Synthetic Studies Towards Dictyoxetane and the Dolabellanes

A thesis presented in partial
fulfilment of the requirements

for the degree of

MASTER OF SCIENCE
in CHEMISTRY

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Abstract

Dictyoxetane (**1**) has been isolated from *Dictyota dichotoma*, a brown alga found in the Indian Ocean. It has an unusual pentacyclic structure which has not yet been synthesised. It is a diterpene which is closely related to the dolabellanes, an important class of bioactive compounds.

A stereoselective synthesis of the linearly fused cyclohept[f]indene system is described. Selective epoxidation of cyclo-octadiene (**142**), followed by hydrolysis to the diol (**143**) and oxidative cleavage allowed preparation of the dialdehyde (**141**) on large scale. Treatment of this with potassium carbonate causes an intramolecular aldol reaction to form cycloheptadiene-carboxaldehyde (**140**). An *E*- selective Wittig reaction is performed with 4-carboxybutyl-triphenylphosphium bromide, to produce the acid (**139**). This is subsequently converted to the vinyl ketone (**138**) followed by an intramolecular Diels Alder reaction to produce the desired cyclohept[f]indene (**137a**).

Utilisation of a *Z*- selective Wittig reaction produced methyl ester (**145*z***). Conversion to cyclohept[f]indene occurred via an intramolecular Diels-Alder of the subsequent vinyl ketone (**138*z***). Conversion of acid (**139**) to the methyl ester (**145**) followed by an intermolecular Diels Alder gave the *endo*- product. Subsequent attempts to cyclise this to the cyclohept[f]indene via an intramolecular Claisen reaction to give the third isomer were unsuccessful.

Cyclohept[f]indene is the backbone for dictyoxetane and can be efficiently synthesised in eight steps from 1,5-cyclo-octadiene (**142**) in a diastereoselective synthesis. This route allows for further modification of functionality to the linearly fused ring system and paves the way for further synthetic studies towards the dolabellanes.

Acknowlegements

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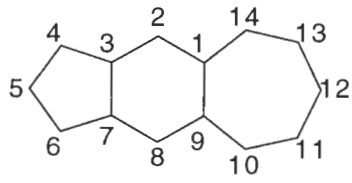
And finally to all my other friends and colleagues who supported me throughout the course of my Masters. Thanks a bunch just for being there. (I've made it!!)

List of Abbreviations

Ac	acetate
acac	2,4-pentanedione
AIBN	azodiisobutylnitrile
Am	amyl
APT	attached proton test
BHT	butylated hydroxytoluene
B.P.	boiling point
Bu	butyl
Bn	benzyl
Bz	benzoyl
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
d	day(s); doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutyl aluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
ECD	1,3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride
EDA	ethylenediamine
ee	enatiomeric excess
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
HETCOR	heteronuclear chemical shift correlation
hr(s)	hour(s)
HMPA	hexamethylphosphoramide
IMDA	intramolecular Diels-Alder
i	iso
Im	imidazole
IR	infrared
KHMDS	potassium hexamethyl disilazide

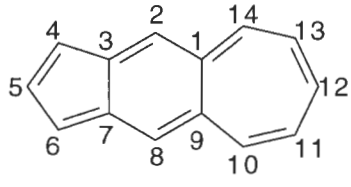
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyl disilazide
*m*CPBA	*meta*chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MeOH	methanol
min(s)	minute(s)
MOM	methoxymethyl
M.P.	melting point
Ms	mesyl (methanesulfonyl)
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NHMDS	sodium hexamethyl disilazide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium-*p*-toluenesulfonate
Pr	propyl
py	pyridine
RT	room temperature
t	tertiary; triplet (spectral)
TBAF	tetra butyl ammonium fluoride
TBS	tertiary butyldimethylsilyl
TBDPS	tertiary butyldiphenylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	tetramethylsilane
Tol	tolyl
TPS	triisopropylsulfonyl
Ts	tosyl

Nomenclature



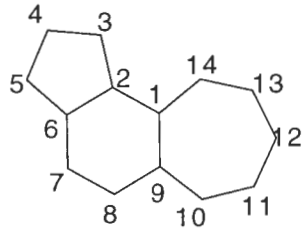
cyclohept[f]indane

The IUPAC name for the linearly fused [5,6,7] ring system shown is tricyclo[7.5.0.$0^{3,7}$]tetradecane. *Chemical Abstracts* refers to this structure as cyclohept[f]indane and the fully conjugated system is named cyclohept[f]indene.



cyclohept[f]indene

The angularly fused system, tricyclo[7.5.0.$0^{2,6}$]tetradecane is referred to as cyclohept[g]indane.

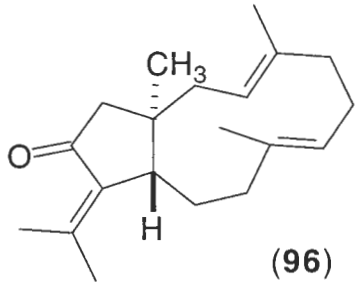


cyclohept[g]indene

Throughout this report cyclohept[f]indene refers to a linearly fused, unsaturated tricyclo[7.5.0.$0^{3,7}$]tetradecene skeleton (i.e. *not* fully conjugated). Further functionality is not differentiated by the use of this term. Cyclohept[g]indene is used in a similar manner.

Stereochemistry

Throughout this work the absolute stereochemistry of dictyoxetane and the dolabellanes are drawn according to Corey.[1] In his enatioselective synthesis of a naturally occurring dolabellatrienone, Corey observed a similar dextrorotation for compound (**96**) to that previously observed for the natural product.



(**96**)

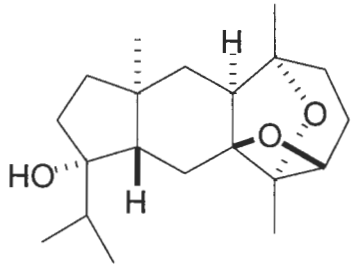
The natural product had previously been assigned the opposite absolute configuration (arbitrarily). Many of the publications relating to the isolation and synthesis of the dolabellanes are therefore believed to depict the wrong enantiomer.

1. Introduction

1.1 Dictyoxetane

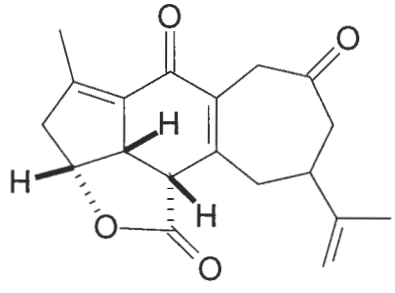
The pentacyclic diterpene dictyoxetane (**1**) is related to the dolabellanes, an important class of compounds displaying a wide range of therapeutic activity. Dictyoxetane was isolated from the cosmopolitan brown alga *Dictyota dichotoma*. This alga is widespread and has been extensively studied for therapeutic activity.

A number of other classes of diterpenes, including the dolabellanes, have been isolated from this alga.[2] Dictyoxetane was extracted from a sample of *Dictyota dichotoma* collected off the coast of India. Its structure was deduced by single crystal x-ray analysis.[3] The absolute stereochemistry of dictyoxetane is yet to be defined.



(1) dictyoxetane

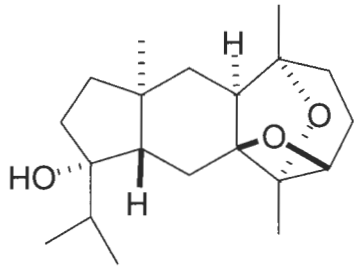
Although five, six and seven membered rings are common in natural products, the [5,6,7] linearly fused ring system is not. The only other example reported in the literature is yonarolide (**2**) which was isolated from a soft coral.[4] The structure of this norditerpenoid was determined by spectroscopic analysis, although its absolute stereochemistry has not been elucidated.



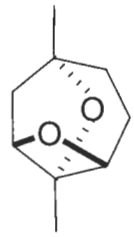
(2) yonarolide

1.1.1 Previous Synthetic Work

Previous synthetic work relating to dictyoxetane is limited to two published papers which describe the synthesis of the dioxatricyclononane moiety (**Figure 1**). The earlier work of Reinecke and Hoffman[5] published in 1995 employed an oxabicyclic ketone as the carbon skeleton and used an intramolecular S_N2 displacement of a tosylate to form the oxetane ring (**Scheme 1**).



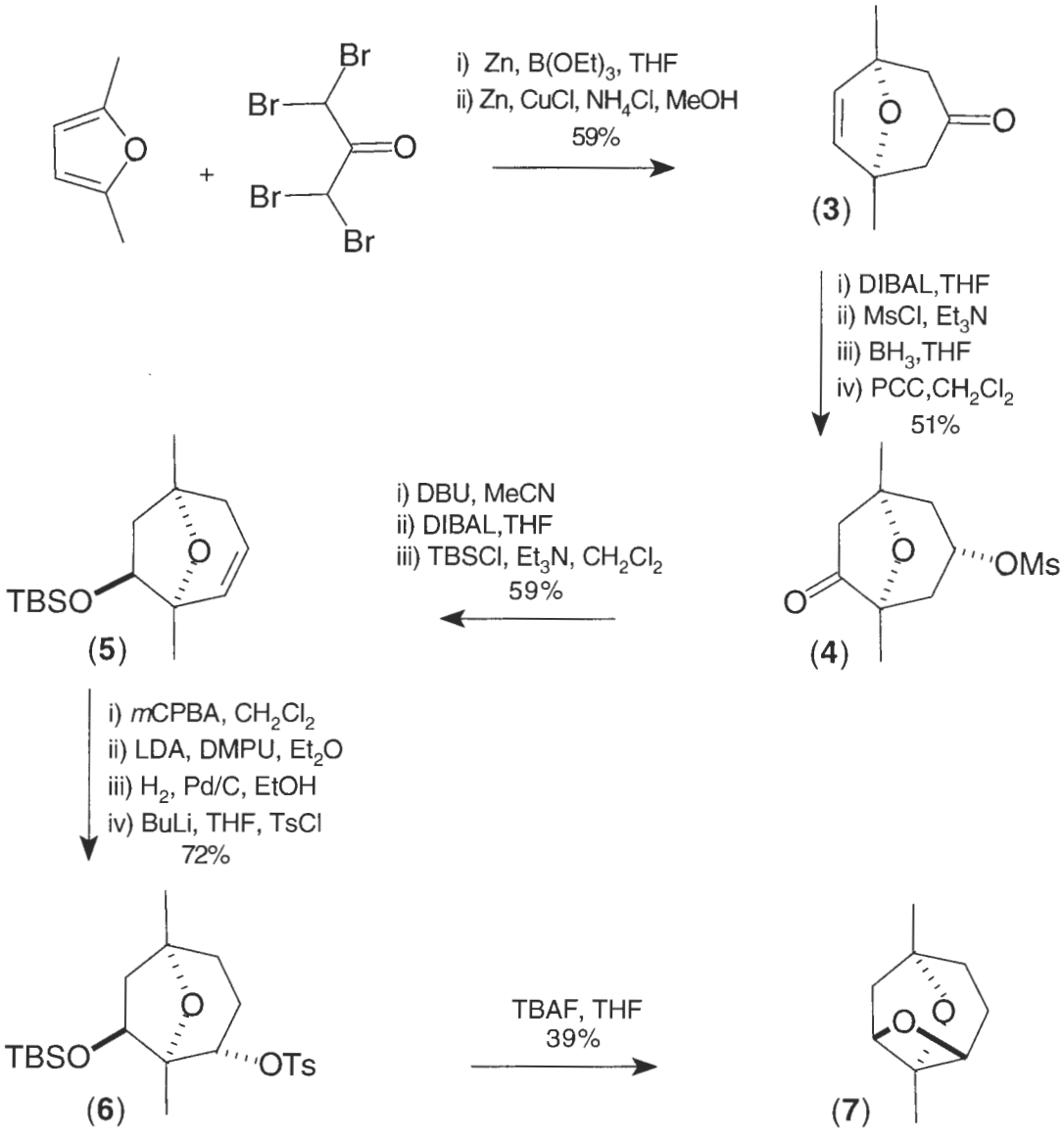
dictyoxetane



2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane

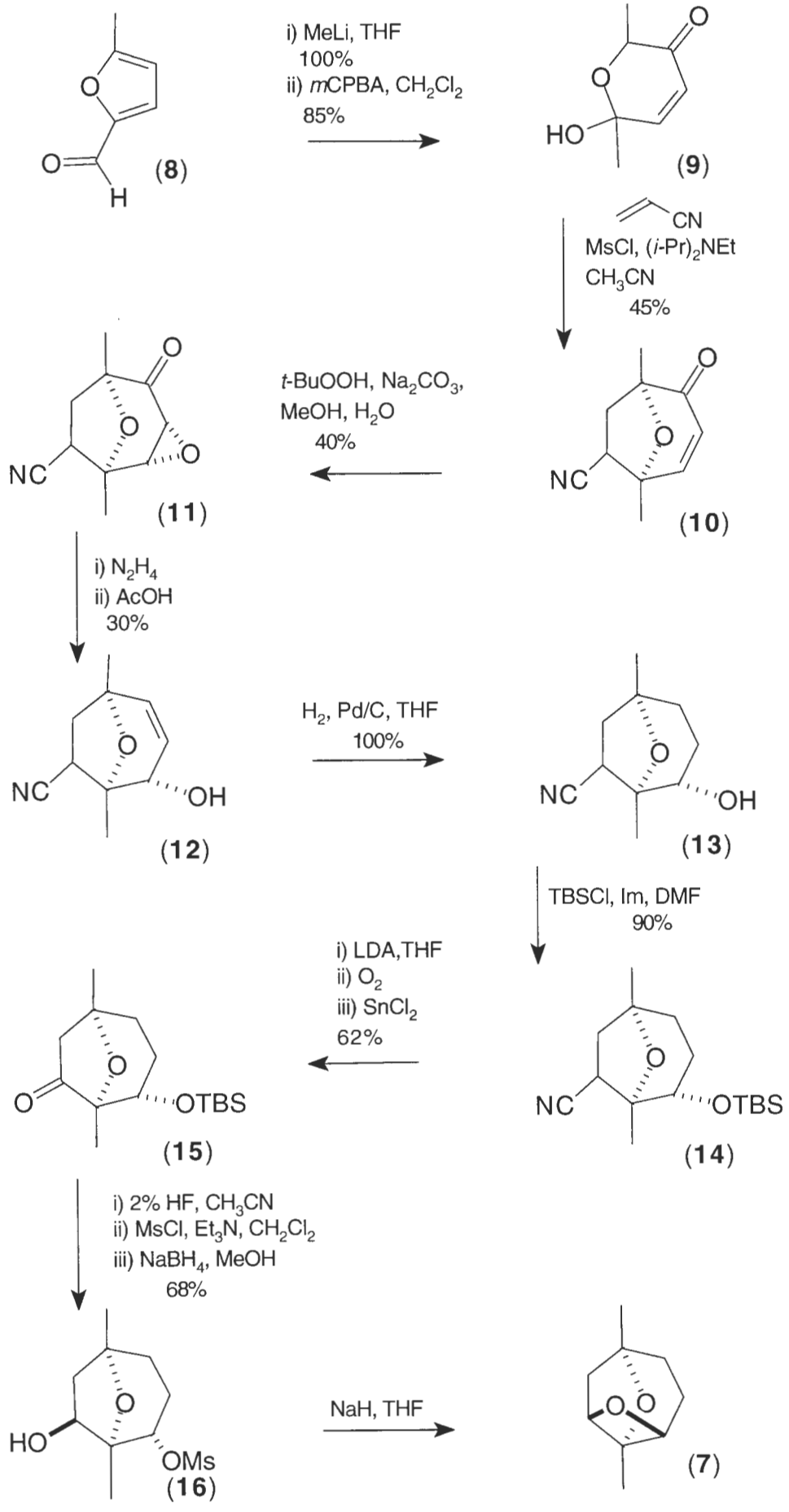
Figure 1

Bicyclic ketone (**3**) was synthesised from 2,5-dimethylfuran and 1,1,3,3-tetrabromo-2-propanone in the presence of copper and zinc powder under sonication. The resulting ketoolefin could be reduced stereoselectively to the alcohol with DIBAL. Mesylation followed by a hydroboration/oxidation gave the ketomesylate (**4**) and its regioisomer in 79% yield. Treatment with DBU gave a mixture of the two possible regioisomeric alkenes in an 8:1 ratio. Reduction with DIBAL produced the secondary alcohol which was protected (**5**) and subsequently epoxidised. The epoxide was subjected to base mediated ring opening (LDA, DMPU) to furnish the allylic alcohol. Hydrogenation followed by tosylation produced 7-*endo*-hydroxy-2-*exo*-tosylate (**6**) which was deprotected and cyclised in a single operation using TBAF to produce (**7**) as a volatile liquid in 39% yield (**Scheme 1**).



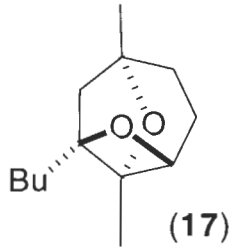
Scheme 1

The more recent work, carried out by the Heathcock group[6] employed a dipolar cycloaddition of a 3-oxidopyrylium salt with acrylonitrile to create the carbon skeleton and a similar intramolecular S_N2 displacement of a mesylate to form the oxetane ring (**Scheme 2**).

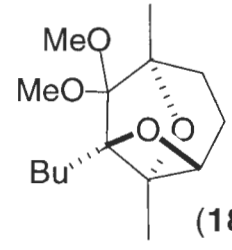

i) MeLi, THF
100%
ii) mCPBA, CH2Cl2
85%
(8)
(9)
CN
MsCl, (i-Pr)2NEt
CH3CN
45%
t-BuOOH, Na2CO3,
MeOH, H2O
40%
(10)
(11)
i) N2H4
ii) AcOH
30%
H2, Pd/C, THF
100%
(12)
(13)
TBSCl, Im, DMF
90%
i) LDA,THF
ii) O2
iii) SnCl2
62%
(14)
(15)
i) 2% HF, CH3CN
ii) MsCl, Et3N, CH2Cl2
iii) NaBH4, MeOH
68%
NaH, THF
(16)
(7)

Scheme 2

Treatment of commercially available 5-methylfurfural (**8**) with MeLi produced 2-furfurylcarbinol in quantitative yield. Oxidative rearrangement with *m*CPBA efficiently converted this to enone (**9**). Cycloadduct (**10**) was produced from (**9**) and acrylonitrile as a mixture of regioisomers (10:1, 45%). Nucleophilic epoxidation of enone (**10**) gave epoxy ketone (**11**) and subsequent Wharton transposition of (**11**) to (**12**) were both low yielding. Allylic alcohol (**12**) was hydrogenated to the saturated alcohol (**13**) which was silylated in high yield (**14**). Ketone (**15**) was obtained by oxidative decyanation of (**14**) with LDA and oxygen. Deprotection of the silyl group afforded the alcohol which was converted to the mesylate. Stereoselective sodium borohydride reduction of (**15**) gave the alcohol precursor (**16**). Treatment with NaH in refluxing THF produced the volatile tricyclic ether (**7**) which was determined only by proton NMR. Analogues of (**7**), compounds (**17**) and (**18**) were also prepared which had decreased volatility thus allowing full characterisation and stereochemical determination (**Figure 2**).



(**17**)



(**18**)

Figure 2

Although Heathcock's synthesis is more recent it is less efficient. It does exhibit similarities to Hoffman's process. Heathcock uses three steps and a [5+2] cycloaddition to produce a similar carbon skeleton to that of Hoffman's. In contrast Hoffman uses two steps and a [4+3] cycloaddition. They both use an intramolecular S_N2 displacement as the final step in the formation of the tricycle. Heathcock uses a mesylated alcohol and an alkoxide formed from the action of a strong base on an alcohol for the intramolecular displacement. Hoffman uses a tosylated alcohol with the alkoxide formed from the deprotection of a silylated alcohol. These racemic syntheses produced the dioxatricyclic component of dictyoxetane. The overall yield for Hoffman's twelve step scheme was 3%. The less efficient synthesis produced by Heathcock required fifteen steps and gave an overall yield of less than 2%. Heathcock was not able to obtain an accurate yield for the cyclisation step or fully characterise his original dioxatricycle due to volatility. Unfortunately these syntheses would appear to be unsuitable for application towards dictyoxetane, as they are not flexible enough to allow production of the tricycle annealated to another ring.

1.1.2 Biosynthesis of Dictyoxetane

Hoffman's synthesis of the dioxatricyclic core formed the basis of a biosynthetic proposal for dictyoxetane, in which a known metabolite, a dolabellane, is cyclised to produce the linearly fused [5,6,7] ring system.

The proposed biosynthetic pathway of dictyoxetane (**Figure 3**) is through the transannular cyclisation of a dolabellane (**19**), also isolated from *Dictyota dichotoma*.[5]

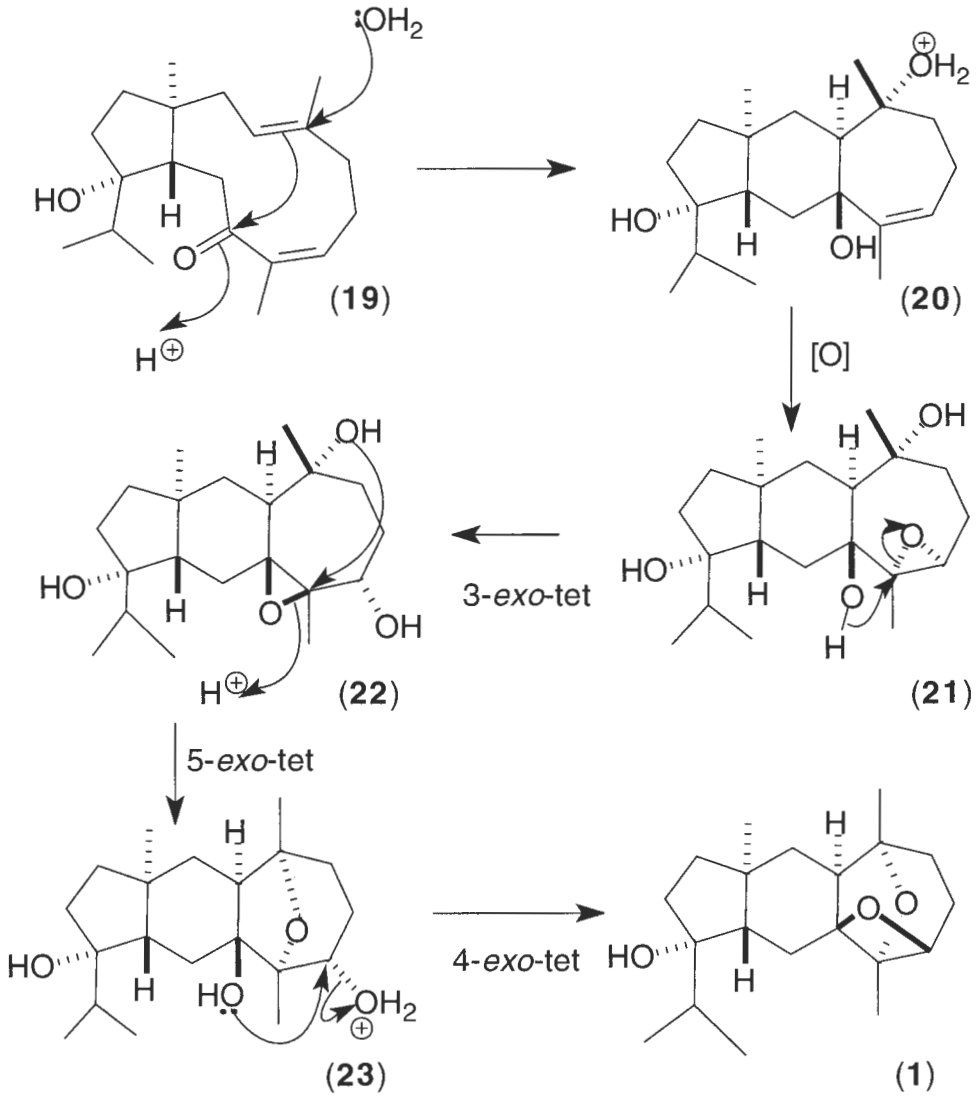
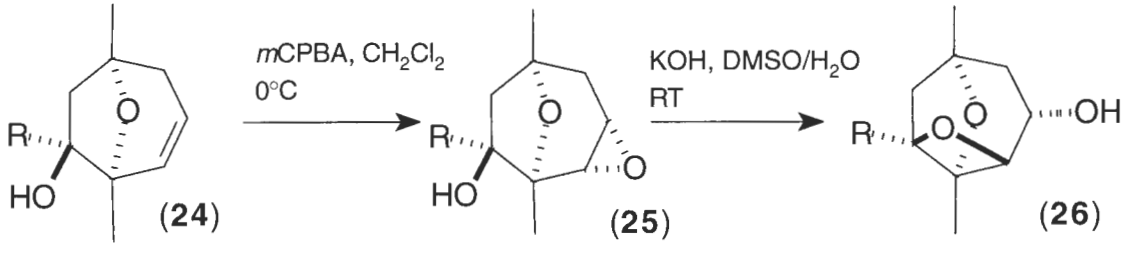


Figure 3

Thus it was proposed that the previously isolated metabolite (**19**) undergoes an acid catalysed transannular cyclisation to produce a tertiary carbocation which is trapped by addition of a water molecule from the bottom face (**20**). Epoxidation of alkene (**21**) produces (**22**) which subsequently undergoes a Payne rearrangement to produce the regioisomeric epoxide (**23**). Two successive transannular cyclisations form (**1**), completing the process.

It has been postulated that the dioxatricyclic moiety is too volatile to be biosynthesised prior to the formation of the linearly fused ring system. Hoffman and Reinecke produced evidence to support this proposal *in vitro.* Their synthesis of the oxatricyclic component of dictyoxetane and the formation of their other hydroxyoxetanes (**Scheme 3**) supports the rapid formation of the tricyclic oxetane core, under mild conditions, in high yields (80-82%).



R=H
R=Me

Scheme 3

Epoxidation of homoallylic alcohol (**24**) was carried out with *m*CPBA affording (**25**) in 75% yield (R=H) or 58% yield (R=Me). Tricyclic oxetane (**26**) was formed in high yield by the reaction of a relatively weak base with epoxyalcohol (**26**). As described above this facile cyclisation suggests that the formation of the hydroxyoxetane ring will occur readily in nature.

1.2 Proposed synthesis

A stereoselective synthesis of dictyoxetane which produces a wide variety of diastereomers and allows flexibility for further modification of structure has yet to be devised. In the review that follows, previous synthetic studies towards the dolabellanes are described. Long synthetic pathways and lack of generality make these schemes inappropriate for the production of many of these marine natural products. An alternative approach is needed. In this study, it is envisaged that a reversal of the biosynthetic pathway of dictyoxetane (**Figure 3**) employing a Grob fragmentation may lead to the production of a large number of dolabellanes (**Figure 4**).

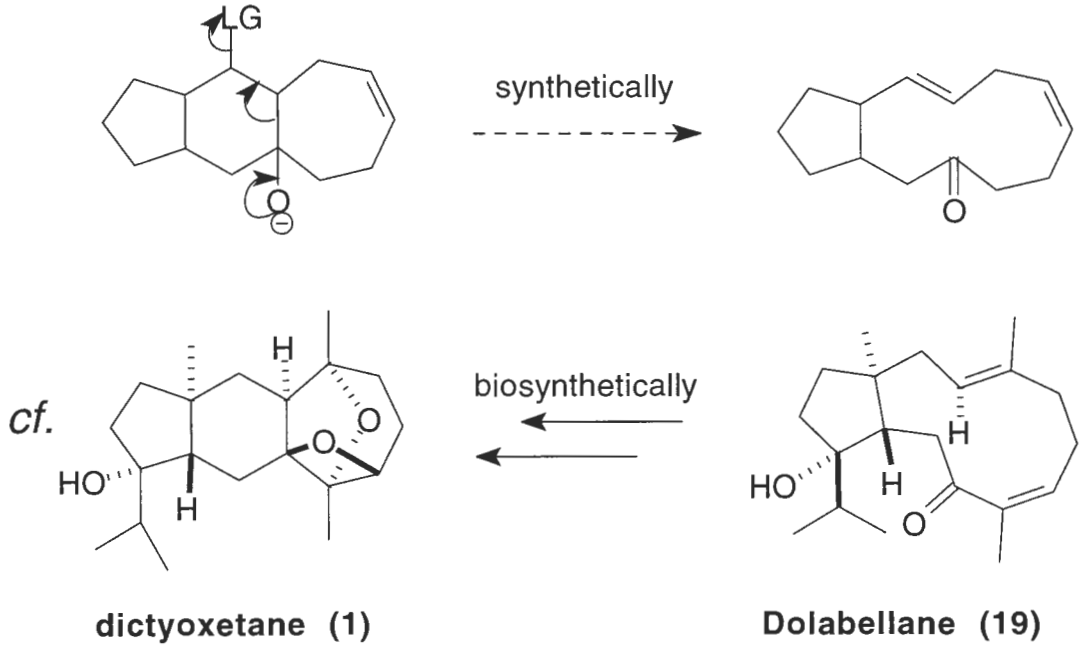
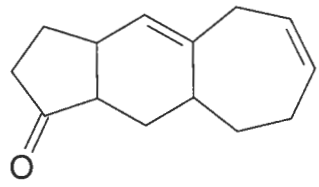


Figure 4

This phase of the project is concerned with the synthesis of cyclohept[f]indene as a model system (**Figure 5**). There are very few previous attempts at the synthesis of this linearly fused ring structure (see **Section 1.4**). The early studies were focused on the synthesis of the fully conjugated molecule. This work represents the first study towards dictyoxetane and the dolabellanes which uses the cyclohept[f]indene system as an intermediate and it is the first stereoselective synthesis of the 6-oxo-tricyclo[7.5.0.0^{3,7}]tetradeca-1,12-diene skeleton.

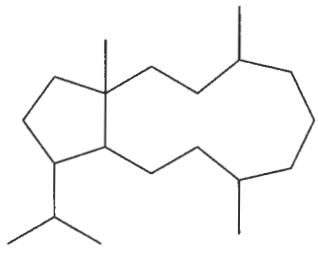


6-oxo-tricyclo[7.5.0.0^{3,7}]tetradeca-1,12-diene

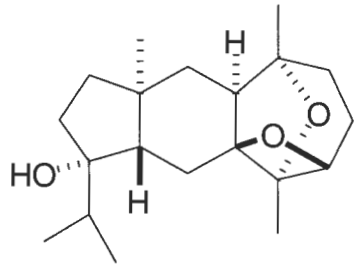
Figure 5

1.3 The Dolabellanes and Related Compounds

The dolabellane class of diterpenes contains a *trans*-fused bicyclo[9.3.0]tetradecane skeleton[7] (**Figure 6**). Members of this important class of compounds were first isolated from the sea hare *Dolabella californica* in 1980.[8]



dolabellane skeleton



dictyoxetane

Figure 6

Many marine ecosystems are in a delicate equilibrium because the organisms are in constant competition for food and light. There are a large number of predators which these organisms need to defend themselves from. Hard external skeletons, spines and colours are prominent deterents but chemical defences, such as the dolabellanes, are also important.[9] The sea hare is known to store algal metabolites, many of which are important defence chemicals.

Dolabellanes have since been isolated from the algae on which the hare feeds. These algae were used traditionally in the treatment of diseases now known to be caused by viruses, bacteria and fungi. Recent reports have confirmed activity against microbes for some of these diterpenes.[10]

The brown alga *Dictyota dichotoma* is a rich source of a variety of biologically active compounds. Extracts from this alga have been shown to exhibit cytotoxic, antibacterial, antifungal and antiviral activity. A further therapeutic effect is antagonism of vasopressin at the V_1 receptors.[11] Vasopressin is an hormone released from the posterior pituitary in response to decreased blood pressure and volume. Constriction of blood vessels is mediated by the action of vasopressin on V_1 receptors. Antagonism at these receptors leads to dilatation of blood vessels and increased diuresis which in turn causes a reduction in blood pressure and volume.

The antibacterial properties of *Dictyota dichotoma* have been studied by Saleh *et al.*[10] Various organic solvents were used to extract components from the alga and these were tested against both gram positive and gram negative bacteria. Subsequently a variety of other microbes; worms, molluscs, yeasts and fungi, were also tested. This study showed a significant antimicrobial effect against helminthics and bacteria, including common human pathogens such as *Pseudommonas aeruginosa*, *Escheria coli* and *Staphlococcus aureus.* No antifungal activity was demonstrated in this study, although *Candida albicans* was the only commonly occuring pathogenic fungi tested. This study did, however, suggest that these extracts were worth persuing as a potential source of pharmacologically active substances.

Other studies[8,12,13] also found antibacterial and antifungal activity in a variety of *dictyota* extracts. The most active constituents of these extracts are the dolabellanes, which are almost exclusively found in marine organisms.[14] By definition dolabellanes have a *trans* fused ring junction. All natural products incorporating this system so far have been isolated from marine organisms, however, similar compounds, with an unsaturated ring junction have been isolated from terrestrial liverworts.[7] Many of the dolabellanes have activity against bacteria, viruses and tumours.[8] The mode of action of these compounds is yet to be established.

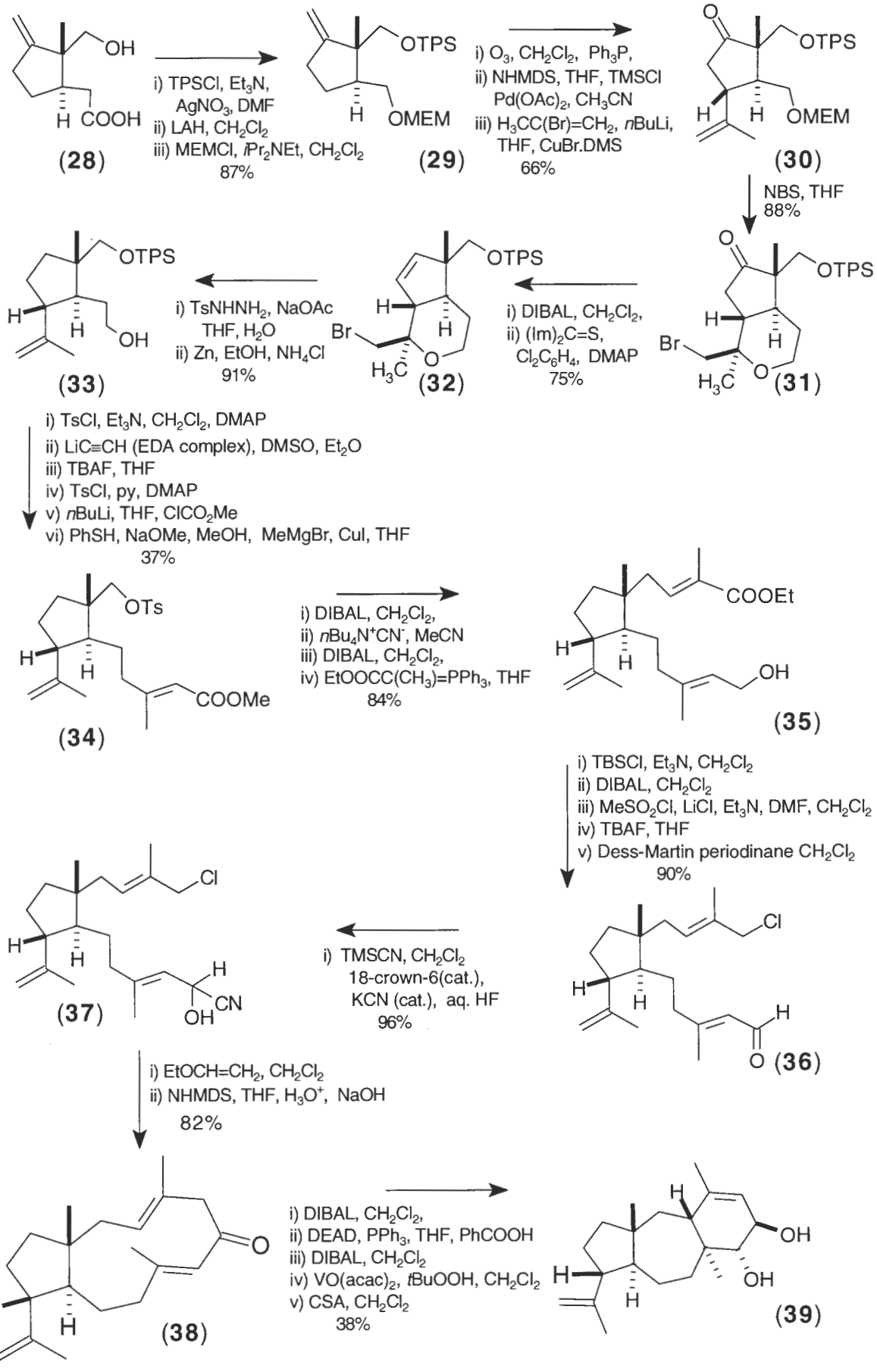
1.3.1 Previous Synthetic Approaches to the Dolabellanes

(See nomenclature *pxiii* for definition of stereochemistry)

Synthetic studies towards the dolabellane class of diterpenes has attracted wide interest. Since a review of this area has not yet appeared in the literature an overview is provided here.

Williams and Coleman[15-18] published four communications of synthetic studies towards the dolabellanes, including the first total synthesis of neodolabellenol (**27**).[18] Neodolabellanol is not strictly a dolabellane, although it has the same bicyclic tetradecane skeleton. The first of these reports Williams *et al*[16] was concerned with the synthesis of a dolabellane which was subsequently converted to a dolastane in a biomimetic approach.

Bis-silylation of hydoxy-carboxylic acid (**28**) (derived from 9,10-dibromocamphor in enatiomerically pure form) and LAH reduction of the silyl ester gave a primary alcohol which was protected to give (**29**). The exocyclic methylene group was cleaved to form the ketone which was subsequently oxidised to the enone. Compound (**30**) was formed by conjugate addition to the enone. Treatment of (**30**) with NBS gave the tetrahydropyran (**31**), a reaction which was carried out to protect the neighbouring olefin. The carbonyl was reduced to the β-alcohol, which underwent elimination on treatment with (thiocarbonyl)diimidazole. The resulting bicyclic alkene (**32**) underwent diimide reduction and deprotection of the hydroxy alkene gave the primary alcohol (**33**). Trisubstituted olefin (**34**) was produced in 25 % yield over 6 steps and contains the required C_6-C_{10} chain of the dolabellanes. DIBAL reduction of (**34**) to the alcohol was followed by cyanide displacement of the tosylate. Another DIBAL reduction to the aldehyde allowed a Wittig olefination with the ylide $EtOOCC(CH_3)=PPh_3$ affording (**35**), which contains the remaining carbons required for the dolabellane skeleton. Standard functional group chemistry was used to convert (**35**) to (**36**) in five steps. The key cyanohydrin (**37**) was formed from α,β-unsaturated aldehyde (**36**) by reaction with TMSCN. Formation of the ethoxyethyl ether then deprotonation provided an acyl anion equivalent for efficient ring closure via S_N2 displacement of the chloride. The resulting dolabellane (**38**) was reduced to the alcohol, epimerised and subsequently converted to the epoxide to allow transannular cyclisation to the desired dolastane (**39**) (**Scheme 4**).

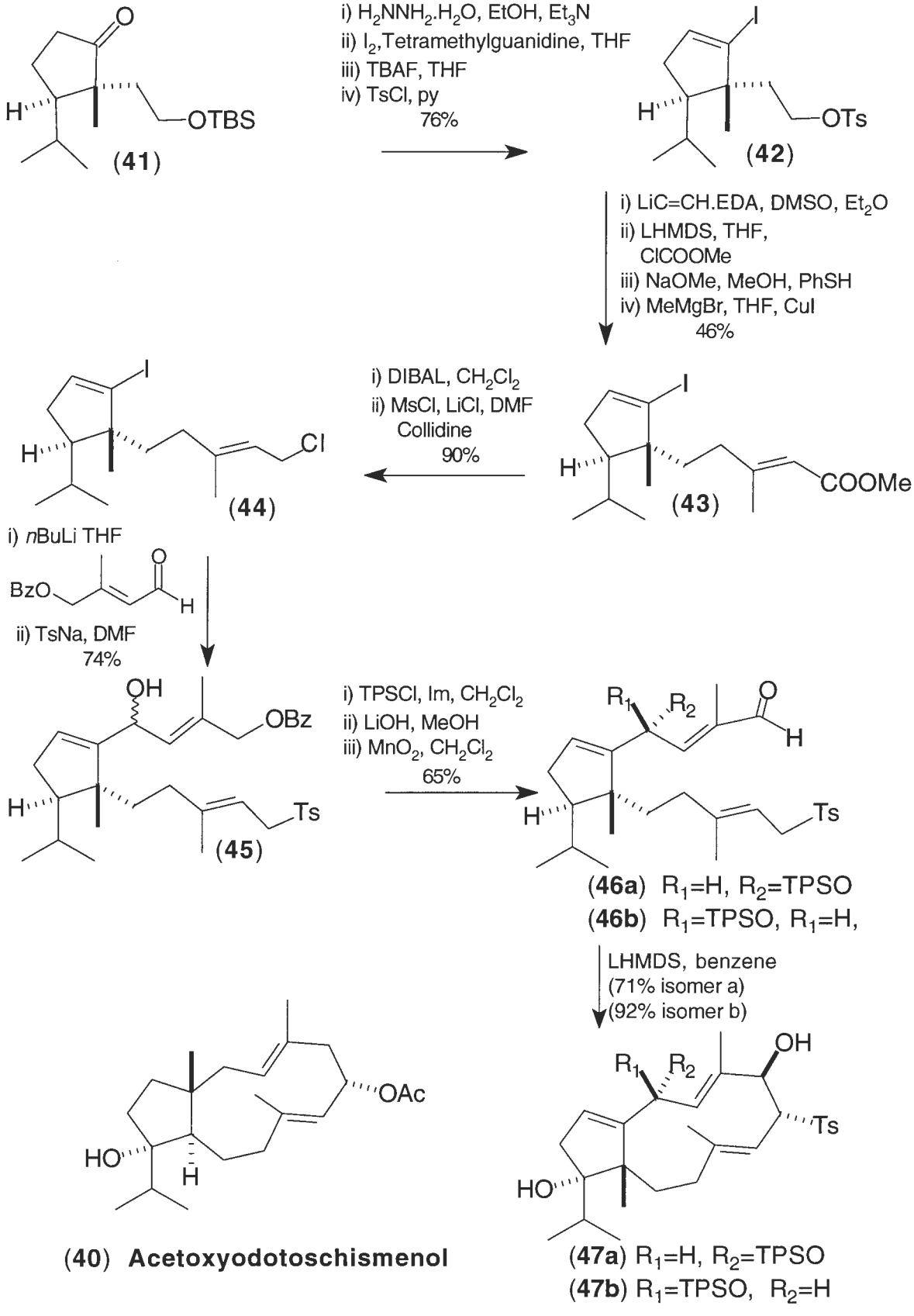

OH
H COOH
(28)
i) TPSCl, Et3N, AgNO3, DMF
ii) LAH, CH2Cl2
iii) MEMCl, iPr2NEt, CH2Cl2
87%
OTPS
H OMEM
(29)
i) O3, CH2Cl2, Ph3P,
ii) NHMDS, THF, TMSCl
Pd(OAc)2, CH3CN
iii) H3CC(Br)=CH2, nBuLi, THF, CuBr.DMS
66%
O
OTPS
H H OMEM
(30)
NBS, THF
88%
O
OTPS
Br H H
H3C O
(31)
i) DIBAL, CH2Cl2,
ii) (Im)2C=S, Cl2C6H4, DMAP
75%
OTPS
H H
Br H
H3C O
(32)
i) TsNHNH2, NaOAc THF, H2O
ii) Zn, EtOH, NH4Cl
91%
OTPS
H H OH
(33)
i) TsCl, Et3N, CH2Cl2, DMAP
ii) LiC≡CH (EDA complex), DMSO, Et2O
iii) TBAF, THF
iv) TsCl, py, DMAP
v) nBuLi, THF, ClCO2Me
vi) PhSH, NaOMe, MeOH, MeMgBr, CuI, THF
37%
OTs
H H
COOMe
(34)
i) DIBAL, CH2Cl2,
ii) nBu4N+CN-, MeCN
iii) DIBAL, CH2Cl2,
iv) EtOOCC(CH3)=PPh3, THF
84%
COOEt
H H
OH
(35)
i) TBSCl, Et3N, CH2Cl2
ii) DIBAL, CH2Cl2
iii) MeSO2Cl, LiCl, Et3N, DMF, CH2Cl2
iv) TBAF, THF
v) Dess-Martin periodinane CH2Cl2
90%
Cl
H H
H
O (36)
i) TMSCN, CH2Cl2
18-crown-6(cat.),
KCN (cat.), aq. HF
96%
Cl
H H
H
CN
OH
(37)
i) EtOCH=CH2, CH2Cl2
ii) NHMDS, THF, H3O+, NaOH
82%
O
H H
(38)
i) DIBAL, CH2Cl2,
ii) DEAD, PPh3, THF, PhCOOH
iii) DIBAL, CH2Cl2
iv) VO(acac)2, tBuOOH, CH2Cl2
v) CSA, CH2Cl2
38%
H
OH
H OH
H
(39)

Scheme 4

Thus the enantiomer of a naturally occuring dolastane was synthesised in a 34 step sequence with an overall yield of 3%. Synthetic (**39**) exhibited an optical rotation with a similar value but opposite sign to the natural product.

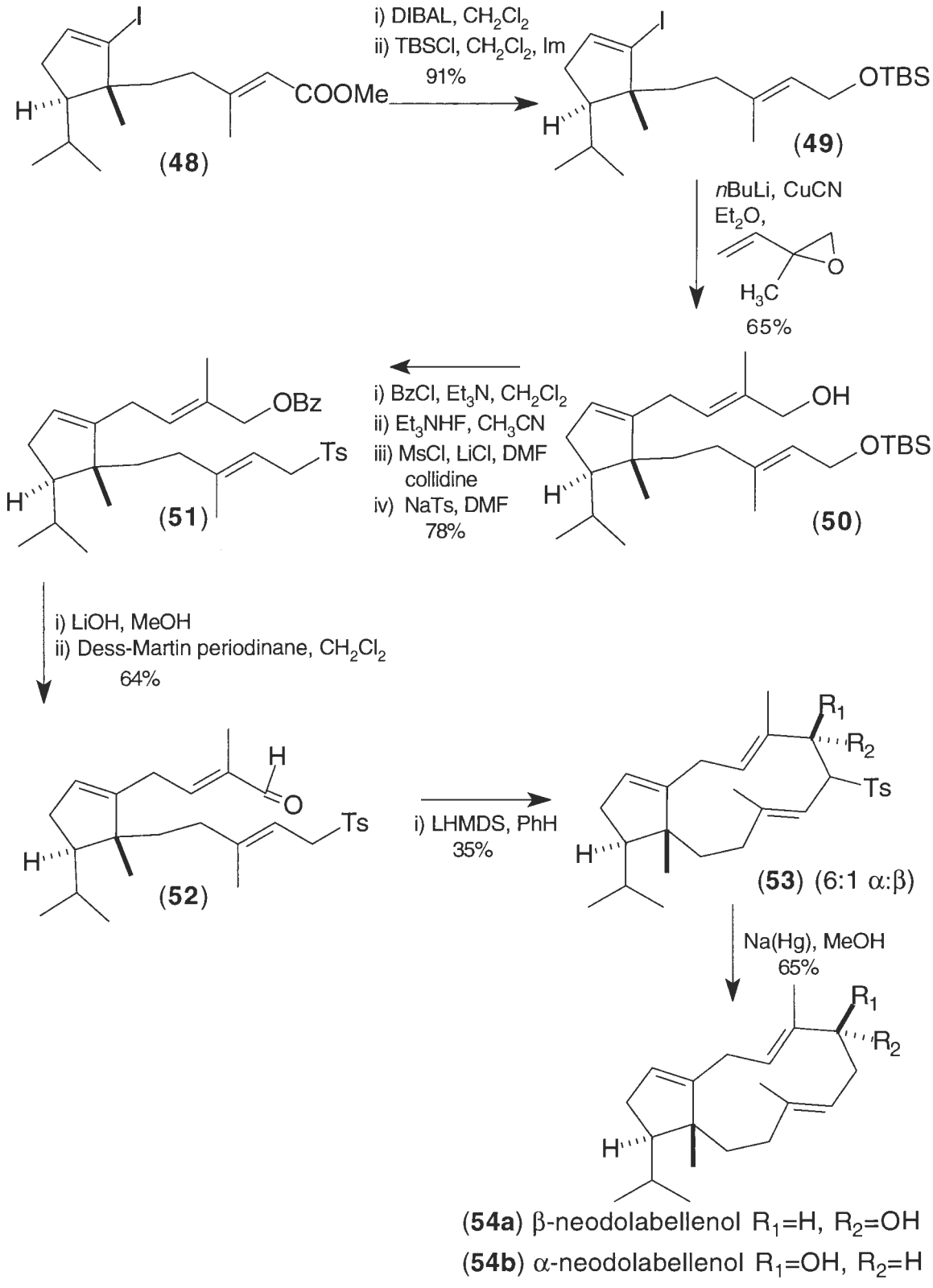
In a shorter racemic route towards acetoxyodontoschismenol (**40**), Williams *et al* [15] performed an intramolecular condensation of an α-sulfonyl carbanion with an α,β-unsaturated aldehyde to produce two novel diterpenes of the dolabellane class in sixteen steps with an overall yield of 14% (**Scheme 5**).

The substituted cyclopentanone (**41**) was synthesised from 2-methyl-2-cyclopentenone. Treatment of its hydrazone with iodine and tetramethylguanidine, followed by desilylation and tosylation, afforded the vinylic iodide (**42**). Nucleophilic displacement of the sulfonate with lithium acetylide followed by conversion to the α,β-acetylenic ester allowed conjugate addition with benzenethiolate, which gave exclusively the *Z*-β-phenylthio-α,β-unsaturated ester. Copper catalysed addition of methyl magnesium bromide produced ester (**43**) which underwent DIBAL reduction to afford the alcohol and subsequent transformation to the chloride (**44**) was carried out under standard conditions. Selective metal-halogen exchange of the iodide was accomplished with *n*-BuLi at low temperature without affecting the chloride moiety. A 1:1 ratio of diastereomeric alcohols (**45**) was produced by displacement of the chloride with sodium tolylsulfinate. The diastereomers were separated after formation of the TBPS ethers. Saponification followed by oxidation gave the aldehydic sulfones (**46**) which were cyclised to form (**47**) on reaction with the strong base LHMDS. Lower yields were obtained with the cyclisation of isomer (**46**), presumably due to unfavourable steric effects of the protecting group in the transition state.


i) $H_2NNH_2.H_2O$, EtOH, Et_3N
ii) I_2,Tetramethylguanidine, THF
iii) TBAF, THF
iv) TsCl, py
76%
(41)
(42)
i) LiC=CH.EDA, DMSO, Et_2O
ii) LHMDS, THF, ClCOOMe
iii) NaOMe, MeOH, PhSH
iv) MeMgBr, THF, CuI
46%
(43)
i) DIBAL, CH_2Cl_2
ii) MsCl, LiCl, DMF
Collidine
90%
(44)
i) *n*BuLi THF
ii) TsNa, DMF
74%
(45)
i) TPSCl, Im, CH_2Cl_2
ii) LiOH, MeOH
iii) MnO_2, CH_2Cl_2
65%
(46a) R_1=H, R_2=TPSO
(46b) R_1=TPSO, R_1=H,
LHMDS, benzene
(71% isomer a)
(92% isomer b)
(40) Acetoxyodotoschismenol
(47a) R_1=H, R_2=TPSO
(47b) R_1=TPSO, R_2=H

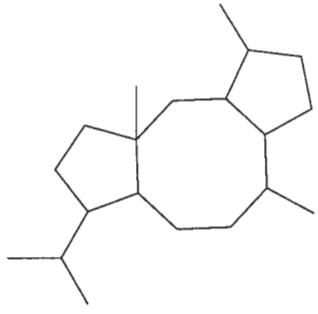
Scheme 5

Modifications to this strategy led to the total synthesis of both C-20 epimers of neodolabellenol.[18] The previously synthesised methyl ester (**48**) was reduced to the primary alcohol and subsequently protected as the silyl ether (**49**). Metal-halogen exchange, was followed by the addition of 3,4-epoxy-3-methyl-1-butene to give a separable 7:1 mixture of *E*- and *Z*- allylic alcohols with the desired *E*- alcohol (**50**) as the major product. Subsequent steps involved protection of the primary alcohol and converting the OTBS group to the sulfone (**51**). Deprotection of the benzoate to the alcohol then oxidation to the aldehyde (**52**) ensured cyclisation on reaction with a relatively strong base. A Julia condensation was successful for the production of the macrocycle (**53**) but was low yielding (25-35%) and gave a mixture of epimers in a 6:1 ratio. Desulfonation gave the desired neodolabellanol (**54a:54b**) as a separable mixture of diastereoisomers in an 11 step racemic synthesis with an overall yield of 7% (**Scheme 6**). Spectral data for α-neodolabellanol matched those of the natural product.


i) DIBAL, CH_2Cl_2
ii) TBSCl, CH_2Cl_2, Im
91%
(48)
(49)
*n*BuLi, CuCN
Et_2O,
H_3C
65%
i) BzCl, Et_3N, CH_2Cl_2
ii) Et_3NHF, CH_3CN
iii) MsCl, LiCl, DMF
collidine
iv) NaTs, DMF
78%
(50)
(51)
i) LiOH, MeOH
ii) Dess-Martin periodinane, CH_2Cl_2
64%
(52)
i) LHMDS, PhH
35%
(53) (6:1 α:β)
Na(Hg), MeOH
65%
(54a) β-neodolabellenol R_1=H, R_2=OH
(54b) α-neodolabellenol R_1=OH, R_2=H

Scheme 6

Another recent paper reported by Williams *et al*,[17] utilised transannular cyclisations of the dolabellane framework to produce the fusicoccane skeleton (**Figure 7**). The fusicoccanes are naturally occuring compounds which, like dictyoxetane and the dolastanes are postulated products of a stereocontrolled transannular cyclisation of the dolabellanes. Williams' synthetic studies towards these compounds involved acid catalysed ring closure of a dolabellane.

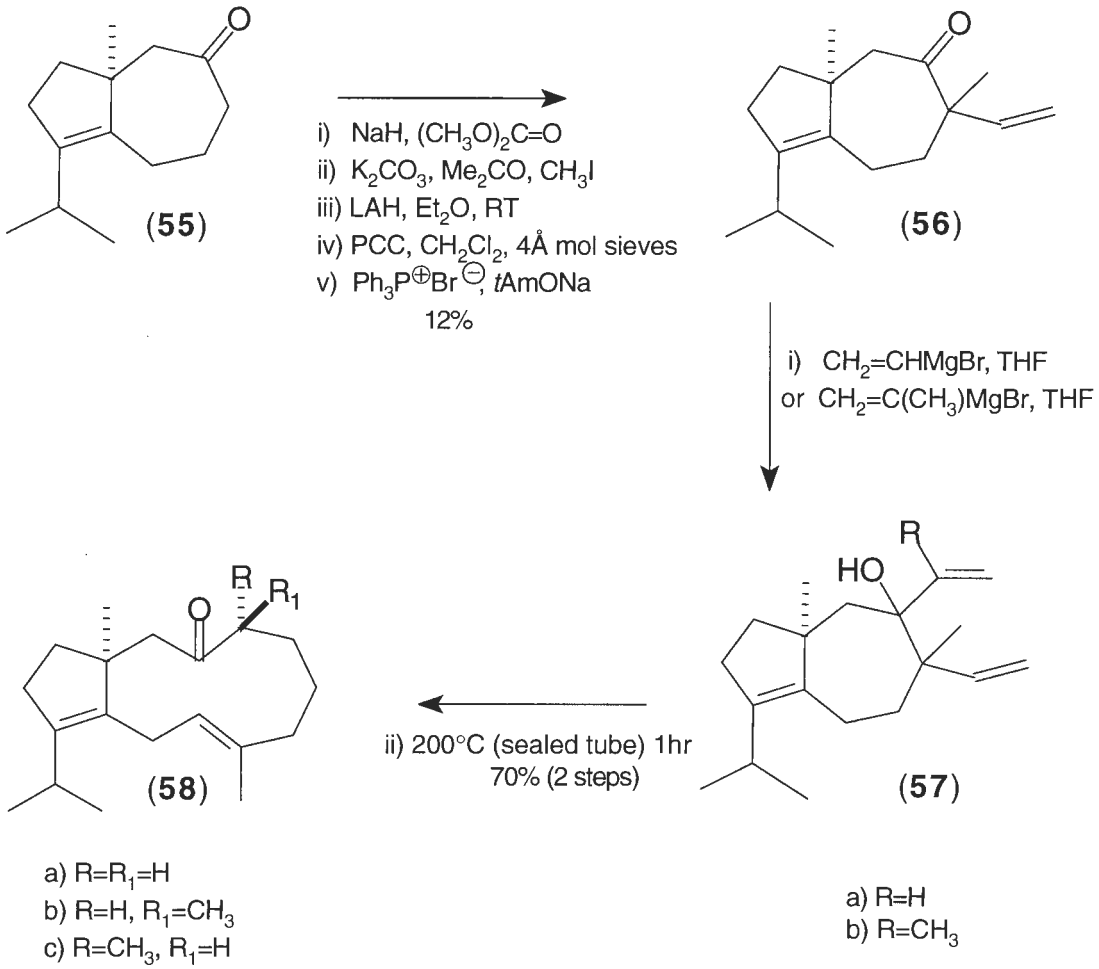


Fusicoccane skeleton

Figure 7

An oxy-Cope rearrangement was reported to produce the bicyclo[9.3.0]tetradecane system in 8% overall yield by Mehta *et al*[19] (**Scheme 7**).

Enantiomerically pure bicyclic ketone (**55**) was formed from (R)-limonene in *ca* 8 steps. Regioselective α-substitution of ketone (**55**) followed by esterification afforded a diastereomeric mixture of products (2:3). Formation of the keto-aldehyde followed by selective methylation of the aldehyde group gave (**56**). A subsequent Grignard reaction with either vinyl magnesium bromide or isopropenyl magnesium bromide produced (**57a**) and (**57b**) respectively. Thermal oxy-Cope rearrangement gave the dolabellane enones (**58a**, **58b**, **58c**). The diastereomers could be separated and equilibrated with sodium methoxide-methanol to give a single diastereomer which could not be determined. This synthesis produces the required skeleton in a short sequence but the low yields encountered converting ketone (**55**) to the vinylic compound (**56**) render it inefficient.

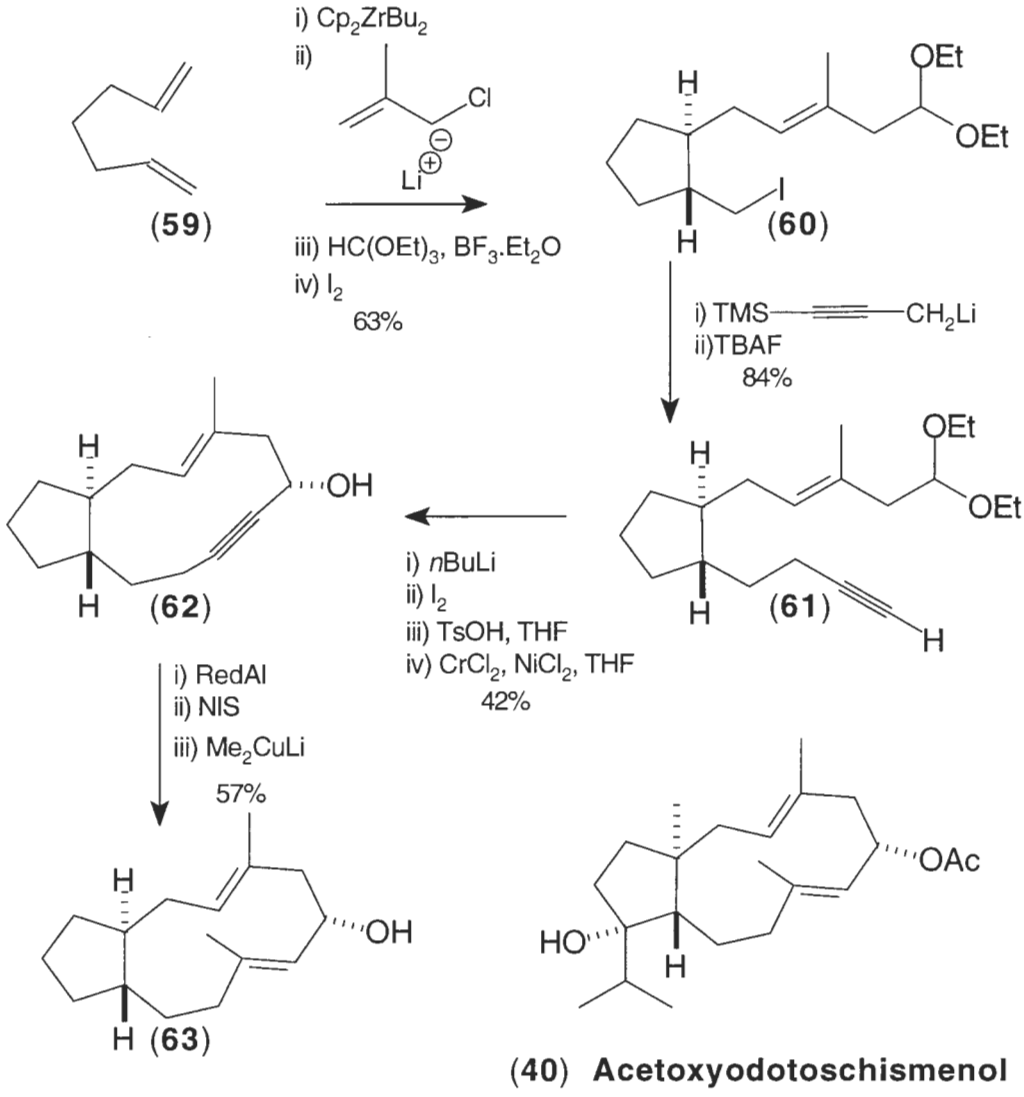


a) $R=R_1=H$
b) $R=H$, $R_1=CH_3$
c) $R=CH_3$, $R_1=H$

a) R=H
b) $R=CH_3$

Scheme 7

Luker and Whitby have reported two similar model studies towards the dolabellane skeleton.[20] Both produce racemic material. The first of these was towards the natural product acetoxyodotoschismenol which gave a 12% overall yield of bicyclic system (**63**) in 13 steps (**Scheme 8**).

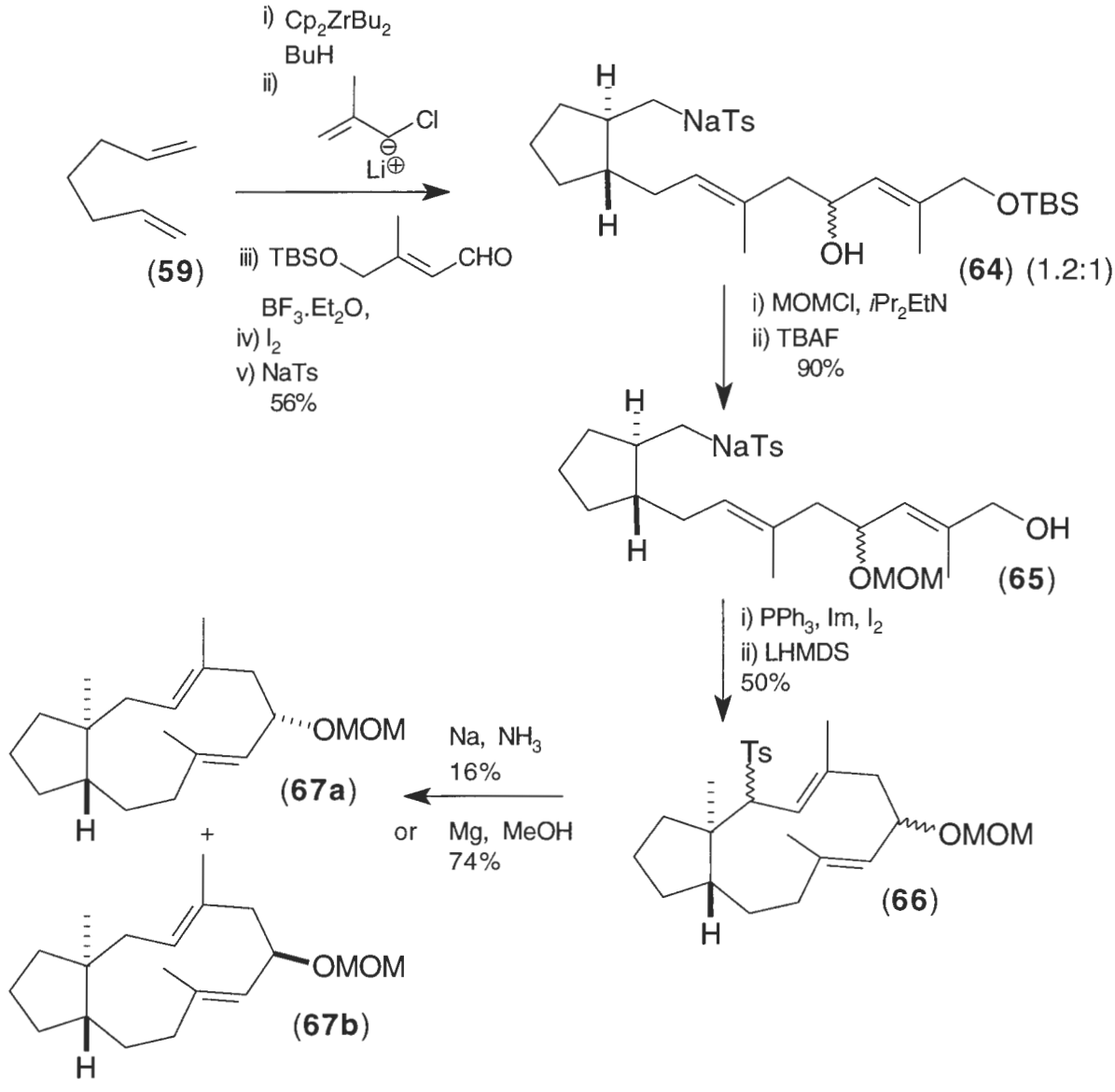


(40) Acetoxyodotoschismenol

Scheme 8

Thus cyclisation of 1,6-heptadiene (**59**) was mediated by zirconocene(1-butene) to form a *trans*-zirconacyclopentane. Insertion of lithiumchloromethallylide followed by reaction with triethylorthoformate and an iodinolytic work up produced compound (**60**). Homologation with 3-lithio-1-(trimethylsilyl)-1-propyne followed by desilylation gave alkyne (**61**) which was converted to the alkynyl iodide then to the iodo-aldehyde. Subsequent cyclisation using an intramolecular Nozaki - Hiyama reaction mediated by Cr(II) produced a single diastereoisomer of the acetylenic alcohol (**62**). The alkyne was converted to the substituted alkene (**63**) through a hydroalumination-iodination procedure.

Slight modifications to this strategy furnished a better overall yield of 19% over 10 steps but is not stereoselective (**Scheme 9**).

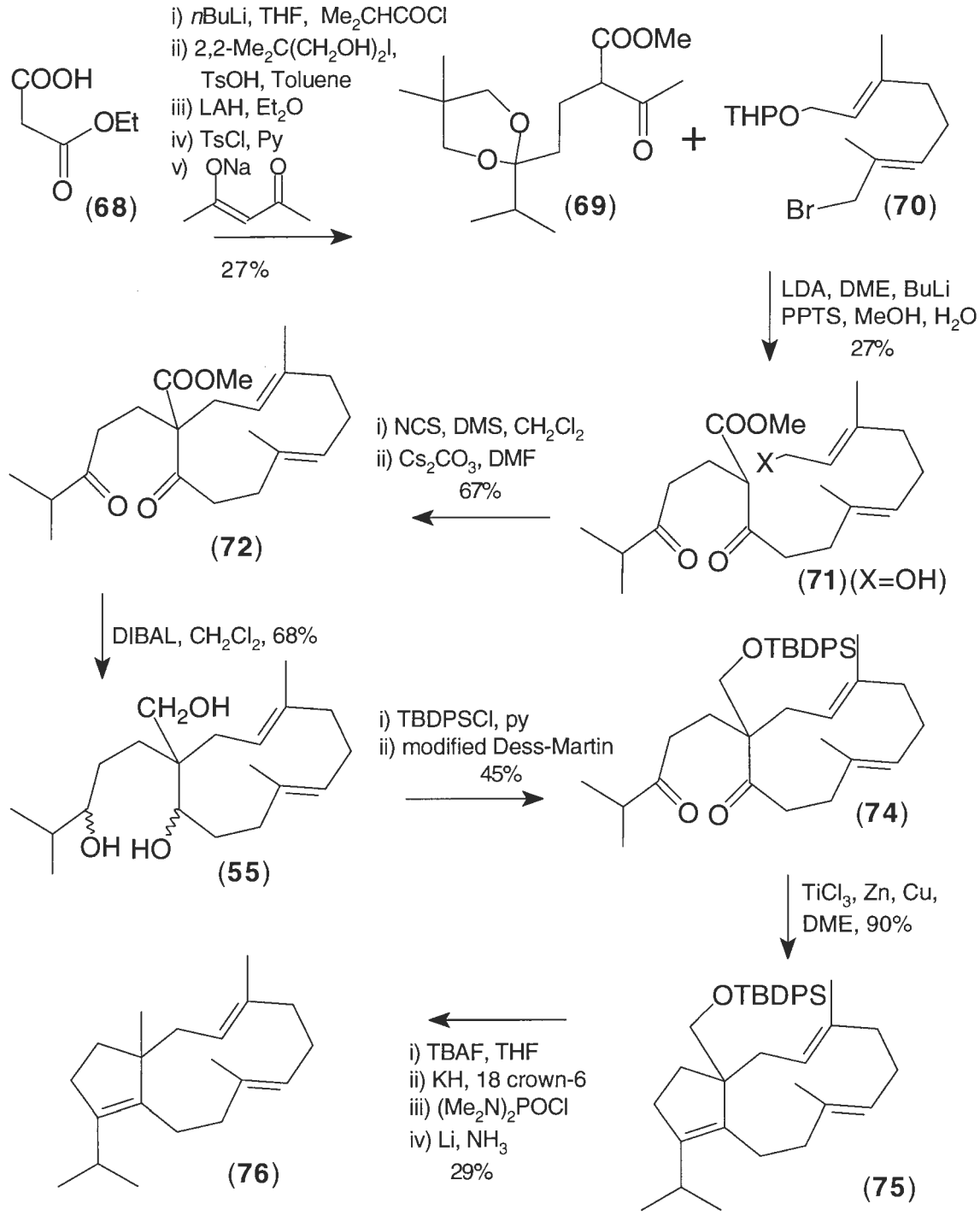


Scheme 9

The first two steps were the same as the previous synthesis. Lewis acid catalysis with the methallyl zirconocene complex afforded (**64**) in a 1.2:1 diastereomeric ratio following reaction with 4-TBSO-3-methyl-2-butenal, an iodinolytic work up and formation of the sulfone. Simple protection and deprotection steps allowed formation of the allylic alcohol (**65**) which was converted to the allylic iodide then cyclised to give (**66**) on addition of a strong base which caused the formation of the α-sulfonyl carbanion. Two different types of desulfonation were tried. Na / NH_3 gave good stereoselectivity (**67a:67b**) (20:1) but was very low yielding as one diastereomer was destroyed. Using Mg / MeOH gave higher yields but low stereoselectivity (1:1.6).

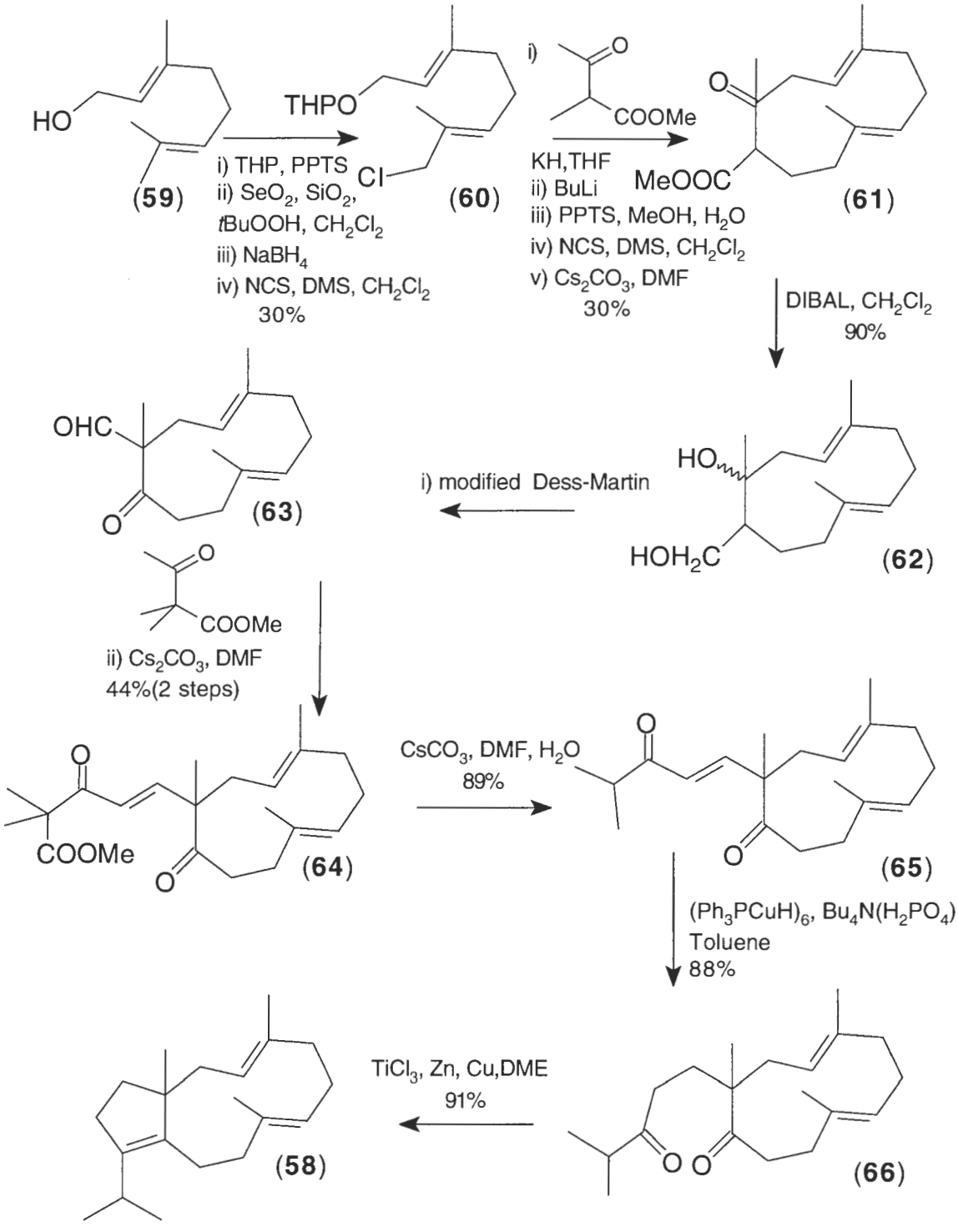
δ-Araneosene (**76**) has been synthesised from geraniol in two different ways, in racemic syntheses by Luzi.[21] This compound is not strictly a dolabellane (*cf,* neodolabellanol (**54b**)), due to unsaturation at the ring junction, but it has the same tetradecane ring system.

Ethyl hydrogen malonate (**68**) was converted to the β-keto ester (**69**) in five steps. The dianion formed from (**69**) reacted with (**70**) (synthesised from geraniol) to produce (**71**) (X=OH) after removal of the protecting group. The derived allylic chloride (**71**) (X=Cl) underwent ring closure upon treatment with Cs_2CO_3 to give (**72**) which was reduced to the triol (**73**) and the primary alcohol was selectively protected. The resulting diol was oxidised to the diketone (**74**) by a *t*butoxy modified version of Dess-Martin periodinane. The reductive coupling of the 1,5-dicarbonyl compound produced the desired skeleton (**75**) from which the (**76**) was obtained in 4 steps with an overall yield of 29% (**Scheme 10**).


i) nBuLi, THF, Me2CHCOCl
ii) 2,2-Me2C(CH2OH)2I,
TsOH, Toluene
iii) LAH, Et2O
iv) TsCl, Py
v) ONa O
27%
COOH
OEt
O
(68)
COOMe
O
O
O
(69)
+
THPO
Br
(70)
LDA, DME, BuLi
PPTS, MeOH, H2O
27%
COOMe
X
O O
(71)(X=OH)
i) NCS, DMS, CH2Cl2
ii) Cs2CO3, DMF
67%
COOMe
O O
(72)
DIBAL, CH2Cl2, 68%
CH2OH
OH HO
(55)
i) TBDPSCl, py
ii) modified Dess-Martin
45%
OTBDPS
O O
(74)
TiCl3, Zn, Cu,
DME, 90%
OTBDPS
(75)
i) TBAF, THF
ii) KH, 18 crown-6
iii) (Me2N)2POCl
iv) Li, NH3
29%
(76)

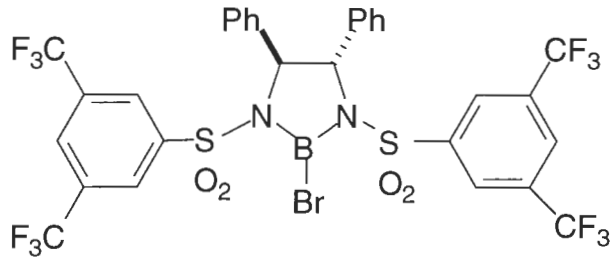
Scheme 10

The same workers undertook further investigation to shorten the synthesis and improve efficiency. Geraniol (**77**) was protected, oxidised with SeO_2 and subsequently reduced with $NaBH_4$ to produce the monoprotected diol. The allylic chloride (**78**) was prepared and used as an alkylating agent for the reaction with methyl-2-methyl-3-oxo-butanoate. Deprotection gave the allylic alcohol which was converted to the corresponding chloride, in preparation for a $CsCO_3$ mediated intramolecular β-keto ester alkylation to form (**79**). DIBAL reduction of (**79**) gave a mixture of diols (**80**) which could be oxidised to the keto-aldehyde (**81**). Crossed aldol reaction between the aldehyde group of (**81**) and methyl 2,2-dimethyl-3-oxobutanoate with Cs_2CO_3 gave (**82**) which was hydrolysed and decarboxylated with Cs_2CO_3 in aqueous DMF to give (**83**). Subsequent reduction of (**83**) to (**8 4**) with $(Ph_3PCuH)_6$ followed by intramolecular McMurray coupling afforded (**76**) in high yield. This scheme gives an overall yield of 2.5% in 15 steps (**Scheme 11**).



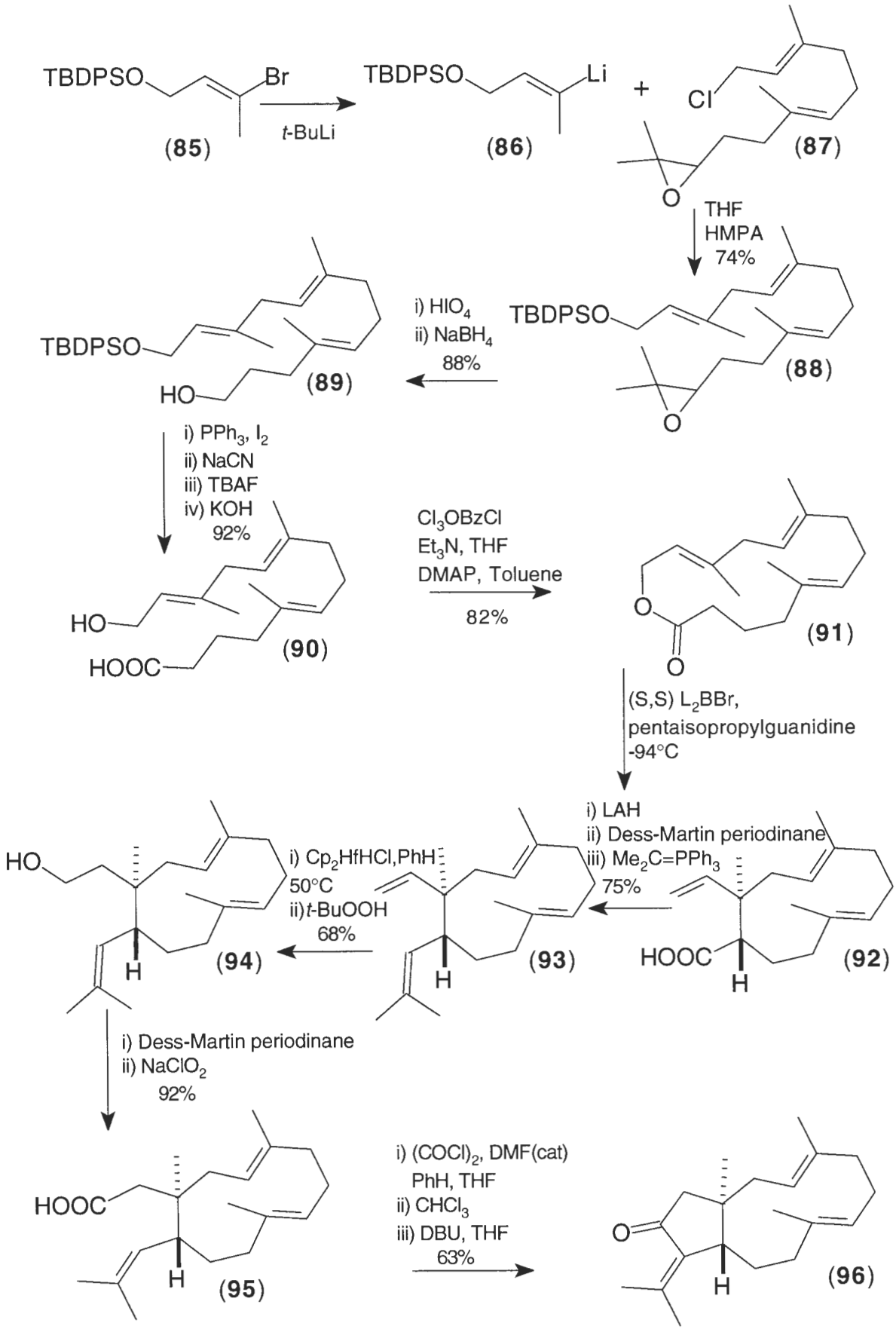
Scheme 11

The first enantioselective total synthesis of a naturally occurring dolabellane was reported by Corey.[1] This strategy for simultaneously creating the eleven membered ring and the correct absolute configuration at the two stereogenic centres uses an highly enantioselective Claisen rearrangement (ee >98%).



L_2BBr

Protected alcohol (**85**) was lithiated (**86**) and coupled with chloro-epoxide (**87**), prepared from *EE*-farnesol in 4 steps, to afford (**88**). Periodic acid cleavage of epoxide (**88**) was followed by reduction to give the primary alcohol (**89**). Cyclisation of (**90**) to the macrolactone (**91**) was carried out under Yamaguchi conditions. A very hindered base (pentaisopropylguanidine) was used in conjunction with the chiral diazaborolidine reagent (L_2BBr) to effect formation of (**92**) by a Claisen rearrangement. Tetraene (**93**) was synthesised from triene acid (**92**) via hydride reduction to the alcohol, oxidation with Dess-Martin periodinane to the aldehyde and a Wittig reaction. Tetraene (**93**) was converted to alcohol (**94**) by selective hydrometallation with Cp_2HfHCl then oxidation of the intermediate organometallic with *t*-BuOOH. A two step oxidation involving Dess-Martin periodinane and $NaClO_2$ afforded carboxylic acid (**95**). The corresponding acid chloride formed by reaction with oxalyl chloride spontaneously cyclised in chloroform at RT to a mixture of bicyclic products. Treatment with DBU, converted the mixture to dolabellatrienone (**96**) and absolute stereochemistry was determined by optical rotation. Comparison of (**96**) with the natural product gave a similar optical rotation suggesting the opposite configuration to that previously assigned to the natural product. Subsequent x-ray analysis with the Mosher ester derivative confirmed the absolute stereochemistry. The overall yield for this 18 step synthesis is 12 % (**Scheme 12**).

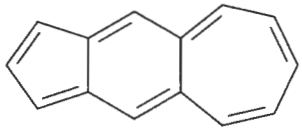

TBDPSO
Br
(85)
t-BuLi
TBDPSO
Li
(86)
+
Cl
(87)
O
THF
HMPA
74%
TBDPSO
(88)
O
i) HIO4
ii) NaBH4
88%
TBDPSO
HO
(89)
i) PPh3, I2
ii) NaCN
iii) TBAF
iv) KOH
92%
HO
HOOC
(90)
Cl3OBzCl
Et3N, THF
DMAP, Toluene
82%
O
O
(91)
(S,S) L2BBr,
pentaisopropylguanidine
-94°C
i) LAH
ii) Dess-Martin periodinane
iii) Me2C=PPh3
75%
HOOC
H
(92)
i) Cp2HfHCl,PhH
50°C
ii) t-BuOOH
68%
H
(93)
HO
H
(94)
i) Dess-Martin periodinane
ii) NaClO2
92%
HOOC
H
(95)
i) (COCl)2, DMF(cat)
PhH, THF
ii) CHCl3
iii) DBU, THF
63%
O
H
(96)

Scheme 12

1.4 Literature approaches to cyclohept[f]indene systems

1.4.1 Aromatic Cyclohept[f]indenes

In the 1960s synthetic studies towards the cyclohept[f]indene system focussed on the fully conjugated system which may have aromatic activity (**Figure 8**).

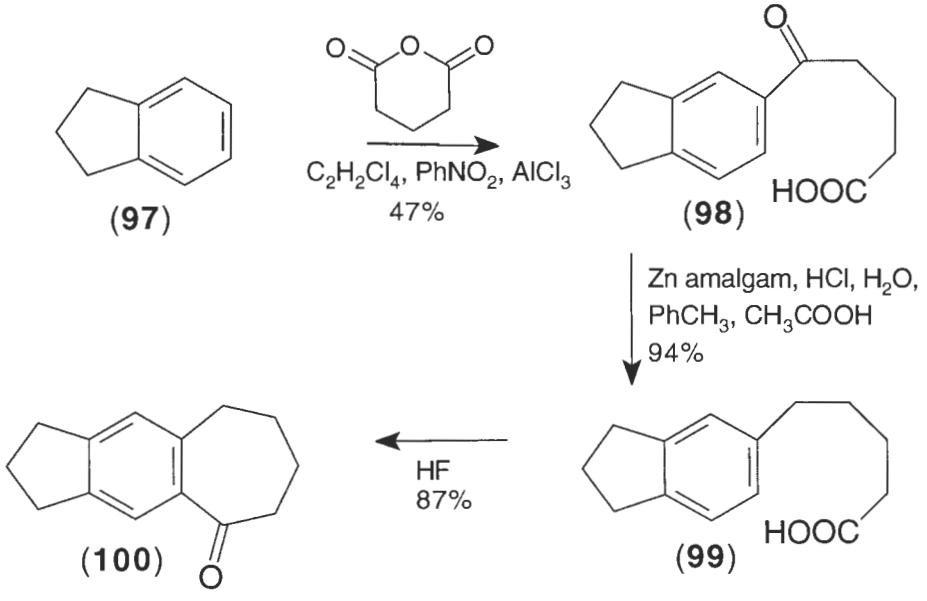


Cyclohept[f]indene

Figure 8

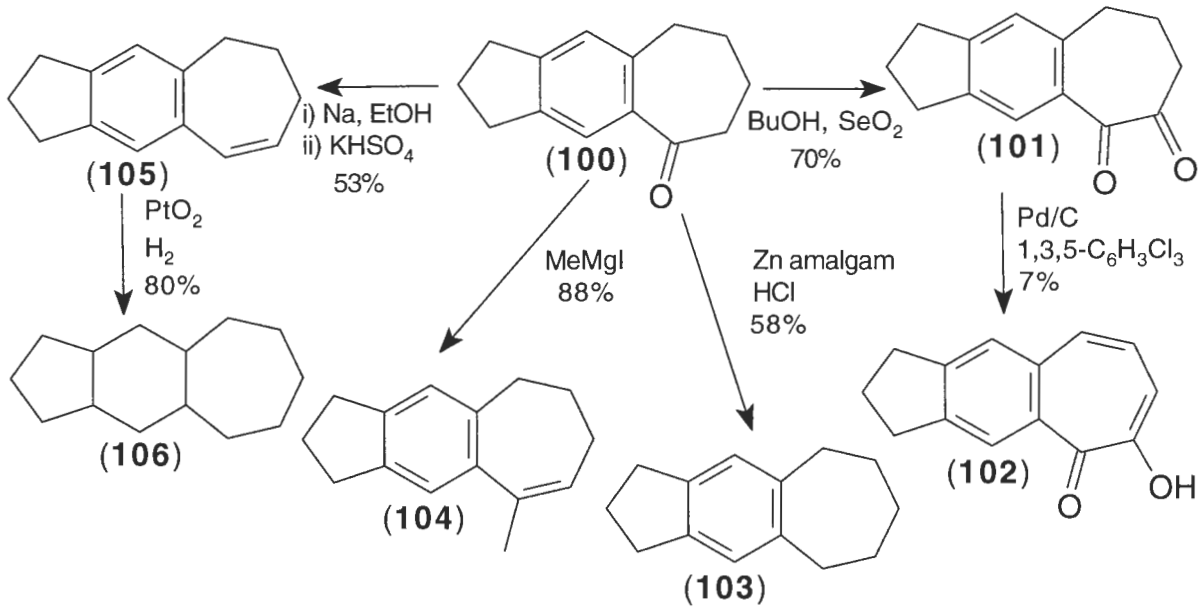
Synthetic endeavours towards this system involved a range of different strategies[22-26] but the fully aromatic system remains elusive.

Campbell[22] synthesised ketone (**100**) in 38% yield over three steps from indan (**97**). Thus, intermolecular Friedel-Crafts acylation of indan (**97**) with glutaric anhydride afforded keto-acid (**98**) which was subsequently reduced under Clemmensen conditions. The resulting acid (**99**) was cyclised to cyclohep[f]inden-10-one (**100**) in an intramolecular Friedel-Crafts acylation reaction (**Scheme 13**).



Scheme 13

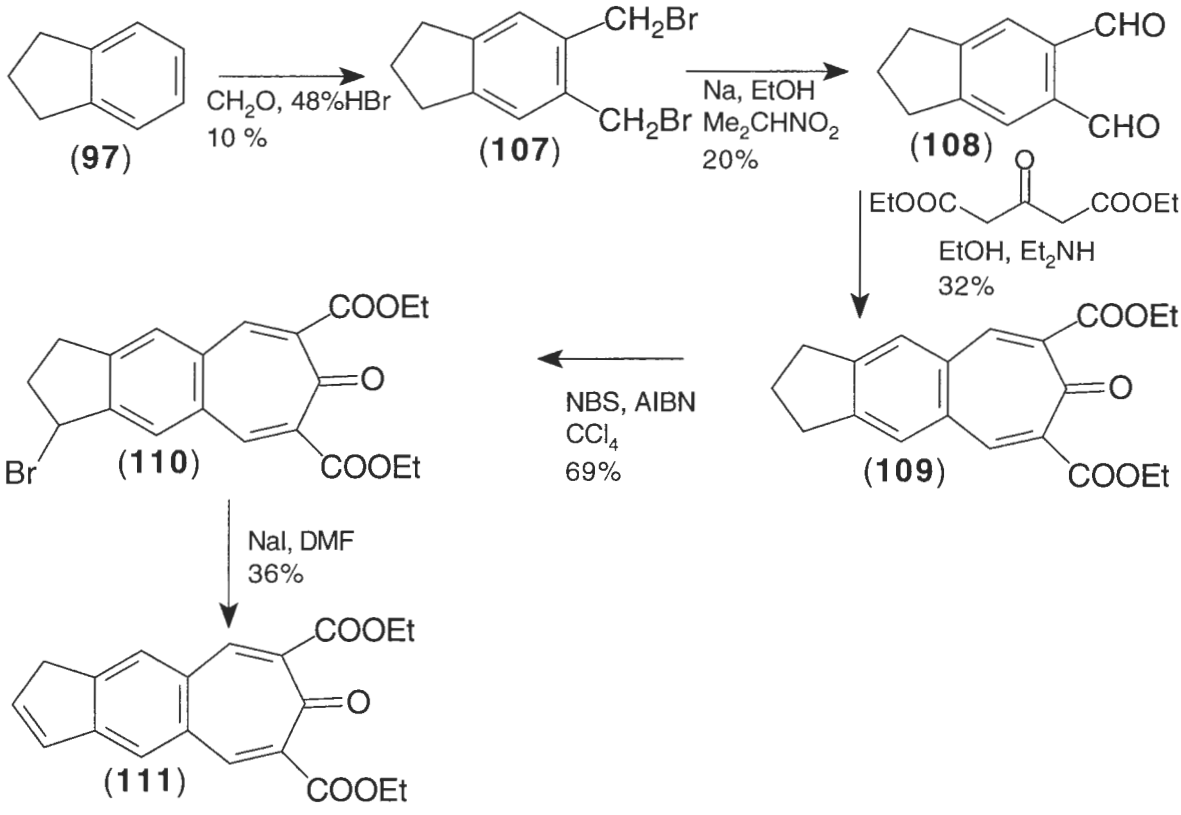
Subsequent attempts to form the conjugated system from ketone (**100**) produced a number of cyclohept[f]indenes. Oxidation of the cyclohept[f]inden-10-one (**100**) with selenium dioxide afforded the dione (**101**) which was dehydrogenated to tropolone (**102**) by palladium on charcoal. The Clemmensen reduction converted ketone (**100**) to the cyclohept[f]indene (**103**). Reaction of methyl magnesium iodide with the ketone (**100**) afforded the alcohol which was dehydrated to alkene (**104**) on distillation. Reduction with sodium metal in EtOH followed by dehydration furnished (**105**) which could be further reduced to the saturated system (**106**) (**Scheme 14**).



Scheme 14

A similar synthesis involving the intermolecular Friedel-Crafts acylation between glutaric anhydride and a methyl-dihydroxy derivative of indane was reported by Procter.[26] This synthesis produced only trace amounts of the 2,8-dihydroxy-4-methyl-cyclohept[f]inden-10,14-dione, however.

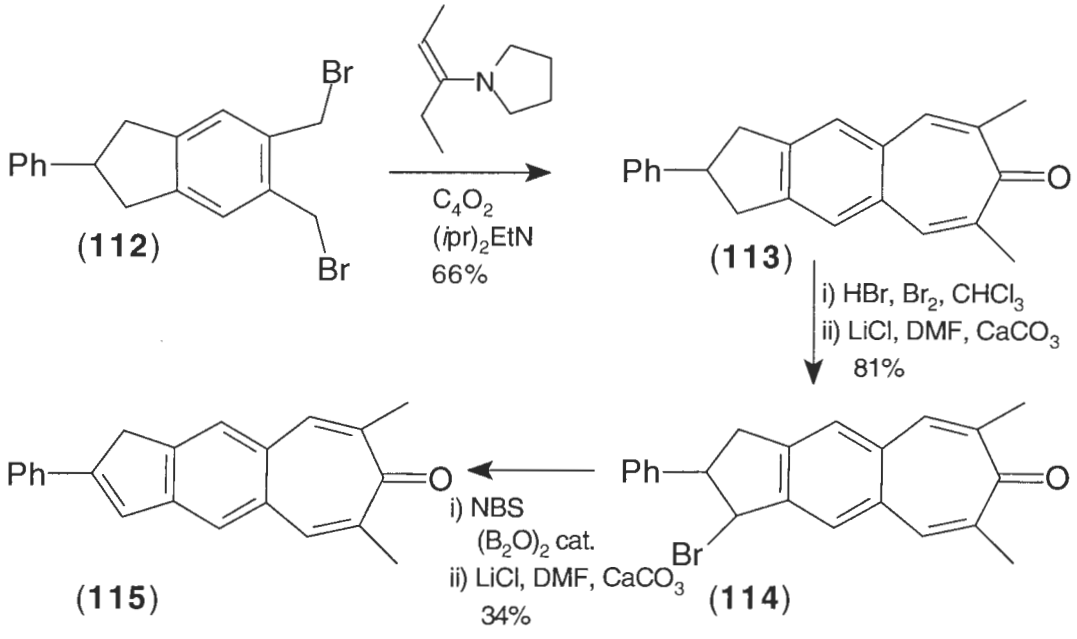
Bertelli[24] produced cyclohept[f]indene in an overall yield of 6% *via* a condensation of an aldehyde derived from indan (**97**) and diethylacetonedicarboxylate.



Scheme 15

Thus indan (**97**) was converted to the 1,9-dibromomethyl derivative (**107**) in low yield. Dialdehyde (**108**) was produced from (**107**) by reaction of the sodium salt of 2-nitropropane and was subsequently converted to (**109**) by annelation with diethylacetonedicarboxylate. Bromination with NBS afforded bromo compound (**110**) which was subsequently dehydrohalogenated to give highly unsaturated keto-diester (**111**). The overall yield for this 5 step synthesis is 0.2%.

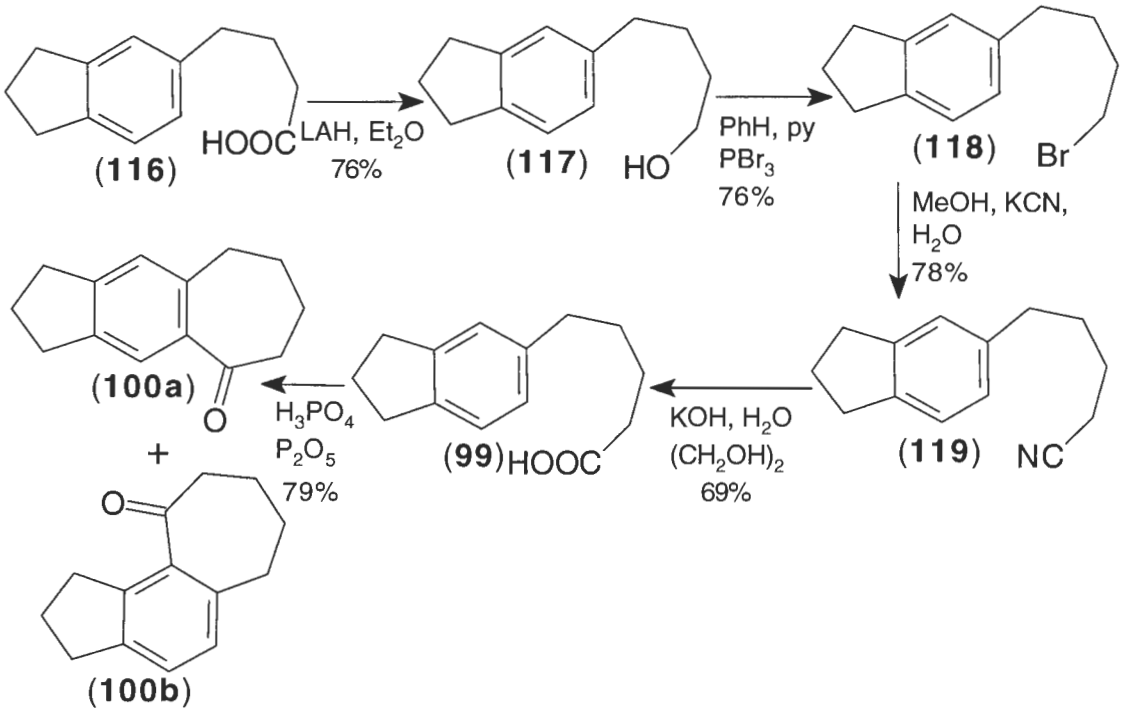
A similar compounds was prepared by Bordwell and Winn[23] in a more respectable yield of 18% (**Scheme 16**).



Scheme 16

Thus indenotropone (**115**) was synthesised through a series of 5 steps using an enamine reaction of 2-phenyl-5,6-*bis*(bromomethyl)indane (**112**) to afford ketone (**113**). Bromination followed by dehydrobromination gave indanotropenone (**114**). The C=C bond was introduced into the five membered ring by an additional bromination-dehydrobromination affording (**115**).

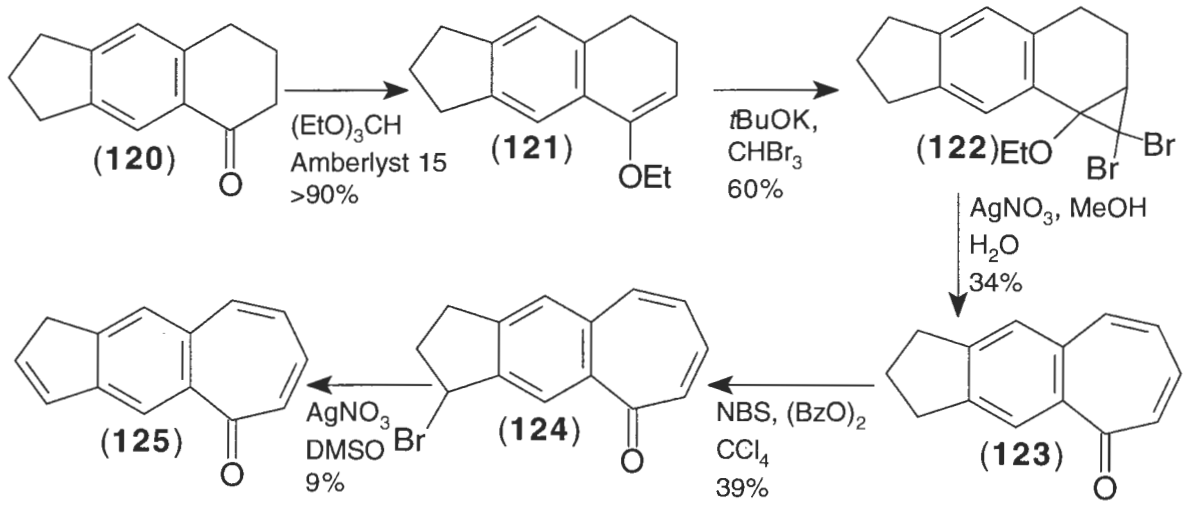
Patwardhan[25] used relatively harsh conditions to produce the cyclohept[f]indenone (**100**) from a carboxylic acid in a 5 step synthesis with an overall yield of 25%. LAH reduction of acid (**116**) to primary alcohol (**117**) followed by bromination produced the bromide (**118**). Refluxing compound (**118**) with KCN afforded the cyanide (**119**) which was hydrolysed to acid (**100**) and subsequently cyclised *via* an intramolecular Friedel-Crafts acylation to produce a 93:7 mixture of regioisomers (**Scheme 17**).



Scheme 17

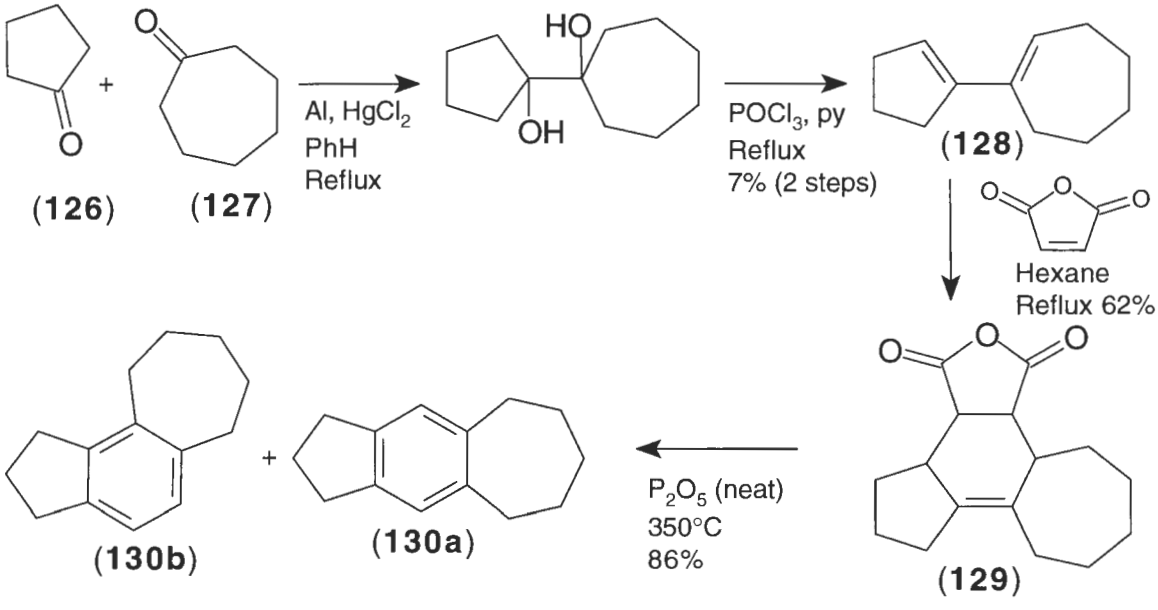
Patwardhan, S and Dev, S[27] utilised 6,7-cyclopentano-1-tetralone as their starting material to form indeno(5',6'-6,7)troponone. Several types of unsaturated indenones were formed. (**Scheme 18**)

An ion exchange resin proved to be an effective catalyst for the preparation of the enol ether (**121**) from ketone (**120**). Dibromocyclopropane (**122**) was formed by the reaction of dibromocarbene with (**121**) and subsequent dehydrobromination rearrangement gave enone (**123**). NBS bromination gave the single regioisomeric bromo derivative (**124**), which was dehydrohalogenated with silver nitrate to produce cyclohept[f]indene (**125**).



Scheme 18

Wightman *et al* [28] produced cyclohept[f]indene in a very low yielding (0.4%) 4 step synthesis (**Scheme 19**).



Scheme 19

Thus, a crossed pinacol reaction between cyclopentanone (**126**) and cycloheptanone (**127**) produced a mixture of three possible diols which proved difficult to separate. The mixture of diols was then dehydrated using phosphorous oxychloride in pyridine to give a mixture of dienes from which the desired compound (**128**) could be isolated in 7% overall yield. Following an intermolecular Diels-Alder reaction of (**128**) with maleic anhydride the resulting anhydride (**129**) was heated with an excess of phosphorous pentoxide to produce an inseparable mixture of regioisomers (9:1**130a:130b**).

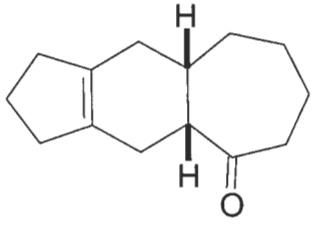
A wide variety of functionalised cyclohept[f]indene systems have been synthesised. The majority of these are cyclohept[f[indenones with the keto functional group incorporated in the seven membered ring. There is no evidence to support the production of the enol tautomer suggesting the fully conjugated system is not as aromatic as previously thought.

In general these synthetic studies towards cyclohept[f]indene are not suitable as a route for the synthesis for dictyoxetane due to the presence of the benzene ring. It is unlikely that the harsh conditions (eg Birch reduction) needed for the dearomatisation of the central six membered ring would leave the complex functionality required on the five and seven membered rings intact. Moreover, the stereoselectivity of such reactions is poor.

1.4.2 Non-aromatic cyclohept[f]indenes

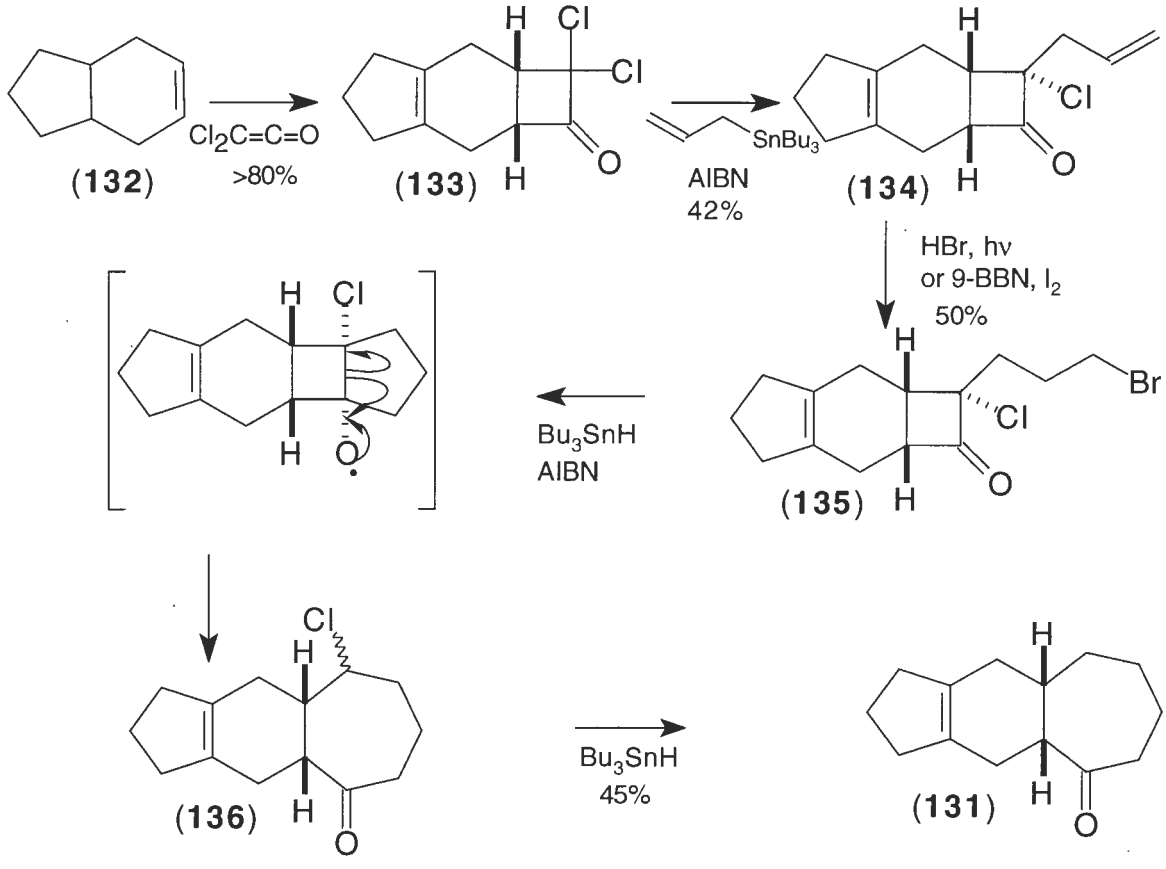
As mentioned in the previous subsection, cyclohept[f]indane (**106**) was formed by Campbell et al.[22] by catalytic hydrogenation of (**105**) using Adams catalyst to form the unsaturated cyclohept[f]indane (**106**) in 49% from ketone (**100**) (**Scheme 14**).

To our knowledge there is only one other study reported in the literature of the non-aromatic system which was reported by Dowd *et al*[29,30]Free radical promoted ring expansion occurred stereoselectively to produce the $\Delta^{3,7}$-cyclohept[f]inden-10-one (**131**) in a four step synthesis with an overall yield of 9% from dichlorocyclobutanone. This compound was produced as part of a wider synthetic study into the annelation of a seven membered ring onto an alkene.



(131) Cyclohept[f]indenone

Dichloroketene reacts *via* a [2+2] cycloaddition with tetrahydroindan (**132**) to produce the dichlorocyclobutane (**133**). Radical allylation of (**133**) with allyltributyl tin produces solely the *exo*-adduct (**134**) which undergoes free radical hydrobromination to give (**135**). Tributyltinhydride-mediated ring expansion afforded *cis*-fused cycloheptanone (**136**), which was subsequently reduced, again with tributyl tin hydride, to give the annelated product (**131**) (**Scheme 20**).



Scheme 20

It is thought that neither of these routes is suitable for application towards the synthesis of dictyoxetane and the dolabellanes. Campbell[22] produces the cyclohept[f]indane with an overall yield of 18% from indan (**97**). Stereochemistry at the ring junction was not defined in this work but most catalytic hydrogenations of aromatic rings have been shown to be *syn*, with the hydrogens entering from the less hindered side of the molecule, resulting in *cis* stereochemistry at the ring junction.[31] The dolabellanes require *trans* fusion. Dowd[29,30] produced a diastereoselective synthesis of cyclohept[f]indenone in 9% overall yield, however, the ring junction is unsaturated making it difficult to control stereochemistry at this position. Moreover, Dowd's [2+2] cycloaddition

would produce a mixture of regioisomers if carried out on unsymmetrical tetrahydroindan starting material.

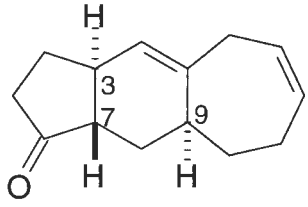
The purpose of the following study was to devise a stereocontrolled route towards dictyoxetane. The overall aim of this chemistry was to reach the target in an efficient, (i.e. short route, high yield) and stereocontrolled manner. Once the cyclohept[f]indene system has been synthesised it is envisaged that this sequence could be adopted to produce members of the dolabellane class of diterpenes. Modifications to this framework must be easily incorporated into earlier parts of the scheme and still afford high yields, to enable a wide variety of dolabellanes to be synthesised. It is therefore important that the synthetic scheme allows for flexibility of reagents and conditions to ensure the addition of various functional groups. The retrosynthetic analysis was conceived with the hope of both stereocontrol and flexibility.

2. Discussion

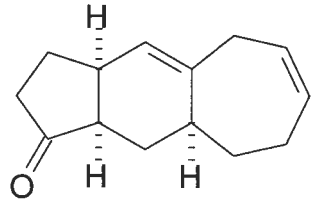
2.1 Stereocontrol

In the hope of finding compounds which are therapeutically useful it is desireable to synthesise a range of diastereoisomers. Many bioactive chemicals isolated from nature are lead compounds in drug development. Often the lead compound can not be utilised directly because of problems of solubility, side effects or toxicity. The structure must therefore be modified to remove these undesireable properties. Stereochemistry is an important component in the biological effect of medicines and by controlling the stereochemistry it may be possible to reduce many adverse reactions.

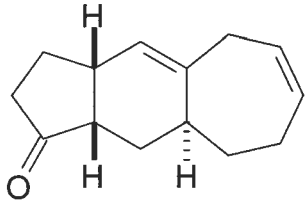
The approach that is outlined by the retrosynthetic analysis will produce the four diastereoisomers that are shown in **Figure 9**.



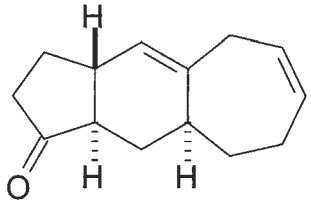
(**137a**) From *E*-starting material with intramolecular Diels-Alder
H_3, H_9-*syn*
H_7, H_9-*anti*



(**137b**) From *E*-starting material with intermolecular Diels-Alder
H_3, H_9-*syn*
H_7, H_9-*syn*



(**137c**)From *Z*-starting material with intramolecular Diels-Alder
H_3, H_9-*anti*
H_7, H_9-*anti*



(**137d**) From *Z*-starting material with intermolecular Diels-Alder
H_3, H_9-*anti*
H_7, H_9-*syn*

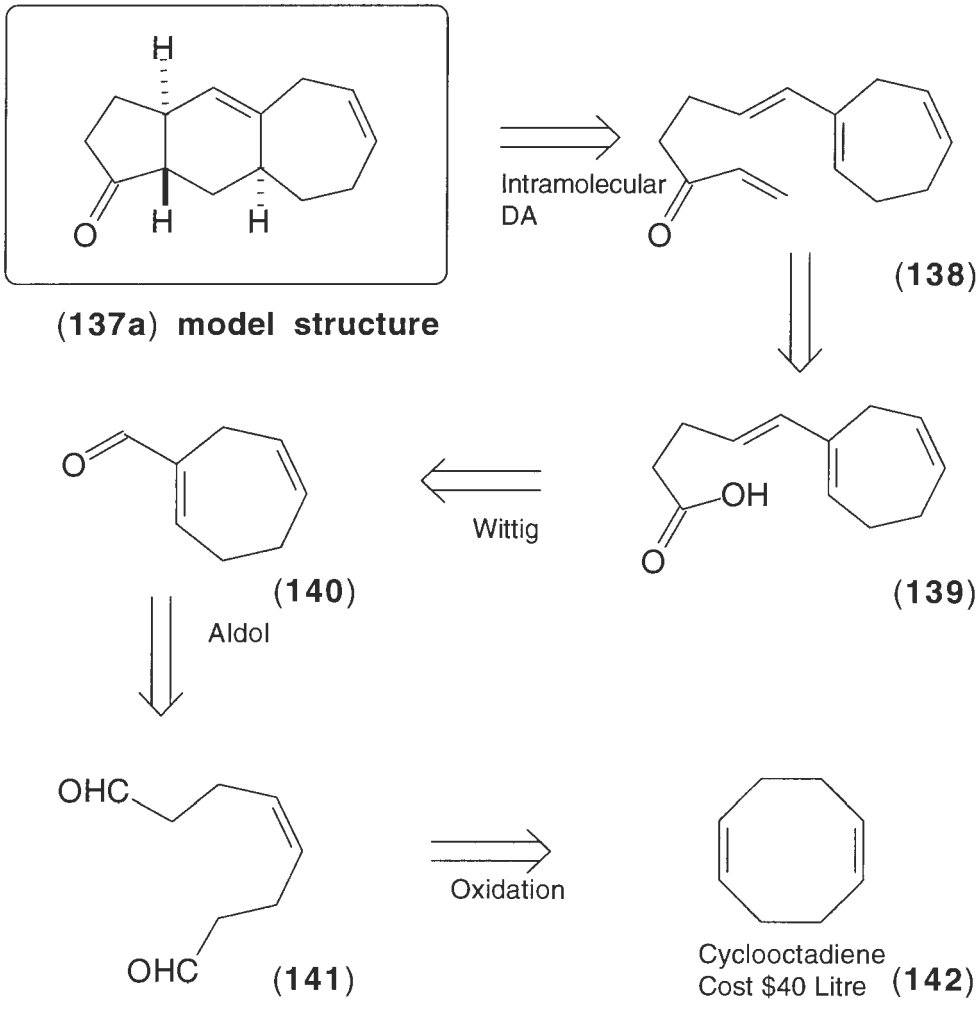
Figure 9

It is important to be able to synthesise a range of diastereoisomers for qualitative structure activity relationships. Structure (**137a**), that with *trans*

fusion between the five and six membered rings, has the same relative stereochemistry as the dolabellanes.

2.2 Retrosynthetic Analysis

In order to synthesise the cyclohept[f]indene system in an efficient manner it was necessary to utilise inexpensive, readily available starting materials. The retrosynthetic analysis of the cyclohept[f]indene system is shown in **Scheme 21**.



Scheme 21

The model structure (**137a**) can be made through an intramolecular Diels-Alder reaction of the vinyl ketone (**138**). This compound may be synthesised from a Weinreb amide, through a Stille coupling or *via* a longer procedure involving a Grignard reagent. The acid (**139**) could be generated through a Wittig reaction with the cycloheptadiene carboxaldehyde (**140**) and the appropriate ylid. The seven membered ring with aldehyde functionality could be generated in three

steps from cyclooctadiene (**142**), a cheap, readily available material. Thus starting from an eight membered ring it should be possible to form the linearly fused [5,6,7] ring system.

As with most reactions, the Diels-Alder reaction may be carried out in an intramolecular or an intermolecular fashion. With substrates like the vinyl ketone (**138**) the intramolecular Diels-Alder reaction results in the *exo* product, whereas the *endo* product is observed in most intermolecular Diels-Alder reactions. Both types of Diels-Alder reactions are concerted with the stereochemistry of the diene and dienophile being conserved. Therefore *Z*-dienes result in *anti* products and *syn* products result when *E*-dienes are employed[32] (**Figure 10**). It is possible, therefore, to produce the range of diastereoisomers by carefully controlling the conditions used in the Wittig reaction and carrying out either an intramolecular or intermolecular Diels-Alder reaction.

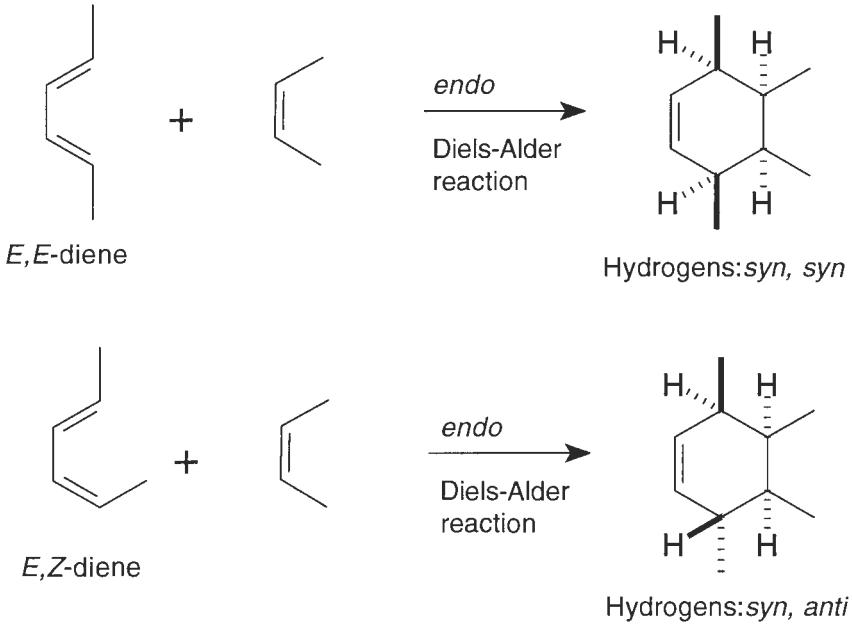
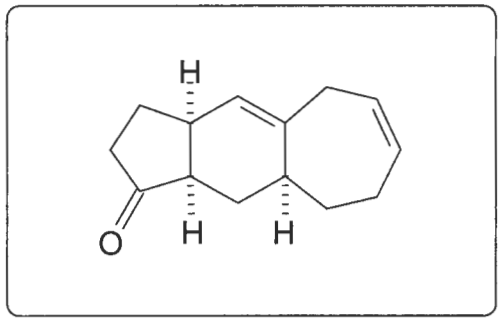
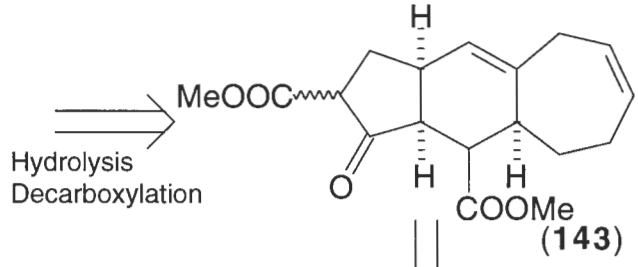


Figure 10

Thus an intermolecular Diels-Alder strategy was also developed (**Scheme 22**) involving a reaction between maleic anhydride and the methyl ester (**145**) of the acid (**139**) previously synthesised in **Scheme 21**. The H_3, H_9-*syn*, H_7, H_9-*syn* of the cyclohept[f]indene system (**137b**) is produced by decarboxylation and hydrolysis of the keto-diester (**143**). This should be formed by a Dieckmann -type reaction of anhydride (**144**), which in turn may be formed by refluxing the methyl ester (**145**) with maleic anhydride.

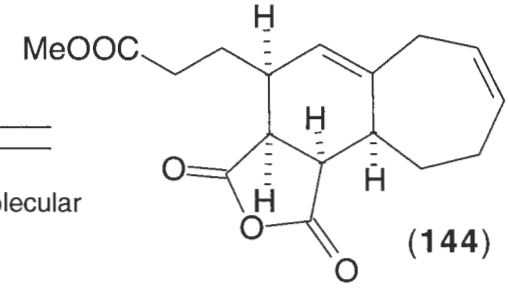


(137b) model structure

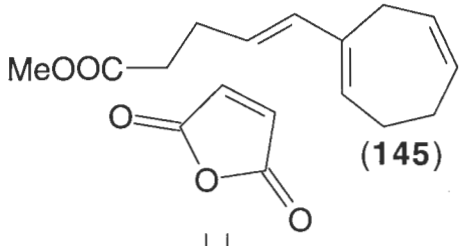


(143)

Dieckman cyclisation

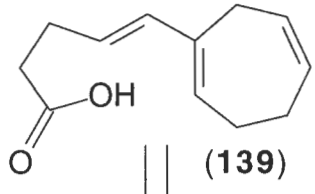


(144)



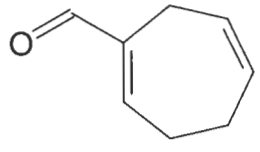
(145)

Esterification

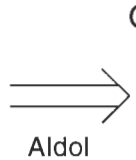


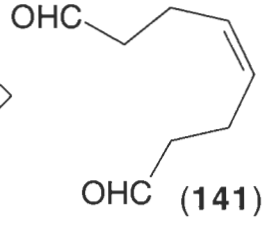
(139)

Wittig

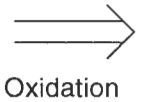


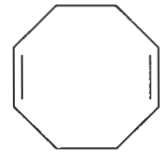
(140)





(141)





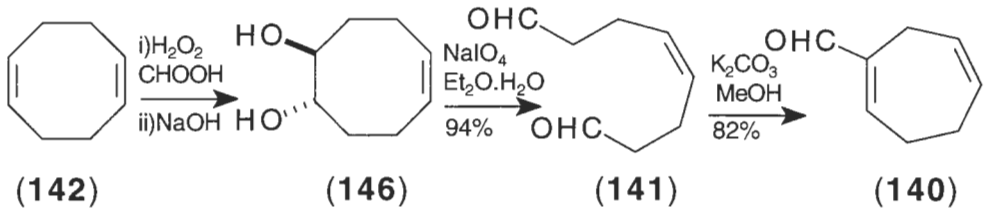
(142)
Cyclooctadiene
Cost $40 Litre

Scheme 22

The major advantage of this work over previous studies towards dictyoxetane, the dolabellanes and cyclohept[f]indene is that it enables all diastereomers to be synthesised, although it is likely that only the *trans* fused 5,6-ring systems will be necessary for the production of dolabellanes. Further functionality may be introduced by modification of the phosphonium salt used in the Wittig reaction and by elaboration of the alkenes present in the 6 and 7 membered rings.

The proposed syntheses of the cyclohept[f]indene are dependent on the generation of the functionalised cycloheptadiene (**140**). The preparation of functionalised seven membered carbocycles is an area of considerable interest because the cycloheptane moiety is present in a wide variety of natural products. Previous synthetic approaches to seven membered rings have included ring expansion of six membered rings,[33,34] [4+3] annelation of dienes and allyl cations,[35] [5+2] cycloadditions[36] and Cope rearrangements.[37,38]

2.3 Synthesis of Cyclohepta-1,5-diene Carboxaldehyde



(142) (146) (141) (140)

Scheme 23

Z-cyclooct-5-ene-trans-1,2-diol (**146**) was produced in 39% overall yield from cycloocta-1,5-diene (**142**) according to the two step procedure developed by Yates *et al.*[39] Thus selective monoepoxidation of 1,4-cyclo-octadiene (**142**) then hydrolysis of the monoepoxide gave diol (**146**) which was purified by distillation to a clear oil. This preparation gave only moderate yields but was easily scaled to produce 15 grams of diol. In our hands synthesis of diol (**146**) was less efficient using the conditions developed by Singh *et al.*[40] Yields were considerably lower (7-21%) than those reported (65%) and purification was difficult due to codistillation of an unidentified byproduct.

Z-oct-4-enedial (**141**) was produced in 94% yield by oxidative cleavage of diol (**146**)[41,42] with $NaIO_4$ according to the procedure developed by Singh *et al.*[40] This paper describes dissolving the diol in moist ether at RT. We found optimal results were obtained when diethyl ether was saturated with water and the reaction was carried out at 31°C.

Initially *Cyclohepta-1,5-diene carboxaldehyde* (**140**) was synthesised in 40% yield from the dialdehyde (**141**) using the phase transfer catalyst tetrabutyl ammonium iodide, between an aqueous solution of sodium hydroxide and CH_2Cl_2. This was fully characterised.

The ^1H NMR spectrum of (**140**) exhibited a singlet at δ9.3 ppm which is characteristic of an aldehyde with no α protons. A two proton multiplet at 3.1 ppm is consistent with a doubly allylic methylene. ^{13}C NMR analysis showed eight non equivalent carbons with the aldehydic carbon resonating at 193.8 ppm. The α,β-unsaturated alkene is evidenced by a quaternary carbon with a chemical shift of 142.8 ppm and a methine carbon further down field at 154.9 ppm. There are two other alkenic carbons with chemical shifts of 130.8 ppm and 127.5 ppm. The remaining three carbons were aliphatic methylenes with chemical shifts ranging from 27.9-22.8. Strong peaks in the C=O stretching

region (1683 cm^{-1}), exhibiting a conjugated aldehyde and (1643cm^{-1}), exhibiting an alkene were present in the IR spectrum. High resolution mass spectral analysis gave a molecular ion of 122.0732.

2.3.1 Optimisation of the Intramolecular Aldol Reaction

Both weak acid and weak bases were trialled in order to optimise the yield of the cycloheptadiene carboxaldehyde (**140**) (**Table 1**). Reactions were carried out at RT unless otherwise stated.

Base	[Base]	Equivalents	Solvent	Yield
NaOH	40%	10	CH_2Cl_2	40%[1]
CSA	5 mmol L^{-1}	0.1	CH_2Cl_2	0%
CSA	50 mmol L^{-1}	0.1	CH_2Cl_2	0%
PTSA	5 mmol L^{-1}	0.1	CH_2Cl_2	0%
PTSA	50 mmol L^{-1}	0.1	CH_2Cl_2	0%
DBU	5 mmol L^{-1}	0.1	CH_2Cl_2	0%
DBU	5 mmol L^{-1}	1	CH_2Cl_2	8%
K_2CO_3	5 mmol L^{-1}	1	MeOH	59%
K_2CO_3	50 mmol L^{-1}	1	MeOH	22%
K_2CO_3	9 mmol L^{-1}	2	MeOH	82%

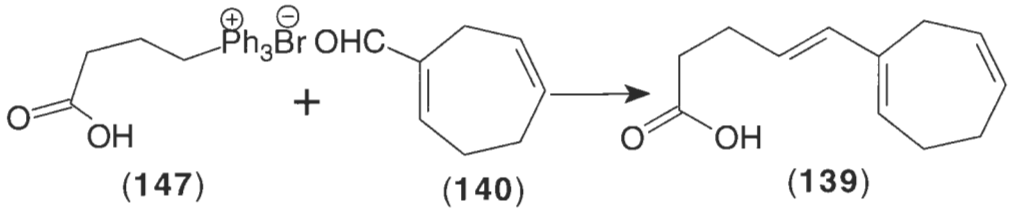
[1] This reaction was carried out using a phase transfer catalyst at 40°C

Table 1

Attempts to mediate the reaction with camphor-sulfonic acid and *para*-toluene-sulfonic acid, led to the formation of polymers. Base mediated reactions were then tried, which proved to be more successful. DBU,[43] a strong hindered amine base, was, however, also ineffective. A total of one equivalent was added over six days and very little product was obtained. More promising results were obtained with the use of methoxide. The initial reaction with this base produced the aldehyde (**140**) in 59% yield. Modifications were made to the concentration of base ultimately leading to a significant improvement in yield. Thus, reaction of dialdehyde (**141**) with two equivalents of K_2CO_3 in MeOH using a base concentration of 9 mmol L^{-1} gave the cyclohepta-1,5-diene carboxaldehyde in high yield (84%). Altering the concentration of the aldehyde also caused a change in yield with the optimum yield at a concentrations of 50 mmol L^{-1}.

Yields after column chromatography were consistently low (22-44%) due to the weakly acidic nature of SiO_2 and the acid sensitivity of the aldehyde. This problem was easily circumvented by using vacuum distillation (B.P. 150°C 0.01 mmHg) as the preferred method of purification. Up to 5 g of cycloheptadienal was purified, in this way using Kugelrohr apparatus.

2.4 The Wittig Reaction



(147) (140) (139)

Scheme 24

A Wittig reaction of cycloheptadiene carboxaldehyde (**140**) was used to produce the acid (**139**). As discussed earlier, this reaction is an essential factor in controlling the stereochemistry of the desired cyclohept[f]indene.

Wittig reactions produce olefins by reactions between between an aldehyde (or ketone) and a phosphorous ylid. The sterereochemical outcome of the Wittig is controlled by the nature of the ylid, base, aldehyde, solvent and temperature.[44-46]

1) The Nature of the Ylid

Ylids may either be stabilised, semistabilised or nonstabilised. Only nonstabilised, phosphorous ylids are relevant for the purpose of this discussion. Formation of *Z*-alkenes is favoured by the use of a nonstabilised ylid at room temperature. There is a trend towards formation of *E*-alkenes with increasing bulk of phosphorous ligands. Anionic, nucleophilic groups in the side chain (*eg* carboxylate groups) favour *E*- alkenes, although this effect is very dependent on the distance of the anionic group from the phosphorous atom.

2)The Nature of the Base

Lithium reagents (*eg* LDA, LHMDS) tend to favour the formation of *E*-alkenes. As the concentration of the lithium cation increases the *Z:E* ratio decreases.

3) The Nature of the Aldehyde

Z-Alkene selectivity is higher for tertiary aldehydes than for unbranched aliphatic aldehydes. The combination of a tertiary aldehyde with bulky phosphorous ligands on the ylid result in the highest *Z*-ratios.

4) Temperature

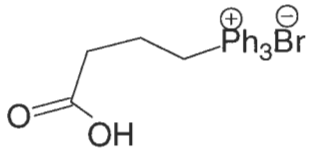
Z- selectivity is highest at low temperatures.

5) Solvent Effects

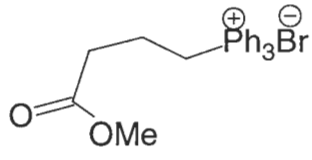
A lithium salt free reaction performed in DMF will give the same *E:Z* ratio as a lithium salt containing reaction carried out in the same conditions as DMF is an efficient lithium complexing agent.[46] Other polar solvents may behave in a similar way. *Z*- stereoselectivity is maximised by polar aprotic solvents.[44]

From these observations it is likely that a Wittig reaction performed at RT, in the prescence of a lithium salt and a carboxylate anion would favour the formation of the *E* alkene. Formation of the *Z* alkene should be favoured using lithium salt free conditions, *ie* the methyl ester rather than the carboxylate anion and a potassium or sodium derived base, at low temperature.

2.4.1 The Ylids



(**147**)

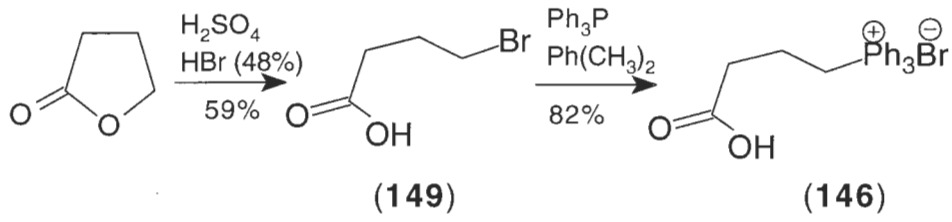


(**148**)

Figure 11

The ylids used in the Wittig reactions in this model system towards dictyoxetane were derived from (4-carboxybutyl)triphenylphosphonium bromide (**146**) and its methyl ester (methyl-4-carboxybutyl)triphenylphosphonium bromide (**147**). γ-butyrolactone, was hydrolysed with concentrated sulphuric acid and bromic acid (48%) yielding 4-bromobutanoic acid (**149**) in 59% yield after purification by vacuum distillation (B.P. 98°C, 1.0 mmHg).[47] Conversion to the phosphonium salt (**149**) in 82% yield (M.P. 241-242°C) was accomplished by refluxing (**148**) in xylene with triphenylphosphine (**Scheme 25**). This phosphonium salt was hygroscopic and could not be used in a Wittig reaction until it was thoroughly dried. All data collected was in agreement with literature values. (4-

bromobutanoic acid B.P. 128-131°C, 11 mmHg and 4-carboxybutyl triphenyl phosphonium bromide M.P. 241°C.)



(**149**) (**146**)

Scheme 25

The corresponding methyl ester, 4-methylcarboxybutyl triphenylphosphonium bromide, was obtained by esterifying the phosphonium salt (**146**) with diazomethane (94%), or by refluxing acid (**148**) in MeOH and sulfuric acid[47] then refluxing the resulting ester with triphenyl phosphine in xylene (64%). The latter was the preferred method for large scale work due to the toxicity and hazards associated with diazomethane.

Discussion of the synthesis of related compounds is found in appendix A.

2.4.2 The *E*-series

Generation of the non-stabilised ylid of 4-carboxybutyl triphenylphosphonium bromide was first attempted using the dimsyl anion.[48-50] NaH and DMSO were heated at 75°C until no further H_2 gas was released (*ca.* 30 min.) and a solution of phosphonium salt (**147**) in DMSO was added. On formation of an orange-red suspension aldehyde (**140**) was added causing decolourisation to a grey suspension. Starting material was consumed but on completion of an acid work-up there was none of the desired product as determined by ^{1}H NMR.

Following initial difficulties forming the acid, trial reactions were attempted using benzaldehyde. A solution of LHMDS was generated by adding butyl lithium to a stirred solution of hexamethyldisilane in THF.[48,51] Dropwise addition of LHMDS solution to a suspension of phosphonium salt (**147**) generated an intense red solution of ylid. On addition of benzaldehyde, the desired acid was produced in 63% yield[52] and was subsequently esterified to the methyl ester using diazomethane (70%).

After the success with benzaldehyde, the reaction was repeated with cycloheptadiene carboxaldehyde (**140**) to give the desired acid (**139**) in 43%

yield. This was subsequently esterified with freshly prepared diazomethane[53] and purified by column chromatography to give the methyl ester (41% 2 steps). Subsequent reactions, without esterification, resulted in improved yields of the acid varying from 55% to 82%.

^{1}H and ^{13}C NMR spectroscopy revealed the formation of only one isomer. A quaternary carbon with a chemical shift of δ179.3 ppm is characteristic of an aldehydic carbonyl carbon. A second quaternary carbon which resonates at δ139.8 ppm has a similar chemical shift to the corresponding carbon in the aldehyde (**140**). The two new alkenic carbons have a chemical shift of δ134.7 ppm and δ131.3 respectively. In the ^{1}H NMR spectrum a broad one proton singlet at 10.1 ppm is characteristic of a carboxylic acid. The new one proton doublet at 6.1 ppm (J=15.6 Hz) is indicative of the *E*-isomer. A new three proton multiplet at 5.61 ppm is consistent with protons H_4, H_{10} and H_{11}. A broad singlet at 3.0 ppm shows the presence of a doubly allylic methylene. Eight other protons are seen in the six proton multiplet at 2.4 ppm and a two proton multiplet at 2.2 ppm indicative of a new alkyl chain. A strong, broad peak in the IR spectrum between 3017 - 2934 cm^{-1} and a strong C=O stretch peak at 1709 cm^{-1} are characteristic of a carboxylic acid. Low resolution mass spectral analysis gave a molecular ion of 192. This data is consistent with the desired *5-(cyclohepta-1',5'-diene)-4-E-pentenoic acid*

Esterification of the acid with diazomethane resulted in the formation of *methyl-(cyclohepta-1',5'-diene)-4-E-pentenoate.* ^{1}H NMR spectral data of this ester was similar to the acid with both the multiplets in the methylenic region and the peaks in the alkenic region at the same chemical shift. A new methoxy peak was exhibited at 3.66 ppm. The ^{13}C NMR are also very similar but a new methoxy peak is apparent at 51.47 ppm. The major differences in the IR spectrum are due to the prescence of the broad C-C(=O)-O band at 1253-1164 cm^{-1}, which is absent in the acid spectrum and strong CH_3 bending peaks at 1436 and 1362 cm^{-1}. Mass spectral analysis gave a molecular ion of 206.

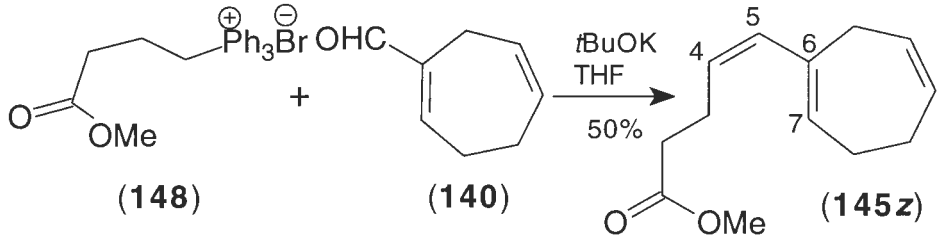
2.4.3 The *Z*-series

Initially it was thought using lithium salt free conditions would give better *Z*-selectivity[46] so similar conditions were tried substituting KHMDS, for LHMDS. KHMDS was synthesised from KH and hexamethyl disilane according to the procedure of Brown.[54] The conditions reported by Perlmutter[55] were employed for the *Z*-selective Wittig reaction but were unsuccessfully adopted in our

procedure, as starting material was consumed but no products could be isolated. Two probable reasons for this are;

1. Perlmutter uses 3.2 equivalents of base and 2.9 equivalents of phosphonium salt with respect to the aldehyde. Our aldehyde is probably base sensitive and these conditions could thus result in its decomposition.
2. It was not possible to determine if the generation of KHMDS was complete. Inadequate generation of KHMDS would result in free KH present in solution which could also cause decomposition of the starting material.

The lithium free bases, KH and dimsyl sodium were also unsuccessful, this time leading to the recovery of starting material. Addition of cosolvents such as DMPU did not alter the outcome. In frustration two and a half equivalents of *t*BuOK were added to an unsuccessful reaction mixture, containing KHMDS and DMPU in THF, resulting in the production of a 10:1 *Z:E* mixture of methyl ester (**145**) in 11% isolated yield. These conditions were subsequently optimised to produce methyl ester (**145**) (50%) in a 16:1 *Z:E* ratio as determined by ^{1}H NMR (**Scheme 26**).

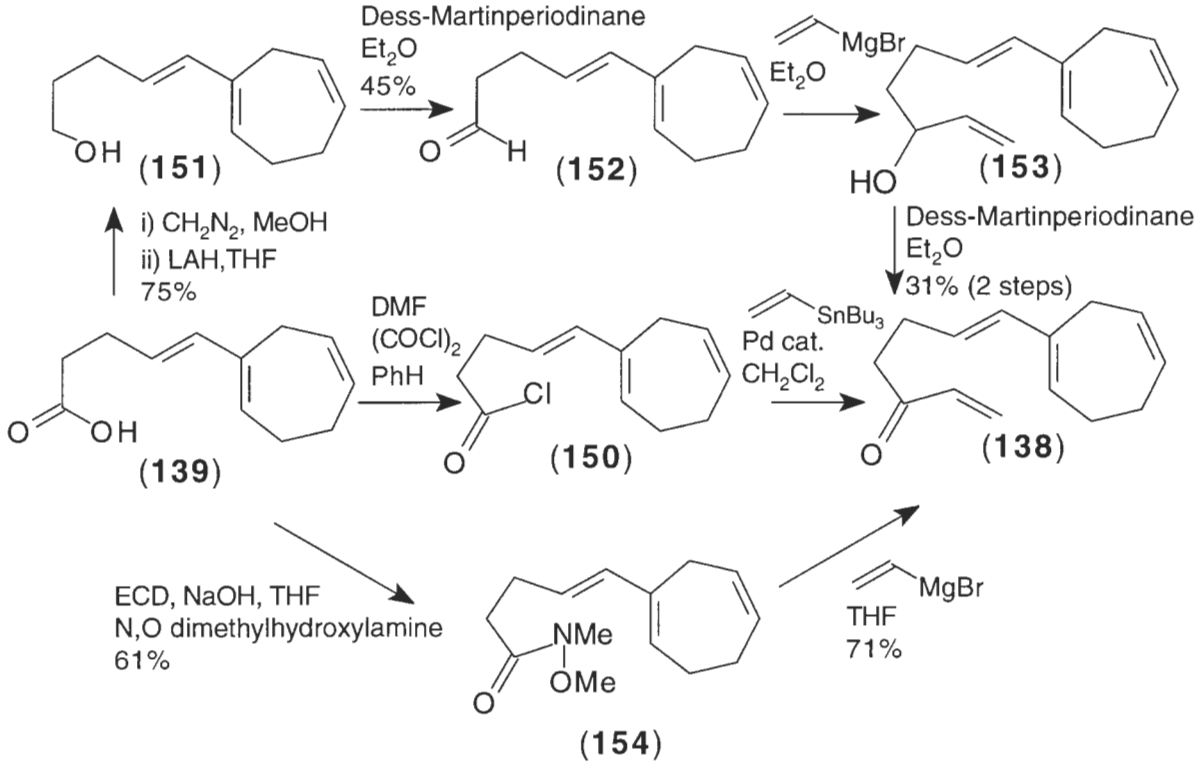


Scheme 26

In the^{1}H NMR spectrum, the aliphatic region of the spectrum has changed noticeably. The doublet of H_5 has moved upfield by 0.22 ppm to 5.85 ppm (J=11.4 Hz). The doublet of triplets of H_4 has become clearly defined and has moved upfield by 0.33 ppm to 5.28 ppm. The methoxy singlet occurs at the same chemical shift as the *E*- isomer but the singlet due to the doubly allylic methylene has moved upfield by 0.08 ppm and the methylenic protons now give three distinct multiplets in contrast to the two seen in the *E*-isomer. The most noticeable changes in the ^{13}C spectrum are a 2.13 ppm upfield shift of C_4 and a 2.03 ppm downfield shift of C_3. Smaller changes of 1.02 ppm downfield shift of the quaternary C_6 and 1.27 ppm downfield shift of C_7 are also observed. IR spectra are very similar except for the absence of a strong peak at 964 cm^{-1} (*trans* double bond) and the prescence of a medium peak at 733 cm^{-1} characteristic of a *cis* alkene.

2.5 Synthesis of the Vinyl Ketone

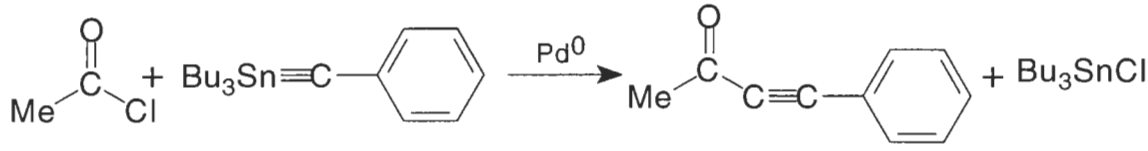
An intramolecular Diels-Alder reaction on vinyl ketone (**138**) should produce the required linearly fused ring system (**137**). Three possible routes for the synthesis of this vinyl ketone from acid (**139**) were attempted as shown in **Scheme 27**



Scheme 27

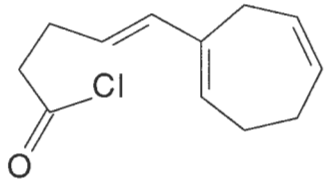
2.5.1 Stille Coupling

Acyl chlorides couple with alkenyltributyl stannanes in the presence of catalytic amounts of palladium (II) or palladium (0) complexes to produce alkenyl ketones[56] Stille and Milstein[57] first reported this conversion with tetraorganotin reagents. They subsequently found when vinyl trialkylstannanes were used, only the vinyl group was transferred to form the corresponding ketones in high yields (>90%) (**Scheme 28**)



Scheme 28

Initially a series of reactions of this type were tried on the *E*-isomer of acyl chloride (**150**). This was synthesised by DMF-catalysed reaction of acid (**139**) with oxalyl chloride in a solution of benzene.[58-61] The reaction was stirred until effervescence subsided at which time the presence of new multiplets at 5.6-5.4 ppm and 3.2-2.9 ppm in the ^1H NMR spectrum suggested an efficient transformation. Because of the susceptibility of acyl chlorides to hydrolysis by water, this reaction was carried out in strictly anhydrous conditions. The reaction was also attempted in CH_2Cl_2, as it was anticipated this would facilitate a sequential Stille coupling, however, no reaction was apparent, even after the addition of five equivalents of oxalyl chloride.



(**150**)

A Stille coupling with vinyl tributyl stannane and acyl chloride (**150**) was attempted using three palladium catalysts[56,62,63] and a variety of solvents.
The catalysts:

Dichlorobistriphenylphosphine palladium II	$[PdCl_2(PPh_3)_2]$
Dichlorobis(tri-o-tolyl phosphine) palladium II	$[PdCl_2[(o\text{-}tolyl_3)_2]$
Tetrakistriphenyl phosphine palladium II	$[Pd(PPh_3)_4]$

were used at a loading of 2 mol% with respect to the acid chloride unless stated otherwise. A comparison of four different palladium catalysts in the synthesis of alkynyl ketones was carried out by Logue[56] which suggested that $[PdCl_2(PPh_3)_2]$ would give the most promising results, although in some cases $[Pd(PPh_3)_4]$ gave very similar results. $[PdCl_2[(-o\text{-}tolyl_3)_2]$ is a more recently developed catalyst which been shown to have enhanced activity in other palladium catalysed reactions.[64]

The first palladium catalyst, $[PdCl_2(PPh_3)_2]$ was added to a solution of 1.2 equivalents of vinyltributyl stannane and 1 equivalent of acid chloride (**150**) and was refluxed for 8 hours in benzene. TLC showed starting material was still present, so a further 2 mol% of catalyst was added and the reaction was left to reflux for a further 14 hours. At the end of this time visualisation by TLC showed there was no remaining starting material and the vinyl ketone was starting to cyclise (**Figure 12**). In order to continue this cascade reaction, refluxing was continued for a further 90 hours, at which time the ratio of (**138**):(**137**) was 1:1 as evidenced by ^1H NMR. TLC analysis indicated a significant quantity of decomposition products, so a work up according to the procedure developed by Chuang *et al*[63]was used to remove the tin residues. Following purification by column chromatography, only 40% of the mass balance was recovered. Of this 62% was vinyl ketone and 28% was cyclohept[f]indene. Further attempts to encourage this cascade reaction towards completion resulted in disappointing yields. As the reaction was sluggish in benzene, CH_2Cl_2 was used as the solvent and the possibility of a cascade reaction was not pursued. A similar study involving a tandem Stille coupling and intermolecular Diels-Alder reaction has been reported.[65]

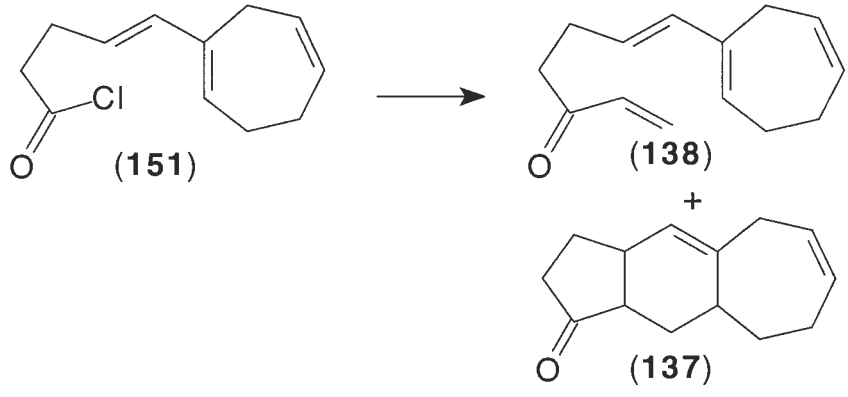


Figure 12

The ^1H NMR spectrum of the vinyl ketone shows a very complicated alkenic region. The terminal alkenes give two doublets of doublets at 6.3 ppm (J=10.1 Hz, 17.6 Hz) and 6.1 ppm (J=1.5 Hz, 17.6 Hz). The doublet indicative of the *E* -alkene has a chemical shift of 6.0 ppm (J=15.6 Hz) The multiplet at 5.7 ppm comprises 2 different signals. A doublet of doublets is due to the terminal alkene (J=1.5 Hz, 10.1 Hz) and a triplet due to the diene proton in the seven membered ring (J=6.5 Hz). The IR spectrum gives a strong C=O stretch at 1701

cm^{-1} and 1681 cm^{-1} characteristic of an α,β unsaturated ketone. Mass spectrometry data gave a molecular ion of 206. [1]

A similar reaction was carried out using this catalyst in refluxing CH_2Cl_2 (35°C). Large amounts of starting material were still present after 14 hrs so a further 1.5 mol% of catalyst was added and the reaction was continued to reflux for 24 hrs. Starting material had been consumed by this stage but the isolated yield of the vinyl ketone (10%) was very disappointing.

An alternative catalyst, $[PdCl_2[(o\text{-}tolyl_3)_2]$ was tried as it has been shown to have enhanced activity.[64] The reaction was again sluggish when carried out at RT in CH_2Cl_2 for 20 hours. At the end of this time no cycloadduct was present and the formation of the vinyl ketone (**138**) was slow. The mixture was refluxed for 5 hours then stirred at room temperature for 14 hours, at which time there was no starting material remaining. The same work up was used as in the previous reaction. After purification by column chromatography it appeared there was a mass balance yield of 85%, however, it was apparent from ^1H NMR that the vinyl ketone was contaminated with Bu_3SnCl residues. Upon freezing overnight the vinyl ketone started to undergo an intramolecular Diels-Alder reaction presumably catalysed by Bu_3SnCl acting as a Lewis acid catalyst.

The work up of the vinyl ketone reaction was modified in anticipation of more efficient removal of tin residues. Both aqueous ammonia (33%) solution and a saturated solution of KF were used in an attempt to remove the tin residues prior to purification but contamination was evident nevertheless.

Following unsatisfactory results with two palladium II catalysts, a third, tetrakistriphenylphosphine palladium 0 was trialled. The reactants were refluxed in CH_2Cl_2 for a total of 28 hours but starting material was sill apparent as visualised by TLC. Vinyl ketone (**138**) was isolated in 4% yield, the remaining material formed polar impurities.

Many further reactions were tried including the use of a sealed tube and exchanging vinyl tributyl stannane for the ethynyl compound. Even though the acyl chloride could be successfully generated from the acid, attempts to couple this to a vinyl stannane were futile. Despite rigorous efforts to purify the products, tin residues continued to be a major source of contamination. A

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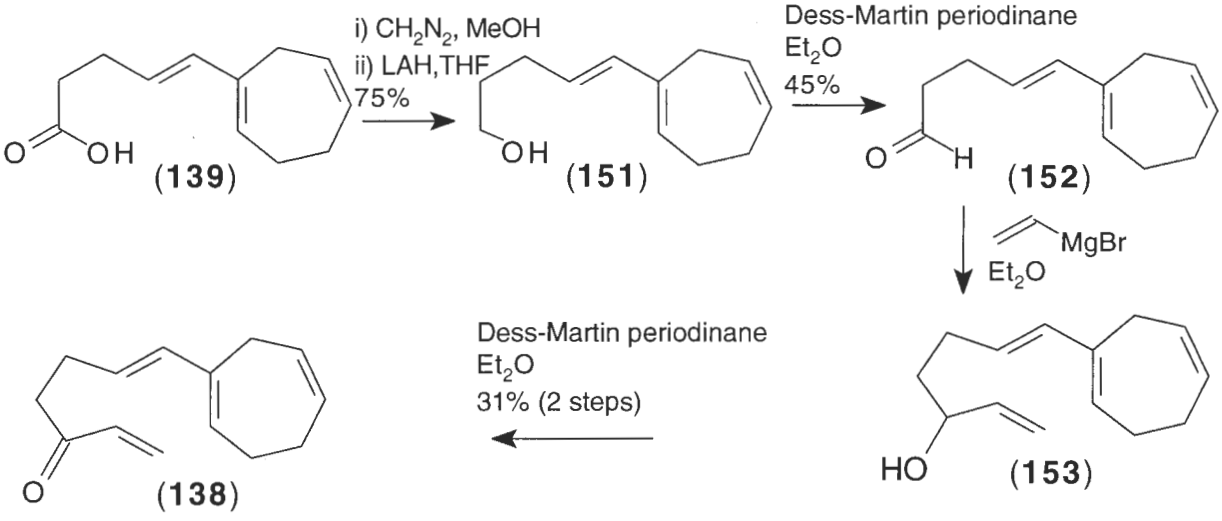
[1]Characterisation of the cyclohept[f]indene is discussed in a later section.

longer, more traditional approach involving the use of Grignard reagents was attempted.

2.5.2 The Grignard Approach: *E*-Series

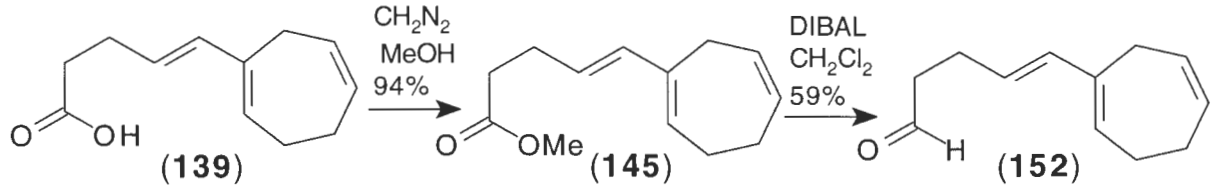


Scheme 29

Hydride reduction of acid (**139**) produced the alcohol (**151**) which was subsequently oxidised using Dess-Martin periodinane to give the corresponding aldehyde (**152**). Reaction of aldehyde (**152**) with the Grignard reagent vinyl MgBr afforded the vinyl alcohol (**153**) which was also oxidised using Dess-Martin periodinane to give the required vinyl ketone (**138**). Despite adding two steps to the synthesis, more traditional chemistry used in this route would ensure a successful synthesis.

2.5.2.1 Synthesis of the Aldehyde

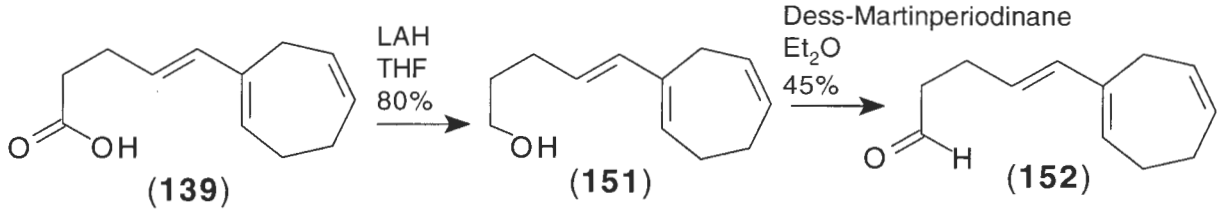
Hydride reduction of acid (**139**) to aldehyde (**152**) was successful using two similar types of reaction (**Schemes 30 and 31**).



Scheme 30

Esterification of the acid (**139**) to the methyl ester (**145**) was carried out using diazomethane (94%). This ester was selectively reduced to the aldehyde (**152**)

in 59% yield using DIBAL. A subsequent reaction resulted in a mixture of the alcohol and aldehyde being produced. This mixture could be converted to the aldehyde with Dess-Martin periodinane although the overall yield of 45% was lower.



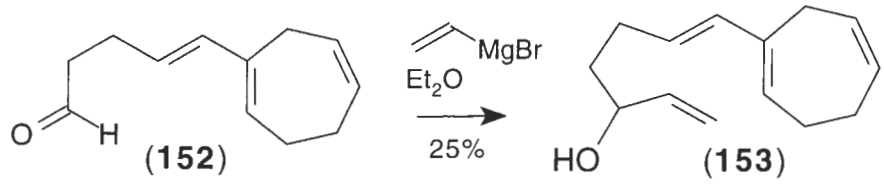
Scheme 31

Acid (**139**) was directly reduced to the alcohol (**151**) using LAH[66] and subsequently oxidising this to aldehyde (**152**) using Dess-Martin[67-70] periodinane. The overall yield for these two steps was 53%.

Formation of the alcohol (**151**) was verified by a broad hydroxyl peak at 3353 cm^{-1} in the IR spectrum and a new singlet at 2.4 ppm in the ^{1}H NMR. The ^{13}C spectrum showed a peak at 62.1 ppm which was indicative of an hydroxyl group attached to the terminus. Low resolution mass spectrometry data gave a molecular ion of 178.

NMR showed a prominent triplet in the ^{1}H spectrum (J=1.53 Hz) at 9.8 ppm and a peak at 199.7 ppm in the ^{13}C spectrum, characteristic of an aldehyde. IR also showed aldehydic C-H stretches at 2830 cm^{-1} and 2720 cm^{-1} and a C=O stretch at 1724 cm^{-1}. Low resolution mass spectrometry data gave a molecular ion of 176.

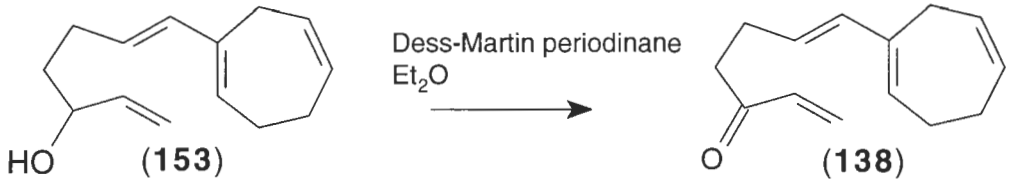
2.5.2.2 Synthesis of the Vinyl Alcohol



Scheme 32

The vinyl alcohol (**153**) was obtained in 25% yield by reacting the aldehyde (**152**) with vinyl magnesium bromide. This alcohol was labile as after storage in benzene at 0°C significant decomposition was seen after only 14 hours. On the basis of a 1.5 $molL^{-1}$ solution of freshly prepared vinyl magnesium bromide, 1.2 equivalents were required before all of the starting material was consumed, however, subsequent reactions required a greater volume due to crystallisation of the reagent.

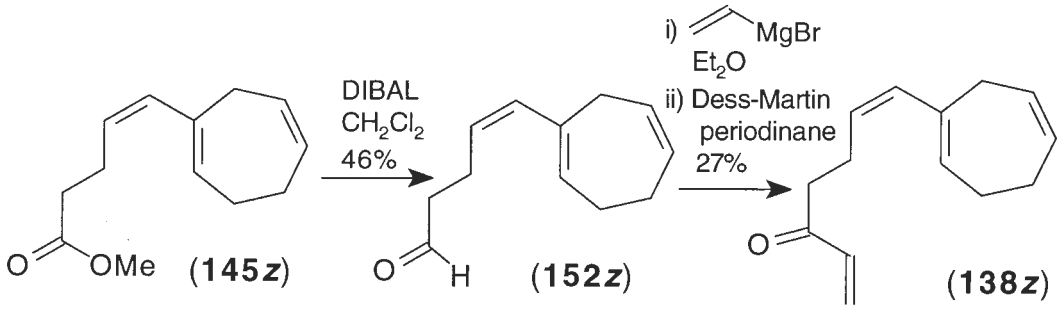
The ^1H spectrum of the vinyl alcohol produced an interesting array of peaks. ABX coupling was apparent in the terminal alkene, with a doublet of triplets at 5.2 (J=1.3 Hz, 17.4 Hz) and 5.1 ppm (J=1.3 Hz,10.3 Hz) respectively. The broad hydroxyl peak at 3360 cm^{-1} in the IR confirmed the presence of the hydroxyl group. The presence of seven alkenic carbons, one quaternary carbon and a carbon with a hydroxyl group (72.6 ppm) was indicated by ^{13}C NMR. Low resolution mass spectrometry data gave a molecular ion of 204. Because of the lability of the vinyl alcohol (**153**) it was isolated for characterisation, but in subsequent reactions was immediately oxidised to the vinyl ketone (**138**) thus increasing the overall yield to 31%.



Scheme 33

Once the vinyl alcohol (**153**) was formed from aldehyde (**152**) it was oxidised to the vinyl ketone (**138**), using Dess-Martin periodinane (31% over two steps). This disappointing result was largely due to the instability of the vinyl alcohol. The overall formation of the *E*-vinyl ketone (**138**) from the acid (**139**) via the grignard route was 17%.

2.5.2.3 The Grignard Route: *Z*- Series



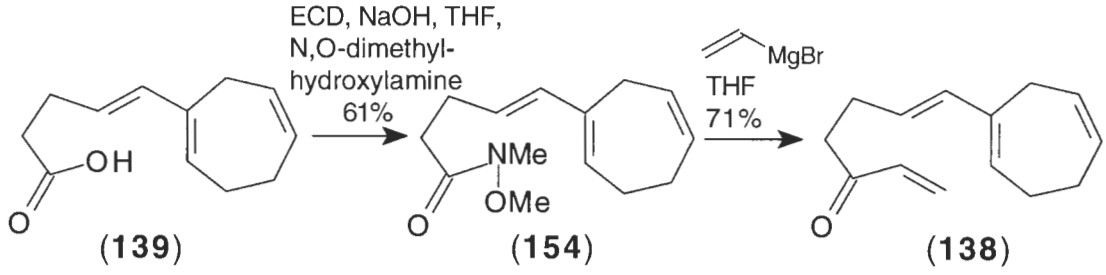
Scheme 34

The *Z*-Grignard route proceeded in a similar fashion to the *E* series. DIBAL reduction of the methyl ester (**145**) to the aldehyde (**152*z***) proceeded in 46% yield. Grignard reaction with vinyl magnesium bromide followed by Dess-Martin oxidation produced the vinyl ketone (**138*z***) in 27% over two steps from the aldehyde (**152*z***) (**Scheme 34**). The vinyl alcohol was not isolated due to stability problems encountered with the *E*-series. Overall reactivity with the *Z*-alkene was similar to that of the *E*- alkene with similar yields being obtained.

Changes in spectroscopy of the *Z*-isomer of the aldehyde showed similar changes to that of the *Z*-methyl ester, with the ^{1}H NMR spectrum giving a clear indication that the *Z*- isomer was present. The regions formed by the aliphatic portion of the diene have noticeably changed with the doublet of H5 moved upfield by 0.20 ppm to 6.04 ppm. The coupling constant has decreased by 4.2 Hz (J=11.4 Hz). The triplet due to H7 has also moved down field by 0.1 ppm. The doublet of triplets of H4 has become more clearly defined and has moved upfield by 0.35 ppm to 5.25 ppm. Methylenic signals have moved upfield with the singlet due to the doubly allylic methylene shifting by 0.08 ppm. The most noticeable changes in the ^{13}C spectrum are a 2.08 ppm downfield shift of the aldehydic C, 2.13 ppm upfield shift of C4 and a 2.03 ppm upfield shift of C5 α to the ring. A 3.02 ppm shift of the aliphatic C γ to the ring is the largest chemical shift and indicates *Z*- geometry. Smaller changes of 1.00 ppm downfield shift of the quaternary C and 1.27 ppm shift of diene C of the ring are also observed.

2.5.3 Weinreb Amide: *E*-series

N-methoxy-N-methyl amides which can be readily prepared from N,O-dimethyl hydroxylamine hydrochloride and a carboxylic acid, combine cleanly with Grignard reagents to form ketones.[71] This was the third route used for the synthesis of vinyl ketone (**138**) and is shown in **Scheme 35**.

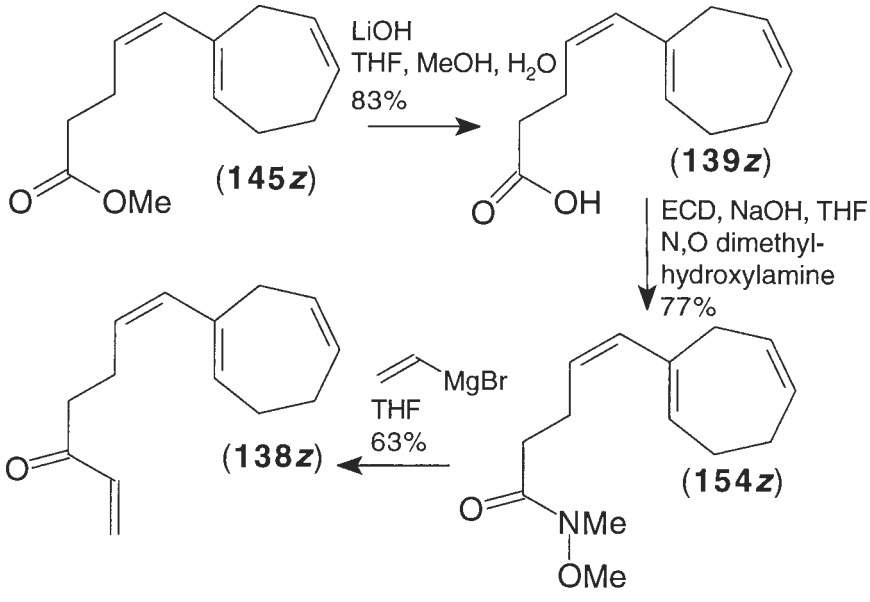


Scheme 35

N,O-dimethyl hydroxylamine hydrochloride was prepared according to the procedure developed by Goel[72] and was subsequently used in a reaction with acid (**139**) according to the procedure developed by Guanti[73] to produce the amide (**154**) (61%). The Weinreb amide was converted to the vinyl ketone (**138**) with vinyl magnesium bromide, following the same procedure. The overall formation of the vinyl ketone (**138**) from the acid (**139**) via the Weinreb amide was 43% rendering this the most efficient and therefore the most favoured route.

The presence of the amide functional group was confirmed by ^{1}H NMR spectroscopy with a methoxy peak at 3.7 ppm and an N-methyl peak at 3.2 ppm. A doublet at 6.1 ppm (J=16.2 Hz) indicates the presence of the *E*-isomer. Coupling of the N with the carbonyl group causes line broadening and decreases the amplitude resulting in a very broad, low amplitude peak at 173.6 ppm in the ^{13}C NMR. Substituent effects of the methyl and methoxy groups cause an upfield shift of the carbonyl C to 173.6 ppm in contrast to the carbonyl of the acid at 179.3 ppm. Low resolution mass spectrometry data gave a molecular ion of 235. A strong C=O stretch at 1665 cm^{-1} and N-H bending at 1432, 1384 cm^{-1} was apparent in IR.

2.5.3.1The Weinreb Amide-Z-series



Scheme 36

Once again this proved to be the most efficient route with only three steps producing the vinyl ketone (**138**) in 41% yield from the methyl ester (**145**). Hydrolysis of the methyl ester (**145**) to acid (**139**) was an efficient reaction utilising the procedure developed by Hung *et al* .[74] Base hydrolysis with LiOH in THF, methanol and water produced the acid in 83% yield. Production of the Weinreb amide (77%) proceeded under the same conditions as those used for the *E* series.

Spectra of the *E* -acid versus *Z* -acid show similar patterns as those observed for the methyl ester. In the ^{1}H NMR the regions formed by the aliphatic portion of the diene have noticeably changed with H5 having moved upfield by 0.21 ppm to 6.07 ppm. The coupling constant has decreased by 4.0 Hz (J=11.6 Hz). The triplet due to H7 has also moved upfield by 0.1 ppm. The doublet of triplets of H4 has become more clearly defined and has moved upfield to 5.32 ppm. The signal of the doubly allylic methylene is now a doublet of doublets in contrast to the singlet of the ester and has moved upfield by 0.08 ppm but other methylenic signals show very little movement. The most noticeable changes in the ^{13}C spectrum are a 2.42 ppm downfield shift of C4 and a 2.31 ppm downfield shift of C3 which indicates *Z* geometry. IR spectra are very similar except for the absence of a strong peak at 963 cm^{-1} indicative of the *trans* double bond which is replaced by medium, broad peak at 937 cm^{-1} of the *Z*- acid indicating the O-H

out of plane stretch. A medium broad peak at 715 cm^{-1} is characteristic of a *Z*-alkene.

The spectra for the Weinreb amide demonstrated similar changes, with ^1H NMR showing significant changes of the diene protons. The coupling constant of the aliphatic portion of the diene has decreased (J=16.62 Hz to J=11.87 Hz) and has moved upfield forming a multiplet. The doublet due to the doubly allylic methylene has moved upfield by 0.02 ppm. Singlets due to the methoxy and N-methyl peaks show very little movement. The mass spectroscopy fragmentation patterns are the same for both the *Z*- and *E*-isomers. IR spectroscopy shows a broad, weak N-H stretch at 3478 cm^{-1} for the *Z*-isomer, which occurs at 3497 cm^{-1} for the *E*-amide. The overlapping ketone stretch and amide I band is much more apparent in the *Z*- isomer at 1667-1651 cm^{-1}.

Formation of the vinyl ketone from the Weinreb amide (63%) was carried out under the same conditions used for the *E* series. Comparison of ^1H NMR spectral data for the *Z*- isomer to that of the *E*-isomer shows an upfield shift of 0.06 ppm for the two doublet of doublets due to the terminal alkene. The doublet due to H2 has moved upfield by 0.08 ppm. The doublet of triplets due to the *Z*- alkenic proton β to the ring has also moved upfield 0.30 ppm. The multiplet due to the doubly allylic methylene has moved upfield by 0.09 ppm. The IR spectra are very similar (correlation factor 0.8709 ±0.005), once again the *Z* isomer has a broad peak at 745-702 cm^{-1} indicative of the *cis* geometry, in contrast with the *E* isomer which shows a *trans* -peak at 962 cm^{-1}.

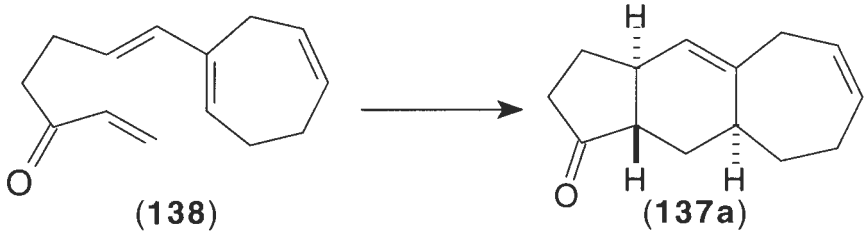
2.6 The Diels-Alder Reaction

The Diels-Alder reaction involves the [4+2] cycloaddition of an alkene to a conjugated diene. It proceeds stereoselectively *syn* with respect to both the diene and the dienophile.[75] Its ability to generate simultaneously up to four chiral centres in an highly stereoselective and largely predictable fashion has resulted in its application to numerous syntheses.[76]

For the intermolecular Diels-Alder reaction *endo*- orientation is prefered due to secondary orbital overlap of the highest occupied molecular orbital of the diene and the lowest unoccupied molecular orbital of the dienophile. These reactions are thermally allowed.

Stereocontrol of the intramolecular Diels-Alder reaction is much more complex. It appears that secondary orbital overlap is unimportant in determining product ratio's. A delicate and subtle balance of structural factors affects the stereochemical outcome of these reactions which is beyond the scope of this discussion. For a review see Craig.[76] The terms *exo-* and *endo-* refer to the orientation of the dienophile activating group with respect to diene function. Flat conjugated π systems have a high ratio of *exo-* products although this is dependent on the linking chain between the diene and dienophile.

2.6.1 Intramolecular Diels Alder Reaction



(138) (137a)

Scheme 37

For the required stereochemistry of the dolabellanes a Diels-Alder reaction that favours the *exo-* mode of cycloaddition is required. To optimise diastereoselectivity of this reaction both thermal and Lewis acid catalysed conditions were attempted.

2.6.1.2 Lewis Acid Catalysed Conditions

Literature precedent suggests Lewis acid catalysis gives high stereoselectivity.[77] A variety of Lewis acids were tried on small scale with varying levels of success (**Table 2**). All reactions used the *E*-vinyl ketone as this has more favourable orientation of the dienophile and would therefore have enhanced reactivity towards the Diels-Alder reaction. They were all stirred at room temperature using CH_2Cl_2 as the solvent and catalysts were used at a concentration of 10 mol%. TLC was used to monitor the progress of the reaction. At the end of 6 hours the reaction was quenched using a 5% solution of $NaHCO_3$.

Catalyst	Observation	Result
$LiClO_4$	no change	no reaction[1]
$TiCl_4$	cloudy, dark brown, solution	Starting material destroyed
$(C_2H_2)_2O.BF_3$	clear, reddy brown solution	Starting material destroyed
$SnCl_4$	clear, pale brown solution	Starting material destroyed
$AlCl_3$	cloudy, white suspension	Cyclohept[f]indene formed
$ZrCl_2$	cloudy, pink suspension	Cyclohept[f]indene formed

[1] $LiClO_4$ was also used in stoichiometric quantities with the same result

Table 2

Although some product was seen with aluminium chloride (1:1 starting material : product) and zirconium tetrachloride (10:1) the reactions were sluggish and starting material was not consumed. Large amounts of polar impurities were also seen on visualisation by TLC. From the results of these reactions it was decided to try diethyl aluminium chloride. This reagent is not as harsh as aluminium chloride and literature precedent suggested good results would be obtained. Initially diethylaluminium chloride was used in CH_2Cl_2 at -78° in catalytic quantities.[78] When this was ineffective stoichiometric quantities were tried at the same low temperature.[79-82] Although the starting material (**138**) was fully consumed no cyclohept[f]indene (**137**) was isolated. ^1H NMR suggested the formation of oligomers and polymers.

A much milder Lewis acid, ZnCl was then tried using the same reaction conditions. No reaction occurred after five hours at low temperature so the reaction was heated to RT, still with no success. A further attempt using an excess of zinc chloride at RT showed no change after three hours.

Rather than persuing further Lewis acid catalysed reactions, thermal conditions were developed.

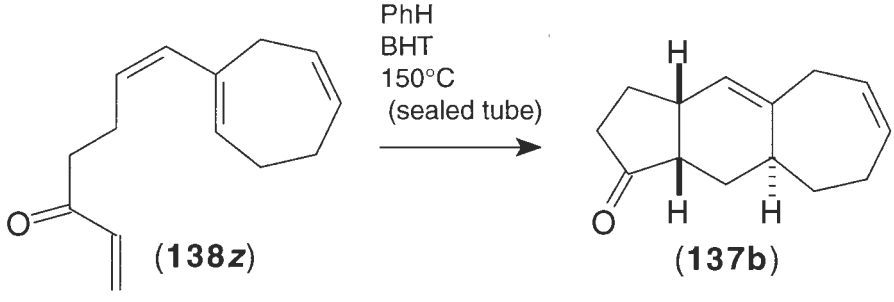
2.6.1.3 Thermal Intramolecular Diels Alder-*E*-series

The thermal IMDA was first attempted by refluxing vinyl ketone (**138**) in benzene with a catalytic amount of BHT. This reaction proved sluggish so the benzene was removed and replaced by toluene. Very low yields were obtained.

In an attempt to improve yields and diastereoselectivity thermally invoked IMDA was tried at various temperatures and pressures. A sealed tube reaction at 200°C for two hours produced the desired cyclohept[f]indene (**137a**) in low yield (25%). By ^{13}C NMR a mixture of diastereomers was apparent in a 5:1 ratio. As these conditions were too harsh lower temperatures and shorter time periods were experimented. At 150°C for one and a half hours some starting material was still visible. Pure cyclohept[f]indene (**137a**), once again as a 5:1 ratio of diasteroisomers, was isolated in 35% yield.

At this stage it was realised the vinyl ketone (**138**) had degraded somewhat. Repurification followed by refluxing for 18 hours in toluene with BHT produced cyclohept[f]indene in 77% yield. A diastereomeric ratio of 7.6:1 was obtained as determined by NMR.

2.6.1.4 Intramolecular Diels Alder- *Z*–series



(**138*z***) (**137b**)

Scheme 38

As predicted the reactivity of the *Z* alkene towards an intramolecular Diels -Alder reaction was retarded in comparison to the *E* alkene. On simple reflux in toluene, the same conditions used for the *E*- series the reaction was only 50% completed after 63 hours. Refluxing was continued for an extra 96 hours (4 days) at which time no starting material remained. Side reactions resulted in an array of products so the reaction was repeated at increased pressure. After 6 hours at 150°C in a sealed tube the reaction was virtually complete. On

purification two diastereomisomers were obtained which proved very difficult to separate.

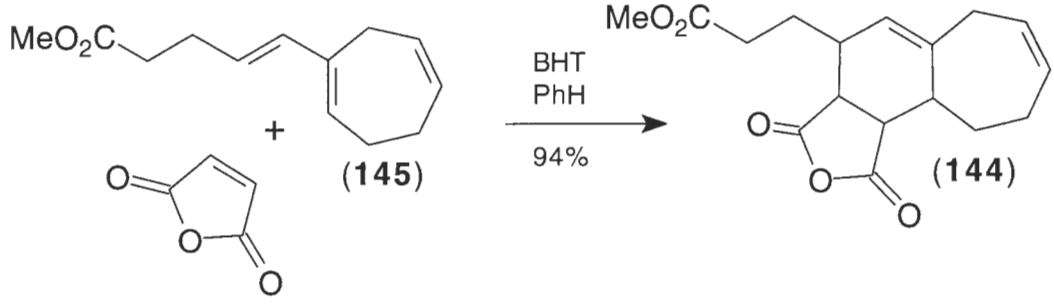
This series provided a mixture of diastereoisomers. The Wittig reaction provided a 16:1 mixture of *Z:E* isomers which subsequently produced a mixture of diastereoisomers on cyclisation. The Diels-Alder reaction had a high degree of *exo-* selectivity however a diastereomeric mixture was still produced.

2.6.2 The Intermolecular Diels-Alder Route

Two of the four possible diastereomers have been made with high distereoselectivity. An intermolecular approach was required to produce the other two.

2.6.2.1 Intermolecular Diels-Alder Reaction

2.6.2.1 *E*-Series



Scheme 39

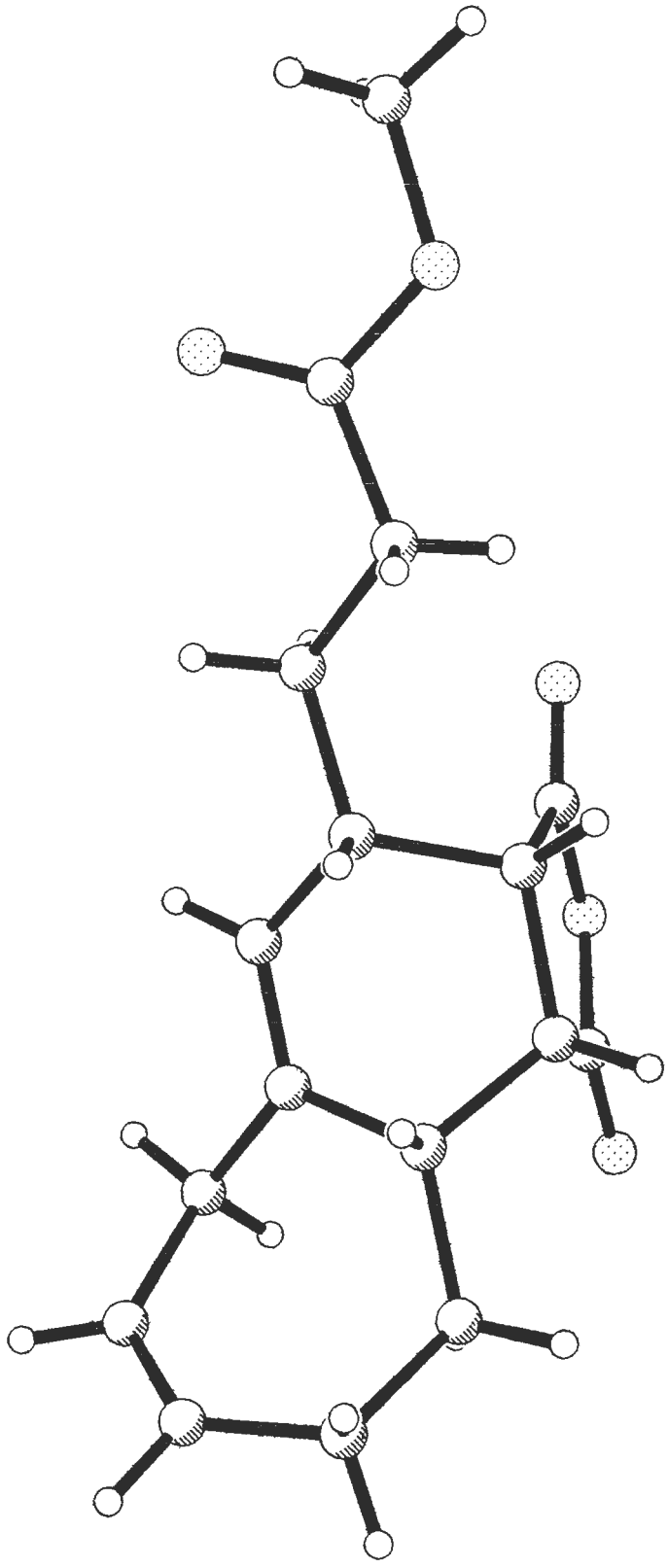
Maleic anhydride is refluxed with *Methyl-5-cyclohepta1,5-diene-E-4-pentenoate* (**145**) to produce the *syn-* anhydride (**144**) as a white crystalline solid.[83] Initially 1.5 equivalents were used and the reaction was complete in two hours. Purification by column chromatography isolated the anhydride (**144**) in 94% yield when the reaction was performed on small scale. Column chromatography however proved difficult on large scale with a detrimental effect on yields. As an alternative 1.05 equivalents of maleic anhyride was tried and although the reaction took a further hour to complete yields remained high. This product could then be recrystallised in 55% yield.

The ^{1}H NMR spectrum proved very difficult to assign so two dimensional NMR studies were carried out. NOESY, COSY and HETCOR data were collected. A complicated array of peaks was too difficult to assign completely, despite this

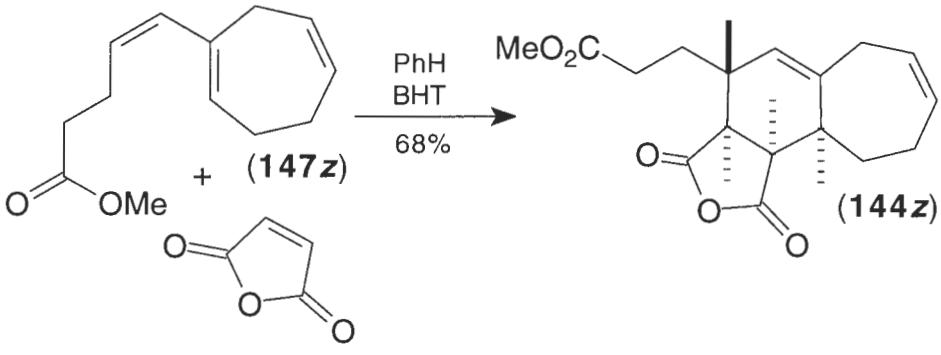
extra data. Deuterated acetone and deuterated benzene were tried as solvents in an attempt to get better separation of peaks, however, this failed to elucidate any further information. A shift reagent proved to be useful in determining a complete assignment. Tris(6,6,7,7,8,8heptafluoro-2,2-dimethyl-3,5-octanedionate) Europium (III) induced a chemical shift down field. After 3 mg of shift reagent had been added a triplet was seen at 2.9 ppm, having shifted from a multiplet at 2.5 ppm. On addition of 5 mg of this reagent a doublet of doublets was apparent at 3.5 ppm which had shifted down field from 3.3 ppm and were now were almost first order. Unfortunately further addition of shift reagent made the spectrum more complicated as multiplets merged together.

As it was possible to purify the anhydride by recrystallisation, attempts to grow crystals suitable for obtaining x-ray data were carried out. Following successful attempts with *t*BuMe ether as a solvent for recrystallisation x-ray data confirmed the formation of the *endo*- Diels-Alder adduct.

Anhydride (**144**) ($C_{17}H_{20}O_5$) was crystallised in the orthorombic system in space group $P2_12_12_1$, with unit cell dimensions: a=8.850 (2), b=9.621 (2), c=18.122(4) Å. 1644 reflections were collected of which 1630 were considered observed ($I>2\sigma(I)$) and used in the subsequent refinement. The structure was refined using Full-matrix least-squares on F^2 with final R indices of 3.52%. It is illustrated in the figure and shows the relative stereochemistry of the *endo* product.



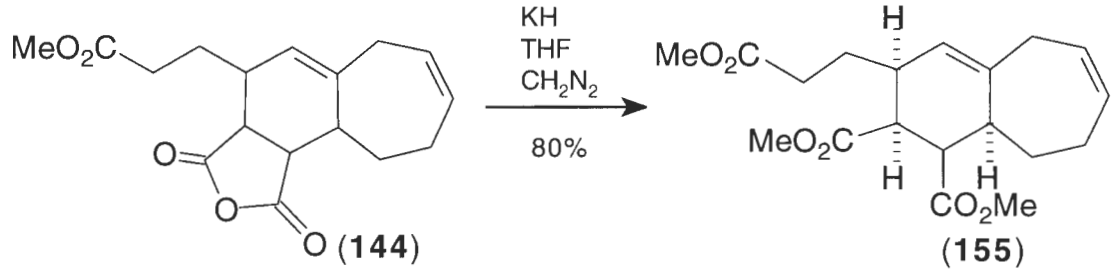
2.6.2.2 Z series



Scheme 40

Maleic anhydride was refluxed with *Methyl-5-cyclohepta1,5-diene-Z-4-pentenoate* affording the *anti*-anhydride (**144z**) as a white crystalline solid. The reaction was not purified on small scale as flushing through a plug of silica was sufficient to remove the majority of impurities. Initially the reaction was tried with 1.05 equivalents of Maleic anhydride but the reaction proved too slow so the amount of maleic anhydride was increased to 1.5 equivalents. Unreacted maleic anhydride was removed by flushing through silica. The residue was then recrystallised in 68% yield. It was difficult to grow crystals appropriate for x-ray analysis, as all attempts resulted in long, needle-like crystals. The ^1H NMR spectrum could be assigned by analogy so a crystal structure was not obtained.

2.7.2 Intramolecular Claisen



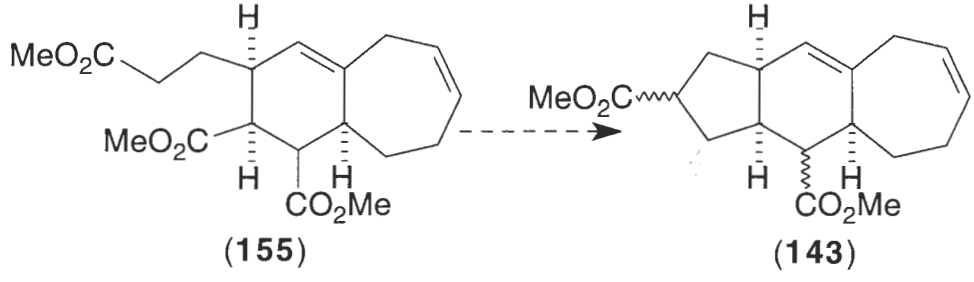
Scheme 41

Attempts to cyclise anhydride (**144**) to the linear ring system using an intramolecular Dieckmann-type reaction were carried out. Initially LHMDS was used to try and obtain the desired tricyclic product[84] but this proved too strong base and the starting material was destroyed. Milder bases were attempted and initially good results were obtained with KH. The reaction was endeavoured on small scale and half the product was immediately reacted with diazomethane to

form the dimethyl ester. Chromatography and spectroscopy of the acid proved difficult so in further experiments the acid was not isolated but was immediately esterified. Although initially the KH reaction looked promising spectral data indicated the trimethyl ester (**155**) had been formed (**Scheme 41**).

^{1}H NMR spectra showed a nine proton multiplet at 3.74-3.62 ppm characteristic of three methyl esters. A multiplet at 5.71 ppm and a singlet at 5.28 ppm are characteristic of the two alkenes. A complicated array of multiplets is present in the methylene region. ^{13}C NMR showed nineteen non equivalent carbons with three carbonyl carbons at 173.45-172.46 ppm. There is one quaternary carbon at 137.67 ppm and three other alkenic carbons. The methoxymethyls resonate at 51.81-51.30 ppm. A strong carbonyl stretch characteristic of a methyl ester is seen at 1735 cm^{-1} in the IR spectrum, along with a broad O-C-C assymetric stretch at 1165 cm^{-1}. Mass spectral analysis gave a molecular ion of 350.

Further attempts at the Dieckmann reaction were also tried. *t*BuOK in THF was used.[85] This produced a mixture of four products as visualised by TLC. These were all isolated but 1H NMR data indicated the desired product was not formed. Refluxing with Na in benzene was then tried.[86-88] Due to difficulties in handling small amounts of Na metal this approach was abandoned after 48 hours. Visualisation by TLC indicated no reaction and this was confirmed by 1H NMR. As these initial reactions proved futile, it was decided to form the desired cyclohept[f]indene (**143**) using an intermolecular Claisen reaction of the trimethyl esther (**155**) (**Scheme 42**).

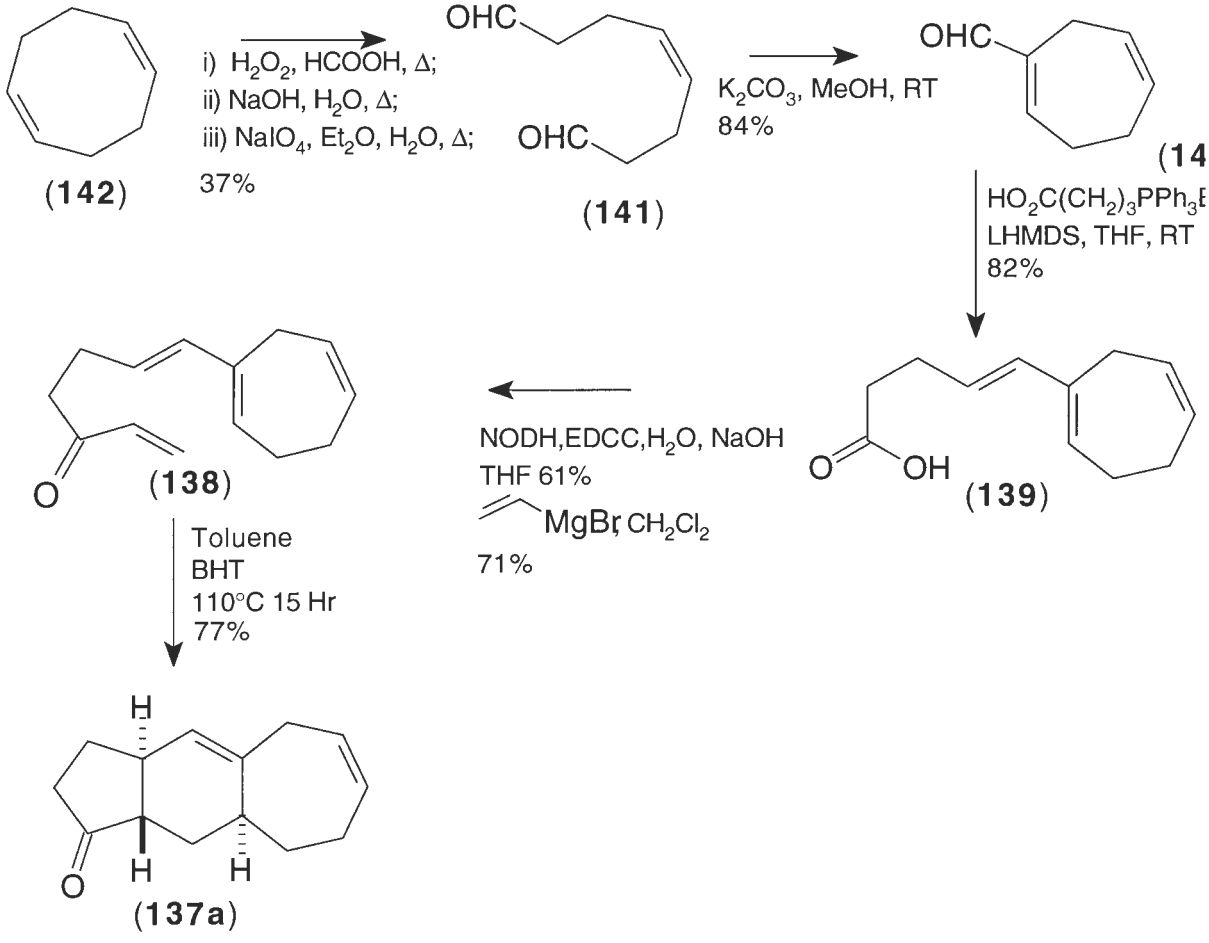


Scheme 42

Two further attempts to form the cycloadduct were made. These involved the base catalysed Claisen reaction of the trimethyl ester. The trimethyl ester was added to a solution of KH in THF at low temperature but again the desired cycloadduct was not obtained. In a subsequent reaction similar conditions were used but at higher temperatures, however, this also was unsuccessful and the starting material was recovered.

2.8 Summary

Two isomers of the desired cyclohept[f]indene (**137**) were formed in an efficent manner from cyclooctadiene. This short, eight step synthesis allows for flexibility in the functionality of the tricyclic structure and is a model study towards the efficient production of a variety of dolabellanes. While it was unfortunate not to synthesise the full range of diastereoisomers future work may enable the synthesis of the entire range. The most important compound for the synthesis of the dolabellanes, has - fusion at the ring junction and can be synthesised in high yield over eight steps as outlined in **Scheme 43**. This can easily be modified to produce a wide range of similar structures.



Scheme 43

Dialdehyde (**141**) was prepared on large scale by selective epoxidation of cyclooctadiene (**142**), hydrolysis to diol (**143**) and oxidative cleavage of the diol with sodium metaperiodate. An intramolecular aldol reaction was invoked by treatment of dialdehyde (**141**) with K_2CO_3 to afford cycloheptadiene-

carboxaldehyde (**140**). An *E*- selective Wittig reaction was performed with 4-carboxybutyl-triphenylphosphonium bromide, to produce acid (**139**). This was converted to vinyl ketone (**138**) in an efficient manner utilising a Weinreb amide. An intramolecular Diels-Alder reaction proceeded with high *exo*- selectivity that produced the desired cyclohept[f]indene (**137a**).

3. Experimental

Infrared spectra were recorded using a Perkin Elmer FTIR spectrometer as thin films between sodium chloride plates for oils or as potassium bromide disks for solids. Absorption maxima are expressed in wave numbers (cm^{-1}) with the following abbreviations: s= strong, m=medium, w=weak and b=broad

^{1}H nuclear magnetic resonance spectra were obtained at 270 MHz using a JEOL GX270 spectrometer. Chemical shifts are expressed in parts per million (ppm) down field shift using $CDCl_3$ as an internal reference standard at 7.27 ppm. Coupling constants (J) are given in Hertz (Hz).

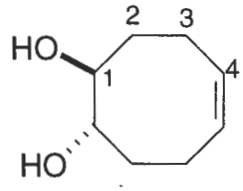
^{13}C nuclear magnetic resonance spectra were obtained at 68 MHz using a JEOL GX270 spectrometer. ^{13}C nuclear magnetic resonance data are expressed in parts per million down field shift using the middle peak of $CDCl_3$ as an internal reference standard at 77.00 ppm.

Mass spectra were recorded using a Varian VG70-250S double focusing magnetic sector mass spectrometer with an ionisation potential of 70 eV. GCMS or EI/DCI mass spectroscopy was used. Major fragmentations are given as percentages relative to base peak intensity.

Merck Kieselgel 60 (230-400 mesh) was used for column chromatography.

Thin layer chromatography was performed using precoated silica gel plates (Merck Kieselgel $60F_{254}$) and compounds were visualised by ultra-violet fluorescence and by staining with vanillin in ethanolic sulphuric acid or potassium permanganate solutions.[53]
Solvents were dried and purified according to the methods of Perrin and Amarego.[89]

Cyclo-oct-5-ene-*E*-1,2-diol

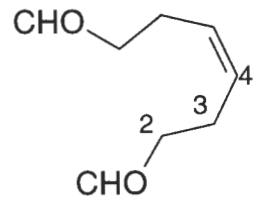


(**146**)

This compound was prepared according to procedure developed by Yates *et al.*[39] Cyclooctadiene (50 g, 0.46 mol) was stirred in a 3 L round bottom flask at 0°C. A mixture of 30% aqueous hydrogen peroxide (50 g, 0.49 mol) and formic acid (378 g, 8.21 mol) was added at a rate such that the temperature was maintained at 40°-45°C (*ca* 30 min). The icebath was removed and reaction stirred for 5 minutes. It was then heated to 65°C until a negative starch-iodide test using starch iodide paper was obtained (*ca* 2 hr).

Solvent was removed *in vacuo* (*ca* 1 hr). A solution of sodium hydroxide (23% w/v, 120 mL) was added at 0°C then the whole reaction mixture was heated to 100°C for 2 hours. Concentrated HCl was added dropwise until pH 7 was obtained. Water was removed *in vacuo*. Precipitated NaCl was rinsed well (3 x 20 mL) with CH_2Cl_2 and removed by filtration to give the crude product as a thick, dark, brown oil. Distillation at reduced pressure gave *cyclo-oct-5-ene-E-1,2-diol* as a colourless, oil. (26 g, 0.18 mol, 39%): BP. 108°/0.1 mm Hg; R_F 0.51 (1:3-hexane:EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.58 (t, J=4.5 Hz, 2H, H1), 3.65 (m, 2H, H4), 3.07 (s, 2H, OH), 2.41-2.22 (m, 2H, H3), 2.19-2.0 (m, 4H, H2, H3), 1.48-2.59 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 128.72 (2,C1), 76.44 (2,C4), 33.12 (2,C2), 22.62 (2,C3); This data is in agreement with the literature values.

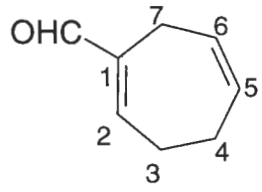
Z-Oct-4-ene-1,8-dial



(141)

This dialdehyde was synthesised according to the procedure developed by Singh, V and Deota, P.[40] *Cyclo-oct-5-ene-E-1,2-diol* (5.0 g, 35 mmol) was dissolved in moist Et_2O (125 mL). Sodium metaperiodate (7.5 g, 35 mmol) was added and the reaction was stirred at 31°C for 45 minutes. The Et_2O layer was decanted and the residue dissolved in the minimum amount of water. The aqueous phase was extracted with Et_2O (3 x 50 mL). Organic layers were combined, washed with H_2O (10 mL), saturated brine (10 mL), dried (Na_2SO_4). and removed *in vacuo* to leave the crude product as a colourless, clear oil. Column chromatography (Et_2O:hexane 1:1 R_F 0.32) provided *Z-oct-4-ene-1,8-dial* as a colourless, clear oil. (4.6 g, 33 mmol, 94%): R_F 0.79 (1:3-hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 9.72 (t, J=1.4 Hz, 2H, CHO), 5.34 (m, Hz, 2H, H1), 2.48 (m, 4H, H3), 2.33 (m, 4H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 201.48 (2, CHO), 128.57 (2, C4), 43.37 (2, C3), 19.87 (2, C2). This data is in agreement with the literature values.

Cyclohepta-1,5-diene-carboxaldehyde

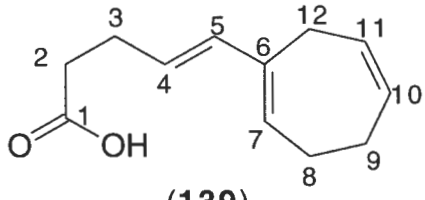


(140)

Z-oct-4-ene-1,8-dial (5.0 g, 36 mmol) was dissolved in MeOH (700 mL) and K_2CO_3 (8.7 g, 71 mmol) was added. The reaction mixture was stirred under Ar at 18°C for 16 hours then the majority of the MeOH was removed *in vacuo* at 18°C (*ca.* 10 mL remained). Saturated aqueous KH_2PO_4 (20 mL) was added and the product extracted with Et_2O (3 x 50 mL). The combined ethereal extracts were washed with H_2O (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and removed *in vacuo* to leave the crude product as a golden brown coloured oil. Vacuum distillation provided *cyclohepta-1,5-diene-carboxaldehyde* as a colourless oil (3.6 g, 29.98 mmol, 84%): BP. 150°/0.1 mm Hg; R_F 0.89 (1:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 9.3 (s, 1H, CHO), 6.81 (t, J=5.7 Hz, 1H, H2), 5.84 (m, 2H, H5, H6), 3.10 (m, 2H, H7), 2.62 (m, 2H, H3), 2.35 (m, 2H, H4); ^{13}C NMR (68 MHz, $CDCl_3$) δ 193.81 (CHO), 154.98 (C2), 142.81 (C1), 130.81 (C6), 127.53 (C7), 27.91 (C8), 25.11 (C4), 22.81 (C3); IR (neat, NaCl plate) 3019, 2940, 2834, 2724, 1683, 1643, 1450, 1433, 1309, 1252, 1180, 1144, 1095, 1047, 993, 923, 863, 845, 796, 710, 682, 637 cm^{-1}; MS (GCMS) calculated for $C_8H_{10}O$: m/e 122.073165, found 122.073162; 122.0732 (M+, 54%), 107.0514 (M+-CH_3, 34%), 91.0522 (M+-CHO, 72%), 77.0390 (M+-C_2H_5O, 100%), 65.0381 (M+-C_3H_5O, 22%), 53.0382 (M+-C_4H_5O, 14%), 39.0228 (M+-C_5H_7O, 38%).

Wittig Reaction

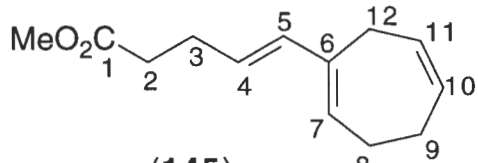
5-(Cyclohepta-1',5'diene)-*E*-4-pentenoic acid



(139)

The *E*-Selective Wittig conditions used were developed by Maryanoff and Duhl-Emswiler.[52] 4-(Carboxybutyl)-triphenyl phosphonium bromide (3.51 g, 8.19 mmol) was suspended in THF (20 mL), under Ar. Freshly prepared LHMDS (2.74 g, 16.4 mmol) was added dropwise at RT. A deep red solution forms after 15 mins. *Cyclohepta-1,5-diene-carboxaldehyde* (1.00 g, 8.19 mmol) was added decolourising the solution, orange. The reaction was stirred at RT for 15 mins, then quenched with a mixture of 1:1 Et_2O:H_2O. The Et_2O layer was washed with water and the aqueous phases combined, acidified to pH 2 (1% HCl) and subsequently extracted with EtOAc (4 x 30 mL). Organic layers were combined, washed with H_2O (30 mL), saturated brine (30 mL), dried ($MgSO_4$) and removed *in vacuo* to give the crude product as a straw coloured oil. Column chromatography (3:1 hexane:EtOAc + AcOH) provided *5-(cyclohepta-1',5'diene)-E-4-pentenoic acid* as a colourless, clear oil (1.32 g, 6.87 mmol, 84%). : R_F 0.22 (3:1 hexane:EtOAc + AcOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.97 (s, 1H, COOH), 6.07 (d, J=15.6 Hz, 1H, H5), 5.83 (t, J=0.03 Hz, 1H, H7), 5.61 (m, 3H, H4, H10, H11), 2.98 (s, 2H, H12), 2.4 (m, 6H, H8, H9, H3), 2.2 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 179.31 (C1), 139.78 (C6), 134.77 (C4), 131.30 (C10), 130.91 (C11), 126.17 (C5), 123.82 (C7), 34.15 (C12), 27.81 (C3), 26.79 (C2), 26.33 (C8, C9); IR (neat) 3017, 2934, 2677, 1709, 1431, 1286, 1254, 1208, 1166, 963, 850, 816, 626 cm^{-1}; MS (EI DCI) 192 (M+47%), 149 (M+-CO_2, 14%), 132 (M+-$C_2H_4O_2$,27%), 117 (M+-$C_3H_8O_7$, 51%), 105 (M+-$C_4H_7O_2$, 62%), 91 (M+-$C_5H_9O_2$, 100%), 79 (M+-$C_6H_9O_2$, 55%), 55 (M+-$C_8H_9O_2$, 54%), 41 (M+-$C_9H_{11}O_2$, 86%).

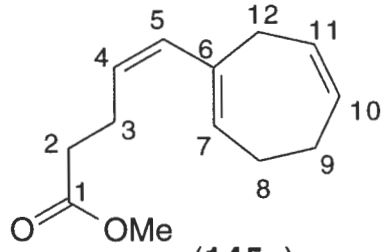
Methyl-5-(Cyclohepta1',5'-diene)-*E*-4-pentenoate



(**145**)

5-(Cyclohepta-1',5'diene)-E-4-pentenoic acid (236 mg, 1.23 mmol) was dissolved in methanol (10 mL) and cooled to 0°C. Diazomethane was added until the reaction reached a yellow endpoint. Excess diazomethane was destroyed on addition of one drop of acetic acid. The methanol was removed *in vacuo*. *Methyl-5-(cyclohepta1',5'-diene)-E-4-pentenoate* was a straw coloured oil (241 mg, 1.16 mmol, 94%) : R_F 0.45 (3:1 hexane:EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.06 (d, J=15.6 Hz, 1H, H7), 5.80 (t, J=6.5 Hz, 1H, H7), 5.64 (m, 3H, H10, H11, H4), 3.66 (s, 3H, OCH_3), 2.96 (d, J=3.9 Hz, 2H, H12), 2.39-2.29 (m, 6H, H3, H8, H9), 2.19-2.14 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.21 (C, 1), 139.77 (C6), 134.55 (C4), 131.07 (C10), 130.83 (C11), 126.13 (C5), 124.11 (C7), 51.47 (OCH_3), 34.08 (C12), 28.09 (C3), 26.76 (C2), 26.27 (2, C8, C9); IR (neat, NaCl Plate) 3015, 2948, 2905, 2845, 1736, 1645, 1435, 1362, 1308, 1252, 1197, 1163, 1090, 1069, 1012, 963, 849, 832, 816, 628 cm-1; MS (GC MS) 206 (M+), 146 (M+-$C_2H_4O_2$, 8%), 132 (M+-$C_3H_6O_2$, 20%), 119 (M+-C_4H_8O, 25%), 106 (M+-C_5H_9O, 26%), 91 (M+-$C_6H_{11}O$, 89%), 79 (M+-$C_7H_{10}O_2$, 95%), 67 (M+-$C_8H_{11}O_2$, 56%), 41 (M+-$C_{10}H_{13}O_2$, 100%).

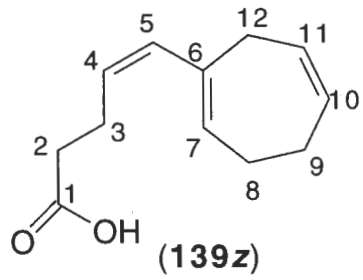
Methyl-5-(Cyclohepta1',5'-diene)-*Z*-4-pentenoate



(**145*z***)

4-(Methylcarboxybutyl) triphenyl phosphonium bromide (4.66 g, 10.5 mmol) was suspended in THF (20 mL) under Ar. A solution of tBuOK(1.0 g, 9.1 mmol) in THF (15 mL) was added dropwise and the mixture was stirred at RT for 15 minutes. At the end of this time the dark orange suspension was cooled to 0°C. A solution of*cyclohepta-1,5-diene carboxaldehyde* (0.856 g, 7.01 mmol) in THF (10 mL) was added to the ylid and the whole reaction was stirred at 0°C for 15 mins. The pale orange suspension was quenched with MeOH (50 mL), Et_2O:H_2O 1:1 (20 mL) was added and the aqueous layer was extracted with Et_2O (3 x20 mL). Combined ethereal extracts were washed with H_2O (10 mL), saturated brine (10 mL), dried ($MgSO_4$) and removed *in vacuo*. The resulting *Methyl-5-(cyclohepta1',5'-diene)-Z-4-pentenoate* was a straw coloured oil. (0.715g, 3.47 mmol, 50%) : R_F 0.62 (10:1 Hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 5.85 (d, J=11.5 Hz, 1H, H5), 5.76 (t, J=6.3 Hz, 1H, H7), 5.64 (m, 2H, H10, H11), 5.28 (dt, J=11.5, 6.9 Hz, 1H, H4), 3.68 (s, 3H, CH_3), 2.90 (m, 2H, H12), 2.54 (dt, J=1.3, 5.7 Hz, 2H, H3), 2.38 (m, 4H, H8, H9), 2.19 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.41 (C1), 138.77 (C6), 133.27 (C4), 130.87 (C11), 130.06 (C10), 127.04 (C5), 126.25 (C7), 51.58 (CH3), 34.56 (C12), 31.56 (C2), 26.85 (C9), 26.19 (C8), 24.24 (C3); IR (neat) 3009, 2948, 2905, 2832, 1739, 1687, 1645, 1435, 1360, 1252, 1196, 1162, 733 cm-1; MS (DCI probe) calculated for $C_{13}H_{18}O_2$: m/e 206.130680, found 206.130817; 206.1308 (M+, 71%), 175.1085 (M+ - C_2H_5O, 8%), 146.1126 (M+ -$C_3H_6O_2$, 22%), 132.0922 (M+ -$C_4H_9O_2$, 43%), 117.0700 (M+ -$C_5H_{11}O_2$, 64%), 105.0715 (M+ -$C_6H_{11}O_2$, 60%), 91.0543 (M+ -$C_7H_{13}O_2$, 100%), 79.0536 (M+ -$C_8H_7O_2$, 31%), 67.0554 (M+ -$C_9H_{13}O_2$, 18%), 41.0388 (M+ -$C_{11}H_{15}O_2$, 26%).

5-(Cyclohepta-1',5'diene)-*Z*-4-pentenoic acid

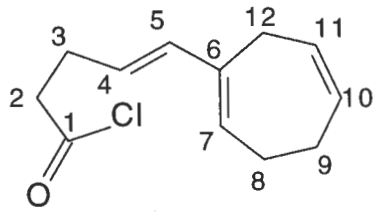


(**139*z***)

Methyl-5-(cyclohepta1',5'-diene)-Z-4-pentenoate (300 mg, 1.45 mmol) was dissolved in 4:1:1 THF:MeOH:H_2O (12 mL). LiOH was added and the reaction was stirred for 4 hours. The dark orange solution was quenched with dilute HCl until pH 2 was obtained. The aqueous layer was extracted with EtOAc (3x10 mL). Organic layers were combined, washed with H_2O (5 mL), saturated brine (5 mL), dried ($MgSO_4$) and removed *in vacuo*. The resulting straw coloured oil was purified using column chromatography, eluting solvent 3:1 hexane:ethylacetate + AcOH to give *5-(cyclohepta-1',5'diene)-Z-4-pentenoic acid* (0.234 g, 1.22 mmol, 84%): R_F 0.56 (3:1 hexane:ethylacetate); ^1H NMR (270 MHz, $CDCl_3$) δ 8.0 (s, 1H, OH), 5.86 (d, J=11.6 Hz, 1H, H5), 5.76 (t, J=6.48 Hz, 1H, H7), 5.70-5.58 (m, 2H, H10, H11), 5.32-5.24 (dt, J=11.4, 7.0 Hz, 1H, H4), 2.90 (dd, J=0.9, 2.2 Hz, 1H, H6), 2.57 (m, 2H, H3), 2.46-2.35 (m, 4H, H8, H9), 2.24 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 179.14 (C1), 138.74 (C6), 133.54 (C4), 130.90 (C10), 130.13 (C11), 126.68 (C7), 126.23 (C5), 34.55 (C12), 31.53 (C3), 26.85 (C8), 26.19 (C9), 23.94 (C2); IR (neat) 3010, 2936, 2681, 1710, 1430, 1412, 1280, 1253, 1209, 1161, 937, 846, 715 cm-1; MS (EI DCI) calculated for: m/e 192.115030, found 192.114712; 192 (M+, 70%), 164.0850 (M+ -$C_2H_4$10%), 132.0943 (M+ -$C_2H_4O_2$, 29%), 117.0699 (M+ -$C_3H_7O_2$, 52%), 105.0683 (M+ -$C_4H_7O_2$, 69%), 91.0553 (M+-$C_5H_9O_2$, 100%), 79.0550 (M+ -$C_6H_9O_2$, 34%), 67.0551 (M+ -$C_9H_{11}O_2$, 30%).

Stille Coupling

5-(Cyclohepta-1',5'diene)-*E*-4-pentenyl chloride

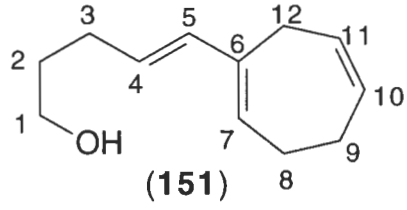


(150)

It was imperative that all glassware used in this reaction was thoroughly dried. *5-(Cyclohepta-1',5'diene)-E-4-pentenoic acid* (0.10 g, 0.52 mmol) was dissolved in benzene (1.5 mL) to which oxalyl chloride (132 mg, 1.04 mmol) was added. DMF (cat. 3μL) was added and the reaction was stirred at RT until effervescence subsided. (*ca* 15 min.) Benzene was removed *in vacuo.* The residue was flushed with benzene (1 mL x 2). Care must be taken not to expose the resultant *5-(cyclohepta-1',5'diene)-E-4-pentenyl chloride* to air or water at any time of this preparation.: ^{1}H NMR (270 MHz, $CDCl_3$) δ6.09 (d, J=16.0 Hz, 1H, H5), 5.85 (t, J=7.0 Hz, 1H, H7), 5.74-5.43 (m, 3H, H4, H10, H11), 3.0-2.90 (m, 4H, H12, H2), 2.57-2.34 (m, 4H, H8, H9), 2.28-2.14 (m, 2H, H3); ^{13}C NMR (68 MHz, $CDCl_3$) δ172.96 (C1), 139.48 (C6), 135.87 (C4), 132.11 (C10), 130.96 (C11), 126.00 (C5), 121.97 (C7), 47.09 (C2), 28.27 (C12), 26.70 (C3), 26.32 (C8) 26.23 (C9); IR (neat, NaCl Plate) 3334, 3015, 2932, 1655, 1432, 1376, 1349, 1255, 1170, 1052, 962, 919, 841, 815, 788, 701, 628 cm-1.

Grignard Approach

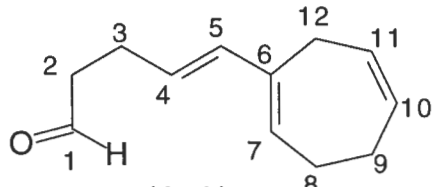
5-(Cyclohepta1',5'-diene)-*E*-4-penten-1-ol



(151)

5-(Cyclohepta-1',5'diene)-E4--pentenoic acid (0.46 g, 2.0 mmol) was dissolved in THF (18 mL) and the mixture was cooled to 0°C. LAH (124 mg, 3.26 mmol) was added and the reaction was stirred at 0°C for 10 min. It was then warmed to reflux for 55 min. The reaction was quenched at 0°C with 9 mL of THF:H_2O 1:1.25 and stirred for 2 hours until a thick white precipitate was formed. The solvent was removed *in vacuo* and the residue dissolved in MeOH. The precipitate was filtered through celite. The resulting *5-(cyclohepta1',5'-diene)-E-4-penten-1-ol* was highly unstable so was reacted immediately with Dess-Martin Periodinane to form the subsequent aldehyde.: R_F 0.44 (3:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 6.01 (d, J=15.4 Hz, 1H, H5), 5.78 (t, J=6.6 Hz, 1H, H7), 5.68-5.49 (m, 3H, H4, H10, H11), 3.61 (dt, J=2.0, 6.6 Hz, 1H, H3), 2.96 (m, 2H, H12), 2.44 (s, 1H, OH), 2.36 (m, 2H, H3), 2.17 (m, 4H, H8, H9), 1.64 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.99 (C6), 133.81 (C4), 130.81 (C10), 130.37 (C11), 126.10 (C5), 125.78 (C7), 62.14 (C1), 32.44 (C12), 29.12 (C3), 26.78 (C2), 26.18 (2, C8, C9); IR (neat, NaCl Plate) 3015, 2932, 1655, 1432, 1376, 1349, 1255, 1170, 1052, 962, 919, 841, 815, 768, 701, 628 cm-1; MS (GC MS) 178 (M+), 151(M+ -CH_{15}), 147(M+ -$H_{15}O$), 142(M+ -CH_8O), 137(M+ -$CH_{13}O$), 134(M+ -$CH_{16}O$), 131(M+ -C_2H_7O), 123(M+ -$C_2H_{15}O$), 119(M+ -C_3H_7O), 110(M+ -$C_3H_{16}O$), 105(M+ -$C_4H_{11}O$).

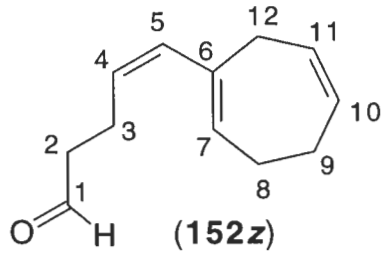
5-(Cyclohepta1',5'-diene)-*E*-4-pentenal



(152)

5-(Cyclohepta1',5'-diene)-E-4-penten-1-ol (255 mg, 1.43 mmol) was dissolved in CH_2Cl_2 (10 mL) under Ar. Dess-Martin Periodinane (849 mg, 2.00 mmol) was added while stirring. On completion saturated $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (10 mL) were added with Et_2O (20 mL) and the mixture was left to stir vigorously for 5 min. The Et_2O layer was drawn off and the aqueous layer extracted with Et_2O (3 x 10 mL). Organic layers were washed, H_2O (10 mL), saturated brine (10 mL), dried (Na_2SO_4) and removed *in vacuo*. Column chromatography, (EtOAc:hexane 1:9) provided *5-(cyclohepta1',5'-diene)-E-4-pentenal* as a straw coloured oil sensitive to acid so any residual SiO_2 was removed by filtration. (115 mg, 0.65 mmol, 46%): R_F 0.76 (3:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 9.77 (t, J=1.5 Hz, 1H, CHO), 6.04 (d, J=15.6 Hz, 1H, H5), 5.81 (t, J=6.6 Hz, 1H, H7), 5.60 (m, 3H, H4, H10, H11), 2.96 (d, J=4.2 Hz, 2H, H12), 2.54 (m, 2H, H3), 2.37 (m, 4H, H8, H9), 2.18 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 201.63 (C1), 139.67 (C6), 134.55 (C4), 131.15 (C10), 130.81 (C11), 125.98 (C5), 123.83 (C7), 43.52 (C2), 26.68 (C12), 26.19 (C9), 26.10 (C8), 25.33 (C3); IR (neat) 3014, 2900, 2830, 2719, 1724, 1645, 1622, 1432, 1408, 1388, 1354, 1255, 1208, 1182, 1050, 1012, 964, 904, 844, 815, 783, 732, 705, 647, 626 cm^{-1}; MS (DCI) 176.1199 (M+, 50%), 161.9891 (M+-H4, 9%), 143.0870 (M+-H_20, 13%), 132.0927 (M+-C_2H_40, 22%), 117.0706 (M+-C_3H_70, 56%), 105.0676 (M+-C_4H_7O, 52%), 91.0444 (M+-C_5H_9O, 100%), 78.9801 (M+-C_6H_9O, 43%), 67.07367 (M+-$C_{12}H_9O$, 23%), 53.1733 (M+-C_8H_{11}, 14%).

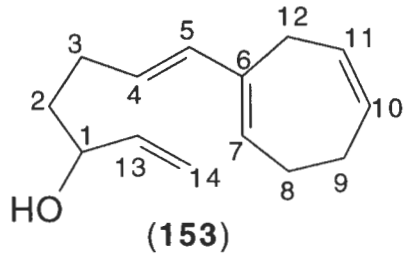
5-(Cyclohepta1',5'-diene)-*Z*-4-pentenal



(**152*z***)

Methyl-5-(cyclohepta-1',-5' diene)-Z-4-pentenoate (150 mg, 0.727 mmol) was dissolved in CH_2Cl_2 (10 mL) under Ar and cooled to -95°C. DIBAL (0.48 mL, 0.72 mmol) was added via syringe pump slowly over 2hr. The reaction was stirred for 30 min then quenched with 2% NaOH (2 mL) and slowly warmed to RT. A solution of 1:1 CH_2Cl_2 :H_2O (30 mL) was added, forming an emulsion to which saturated aqueous Rochelles salt was added. Once the emulsion cleared the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layers were washed with Rochelles salt (5 mL), saturated brine (5 mL), dried (Na_2SO_4) and solvent removed *in vacuo*. Resultant oil *5-(cyclohepta1',5'-diene)-Z-4-pentenal* was purified using column chromatography, eluting solvent EtOAc:hexane 1:20. (73.7 mg, 0.42 mmol, 56%) *5-(cyclohepta1',5'-diene)-Z-4-pentenal* was sensitive to acid so any residual SiO_2 was removed by filtration: R_F 0.83 (5:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 9.75 (s, 1H, H1), 5.84 (d, J=11.42 Hz, 1H, H5), 5.74 (t, J=6.5 Hz, 1H, H7), 5.68-5.54 (m, 2H, H10, H11), 5.25 (m, 1H, H4), 2.88 (d, J=4.0 Hz, 2H, H12), 2.57-2.47 (m, 4H, H3, H8), 2.34 (m, 2H, H9), 2.18 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 201.79 (C1), 138.70 (C6), 133.38 (C4), 130.82 (C10), 130.07 (C11), 126.74 (C5), 126.07 (C7), 44.166 (C2), 31.45 (C12), 26.78 (C9), 26.09 (C8), 21.42 (C3).

-(Cyclohept-1',5'-diene)-*E*-1,6-heptadien-3-ol

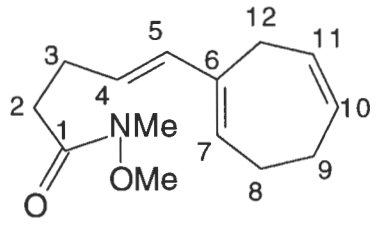


(**153**)

5-(Cyclohepta1',5'-diene)-E-4-pentenal (310 mg, 1.8 mmol) was dissolved in Et_2O (30 mL) under Ar and cooled to 0°C. A solution of vinyl magnesium bromide in THF (6.5 mL, 1.5 molL-1, 9.8 mmol) was added dropwise. On completion the reaction was quenched with a saturated solution of NH_4Cl and extracted with Et_2O (3 x20 mL). Ethereal layers were combined, washed with H_2O (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and removed *in vacuo.* Due to the lability of *7-(cyclohept-1',5'-diene)-E-1,6-heptadien-3-ol* the reaction mixture was cleaned by flushing through a plug of silica and immediately oxidised to the vinyl ketone. (20.5 mg, 0.1 mmol, 25%): R_F 0.61 (3:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 6.05 (d, J=15.6 Hz, 1H, H5), 5.94-5.78 (m, 2H, H7), 5.69-5.73 (m, 3H, H10, H11, H4), 5.27-5.20 (dt, J= 17.4 Hz,1.5 Hz 1H, H14), 5.15-5.10 (dt, J=10.3 Hz, 1.5 Hz 1H, H14), 2.99 (s, 2H, H12), 2.49-2.35 (m, 2H, H3), 2.21-2.16 (m, 4H, H8, H9), 1.68-1.62 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 140.85 (C6), 140.08 (C13), 133.98 (C5), 130.92 (C10), 130.54 (C11), 126.18 (C4), 125.81 (C7), 114.63 (C14), 72.58 (C1), 36.77 (C12), 28.78 (C2), 26.85 (C3), 26.28 (2, C8, C9); IR (neat, NaCl Plate) 3360, 3076, 3014, 2932, 2849, 1846, 1708, 1642, 1510, 1430, 1320, 1255, 1183, 1123, 1051, 991, 962, 921, 846, 816, 627 cm^{-1}; MS (DCI PROBE) calculated for $C_{14}H_{20}O$: m/e 204.151415, found 204.152134; 204.1521 (M+), 176.1193 (M+-C_2H_4, 10%), 157.1014 (M+-C_2H_7O, 5%), 145.1016 (M+-C_3H_7O, 15%), 131.0856 (M+-C_4H_9O, 24%), 117.0706 (M+-$C_5H_{11}O$, 46%), 105.0699 (M+-$C_6H_{11}O$, 39%), 91.0535 (M+-$C_7H_{13}O$, 10%), 79.0541 (M+-$C_8H_{13}O$, 56%), 67.0544 (M+-$C_9H_{13}O$, 41%), 55.0551 (M+-$C_{10}H_{13}O$, 32%), 41.0401 (M+-$C_{11}H_{15}O$, 48%)

Weinreb Amide

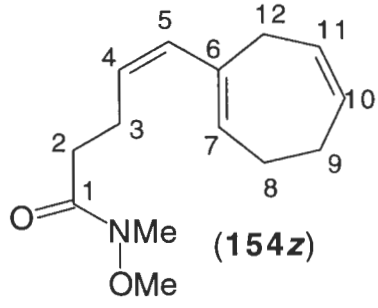
5-(Cyclohepta-1',5'-diene)-N-methyl-N-methoxy-E-4-pentenamide



(154)

5-(cyclohepta-1,5diene)-E-4-pentenoic acid (180 mg, 0.94 mmol) was dissolved in THF (2 mL) to which a solution of N,O,dimethylhydroxylamine (155 mg,1.59 mmol) in H_2O (2 mL) was added. 0.1 N NaOH was added until the pH was 4.5. 1,3-dimethylaminopropyl-3-ethylcarbodiimide (449 mg, 2.34 mmol) dissolved in H_2O (7 mL) was added over a period of 15 min during which time the pH was maintained at pH4.5. The reaction was stirred for 1 hr then quenched by saturating the solution with NaCl. The aqueous layer was extracted with EtOAc (10 mL x 4). Organic extracts were combined, washed with H_2O (5 mL), saturated brine (5 mL), dried (Na_2SO_4) and removed *in vacuo* to give the crude product as a straw coloured oil. Column chromatography (3:1 hexane:EtOAc) provided *5-(cyclohepta-1',5'-diene)-N-methyl-N-methoxy-E-4-pentenamide* (133 mg, 0.57 mmol, 61%) as a straw coloured oil.: R_F 0.54 (3:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 6.01 (d, J=16.2 Hz, 1H, H5), 5.80 (t, J=6.6 Hz, 1H, H7), 5.67-5.59 (m, 3H, H10, H11, H4), 3.69 (s, 3H, OCH_3), 3.19 (s, 3H, NCH_3), 3.00 (d, J=3.9 Hz, 2H, H12), 2.55-2.34 (m, 6H, H8,H9,H3), 2.20 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.66 (C1), 140.01 (C6), 134.20 (C4), 130.85 (C10), 130.79 (C11), 126.19 (C5), 125.13 (C7), 61.20 (OCH_3), 32.30 (NCH_3), 32.04 (C12), 27.85 (C2), 26.82 (C3), 26.28 (C8), 25.25 (C9); IR (neat, NaCl Plate) 3013, 2935, 2848, 1665, 1432, 1384, 1341, 1255, 1177, 1113, 994, 964, 849, 817, 741, 628 cm^{-1}; MS (EI/DCI) calculated for $C_{14}H_{21}NO_2$: m/e 235.157229, found 235.156872; 235.1569 (M+), 204.1315 (M+-CH_3O, 51%), 175.1074 (M+-C_3H_7O, 8%), 147.1233 (M+-$C_3H_6NO_2$, 12%), 131.0844 (M+-$C_4H_{10}NO_2$, 34%), 117.0702 (M+-$C_5H_{12}NO_2$, 22%), 105.0659 (M+-$C_6H_{12}NO_2$, 43%), 91.0576 (M+-$C_7H_{14}NO_2$, 100%), 79.0571 (M+-$C_8H_{14}NO_2$, 56%), 67.0547 (M+-$C_{10}H_{16}O_2$, 40%), 41.0409 (M+-$C_{11}H_{16}NO_2$, 32%).

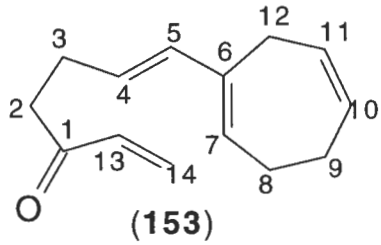
5-(Cyclohepta1',5'-diene)-N-methyl-N-methoxy-*Z*-4-pentenamide



(**154*z***)

5-(cyclohepta1',5'-diene)-N-methyl-N-methoxy-Z-4-pentenamide was produced in the same manner as the *E* isomer. *5-(Cyclohepta-1',5'diene)-Z-4-pentenoic acid*(210 mg, 1.09 mmol)was reacted with N,O-dimethyl hydroxylamine(181 mg, 1.86 mmol) and ECD (523 mg, 2.73 mmol) to produce a straw coloured oil,*5-cyclohepta1,5-diene-N-methyl-N-methoxy-Z-4-pentenamide* (199 mg, 0.846 mmol, 78%) : R_F 0.45 (3:1 hexane:EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 5.82 (d, J=11.9 Hz, 1H, H5), 5.76 (d, J=6.8 Hz, 1H, H7), 5.65-5.60 (m, 2H, H10, H11), 5.32-5.28 (dt, J=11.4, 6.3 Hz, 1H, H4), 3.67 (s, 3H, OCH_3), 3.18 (s, 3H, NCH_3), 2.9 (d, J=3.5 Hz, 2H, H12), 2.55-2.51 (m, 4H, H8, H9), 2.37-2.32 (m, 2H, H3), 2.21-2.27 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.83 (C6), 132.84 (C4), 130.77 (C10), 129.34 (C11), 127.76 (C7), 126.24 (C5), 61.19 (OCH_3), 32.63 (NCH_3), 31.51 (C12), 26.82 (C8, C9), 26.13 (C3), 23.89 (C2); IR (neat, NaCl plate) 3478, 3007, 2936, 2830, 1728, 1667, 1651, 1433, 1384, 1322, 1254, 1178, 1104, 996, 912, 846, 732, 640 cm-1; MS (DCI) calculated for: m/e 235.157229, found 235.157124; 235.1571 (M+, 15%), 204.1370 (M+-CH_3, 79%), 175.1066 (M+-C_3H_8, 9%), 147.1159 (M+-$C_3H_6NO_2$, 14%), 131.0874 (M+-$C_4H_{11}NO_2$, 41%), 117.0711 (M+-$C_5H_{11}NO_2$, 25%), 105.0739 (M+ -$C_6H_{11}NO_2$, 47%), 91.0577 (M+ -$C_7H_{14}NO_2$, 100%), 79.0695 (M+-$C_8H_{14}NO_2$, 57%), 67.0524 (M+-$C_9H_{14}NO_2$, 48%), 55.0522 (M+-$C_{11}H_{18}N$, 19%), 41.0392 ($C_{11}H_{16}NO_2$, 26%).

5-(Cyclohept-1',5'-diene)-ethynyl-*E*-4-pentenone



(153)

5-(Cyclohepta-1',5'-diene)-N-methyl-N-methoxy-E-4-pentenamide (440 mg, 1.87 mmol) was dissolved in THF (10 mL) and cooled to -78°C. Vinyl MgBr (6.5 mL, 7.47 mmol) was added dropwise and the reaction was stirred for 1 hr, during which time the temperature was kept between -66°C and -72°C. The reaction was quenched at -66°C with saturated aqueous NH_4Cl and the whole mixture was warmed to RT. The solid formed was dissolved in the minimum amount of H_2O and the aqueous layer extracted with Et_2O (4 x 10 mL). Combined ethereal extracts were washed with H_2O (5 mL), saturated brine (5 mL), dried (Na_2SO_4) and removed *in vacuo*. (266 mg, 1.32 mmol, 71%)

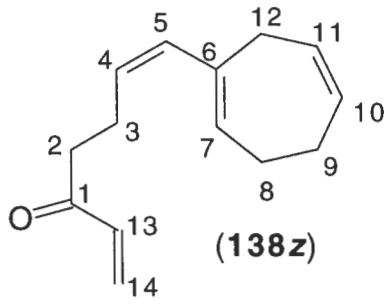
Alternatively

7-(Cyclohept-1',5'-diene)-E-1,6-heptadien-3-ol (0.36 g, 1.8 mmol) was dissolved in CH_2Cl_2 (10 mL) under Ar. Dess-Martin Periodinane (1.06 g, 2.50 mmol) was added while stirring. On completion, saturated $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (10 mL) was added with Et_2O (20 mL) and the mixture was left to stir vigorously for 5 min. The Et_2O layer was drawn off and the aqueous layer extracted with Et_2O (3 x 10 mL). Organic layers were combined, washed with H_2O (5 mL), saturated brine (5 mL), dried (Na_2SO_4), filtered, and removed *in vacuo*. The resultant oil was purified using column chromatography, eluting solvent CH_2Cl_2:hexane 2:3. Any residual SiO_2 was removed by filtration. (113 mg, 0.5 mmol, 31% (2 steps))

5-(Cyclohept-1',5'-diene)-ethynyl-E-4-pentenone was a straw coloured oil and was labile so was stored in benzene.: R_F 0.49 (3:1 hexane:EtOAc); 1H NMR (270 MHz, $CDCl_3$) δ 6.32-6.22 (dd, J=10.1, 17.6 Hz, 1H, H14), 6.16-6.09 (dd, J=17.6, 1.5 Hz, 1H, H14), 5.95 (d, J=15.6 Hz, 1H, H5), 5.77-5.72 (dd, J=1.5, 10.11 Hz, 1H, H13), 5.72 (t, J=6.5 Hz, 1H, H7), 5.61-5.43 (m, 3H, H10, H11, H4), 2.98 (m, 2H, H12), 2.73-2.65 (m, 2H, H3), 2.54-2.34 (m, 4H, H8, H9), 2.21-2.17 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 201.85 (C1), 138.83 (C6), 136.42 (C13), 134.35 (C4), 130.97 (C10), 130.94 (C11), 127.95 (C5), 126.19 (C7), 124.71 (C14), 39.52 (C12), 27.12 (C2), 26.85 (C3), 26.30 (2, C8, C9); IR (neat, NaCl Plate) 3016, 2926, 2851, 1701, 1681, 1614, 1450, 1432, 1400,

1363, 1255, 1184, 1098, 962, 912, 848, 816, 748, 627 cm-1; MS (GC MS) 202 (M+), 145 (M+-C_4H_7, 28%), 131 (M+-C_4H_6O, 33%), 117 (M+-C_5H_9O, 46%), 104 (M+-C_6H_9O, 56%), 91 (M+-C_7H_9O, 100%), 79 (M+-$C_8H_{11}O$, 36%).

5-(Cyclohepta-1',5'diene)ethenyl-*Z*-4pentenone



(138*z*)

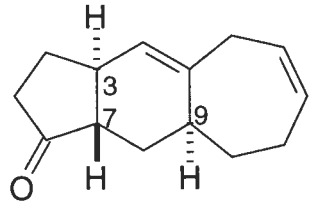
The *Z* isomer was prepared using the same procedure as the *E* isomer.
Vinyl MgBr (1.1 mL, 1.3 mmol) was added to *5-(cyclohepta1',5'-diene)-N-methyl-N-methoxy-Z-4-pentenamide* (75 mg, 0.32 mmol) dissolved in THF (2 mL) to produce *5-(cyclohepta-1',5'diene)ethenyl-Z-4pentenone* (41 mg, 0.20 mmol, 63%)

Alternatively

Vinyl MgBr (0.36 mL, 0.42 mmol) was added to *5-(cyclohepta1',5'-diene)-Z-4-pentenal* (59 mg, 0.34 mmol) in Et_2O (5 mL). Because of the lability of *7-(Cyclohept-1',5'-diene)-E-1,6-heptadien-3-ol* a quantitative yield was assumed and it was oxidised immediately. Dess-Martin Periodinane (200 mg, 0.47 mmol) was added to*7-(cyclohept-1',5'-diene)-E-1,6-heptadien-3-ol* (68 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) to produce *5-(cyclohepta-1',5'diene)ethenyl-Z-4pentenone* (19 mg, 0.091 mmol, 27% (2 steps)): R_F 0.85 (3:1 hexane:ethy lacetate); ^1H NMR (270 MHz, $CDCl_3$) δ 6.36 (dd, J=10.2, 17.7 Hz, 1H, H14), 6.22 (dd, J=1.5, 17.7 Hz, 1H, H14), 5.83 (dd, J=1.54, 10.2 Hz, 1H, H13), 5.74 (t, J=6.4 Hz, 1H, H7), 5.62 (m, 2H, H10, H11), 5.27 (dt, J=11.4, 4.4 Hz, 1H, H4), 2.89 (m, 2H, H12), 2.67 (m, 2H, H3), 2.52 (m, 2H, H8), 2.35 (m, 2H, H9), 2.18 (m, 2H, H2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 199.88 (C1), 138.83 (C6), 136.33 (C13), 133.45 (C4), 130.84 (C10), 130.13 (C11), 129.98 (C5), 127.96 (C14), 126.77 (C7), 40.05 (C2), 31.66 (C12), 28.25 (C9), 27.15 (C8), 22.60 (C3); IR (neat) 3010, 2930, 2852, 1725, 1701, 1681, 1614, 1450, 1432, 1400, 1360, 1254, 1184, 1096, 986, 963, 845, 745, 638 cm-1; MS (DCI) calculated for: m/e 202.135765, found 202.136326; 202.1363 (M+, 27%), 161.9911 (M+ -C_2H_{16}, 6%), 147.1048 (M+ -C_4H_{17}, 9%), 132.0897 (M+ -C_4H_6O, 37%), 117.0698 (M+ -C_5H_8O, 78%), 105.0716 (M+ -C_6H_9O, 30%), 91.0531 (M+ -$C_7H_{11}O$, 100%),

79.0550 (M+ -$C_8H_{11}O$, 37%), 55.0190 (M+ -$C_{11}H_{15}$, 79%), 41.0405 (M+ -$C_{11}H_{13}O$, 44%).

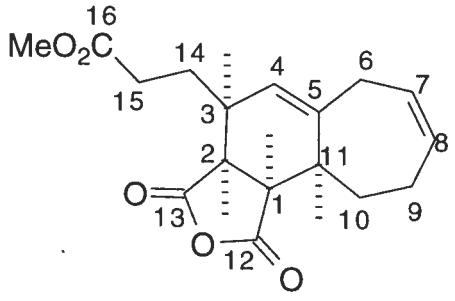
3,7*syn*- 7,9*anti*-Tricyclo[7.5.0.0^{3,7}]tetradecane



(**137a**)

5-(Cyclohept-1',5'-diene)-ethynyl-E-4-pentenone (0.035 g, 0.173 mmol) was dissolved in toluene (27 mL) and a small crystal of BHT was added. The reaction was refluxed under Ar for 18 hr. Toluene was removed *in vacuo* and the resulting oil was purified by column chromatography. (0.025 g, 0.124 mmol, 72%): R_F 0.43 (3:1 hexane:EtOAc). ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.87-5.42 (m, 3H, H8, H9, H5), 3.00-2.65 (m, 3H), 2.50-1.82 (m, 8H) 1.77-1.41(m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 221.59 (C6), 141.15 (C1), 130.07 (C13), 127.97 (C12), 123.88 (C2), 46.48 (C7), 38.60 (C9), 37.04 (C5), 36.22 (C10), 31.48 (C8), 28.56 (C8), 27.94 (C3), 28.9 (C11), 26.27 (C4); MS (DCI) calculated for: m/e 202.135765, found 202.136326; 202.1363 (M+, 100%), 117.0698 (M+ -C_5H_8O, 41%), 105.0716 (M+ -C_6H_9O, 41%), 91.0576 (M+ -$C_7H_{11}O$, 75%), 79.0550 (M+ -$C_8H_{11}O$, 33%), 55.0190 (M+ -$C_{11}H_{15}$, 11%), 41.0405 (M+ -$C_{11}H_{13}O$, 24%).

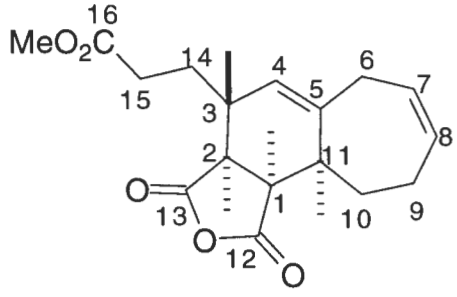
^{3,11}*Syn*-3-(Methylpropanoate)[5.4.0^{5,11}]-bicyclo-4,7-undecadiene1,2-dicarboxylic anhydride



(144)

Methyl-5-(Cyclohepta1',5'-diene)-E-4-pentenoate (210 mg, 1.02 mmol) and maleic anhydride (105 mg, 1.07 mmol) were dissolved in 5 mL of dry benzene with a catalytic amount of BHT. The mixture was refluxed under Ar for 3 hours. The benzene was removed *in vacuo* and the resulting solid purified by recrystallisation in *t*BuOMe to give *^{3,11}syn-3-(Methylpropanoate)[5.4.0^{5,11}]-bicyclo-4,7-undecadiene1,2-dicarboxylic anhydride* as white square crystals. (171 mg, 0.562 mmol, 55%): R_F 0.53 (1:1 hexane:EtOAc + triethylamine); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.59-5.42 (m, 3H, H7, H8, H4), 3.68 (s, 3H, OCH_3), 3.40-3.35 (m, 2H, H1, H2), 3.24 (d, J=15.8 Hz, 1H, H6), 2.75-2.62 (m, 1H), 2.58-2.22 (m, 6H), 2.20-2.03 (m, 3H), 1.85 (d, J=14.1 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.14 (C16), 171.43 (C13), 171.10 (C12), 146.00 (C5), 124.60 (C4), 124.19 (C7), 124.11 (C8), 47.52 (OCH_3), 44.80, 40.76, 35.39, 32.83 (C6), 31.99 (2, C9, C10), 26.21 (C15), 25.96 (C14); IR (neat, NaCl Plate) 3448, 3022, 2940, 2869, 2832, 1849, 1830, 1774, 1734, 1451, 1436, 1388, 1364, 1330, 1278, 1249, 1230, 1193, 1171, 1078, 983, 925, 892, 786, 652 cm-1; MS (DCI PROBE) calculated for $C_{16}H_{20}O_5$: m/e 304.131074, found 304.131302; 304.1313 (M+), 292.0894 (M+ -$C_4H_6O_3$ 39%), 276.1361 (M+ -CO 88%), 230.0949 (M+ -$C_3H_6O_2$ 100%), 157.1031 (M+ -$C_5H_7O_5$ 100%), 117.0713 (M+ -$C_8H_{11}O_5$ 44%), 91.0547 (M+ -$C_{10}H_{13}O_5$ 72%).

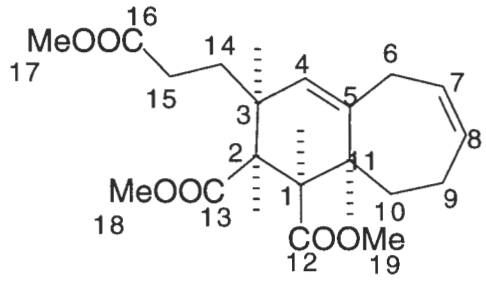
^{3,11}*Anti*-3-(Methylpropanoate)[5.4.0^{5,11}]-bicyclo-4,7-undecadiene1,2-dicarboxylic anhydride



(**144*z***)

Methyl ester (300 mg, 1.45 mmol) and maleic anhydride (214 mg, 2.18 mmol, 1.5 equiv) were dissolved in benzene (20 mL) with a catalytic amount of BHT. The mixture was refluxed under Ar for 3 days. The benzene was removed *in vacuo* and the resulting solid purified by recrystalisation *t*BuOMe/Et_2O to give *^{3,11}anti-3-(Methylpropanoate)[5.4.0^{5,11}]-bicyclo-4,7-undecadiene-1,2-dicarboxylic anhydride* as a white, needlelike, crystalline solid (345 mg, 0.99 mmol 68%).: R_F 0.53 (1:1 hexane:EtOAc + triethylamine). ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.68-5.43 (m, 3H, H7, H8, H4), 3.69 (s, 3H, OCH_3), 3.45-3.39 (m, 1H, H12), 3.28-3.25 (m, 1H, H6), 3.21-3.14 (m, 1H, H5) 2.89-2.78 (m, 1H, H1), 2.75-2.66 (m, 1H, H3) 2.64-2.40 (m, 1H, H6), 2.59-2.40 (m, 4H, H9, H15) 2.21-2.07 (m, 2H, H10), 1.98-1.89 (m, 1H, H14); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.91 (C16), 173.16 (C13), 171.62 (C12), 143.89 (C5), 128.29 (C4), 125.50 (C7), 122.28 (C8), 51.84 (OCH_3), 46.05 (C2), 45.44 (C1), 37.41 (C11), 35.55 C3) 35.16 (C6), 32.17 (C9), 29.92 (C10), 29.29 (C15), 26.66 (C14); IR (neat, NaCl Plate) 3448, 3022, 2940, 2869, 2832, 1849, 1830, 1774, 1734, 1451, 1436, 1388, 1364, 1330, 1278, 1249, 1230, 1193, 1171, 1078, 983, 925, 892, 786, 652 cm-1; MS (DCI PROBE) calculated for $C_{16}H_{20}O_5$: m/e 304.131074, found 304.131302; 304.1313 (M+), 292.0894 (M+ -$C_4H_6O_3$ 39%), 276.1361 (M+ -CO 88%), 230.0949 (M+ -$C_3H_6O_2$ 100%), 157.1031 (M+ -$C_5H_7O_5$ 100%), 117.0713 (M+ -$C_8H_{11}O_5$ 44%), 91.0547 (M+ -$C_{10}H_{13}O_5$ 72%).

Dimethyl-3-(Methylpropanoate)[5.4.0^{5,11}]-bicyclo-4,7-undecadiene1,2-dicarboxylate



(**155**)

KH (35% dispersion in oil) (20 mg, 0.17 mmol) was dissolved in THF (1 mL) and cooled to -78°C. On addition of the anhydride (48 mg, 0.16 mmol) the reaction was left to warm to RT slowly, then quenched with MeOH (1 mL) at 0°C. Et_2O : NH_4Cl 1:1 (2 mL) was added, the aqueous layer was drawn off and acidified to pH 2 (10% HCl) then extracted with Et_2O (3 x 5 mL). Ethereal extracts were combined, washed with H_2O (5 mL), saturated brine (5 mL), dried ($MgSO_4$) and removed *in vacuo*.: R_F 0.08 (3:1 hexane:EtOAc) The residue was dissolved in MeOH and cooled to 0°C. Diazomethane was added until the yellow endpoint was reached. Excess diazomethane was destroyed using acetic acid and the solvent was removed under reduced pressure.: R_F 0.52 (3:1 hexane:EtOAc). ^1H NMR (270 MHz, $CDCl_3$) δ 5.71 (m, 2H, H7, H8), 5.28 (s, 1H, H4), 3.74-3.62 (m, 9H, H17, H18, H19), 3.17-3.04 (m, 2H, H6), 3.02-2.92 (m, 1H, H2), 2.80-2.60 (m, 2H, H14), 2.46-2.24 (m, 4H, H9, H10), 2.18-2.02 (m, 1H, H1), 1.85-1.70 (m, 3H, H15, H11), 1.62-1.51 (m, 1H, H3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.48 (C1), 172.93 (C15), 172.46 (C16), 137.67 (C6), 130.51 (C5), 127.46 (C8), 121.94 (C9), 51.81 (C18), 51.56 (C19), 51.30 (C17) 47.24 (C14), 42.45(C13), 41.75 (C12), 37.27 (C7), 36.94 (C2), 32.04 (C4), 29.00 (C10), 27.94 (C11), 27.60 (C3); IR (neat, NaCl Plate) 3453, 2950, 1735, 1654, 1572, 1435, 1164, 1020, 875, 812, 775, 745, 716, 690, 659 cm-1; MS (DCI PROBE) calculated for $C_{19}H_{26}O_6$: m/e 350.172939, found 350.172165; 350.1722 (M+), 318.1482 (M+ -CH_4O 14%), 290.1506 (M+ -C_2H_4O 100%), 258.1230 (M+ -$C_3H_8O_2$ 60%), 230.1273 (M+ -$C_{11}H_8O_3$ 34%), 199.1129 (M+ -$C_{12}H_{11}O_5$ 58%), 157.1033 (M+ -$C_{14}H_{23}O_6$ 84%), 91.0551 (M+ -$C_{12}H_{19}O_6$ 28%), 59.0134 (M+ -$C_{17}H_{23}O_3$ 13%).

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Appendix A

Synthesis of the Phosphonium Salts

It was anticipated that modifications to the ylid would result in the introduction of functionality to the 5 membered ring and thus, allow the synthesis of a variety of dolabellanes. For this reason the syntheses of two other phosphonium salts were attempted. Hydrobromic acid and concentrated sulfuric acid were used to convert δ-valerolactone and γ-valerolactone to the corresponding bromo-carboxylic acids,[47] which were subsequently converted to the phosphonium salts by refluxing with triphenylphosphine. [29,49,90-92]

Dictyoxetane and the dolabellanes have a methyl position at C_3. To synthesise cyclohept[f]indene (**156**) with the methyl at position C_3, the phosphonium salt 1-methyl-4carboxybutyl triphenyl phosphonium bromide is needed (**Figure 13**).

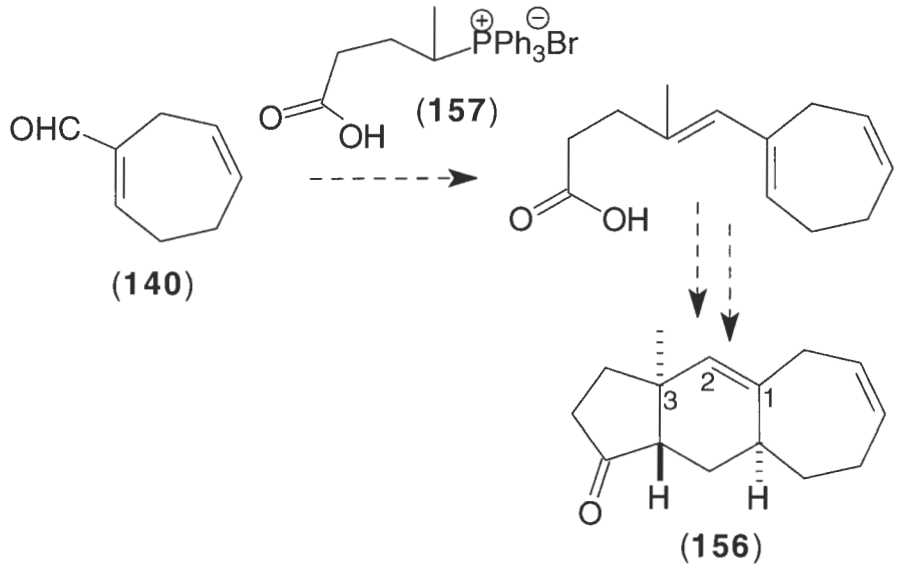
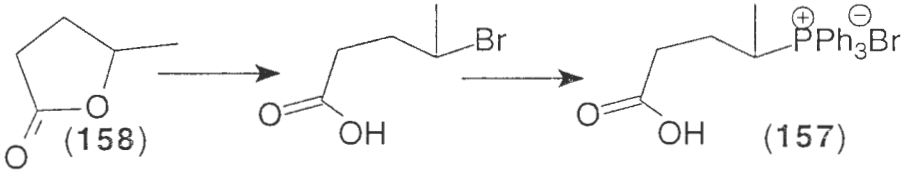


Figure 13

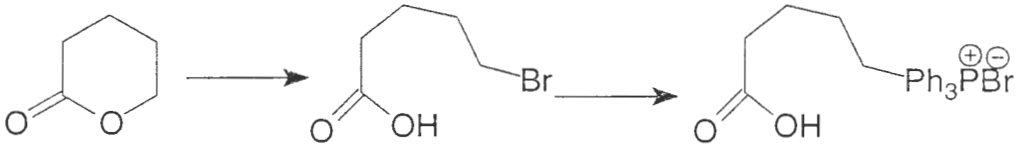
Thus the synthesis of 1-methyl-4-carboxybutyl triphenyl phosphonium bromide was attempted (**Scheme 44**). Reaction of γ-valerolactone (**158**) with hydrobromic and sulfuric acids was very slow and the carboxylic acid derivative of γ-valerolactone (4-bromo,4-methyl butanoic acid) was difficult to isolate from starting material. Initially purification was attempted using column chromatography and subsequently by distillation (B.P. 88°C, 0.1 mmHg). By NMR the two fractions obtained gave a 3:1 and 1:2 mixture of starting material

: product respectively. A revised work up, which involved washing with 5% $NaHCO_3$, reacidification, then extraction with ether (4 x 20 ml) also failed to separate the desired bromo-acid. Distillation was made easier by esterification of the carboxylic acid to the corresponding methyl ester (B.P. 74°C, 0.3 mmHg) using diazomethane. The greatest yield obtained using this procedure was 13%. Upon refluxing this with triphenylphosphine in toluene and xylene, a yellow intractable solid was formed in 8% yield that was not able to be recrystalised.



Scheme 45

In a further attempt to synthesis alternative phosphonium salts 5-bromo-pentanoic acid (**159**) was synthesised from δ valerolactone (**160**) (60%) and subsequently converted to its phosphonium salt (**161**) (**Scheme 46**). 5-bromo-pentanoic acid was purified by vacuum distillation (B.P. 120°C 0.3 mmHg). A low yielding attempt to synthesise the phosphonium salt by refluxing the bromo-acid with triphenylphosphine in acetonitrile,[49] was difficult to purify. The phosphonium salt was formed by refluxing 5-bromopentanoic acid with triphenylphosphine in toluene. Purification was not required as phosphonium salt crystalised in pure form from toluene during the course of the reaction. Attempts to increase the yield by refluxing in xylene resulted in the formation of unidentified byproducts.



(160) (159) (161)

Scheme 46

Experimental Data

Phosphonium salt:

^1H NMR (270 MHz, $CDCl_3$) δ 10.0-9.8 (s, 1H, COOH), 7.77-7.57 (m, 15H, Ph_3), 3.65-3.34 (m, 2H, Br-CH_2), 2.54-2.34 (t J=7.0 Hz 2H, H_2COO), 1.90-1.53 (m, 4H, CH_2CH_2);