{O}$ ) of the acquired solid, afforded 112 mg (44%) of acid (264) as fine colourless crystals (mp 165-166°C dec.). This material exhibited IR (KBr): 3750-2400, 2256, 1709, 1436, 1252  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 2.94 (dm, 1H,  $J = 14$  Hz,  $\text{H}_b$ ), 3.07-3.22 (m, 4H,  $\text{H}_c$ , 3 of  $\text{H}_d$ ), 3.32 (br d, 1H,  $J = 16$  Hz, one of  $\text{H}_d$ ), 3.88 (br s, 1H,  $\text{H}_a$ ); NOE difference experiment: irradiation of the signal at  $\delta$  2.94 ( $\text{H}_b$ ) enhanced the signal at  $\delta$  3.88 ( $\text{H}_a$ ); irradiation of the signal at  $\delta$  3.88 ( $\text{H}_a$ ) enhanced the signals at  $\delta$  2.94 ( $\text{H}_b$ ) and  $\delta$  3.07-3.15 (one of  $\text{H}_d$ ). Anal. calcd. for  $\text{C}_{13}\text{H}_8\text{O}_2\text{N}_4$ : C 61.90, H 3.20, N 22.21 found: C 61.88, H 3.30, N 22.18. Exact Mass calcd. for  $\text{C}_{13}\text{H}_8\text{O}_2\text{N}_4$ : 252.0647; found: 252.0646.

### 13.2 General Procedure 15: Preparation of the keto esters (252)



To a cold ( $-78^{\circ}\text{C}$ ), stirred solution of the appropriate diene (**221**) (1 equiv.) in dry dichloromethane (10-12 mL/mmol ester) was added sequentially methyl vinyl ketone (MVK) (5 equiv.) and boron trifluoride-etherate (1 equiv.). The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1.5-3.5 hours (unless noted otherwise). Saturated aqueous  $\text{NH}_4\text{Cl}$ - $\text{NH}_4\text{OH}$  (pH 8) (equal volume to the total volume of the reaction mixture) was added, the resultant mixture was allowed to warm to room temperature, and the mixture was thoroughly extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. The residual oil was subjected to either flash or radial chromatography and traces of solvent were removed (vacuum pump) from the acquired material to afford the corresponding keto ester (**252**).

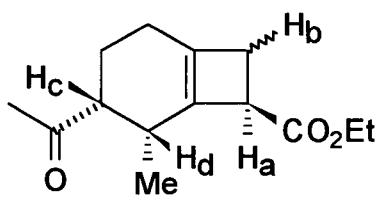
### Preparation of the keto ester (14)



Following general procedure 15 outlined above, ethyl (Z)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**) was converted into the keto ester (**14**). The reaction time was 3 hours. The following amounts of reagents and solvents were used: ethyl (Z)-2-ethylidene-3-methylenecyclobutanecarboxylate (**55**) (225 mg, 1.35 mmol) in 15 mL of dry  $\text{CH}_2\text{Cl}_2$ , methyl vinyl ketone (475 mg, 6.77 mmol), and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (192 mg, 1.35 mmol). Normal workup, followed by radial chromatography (4 mm plate, 3:1 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and removal of traces of solvent (vacuum pump) from the acquired liquid afforded 185 mg (58%) of the keto ester (**14**) as a colourless oil, which exhibited IR (neat): 1731, 1712, 1177, 1033  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.88 (d, 3H,  $J = 7$  Hz,  $-\text{CHCH}_3$ ), 1.24 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.59-1.69 (m, 1H,  $\text{H}_e$ ), 1.89-1.94 (m, 1H,  $\text{H}_f$ ), 1.95-2.02 (m, 1H,  $\text{H}_g$ ), 2.08-2.14 (m, 1H,  $\text{H}_{g'}$ ), 2.15 (s, 3H,  $-\text{COCH}_3$ ), 2.40 (ddd, 1H,  $J = 11, 8, 3$  Hz,  $\text{H}_c$ ), 2.50-2.58 (m, 1H,  $\text{H}_d$ ), 2.58-2.66 (m, 2H,  $\text{H}_b$ ), 3.52-3.57 (m, 1H,  $\text{H}_a$ ), 4.11 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.63 ( $\text{H}_e$ ) simplified the multiplets at  $\delta$  1.89-1.94 ( $\text{H}_f$ ), 1.95-2.02 ( $\text{H}_g$ ),  $\delta$  2.08-2.14 ( $\text{H}_{g'}$ ) and  $\delta$  2.40 ( $\text{H}_c$ ); irradiation at  $\delta$  1.91 ( $\text{H}_f$ ) simplified the multiplets at  $\delta$  1.59-1.69 ( $\text{H}_e$ ), 1.95-2.02 ( $\text{H}_g$ ), and  $\delta$  2.08-2.14 ( $\text{H}_{g'}$ ) and converted the signal at  $\delta$  2.40 ( $\text{H}_c$ ) to a doublet of doublets ( $J = 11, 8$  Hz); irradiation at  $\delta$  2.00 ( $\text{H}_g$ ) simplified the multiplets at  $\delta$  1.59-1.69 ( $\text{H}_e$ ),  $\delta$  1.89-1.94 ( $\text{H}_f$ ) and 2.08-2.14 ( $\text{H}_{g'}$ ); irradiation at  $\delta$  2.12 ( $\text{H}_{g'}$ ) simplified the multiplets at  $\delta$  1.59-1.69 ( $\text{H}_e$ ),  $\delta$  1.89-1.94 ( $\text{H}_f$ ) and 1.95-2.02 ( $\text{H}_g$ ); irradiation at  $\delta$  2.40 ( $\text{H}_c$ ) simplified the multiplets at  $\delta$  1.59-1.69 ( $\text{H}_e$ ),  $\delta$  1.89-1.94 ( $\text{H}_f$ ), and  $\delta$  2.50-2.58 ( $\text{H}_d$ ); irradiation at  $\delta$  2.54 ( $\text{H}_d$ ) converted the doublet at  $\delta$  0.88

(-CHCH<sub>3</sub>) to a singlet and converted the signal at  $\delta$  2.40 (H<sub>c</sub>) to a doublet of doublets ( $J = 11$ , 3 Hz); irradiation at  $\delta$  3.55 (H<sub>a</sub>) simplified the multiplet at 2.58-2.66 (H<sub>b</sub>). NOE difference experiments: irradiation at  $\delta$  0.88 (-CHCH<sub>3</sub>) enhanced the signals at  $\delta$  2.40 (H<sub>c</sub>) and  $\delta$  2.50-2.58 (H<sub>d</sub>); irradiation at  $\delta$  1.64 (H<sub>e</sub>) caused enhancement of the signals at  $\delta$  1.89-1.94 (H<sub>f</sub>),  $\delta$  1.95-2.02 (H<sub>g</sub>), 2.15 (-COCH<sub>3</sub>), and 2.50-2.58 (H<sub>d</sub>); irradiation at  $\delta$  2.08-2.16 (H<sub>g'</sub>, -COCH<sub>3</sub>) caused enhancement of the signals at  $\delta$  1.89-1.94 (H<sub>f</sub>),  $\delta$  2.40 (H<sub>c</sub>) and  $\delta$  2.50-2.58 (H<sub>d</sub>); irradiation at  $\delta$  2.40 (H<sub>c</sub>) caused enhancement of the signals at  $\delta$  0.88 (-CHCH<sub>3</sub>),  $\delta$  1.89-1.94 (H<sub>f</sub>), 2.08-2.16 (H<sub>g'</sub>), and  $\delta$  2.15 (-COCH<sub>3</sub>); irradiation at  $\delta$  2.54 (H<sub>d</sub>) caused enhancement of the signals at  $\delta$  0.88 (-CHCH<sub>3</sub>),  $\delta$  1.59-1.69 (H<sub>e</sub>) and  $\delta$  3.52-3.57 (H<sub>a</sub>). <sup>13</sup>C NMR (100.4 MHz)  $\delta$ : 14.2, 16.3, 24.2, 25.6, 29.5, 31.9, 33.8, 45.3, 55.9, 60.3, 143.1, 143.2, 177.8, 206.9. Anal. calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>3</sub>: C 71.15, H 8.54; found: C 71.35, H 8.75. Exact Mass calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>3</sub>: 236.1412; found: 236.1417.

#### Preparation of the keto ester (11)

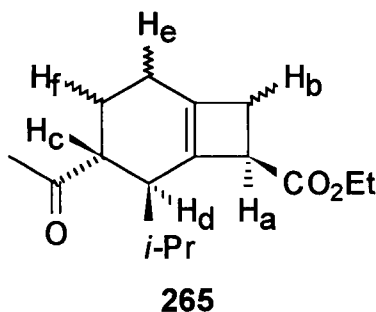


11

Following general procedure 15 outlined above, ethyl (*E*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**54**) was converted into the keto ester (**11**). The reaction time was 1.5 hours. The following amounts of reagents and solvents were used: ethyl (*E*)-2-ethylidene-3-methylenecyclobutanecarboxylate (**54**) (150 mg, 0.903 mmol) in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, methyl vinyl ketone (317 mg, 4.52 mmol), and BF<sub>3</sub>•Et<sub>2</sub>O (128 mg, 0.903 mmol). Normal workup, followed by radial chromatography (4 mm plate, 3:1 hexanes-Et<sub>2</sub>O) of the crude product and removal of traces of solvent (vacuum pump) from the

acquired liquid, afforded 187 mg (88%) of keto ester (**11**) as a colourless oil, which exhibited IR (neat): 1730, 1709, 1179, 1038  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.81 (d, 3H,  $J = 7$  Hz,  $-\text{CHCH}_3$ ), 1.27 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.62-1.72 (m, 1H), 1.78 (ddd, 1H,  $J = 14, 2.5, 2.5$  Hz), 1.94-2.00 (m, 2H), 2.13 (s, 3H,  $-\text{COCH}_3$ ), 2.60-2.70 (m, 2H,  $\text{H}_b$ ), 2.70-2.77 (m, 1H,  $\text{H}_d$ ), 2.81 (ddd, 1H,  $J = 12, 5, 2.5$  Hz,  $\text{H}_c$ ), 3.58-3.62 (m, 1H,  $\text{H}_a$ ), 4.15 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ). irradiation at  $\delta$  0.81 ( $-\text{CHCH}_3$ ) sharpened the multiplet at  $\delta$  2.70-2.77 ( $\text{H}_d$ ); irradiation at  $\delta$  3.60 ( $\text{H}_a$ ) sharpened the multiplet at  $\delta$  2.60-2.70 ( $\text{H}_b$ ). NOE difference experiments: irradiation at  $\delta$  0.81 ( $-\text{CHCH}_3$ ) caused enhancement of the signals at  $\delta$  1.62-1.72,  $\delta$  2.70-2.77 ( $\text{H}_d$ ) and  $\delta$  3.58-3.62 ( $\text{H}_a$ ); irradiation at  $\delta$  3.60 ( $\text{H}_a$ ) caused enhancement of the signals at  $\delta$  0.81 ( $-\text{CHCH}_3$ ) and  $\delta$  2.60-2.66 ( $\text{H}_b$ ).  $^{13}\text{C}$  NMR (100.4 MHz)  $\delta$ : 13.5, 14.3, 19.1, 25.0, 28.7, 29.8, 34.2, 43.7, 51.6, 60.3, 143.4, 160.9, 175.5, 207.8. Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : C 71.15, H 8.54; found: C 71.40, H 8.48. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : 236.1412; found: 236.1414.

#### Preparation of the keto ester (265)

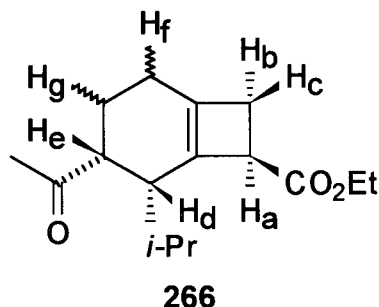


Following a modified version of general procedure 15 outlined above, in which the reaction mixture was warmed to  $-48^\circ\text{C}$  after the addition of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , ethyl (*Z*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**234**) was converted into the keto ester (**265**). The reaction time was 8 hours. The following amounts of reagents and solvents were used: ethyl (*Z*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**265**) (40 mg, 0.21 mmol) in 4 mL of dry  $\text{CH}_2\text{Cl}_2$ , methyl vinyl ketone (72 mg, 1.0 mmol), and

$\text{BF}_3 \cdot \text{Et}_2\text{O}$  (30 mg, 0.21 mmol). Normal workup, followed by flash chromatography (10 g silica/4:1 hexanes- $\text{Et}_2\text{O}$ ) of the crude product and removal of traces of solvent (vacuum pump) from the acquired liquid, afforded 28 mg (50%) of ketó ester (**94**) as a colourless oil, which exhibited IR (neat): 1733, 1705, 1469, 1369, 1155  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.82 (d, 6H,  $J = 6.5$  Hz,  $-\text{CH}(\text{CH}_3)_2$ ), 1.23 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.65-1.77 (m, 2H,  $-\text{CH}(\text{CH}_3)_2$ , one of  $\text{H}_f$ ), 1.81-1.87 (m, 1H, one of  $\text{H}_f$ ), 1.87-1.96 (m, 1H, one of  $\text{H}_e$ ), 2.02-2.12 (m, 1H, one of  $\text{H}_e$ ), 2.17 (s, 3H,  $-\text{COCH}_3$ ), 2.48-2.53 (m, 1H,  $\text{H}_d$ ), 2.54-2.65 (m, 2H,  $\text{H}_b$ ), 2.66-2.72 (ddd, 1H,  $J = 8, 7, 3$  Hz,  $\text{H}_c$ ), 3.54-3.58 (m, 1H,  $\text{H}_a$ ), 4.06-4.16 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.65-1.77 ( $-\text{CH}(\text{CH}_3)_2$ , one of  $\text{H}_f$ ) converted the doublet at  $\delta$  0.82 into a singlet, sharpened the multiplet at  $\delta$  1.83 (one of  $\text{H}_f$ ), converted the multiplet at  $\delta$  2.02-2.12 (one of  $\text{H}_e$ ) into a broad doublet ( $J = 14$  Hz), and converted the signal at  $\delta$  2.66-2.72 ( $\text{H}_c$ ) to a doublet of doublets ( $J = 8, 7$  Hz); irradiation at  $\delta$  2.48-2.53 ( $\text{H}_d$ ) sharpened the multiplets at  $\delta$  1.65-1.77 ( $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  1.87-1.96 (one of  $\text{H}_e$ ), converted the doublet of doublet of doublets at  $\delta$  2.66-2.72 ( $\text{H}_c$ ) into a doublet of doublets ( $J = 8, 3$  Hz), and sharpened the multiplet at  $\delta$  3.54-3.58 ( $\text{H}_a$ ); irradiation at  $\delta$  3.54-3.58 ( $\text{H}_a$ ) sharpened the multiplets at  $\delta$  2.48-2.53 ( $\text{H}_d$ ) and  $\delta$  2.54-2.65 ( $\text{H}_b$ ). NOE difference experiments: irradiation at  $\delta$  2.50 ( $\text{H}_d$ ) enhanced the signals at  $\delta$  0.82,  $\delta$  1.65-1.77 ( $-\text{CH}(\text{CH}_3)_2$ ), 2.17 ( $-\text{COCH}_3$ ), and 3.54-3.58 ( $\text{H}_a$ ); irradiation at  $\delta$  2.69 ( $\text{H}_c$ ) caused enhancement of the signals at  $\delta$  0.82,  $\delta$  1.81-1.87 (one of  $\text{H}_f$ ),  $\delta$  2.17 ( $-\text{COCH}_3$ ), and  $\delta$  2.48-2.53 ( $\text{H}_d$ ); irradiation at  $\delta$  3.56 ( $\text{H}_a$ ) caused enhancement of the signals at  $\delta$  2.48-2.53 ( $\text{H}_d$ ) and  $\delta$  2.54-2.62 ( $\text{H}_b$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 14.2, 19.6, 20.1, 23.4, 25.5, 28.7, 29.1, 34.0, 43.0, 46.5, 49.1, 60.3, 141.2, 145.6, 174.1, 211.6. Anal. calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : C 72.69, H 9.16; found: C 72.73, H 9.11. Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : 264.1725; found: 264.1731.



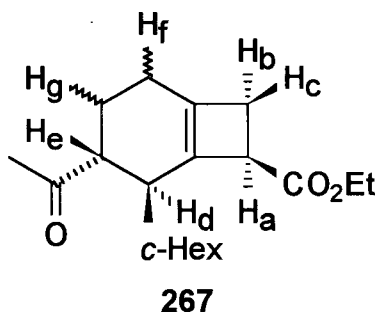
### Preparation of the keto ester (266)



Following general procedure 15 outlined above, ethyl (*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**) was converted into the keto ester (**266**). The reaction time was 2 hours. The following amounts of reagents and solvents were used: ethyl (*E*)-2-(2-methylpropylidene)-3-methylenecyclobutanecarboxylate (**233**) (50 mg, 0.26 mmol) in 4 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, methyl vinyl ketone (91.0 mg, 1.30 mmol), and BF<sub>3</sub>•Et<sub>2</sub>O (37 mg, 0.26 mmol). Normal workup, followed by flash chromatography (10 g silica/4:1 hexanes-Et<sub>2</sub>O) of the crude product and removal of traces of solvent (vacuum pump) from the acquired liquid, afforded 57 mg (84%) of keto ester (**266**) as a colourless oil, which exhibited IR (neat): 1731, 1709, 1177 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.82 (d, 3H, *J*= 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 0.92 (d, 3H, *J*= 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.26 (t, 3H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.57-1.65 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.75-1.85 (m, 1H, one of H<sub>g</sub>), 1.85-1.94 (m, 1H, one of H<sub>g</sub>), 1.95-2.01 (m, 2H, H<sub>f</sub>), 2.15 (s, 3H, -COCH<sub>3</sub>), 2.50-2.59 (m, 2H, H<sub>c</sub>, H<sub>d</sub>), 2.72-2.78 (m, 1H, H<sub>b</sub>), 2.80-2.87 (m, 1H, H<sub>e</sub>), 3.62-3.67 (m, 1H, H<sub>a</sub>), 4.15 (q, 2H, *J*= 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>); in a series of decoupling experiments, irradiation at δ 1.60 (-CH(CH<sub>3</sub>)<sub>2</sub>) converted the doublets at δ 0.82 (one of -CH(CH<sub>3</sub>)<sub>2</sub>) and δ 0.92 (one of -CH(CH<sub>3</sub>)<sub>2</sub>) into singlets; irradiation at δ 1.80 (one of H<sub>g</sub>) simplified the multiplet at δ 1.85-1.94 (one of H<sub>g</sub>) and converted the multiplet at δ 2.80-2.87 (H<sub>e</sub>) into a doublet of doublets (*J*= 9, 6 Hz); irradiation at δ 1.90 (one of H<sub>g</sub>) sharpened the multiplets at δ 1.75-1.85 (one of H<sub>g</sub>) and δ 1.95-2.01 (H<sub>f</sub>) and converted the multiplet at δ 2.80-2.87 (H<sub>e</sub>) into a broad doublet (*J*= 6 Hz); irradiation at δ 2.55 (H<sub>c</sub>, H<sub>d</sub>) converted the multiplet at δ 1.57-1.65 (-CH(CH<sub>3</sub>)<sub>2</sub>) into a heptet (*J*= 7 Hz),

converted the multiplet at  $\delta$  2.72-2.78 ( $H_b$ ) into a doublet ( $J = 5$  Hz), simplified the multiplet at  $\delta$  2.80-2.87 ( $H_e$ ) into a doublet of doublets ( $J = 9, 3$  Hz), and simplified the multiplet at  $\delta$  3.62-3.67 ( $H_a$ ); irradiation at  $\delta$  2.76 ( $H_b$ ) sharpened the multiplets at  $\delta$  2.50-2.58 ( $H_c$ ) and  $\delta$  3.62-3.67 ( $H_a$ ); irradiation at  $\delta$  2.84 ( $H_e$ ) simplified the multiplets at  $\delta$  1.75-1.85 (one of  $H_g$ ),  $\delta$  1.85-1.94 (one of  $H_g$ ), and  $\delta$  2.50-2.59 ( $H_d$ ); irradiation at  $\delta$  3.64 ( $H_a$ ) simplified the multiplet at  $\delta$  2.50-2.58 ( $H_c$ ) and converted the signal at  $\delta$  2.72-2.78 ( $H_b$ ) into a broad doublet ( $J = 14$  Hz). NOE difference experiments: irradiation at  $\delta$  1.60 ( $-\underline{\text{CH}}(\text{CH}_3)_2$ ) enhanced the signals at  $\delta$  0.82 (one of  $-\text{CH}(\underline{\text{CH}}_3)_2$ ),  $\delta$  0.92 (one of  $-\text{CH}(\underline{\text{CH}}_3)_2$ ), and  $\delta$  2.54-2.59 ( $H_d$ ); irradiation at  $\delta$  2.76 ( $H_b$ ) caused enhancement of the signals at  $\delta$  2.50-2.58 ( $H_c$ ) and  $\delta$  3.62-3.67 ( $H_a$ ); irradiation at  $\delta$  2.82 ( $H_e$ ) caused enhancement of the signals at  $\delta$  1.75-1.85 (one of  $H_g$ ),  $\delta$  1.85-1.94 (one of  $H_g$ ),  $\delta$  1.95-2.01 ( $H_f$ ),  $\delta$  2.15, and  $\delta$  2.54-2.59 ( $H_d$ ); irradiation at  $\delta$  3.65 ( $H_a$ ) caused enhancement of the signals at  $\delta$  0.82 (one of  $-\text{CH}(\underline{\text{CH}}_3)_2$ ),  $\delta$  0.92 (one of  $-\text{CH}(\underline{\text{CH}}_3)_2$ ),  $\delta$  1.26, and  $\delta$  2.72-2.78 ( $H_b$ );  $^{13}\text{C}$  NMR (75.3 MHz)  $\delta$ : 14.3, 20.0, 21.4, 23.6, 23.8, 25.5, 29.2, 34.6, 41.5, 49.9, 51.7, 60.3, 139.7, 145.9, 173.6, 210.6. Anal. calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : C 72.69, H 9.16; found: C 72.72, H 9.19. Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : 264.1725; found: 264.1725.

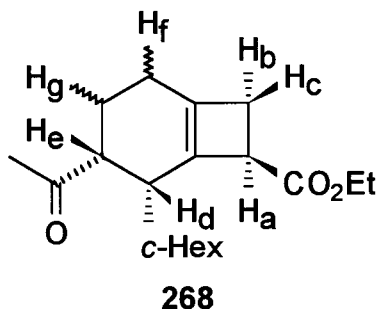
#### Preparation of the keto ester (267)



Following a modified version of general procedure 15 outlined above in which the reaction mixture was warmed to  $-48^\circ\text{C}$  after the addition of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , ethyl (Z)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (236) was converted into the

keto ester (**267**). The reaction time was 10 hours. The following amounts of reagents and solvents were used: ethyl (*Z*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**236**) (200 mg, 0.854 mmol) in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, methyl vinyl ketone (298 mg, 4.27 mmol), and BF<sub>3</sub>-Et<sub>2</sub>O (122 mg, 0.855 mmol). Normal workup, followed by radial chromatography (4 mm plate/4:1 hexanes-Et<sub>2</sub>O) of the crude product and removal of traces of solvent (vacuum pump) from the acquired liquid, afforded 194 mg (75%) of keto ester (**267**) as a colourless oil, which exhibited IR (neat): 1734, 1714, 1155 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.90-1.20 (m, 4H), 1.26 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.30-1.39 (m, 2H), 1.53-1.75 (m, 6H), 1.80-1.95 (m, 2H, one of H<sub>f</sub>, one of H<sub>g</sub>), 2.01-2.11 (m, 1H, one of H<sub>g</sub>), 2.16 (s, 3H, -COCH<sub>3</sub>), 2.44-2.50 (m, 1H, H<sub>d</sub>), 2.54-2.63 (m, 2H, H<sub>b</sub>, H<sub>c</sub>), 2.70-2.76 (m, 1H, H<sub>e</sub>), 3.52-3.58 (m, 1H, H<sub>a</sub>), 4.08-4.16 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>); in a series of decoupling experiments, irradiation at  $\delta$  1.85 (one of H<sub>f</sub>, one of H<sub>g</sub>) converted the multiplet at  $\delta$  2.70-2.76 (H<sub>e</sub>) into a doublet of doublets (*J* = 7, 7 Hz); irradiation at  $\delta$  2.47 (H<sub>d</sub>) sharpened the multiplet at  $\delta$  1.30-1.39 and converted the multiplet at  $\delta$  2.70-2.76 (H<sub>e</sub>) into a doublet of doublets (*J* = 7, 3 Hz); irradiation at  $\delta$  2.60 (H<sub>b</sub>, H<sub>c</sub>) sharpened the multiplets at  $\delta$  1.89-1.95 (H<sub>f</sub>) and  $\delta$  3.52-3.58 (H<sub>a</sub>); irradiation at  $\delta$  2.73 (H<sub>e</sub>) simplified the multiplets at  $\delta$  1.80-1.89 (one of H<sub>g</sub>) and sharpened the signal at  $\delta$  2.44-2.50 (H<sub>d</sub>); irradiation at  $\delta$  3.55 (H<sub>a</sub>) sharpened the multiplets at  $\delta$  2.44-2.50 (H<sub>d</sub>) and  $\delta$  2.54-2.63 (H<sub>b</sub>, H<sub>c</sub>). NOE difference experiments: irradiation at  $\delta$  1.35 enhanced the signal at  $\delta$  2.44-2.50 (H<sub>d</sub>); irradiation at  $\delta$  1.85 (one of H<sub>f</sub>, one of H<sub>g</sub>) enhanced the signals at  $\delta$  1.56-1.75 and  $\delta$  2.70-2.76 (H<sub>e</sub>); irradiation at  $\delta$  2.47 (H<sub>d</sub>) enhanced the signals at  $\delta$  1.30-1.39,  $\delta$  2.16,  $\delta$  2.70-2.76 (H<sub>e</sub>) and  $\delta$  3.52-3.58 (H<sub>a</sub>); irradiation at  $\delta$  2.75 (H<sub>e</sub>) caused enhancement of the signals at  $\delta$  0.90-1.05,  $\delta$  1.80-1.90 (one of H<sub>g</sub>),  $\delta$  2.16, and  $\delta$  2.44-2.50 (H<sub>d</sub>); irradiation at  $\delta$  3.55 (H<sub>a</sub>) enhanced the signals at  $\delta$  2.44-2.50 (H<sub>d</sub>) and  $\delta$  2.54-2.60 (H<sub>b</sub>); <sup>13</sup>C NMR (75.3 MHz)  $\delta$ : 14.2, 23.4, 25.4, 26.4, 26.82, 26.83, 28.7, 30.0, 31.2, 33.9, 39.8, 42.6, 46.6, 49.1, 60.4, 141.3, 145.3, 174.2, 211.5. Anal. calcd. for C<sub>19</sub>H<sub>28</sub>O<sub>3</sub>: C 74.96, H 9.28; found: C 74.79, H 9.28. Exact Mass calcd. for C<sub>19</sub>H<sub>28</sub>O<sub>3</sub>: 304.2039; found: 304.2038.

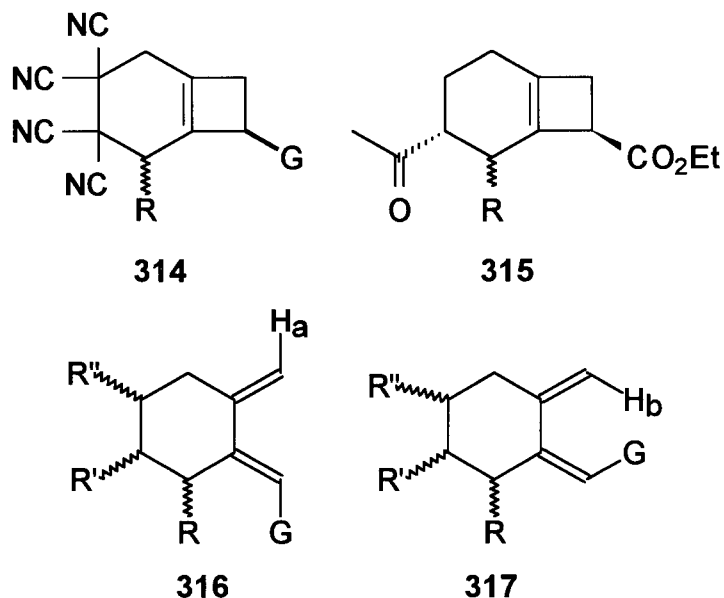
### Preparation of the keto ester (268)



Following general procedure 15 outlined above, ethyl (*E*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**235**) was converted into the keto ester (**268**). The reaction time was 3.5 hours. The following amounts of reagents and solvents were used: ethyl (*E*)-2-cyclohexylmethylene-3-methylenecyclobutanecarboxylate (**238**) (125 mg, 0.533 mmol) in 5 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, methyl vinyl ketone (186 mg, 2.66 mmol), and BF<sub>3</sub>•Et<sub>2</sub>O (76 mg, 0.53 mmol). Normal workup, followed by radial chromatography (4 mm plate/4:1 hexanes-Et<sub>2</sub>O) of the crude product and removal of traces of solvent (vacuum pump) from the acquired liquid, afforded 142 mg (87%) of keto ester (**268**) as a colourless oil, which exhibited IR (neat): 1729, 1709, 1177 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.80-0.92 (m, 1H), 1.02-1.18 (m, 4H), 1.26 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.46-1.74 (m, 7H), 1.80-1.90 (m, 1H, one of H<sub>g</sub>), 1.92-2.00 (m, 2H, H<sub>f</sub>), 2.15 (s, 3H, -COCH<sub>3</sub>), 2.52-2.60 (m, 2H, H<sub>c</sub>, H<sub>d</sub>), 2.70-2.77 (m, 1H, H<sub>b</sub>), 2.78-2.85 (m, 1H, H<sub>e</sub>), 3.63-3.68 (m, 1H, H<sub>a</sub>), 4.11-4.19 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>); in a series of decoupling experiments, irradiation at δ 1.85 (H<sub>g</sub>) converted the multiplet at δ 2.78-2.85 (H<sub>e</sub>) into a broad doublet of doublets (*J* = 4, 4 Hz) and sharpened the multiplet at δ 1.92-2.00 (H<sub>f</sub>); irradiation at δ 2.54 (H<sub>c</sub>, H<sub>d</sub>) simplified the multiplet at δ 2.70-2.77 (H<sub>b</sub>), converted the multiplet at δ 2.78-2.85 (H<sub>e</sub>) into a doublet of doublets (*J* = 10, 4 Hz), and sharpened the multiplet at δ 3.63-3.68 (H<sub>a</sub>); irradiation at δ 2.75 (H<sub>b</sub>) sharpened the multiplets at δ 2.52-2.60 (H<sub>c</sub>) and δ 3.63-3.68 (H<sub>a</sub>); irradiation at δ 3.68 (H<sub>a</sub>) simplified the multiplet at δ 2.52-2.60 (H<sub>c</sub>) and converted the multiplet at δ 2.70-2.77 (H<sub>b</sub>) into a doublet of doublets (*J* = 12, 1.5 Hz). NOE difference experiments: irradiation at δ 1.66 caused

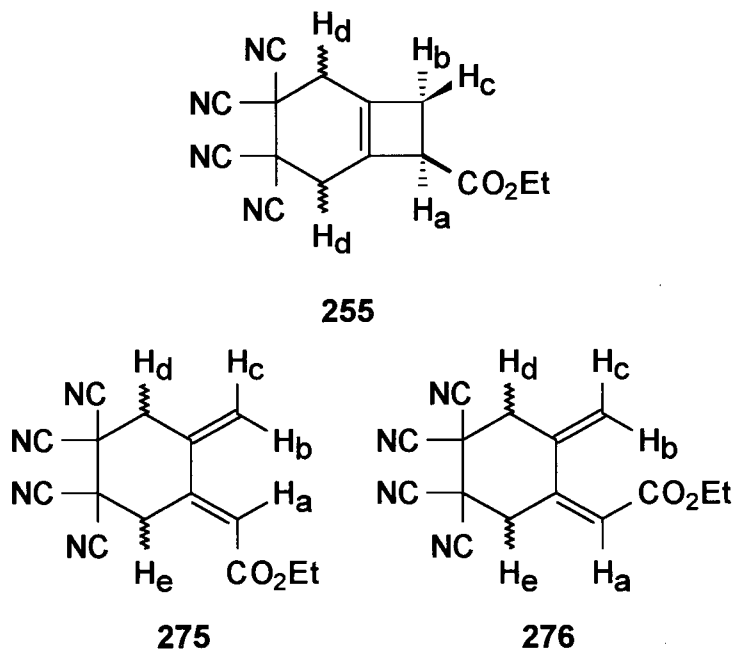
enhancement of the signals at  $\delta$  0.80-0.90 and  $\delta$  1.02-1.18; irradiation at  $\delta$  1.84 (one of  $H_g$ ) caused enhancement of the signal at  $\delta$  2.78-2.85 ( $H_e$ ); irradiation at  $\delta$  1.97 ( $H_f$ ) caused enhancement of the signal at  $\delta$  2.78-2.85 ( $H_e$ ); irradiation at  $\delta$  2.15 ( $COCH_3$ ) caused enhancement of the signals at  $\delta$  2.52-2.60 ( $H_d$ ) and  $\delta$  2.78-2.85 ( $H_e$ ); irradiation at  $\delta$  2.54 ( $H_c$ ,  $H_d$ ) caused enhancement of the signals at  $\delta$  2.15 ( $COCH_3$ ),  $\delta$  2.70-2.77 ( $H_b$ ) and  $\delta$  2.78-2.85 ( $H_e$ ); irradiation at  $\delta$  2.75 ( $H_b$ ) caused enhancement of the signals at  $\delta$  2.52-2.60 ( $H_c$ ) and  $\delta$  3.63-3.68 ( $H_a$ ); irradiation at  $\delta$  2.82 ( $H_e$ ) caused enhancement of the signals at  $\delta$  1.80-1.90 ( $H_g$ ) and  $\delta$  2.52-2.60 ( $H_d$ ); irradiation at  $\delta$  3.68 ( $H_a$ ) enhanced the signals at  $\delta$  2.52-2.56 ( $H_c$ ) and  $\delta$  2.70-2.77 ( $H_b$ );  $^{13}C$  NMR (75.3 MHz)  $\delta$ : 14.3, 21.9, 24.0, 26.2, 26.3, 26.8, 29.3, 31.0, 33.6, 34.5, 39.3, 41.3, 47.0, 51.8, 60.3, 140.3, 145.3, 173.7, 210.8. Anal. calcd. for  $C_{19}H_{28}O_3$ : C 74.96, H 9.28; found: C 74.98, H 9.34. Exact Mass calcd. for  $C_{19}H_{28}O_3$ : 304.2039; found: 304.2043.

14. General Procedure 16: Preparative thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)enes



A solution of the appropriate bicyclo[4.2.0]oct-1(6)ene (**314**) or (**315**) in dry mesitylene (10-15 mL/mmol of substrate) was heated to and refluxed at 165°C for 4 hours (unless noted otherwise) under an argon atmosphere. The reaction mixture was cooled to room temperature and then subjected to radial chromatography to afford a mixture of outward rotation isomer (**316**) and inward rotation isomer (**317**) as thermolysis products. After determining the ratio of (**150**):(**151**) by <sup>1</sup>H NMR spectroscopic analysis (ratio of H<sub>a</sub>:H<sub>b</sub> in all cases unless noted otherwise), the crude product was again subjected to radial chromatography. Removal of traces of solvent (vacuum pump) from the acquired products gave the corresponding outward (**316**) and inward (**317**) rotation products.

Preparation of the tetranitrile ester dienes (275) and (276) from the ester (255)



Following a modified version of general procedure 16, in which the reaction mixture was heated to 145°C for 3.5 hours before cooling to room temperature, the ester (255) was converted into the tetranitrile ester dienes (275) and (276). The following amounts of substrate and solvent were used: ester (255) (75 mg, 0.27 mmol) in 3 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes then Et<sub>2</sub>O) afforded 72 mg (96%) of a mixture of the diene (275) and the diene (276) in a ratio of 18:1, respectively (<sup>1</sup>H NMR analysis of signals H<sub>c</sub> (275) and H<sub>b</sub> (276)). The mixture was again subjected to radial chromatography (1 mm plate, 3:1 hexanes-Et<sub>2</sub>O). Recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solids afforded 60 mg (80%) of the diene (275) as a colourless solid (melting point 84-85°C), and 3.5 mg (5%) of the diene (276), also as a colourless solid (melting point 56-57°C).

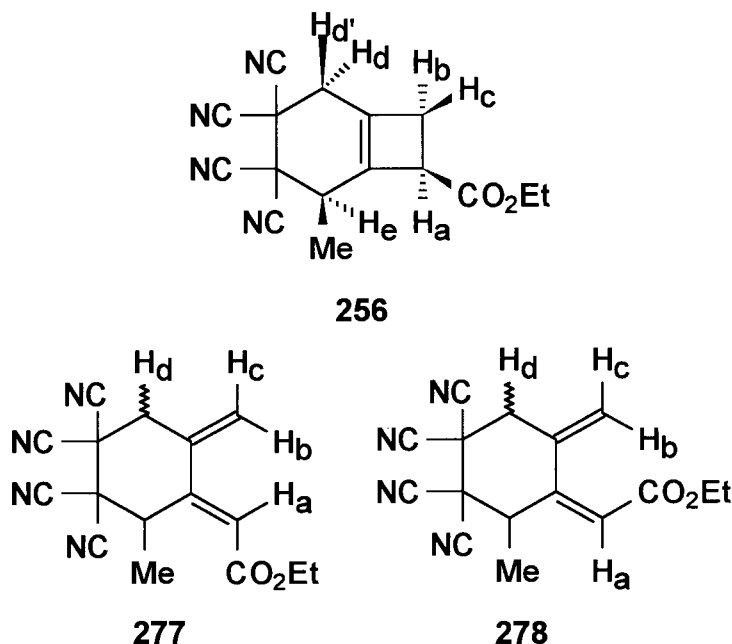
The major isomer, resulting from outward rotation of the ester group, the diene (275), exhibited IR (KBr): 2264, 1716, 1649, 1193 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.29 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 3.25 (s, 2H, H<sub>d</sub>), 4.01 (br s, 2H, H<sub>e</sub>), 4.23 (q, 2H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.36 (s, 1H, H<sub>c</sub>), 5.58 (s, 1H, H<sub>b</sub>), 6.21 (br s, 1H, H<sub>a</sub>); NOE difference experiments:

irradiation at  $\delta$  3.25 ( $H_d$ ) caused enhancement of the signal at  $\delta$  5.36 ( $H_c$ ); irradiation at  $\delta$  5.36 ( $H_c$ ) caused enhancement of the signals at  $\delta$  3.25 ( $H_d$ ) and  $\delta$  5.58 ( $H_b$ ); irradiation at  $\delta$  5.58 ( $H_b$ ) caused enhancement of the signals at  $\delta$  5.36 ( $H_c$ ) and  $\delta$  6.21 ( $H_a$ ); irradiation at  $\delta$  6.21 ( $H_a$ ) caused enhancement of the signal at  $\delta$  5.58 ( $H_b$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.93 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.92 (br s, 2H,  $H_d$ ), 3.47 (d, 2H,  $J = 2$  Hz,  $H_e$ ), 3.84 (q, 2H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 4.22 (s, 1H,  $H_c$ ), 4.56 (s, 1H,  $H_b$ ), 5.65 (t, 1H,  $J = 2$  Hz,  $H_a$ );  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 14.0, 33.0, 39.2, 40.2, 40.7, 61.2, 109.63, 109.67, 109.71, 109.73, 121.8, 122.3, 134.6, 142.2, 164.6. Anal. calcd. for  $C_{15}H_{12}O_2N_4$ : C 64.28, H 4.32, N 19.99; found: C 64.35, H 4.45, N 20.00. Exact Mass calcd. for  $C_{15}H_{12}O_2N_4$ : 280.0960; found: 280.0967.

The minor isomer, resulting from inward rotation of the ester group, the diene (276), exhibited IR (KBr): 2259, 1713, 1650, 1200  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 1.26 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 3.14 (br s, 2H,  $H_e$ ), 3.21 (br s, 2H,  $H_d$ ), 4.18 (q, 2H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 5.54 (s, 1H,  $H_b$ ), 5.56 (br s, 1H,  $H_c$ ), 6.01 (br s, 1H,  $H_a$ ); NOE difference experiments: irradiation at  $\delta$  3.14 ( $H_e$ ) caused enhancement of the signal at  $\delta$  6.01 ( $H_a$ ); irradiation at  $\delta$  3.21 ( $H_d$ ) caused enhancement of the signal at  $\delta$  5.56 ( $H_c$ ); irradiation at  $\delta$  5.56 ( $H_c$ ) caused enhancement of the signal at  $\delta$  3.21 ( $H_d$ ); irradiation at  $\delta$  6.01 ( $H_a$ ) caused enhancement of the signal at  $\delta$  3.14 ( $H_e$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.87 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.76 (br s, 2H,  $H_e$ ), 1.94 (br s, 2H,  $H_d$ ), 3.83 (q, 2H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 4.59 (s, 1H,  $H_b$ ), 5.02 (br s, 1H,  $H_c$ ), 5.23 (br s, 1H,  $H_a$ ); Anal. calcd. for  $C_{15}H_{12}O_2N_4$ : C 64.28, H 4.32, N 19.99; found: C 64.47, H 4.34, N 20.07. Exact Mass calcd. for  $C_{15}H_{12}O_2N_4$ : 280.0960; found: 280.0959.



Preparation of the tetranitrile ester dienes (278) and (277) from the ester (256)



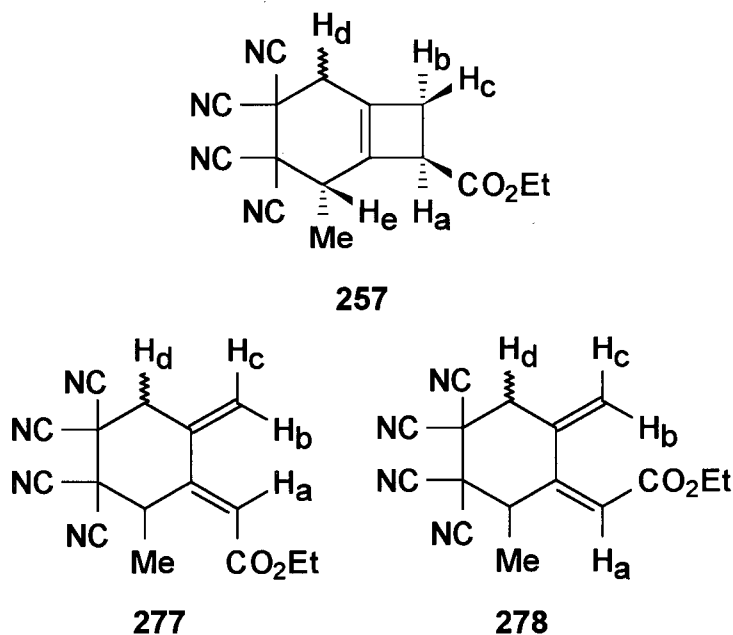
Following general procedure 16 outlined above, the ester (**256**) was converted into the tetranitrile ester dienes (**278**) and (**277**). The following amounts of substrate and solvent were used: ester (**256**) (50 mg, 0.17 mmol) in 2 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, followed by  $\text{CH}_2\text{Cl}_2$ ) afforded 42 mg (84%) of a mixture of the diene (**277**) and the inward rotation diene (**278**) in a ratio of 2.6:1, respectively ( $^1\text{H}$  NMR analysis of signals  $\text{H}_\text{C}$  (**277**) and  $\text{H}_\text{b}$  (**278**)). The mixture was again subjected to radial chromatography (1 mm plate,  $\text{CH}_2\text{Cl}_2$ ). Recrystallization (1:1 petroleum ether- $\text{Et}_2\text{O}$ ) of the solids obtained afforded 26.5 mg (53%) of the diene (**277**), as a colourless solid (melting point  $127\text{--}128^\circ\text{C}$ ), and 10.5 mg (21%) of the diene (**278**), also as a colourless solid (melting point  $85\text{--}86^\circ\text{C}$ ).

The major isomer, resulting from outward rotation of the ester group, the diene (**277**), exhibited IR (KBr):  $2255, 1714, 1645, 1207, 1133\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.29 (t, 3H,  $J = 7\text{ Hz}$ ,  $-\text{OCH}_2\text{CH}_3$ ), 1.60 (d, 3H,  $J = 7\text{ Hz}$ ,  $-\text{CHCH}_3$ ), 3.21–3.31 (m, 2H,  $\text{H}_\text{d}$ ), 4.21 (q, 2H,  $J = 7\text{ Hz}$ ,  $-\text{OCH}_2\text{CH}_3$ ), 5.00 (q, 1H,  $J = 7\text{ Hz}$ ,  $-\text{CHCH}_3$ ), 5.42 (br s, 1H,  $\text{H}_\text{c}$ ), 5.57 (d, 1H,  $J = 2\text{ Hz}$ ,  $\text{H}_\text{b}$ ), 6.09 (s, 1H,  $\text{H}_\text{a}$ ); NOE difference experiments: irradiation at  $\delta$  3.27 ( $\text{H}_\text{d}$ ) caused

enhancement of the signal at  $\delta$  5.42 ( $H_C$ ); irradiation at  $\delta$  5.42 ( $H_C$ ) caused enhancement of the signals at  $\delta$  3.21-3.31 ( $H_D$ ) and  $\delta$  5.57 ( $H_B$ ); irradiation at  $\delta$  5.57 ( $H_B$ ) caused enhancement of the signals at  $\delta$  5.42 ( $H_C$ ) and  $\delta$  6.09 ( $H_A$ ); irradiation at  $\delta$  6.09 ( $H_A$ ) caused enhancement of the signal at  $\delta$  5.57 ( $H_B$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.88 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.26 (d, 3H,  $J = 7$  Hz,  $-CHCH_3$ ), 1.82 (ddd, 1H,  $J = 16, 2, 2$  Hz, one of  $H_D$ ), 2.19 (ddd, 1H,  $J = 16, 2, 2$  Hz, one of  $H_D$ ), 3.78-3.86 (m, 2H,  $-OCH_2CH_3$ ), 4.33 (dd, 1H,  $J = 2, 2$  Hz,  $H_C$ ), 4.60 (dd, 1H,  $J = 2, 2$  Hz,  $H_B$ ), 4.93 (q, 1H,  $J = 7$  Hz,  $-CHCH_3$ ), 5.60 (br s, 1H,  $H_A$ );  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 14.0, 16.6, 38.0, 39.4, 39.5, 44.2, 61.2, 109.9, 110.5, 110.6, 110.9, 120.9, 123.1, 133.3, 149.0, 164.4. Anal. calcd. for  $C_{16}H_{14}O_2N_4$ : C 65.29, H 4.80, N 19.04; found: C 65.45, H 4.82, N 19.14. Exact Mass calcd. for  $C_{16}H_{14}O_2N_4$ : 294.1116; found: 294.1115.

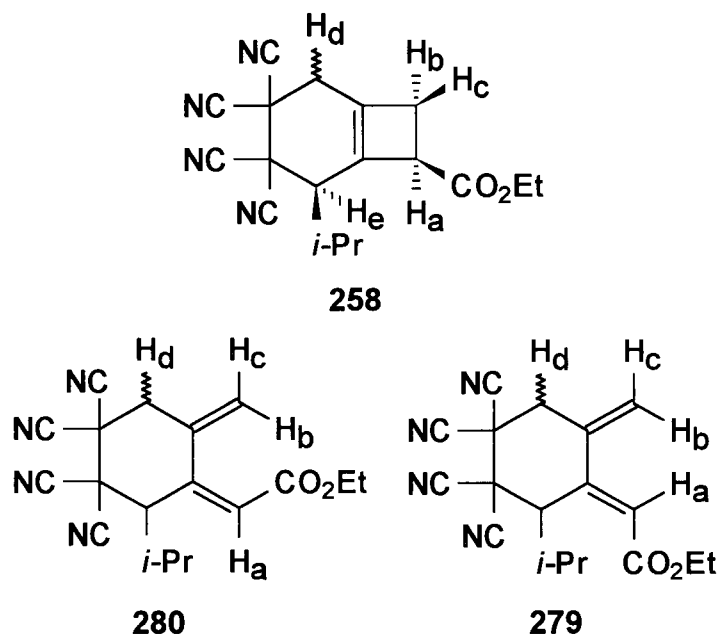
The minor isomer, resulting from inward rotation of the ester group, the diene (**278**), exhibited IR (KBr): 2256, 1729, 1648, 1193  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 1.25 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.61 (d, 3H,  $J = 7$  Hz,  $-CHCH_3$ ), 3.17 (dq, 1H,  $J = 2.5, 7$  Hz,  $-CHCH_3$ ), 3.20-3.24 (m, 2H,  $H_D$ ), 4.18 (q, 2H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 5.38 (br s, 1H,  $H_B$ ), 5.45 (br s, 1H,  $H_C$ ), 5.96 (d, 1H,  $J = 2.5$  Hz,  $H_A$ ); NOE difference experiments: irradiation at  $\delta$  5.38 ( $H_B$ ) caused enhancement of the signal at  $\delta$  5.45 ( $H_C$ ); irradiation at  $\delta$  5.45 ( $H_C$ ) caused enhancement of the signals at  $\delta$  5.38 ( $H_B$ ) and  $\delta$  3.20-3.24 ( $H_D$ ); irradiation at  $\delta$  5.96 ( $H_A$ ) caused enhancement of the signals at  $\delta$  1.61 ( $-CHCH_3$ ) and  $\delta$  3.17 ( $-CHCH_3$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.63 (d, 3H,  $J = 7$  Hz,  $-CHCH_3$ ), 0.82 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 2.30-2.38 (m, 3H,  $H_D$ ,  $-CHCH_3$ ), 3.75-3.85 (m, 2H,  $-OCH_2CH_3$ ), 4.67 (d, 1H,  $J = 2$  Hz,  $H_B$ ), 4.88 (d, 1H,  $J = 2$  Hz,  $H_C$ ), 5.35 (d, 1H,  $J = 2.5$  Hz,  $H_A$ ).  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 13.9, 14.2, 40.5, 42.1, 43.2, 48.2, 61.2, 107.9, 109.7, 110.3, 110.4, 122.1, 122.4, 132.7, 144.3, 164.4. Anal. calcd. for  $C_{16}H_{14}O_2N_4$ : C 65.29, H 4.80, N 19.04; found: C 65.50, H 4.79, N 19.00. Exact Mass calcd. for  $C_{16}H_{14}O_2N_4$ : 294.1116; found: 294.1120.

Preparation of the tetranitrile ester dienes (278) and (277) from the ester (257)



Following general procedure 16 outlined above, the ester (257) was converted into the tetranitrile ester dienes (278) and (277). The following amount of substrate and solvent were used: ester (257) (50 mg, 0.17 mmol) in 2 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then  $\text{CH}_2\text{Cl}_2$ ) afforded 40 mg (80%) of a mixture of the diene (277) and the diene (278) in a ratio of 4.3:1, respectively ( $^1\text{H}$  NMR analysis of signals  $\text{H}_c$  (277) and  $\text{H}_b$  (278)). The mixture was again subjected to radial chromatography (1 mm plate,  $\text{CH}_2\text{Cl}_2$ ). Recrystallization (1:1 petroleum ether- $\text{Et}_2\text{O}$ ) of the acquired solids afforded 28 mg (56%) of the diene (277) as a colourless solid (melting point, 127-128°C) and 7 mg (14%) of the diene (278), also as a colourless solid (melting point 85-86°C). The spectral data derived from these substances were identical with those reported in the last experiment.

Preparation of the tetranitrile ester dienes (279) and (280) from the ester (258)



Following a modified version of general procedure 16 in which the reaction time was 6 hours, the ester (**258**) was converted into the tetranitrile ester dienes (**279**) and (**280**). The following amounts of substrate and solvent were used: ester (**258**) (50 mg, 0.16 mmol) in 2.5 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 43 mg (86%) of a mixture of the outward rotation diene (**279**) and inward rotation diene (**280**) in a ratio of 1:1.5 respectively (<sup>1</sup>H NMR analysis of the signals H<sub>c</sub> (**279**) and H<sub>b</sub> (**280**)). The mixture was again subjected to radial chromatography (1 mm plate, CH<sub>2</sub>Cl<sub>2</sub>). Recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the solids obtained afforded 16 mg (32%) of the diene (**279**), as a colourless solid (melting point 142-143°C), and 22 mg (44%) of the diene (**280**), also as a colourless solid (melting point, 98-99°C).

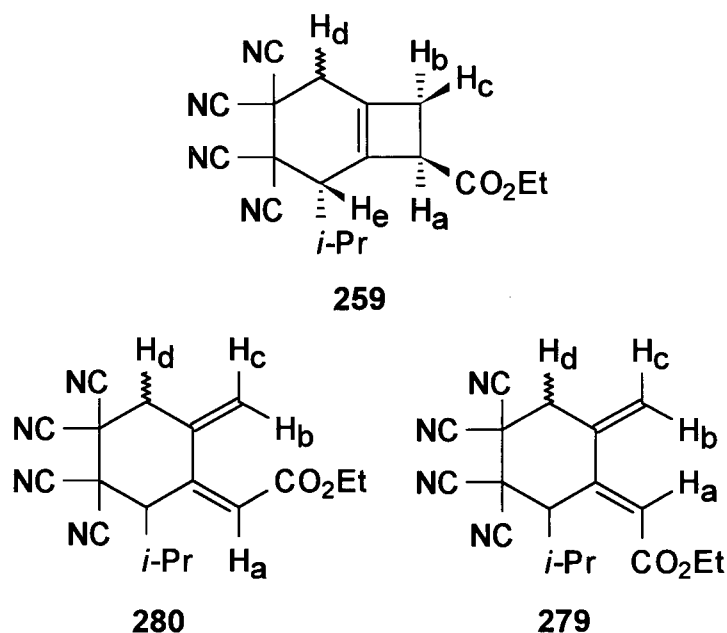
The minor isomer, resulting from outward rotation of the ester group, the diene (**279**), exhibited IR (KBr): 2256, 1716, 1202 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.93 (d, 3H, *J* = 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.30 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (d, 3H, *J* = 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 2.36-2.46 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 3.23-3.33 (m, 2H, H<sub>d</sub>), 4.21 (q, 2H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.76 (d, 1H, *J* = 9 Hz, -CH(*i*-Pr)), 5.35 (br s, 1H, H<sub>c</sub>), 5.46 (br s, 1H, H<sub>b</sub>), 6.16

(s, 1H,  $H_a$ ); NOE difference experiments: irradiation at  $\delta$  3.30 ( $H_d$ ) caused enhancement of the signal at  $\delta$  5.35 ( $H_c$ ); irradiation at  $\delta$  5.35 ( $H_c$ ) caused enhancement of the signals at  $\delta$  3.23-3.33 ( $H_d$ ) and  $\delta$  5.46 ( $H_b$ ); irradiation at  $\delta$  5.46 ( $H_b$ ) caused enhancement of the signals at  $\delta$  5.35 ( $H_c$ ) and  $\delta$  6.16 ( $H_a$ ); irradiation at  $\delta$  6.16 ( $H_a$ ) caused enhancement of the signal at  $\delta$  5.46 ( $H_b$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.62 (d, 3H,  $J = 7$  Hz, one of  $-CH(CH_3)_2$ ), 0.88 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.20 (d, 3H,  $J = 7$  Hz, one of  $-CH(CH_3)_2$ ), 1.95 (br d, 1H,  $J = 16$  Hz, one of  $H_d$ ), 2.20 (br d, 1H,  $J = 16$  Hz, one of  $H_d$ ), 2.21-2.31 (m, 1H,  $-CH(CH_3)_2$ ), 3.77-3.87 (m, 2H,  $-OCH_2CH_3$ ), 4.28 (br s, 1H,  $H_c$ ), 4.55 (br s, 1H,  $H_b$ ), 4.79 (d, 1H,  $J = 9$  Hz,  $-CH(i-Pr)$ ), 5.74 (s, 1H,  $H_a$ ).  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 14.0, 20.3, 22.8, 30.0, 38.7, 39.6, 43.0, 48.7, 61.2, 110.5, 110.7, 110.92, 110.94, 120.9, 123.9, 135.2, 147.7, 164.7. Anal. calcd. for  $C_{18}H_{18}O_2N_4$ : C 67.06, H 5.63, N 17.38; found: C 67.08, H 5.84, N 16.95. Exact Mass calcd. for  $C_{18}H_{18}O_2N_4$ : 322.1429; found: 322.1423.

The major isomer, resulting from inward rotation of the ester group, the diene (**280**), exhibited IR (KBr): 2256, 1716, 1202  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 1.18 (d, 3H,  $J = 7$  Hz, one of  $-CH(CH_3)_2$ ), 1.26 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.39 (d, 3H,  $J = 7$  Hz, one of  $-CH(CH_3)_2$ ), 2.37-2.46 (m, 1H,  $-CH(CH_3)_2$ ), 2.86 (d, 1H,  $J = 7$  Hz,  $-CH(i-Pr)$ ), 3.28-3.36 (m, 2H,  $H_d$ ), 4.17 (q, 2H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 5.30 (br s, 1H,  $H_b$ ), 5.43 (br s, 1H,  $H_c$ ), 6.00 (s, 1H,  $H_a$ ); NOE difference experiments: irradiation at  $\delta$  2.86 ( $-CH(i-Pr)$ ) caused enhancement of the signals at  $\delta$  1.18 (one of  $-CH(CH_3)_2$ ),  $\delta$  1.39 (one of  $-CH(CH_3)_2$ ),  $\delta$  2.37-2.46 ( $-CH(CH_3)_2$ ) and  $\delta$  6.00 ( $H_a$ ); irradiation at  $\delta$  3.33 ( $H_d$ ) caused enhancement of the signal at  $\delta$  5.43 ( $H_c$ ); irradiation at  $\delta$  5.43 ( $H_c$ ) caused enhancement of the signals at  $\delta$  3.28-3.36 ( $H_d$ ) and  $\delta$  5.30 ( $H_b$ ); irradiation at  $\delta$  6.00 ( $H_a$ ) caused enhancement of the signals at  $\delta$  2.37-2.46 ( $-CH(CH_3)_2$ ) and  $\delta$  2.86 ( $-CH(i-Pr)$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.47 (d, 3H,  $J = 7$  Hz, one of  $-CH(CH_3)_2$ ), 0.84 (t, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 0.85 (d, 3H,  $J = 7$  Hz, one of  $-CH(CH_3)_2$ ), 1.77-1.87 (m, 1H,  $-CH(CH_3)_2$ ), 2.13 (d, 1H,  $J = 7$  Hz,  $-CH(i-Pr)$ ), 2.25-2.37 (m, 2H,  $H_d$ ), 3.87 (q, 2H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 4.65 (br s, 1H,  $H_b$ ), 4.83 (br s, 1H,  $H_c$ ), 5.52 (br s, 1H,  $H_a$ ).  $^{13}C$  NMR (100.4 MHz)  $\delta$ : 14.0, 21.0, 21.1, 29.3, 29.7, 40.6, 44.3, 55.4, 61.2, 109.6, 110.5, 110.6, 111.0, 121.5, 124.5, 132.1, 143.8, 164.0. Anal. calcd. for  $C_{18}H_{18}O_2N_4$ :

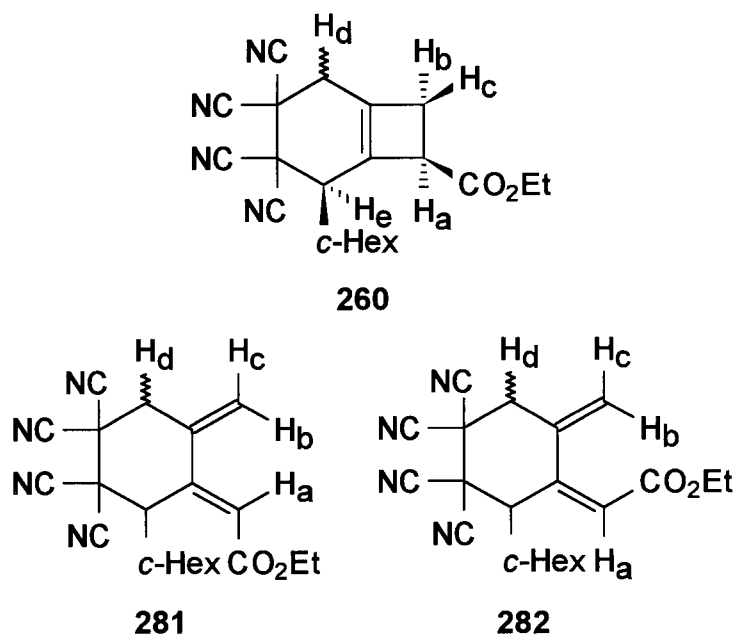
C 67.06, H 5.63, N 17.38; found: C 67.36, H 5.72, N 16.91. Exact Mass calcd. for  $C_{18}H_{18}O_2N_4$ : 322.1429; found: 322.1423.

Preparation of the tetranitrile ester dienes (279) and (280) from the ester (259)



Following a modified version of general procedure 16 in which the reaction time was 6 hours, the ester (259) was converted into the tetranitrile ester dienes (279) and (280). The following amounts of substrate and solvent were used: ester (259) (50 mg, 0.16 mmol) in 2.5 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes then  $Et_2O$ ) afforded 46 mg (92%) of a mixture of the outward rotation diene (279) and the inward rotation diene (280) in a ratio of 1:1.6 respectively ( $^1H$  NMR analysis of signals  $H_c$  (279) and  $H_b$  (280)). The mixture was again subjected to radial chromatography (1 mm plate,  $CH_2Cl_2$ ). Recrystallization (1:1 petroleum ether- $Et_2O$ ) of the acquired solids afforded 13.5 mg (27%) of the diene (279) as a colourless solid (melting point 142-143°C) and 20.5 mg (41%) of the diene (280), also as a colourless solid (melting point, 98-99°C). The spectral data obtained from these materials was identical with those reported for the last experiment.

Preparation of the tetranitrile ester dienes (281) and (282) from the ester (260)



Following a modified version of general procedure 16 in which the reaction time was 6 hours, the ester (260) was converted into the tetranitrile ester dienes (281) and (282). The following amounts of substrate and solvent were used: ester (260) (100 mg, 0.276 mmol) in 3 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then  $\text{CH}_2\text{Cl}_2$ ) afforded 84 mg (84%) of a mixture of the diene (281) and the diene (282), in a ratio of 1:1.2 respectively ( $^1\text{H}$  NMR analysis of signals  $\text{H}_c$  (281) and  $\text{H}_b$  (282)). The mixture was again subjected to radial chromatography (1 mm plate,  $\text{CH}_2\text{Cl}_2$ ). Recrystallization (1:1 petroleum ether- $\text{Et}_2\text{O}$ ) of the solids obtained gave 32 mg (32%) of the diene (281) as a colourless solid (melting point  $148\text{--}149^\circ\text{C}$ ) and 39 mg (39%) of the diene (282), also as a colourless solid (melting point,  $102\text{--}103^\circ\text{C}$ ).

The minor isomer, resulting from outward rotation of the ester group, the diene (281), exhibited IR (KBr):  $2253, 1708, 1645, 1208\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.93-1.02 (m, 2H), 1.10-1.22 (m, 2H), 1.30 (t, 3H,  $J = 7\text{ Hz}$ ,  $-\text{OCH}_2\text{CH}_3$ ), 1.42-1.51 (m, 1H), 1.56-1.82 (m, 4H), 2.02-2.11 (m, 1H), 2.26-2.34 (m, 1H), 3.23-3.31 (m, 2H,  $\text{H}_d$ ), 4.22 (q, 2H,  $J = 7\text{ Hz}$ ,

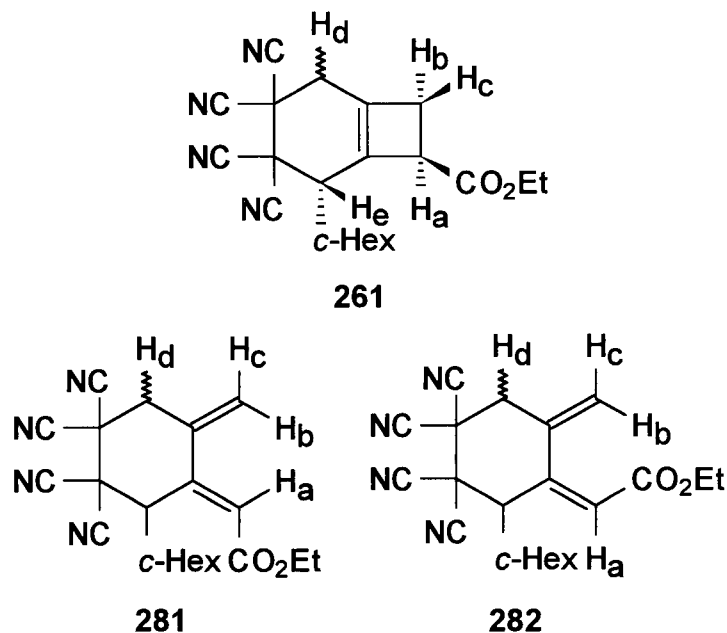
-OCH<sub>2</sub>CH<sub>3</sub>), 4.75 (d, 1H,  $J = 8$  Hz, =CCH(*c*-Hex)), 5.34 (br s, 1H, H<sub>C</sub>), 5.46 (br s, 1H, H<sub>b</sub>), 6.16 (s, 1H, H<sub>a</sub>); NOE difference experiments: irradiation at  $\delta$  3.28 (H<sub>d</sub>) caused enhancement of the signal at  $\delta$  5.34 (H<sub>C</sub>); irradiation at  $\delta$  5.34 (H<sub>C</sub>) caused enhancement of the signals at  $\delta$  3.23-3.31 (H<sub>d</sub>) and  $\delta$  5.46 (H<sub>b</sub>); irradiation at  $\delta$  5.46 (H<sub>b</sub>) caused enhancement of the signals at  $\delta$  5.34 (H<sub>C</sub>) and  $\delta$  6.16 (H<sub>a</sub>); irradiation at  $\delta$  6.16 (H<sub>a</sub>) caused enhancement of the signals at  $\delta$  5.46 (H<sub>b</sub>). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz)  $\delta$ : 0.87-1.14 (m, 7H, including triplet at  $\delta$  0.92, -OCH<sub>2</sub>CH<sub>3</sub>),  $\delta$  1.32-1.54 (m, 5H), 1.93 (d, 1H,  $J = 16$  Hz, one of H<sub>d</sub>), 2.10-2.20 (m, 1H), 2.23 (ddd, 1H,  $J = 16, 2, 2$  Hz, one of H<sub>d</sub>), 2.30-2.37 (m, 1H), 3.81-3.91 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.30 (d, 1H,  $J = 2$  Hz, H<sub>C</sub>), 4.60 (d, 1H,  $J = 2$  Hz, H<sub>b</sub>), 4.83 (d, 1H,  $J = 7$  Hz, =CCH(*c*-Hex)), 5.79 (s, 1H, H<sub>a</sub>). <sup>13</sup>C NMR (100.4 MHz)  $\delta$ : 14.1, 25.4, 25.7, 26.1, 26.2, 29.6, 33.6, 38.5, 39.6, 43.0, 47.7, 61.1, 110.4, 110.6, 110.9, 111.0, 121.0, 124.0, 136.0, 147.1, 163.6. Anal. calcd. for C<sub>21</sub>H<sub>22</sub>O<sub>2</sub>N<sub>4</sub>: C 69.59, H 6.12, N 15.46; found: C 69.43, H 6.08, N 15.51. Exact Mass calcd. for C<sub>21</sub>H<sub>22</sub>O<sub>2</sub>N<sub>4</sub>: 362.1743; found: 362.1753.

The major isomer, resulting from inward rotation of the ester group, the diene (**282**), exhibited IR (KBr): 2265, 1719, 1639, 1204 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 1.25-1.40 (m, 7H, includes triplet at  $\delta$  1.28,  $J = 7$  Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.69-1.75 (m, 1H), 1.80-1.91 (m, 4H), 1.96-2.02 (m, 1H), 2.04-2.11 (m, 1H), 2.87 (d, 1H,  $J = 6$  Hz, =CCH(*c*-Hex)), 3.29-3.34 (m, 2H, H<sub>d</sub>), 4.16 (q, 2H,  $J = 7$  Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 5.30 (br s, 1H, H<sub>b</sub>), 5.43 (br s, 1H, H<sub>C</sub>), 5.95 (s, 1H, H<sub>a</sub>); NOE difference experiments: irradiation at  $\delta$  2.87 (=CCH(*c*-Hex)) caused enhancement of the signal at  $\delta$  5.95 (H<sub>a</sub>); irradiation at  $\delta$  3.32 (H<sub>d</sub>) caused enhancement of the signal at  $\delta$  5.43 (H<sub>C</sub>); irradiation at  $\delta$  5.30 (H<sub>b</sub>) caused enhancement of the signals at  $\delta$  5.43 (H<sub>C</sub>); irradiation at  $\delta$  5.43 (H<sub>C</sub>) caused enhancement of the signals at  $\delta$  3.29-3.34 (H<sub>d</sub>) and  $\delta$  5.30 (H<sub>b</sub>); irradiation at  $\delta$  5.95 (H<sub>a</sub>) caused enhancement of the signal at  $\delta$  2.87 (=CCH(*c*-Hex)). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz)  $\delta$ : 0.77-1.05 (m, 8H, including triplet at  $\delta$  0.89,  $J = 7$  Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.30-1.48 (m, 3H), 1.60-1.71 (m, 1H), 1.95-2.03 (m, 1H), 2.25-2.40 (m, 3H), 3.88 (q, 2H,  $J = 7$  Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.57 (br s, 1H, H<sub>b</sub>), 4.72 (br s, 1H, H<sub>C</sub>), 5.56 (br s, 1H, H<sub>a</sub>). <sup>13</sup>C NMR (100.4 MHz)  $\delta$ : 14.1, 25.4, 26.1, 26.2, 26.3, 29.7, 33.61, 33.62, 39.62, 39.63, 47.7, 61.2, 110.4,



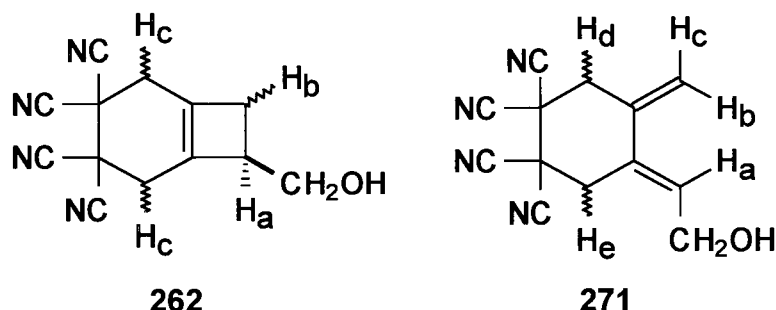
110.6, 110.9, 111.0, 121.1, 124.0, 135.6, 147.1, 164.7. Anal. calcd. for  $C_{21}H_{22}O_2N_4$ : C 69.59, H 6.12, N 15.46; found: C 69.69, H 6.10, N 15.60. Exact Mass calcd. for  $C_{21}H_{22}O_2N_4$ : 362.1743; found: 362.1739.

Preparation of the tetranitrile ester dienes (281) and (282) from the ester (261)



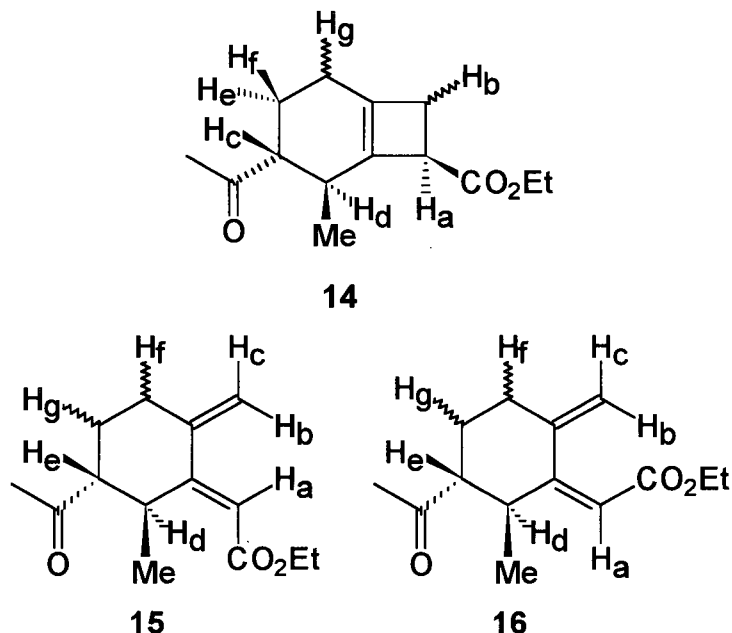
Following a modified version of general procedure 16 in which the reaction time was 6 hours, the ester (261) was converted into the tetranitrile ester dienes (281) and (282). The following amounts of substrate and solvent were used: ester (261) (100 mg, 0.276 mmol) in 3 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes then  $CH_2Cl_2$ ) afforded 94 mg (94%) of a mixture of the outward rotation diene (281) and the inward rotation diene (282) in a ratio of 1:1.3 respectively ( $^1H$  NMR analysis of signals  $H_c$  (281) and  $H_b$  (282)). The mixture was again subjected to radial chromatography (1 mm plate,  $CH_2Cl_2$ ). Recrystallization (1:1 petroleum ether- $Et_2O$ ) of the acquired solids afforded 36 mg (36%) of the diene (281) as a colourless solid (melting point, 148-149°C) and 51 mg (51%) of the diene (282), also as a colourless solid (melting point, 102-103°C). The spectral data obtained from these materials was identical with those reported for the last experiment.

Preparation of the tetranitrile alcohol diene (271) from the alcohol (262)



Following general procedure 16 outlined above, the alcohol (**262**) was converted into the alcohol (**271**). The following amounts of substrate and solvent were used: alcohol (**262**) (50 mg, 0.21 mmol) in 2.5 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) and recrystallization (1:1 petroleum ether-ether) afforded 42 mg (84%) of the diene (**271**) as colourless crystals (melting point, 118-119°C), which exhibited IR (KBr): 3466 (br), 1642, 1441, 1007 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.55 (br s, 1H, -CH<sub>2</sub>OH), 3.15 (s, 2H, H<sub>d</sub>), 3.34 (s, 2H, H<sub>e</sub>), 4.32 (d, 2H, *J* = 7 Hz, -CH<sub>2</sub>OH), 5.20 (s, 1H, H<sub>c</sub>), 5.42 (s, 1H, H<sub>b</sub>), 6.13 (t, 1H, *J* = 7 Hz, H<sub>a</sub>); NOE difference experiments: irradiation at δ 3.15 (H<sub>d</sub>) caused enhancement of the signal at δ 5.20 (H<sub>c</sub>); irradiation at δ 3.34 (H<sub>e</sub>) caused enhancement of the signal at δ 4.32 (-CH<sub>2</sub>OH); irradiation at δ 4.32 (-CH<sub>2</sub>OH) caused enhancement of the signals at δ 3.34 (H<sub>e</sub>) and δ 6.13 (H<sub>a</sub>); irradiation at δ 5.20 (H<sub>c</sub>) caused enhancement of the signals at δ 3.15 (H<sub>d</sub>) and δ 5.42 (H<sub>b</sub>); irradiation at δ 5.42 (H<sub>b</sub>) caused enhancement of the signals at δ 5.20 (H<sub>c</sub>) and δ 6.13 (H<sub>a</sub>); irradiation at δ 6.13 (H<sub>a</sub>) caused enhancement of the signals at δ 4.32 (-CH<sub>2</sub>OH) and δ 5.42 (H<sub>b</sub>). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz) δ: 0.52 (t, 1H, *J* = 7 Hz, -CH<sub>2</sub>OH), 1.95 (br s, 2H, H<sub>d</sub>), 2.30 (br s, 2H, H<sub>e</sub>), 3.34 (dd, 2H, *J* = 7, 7 Hz, -CH<sub>2</sub>OH), 4.25 (br s, 1H, H<sub>c</sub>), 4.63 (br s, 1H, H<sub>b</sub>), 5.37 (t, 1H, *J* = 7 Hz, H<sub>a</sub>). Anal. calcd. for C<sub>13</sub>H<sub>10</sub>ON<sub>4</sub>: C 65.54, H 4.23, N 23.52; found: C 65.36, H 4.33, N 23.58. Exact Mass calcd. for C<sub>13</sub>H<sub>10</sub>ON<sub>4</sub>: 238.0855; found: 238.0856.

Preparation of the keto ester dienes (15) and (16)<sup>16</sup>



Following general procedure 16 outlined above, the keto ester (14) was converted into the keto ester dienes (15) and (16). The following amounts of substrate and solvent were used: keto ester (14) (75 mg, 0.32 mmol) in 3.2 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 63 mg (83%) of a mixture of the outward rotation diene (15) and the inward rotation diene (16) in a ratio of 1:1 respectively (<sup>1</sup>H NMR analysis of signals H<sub>b</sub> (15) and H<sub>c</sub> (16)). The mixture was again subjected to radial chromatography (1 mm plate, 3:1 hexanes-Et<sub>2</sub>O). Removal of trace amounts of solvent (vacuum pump) from the acquired liquids afforded 28 mg (37%) of the diene (15), as a colourless oil, and 29 mg (38%) of the diene (16), also as a colourless oil.

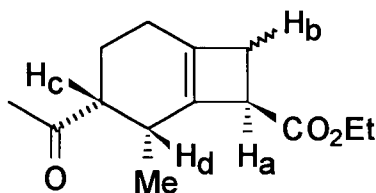
The product resulting from outward rotation of the ester group, the diene (15), exhibited IR (neat): 1713, 1635, 1176, 1137 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 1.15 (d, 3H, *J* = 7 Hz, -CHCH<sub>3</sub>), 1.28 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.84-1.90 (m, 1H, one of H<sub>g</sub>), 1.97-2.04 (m, 1H, one of H<sub>g</sub>), 2.18 (s, 3H, -COCH<sub>3</sub>), 2.25-2.40 (m, 2H, H<sub>f</sub>), 2.50-2.55 (m, 1H, H<sub>e</sub>), 4.12-4.20 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.52 (br q, 1H, *J* = 7 Hz, H<sub>d</sub>), 4.83 (d, 1H, *J* = 2 Hz, H<sub>c</sub>), 5.00

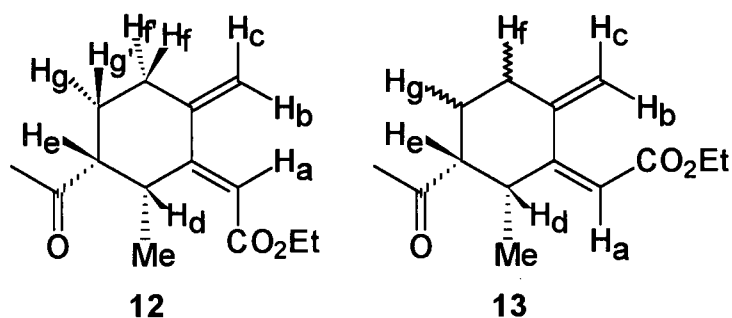
(dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 5.80 (s, 1H,  $H_a$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.15 ( $-\text{CHCH}_3$ ) simplified the quartet at  $\delta$  4.52 ( $H_d$ ) to a broad singlet; irradiation at  $\delta$  1.86 (one of  $H_g$ ) sharpened the multiplets at  $\delta$  1.97-2.04 (one of  $H_g$ ), 2.25-2.40 ( $H_f$ ), and 2.50-2.55 ( $H_e$ ); irradiation at  $\delta$  1.99 (one of  $H_g$ ) sharpened the multiplets at  $\delta$  1.84-1.90 (one of  $H_g$ ),  $\delta$  2.25-2.40 ( $H_f$ ), and  $\delta$  2.50-2.55 ( $H_e$ ); irradiation at  $\delta$  2.31 ( $H_f$ ) converted the signal at  $\delta$  1.84-1.90 (one of  $H_g$ ) into a doublet of doublets ( $J = 16, 4$  Hz), the signal at  $\delta$  1.97-2.04 (one of  $H_g$ ) into a doublet of doublets ( $J = 16, 2$  Hz), and the signals at  $\delta$  4.83 ( $H_c$ ) and  $\delta$  5.00 ( $H_b$ ) to singlets; irradiation at  $\delta$  2.53 ( $H_e$ ) sharpened the multiplets at  $\delta$  1.84-1.90 (one of  $H_g$ ),  $\delta$  1.97-2.04 (one of  $H_g$ ) and the broad quartet at  $\delta$  4.52 ( $H_d$ ); irradiation at  $\delta$  4.52 ( $H_d$ ) converted the doublet at  $\delta$  1.15 ( $-\text{CHCH}_3$ ) to a singlet, and simplified the multiplet at  $\delta$  2.50-2.55 ( $H_e$ ). NOE difference experiments: irradiation at  $\delta$  1.15 ( $-\text{CHCH}_3$ ) caused enhancement of the signals at  $\delta$  2.50-2.55 ( $H_e$ ) and  $\delta$  4.52 ( $H_d$ ); irradiation at  $\delta$  5.80 ( $H_a$ ) caused enhancement of the signal at  $\delta$  5.00 ( $H_b$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.2, 20.1, 21.9, 28.3, 31.0, 32.2, 54.3, 59.7, 113.0, 113.8, 146.5, 162.8, 166.3, 210.1. Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : C 71.15, H 8.54; found: C 70.81, H 8.60. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : 236.1412; found: 236.1410.

The product resulting from inward rotation of the ester group, the diene (16), exhibited IR (neat): 1721, 1713, 1635, 1192, 899  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.00 (d, 3H,  $J = 7$  Hz,  $-\text{CHCH}_3$ ), 1.22 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.60-1.70 (m, 1H, one of  $H_g$ ), 1.92-2.00 (m, 1H, one of  $H_g$ ), 2.15 (s, 3H,  $-\text{COCH}_3$ ), 2.26-2.35 (m, 1H, one of  $H_f$ ), 2.45 (dd, 1H,  $J = 10, 4$  Hz,  $H_e$ ), 2.49 (ddd, 1H,  $J = 14, 4, 4$  Hz, one of  $H_f$ ), 2.60-2.65 (m, 1H,  $H_d$ ), 4.10 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.80 (br s, 1H,  $H_b$ ), 4.91 (br s, 1H,  $H_c$ ), 5.59 (d, 1H,  $J = 2$  Hz,  $H_a$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.00 ( $-\text{CHCH}_3$ ) converted the multiplet at  $\delta$  2.60-2.65 ( $H_d$ ) to a doublet ( $J = 10$  Hz); irradiation at  $\delta$  1.65 (one of  $H_g$ ) simplified the multiplets at  $\delta$  1.92-2.00 (one of  $H_g$ ) and  $\delta$  2.26-2.35 (one of  $H_f$ ), and simplified the doublet of doublets at  $\delta$  2.49 (one of  $H_f$ ) to a doublet of doublets ( $J = 14, 4$  Hz); irradiation at  $\delta$  1.95 (one of  $H_g$ ) simplified the multiplets at  $\delta$  1.60-1.70 (one of  $H_g$ ) and  $\delta$  2.26-2.35 (one of  $H_f$ ), simplified the doublet of doublets at  $\delta$  2.45 ( $H_e$ ) to a broad doublet ( $J = 10$  Hz), and

simplified the doublet of doublet of doublets at  $\delta$  2.49 (one of  $H_f$ ) to a doublet of doublets ( $J=14, 4$  Hz); irradiation at  $\delta$  2.30 (one of  $H_f$ ) simplified the multiplets at  $\delta$  1.60-1.70 (one of  $H_g$ ) and  $\delta$  1.92-2.00 (one of  $H_g$ ), and simplified the signal at  $\delta$  2.49 (one of  $H_f$ ) to a broad doublet of doublets ( $J=4, 4$  Hz); irradiation at  $\delta$  2.45 ( $H_e$ ) simplified the multiplet at  $\delta$  1.60-1.70 (one of  $H_g$ ) to a broad doublet of doublets ( $J=15, 15$  Hz), converted the multiplet at  $\delta$  1.92-2.00 (one of  $H_g$ ) to a broad doublet of doublets ( $J=15, 4$  Hz), and simplified the multiplet at  $\delta$  2.60-2.65 ( $H_d$ ); irradiation at  $\delta$  2.49 (one of  $H_f$ ) simplified the multiplets at  $\delta$  1.60-1.70 (one of  $H_g$ ),  $\delta$  1.92-2.00 (one of  $H_g$ ), and 2.26-2.35 (one of  $H_f$ ); irradiation at  $\delta$  2.64 ( $H_d$ ) converted the doublets at  $\delta$  1.00 ( $-\text{CHCH}_3$ ) and  $\delta$  5.59 ( $H_a$ ) to singlets, and the doublet of doublets at  $\delta$  2.45 ( $H_e$ ) to a doublet ( $J=4$  Hz); irradiation at  $\delta$  5.59 ( $H_a$ ) simplified the multiplet at  $\delta$  2.60-2.65 ( $H_d$ ). NOE difference experiments: irradiation at  $\delta$  1.00 ( $-\text{CHCH}_3$ ) caused enhancement of the signals at  $\delta$  2.45 ( $H_e$ ),  $\delta$  2.60-2.65 ( $H_d$ ), and  $\delta$  5.59 ( $H_a$ ); irradiation at  $\delta$  2.30 (one of  $H_f$ ) caused enhancement of the signals at  $\delta$  1.60-1.70 (one of  $H_g$ ),  $\delta$  1.92-2.00 (one of  $H_g$ ),  $\delta$  2.49 (one of  $H_f$ ), and  $\delta$  4.91 ( $H_c$ ); irradiation at  $\delta$  2.60 ( $H_d$ ) caused enhancement of the signals at  $\delta$  1.60-1.70 (one of  $H_g$ ), 1.00 ( $-\text{CHCH}_3$ ), and  $\delta$  5.59 ( $H_a$ ); irradiation at  $\delta$  4.78 ( $H_b$ ) caused enhancement of the signal at  $\delta$  4.91 ( $H_c$ ); irradiation at  $\delta$  4.91 ( $H_c$ ) caused enhancement of the signals at  $\delta$  4.80 ( $H_b$ ) and  $\delta$  2.49 (one of  $H_f$ ); irradiation at  $\delta$  5.59 ( $H_a$ ) caused enhancement of the signals at  $\delta$  2.60-2.65 ( $H_d$ ), and  $\delta$  1.00 ( $-\text{CHCH}_3$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.0, 16.2, 29.1, 29.4, 34.8, 40.9, 58.3, 60.0, 111.7, 114.0, 145.3, 159.2, 167.0, 210.1. Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : C 71.15, H 8.54; found: C 71.40, H 8.63. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : 236.1412; found: 236.1420.

Preparation of the keto ester dienes (12) and (13)<sup>16</sup>





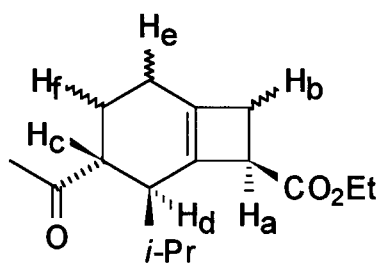
Following general procedure 16 outlined above, the keto ester (11) was converted into the keto ester dienes (12) and (13). The following amounts of substrate and solvent were used: keto ester (11) (75 mg, 0.32 mmol) in 3.2 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 60 mg (79%) of a mixture of the outward rotation diene (12) and the inward rotation diene (13) in a ratio of 11.5:1 respectively (<sup>1</sup>H NMR analysis of signals H<sub>c</sub> (12) and H<sub>b</sub> (13)). The mixture was again subjected to radial chromatography (1 mm plate, 3:1 hexanes-Et<sub>2</sub>O). Removal of trace amounts of solvent (vacuum pump) from the liquids obtained afforded 46 mg (61%) of the diene (12), as a colourless oil, and 4.5 mg (6%) of the diene (13), also as a colourless oil.

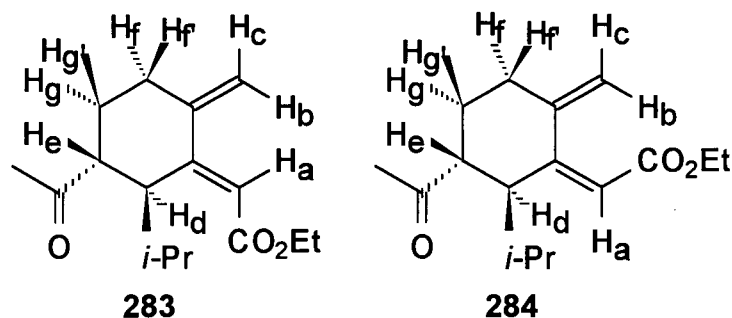
The major isomer, resulting from outward rotation of the ester group, the diene (12) exhibited IR (neat): 1712, 1635, 1184, 1137 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.84 (d, 3H, *J* = 7 Hz, -CHCH<sub>3</sub>), 1.28 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.70-1.77 (m, 1H, H<sub>g'</sub>), 1.83 (ddd, 1H, *J* = 13, 13, 5.5 Hz, H<sub>g</sub>), 2.06-2.20 (m, 1H, H<sub>f</sub>), 2.18 (s, 3H, -COCH<sub>3</sub>), 2.48 (ddd, 1H, *J* = 14, 5.5, 2 Hz, H<sub>f</sub>), 2.67 (ddd, 1H, *J* = 13, 4, 4 Hz, H<sub>e</sub>), 4.17 (q, 2H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.54-4.63 (m, 1H, H<sub>d</sub>), 4.87 (dd, 1H, *J* = 2, 2 Hz, H<sub>c</sub>), 5.00 (dd, 1H, *J* = 2, 2 Hz, H<sub>b</sub>), 5.79 (s, 1H, H<sub>a</sub>); in a series of decoupling experiments, irradiation at δ 0.84 (-CHCH<sub>3</sub>) converted the multiplet at δ 4.54-4.63 (H<sub>d</sub>) to a doublet (*J* = 4 Hz); irradiation at δ 2.10 (H<sub>f</sub>) simplified the multiplet at δ 1.70-1.77 (H<sub>g'</sub>), and converted the signal at δ 2.48 (H<sub>f</sub>) to a doublet of doublets (*J* = 2, 5.5 Hz) and converted the signals at δ 4.87 (H<sub>c</sub>) and δ 5.00 (H<sub>b</sub>) to doublets (*J* = 2 Hz); irradiation at δ 2.48 (H<sub>f</sub>) simplified the multiplet at δ 1.70-1.77 (H<sub>g'</sub>), converted the doublet of doublet of doublets at δ 1.83 (H<sub>g</sub>) into a doublet of doublets (*J* = 13, 13 Hz), and simplified the multiplet at

$\delta$  2.06-2.20 ( $H_f$ ); irradiation at  $\delta$  2.67 ( $H_e$ ) sharpened the signal at  $\delta$  1.70-1.77 ( $H_{g'}$ ), converted the signal at  $\delta$  1.83 ( $H_g$ ) into a doublet of doublets ( $J= 5.5, 13$  Hz) and converted the multiplet at  $\delta$  4.54-4.63 ( $H_d$ ) to a broad quartet ( $J= 7$  Hz); irradiation at  $\delta$  4.56 ( $H_d$ ) converted the doublet at  $\delta$  0.84 ( $-\text{CHCH}_3$ ) to a singlet and the signal at  $\delta$  2.67 ( $H_e$ ) to a doublet of doublets ( $J= 13, 4$  Hz). NOE difference experiments: irradiation at  $\delta$  2.48 ( $H_f$ ) caused enhancement of the signals at  $\delta$  1.83 ( $H_g$ ),  $\delta$  2.06-2.20 ( $H_f$ ), and  $\delta$  4.87 ( $H_c$ ); irradiation at  $\delta$  2.67 ( $H_e$ ) caused enhancement of the signals at  $\delta$  4.54-4.63 ( $H_d$ ), and  $\delta$  1.70-1.77 ( $H_{g'}$ ); irradiation at  $\delta$  4.59 ( $H_d$ ) caused enhancement of the signals at  $\delta$  0.84 ( $-\text{CHCH}_3$ ), 2.18 ( $-\text{COCH}_3$ ), and  $\delta$  2.67 ( $H_e$ ); irradiation at  $\delta$  4.87 ( $H_c$ ) caused enhancement of the signals at  $\delta$  2.48 ( $H_f$ ) and  $\delta$  5.00 ( $H_b$ ); irradiation at  $\delta$  5.00 ( $H_b$ ) caused enhancement of the signals at  $\delta$  4.87 ( $H_c$ ), and  $\delta$  5.79 ( $H_a$ ); irradiation at  $\delta$  5.79 ( $H_a$ ) caused enhancement of the signal at  $\delta$  5.00 ( $H_b$ ).  $^1\text{H}$  ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 0.91 (d, 3H,  $J= 7$  Hz,  $-\text{CHCH}_3$ ), 1.01 (t, 3H,  $J= 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.51-1.57 (m, 1H), 1.75-1.84 (m, 5H, includes singlet at  $\delta$  1.77,  $-\text{COCH}_3$ ), 2.13-2.24 (m, 2H), 4.03 (q, 2H,  $J= 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.60 (dd, 1H,  $J= 2, 2$  Hz,  $H_c$ ), 4.75-4.81 (m, 1H,  $H_d$ ), 4.83 (dd, 1H,  $J= 2, 2$  Hz,  $H_b$ ), 5.94 (br s, 1H,  $H_a$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.1, 14.2, 20.9, 28.1, 32.5, 33.5, 53.6, 59.9, 112.9, 113.4, 146.2, 163.5, 166.3, 209.5. Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : C 71.15, H 8.54; found: C 71.00, H 8.50. Exact Mass calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : 236.1412; found: 236.1411.

The minor isomer, resulting from inward rotation of the ester group, diene (**13**) exhibited spectral characteristics identical to those previously reported.<sup>16</sup>

#### Preparation of the keto ester dienes (**283**) and (**284**)





Following general procedure 16 outlined above, the keto ester (**265**) was converted into the keto ester dienes (**283**) and (**284**). The following amounts of substrate and solvent were used: keto ester (**265**) (60 mg, 0.23 mmol) in 2.5 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 56 mg (93%) of a mixture of the outward rotation diene (**283**) and the inward rotation diene (**284**) in a ratio of 1:2.2 respectively (<sup>1</sup>H NMR analysis of signals H<sub>c</sub> (**283**) and H<sub>b</sub> (**284**)). The mixture was again subjected to radial chromatography (1 mm plate, 4:1 hexanes-Et<sub>2</sub>O). Removal of trace amounts of solvent under (vacuum pump) from the acquired liquids afforded 15 mg (25%) of the diene (**283**), as a colourless oil, and 36 mg (60%) of the diene (**284**), also as a colourless oil.

The minor isomer, resulting from outward rotation of the ester group, the diene (**283**), exhibited IR (neat): 1714, 1635, 1198, 1175, 1037 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.84 (d, 3H, *J* = 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.03 (d, 3H, *J* = 7 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.26 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.64-1.74 (m, 2H, -CH(CH<sub>3</sub>)<sub>2</sub>, H<sub>g'</sub>), 1.96-2.04 (m, 1H, H<sub>g</sub>), 2.18 (s, 3H, -COCH<sub>3</sub>), 2.24-2.33 (m, 1H, H<sub>f</sub>), 2.48-2.61 (m, 1H, H<sub>f</sub>), 2.79-2.83 (m, 1H, H<sub>e</sub>), 4.08-4.17 (m, 3H, H<sub>d</sub>, -OCH<sub>2</sub>CH<sub>3</sub>), 4.76 (dd, 1H, *J* = 2, 2 Hz, H<sub>c</sub>), 4.91 (dd, 1H, *J* = 2, 2 Hz, H<sub>b</sub>), 5.83 (s, 1H, H<sub>a</sub>); in a series of decoupling experiments, irradiation of the signal at δ 1.72 (H<sub>g'</sub>) sharpened the multiplets at δ 1.96-2.04 (H<sub>g</sub>), δ 2.24-2.33 (H<sub>f</sub>), δ 2.48-2.61 (H<sub>f</sub>), and δ 2.79-2.83 (H<sub>e</sub>); irradiation at δ 2.00 (H<sub>g</sub>) sharpened the multiplets at δ 1.64-1.74 (H<sub>g'</sub>), δ 2.24-2.33 (H<sub>f</sub>), and δ 2.48-2.61 (H<sub>f</sub>); irradiation at δ 2.55 (H<sub>f</sub>) simplified the multiplet at δ 2.24-2.33 (H<sub>f</sub>), converted the signal at δ 1.96-2.04 (H<sub>g</sub>) to a doublet of multiplets (*J* = 14 Hz) and converted the signals at δ 4.76 (H<sub>c</sub>) and δ 4.91 (H<sub>b</sub>) to doublets (*J* = 2 Hz). NOE difference experiments:

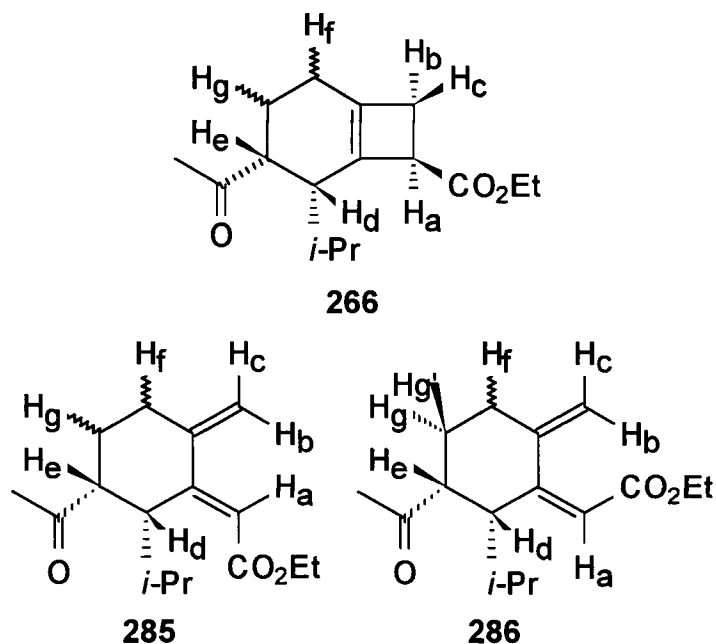


irradiation at  $\delta$  2.54 ( $H_f$ ) caused enhancement of the signals at  $\delta$  1.96-2.04 ( $H_g$ ),  $\delta$  2.24-2.33 ( $H_f$ ); irradiation at  $\delta$  2.81 ( $H_e$ ) caused enhancement of the signals at  $\delta$  1.03 (one of  $-\text{CH}(\text{CH}_3)_2$ ),  $\delta$  1.64-1.74 ( $H_{g'}$ ),  $\delta$  1.96-2.04 ( $H_g$ ),  $\delta$  2.18 ( $-\text{COCH}_3$ ), and  $\delta$  4.08-4.17 ( $H_d$ ); irradiation at  $\delta$  4.91 ( $H_b$ ) caused enhancement of the signals at  $\delta$  4.76 ( $H_c$ ) and  $\delta$  5.83 ( $H_a$ ); irradiation of the signal at  $\delta$  5.83 ( $H_a$ ) caused enhancement of the signal at  $\delta$  4.91 ( $H_b$ ).  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 0.82 (d, 3H,  $J = 7$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.95 (d, 3H,  $J = 7$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.96 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.12-1.20 (m, 1H), 1.30-1.41 (m, 1H), 1.68-1.75 (m, 1H), 1.89-1.94 (m, 1H), 2.05 (s, 3H,  $-\text{COCH}_3$ ), 2.45 (br s, 1H), 2.70-2.78 (m, 1H), 3.96-4.05 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 4.35 (br d, 1H,  $J = 10$  Hz,  $H_d$ ), 4.55 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 4.77 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 6.01 (br s, 1H,  $H_a$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.2, 19.9, 20.2, 21.1, 28.2, 29.2, 31.3, 44.3, 50.4, 59.7, 111.3, 116.0, 147.9, 161.4, 166.5, 210.7. Anal. calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : C 72.69, H 9.16; found: C 72.55, H 9.15. Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : 264.1725; found: 264.1724.

The major isomer, resulting from inward rotation of the ester group, the diene (**284**), exhibited IR (neat): 1713, 1636, 1191, 1035  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.85 (d, 3H,  $J = 6.5$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.95 (d, 3H,  $J = 6.5$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.20 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.69-1.80 (m, 2H,  $-\text{CH}(\text{CH}_3)_2$ ,  $H_{g'}$ ), 2.00-2.08 (m, 1H,  $H_g$ ), 2.14 (s, 3H,  $-\text{COCH}_3$ ), 2.26-2.33 (m, 2H,  $H_d$ ,  $H_f$ ), 2.43-2.54 (m, 1H,  $H_f$ ), 2.73-2.78 (m, 1H,  $H_e$ ), 4.02-4.11 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 4.80 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 4.96 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 5.59 (br s, 1H,  $H_a$ ); in a series of decoupling experiments, irradiation at  $\delta$  2.05 ( $H_g$ ) sharpened part of the multiplet at  $\delta$  1.69-1.75 ( $H_{g'}$ ), converted the multiplet at  $\delta$  2.26-2.33 ( $H_d$ ,  $H_f$ ) to a broad doublet ( $J = 6$  Hz) and doublet of doublets ( $J = 12, 2$  Hz), and converted the multiplet at  $\delta$  2.43-2.54 ( $H_f$ ) to a broad doublet of doublet of doublets ( $J = 12, 12, 2$  Hz); irradiation at  $\delta$  2.50 ( $H_f$ ) converted the multiplet at  $\delta$  2.00-2.08 ( $H_g$ ) to a doublet of multiplets ( $J = 14$  Hz), sharpened the multiplet at  $\delta$  2.29-2.33 ( $H_f$ ) and converted the doublet of doublets at  $\delta$  4.80 ( $H_b$ ) and  $\delta$  4.96 ( $H_c$ ) to doublets ( $J = 2$  Hz); irradiation at  $\delta$  2.75 ( $H_e$ ) sharpened the multiplet at  $\delta$  2.26-2.30 ( $H_d$ ). NOE difference experiments: irradiation at  $\delta$  2.05 ( $H_g$ ) caused enhancement of the signals at  $\delta$  1.69-1.80 ( $H_{g'}$ ),  $\delta$  2.48-2.54 ( $H_f$ ) and  $\delta$  2.73-2.78 ( $H_e$ ); irradiation at  $\delta$  2.50

(H<sub>f</sub>) caused enhancement of the signals at  $\delta$  2.00-2.08 (H<sub>g</sub>) and  $\delta$  2.26-2.33 (H<sub>f</sub>); irradiation at  $\delta$  4.80 (H<sub>b</sub>) caused enhancement of the signal at  $\delta$  4.96 (H<sub>c</sub>); irradiation of the signal at  $\delta$  4.96 (H<sub>c</sub>) caused enhancement of the signals at  $\delta$  2.30-2.33 (H<sub>f</sub>) and  $\delta$  4.80 (H<sub>b</sub>); irradiation of the signal at  $\delta$  5.59 (H<sub>a</sub>) caused enhancement of the signal at  $\delta$  2.26-2.33 (H<sub>d</sub>). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz)  $\delta$ : 0.63 (d, 3H,  $J$ = 6.5 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 0.74 (d, 3H,  $J$ = 6.5 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 0.97 (t, 3H,  $J$ = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.29-1.40 (m, 2H), 1.50-1.58 (m, 1H), 1.67 (s, 3H, -COCH<sub>3</sub>), 1.69-1.74 (m, 1H), 2.05-2.13 (m, 1H), 2.24-2.30 (m, 1H), 2.60-2.70 (m, 1H), 3.93-4.01 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.93 (dd, 1H,  $J$ = 2, 2 Hz, H<sub>b</sub>), 4.97 (dd, 1H,  $J$ = 2, 2 Hz, H<sub>c</sub>), 5.72 (br s, 1H, H<sub>a</sub>). <sup>13</sup>C NMR (125.8 MHz)  $\delta$ : 14.0, 20.2, 20.8, 23.2, 27.8, 28.0, 32.8, 51.8, 54.3, 59.8, 112.6, 117.2, 143.3, 157.5, 165.9, 209.3. Anal. calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>3</sub>: C 72.69, H 9.16 ; found: C 72.43, H 9.33. Exact Mass calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>3</sub>: 264.1725; found: 264.1725.

Preparation of the keto ester dienes (285) and (286)



Following general procedure 16 outlined above, the keto ester (266) was converted into the keto ester dienes (285) and (286). The following amounts of substrate and solvent were used: keto ester (266) (50 mg, 0.19 mmol) in 2 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 46 mg (92%) of a mixture of the outward rotation diene (285) and inward rotation diene (286) in a ratio of 3.9:1, respectively (<sup>1</sup>H NMR analysis). The mixture was again subjected to radial chromatography (1 mm plate, 4:1 hexanes-Et<sub>2</sub>O). Removal of trace amounts of solvent (vacuum pump) from the acquired liquid afforded 34 mg (68%) of the diene (285), as a colourless oil, and 9 mg (18%) of the diene (286), also as a colourless oil.

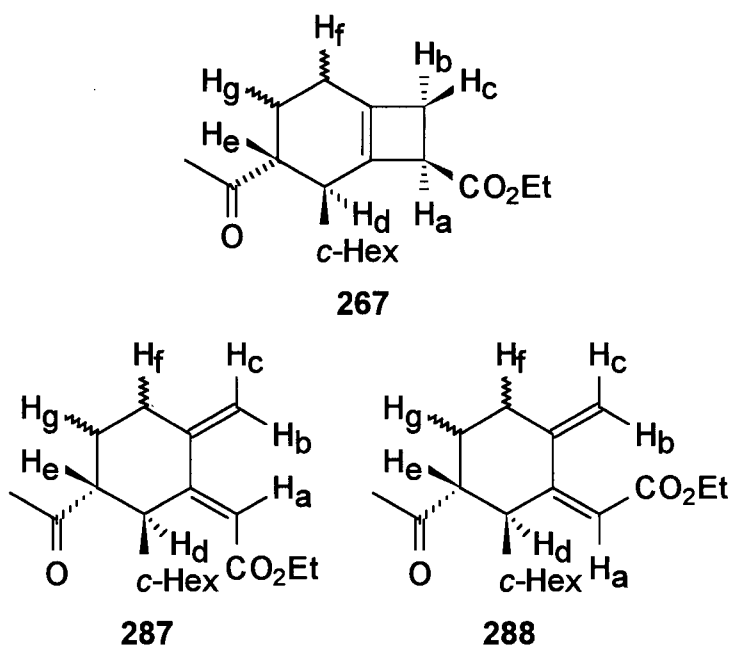
The major isomer, resulting from outward rotation of the ester group, the diene (285), exhibited IR (neat): 1713, 1635, 1369, 1218, 1180 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.76 (d, 3H,  $J$  = 6.5 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 0.79 (d, 3H,  $J$  = 6.5 Hz, one of -CH(CH<sub>3</sub>)<sub>2</sub>), 1.30 (t, 3H,  $J$  = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.68-1.76 (m, 1H, -CH(CH<sub>3</sub>)<sub>2</sub>), 1.80-1.92 (m, 2H, H<sub>g</sub>), 2.10-2.19 (m, 1H, one of H<sub>f</sub>), 2.26 (s, 3H, -COCH<sub>3</sub>), 2.49-2.57 (m, 2H, H<sub>e</sub>, one of H<sub>f</sub>), 4.18 (q, 2H,  $J$  = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.43 (dd, 1H,  $J$  = 8.5, 2 Hz, H<sub>d</sub>), 4.82 (dd, 1H,  $J$  = 2, 2 Hz, H<sub>c</sub>), 4.95 (dd, 1H,  $J$  = 2, 2 Hz, H<sub>b</sub>), 5.81 (s, 1H, H<sub>a</sub>); in a series of decoupling experiments, irradiation at  $\delta$  1.72 (-CH(CH<sub>3</sub>)<sub>2</sub>) converted the doublets at  $\delta$  0.76 (-CH(CH<sub>3</sub>)<sub>2</sub>) and  $\delta$  0.79 (-CH(CH<sub>3</sub>)<sub>2</sub>) to singlets and converted the signal at  $\delta$  4.43 (H<sub>d</sub>) to a broad doublet ( $J$  = 2 Hz); irradiation at  $\delta$  1.84 (H<sub>g</sub>) sharpened the multiplet at  $\delta$  2.10-2.19 (one of H<sub>f</sub>) and converted the multiplet at  $\delta$  2.49-2.57 (H<sub>e</sub>, one of H<sub>f</sub>) to a doublet ( $J$  = 2 Hz, H<sub>e</sub>) and a doublet of doublets ( $J$  = 15, 2 Hz, one of H<sub>f</sub>); irradiation at  $\delta$  2.15 (one of H<sub>f</sub>) sharpened the multiplet at  $\delta$  1.80-1.92 (H<sub>g</sub>), converted the signals at  $\delta$  2.49-2.57 (H<sub>e</sub>, H<sub>f</sub>) into multiplet (H<sub>f</sub>) and doublet of doublet of doublets ( $J$  = 12, 3, 2 Hz, H<sub>e</sub>) and converted the signals at  $\delta$  4.82 (H<sub>c</sub>) and  $\delta$  4.95 (H<sub>b</sub>) into doublets ( $J$  = 2 Hz); irradiation at  $\delta$  2.52 (H<sub>e</sub>, one of H<sub>f</sub>) sharpened the multiplets at  $\delta$  1.80-1.92 (H<sub>g</sub>) and  $\delta$  2.10-2.19 (one of H<sub>f</sub>) and converted the signal at  $\delta$  4.43 (H<sub>d</sub>) to a doublet ( $J$  = 8.5 Hz); irradiation at  $\delta$  4.43 (H<sub>d</sub>) sharpened the multiplet at  $\delta$  2.49-2.57 (H<sub>e</sub>) and converted the multiplet at  $\delta$  1.68-1.76 into a heptet ( $J$  = 6.5 Hz). NOE difference experiments: irradiation at  $\delta$  2.52 (H<sub>e</sub>, one of H<sub>f</sub>) caused enhancement of the signals at  $\delta$  1.80-1.92 (H<sub>g</sub>),  $\delta$  2.10-2.19 (one

of  $H_f$ ),  $\delta$  2.26 ( $-\text{COCH}_3$ ),  $\delta$  4.43 ( $H_d$ ), and  $\delta$  4.82 ( $H_c$ ); irradiation at  $\delta$  4.43 ( $H_d$ ) caused enhancement of the signals at  $\delta$  2.51-2.57 ( $H_e$ ) and  $\delta$  2.26 ( $-\text{COCH}_3$ ); irradiation at  $\delta$  5.81 ( $H_a$ ) caused enhancement of the signal at  $\delta$  4.95 ( $H_b$ ).  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 0.82 (d, 3H,  $J = 6.5$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.88 (d, 3H,  $J = 6.5$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.01 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.61-1.70 (m, 2H), 1.74-1.85 (m, 2H), 2.06 (s, 3H,  $-\text{COCH}_3$ ), 2.12-2.22 (m, 2H), 4.03 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.55 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 4.62 (dd, 1H,  $J = 8.5, 2$  Hz,  $H_d$ ), 4.78 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 5.94 (s, 1H,  $H_a$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.3, 20.61, 20.65, 21.1, 27.6, 28.2, 33.8, 44.8, 55.3, 59.9, 112.2, 114.1, 147.5, 163.3, 166.7, 210.5. Anal. calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : C 72.69, H 9.16; found: C 72.55, H 9.04. Exact Mass calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3$ : 264.1725; found: 264.1724.

The product resulting from inward rotation of the ester group, the diene (**286**) exhibited IR (neat): 1714, 1635, 1198, 1035  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 0.75 (d, 3H,  $J = 7$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 0.81 (d, 3H,  $J = 7$  Hz, one of  $-\text{CH}(\text{CH}_3)_2$ ), 1.23 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.79-1.89 (m, 2H,  $-\text{CH}(\text{CH}_3)_2$ ,  $H_g$ ), 1.90-1.98 (m, 1H,  $H_{g'}$ ), 2.20 (s, 3H,  $-\text{COCH}_3$ ), 2.22-2.28 (m, 1H, one of  $H_f$ ), 2.49-2.55 (m, 2H,  $H_d$ , one of  $H_f$ ), 2.61 (ddd, 1H,  $J = 12, 3.5, 3.5$  Hz,  $H_e$ ), 4.07-4.14 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 4.87 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 5.02 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 5.68 (s, 1H,  $H_a$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.85 ( $-\text{CH}(\text{CH}_3)_2$ ,  $H_g$ ) sharpened the multiplets at  $\delta$  2.22-2.28 (one of  $H_f$ ) and  $\delta$  2.49-2.55 ( $H_d$ , one of  $H_f$ ), converted the doublets at  $\delta$  0.75 ( $-\text{CH}(\text{CH}_3)_2$ ) and  $\delta$  0.81 ( $-\text{CH}(\text{CH}_3)_2$ ) to singlets, and converted the signal at  $\delta$  2.61 ( $H_e$ ) to a doublet of doublets ( $J = 3.5, 3.5$  Hz); irradiation at  $\delta$  1.95 ( $H_{g'}$ ) sharpened the multiplets at  $\delta$  1.79-1.89 ( $H_g$ ) and  $\delta$  2.22-2.28 (one of  $H_f$ ) and converted the signal at  $\delta$  2.61 ( $H_e$ ) to a doublet of doublets ( $J = 12, 3.5$  Hz); irradiation at  $\delta$  2.25 (one of  $H_f$ ) sharpened the multiplets at  $\delta$  1.83-1.89 ( $H_g$ ),  $\delta$  1.90-1.98 ( $H_{g'}$ ), and  $\delta$  2.22-2.28 (one of  $H_f$ ) and converted the signals at  $\delta$  4.87 ( $H_b$ ) and  $\delta$  5.02 ( $H_c$ ) into doublets ( $J = 2$  Hz); irradiation at  $\delta$  2.50 ( $H_d$ , one of  $H_f$ ) sharpened the multiplets at  $\delta$  1.79-1.89 ( $H_g$ ),  $\delta$  1.90-1.98 ( $H_{g'}$ ), and converted the signal at  $\delta$  2.61 ( $H_e$ ) to a broad doublet of doublets ( $J = 12, 3.5$  Hz); irradiation at  $\delta$  2.61 ( $H_e$ ) simplified the multiplets at  $\delta$  1.79-1.89 ( $H_g$ ) and

$\delta$  2.49-2.55 ( $H_d$ ) and converted the multiplet at  $\delta$  1.90-1.98 ( $H_{g'}$ ) to a doublet of doublets ( $J=15, 7$  Hz). NOE difference experiments: irradiation at  $\delta$  4.87 ( $H_b$ ) caused enhancement of the signal at  $\delta$  5.02 ( $H_c$ ); irradiation at  $\delta$  5.02 ( $H_c$ ) caused enhancement of the signals at  $\delta$  2.49-2.55 (one of  $H_f$ ) and  $\delta$  4.87 ( $H_b$ ); irradiation of the signal at  $\delta$  5.68 ( $H_a$ ) caused enhancement of the signal at  $\delta$  2.49-2.55 ( $H_d$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)  $\delta$ : 0.62 (d, 3H,  $J=7$  Hz, one of  $-CH(CH_3)_2$ ), 0.71 (d, 3H,  $J=7$  Hz, one of  $-CH(CH_3)_2$ ), 1.03 (t, 3H,  $J=7$  Hz,  $-OCH_2CH_3$ ), 1.27-1.34 (m, 1H), 1.60-1.73 (m, 2H), 1.75 (s, 3H,  $-COCH_3$ ), 2.01-2.10 (m, 2H), 2.20-2.27 (m, 2H), 3.99-4.06 (m, 2H,  $-OCH_2CH_3$ ), 4.92 (dd, 1H,  $J=2, 2$  Hz,  $H_b$ ), 4.96 (dd, 1H,  $J=2, 2$  Hz,  $H_c$ ), 5.64 (s, 1H,  $H_a$ ).  $^{13}C$  NMR (125.8 MHz)  $\delta$ : 14.1, 20.6, 21.6, 22.6, 26.8, 28.3, 34.5, 55.3, 56.2, 60.0, 113.8, 115.4, 142.9, 159.3, 166.4, 209.7. Anal. calcd. for  $C_{16}H_{24}O_3$ : C 72.69, H 9.16; found: C 72.52, H 9.26. Exact Mass calcd. for  $C_{16}H_{24}O_3$ : 264.1725; found: 264.1728.

Preparation of the keto ester dienes (287) and (288)



Following general procedure 16 outlined above, the keto ester (**267**) was converted into the keto ester dienes (**287**) and (**288**). The following amounts of substrate and solvent were used: keto ester (**267**) (100 mg, 0.329 mmol) in 3.5 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 93 mg (93%) of a mixture of the outward rotation diene (**287**) and the inward rotation diene (**288**) in a ratio of 1:2.6, respectively (<sup>1</sup>H NMR analysis of signals H<sub>C</sub> (**287**) and H<sub>b</sub> (**288**)). The mixture was again subjected to radial chromatography (1 mm plate, 7:3 hexanes-Et<sub>2</sub>O). Removal of trace amounts of solvent (vacuum pump) from the acquired liquid afforded 25 mg (25%) of the diene (**287**), as a colourless oil, and 62 mg (62%) of the diene (**288**), also as a colourless oil.

The minor isomer, resulting from outward rotation of the ester group, the diene (**287**), exhibited IR (neat): 1714, 1633, 1196 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$ : 0.89-1.20 (m, 5H), 1.26 (t, 3H,  $J = 7$  Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.30-1.42 (m, 1H), 1.53-1.73 (m, 4H), 1.73-1.80 (m, 1H), 1.83-1.91 (m, 1H), 1.94-2.02 (m, 1H, one of H<sub>g</sub>), 2.16 (s, 3H, -COCH<sub>3</sub>), 2.24-2.33 (m, 1H, one of H<sub>f</sub>), 2.50-2.61 (m, 1H, one of H<sub>f</sub>), 2.85-2.90 (m, 1H, H<sub>e</sub>), 4.08-4.16 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.18 (d, 1H,  $J = 10$  Hz, H<sub>d</sub>), 4.75 (dd, 1H,  $J = 2, 2$  Hz, H<sub>c</sub>), 4.88 (br d, 1H,  $J = 2, 2$  Hz, H<sub>b</sub>), 5.83 (s, 1H, H<sub>a</sub>); in a series of decoupling experiments, irradiation at  $\delta$  2.00 (one of H<sub>g</sub>) sharpened the multiplets at  $\delta$  2.24-2.33 (one of H<sub>f</sub>) and  $\delta$  2.50-2.61 (one of H<sub>f</sub>) and  $\delta$  2.85-2.90 (H<sub>e</sub>); irradiation at  $\delta$  2.55 (one of H<sub>f</sub>) sharpened the multiplet at  $\delta$  2.24-2.33 (one of H<sub>f</sub>), converted the multiplet at  $\delta$  1.94-2.02 (one of H<sub>g</sub>) to a doublet of multiplets ( $J = 15$  Hz) and converted the doublet of doublets at  $\delta$  4.75 (H<sub>c</sub>) and  $\delta$  4.88 (H<sub>b</sub>) to doublets ( $J = 2$  Hz), respectively; irradiation at  $\delta$  4.18 (H<sub>d</sub>) sharpened the multiplet at  $\delta$  1.30-1.42 and  $\delta$  2.85-2.90 (H<sub>e</sub>). NOE difference experiments: irradiation at  $\delta$  2.55 (one of H<sub>f</sub>) caused enhancement of the signals at  $\delta$  1.94-2.02 (one of H<sub>g</sub>) and  $\delta$  2.30 (one of H<sub>f</sub>); irradiation at  $\delta$  2.85 (H<sub>e</sub>) caused enhancement of the signals at  $\delta$  1.83-1.91,  $\delta$  1.94-2.02 (one of H<sub>g</sub>), and  $\delta$  4.18 (H<sub>d</sub>); irradiation at  $\delta$  4.18 (H<sub>d</sub>) caused enhancement of the signals at  $\delta$  0.92-1.09,  $\delta$  1.30-1.42,  $\delta$  2.16 (-COCH<sub>3</sub>), and  $\delta$  2.85 (H<sub>e</sub>); irradiation at  $\delta$  4.75 (H<sub>c</sub>) caused enhancement of the signals at

$\delta$  2.24-2.33 (one of  $H_f$ ) and  $\delta$  4.88 ( $H_b$ ); irradiation at  $\delta$  4.88 ( $H_b$ ) caused enhancement of the signals at  $\delta$  4.75 ( $H_c$ ) and  $\delta$  5.83 ( $H_a$ ); irradiation at  $\delta$  5.83 ( $H_a$ ) caused enhancement of the signal at  $\delta$  4.88 ( $H_b$ ).  $^1H$  NMR ( $C_6D_6$ , 400 MHz)

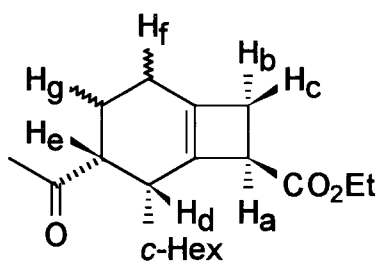
$\delta$ : 0.85-1.10 (m, 7H, includes triplet at  $\delta$  0.94, 3H,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.22-1.42 (m, 4H), 1.55-1.71 (m, 4H), 1.91-1.97 (m, 1H), 2.06-2.13 (m, 4H, includes singlet at  $\delta$  2.09,  $-COCH_3$ ), 2.49-2.53 (m, 1H), 2.72-2.83 (m, 1H), 3.95-4.01 (m, 2H,  $-OCH_2CH_3$ ), 4.43 (br d, 1H,  $J = 10$  Hz,  $H_d$ ), 4.55 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 4.77 (br d, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 6.03 (s, 1H,  $H_a$ ).

$^{13}C$  NMR (125.8 MHz)  $\delta$ : 14.2, 21.2, 26.2, 26.4, 26.5, 28.2, 29.8, 30.4, 31.3, 38.2, 43.0, 49.7, 59.7, 111.3, 116.2, 148.0, 161.2, 166.6, 210.9. Anal. calcd. for  $C_{19}H_{28}O_3$ : C 74.96, H 9.28; found: C 75.16, H 9.27. Exact Mass calcd. for  $C_{19}H_{28}O_3$ : 304.2039; found: 304.2039.

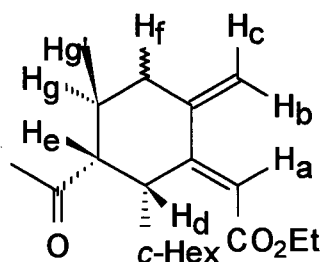
The major isomer, resulting from inward rotation of the ester group, the diene (**288**), exhibited IR (neat): 1713, 1634, 1171  $cm^{-1}$ ;  $^1H$  NMR (400 MHz)  $\delta$ : 0.71-0.91 (m, 2H), 1.09-1.22 (m, 6H includes triplet at  $\delta$  1.21,  $J = 7$  Hz,  $-OCH_2CH_3$ ), 1.37-1.40 (m, 1H,  $-CH$  of *c*-Hex), 1.60-1.82 (m, 6H), 2.00-2.06 (m, 1H, one of  $H_g$ ), 2.14 (s, 3H,  $-COCH_3$ ), 2.28-2.35 (m, 1H, one of  $H_f$ ), 2.38 (br dd, 1H,  $J = 10, 2$  Hz,  $H_d$ ), 2.45-2.55 (m, 1H, one of  $H_f$ ), 2.73-2.78 (m, 1H,  $H_e$ ), 4.01-4.10 (m, 2H,  $-OCH_2CH_3$ ), 4.77 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 4.94 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 5.53 (s, 1H,  $H_a$ ); in a series of decoupling experiments, irradiation at  $\delta$  1.40 ( $-CH$  of *c*-Hex ring) converted the broad doublet of doublets at  $\delta$  2.38 ( $H_d$ ) into a broad doublet ( $J = 2$  Hz); irradiation at  $\delta$  2.03 (one of  $H_g$ ) converted the signal at  $\delta$  2.28-2.35 (one of  $H_f$ ) into a doublet of doublet of doublets ( $J = 14, 4, 2$  Hz) and sharpened the multiplet at  $\delta$  2.45-2.55 (one of  $H_f$ ); irradiation at  $\delta$  2.38 ( $H_d$ ) sharpened the multiplet at  $\delta$  1.37-1.40 ( $-CH$  of *c*-Hex) and converted the multiplet at  $\delta$  2.73-2.78 ( $H_e$ ) into a broad doublet of doublets ( $J = 3.5, 3.5$  Hz); irradiation at  $\delta$  2.50 (one of  $H_f$ ) sharpened the multiplets at  $\delta$  1.94-2.02 (one of  $H_g$ ) and  $\delta$  2.28-2.35 (one of  $H_f$ ) and converted of the doublet of doublets at  $\delta$  4.77 ( $H_b$ ) and  $\delta$  4.94 ( $H_c$ ) and doublets ( $J = 2$  Hz) respectively; irradiation at  $\delta$  2.77 ( $H_e$ ) sharpened the signal at  $\delta$  2.00-2.06 (one of  $H_g$ ) and converted the signal at  $\delta$  2.38 ( $H_d$ ) into a doublet ( $J = 10$  Hz). NOE difference experiments: irradiation at  $\delta$  2.50 (one of  $H_f$ ) caused enhancement of the

signals at  $\delta$  2.28-2.35 (one of  $H_f$ ) and  $\delta$  2.00-2.06 (one of  $H_g$ ); irradiation at  $\delta$  2.75 ( $H_e$ ) caused enhancement of the signals at  $\delta$  1.71-1.82,  $\delta$  2.14 ( $-\text{COCH}_3$ ), and  $\delta$  2.38 ( $H_d$ ); irradiation at  $\delta$  4.77 ( $H_b$ ) caused enhancement of the signal at  $\delta$  4.94 ( $H_c$ ); irradiation at  $\delta$  4.94 ( $H_c$ ) caused enhancement of the signals at  $\delta$  2.28-2.35 (one of  $H_f$ ) and  $\delta$  4.77 ( $H_b$ ); irradiation at  $\delta$  5.53 ( $H_a$ ) caused enhancement of the signal at  $\delta$  2.38 ( $H_d$ ).  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 0.50-0.68 (m, 2H), 0.95 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.05-1.10 (m, 1H), 1.22-1.50 (m, 5H), 1.55-1.72 (m, 7H, includes singlet at  $\delta$  1.70,  $-\text{COCH}_3$ ), 1.88-1.99 (m, 1H), 2.09-2.15 (m, 1H), 2.22 (br d, 1H,  $J = 10$  Hz,  $H_d$ ), 2.29-2.36 (m, 1H), 2.62-2.72 (m, 1H), 3.93-4.03 (m, 2H,  $-\text{OCH}_2\text{CH}_3$ ), 4.92 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 4.95 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 5.71 (s, 1H,  $H_a$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.0, 23.1, 26.1, 26.22, 26.25, 27.8, 30.3, 31.0, 32.7, 36.8, 50.9, 52.7, 59.8, 112.5, 117.3, 143.3, 157.2, 165.8, 209.5. Anal. calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : C 74.96, H 9.28; found: C 75.16, H 9.24. Exact Mass calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : 304.2039; found: 304.2040.

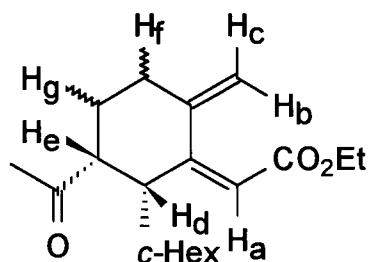
Preparation of the keto ester dienes (289) and (290)



268



289



290



Following general procedure 16 outlined above, the keto ester (268) was converted into the keto ester dienes (289) and (290). The following amounts of substrate and solvent were used: keto ester (268) (100 mg, 0.329 mmol) in 3.5 mL of dry mesitylene. Radial chromatography (1 mm plate, hexanes, then Et<sub>2</sub>O) afforded 93 mg (93%) of a mixture of the outward rotation diene (289) and the inward rotation diene (290) in a ratio of 4:1 respectively (<sup>1</sup>H NMR analysis of signals H<sub>C</sub> (289) and H<sub>b</sub> (290)). The mixture was again subjected to radial chromatography (1 mm plate, 7:3 hexanes-Et<sub>2</sub>O). Recrystallization (1:1 petroleum ether-Et<sub>2</sub>O) of the acquired solids afforded 67 mg (67%) of the diene (289) as a colourless solid (melting point, 72-73°C) and 17 mg (17%) of the diene (290), also as a colourless solid (melting point, 82-83°C).

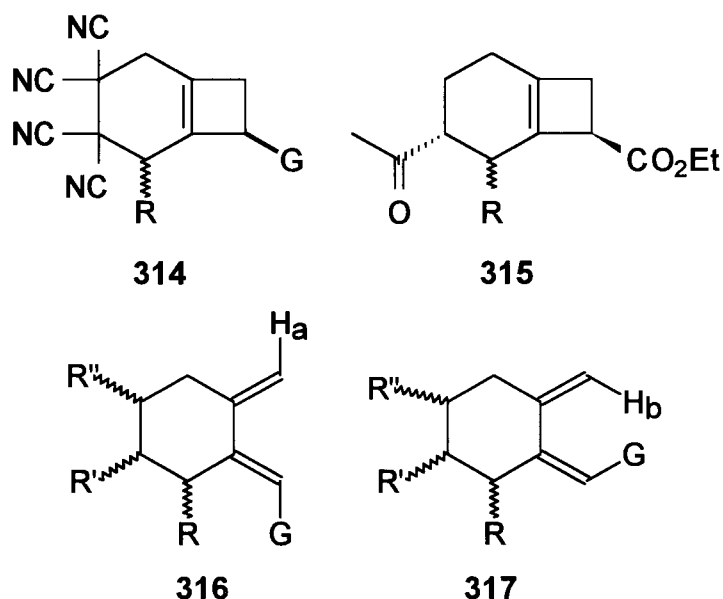
The major isomer, resulting from outward rotation of the ester group, the diene (289), exhibited IR (KBr): 1704, 1654, 1175 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) δ: 0.75-0.93 (m, 2H), 0.99-1.11 (m, 2H), 1.30 (t, 3H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.32-1.44 (m, 1H, -CH of *c*-Hex), 1.44-1.68 (m, 6H), 1.76-1.82 (m, 1H, H<sub>g</sub>), 1.88-1.97 (m, 1H, H<sub>g'</sub>), 2.08-2.22 (m, 1H, one of H<sub>f</sub>), 2.26 (s, 3H, -COCH<sub>3</sub>), 2.47 (ddd, 1H, *J* = 12, 2.5, 2.5 Hz, H<sub>e</sub>), 2.51-2.59 (m, 1H, one of H<sub>f</sub>), 4.18 (q, 2H, *J* = 7 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 4.48 (dd, 1H, *J* = 9, 2.5 Hz, H<sub>d</sub>), 4.83 (dd, 1H, *J* = 2, 2 Hz, H<sub>c</sub>), 4.93 (dd, 1H, *J* = 2, 2 Hz, H<sub>b</sub>), 5.82 (s, 1H, H<sub>a</sub>); in a series of decoupling experiments, irradiation at δ 1.79 (H<sub>g</sub>) sharpened the multiplets at δ 1.88-1.97 (H<sub>g'</sub>) and δ 2.51-2.59 (one of H<sub>f</sub>), converted the signal at δ 2.47 (H<sub>e</sub>) to a broad doublet of doublets (*J* = 2.5, 2.5 Hz); irradiation at δ 1.92 (H<sub>g'</sub>) sharpened the signals at δ 1.76-1.82 (H<sub>g</sub>), δ 2.08-2.20 (one of H<sub>f</sub>) and at δ 2.51-2.59 (H<sub>f</sub>), and converted the signal at δ 2.47 (H<sub>e</sub>) to a doublet of doublets (*J* = 12, 2.5 Hz); irradiation at δ 2.15 (one of H<sub>f</sub>) sharpened the signal at δ 1.76-1.82 (H<sub>g</sub>), converted the signal at δ 1.88-1.97 (H<sub>g'</sub>) into a doublet of multiplets (*J* = 14 Hz), sharpened the signal at δ 2.51-2.59 (one of H<sub>f</sub>) and converted the doublet of doublets at δ 4.83 (H<sub>c</sub>) and δ 4.93 (H<sub>b</sub>) to doublets (*J* = 2 Hz); irradiation at δ 2.47 (H<sub>e</sub>) sharpened the multiplets at δ 1.76-1.82 (H<sub>g</sub>) and δ 1.88-1.97 (H<sub>g'</sub>) and converted the doublet of doublets at δ 4.48 (H<sub>d</sub>) into a doublet (*J* = 9 Hz); irradiation at δ 4.48 (H<sub>d</sub>) simplified the multiplet at δ 1.32-1.44 (-CH

of *c*-Hex) and converted the signal at  $\delta$  2.47 ( $H_e$ ) into a doublet of doublets ( $J = 12, 2.5$  Hz). NOE difference experiments: irradiation at  $\delta$  4.48 ( $H_d$ ) caused enhancement of the signals at  $\delta$  0.79-0.90,  $\delta$  2.26 ( $-\text{COCH}_3$ ), and  $\delta$  2.47 ( $H_e$ ); irradiation at  $\delta$  4.83 ( $H_c$ ) caused enhancement of the signals at  $\delta$  2.51-2.59 (one of  $H_f$ ) and  $\delta$  4.93 ( $H_b$ ); irradiation at  $\delta$  4.93 ( $H_b$ ) caused enhancement of the signals at  $\delta$  4.83 ( $H_c$ ) and  $\delta$  5.82 ( $H_a$ ); irradiation at  $\delta$  5.82 ( $H_a$ ) caused enhancement of the signal at  $\delta$  4.93 ( $H_b$ ).  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 0.75-0.93 (m, 2H), 0.88-1.15 (m, 7H, includes triplet at  $\delta$  1.01,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.45-1.70 (m, 5H), 1.83-1.89 (m, 3H), 2.09 (s, 3H,  $-\text{COCH}_3$ ), 2.12-2.18 (m, 1H), 2.20-2.26 (m, 1H), 4.05 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.57 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 4.74 (dd, 1H,  $J = 9, 2.5$  Hz,  $H_d$ ), 4.79 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 6.00 (br s, 1H,  $H_a$ ).  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.3, 21.0, 26.1, 26.4, 26.5, 28.2, 30.2, 30.6, 33.8, 37.1, 43.7, 55.2, 59.9, 112.2, 114.3, 147.5, 163.2, 166.7, 210.5. Anal. calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : C 74.96, H 9.28; found: C 74.74, H 9.30. Exact Mass calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : 304.2039; found: 304.2030.

The minor isomer, resulting from inward rotation of the ester group, the diene (290) exhibited IR (neat): 1723, 1694, 1650, 1180  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz)  $\delta$ : 1.00-1.13 (m, 2H), 1.00-1.13 (m, 3H), 1.23 (t, 3H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.39-1.70 (m, 6H), 1.74-1.86 (m, 1H, one of  $H_g$ ), 1.91-1.99 (m, 1H, one of  $H_g$ ), 2.20 (s, 3H,  $-\text{COCH}_3$ ), 2.21-2.29 (m, 1H, one of  $H_f$ ), 2.48-2.62 (m, 3H,  $H_d$ ,  $H_e$ , one of  $H_f$ ), 4.11 (q, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.85 (dd, 1H,  $J = 2, 2$  Hz,  $H_b$ ), 5.03 (dd, 1H,  $J = 2, 2$  Hz,  $H_c$ ), 5.66 (s, 1H,  $H_a$ ); In a series of decoupling experiments, irradiation at  $\delta$  1.79 (one of  $H_g$ ) sharpened the multiplets at  $\delta$  1.91-1.99 (one of  $H_g$ ) and  $\delta$  2.48-2.58 ( $H_e$ , one of  $H_f$ ); irradiation at  $\delta$  2.25 (one of  $H_f$ ) simplified the multiplets at  $\delta$  1.74-1.86 (one of  $H_g$ ),  $\delta$  1.91-1.99 (one of  $H_g$ ) and  $\delta$  2.48-2.56 (one of  $H_f$ ), and converted the doublet of doublets at  $\delta$  4.85 ( $H_b$ ) and  $\delta$  5.03 ( $H_c$ ) into doublets ( $J = 2$  Hz) respectively. NOE difference experiments: irradiation at  $\delta$  4.85 ( $H_b$ ) caused enhancement of the signal at  $\delta$  5.03 ( $H_c$ ); irradiation at  $\delta$  5.03 ( $H_c$ ) caused enhancement of the signals at  $\delta$  2.50-2.55 (one of  $H_f$ ) and  $\delta$  4.85 ( $H_b$ ); irradiation at  $\delta$  5.66 ( $H_a$ ) caused enhancement of the signal at  $\delta$  2.56-2.62 ( $H_d$ ).  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$ : 0.58-0.67 (m, 2H), 0.92-1.05 (m, 5H, includes triplet at

$\delta$  1.01,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 1.43-1.60 (m, 7H), 1.63-1.80 (m, 5H, includes singlet at  $\delta$  1.74,  $-\text{COCH}_3$ ), 2.02-2.10 (m, 2H), 2.23-2.30 (m, 1H), 2.30-2.37 (m, 1H), 4.00-4.07 (m, 2H,  $J = 7$  Hz,  $-\text{OCH}_2\text{CH}_3$ ), 4.92 (dd, 1H,  $J = 2, 2$  Hz,  $\text{H}_b$ ), 4.97 (dd, 1H,  $J = 2, 2$  Hz,  $\text{H}_c$ ), 5.67 (s, 1H,  $\text{H}_a$ );  $^{13}\text{C}$  NMR (125.8 MHz)  $\delta$ : 14.1, 22.5, 26.1, 26.36, 26.39, 28.2, 30.6, 31.3, 34.5, 36.1, 54.1, 56.0, 60.0, 113.8, 115.6, 143.0, 160.0, 167.4, 209.4. Anal. calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : C 74.96, H 9.28; found: C 75.08, H 9.18. Exact Mass calcd. for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : 304.2039; found: 304.2037.

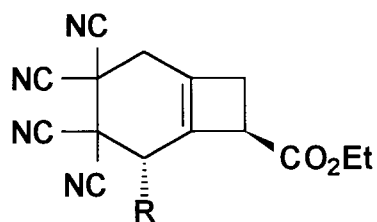
15. General Procedure 17: Small scale thermal ring opening of the functionalized bicyclo[4.2.0]oct-1(6)enes and direct determination of product ratios by  $^1\text{H}$  NMR spectroscopy



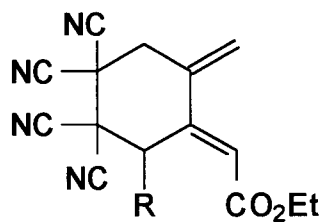
A solution of the appropriate bicyclo[4.2.0]oct-1(6)ene (**314**) or (**315**) in either dry deuteriobenzene (0.8 mL) or deuteriomethylene chloride (1 gram) was placed in a glass tube (10 mm diameter walls 2 mm thick) sealed at one end. The solution was placed under argon atmosphere and cooled with liquid nitrogen until frozen. The glass tube was then evacuated (vacuum pump) and the open end of the glass tube was sealed with a methane/oxygen torch. After the sealing process, the glass tube was allowed to warm to room temperature and was then placed into a hot ( $165 \pm 2^\circ\text{C}$  unless noted otherwise) steel bomb for 4-6 hours. Note that care should be taken at this stage of the experiment as the sealed glass tube may explode if any structural defects are present in the tube. All of the thermolysis cleanly produced two products and, in each case, the ratio of products was determined directly by integration of the signals due to  $\text{H}_a$  and  $\text{H}_b$  (see formulas (**316**) and (**317**)) in the  $^1\text{H}$  NMR spectrum of the reaction mixture. For compound (**255**) the ring opening was carried out at  $143\text{--}145^\circ\text{C}$  (3.5 hours) to avoid sigmatropic rearrangement of the outward rotation product. All experiments were carried out at least in duplicate and were found to be reproducible. To determine product stability a small

sample of each pure product (prepared from the experiments previously mentioned) was dissolved in  $C_6D_6$  and subjected to the above experimental conditions. In each case the starting material showed no signs of decomposition or rearrangement. A summary of the experimental conditions and results can be seen in Charts 1 through 5.

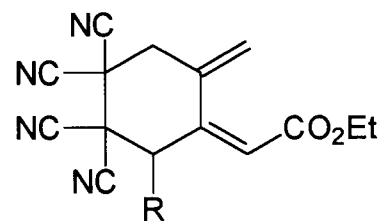
CHART 1.



255 R = H  
 257 R = Me  
 259 R = *i* - Pr  
 261 R = *c* - Hex



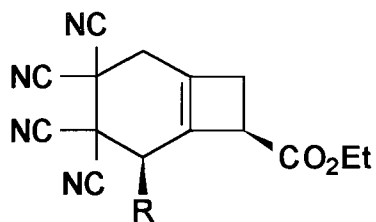
275 R = H  
 277 R = Me  
 279 R = *i* - Pr  
 281 R = *c* - Hex



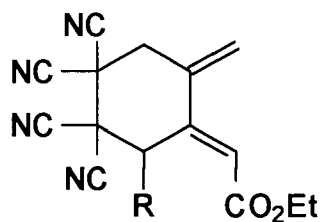
276 R = H  
 278 R = Me  
 280 R = *i* - Pr  
 282 R = *c* - Hex

<u>Expt</u>	<u>Substrate</u>	<u>Mass</u>	<u>Solvent</u>	<u>Time</u>	<u>Temp.</u>	<u>Ratio of Products</u>	
1	255	4 mg	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	16	1
2	255	4 mg	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	18	1
3	257	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.3	1
4	257	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.1	1
5	257	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.3	1
6	259	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
7	259	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4
8	259	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
9	261	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4
10	261	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.3
11	261	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4

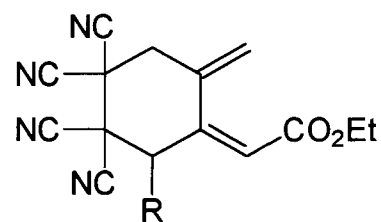
CHART 2.



256 R = Me  
 258 R = *i* - Pr  
 260 R = *c* - Hex



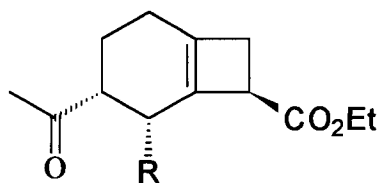
277 R = Me  
 279 R = *i* - Pr  
 281 R = *c* - Hex



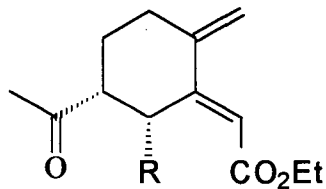
278 R = Me  
 280 R = *i* - Pr  
 282 R = *c* - Hex

<u>Expt</u>	<u>Substrate</u>	<u>Mass</u>	<u>Solvent</u>	<u>Time</u>	<u>Temp.</u>	<u>Ratio of Products</u>	
12	256	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	2.5	1
13	256	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	2.6	1
14	256	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	2.7	1
15	258	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
16	258	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4
17	260	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.5
18	260	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	1	1.4

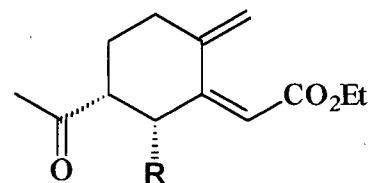
CHART 3.



11 R = Me  
 266 R = *i* - Pr  
 268 R = *c* - Hex



12 R = Me  
 285 R = *i* - Pr  
 289 R = *c* - Hex

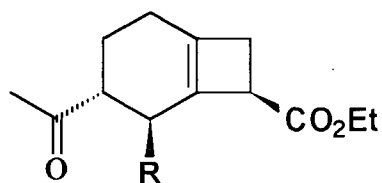


13 R = Me  
 286 R = *i* - Pr  
 290 R = *c* - Hex

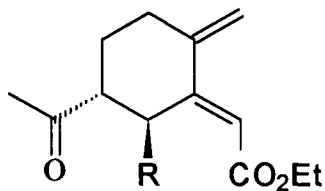
<u>Expt</u>	<u>Substrate</u>	<u>Mass</u>	<u>Solvent</u>	<u>Time</u>	<u>Temp.</u>	<u>Ratio of Products</u>	
19	11	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	10.4	1
20	11	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	11.2	1
21	266	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	4.0	1
22	266	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	3.6	1
23	266	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	4.3	1
24	268	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	3.8	1
25	268	4 mg	C <sub>6</sub> D <sub>6</sub>	6 h	165°C	3.7	1



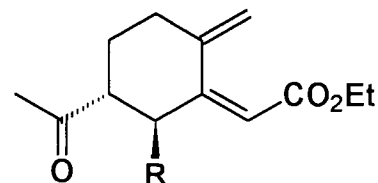
CHART 4.



14 R = Me  
 265 R = *i* - Pr  
 267 R = *c* - Hex



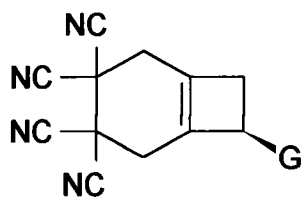
15 R = Me  
 283 R = *i* - Pr  
 287 R = *c* - Hex



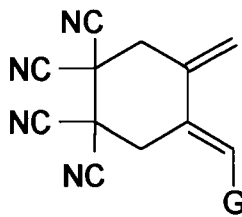
16 R = Me  
 284 R = *i* - Pr  
 288 R = *c* - Hex

<u>Expt</u>	<u>Substrate</u>	<u>Mass</u>	<u>Solvent</u>	<u>Time</u>	<u>Temp.</u>	<u>Ratio of Products</u>	
26	14	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1.0	1
27	14	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1.0	1
28	265	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.4
29	265	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.2
30	265	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.4
31	267	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.6
32	267	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.5
33	267	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	1	2.8

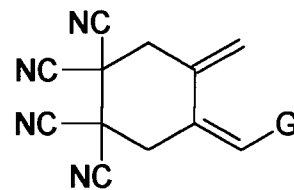
CHART 5.



255 G = - CO<sub>2</sub>Et  
 262 G = - CH<sub>2</sub>OH  
 264 G = - CO<sub>2</sub>H



275 G = - CO<sub>2</sub>Et  
 271 G = - CH<sub>2</sub>OH  
 305 G = - CO<sub>2</sub>H



276 G = - CO<sub>2</sub>Et  
 271bG = - CH<sub>2</sub>OH  
 306 G = - CO<sub>2</sub>H

<u>Expt</u>	<u>Substrate</u>	<u>Mass</u>	<u>Solvent</u>	<u>Time</u>	<u>Temp.</u>	<u>Ratio of Products</u>	
1	255	4 mg	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	16	1
2	255	4 mg	C <sub>6</sub> D <sub>6</sub>	3.5 h	145°C	18	1
34	255	4 mg	CD <sub>2</sub> Cl <sub>2</sub>	3.5h	145°C	17	1
35	262	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	100	0
36	262	4 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	100	0
37	264	0.25 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	7.3	1
38	264	0.25 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	7.4	1
39	264	0.25 mg	C <sub>6</sub> D <sub>6</sub>	4 h	165°C	7.0	1

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## V. APPENDIX

1. Appendix 1: X-ray Crystallographic Data

Compound	<b>332</b>	<b>352</b>
formula	$C_{21}H_{29}NO$	$C_{16}H_{14}N_4O_2$
formula weight	311.47	294.31
crystal system	orthorhombic	monoclinic
space group	$P2_12_12_1$	$P2_1/C$
$a(\text{\AA})$	13.1014(7)	8.604(4)
$b(\text{\AA})$	27.057(1)	19.370(3)
$c(\text{\AA})$	5.280(1)	9.633(3)
$\beta(\text{deg})$	-	104.69(3)
Z	4	4
D <sub>calc</sub> (g/cm <sup>3</sup> )	1.11	1.259
radiation	Cu-K	Cu-K
temperature (°C)	21	21
2 $\theta$ max (deg)	155.1	155.5
No reflections with $I > 3 \sigma(I)$	1640	2287
No. variables	325	200
R	0.030	0.035
R <sub>w</sub>	0.029	0.036
goodness of fit	1.86	2.58
largest residual peak (e $\text{\AA}^{-3}$ )	0.09	0.016