Syntheses Towards Derivatives of Bicyclo[4.4.4]tetradecane.

By

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Contents

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university. To the best of my knowledge, this thesis contains no material previously published or written by any other person, except where due reference has been made in the text.

Guy Yeoman Krippner.

Acknowledgements

It feels like a lot of water has passed under the bridge since I first opened the doors of the G. M. Badger Laboratories of the University of Adelaide. It has been one of the most fruitful times of my life, and I am grateful to Everyone who works and learns there for making it so.

My thanks in particular to my supervisor Dr David P G Hamon for being just that, and a friend as well. I would also like to thank Dr George Gream for his ongoing encouragement since the day I arrived.

The work would not have been possible without the help of the following people and I am grateful for the generosity of spirit that I encountered: Dr Andrea Hounslow and Phil Clemmens (CXP-300), Paul McLaren (glass), Kevin Newton and Lee Paltridge (technical), Tom Blumenthal, Ruth Pavy, Dr Max Tate and Dr Graeme Currie (mass spectrometry at various sites).

My sense of humour and humanity would not have survived without the love and support that I have received from Lorely Marshallsay.

I wish to also express my gratitude to my Mother and Jane, and my Father and Alison, for always being there.

Summary

Considerable attention has been given to theoretical calculations of the strain energies associated with the different bridgehead configurations that are thought to be available for bicyclo[4.4.4]tetradecane and analogous structures. The only successful syntheses of molecules of this type have been the preparation of in-6-*H*-bicyclo[4.4.4]tetradec-1-ene, and the corresponding in,out-bicyclo[4.4.4]tetradecane, by McMurry and Hodge.

Described herein are two synthetic approaches that were developed in an attempt to prepare other bridgehead derivatives of bicyclo[4.4.4]tetradecane. Each of these approaches has, as the key step, an intramolecular zero valent titanium induced carbonyl coupling reaction.

One approach was by way of the cyclisation of derivatives of 6-(4-oxobutyl)cyclodecan-1-one. The compounds 6-(4-butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one, 6-(4-butanal)-5-*E*-cyclodecen-1-one and 6-(4-oxobutylidene)cyclodecan-1-one were prepared and attempts were made to bring about their cyclisation.

The reaction of 6-(4-butanal)-6-(tetrahydropyranyloxy) cyclodecan-1-one with zero valent titanium gave an intractable mixture. The in-6*H*-bicyclo[4.4.4]tetradec-1-ene was prepared as a model study in order to indicate the effectiveness of the zero valent titanium preparation.

The attempted intramolecular coupling of 6-(4-butanal)-5-*E*-cyclodecen-1-one gave a bicyclic diene in low yield. The ^{1}H and ^{13}C nmr spectra of the bicyclic diene were consistent with 1-*E*-6-

E-bicyclo[4.4.4] tetradecadiene. The products that arose from the hydrogenation or hydroboration of the bicyclic diene suggested that, in fact, the product of the coupling reaction was 1,4-bis(cyclopentenyl)butane.

The intramolecular coupling of 6-(4-oxobutylidene)cyclodecan-1-one gave a small yield of a bicyclic diene that has been identified as 1,2-divinylbicyclo[4.4.0]decane. This material had been prepared by Shea and coworkers in an attempt to prepare meso-1,5-bicyclo[4.4.4]tetradecadiene by way of a Cope rearrangement.

The second approach to derivatives of bicyclo[4.4.4]tetradecane was based upon 1,6-bis(2-oxoethyl)cyclodecyl precursors. The reaction of 1,6-bis(2-oxoethyl)cyclodecane with low valent titanium gave a small yield of 1,6-diethylcyclodecane and 6-ethyl-1-(2-propenyl)cyclodecane. This suggested that the pathway to intramolecular coupling of the saturated precursor was too sterically hindered. The attempted intramolecular coupling of 1,6-bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene gave an intractable mixture.

Abbreviations used in this Thesis.

G.C.	Gas Chromatography
G.C./M.S.	Gas Chromatography/Mass Spectrometry
HCOSY	Homonuclear $^{1}J_{H-H}$ Correlation Spectroscopy
IR	Infrared
nmr	nuclear magnetic resonance
p-toluene	*para*-toluene
SFORD	Single Frequency Off Resonance Decoupling
t-butyl	tertiary butyl
TBDMS	Tertiarybutyldimethylsilyloxy
THF	Tetrahydrofuran
THP	Tetrahydropyranyloxy
$TiCl_3$:$(DME)_{1.5}$	Titanium trichloride:(dimethoxyethane)$_{1.5}$ complex
TLC	Thin Layer Chromatography

three orders of magnitude greater than the rate of solvolysis of bicyclo[3.3.3]undecanyl chloride.

2.

Scheme 1

Strain energy in molecular mechanics calculations is derived from the difference between the value for heat of formation for a molecule and the heat of formation of an ideal unstrained counterpart. Olefinic Strain (O.S.)[3] is calculated by the subtraction of the strain energy of a saturated system from the strain energy of the same system containing a double bond. The difference between the heat of formation of a saturated molecule and the heat of formation of an analogous structure that contains a double bond corresponds to the Heat of Hydrogenation, $\Delta H_H°$.

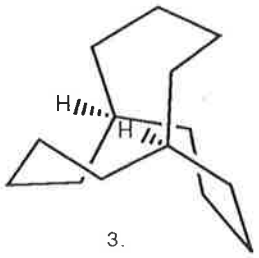
This last value is useful as it can be derived directly from empirical (molecular mechanics) calculations and may also be measured experimentally under favourable circumstances thus providing a means of corroborating the theoretical predictions. When an olefin is unstrained as in 2-*Z*-butene the O.S. is 0 kJ mol^{-1} and the amount of energy released upon hydrogenation[4] is 109·2 kJ mol^{-1}. If the presence of the double bond has increased the strain of the molecule relative to the saturated system then the O.S. value will be positive and this strain energy will be released in addition to the standard Heat of Hydrogenation during hydrogenation.

Conversely, if the presence of the double bond has the effect of reducing the strain energy in the molecule then the O.S. value will be negative and the Heat of Hydrogenation will be less than the standard value, for some of the energy is absorbed in the increased strain energy of the molecule. Schleyer[5] has labelled olefins with negative O.S. values *"hyperstable"* and predicted that such molecules would be characterised by an unreactive double bond.

Two groups[6] have carried out detailed calculational analyses of the geometry and strain energy of the bicyclo[4.4.4]tetradecane molecule. They have put forward three potential isomers for the saturated bicyclo[4.4.4]tetradecane: the in,out- (3) at 197·6 kJ mol^{-1}, the out,out- (1) at 248·7 kJ mol^{-1} and the in,in- (4) at 262·3 kJ mol^{-1}. Two isomers containing a single bridgehead double bond were proposed; the in-alkene (5) at 150·6 kJ mol^{-1} and the out-alkene (6) at 181·6 kJ mol^{-1}. In addition to this there are potentially five isomers containing two bridgehead double bonds, four racemic and one meso. Schleyer and McEwen[7] have calculated the strain energy of four of these five; they are named as types I to V according to the descriptions given in the review article by Warner[8] . The strain energy associated with each is as follows: type I, 1,5-*E,Z*-diene (7), 165·3 kJ mol^{-1}; type II, 1,5-*Z,Z*-diene (8), 168·6 kJ mol^{-1}; type III, 1,6-*E,E*-diene (9), not calculated; type IV, 1,6-*Z,Z*-diene (10), 148·9 kJ mol^{-1}; type V, 1,6-*E,Z*-diene (11), 125·5 kJ mol^{-1}.

The various double bond isomers of bicyclo[4.4.4]tetradecane should clearly show evidence of hyperstability and indeed the hydrogenation of the in-alkene (5) required forcing conditions to go to completion[9]. The out,out-bicyclo[4.4.4]tetradecane (1) is one of

the most strained examples of the out,out- medium sized bicyclic systems so far studied[6] and so hydrogenation of the dienes (7,8,9,10,11) should be even more difficult and could well go in a stepwise manner.



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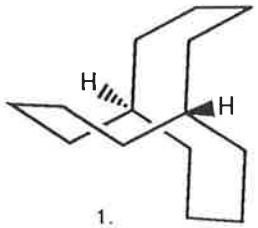

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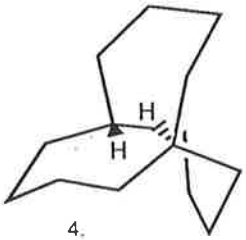

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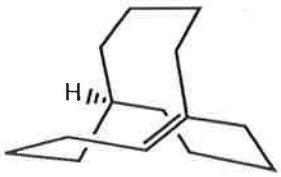

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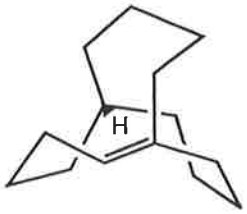

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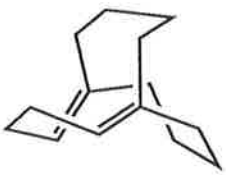
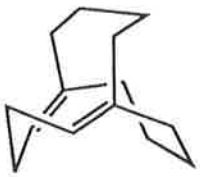
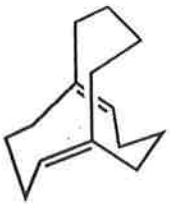


Type II 8.

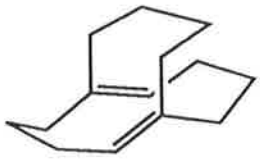


Type I 7.

Type V 11.



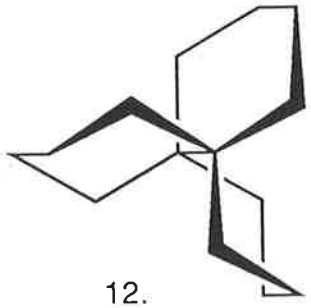
TypeIV 10.



Type III 9.

It appears from the calculations that a good proportion of the strain is associated with the geometry around the bridgehead. A salient example is the theoretical[10] "dehydrogenation" of the out,out- alkane (1) to form the propellane,

tricyclo[4.4.4.$0^{1,6}$]tetradecane (12) which allows the bridgeheads to move considerably closer together. All the six membered rings[11] are in a slightly flattened chair conformation with the average C-C-C bond angle reduced from 118° to 110° , the nonbonded H/H interactions are considerably reduced and the structure (12) is 151 kJ mol^{-1} less strained than the out,out-bicyclo[4.4.4]tetradecane (1).

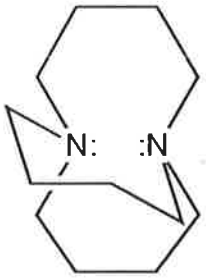


12.

Much of the interesting chemistry that has been observed for derivatives of bicyclo[4.4.4]tetradecane arises from the geometry and strain associated with the bridgeheads.

Alder[10] has used the geometry of the bicyclo[4.4.4]tetradecane as well as other bicyclic molecules to investigate the properties of unusual bonds that arise from the overlap of orbitals through space. Bicyclic molecules have the advantage of locking the bridgeheads into a close spatial relationship. Alder has prepared the bridgehead aza[12] and diaza-bicyclo[4.4.4]tetradecanes[13] (13) and observed that with lone pairs and not hydrogens as bridgehead substituents, the molecule was most stable with the in,in- configuration. The X-ray structure analysis[14] of the diaza bicyclic (13) showed the nitrogens to be inwardly pyramidalised with an N: :N distance of 2·806 Å. The intrabridgehead distance represents the balance between the nitrogen/nitrogen lone pair repulsion and the preferred geometry of

the hydrocarbon framework, which reaches a minimum strain energy in the dication propellane (14) with an intrabridgehead distance (σ bond) of 1·53 Å..



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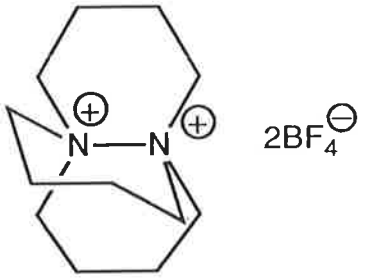
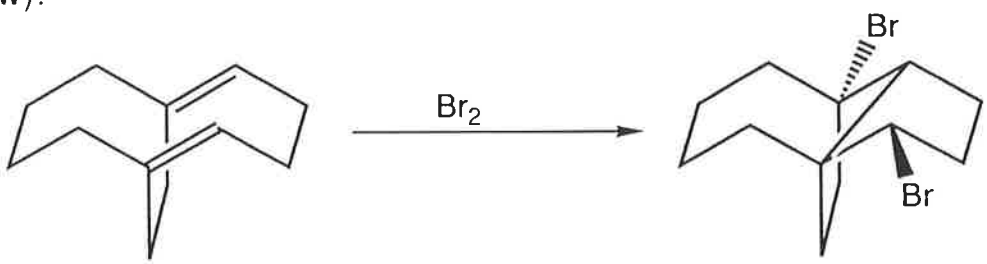


14.

Shea[15] has explored the interaction of the π systems in bicyclic bridgehead dienes prepared by a common strategy of [3.3] sigmatropic rearrangements of 1,2-divinyl precursors. Four dienes were prepared this way; bicyclo[4.3.1]deca-1,5-diene , bicyclo[4.4.1]undeca-1,5-diene , bicyclo[4.3.2]undeca-1,5-diene and bicyclo[4.4.2]dodeca-1,5-diene. His attempt at the preparation of the 1,5-bicyclo[4.4.4]tetradecadiene (8) was unsuccessful (see below).



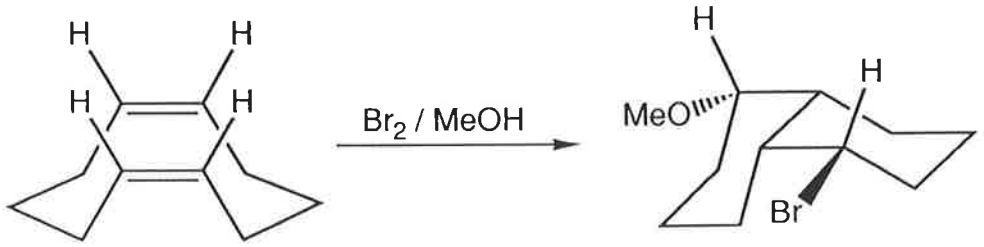
15. 16.

Scheme 2.

The splitting observed in the photoelectron spectra for all four dienes is consistent with π orbital overlap. The bridgehead dienes bicyclo[4.3.2]undeca-1,5-diene and bicyclo[4.4.2]dodeca-1,5-diene (15) were reacted with bromine and formed an intrabridgehead bond-[3.3.0] subunit (scheme 2). These bicyclic systems contain a 1,5-*Z,Z*-cyclooctadiene subunit. This

intrabridgehead bond formation was further evidence that the π systems of the dienes at least partially overlap as 1,5-*Z,Z*-cyclooctadiene reacts with one equivalent of bromine to give 1,2-dibromo-5-*Z*-cyclooctene[16], no transannular reaction was observed to occur.

The reaction of 1,6-*Z,Z*-cyclodecadiene[17] (17) with bromine in methanol (scheme 3) resulted in the formation of a disubstituted decalin, (18). This kind of reaction has also been observed for 1,5-*E,Z*-cyclodecadienes[18] and suggests that the π systems of bicyclo[4.4.4]tetradeca-1,6-dienes (9,10,11) and bicyclo[4.4.4]tetradeca-1,5-dienes (7,8) might be expected to form an intramolecular carbon-carbon bond in reaction with electrophilic reagents.

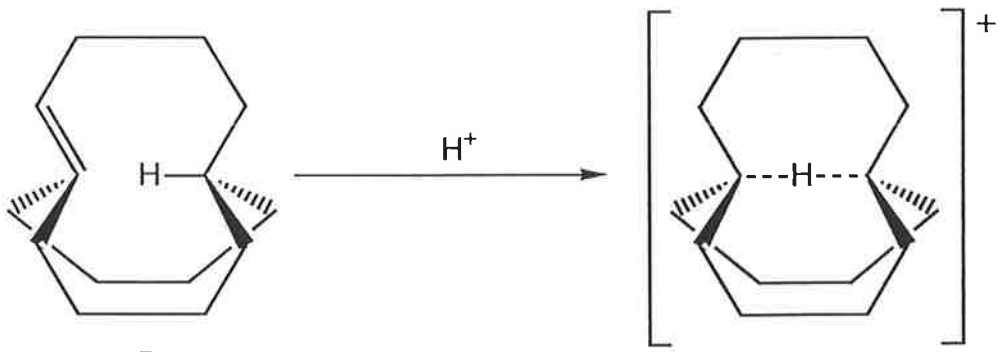


17. 18.

Scheme 3

McMurry and co-workers[9,19] have prepared the in-bicyclo[4.4.4]tetradec-5-ene (5) and made a study of an unusual feature of its intrabridgehead chemistry. McMurry observed that the alkene was readily protonated under acidic conditons to give a symmetrical cation (19) (scheme 4) that was stable indefinitely in polar solvents. That the alkene protonates so readily is probably a result of the strain relief that ensues from the formation of two quasi sp^2 bridgeheads[7]. McMurry proposed that the cation represented a particularly stable example of a molecule containing

a doubly occupied three centre molecular orbital with the nonclassical structure (19)



5. 19.

Scheme 4.

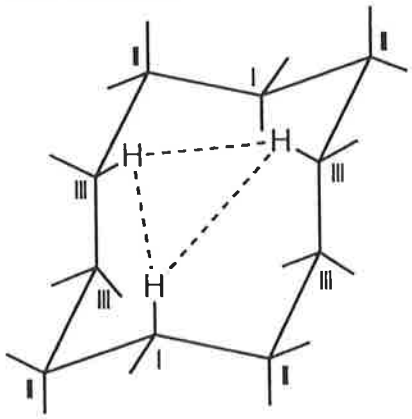
Synthetic Strategy

One of the key considerations in the assembly of the bicyclo[4.4.4]tetradecane skeleton is the recognition that the structure is composed entirely of ten membered rings. There is only a small number of reactions that have been successful in the preparation of eight to eleven membered rings; the *medium* sized rings, as there are both enthalpic and entropic barriers towards cyclisation[20].

The longer the alkyl chain that is to undergo a cyclisation reaction, the more degrees of freedom it will have. Once a chain passes a certain length, usually taken to be seven units, any advantage that may have been gained by linking two potentially reactive sites is lost and it is necessary to utilise high dilution techniques[21] in order to ensure intramolecular reactions are favoured over intermolecular reactions. This is the entropy factor and may be offset by introducing constituents to the alkyl chain that reduce its degrees of freedom; for example the presence of a

double bond or triple bond will restrict rotational degrees of freedom.

The second element that affects a cyclisation to form a medium sized ring is related to the strain inherent in rings of eight to eleven members and is thus an enthalpy factor. Conformations[22] of rings of these sizes represent a balance between nonbonded hydrogen-hydrogen interactions, increased bond angle deformation and imperfect staggering; there are no conformations available in which these elements of strain are absent. The simplest method of alleviating some potential strain is by removing transannular hydrogens, this can be done by introducing unsaturation into the precyclisation alkyl chain either with double or triple bonds or sp^2 centres such as carbonyl groups. The ring will then adopt a conformation that fits this gap into a position usually occupied by an intraannular hydrogen. Figure 1 shows a stable conformation of cyclodecane (20). The structure was determined by X-ray crystallography[22]. The non-bonded interactions of hydrogens on type I and type III carbons are shown.



20.

Figure 1.

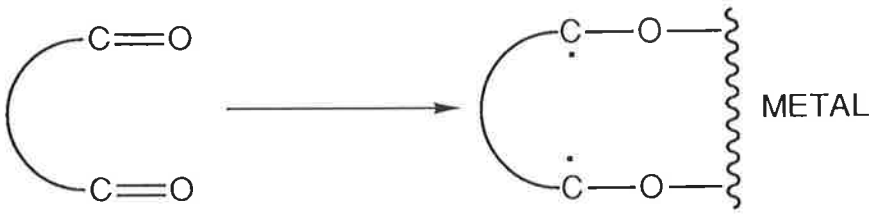
The classic solution to medium ring syntheses has been the acyloin reaction[23,24]; yields of ten membered rings have been in the

range 58% to 69% using trimethylsilyl chloride to suppress base catalysed Dieckmann reactions. The coupling requires two ester moieties; keto-ester couplings have been attempted for the preparation of five membered rings[25] but result in unacceptably low yields and a diverse range of products. This places limitations on the structure of the cyclisation precursor that will be discussed below. The functional group manipulations necessary in order to reduce the acyloin to a hydrocarbon also make for lengthy synthetic sequences[26]. There appears to be a scarcity of examples of acyloin cyclisations being applied to the preparation of strained systems. Under the acyloin reaction conditions α,β-unsaturated esters often couple tail to tail followed by a Dieckmann cyclisation to form a five membered ring keto-ester[27,28].

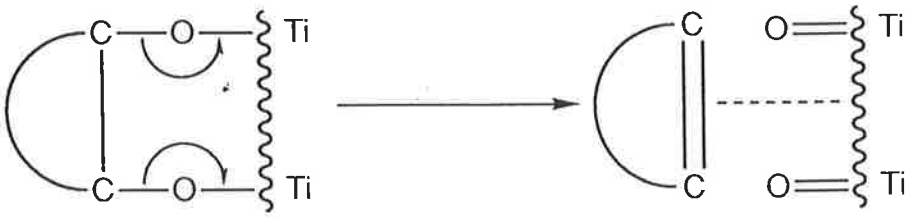
A more recently developed, and highly successful approach to the synthesis of rings of four to twenty members[28] is the zero valent titanium induced dicarbonyl coupling reaction which has given yields for these rings in the range 65% to 90% and in particular the yields of eight to twelve membered rings fall in the range 65% to 71%. Much of the extensive work on the methodology of this reaction has been carried out by Professor J.E. McMurry[29] and coworkers.

The titanium induced carbonyl coupling reaction has a number of advantages over the acyloin reaction even though the mechanisms of both reactions are related to a certain extent[30,31]. In each case the coupling of the radical anions may be the rate determining step (scheme 5), requiring an encounter in correct orientation of two radicals adsorbed in some manner onto the metal surface. It is at this stage that the reaction must overcome

the steric barriers to ring formation. The intermediate titanium pinacolate undergoes a near-concerted deoxygenation step[28,31] (scheme 6) to produce an olefin π-bonded to an oxotitanium species. It is the formation of the titanium oxygen bonds that provides the thermodynamic driving force for the reaction and is the reason why the reaction has been successful in the preparation of strained ethylenic linkages between moieties of considerable steric bulk. It is one of the few available methods for the preparation of strained double bonds, which in combination with the reactions efficiency with intramolecular cyclisations makes the titanium induced carbonyl coupling reaction a considerably powerful technique. There is a growing number of functional groups that have been shown to be compatible or semicompatible towards the reaction conditions[29].The potential of the reaction has been recently reviewed by McMurry[29].



Scheme 5.

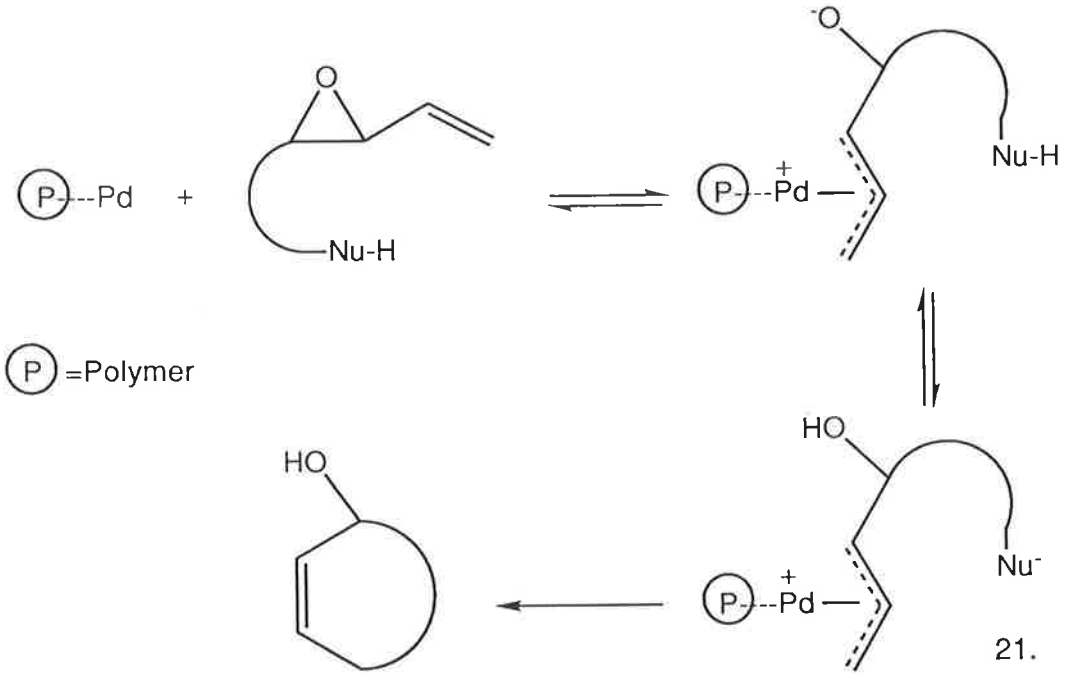


Scheme 6.

Recent reviews[32] of medium ring preparations show that much of the development has concentrated on providing isomers of

the 1,5-cyclodecadiene skeleton, a structural component of the germacrene and germacranolide sesquiterpenes.

Advances have been made in the area of anion induced cyclisation. An interesting variation has been developed by Trost[33] and coworkers which utilises the electrostatic attraction of a zwitterionic precyclisation intermediate (21) to overcome entropy effects (scheme 7). There are no examples yet of this type of reaction being used to cyclise intermediates with significant nonbonded interactions.

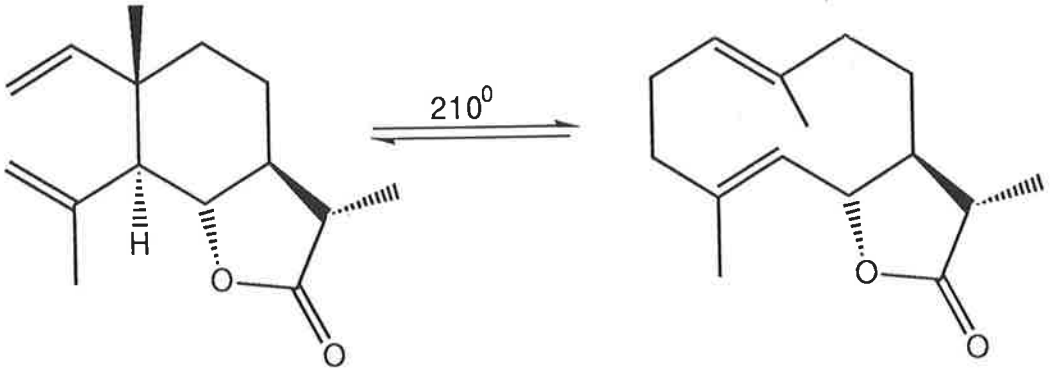


21.

Scheme 7.

An alternative approach to medium sized rings has been to use ring expansion techniques. Six membered rings may be prepared without difficulty. Strategies are then available to make the ring larger. One problem is that the ring expansions are often reversible, for example germacrenes (22) are unstable because of the potential [3.3] sigmatropic migration which can lead to 1,2-divinylcyclohexanes (23)[34] (scheme 8). This problem has been

overcome by making the Cope rearrangement irreversible. An oxy-Cope rearrangement was used to successfully transform the trans-1,2-divinylcyclohexan-1-ol (24) into the 2-*Z*-6-*E*-cyclodecadienone[35] (25) (scheme 9). Both Mander[36] and Marshall[37] have used Grob-like fragmentations to successfully convert decalin systems, for example (26) into 1,5- and 1,6-cyclodecadienes (27) (scheme 10).



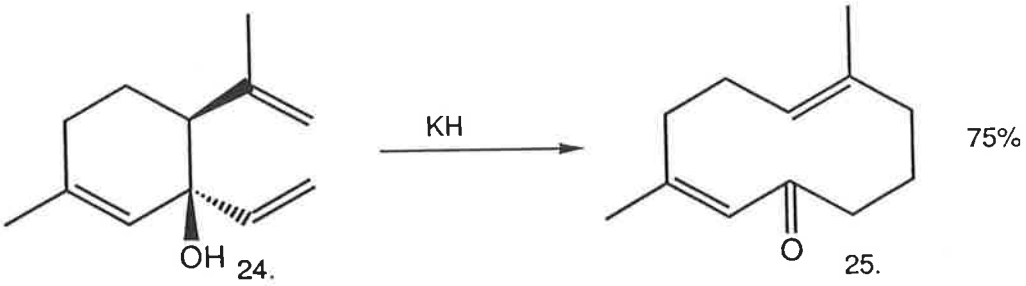
sassurea lactone 23.

50%

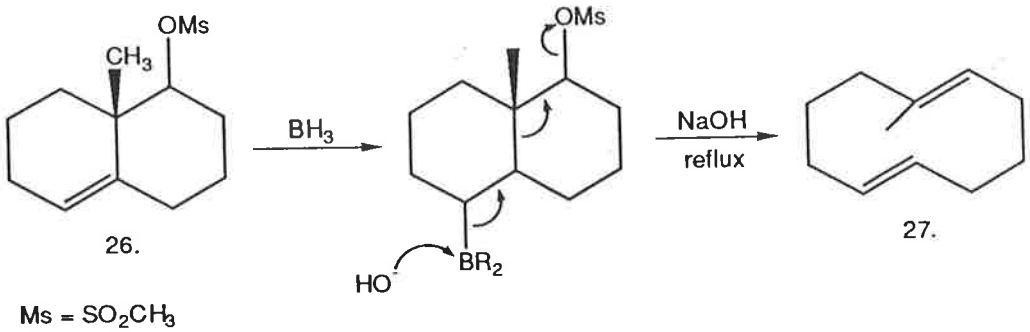
dihydrocostulonide 22.

50%

Scheme 8.



Scheme 9.

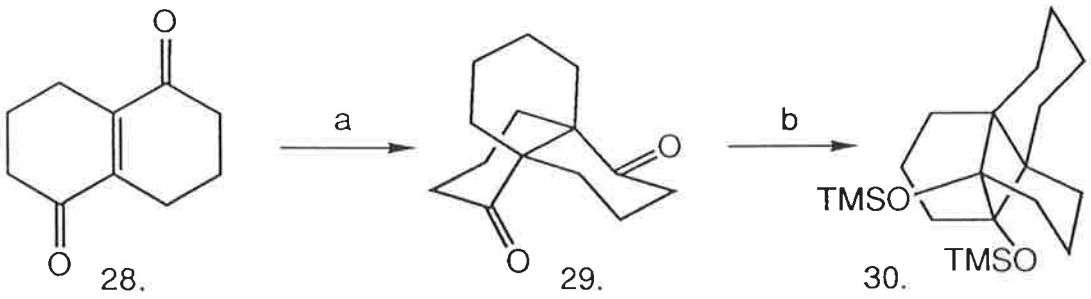


Ms = SO_2CH_3

Scheme 10.

There have been two unsuccessful attempts at the synthesis of isomers of bicyclo[4.4.4]tetradecane. These will be described briefly.

Alder and coworkers[38] hoped to use as the key step a reductive Grob-like fragmentation. The tricyclo[4.4.4.0]tetradeca-2,7-dione (29) was prepared by reductive alkylation of the ene-dione (28) and then subjected to even more vigorous reducing conditions in order to cleave the zero order bond (scheme 11). Instead of the desired cleavage taking place the product of a pinacol coupling, (30), was isolated.

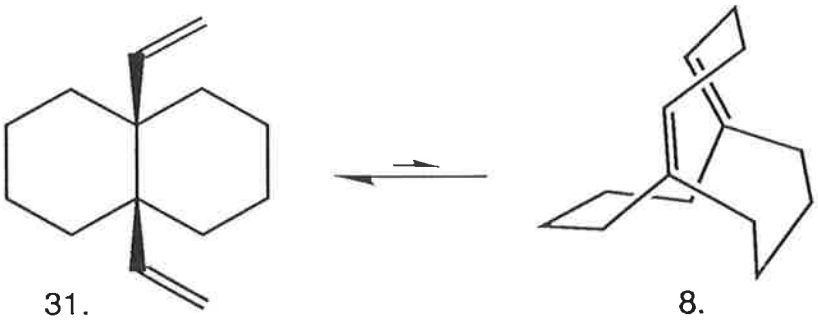


a.Na / NH_3
$Br(CH_2)_4Br$

b.Na-K, TMSCl
benzene, reflux

Scheme 11.

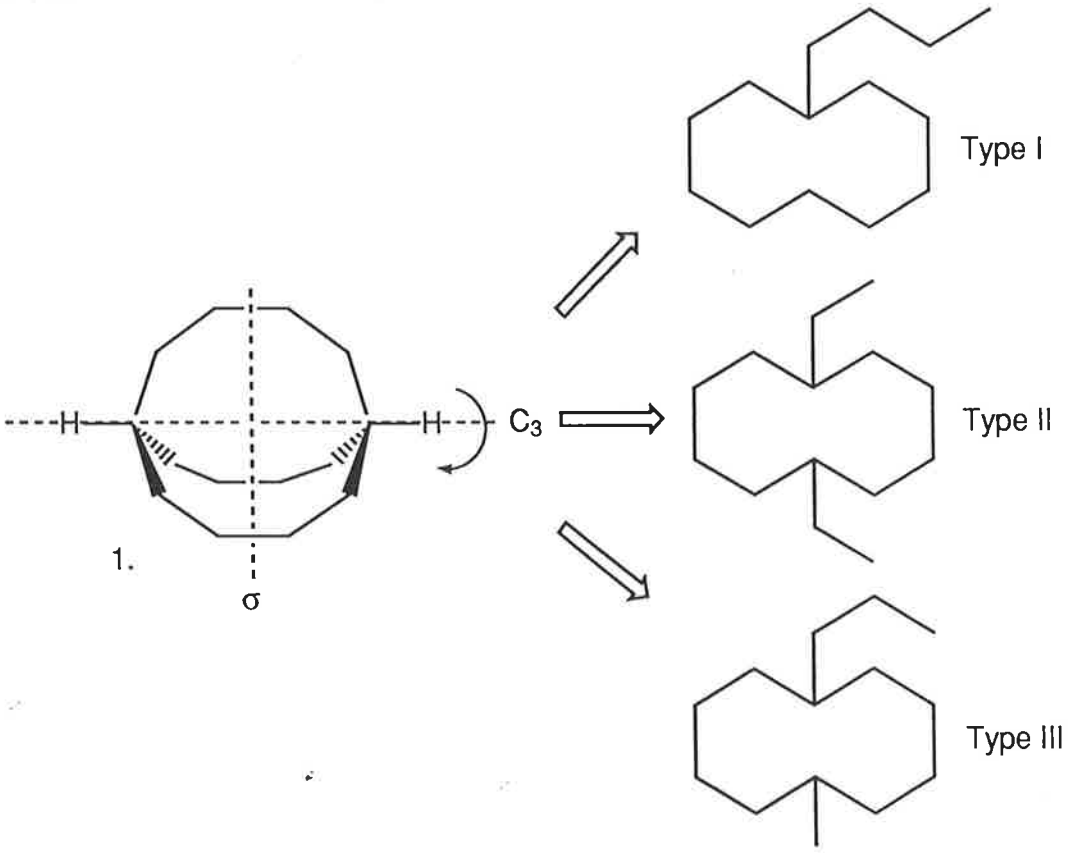
Shea and coworkers made a systematic study of *meso* bridgehead dienes[15] which were prepared by way of a general strategy utilising the Cope rearrangement of *cis* -1,2-divinylbicycloalkanes. Four dienes were prepared by this method (see above) however bicyclo[4.4.4]tetradeca-1,5-diene (8) remained inaccessible (scheme 12). This may be due to the difference in strain energies between the divinyldecalin (31) and the 1,5-[4.4.4]diene (8), the latter is calculated[38] to be more strained by 23 kJ mol^{-1}.



31. 8.

Scheme 12.

It is worthy of note that both these synthetic strategies attempted to avoid the problematic *de novo* synthesis of ten membered rings by assembling first the elements of the bicyclo[4.4.4]tetradecane skeleton from six membered rings.



Scheme 13

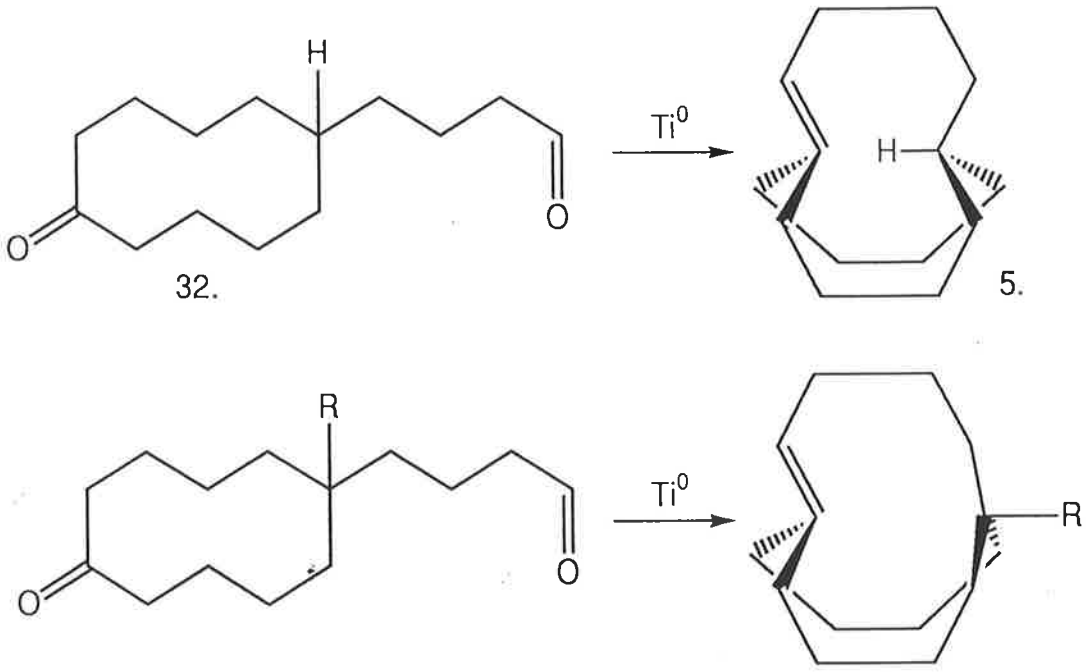
A high degree of symmetry, D_3, in the out,out-bicyclo[4.4.4]tetradecane (1) molecule means the molecule has only three unique single bonds that can be formed as the key step of a

synthetic strategy. This gives rise to key intermediates I, II and III shown in scheme 13. After a consideration of the methods available for the preparation of medium sized rings we decided that the most convergent strategy would utilise an intramolecular titanium induced carbonyl coupling reaction for the crucial cyclisation of these key intermediates. This reaction has the most potential for overcoming the problem of preparing strained, medium sized rings and the key dicarbonyl intermediates should be relatively simple to prepare. The key intermediate III did not appear to offer any particular advantages over type I and type II with regard to simplicity of preparation or convergence of approach and so it was discarded as a potential precursor.

The fundamental structural differences of the key intermediates type I and type II reside in the pro-bridgehead positions. The titanium reaction forms a carbon-carbon double bond by coupling two carbonyl groups. By using a type I key intermediate the coupling reaction performs a dual role; cyclisation, and derivatisation of one of the bridgeheads. In key intermediate II the bridgehead configurations could be established before or after the cyclisation step, depending upon such considerations as; strain of the cyclisation intermediate (see below) and whether or not the pro-bridgehead substituent would survive the coupling conditions. The pivotal role of the pro-bridgehead configuration in the success of the cyclisation strategy will be outlined below.

While preliminary investigations into the preparation of bicyclo[4.4.4]tetradecanes were underway in this research group[39,40], McMurry and Hodge[9] prepared in-6-*H*-bicyclo[4.4.4]tetradec-1-ene (5) in 20% yield by way of a zero

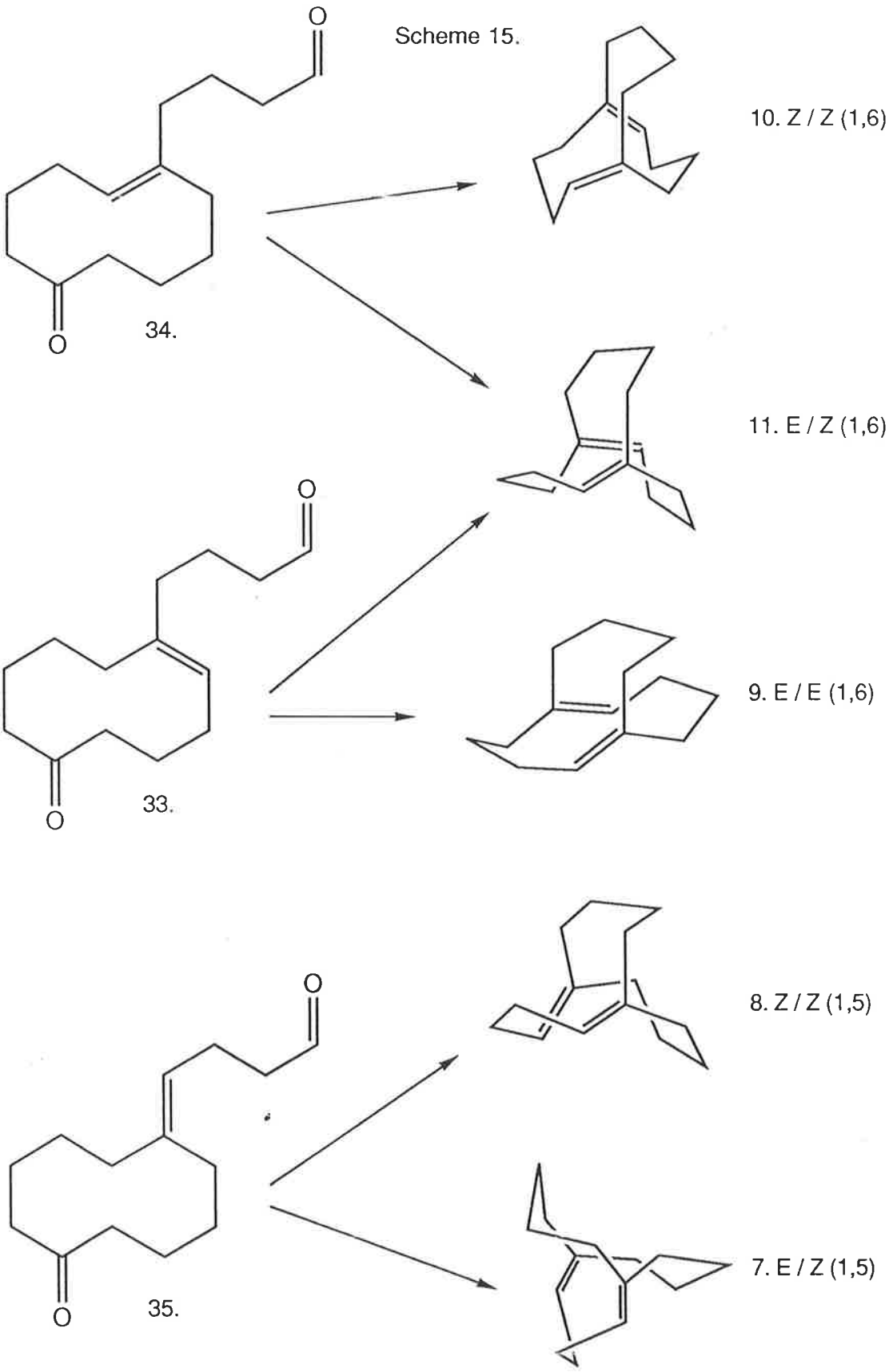
valent titanium induced cyclisation of 6-(4-oxobutyl)-cyclodecanone (32) (scheme 14). This result shows that the configuration of the bridgehead exerts control over the cyclisation pathway. It seemed obvious that for a type I key intermediate with a bulky substituent (R in Scheme 14) at the pro-bridgehead, cyclisation would proceed so as to render the substituent outside the bicyclic framework. This pathway would, by nature of the intermediates and products, involve greater steric hinderance than the successful cyclisation reported by McMurry. It is important to remember that the probable rate determining step of the key carbonyl coupling reaction involves a tetrahedral intermediate and that in-out bicyclo[4.4.4]tetradecane (3) is 51 kJ mol^{-1} less strained than the out-out isomer[6].



Scheme 14.

By placing a double bond at the pro-bridgehead of a type I key intermediate it may be possible to bring about a cyclisation involving intermediates that are less strained than those involved

Scheme 15.

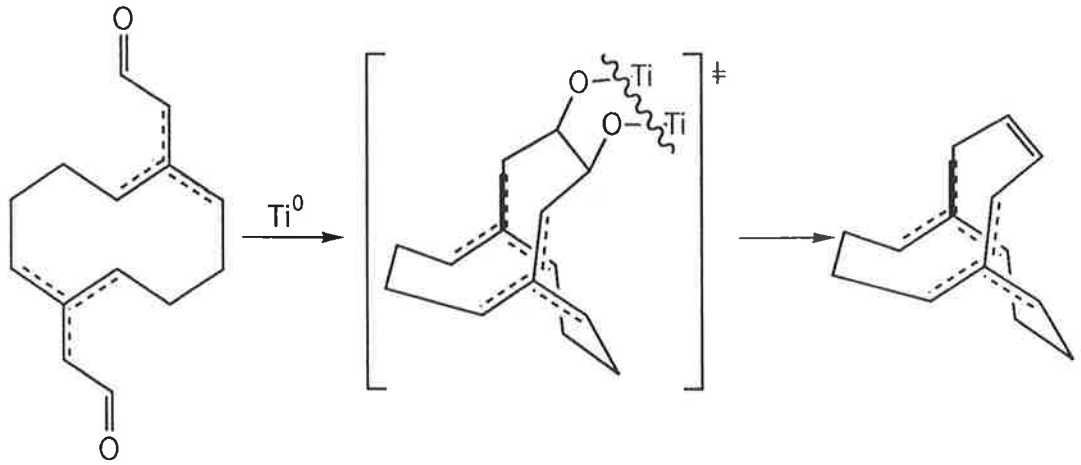


in the route that delivered the in-alkene (5), for the intermediate would be analogous to the out-alkene (6), 16kJ mol^{-1} more stable again than intermediates akin to the in,out-alkane[7,14] (3). This may be a significant alternative to the bicyclo[4.4.4]tetradecane targets if steric hinderance prohibits the cyclisation of the substituted type I key intermediates. As described in scheme (15) the *E*-, *Z*-, and exo- cycloalkenes (33,34,35) may give rise, collectively, to five types (see above) of isomeric bridgehead dienes (7,8,9,10,11). It should be possible to distinguish between the various types on the basis of their symmetry properties using ^{13}C nmr, particularly if the stereochemistry of the precursor could be taken into account.

This product diversity does not detract from the strategy as a means of preparing the target out,out-1-*H*-6-*H*-bicyclo[4.4.4]tetradecane (1) for the catalytic hydrogenation of all the diene isomers (7,8,9,10,11) should give the out,out-alkane (1) as the sole product. The structure of the molecule prevents delivery by the catalyst of hydrogen to the inner face of the double bonds; this does not, however, preclude transannular migrations of hydrogen[41]. Access to substituted derivatives would require the transformation of one or two of the double bonds of the bicyclic dienes (7,8,9,10 or 11) again without transannular reactions (see above)[15,42] taking place. It may be that the hyperstability[7] of the olefinic moieties results in them reacting in a stepwise manner, as was observed in the hydrogenation of the [2.2] (1,4) and [2.2.2] (1,2,4) paracyclophanes prepared by Murad and Hopf[43].

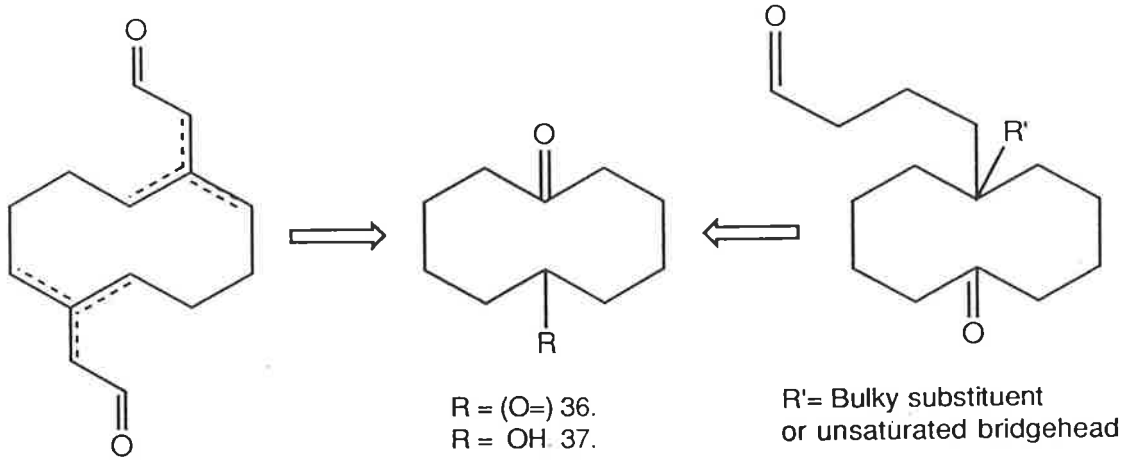
The type II key intermediate represents an alternative approach to the bicyclo[4.4.4]tetradecane framework which is also based upon the strategy of utilising the titanium induced

dicarbonyl coupling reaction for the cyclisation step. The principal advantage of moving the key bond connection away from the bridgeheads concerns the decrease in steric hindrance that would result from a type II key intermediate possessing two pro-bridgehead double bonds. According to the MM2 calculations of Schleyer and McEwen[7] the titanium pinacolate from a type II key intermediate shown in scheme 16 could be 13 to 56 kJ mol^{-1} more stable than the pinacolate corresponding to the out-alkene (6). There are examples[44] of intramolecular couplings of α,β-unsaturated dicarbonyls taking place without the complication of tail to tail coupling that has been observed in the analogous acyloin situation[27].



Scheme 16.

As a secondary consideration the type II key intermediates may provide potential substrates for an acyloin cyclisation; as the key intermediate could be prepared as a diester instead of a dialdehyde. Because of the aforementioned potential that α,β-unsaturated esters have shown for tail to tail coupling[27] under acyloin conditions, the key intermediate would be have to be either a saturated diester or a bis(β,γ-unsaturated ester) .



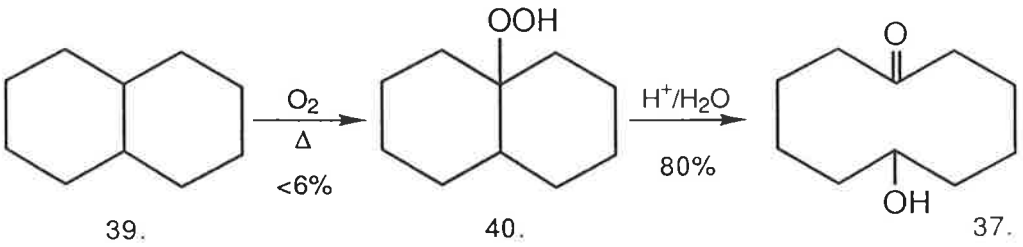
Scheme 17

Retrosynthetic analysis of the type I and II key intermediates (scheme 17) shows that they may derive from a common precursor, a cyclodecyl ring with potential carbonyl groups at the C1 and C6 positions. The sensitivity of 1,6-cyclodecadione (36) towards base[45,46] or acid[39] catalysed transannular aldol type reactions precluded it from being a useful precursor. An alternative precursor was 6-hydroxycyclodecan-1-one (37) in which the second carbonyl group is masked as a hydroxyl function which avoids transannular aldol type reactions. The hydroxyketone (37) has been observed to exist in an equilibrium with its hemiacetal (38) when in solution[47] (scheme 18). This equilibrium could affect attempts to protect either the carbonyl or the hydroxyl group of the hydroxyketone (37).

37. 38.

Scheme 18.

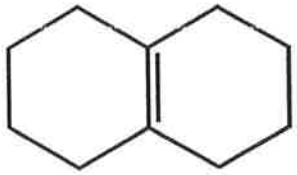
A new synthesis of 6-hydroxycyclodecan-1-one (37) is described in the first part of Chapter 2. This was developed because the principal route to the hydroxyketone (37) described in the literature[47] is particularly low yielding. The literature procedure is a modification of a synthesis developed by Criegee[48] (scheme 19) whereby decalins (39) are oxidised by air to form 9-hydroperoxydecalin (40) in yields of 6% or less based upon starting material. The hydroperoxide (40) may be rearranged *in situ* to give the hydroxyketone (37) in reasonable yield, but the overall yield of the preparation was not satisfactory for its use in preparation of a starting material.



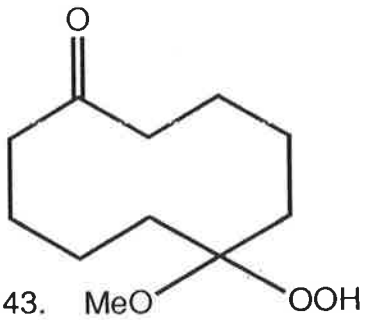
Scheme 19

It appeared to us that the hydroxyketone (37) could be prepared by the selective oxidation of 1,6-cyclodecanediols (41). Selective oxidations have been carried out with silver carbonate-on-celite to prepare ketoöls from the corresponding *meso*-diols[49]. The diols (41) could not be derived from 1,6-cyclodecadione (36) as reduction of the latter with hydride reagents leads to an intractable mixture[39]. A potential source of the diols (41) was from the direct reduction of the ozonide of $\Delta^{9,10}$-octalin (42). Criegee[50] has isolated the α-methoxyhydroperoxide (43) in 88% yield from the ozonolysis of $\Delta^{9,10}$-octalin (42) in methanol. The methoxyhydroperoxide (43) does not share the juxtaposition of the acidic methylenic protons and electrophilic carbonyl group that, in

concert, are the key to the sensitivity of the cyclodecadione (36) towards intramolecular aldol reactions.



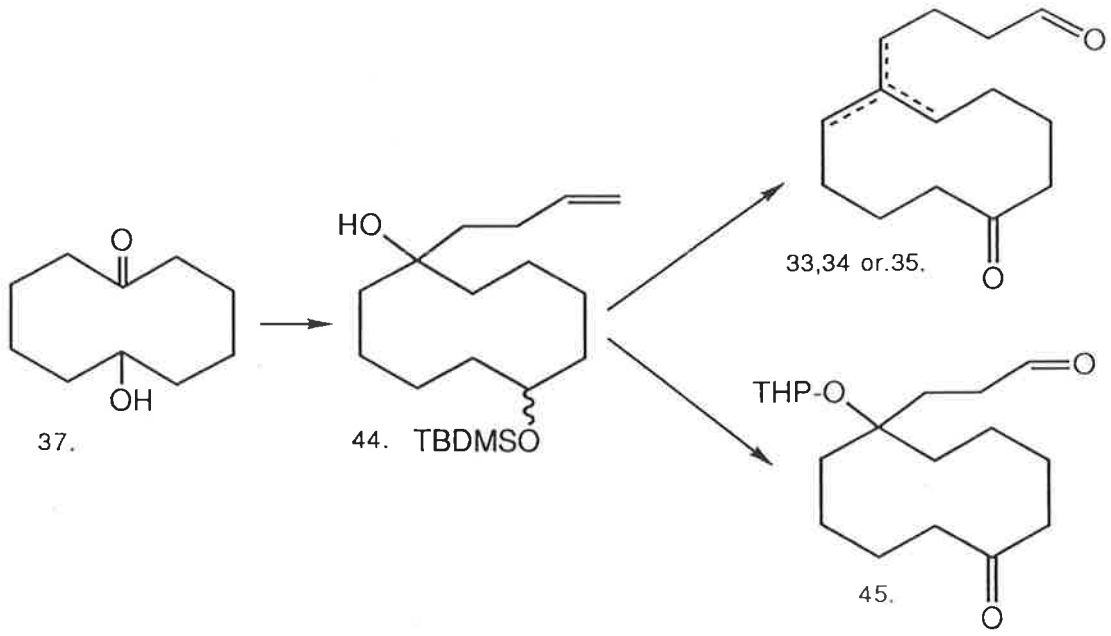
42.



43.

The second part of Chapter 2 describes the transformation of the hydroxyketone (37) into two kinds of type I key intermediate; either with a tetrahydropyranyl (THP) ether or an olefinic moiety at the pro-bridgehead position.

The proposed synthetic route calls for the addition of a butenyl nucleophile to the hydroxyketone (37) to build up the required type I key intermediate skeleton. This addition would give a molecule (44) with a tertiary hydroxyl group at the pro-bridgehead position. The hydroxyl group could be dehydrated to provide the unsaturated key intermediate (33, 34 or 35), left intact for subsequent protection as a THP ether (45), or transformed to provide other substituted key intermediates (scheme 20). The initial synthesis of the saturated type I key intermediate (32) by McMurry and Hodge[9] built up the butyl side chain by way of two successive Wadsworth-Emmons condensations. The route is less convergent and does not offer the flexibility with regard to bridgehead substituents as the routes described herein. McMurry[19] has recently published a modified procedure that uses the Grignard reagent prepared from 4-(benzyloxy)butylmagnesium chloride in the preparation of the saturated key intermediate (32).

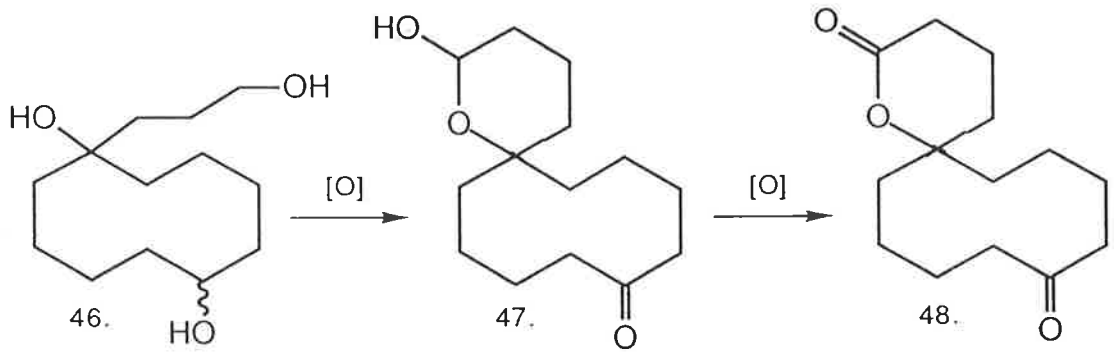


Scheme 20

The route to each key intermediate (33, 34 or 35) and (45) requires that the hydroxyl moiety of the hydroxyketone (37) be protected prior to alkylation to permit selective transformations of the tertiary hydroxyl group to take place. A t-butyldimethylsilyl (TBDMS) ether was thought to be an appropriate protecting group for the hydroxyketone (37). Alkylsilyl ethers[51,52] should be resistant to the reactions required for the subsequent transformation of the butenyl side chain, and may be selectively cleaved by fluoride ions in the presence of THP ethers.

The 3-butenyl Grignard reagent was chosen as the means of adding the four carbon chain. The terminal olefinic moiety represents a masked carbonyl group which can be revealed by the straight forward process of hydroboration with an alkaline peroxide work up followed by an oxidation step[53]. This strategy is applicable to the unsaturated as well as substituted key intermediates as hindered borane reagents should not react with a trisubstituted double bond[53].

The tertiary hydroxyl group should survive the conditions of the titanium induced carbonyl coupling reaction[29]. It was protected as a THP ether because the hydroxyl group of the triol (46) may have participated in the oxidation of the primary butyl hydroxyl group to instead form a six membered lactone (48) (scheme 21). In addition a free tertiary hydroxyl group in the key intermediate could exist in equilibrium with its hemiacetal (47) which may have a deleterious effect upon the carbonyl coupling reaction. THP groups should survive the conditions of the coupling reaction[29,54].



Scheme 21.

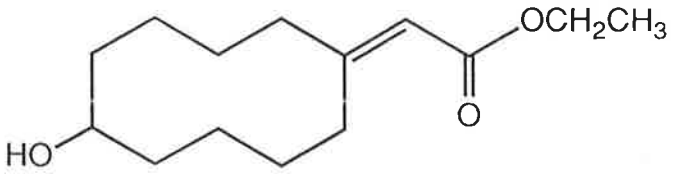
Although it was not investigated, the tertiary hydroxyl moiety could also be transformed to a quaternary methyl substituent using chemistry described by Reetz[55]. The quaternary methyl group key intermediate could not undergo side reactions such as elimination which could occur with the THP derivative (45), and might provide further insight into the ability of substituted type I key intermediates to cyclise.

Chapter 3 describes the attempts that were made to cyclise the key intermediates that had been prepared in Chapter 2. As there was no experience with the techniques involved in carrying out the key titanium induced carbonyl coupling reaction within the research group, considerable efforts were devoted to the coupling

of model systems to ensure the coupling reaction was performing according to the literature. Indeed the cyclisation of the saturated key intermediate 6-(4-butanal)cyclodecan-1-one (32) was carried out to act as a standard for the other cyclisation reactions.

The first part of Chapter 4 describes the transformation of the hydroxyketone (37) into type II key intermediates with either two saturated, or two unsaturated pro-bridgehead moieties. This alternative route to the bicyclo[4.4.4]tetradecane skeleton was undertaken when results of early cyclisation reactions of type I key intermediates did not appear successful.

The proposed synthetic route towards type II intermediates requires the stepwise alkylation of the C1 and C6 carbons of the cyclodecyl precursor with two nucleophilic acetate synthons. The acetate group represents a masked aldehyde function but should be sufficiently unreactive[51] to ensure the second alkylation is selective for the cyclodecyl carbonyl. The preparation of the α,β hydroxyester (49) has been described by McMurry[9], it was formed by the reaction between the hydroxyketone (37) and triethylphosphonoacetate. The use of equivalent synthons for the two alkylation steps should allow the two carbonyl groups of the type II key intermediate to be unmasked simultaneously. The saturated type II key intermediate should be accessible by hydrogenation of any of the precursors to the di-unsaturated key intermediate and so a common approach can be used to prepare both substrates for the cyclisation reactions.



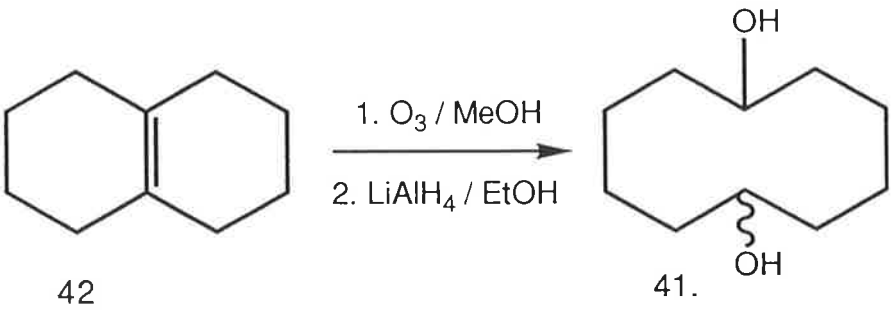
49.

The second part of Chapter 4 decribes the attempts that were made to cyclise the saturated and di-unsaturated type II key intermediates by the titanium induced intramolecular carbonyl coupling reaction. In addition attempts were made to cyclise the 1,6-bis(ethoxycarbonylmethyl)cyclodecanes (50) by way of acyloin coupling reactions.

Chapter 2

Part 1. Preparation of 6-Hydroxycyclodecan-1-one (37).

Preliminary investigations in this research group[39,40] had demonstrated that the crude product from the ozonolysis in methanol of 1,2,3,4,5,6,7,8-octahydronaphthalene ($\Delta^{9,10}$-octalin) (42), would yield, upon reduction with lithium aluminium hydride, 1,6-cyclodecanediols (41) in 25% to 30% yield after recrystallisation (scheme 22). A solitary experiment that yielded 60% of the diols (41) suggested that the reaction warranted further investigation.



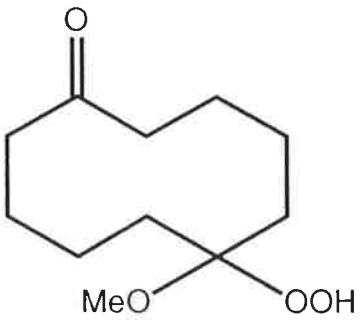
42 41.

Scheme 22.

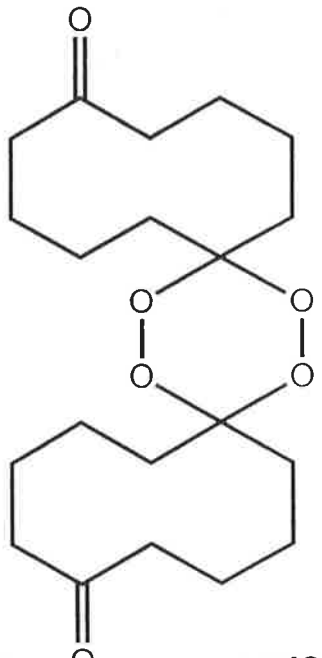
The ozonolysis of $\Delta^{9,10}$-octalin (42) had been explored by Criegee[50] who had isolated the α-methoxyhydroperoxide (43) in 88% yield as a crystalline solid with a melting point of 94°C.

The α-methoxyhydroperoxide (43) represented a molecule which should be reduced by lithium aluminium hydride to provide the diols (41) in good yield for the reasons that have been discussed in the introduction. Consequently the low yield of diols (41) was felt to reflect a failure in the ozonolysis step. Even though the products that Criegee isolated from the ozonolysis of

$\Delta^{9,10}$-octalin (42) in methanol to give (43) or hexane to give (51) had been shown to be stable, Bailey's monograph[56] alludes to a traditional fear of the "explosive ozonide" which he attributes to "polymeric peroxides or ozonides contaminated with such". We devised a procedure that kept the crude ozonolysis product cold; by substituting dichloromethane for methanol this product could be reduced by lithium aluminium hydride without the necessity for solvent removal.



43. m.p. 94°- 95°C



51. m.p. 166°C

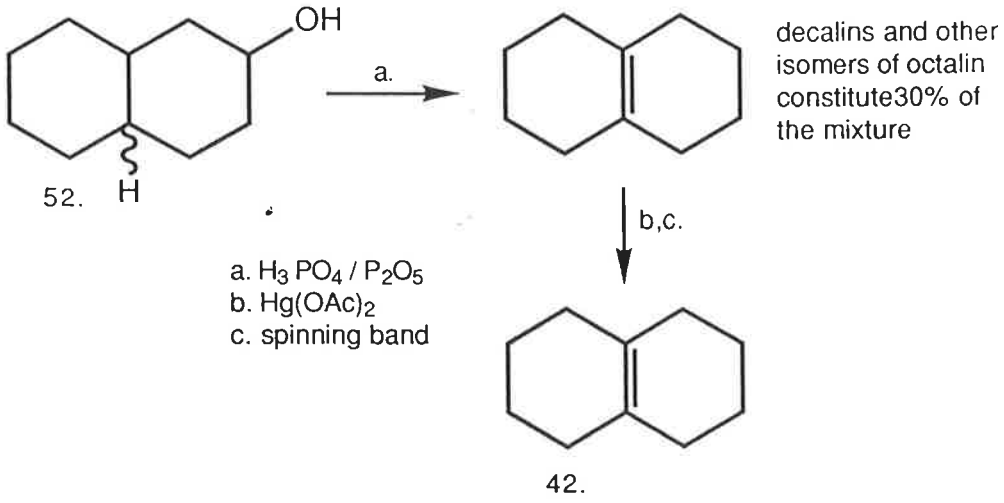
This modified procedure improved the yield of cyclodecanediols (41) to 45%. The isolation of the diols (41) was made considerably more difficult by the presence of unidentified components with solubility and polarity characteristics resembling those of the cyclodecanediols (41). Recrystallisation was unsuccessful. Instead the complex mixture required repetitive chromatography which made scale up of the procedure impractical.

The $\Delta^{9,10}$-octalin (42) we were using for the ozonolysis step was obtained from the dehydration of β-decalols[57] (52). The product contained contaminants present in the range of 5% to 10%

by gas chromatographic analysis that were not removed by repetitive oxymercuration[58]. These contaminants were tentatively assigned as *cis/trans*-decalins (39) as they co-eluted with authentic samples of *cis/trans*-decalins and show a molecular ion of *m/z* 138. The ^1H nmr spectrum for the mixture shows no olefinic hydrogens.

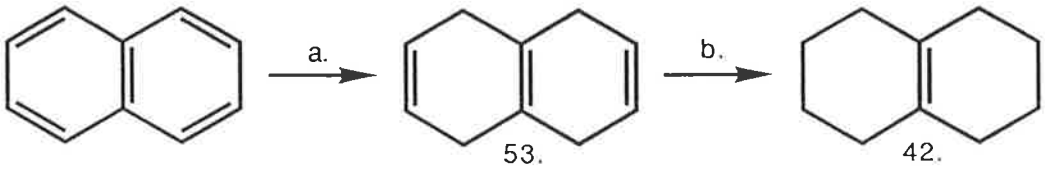
The only rationale we could provide for any interference by decalins was that peroxides may have arisen from the oxidation of the decalins either by contact with oxygen or ozone and that these peroxides were participating with a deleterious effect on the ozonolysis process.

The decalins (39) could be successfully removed by careful distillation using a one metre spinning band column to give $\Delta^{9,10}$-octalin (42) of at least 97% purity by gas chromatography. The boiling point of *cis/trans*-decalins[59], 189°-190°C / 760 mmHg, and $\Delta^{9,10}$-octalin[57], 190°-191°C / 760 mmHg, are very similar. Pure $\Delta^{9,10}$-octalin (42) was obtained in 33% yield from a mixture containing 70% $\Delta^{9,10}$-octalin (42) by sequential oxymercuration/spinning band distillation .



Scheme 23.

An alternative synthesis of $\Delta^{9,10}$-octalin (42) had been devised by Birch and Walker[60]. The hydrogenation of 1,4,5,8-tetrahydronaphthalene (isotetralin) (53) with tris(triphenylphosphine)rhodium chloride in benzene gave $\Delta^{9,10}$-octalin (42) in 87% yield and better than 97% pure[61]. Initial problems were caused by the inactivation of the catalyst by hydrogen contaminated with oxygen. This was overcome by passing the hydrogen through a manganese oxide column[61] to ensure the reaction was carried out under oxygen free conditions. Wilkinson[62] has reported the formation of an insoluble polymer of the rhodium catalyst and oxygen when oxygen comes into contact with a solution of the catalyst.



a. Na/NH_3, EtOH, 79%
b. H_2 / $(Ph_3P)_3RhCl$, 87%

Scheme 24.

When the pure $\Delta^{9,10}$-octalin (42) was ozonolysed in methanol and the crude ozonide, stripped of methanol, was reduced with lithium aluminium hydride, the 1,6-cyclodecanediols (41) were isolated in 70% to 78% yields; highlighting the importance of pure reaction precursors.

An additional observation that was made during the development of this procedure was that the ozonolysis step was best carried out quickly. Short reaction times produced a white solid upon solvent removal from the crude product, and the subsequent yield of diols (41) was good. If the ozonolysis took in

excess of 2 hours the crude ozonide was often a clear liquid and yield of the diols (41) was reduced to 60% to 65%.

The removal of methanol can be avoided by the use of sodium borohydride in ethanol as the reducing agent. Ozonides may be effectively reduced to alcohols by either lithium aluminium hydride or sodium borohydride[56]. When $\Delta^{9,10}$-octalin (42) of >97% purity was used in the ozonolysis, reduction with sodium borohydride gave the diols (41) in 64% yield. Although the yield is lower, the use of sodium borohydride avoided the need for solvent removal prior to the reduction step and the reaction workup was simpler than when lithium aluminium hydride was used.

The 1,6-cyclodecanediols (41) may be oxidised to 6-hydroxycyclodecan-1-one (37) in yields of 70% - 75% using Fetizon's reagent, silver carbonate-on-celite[63,64]. The hydroxyketone (37) had the correct melting point[48] and the ^{13}C nmr spectrum showed the resonances of both the hydroxyketone (37) and its hemiacetal tautomer (38) (see scheme 18) which corresponded to literature observations[65].

The oxidation reaction was most efficient when monitored by gas chromatography, as the duration of the oxidation was not reproducible and after a certain period the oxidation of 6-hydroxycyclodecan-1-one (37) to 1,6-cyclodecanedione (36) becomes significant. The solid phase must be separated from the hot suspension as soon as possible after the reaction has gone to the optimum point in order to prevent over-oxidation. The table of results (table 1) was included to show the erratic nature of the reaction.

The three components of the crude product were effectively separated by short column chromatography[66].

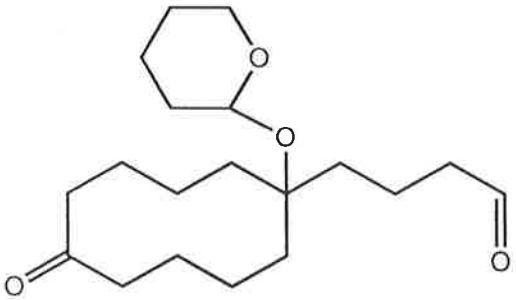
Table 1.

$AgCO_3$ equiv.	$AgCO_3$ conc.(M)	Reaction time (min.)	ketøl (37)	diol (41)	dione (36)
3·7	1·0	7·5	72%	7%	15%
3·5	0·37	23	76	10	13
3·3	0·4	25	42	48	2
3·5	0·4	55	57		40
4·1	0·06	5	60	30	
4·0	0·06	5	68	23	
3·7	0·05	7	72	6	17
3·0	0·05	7	64		25
2·5	0·05	7	70	3	21

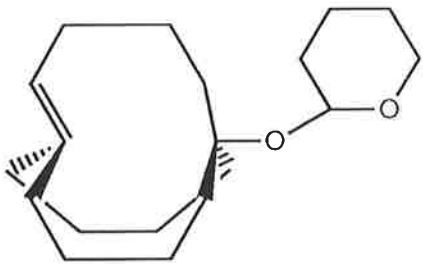
McKillop and Young[64] propose that the reaction is selective because of differences in the adsorption characteristics of various substrates onto the silver carbonate on celite reagent. This suggests that the reaction is bi-molecular, dependent upon the concentrations of both the silver carbonate reagent and the compound to be oxidised. The reaction must be monitored because the reagent is in excess and as the hydroxyketone (37) concentration becomes high the rate of its oxidation becomes significant.

Part 2. The Preparation of 6-(4-Butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45), a Substituted Type I Key Intermediate.

The key step of our synthesis towards 1-(tetrahydropyranyloxy)-out-6-H-bicyclo[4.4.4]tetradecane (54) required as its substrate 6-(4-butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45). The synthetic route by which this key intermediate was prepared is outlined in scheme 25. The precursor for this sequence was 6-hydroxycyclodecan-1-one (37).



45.

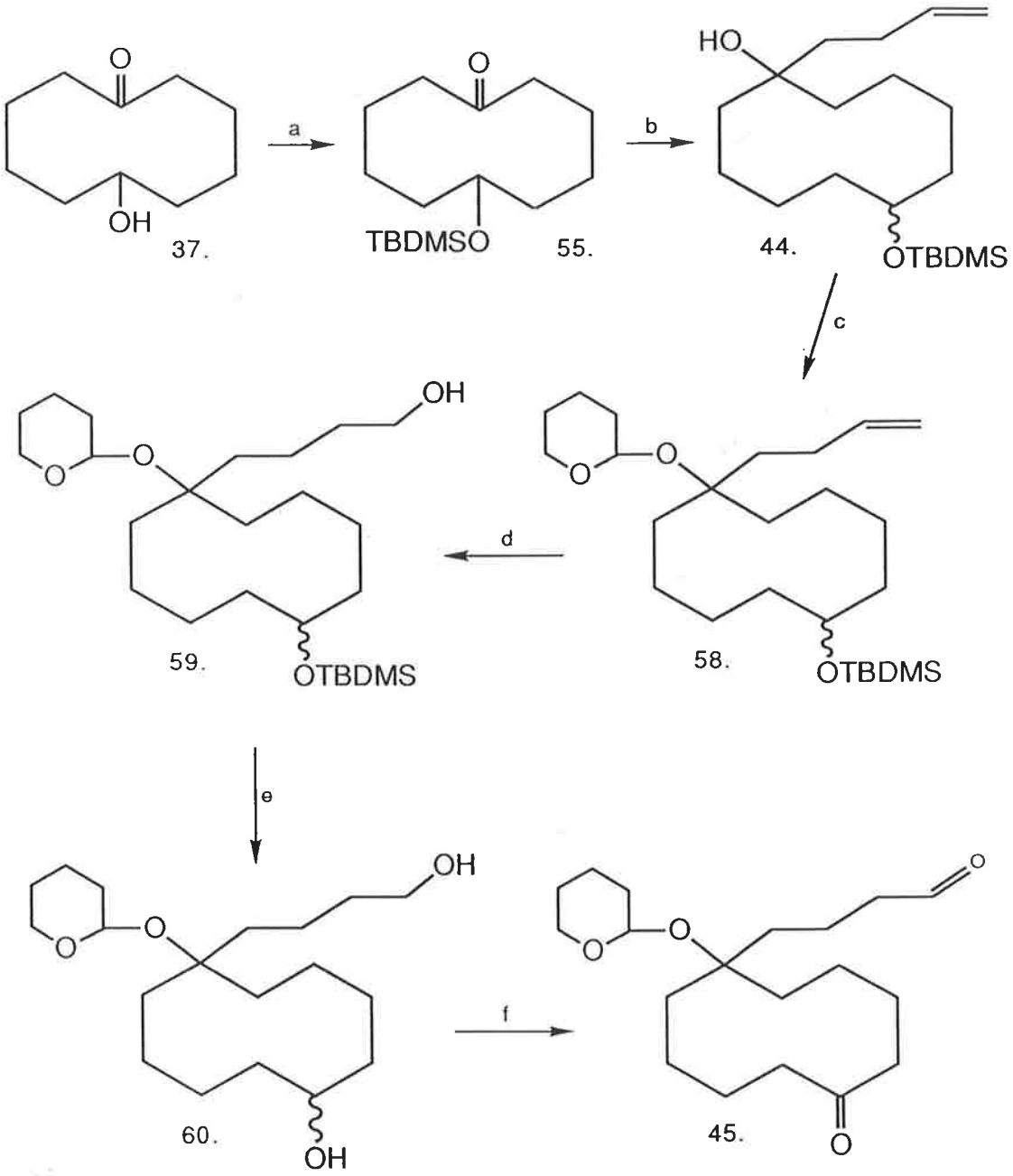


54.

The reaction between the hydroxyketone (37) and t-butyldimethylsilyl chloride in the presence of a catalytic amount of 4-dimethylaminopyridine produced 6-(t-butyldimethylsilyloxy)cyclodecan-1-one (55) in greater than 90% yield after purification by short path distillation. This is a general procedure for the preparation of alkyl silyl ethers[67,68,69].

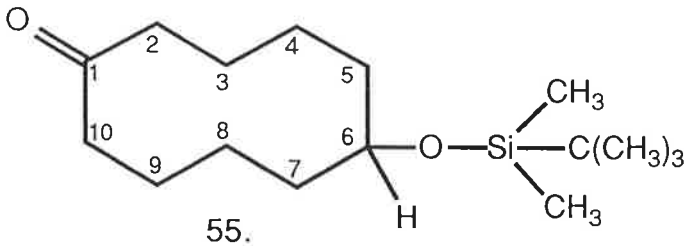
The hydroxyketone (37) has been observed[47] to exist in equilibrium with its hemiacetal (38) in solution. It was important to establish that there was no hemiacetal protected as a silyl

Scheme 25.

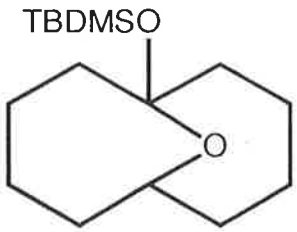


a. TBDMSCl, DMAP, Et_3N/CH_2Cl; b. (57), Toluene, -10°C; c. Dihydropyran/H^+; d. i.Disiamylborane,THF,ii. NaOH / H_2O_2; e. $(n\text{-Butyl})_4NF$, THF; f. PCC or DMSO / $(COCl)_2$.

ether (56) contaminating the product. The infrared spectrum has a strong absorption at 1706 cm^{-1} for the cyclodecyl carbonyl group and the O-H stretch of the hydroxyketone (37) was absent. The ^{13}C nmr spectrum of the product shows a resonance at δ 214·07 for the C1 carbonyl function and at δ 70·1 for the C6 carbon bearing the silyloxy substituent but there are no resonances in the range δ 85 to 100 which is where the acetal carbon of the silylated hemiacetal (56) might be expected to occur. This observation is consistent with the product being only the TBDMS cyclodecanone (55). Three of the seven resonances in the aliphatic region of the ^{13}C nmr spectrum are attributed to the carbons of the TBDMS group. The resonance at δ 25·7 is due to the equivalent methyl carbons of the t-butyl group, and the weak signal at δ 17·8 and the resonance at δ -4·7 represent respectively the quaternary carbon and the methyl carbon that are bonded directly to the silicon of the TBDMS group.



55.



56.

Cyclodecyl rings that are 1,6- disubstituted have a plane of symmetry through the C1 and C6 carbons[22] which should simplify the ^{13}C nmr spectrum. The fact that the spectrum contains only five resonances due to the cyclodecyl ring may be attributed to the further equivalences of C9 to C8 and C3 to C4, which are a long distance from the points of substitution and so would be in similar environments.

The ^1H nmr spectrum shows the C6 hyrogen as a multiplet at δ 3·64. Two singlets at δ 0·88 and 0·05 are diagnostic of the t-butyl hydrogens and methyl hydrogens, respectively of the t-butyldimethylsilyloxy group. The methyl signals are upfield due to the influence of the adjacent electropositive silicon.

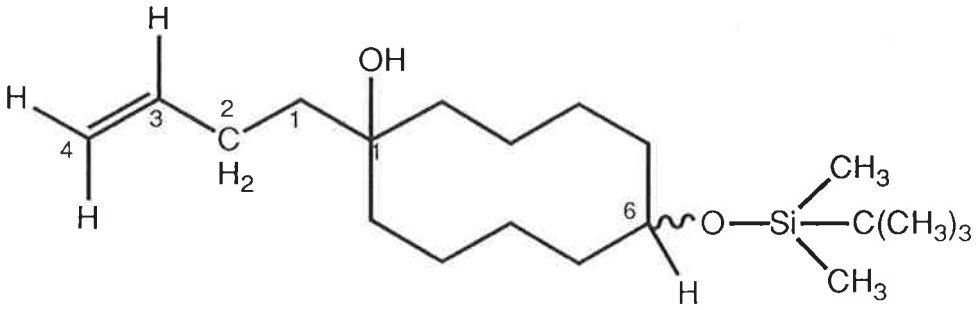
The Grignard reagent, 3-butenylmagnesium bromide (57) was prepared in 75% yield by way of a literature procedure[70].

A preliminary observation made concerning the reaction between the TBDMS-cyclodecanone (55) and 3-butenylmagnesium bromide (57) in refluxing ether was the recovery of a large proportion of unreacted ketone (55) and less than 30% yield of the desired product (44). This was attributed to the removal of protons α to the carbonyl group by the Grignard reagent resulting in the formation of its enolate anion which was immune to nucleophilic attack. The steric bulk of the cyclodecyl ring in concert with the favourable energetics of enolisation, that is by the introduction of a double bond into a ten membered ring transannular strain is reduced, make the hydrogens α to the carbonyl group more susceptible to attack than the electrophilic carbonyl carbon.

Cannone *et al.*[71] have observed that carbonyl groups that are prone to enolisation undergo efficient addition reactions with organomagnesium reagents when the reaction is carried out in aromatic hydrocarbon solvents. The reaction between the 3-butenylmagnesium bromide (57) and the TBDMS-cyclodecanone (55) in benzene at 50°C gave 6-(t-butyldimethylsilyloxy)-1-(3-butenyl)cyclodecan-1-ol (44) in 39% yield.

The enolisation of carbonyl groups has also been suppressed by carrying out the reaction at lower temperatures. When the reaction was carried out at room temperature in benzene the

TBDMS-butenylcyclodecanol (44) was isolated in 48% yield. The substitution of toluene for benzene permitted the reaction to be carried out at -10°C and the yield of addition product (44) improved to 60%. Although lower temperatures were tried, no further improvements in yield were observed. In addition to some recovered TBDMS-cyclodecanone (55) the reaction produced an alcohol, 6-(t-butyldimethylsilyloxy)cyclodecan-1-ol (61) in 7% to 10% yield.



44.

The infrared spectrum of (44) shows a strong OH stretch at 3375 cm^{-1} and sharp absorptions at 3060 cm^{-1} and 1640 cm^{-1} from the terminal olefinic C-H and C=C stretching respectively. The carbonyl stretch at 1706 cm^{-1} is absent. The mass spectrum does not show a molecular ion. There are fragment ions at *m/z* 283 and 265 which correspond to the sequential loss from the parent ion of a t-butyl fragment and then a molecule of water, a facile process for a tertiary alcohol.

A significant consequence of the alkylation step was the production of *cis/trans*- diastereomers of the cyclodecyl system. Analytical thin layer chromatography (TLC) resolved the product isolated from the reaction into two components that were not readily separable by preparative techniques. It was important to

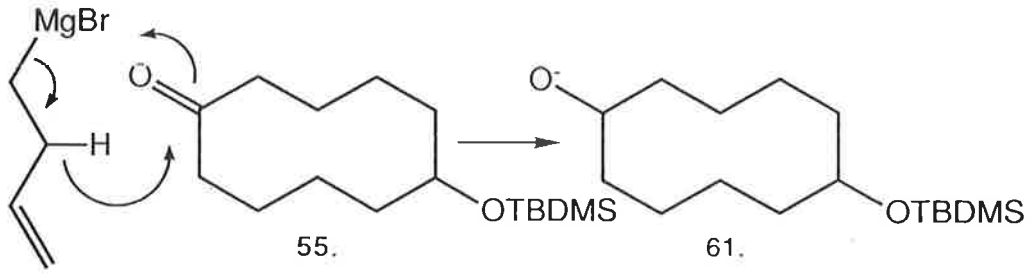
establish that the product was indeed a mixture of the diastereomers of TBDMS-butenylcyclodecanol (44).

The elemental analysis of the product was consistent with the formula $C_{20}H_{40}O_2Si$. Many of the resonances in the ^{13}C nmr spectrum occurred as closely shifted pairs, the principal exceptions being the signals associated with the TBDMS group. The ^{13}C nmr spectrum shows the resonances of C3 and C4 of the butenyl chain at δ 139·25 and 114· 29, 114·24. In addition both of the carbons bonded to oxygen, C1 and C6, display paired resonances of δ75·92, 75·88 and 72·14, 72·07; the C1 carbon being more deshielded by greater alkyl substitution would resonate further downfield. The symmetry of the cyclodecyl ring again contributes to the simplicity of the spectrum in the aliphatic region. Of the five isomeric pairs of signals in the aliphatic region, two would be due to C1 and C2 of the butenyl chain, leaving three pairs for assignment to the relevant cyclodecyl carbons.

The ^1H nmr spectrum shows a coupling pattern which is consistent with the hydrogens of a terminal double bond. The vinylic C3 hydrogen at δ 5·85 occurs as a doublet of doublet of triplets: a coupling constant of 17·1 Hz to the resonance at δ 5·04 and 10·6 Hz to the resonance at δ 4·94 indicates a trans and cis arrangement respectively to the C4 geminal vinylic hydrogens. The C4 hydrogens are coupled to each other with a coupling constant of 1·7 Hz.

The byproduct of the Grignard reaction, 6-(t-butyldimethylsilyloxy)cyclodecan-1-ol (61), was successfully reverted to the TBDMS cyclodecanone (55) in 94% yield by oxidation with pyridinium chlorochromate[72,73]. The TBDMS-cyclodecanol (61) would have been formed as a result of a β-hydride elimination from

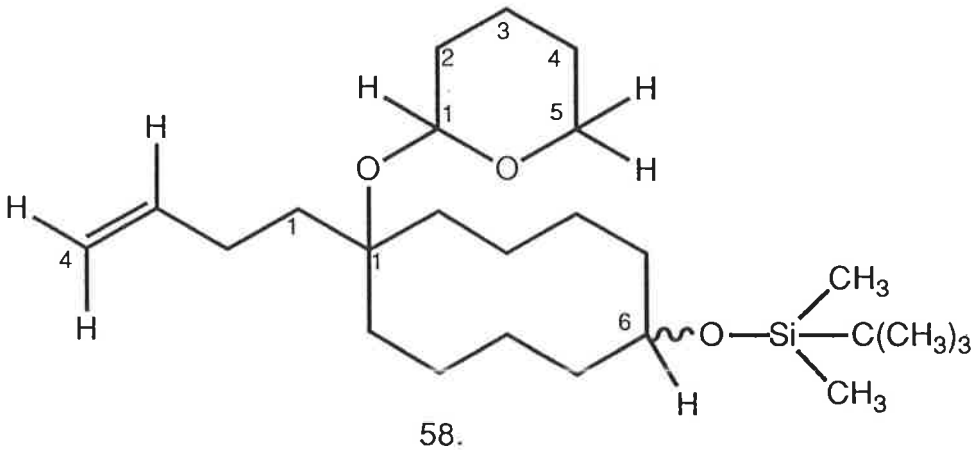
the organomagnesium species[74] (scheme 26). This process has been observed to occur particularly with sterically crowded ketones where the usual course of nucleophilic addition is inhibited[75].



55. 61.

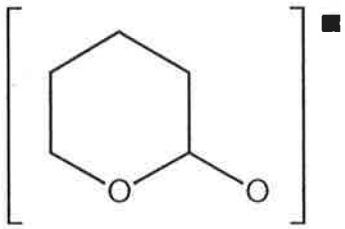
Scheme 26.

The tertiary alcohol moiety of the TBDMS butenylcyclodecanol (44) was successfully protected as the tetrahydropyranyloxy ether (58) by reaction with pyridinium *p*-toluenesulphonate[76] in neat dihydropyran. The product, 1-(3-butenyl)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy) cyclodecane (58) was isolated in 92% yield by chromatography. When *p*-toluenesulphonic acid[77] was used as the acid catalyst the yield of TBDMS-THP-butenylcyclodecane (58) was 82%. The formation of the THP ether was particularly sluggish if the dihydropyran was diluted with dichloromethane as recommended by the literature procedures[76,76] for the general preparation of THP ethers.



58.

No O-H stretch is evident in the infrared spectrum of the THP ether (58) which indicates the successful protection of the C1 hydroxyl group. The mass spectrum of the TBDMS-THP-butenylcyclodecane (58) shows a weak molecular ion of *m/z* 424 with strong fragment ions at *m/z* 367 for the loss of the t-butyl fragment and at *m/z* 323 which gives a high resolution mass spectrum consistent with $C_{20}H_{39}OSi$. This ion could be attributed to the ready loss of the tetrahydropyranyloxy fragment (62) from a tertiary position.



62.

The ^1H nmr spectrum contains a new multiplet at δ 4·70 that is consistent with the hydrogen of the C1 acetal carbon of the THP moiety. The two oxygens deshield the acetal hydrogen and cause it to be shifted almost 1 ppm further downfield from hydrogens adjacent to a single ether or hydroxyl group. There are also two new multiplets at δ 3·95 and 3·44 of a single hydrogen each. A decoupling experiment showed that these resonances are mutually coupled as well as being further coupled to the aliphatic region and are consistent with the geminal hydrogens on the C5 of the THP group. There was no obvious indication from the ^1H nmr spectrum that TBDMS-THP-butenylcyclodecane (58) was a mixture of *cis*- and *trans*-isomers.

The ^{13}C nmr spectrum, however, still exhibits the resonance pairs attributed to the occurrance of *cis/trans*- isomerism. The spectrum contains a new pair of resonances at δ 93·17 and 92·99 as

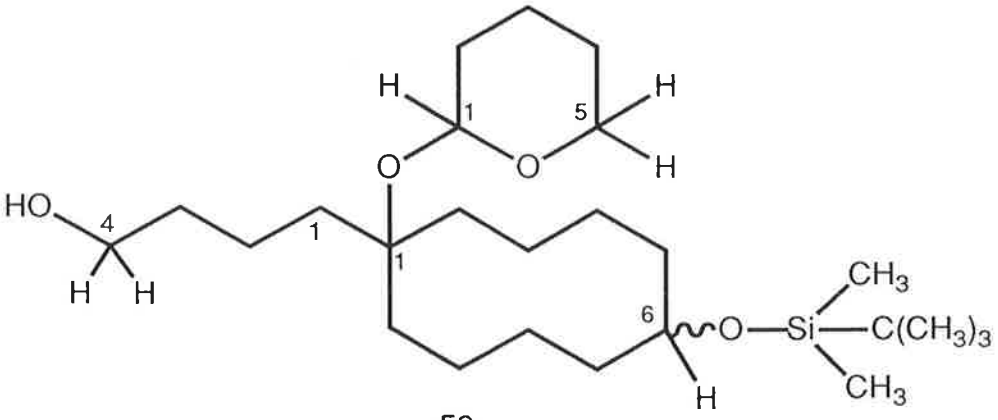
well as a pair further upfield at δ 63·64 and 63·40. These are consistent, respectively, with the acetal C1 of the THP group deshielded by two oxygen substituents, and the THP C5 carbon. The latter carbon occurs upfield of the other carbons singly bonded to oxygen because it has only one alkyl substituent and so is not as deshielded as the rest. In addition the cyclodecyl C1 carbon has shifted downfield from δ 75·92 to 81·62, which demonstrates the deshielding effect of replacing a hydroxyl group with an alkoxy substituent.

The resonances of the aliphatic region have not assigned except for the resonances that are characteristic of the TBDMS group. The introduction of the chiral THP group has clearly affected the ^{13}C nmr spectrum for it no longer displays the spectral properties of a plane of symmetry. This apparent loss of symmetry would arise as a result of the presence of the chiral centre in the THP ether. Each of the methylene groups of the cyclodecyl ring has become diastereotopic and as a result may have a unique resonance.

The ^{13}C nmr spectrum of a later derivative of this synthetic sequence, 6-(4-butanal)-6-(tetrahydropyranyloxy) cyclodecan-1-one (45) helps elucidate why there was not a full set of resonances for each diastereomer. The spectrum of the THP-butanalcyclodecanone (45), which lacks the complication of *cis/trans* isomerism, suggests that the plane of symmetry is still intact around the C6 region, thus the effects of the THP chiral centre appear to diminish with distance.

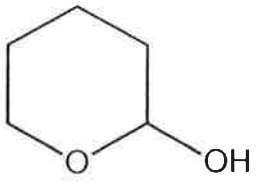
The hydroboration/oxidation step which used disiamylborane to hydrate the terminal olefin in an anti-Markownikoff sense exhibited the expected[53] selectivity to give 1-(4-butanol)-1-(tetrahydropyranyloxy)-6-(t-

butyldimethylsilyloxy)cyclodecane (59) in 93% yield. There was no evidence of butyl C3 carbons bearing hydroxyl functions in either the ^{13}C nmr spectrum or ^{1}H nmr spectrum, and the product was a single component by analytical TLC. A more complex mixture of products was obtained if the oxidation of the intermediate alkylborane was heated above 45°C - 50°C. The TBDMS-THP-butanolcyclodecane (59) was an unusually labile compound and could not be stored for long periods of time without decomposition to form an intractable mixture of products.



59.

The elemental analysis of the product (59) was consistent with the formula $C_{25}H_{50}O_4Si$. The resonances which characterise the olefinic moiety of the butenyl side chain are absent from the ^{1}H nmr and ^{13}C nmr spectra. The infrared spectrum of the TBDMS-THP-butanolcyclodecane (59) has a strong OH stretch at 3400 cm^{-1} and the olefinic absorptions of the butenyl precursor were absent. The F.A.B. mass spectrum did not show a molecular ion but fragment ions at *m/z* 425 and 341 correspond to the loss from the protonated molecular ion $(M+H)^+$ of either a molecule of water, or a fragment of 102 mass units which is consistent with a tetrahydropyranol fragment (63).

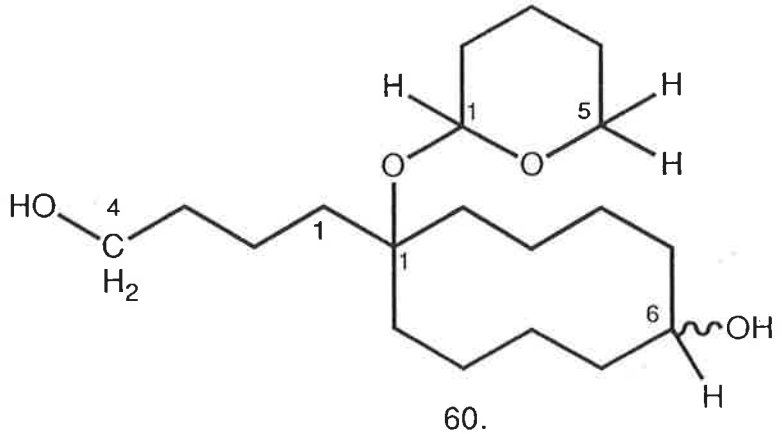


63.

The ^{13}C nmr spectrum shows a new single resonance at δ 61·93 that was consistent with the primary C4 bearing a hydroxyl group. If the C3 carbon of the butyl chain had been hydroxylated, the resonance would occur further downfield at δ 70 to 75 as a consequence of the additional deshielding brought about by greater alkyl substitution. An additional signal at δ 18·43 was initially mistaken for an isomeric quaternary carbon of the TBDMS group, however its persistence in the deprotected THP-butanolcyclodecanol (60) suggested it was the C2 of the butanol chain. The carbon γ to a hydroxyl group can experience an upfield shift of up to 5 ppm relative to the unsubstituted hydrocarbon. This shift is due to a shielding effect that arises from the gauche interactions of the hydroxyl group and the hydrogens of the γ carbon[78]. The ^{1}H nmr spectrum shows a two hydrogen multiplet at δ 3·59 for the hydrogens of the primary alcohol moiety.

The cleavage of the t-butyldimethylsilyloxy ether of the TBDMS-THP-butanolcyclodecane (59) with a solution of tetrabutylammonium fluoride in THF took five days to go to completion. This is a general procedure for the cleavage of alkyl silyl ethers[67,69] though the reactions are not reported to take so long. The reaction may have been sluggish because of the considerable steric bulk surrounding the silicon atom. The product, 1-(4-butanol)-1-(tetrahydropyranyloxy)cyclodecan-6-ol (60) was readily isolated by removal of the solvent *in vacuo* and passage of

the crude residue down a column of silica gel. The yields were in the range 80% - 85%. Analytical TLC clearly resolved the two diastereomers of the THP-butanolcyclodecanol (60)

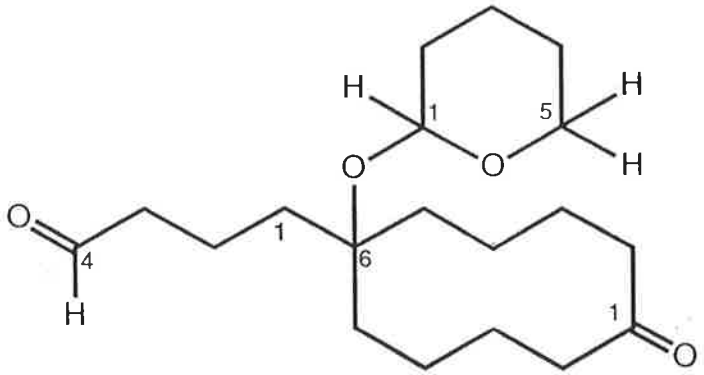


60.

The key feature of the ^{1}H nmr spectrum of the THP-butanolcyclodecanol (60) is the absence of the singlets at δ 0·88 and 0·03 which characterised the presence of the t-butyldimethylsilyloxy ether. In addition the C6 hydrogen has undergone a downfield shift of 0·04 ppm possibly as a result of the absence of the electropositive silicon. The resonances at δ 25·8, 18·1 and -4·7 due to the TBDMS group are absent from the ^{13}C nmr spectrum but the butyl C2 resonance remains at δ 18·39. The infrared spectrum shows a strong absorption at 3360 cm^{-1} for the OH stretch of the diol (60). The F.A.B. mass spectrum shows a protonated molecular ion at *m/z* 329.

The oxidation of the THP-butanolcyclodecanol (60) to prepare the key intermediate 6-(4-butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45) was carried out using either pyridinium chlorochromate[72,73] or activated dimethyl sulphoxide[79]. The yield of THP-butanalcyclodecanone (45) from the Swern oxidation was slightly higher, 72% vs. 65%, however the

manipulations required by that reaction were considerably more complex.



45.

The infrared spectrum shows a sharp, weak absorption at 2724 cm^{-1} and a strong absorption at 1725 cm^{-1} which represent the C-H and C=O stretch of the aldehyde moiety and the strong band at 1707 cm^{-1} is consistent with the C=O stretch of the cyclodecyl ketone. The mass spectrum of the THP-butanalcyclodecanone (45) has a weak molecular ion at *m/z* 324 and the high resolution mass spectrum is consistent with $C_{19}H_{32}O_4$. There are significant fragment ions at *m/z* 223, 205 and 187 which are consistent with the consecutive loss of (62) and then two molecules of water. The loss of H_2O fragments is characteristic of the presence of ketone and aldehyde groups.

The ^1H nmr spectrum shows a narrow triplet downfield at δ 9·69 with a coupling constant of 1·9 Hz, assigned to the C4 aldehyde hydrogen. The multiplet associated with the THP C1 acetal hydrogen persists at δ 4·56.

A notable feature of the ^{13}C nmr spectrum of the THP-butanalcyclodecanone (45) is the absence of chemical shift "pairs". These have been attributed to the presence of *cis*- and *trans*-isomers of the cyclodecanol intermediates and with the oxidation

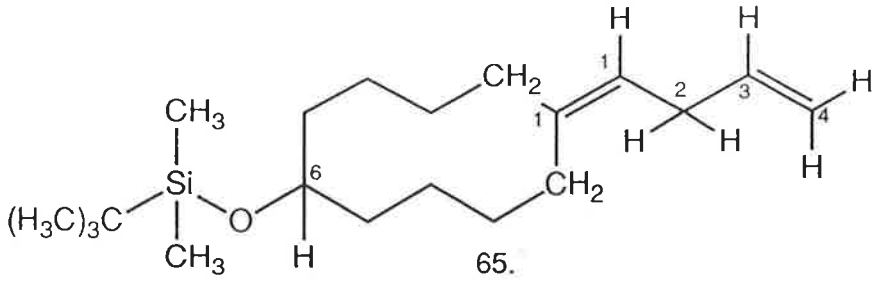
to form the carbonyl C1 carbon they cease to exist. The spectrum contains two carbonyl signals at δ 214·81 and 202·77. The higher field resonance corresponds to the C4 aldehyde, less deshielded because of only a single alkyl substituent. Aside from the resonances at δ 93·49, 80·96 and 63·61 associated with the presence of the THP group there remain twelve aliphatic signals and fourteen carbons to which they can be assigned. There are three carbons which should be deshielded by their proximity to carbonyl groups, but only two resonances occur in the appropriate region of the spectrum, at δ 44·01 and 42·51. One explanation is that the cyclodecyl C2 and C10 carbons are equivalent which indicates that the molecule retains some symmetry in positions distant from the chiral THP group. If this symmetry is extended to make C3 equivalent to C9 twelve environments exist to account for the signals in the aliphatic region of the spectrum.

The THP-butanalcyclodecanone (45) was particularly sensitive to aerial oxidation and was best prepared just prior to use in the titanium induced intramolecular carbonyl coupling reaction.

Part 3. The Preparation of 6-(4-Butanal)-5-*E*-cyclodecen-1-one (33) and 6-(4-Butylidene)cyclodecan-1-one (35), Unsaturated Type I Key Intermediates.

A second approach to the out-out-bicyclo[4.4.4]tetradecane (1) required the placement of a double bond at the pro-bridgehead carbon of the type I key intermediate.

Preliminary attempts were made to alkylate the TBDMS-cyclodecanone (55) with the ylid (64) from 3-butenylphosphonium bromide. When sodium methylsulphinylmethide in dimethylsulphoxide[80] was used as the base to deprotonate 3-butenylphosphonium bromide a new compound, tentatively assigned as 1-(3-butylidene)-6-(t-butyldimethylsilyloxy) cyclodecane (65), was isolated in 3% yield. The ^1H nmr spectrum is consistent with the presence of a 3-butenylidene chain attatched to the cyclodecyl ring. The vinylic region shows a similar coupling pattern to that observed for the terminal olefinic moiety in the TBDMS-butenylcyclodecanol (44) spectrum with multiplets at δ 5·83, 5·03 and 4·96. In addition there is a second vinylic triplet at δ 5·13 which corresponds to the hydrogen of the butyl C1 carbon. The doubly allylic methylenic hydrogens of C2 of the butyl chain are significantly deshielded by the proximity of two vinylic groups and occur as a two hydrogen triplet at δ 2·83. Further upfield there is a four hydrogen triplet at δ 2·16 consistent with the allylic hydrogens of the cyclodecyl C2 and C10 carbons. The presence of the t-butyldimethylsilyloxy ether is characterised by the multiplet at δ 3·76 and the singlets at 0·88 and 0·04.



65.

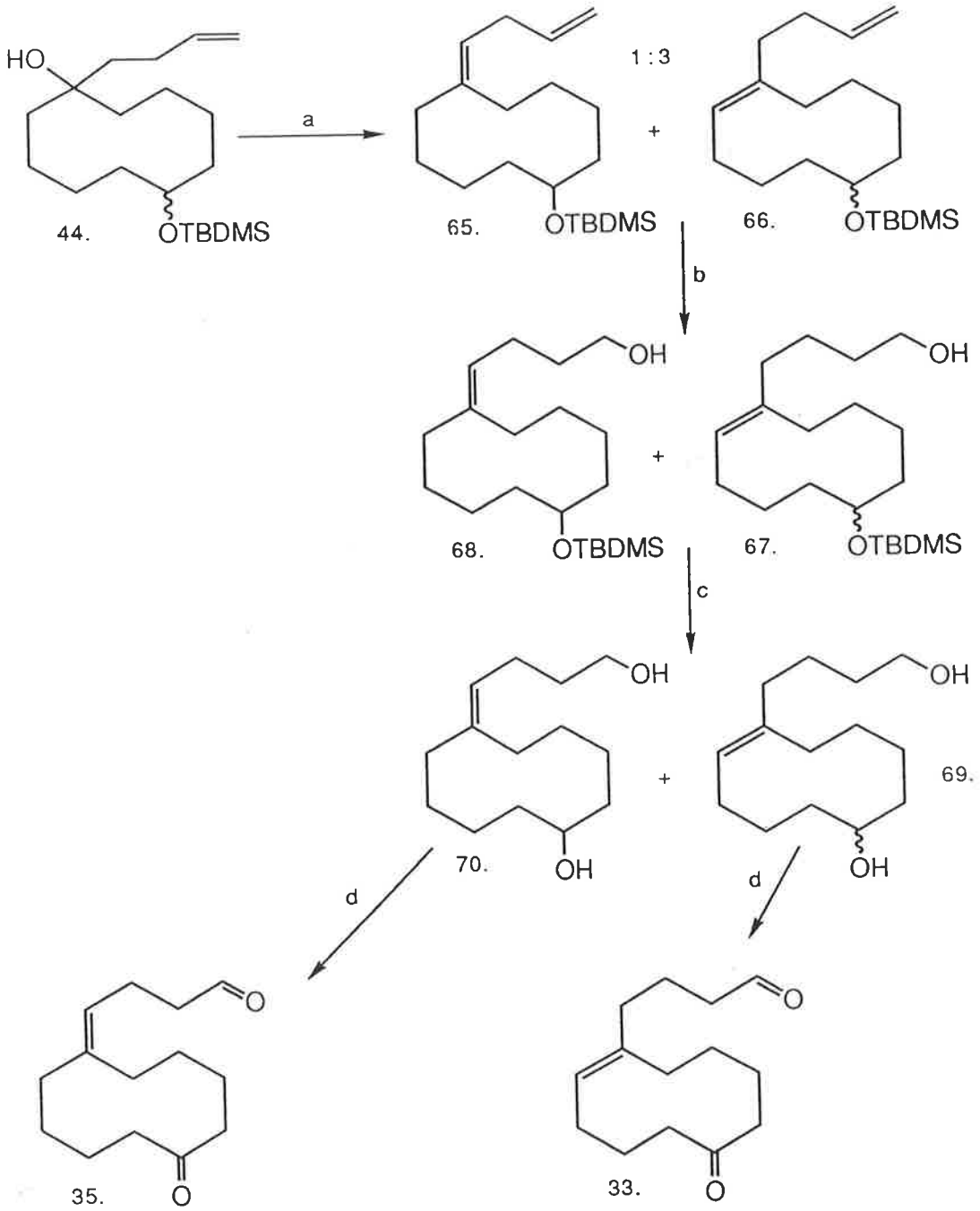
$Ph_3P{=}CH\text{-}CH_2CH{=}CH_2$

64.

The predominance of TBDMS-cyclodecanone (55) in the reaction product suggested that the protons α to the carbonyl group were being removed to form the enolate of (55) in a process analogous to that which was observed for the reaction between 3-butenylmagnesium bromide (57) and TBDMS-cyclodecanone (55). The 3-butenylphosphonium bromide was deprotonated by n-butyllithium in THF to enable a low temperature reaction between the ylid (64) and the TBDMS ketone (55) and thereby discourage any enolisation process. This reaction, carried out from -70° to room temperature, returned only starting material and this suggested that the ylid (64) was not reactive enough to alkylate the ketone at the low temperature.

An alternative route which provides unsaturated key intermediates 6-(4-butanal)-5-*E*-cyclodecen-1-one (33) and 6-(4-oxobutylidene)cyclodecan-1-one (35) was developed and is described in scheme 27. The preparation of the precursor to the sequence described in scheme 27, TBDMS-butenylcyclodecanol (44), has been described above.

Scheme 27.



a. $SOCl_2$ / Pyridine, Toluene; b. i.Disiamylborane, THF, ii. NaOH / H_2O_2;
c. AcOH, H_2O, THF; d. PCC or DMSO / $(COCl)_2$.

The C1 tertiary hydroxyl group of the TBDMS-butenylcyclodecanol (44) was dehydrated by reaction with thionyl chloride in the presence of pyridine to give an isomeric mixture of trisubstituted double bonds. This is a general procedure for the dehydration of tertiary alcohols[81]. The reaction gave 94% yield when neat pyridine was used as solvent and 90% yield when the reaction was carried out in toluene with an excess of pyridine present.

This dehydration could theoretically give three isomers; the double bond could be exo to the cyclodecyl ring as in 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65) or the double bond could be endo to the cyclodecyl ring in which case it would be either cisoid or transoid within the cyclodecyl framework. The dehydration of a tertiary alcohol would go via an E1 mechanism so the stereochemistry of the double bond would arise from thermodynamic control. Cope *et al*[82] have observed that the acid catalysed isomerisation of methylenecyclodecane favours a cisoid cyclodecyl double bond, the equilibrium mixture contained 99% 1-methyl-1-*Z*-cyclodecene. In addition the measured heats of hydrogenation[4] for *Z*- and *E*- isomers of cyclodecene show that the *Z*- isomer has the lower strain energy.

The stereochemistry of the double bond will determine the bicyclic diene isomers that are available from the cyclisation of the key intermediate. Each double bond configuration is able to yield only two of the five bicyclic diene isomers (see introduction) so prior knowledge of the stereochemistry of the key intermediate would aid in identifying the products from the cyclisation.

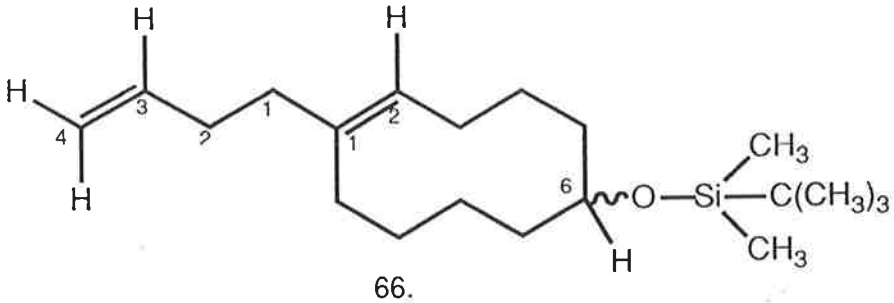
Neither capillary gas chromatography nor analytical TLC were able to resolve the double bond isomers contained in the

product of the dehydration reaction. The ^{13}C nmr spectrum contains 31 resonances which is consistent with the presence of only two double bond isomers. The ^{1}H nmr spectrum shows a triplet at δ 2·83 which has been previously assigned to the 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy) cyclodecane (65). The integration of the ^{1}H nmr spectrum suggested that the ratio of endocyclic to exocyclic isomers was 3:1. At this stage of the sequence the stereochemistry of the endocyclic trisubstituted double bond could not be determined from either the ^{1}H nmr or ^{13}C nmr spectra, and instead we based the assignment of 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) on the above thermodynamic observations.

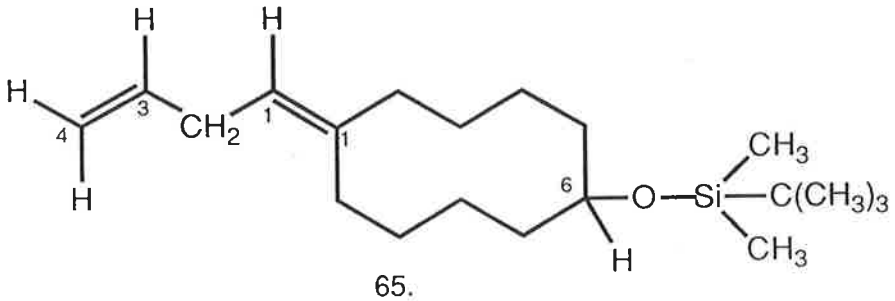
The infrared spectrum of the diene mixture shows that the OH stretch at 3375 cm^{-1} of the tertiary alcohol is absent and in addition to the absorptions associated with the terminal olefin at 3060 and 1640 cm^{-1} there was a new weak absorption at 1645 cm^{-1} attributed to the C=C stretch of the trisubstituted double bond. The elemental analysis of the mixture was consistent with $C_{20}H_{38}OSi$. The mass spectrum has fragment ions at *m/z* 321 for $(M-H)^{+}$ and 265 for $(M$ - t-butyl$)^{+}$.

The ^{1}H nmr spectrum shows a new set of overlapping triplets in the vinylic region at δ 5·19 and 5·17 which correspond respectively to the butenylidene C1 hydrogen and the *E*-cyclodecenyl C2 hydrogen. The triplet at δ 2·83, which integrates for 0·25 hydrogens has been assigned to the doubly-allylic butenylidene C2 hydrogens and as well there is a large multiplet from δ 2·0 to 2·3 corresponding to the various allylic resonances arising from the hydrogens of five allylic positions in the two isomers. Other aspects of the spectrum confirm the presence of the

TBDMS ether and the terminal olefinic moiety but do not distinguish between the two isomers.



66.



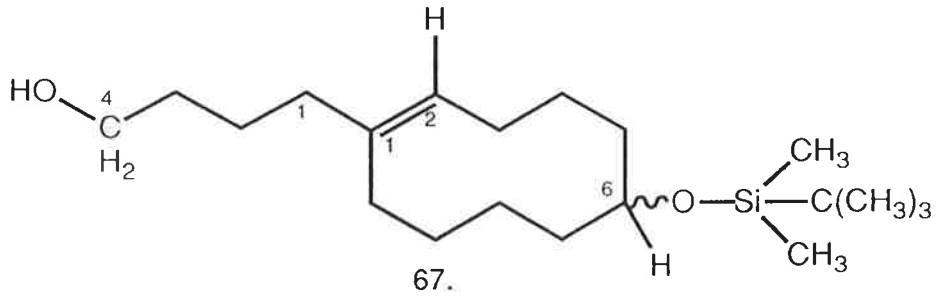
65.

All three of the double bond isomers are asymmetric and should each show 14 distinct resonances for the butylcyclodecyl skeleton. The ^{13}C nmr spectrum provided the evidence that the dehydration mixture contained only two isomers of the trisubstituted double bond configuration. The olefinic region contains six signals. The resonances at δ 138·91 and 114·24 are consistent with C3 and C4 of the terminal olefinic and do not differentiate between the two isomers except for some broadening of the upfield signal. Of the four remaining olefinic signals those at δ 137·62 and 137·29 are particularly weak, consistent with assignment to the isomeric quaternary cyclodecyl carbons. The relative intensity of the signals suggest that the downfield resonance is due to the more abundant *E*- cyclodecene C1. The signals at δ 125·71 and 122·71 are attributed to the tertiary vinyl carbons and again on the basis of intensity the downfield resonance

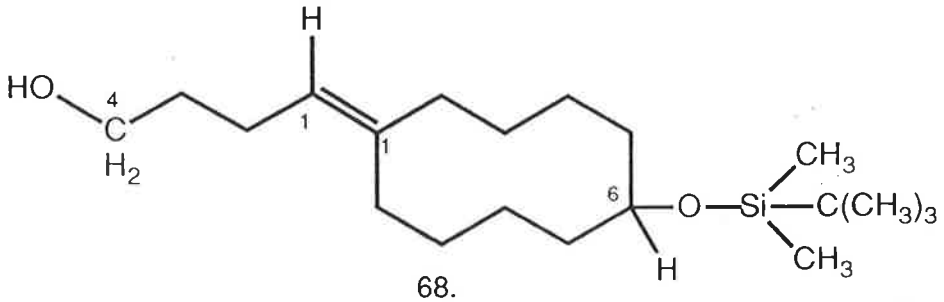
corresponds to the *E*- cyclodecene C2. The two resonances at δ 71·90 and 71·56 are due to the cyclodecyl C6 bearing the TBDMS ether. Of the characteristic TBDMS group resonances only the silyl methyl signals distinguish between the two isomers. There remain 18 resonances in the aliphatic region, corresponding to 18 unassigned carbons of the TBDMS-butenyl-*E*-cyclodecene (66) and TBDMS-butenylidenecyclodecane (65).

The hydroboration[53] of the mixture of TBDMS-dienes (65,66) was carried out to give almost quantitative yields of the mixture containing 1-(4-butanol)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (67) and 1-(4-hydroxybutylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (68). In order to eliminate the possibility of over reduction the reaction was routinely carried out by adding disiamylborane to a cold solution of the dienes (65,66), thereby favouring terminal selectivity by keeping a low relative concentration of borane. The trial reaction for this procedure was performed by adding the dienes (65,66) to a cold solution of excess disiamylborane and even under these circumstances there was no evidence of undesired hydration products.

The infrared spectrum of the product shows a strong OH stretch at 3300 cm^{-1}, and the absorptions of the terminal olefin at 3060 cm^{-1} and 1640 cm^{-1} have disappeared. A weak absorption still remains at 1645 cm^{-1} for the C=C stretch of the trisubstituted olefin. The mass spectrum of the mixture shows a weak molecular ion at *m/z* 340 which has the appropriate high resolution mass spectrum for $C_{20}H_{40}O_2Si$.



67.



68.

The ^{1}H nmr spectrum shows clearly the absence of the terminal olefinic resonances, replaced by a two hydrogen triplet at δ 3·62 consistent with the butyl C4 hydrogens of the new hydroxyl group. The only evidence for the product being a mixture was the presence at δ 0·87 and 0·03 of smaller isomeric singlets of the minor isomer (68) for the t-butyl and silyl methyl resonances of the TBDMS ether, adjacent to δ 0·88 and 0·04 for the major isomer (67).

The ^{13}C nmr spectrum shows the appearance of two new carbons bearing hydroxyl groups at δ 62·83 and 62·68. Resonances this far upfield are characteristic of primary hydroxylated carbons. A second alkyl substituent would further deshield the carbon and the resonance would occur further downfield. There are only two resonances in this region at δ 71·86, 71·53 and these have been assigned previously to the cyclodecyl C6 carbons bearing the TBDMS ether. The absence of any further peaks in this region suggests that the hydroboration has hydroxylated the butyl C4 carbon with good selectivity.

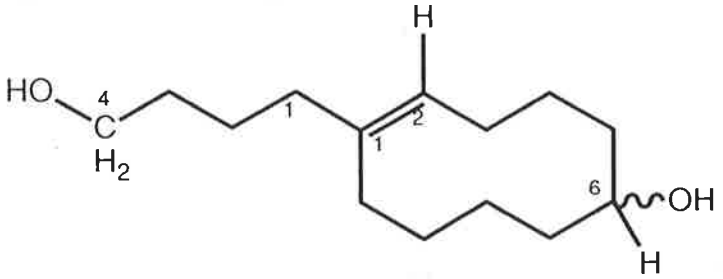
The remainder of the ^{13}C nmr spectrum again characterises the mixture as containing two isomeric components in unequal proportions. There is a total of thirty one resonances. This indicates that in addition to the resonances of the t-butyl group, which do not distinguish between isomers, only two carbons share a co-incident resonance in the spectrum.

The reaction of the mixture of alcohols (67,68) with tetrabutylammonium fluoride in THF in an attempt to cleave the t-butyldimethylsilyloxy protecting group went to only 80% completion after 5 days. A similar slow rate had been observed for the THP analogue (59). As the TBDMS-butanolcyclodecene (67) and its isomer (68) did not contain any acid sensitive functional groups it was feasible to attempt an acid hydrolysis of the silyl ether moiety. When the mixture of alcohols (67,68) was stirred with acetic acid the silyl ether cleavage went to completion in 1·5 days. The isomeric diols were isolated in 86% yield after chromatography. Both procedures[51,52] are well known methods of removing t-butyldimethylsilyloxy ether protection.

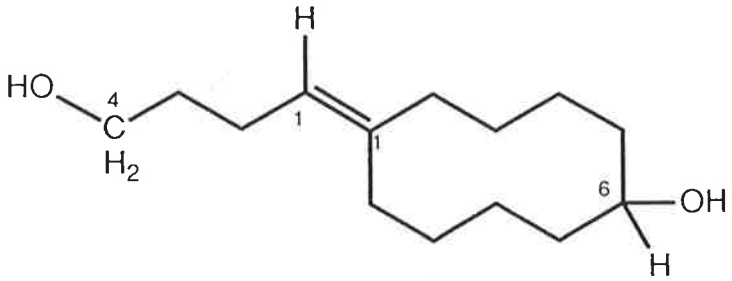
At this stage it was possible to separate 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) by repetitive flash chromatography. The major component of the mixture (69) eluted first.

The absence of the diagnostic singlets at δ 0·8 and 0·04 from the ^{1}H nmr spectrum and the resonances at δ 25·87, 18·12 and -4·6/-4·7 from the ^{13}C nmr spectrum is clear evidence that the TBDMS group has been removed from the C6 hydroxyl function. The infrared spectrum of each of the diol isomers (69) and (70) has a strong absorption at 3345 cm^{-1} corresponding to the OH stretch. The mass spectrum of the butanolcyclodecenol (69) has a molecular

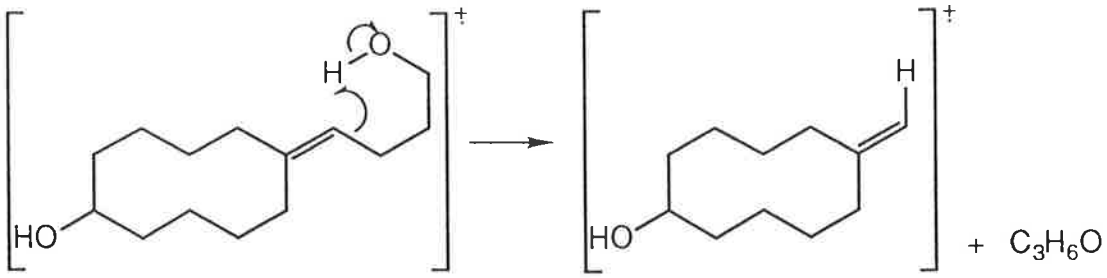
ion of *m/z* 226 with the appropriate high resolution value for $C_{14}H_{26}O_2$. The minor isomer (70) does not show a molecular ion, the highest fragment ion of *m/z* 168 arises from the loss of C_3H_6O perhaps by way of the cleavage shown in scheme 28.



69.



70.



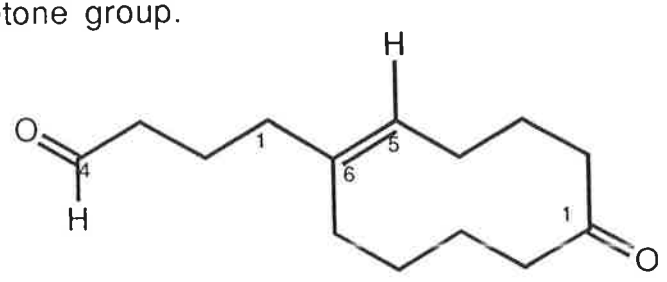
Scheme 28

It was of considerable importance that the stereochemistry of the double bonds of the major and minor isomers had been assigned at an earlier stage of the synthetic sequence as it is difficult to distinguish between the exo and endocyclic double bond isomers on the basis of their nmr spectra, which are strikingly similar. The chemical shifts for the vinylic hydrogen, the hydrogens of the butyl C4 alcohol and the hydrogen of the C6 alcohol moiety each differed by less than 0·1 ppm. The principal differences

between the two spectra occur in the region δ 2·0 to 2·5 where the resonances of the allylic hydrogens of the butanolcyclodecenol (69) are partially resolved into multiplets. Both diols (69) and (70) give ^{13}C nmr spectra that are consistent with the presence of a trisubstituted double bond and two carbons bearing hydroxyl groups.

The oxidation of the butanolcyclodecenol (69) to give the key intermediate 6-(4-butanal)-5-*E*-cyclodecan-1-one (33) was accomplished by the use of either pyridinium chlorochromate[72,73] with powdered 4Å molecular sieves or by way of a Swern oxidation[79]. The latter procedure gave a better slightly better yield, 82% compared to 75%.

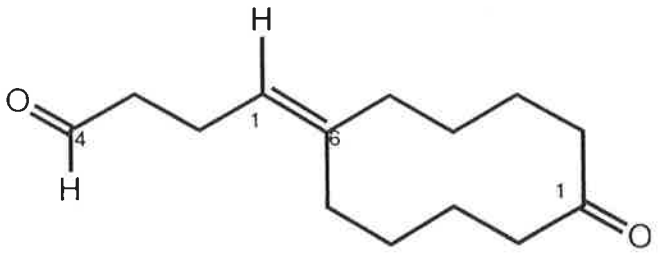
The dicarbonyl nature of the butanalcyclodecenone (33) is established by its infrared spectrum which shows new absorptions at 2716 , 1724 and 1704 cm^{-1}. The first two absorptions are consistent with the C(O)-H and C(H)=O stretches of the aldehyde group and the latter absorption corresponds to the C=O stretch of the ketone moiety. The butanalcyclodecenone (33) is rather unstable and was not submitted for elemental analysis. The high resolution mass spectrum is consistent with $C_{14}H_{22}O_2$ and the mass spectrum also shows fragment ions at 204 and 186 which correspond to the sequential loss of two H_2O fragments. The loss of H_2O is a typical fragmentation process of compounds containing an aldehyde or ketone group.



33.

The ^{1}H nmr spectrum shows a narrow triplet at δ 9·72 for the butyl C4 hydrogen deshielded by the proximity to the π system of the carbonyl group. Such downfield shifts are characteristic of aldehyde hydrogens. In the ^{13}C nmr spectrum two new resonances occur in the carbonyl region at δ 213·46 and 201·61 and these are consistent with the presence of ketone and aldehyde functions. In addition the resonances associated with the hydroxylated C6 and butyl C4 carbons are absent. The remainder of the spectrum establishes the persistence of trisubstituted double bond and the characteristic lack of symmetry of the butylcyclodecene skeleton.

The oxidation of the hydroxybutylidenecyclodecanol (70) to give the key intermediate 6-(4-oxobutylidene)cyclodecan-1-one (35) was carried out using the Swern oxidation[79] conditions but the yield of 53% was considerably poorer than for the oxidation of the isomeric diol (69). The purification of the dicarbonyl (35) was complicated by a mixture of components in the product.



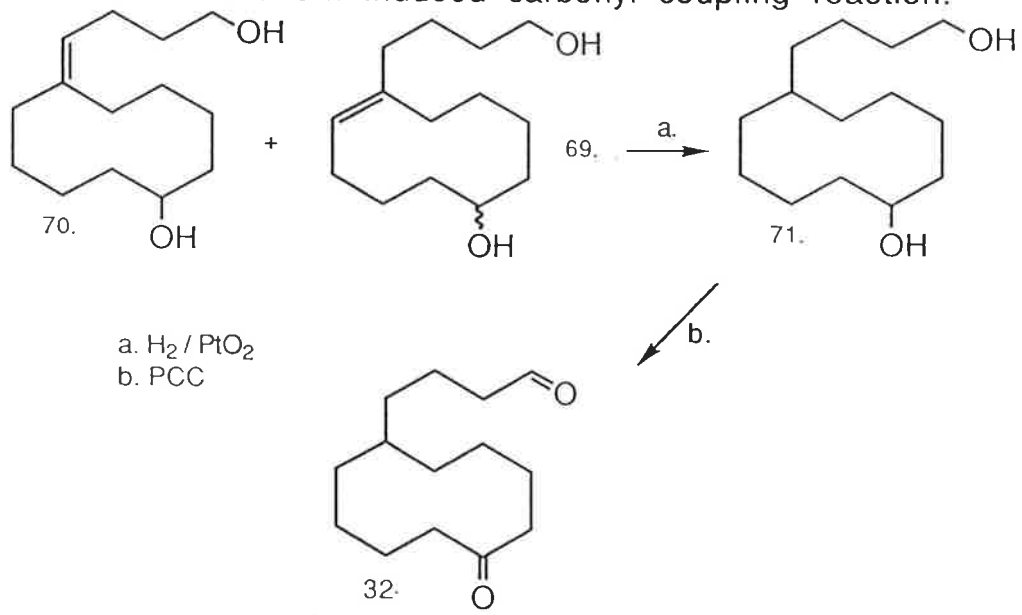
35.

The key features of the spectral data for the butylidene isomer (35) are very similar to those of the isomeric butanalcyclodecenone (33). This confirms the dicarbonyl, unsaturated nature of the molecule. The butylidene isomer (35) differs in the region of the ^{1}H nmr spectrum at δ 2·0 to 2·5 associated with hydrogens α to vinylic and carbonyl groups, which

shows considerable but differing complexity for each of the isomers.

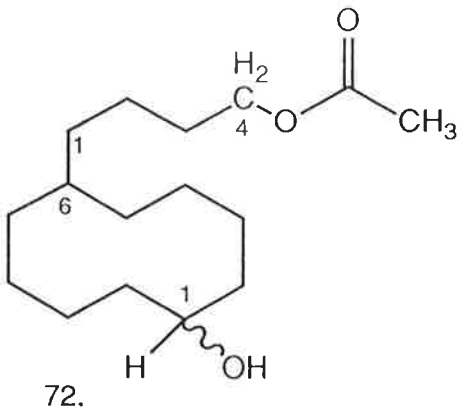
Part 4. Preparation of 6-(4-Butanal)cyclodecan-1-one (32), the Key Intermediate for the Preparation of in-Bicyclo[4.4.4]tetradecene (5): a Model Study.

The synthetic sequence described above also provided access to 6-(4-butanal)cyclodecan-1-one (32) by way of the route shown in scheme 29. This compound was used as a model system to test the zero valent titanium induced carbonyl coupling reaction.



Scheme 29.

The hydrogenation of the mixture containing 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) in ethyl acetate over platinum oxide catalyst provided 6-(4-butanol)cyclodecan-1-ol (71) in 72% yield with spectral properties identical to those reported in the literature[19]. In addition 1-(4-butylacetate)cyclodecan-1-ol (72) was isolated in 16% yield.



72.

This compound is the result of a transesterification reaction between the primary hydroxyl group of the diol (71) and the solvent, ethyl acetate. The infrared spectrum of the acetate (72) shows an ester carbonyl stretch at 1738 cm^{-1} as well as an OH stretch at 3410cm^{-1}. The ^1H nmr spectrum is similar to the diol (71) except that the triplet associated with the butyl C4 hydrogens is shifted downfield to δ 4·07 due to the electron withdrawing effects of the acetate group. As well there is a three hydrogen singlet at δ 2·05 for the methyl hydrogens of the acetate group. The hydroxy acetate (72) could be reverted to the diol (71) in 90% yield by reduction with lithium aluminium hydride.

The diol (71) was oxidised with pyridinium chlorochromate to give 6-(4-butanal)cyclodecan-1-one (32) in 71% yield. The preparation of the butanalcyclodecanone (32) is a literature procedure[19] and the spectral characteristics of the product corresponded to those reported in the literature.

Chapter 3

Intramolecular Reactions of Type I Key Intermediates.

The key reaction of the two synthetic routes directed towards the preparation of derivatives of out,out-bicyclo[4.4.4]tetradecane was the titanium induced dicarbonyl coupling reaction.

At the outset of this project there was no experience within the research group related to this particular reaction. The literature[83] contained many examples of the successful application of the coupling reaction to molecules of unusual structure, but the procedures that were described were as many in number as there were groups reporting them.

We chose to follow the guidelines set down by McMurry and co-workers[28] because of their obvious experience with this particular reaction. A zinc-copper couple was used to reduce titanium trichloride to the active zero valent titanium with dimethoxyethane as the solvent.

Part 1. The Attempted Cyclisation of 6-(4-Butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45) and Model Studies.

The first intramolecular dicarbonyl coupling reaction was attempted with the THP-butanalcyclodecanone (45) as the substrate. The crude product from early attempts at this reaction

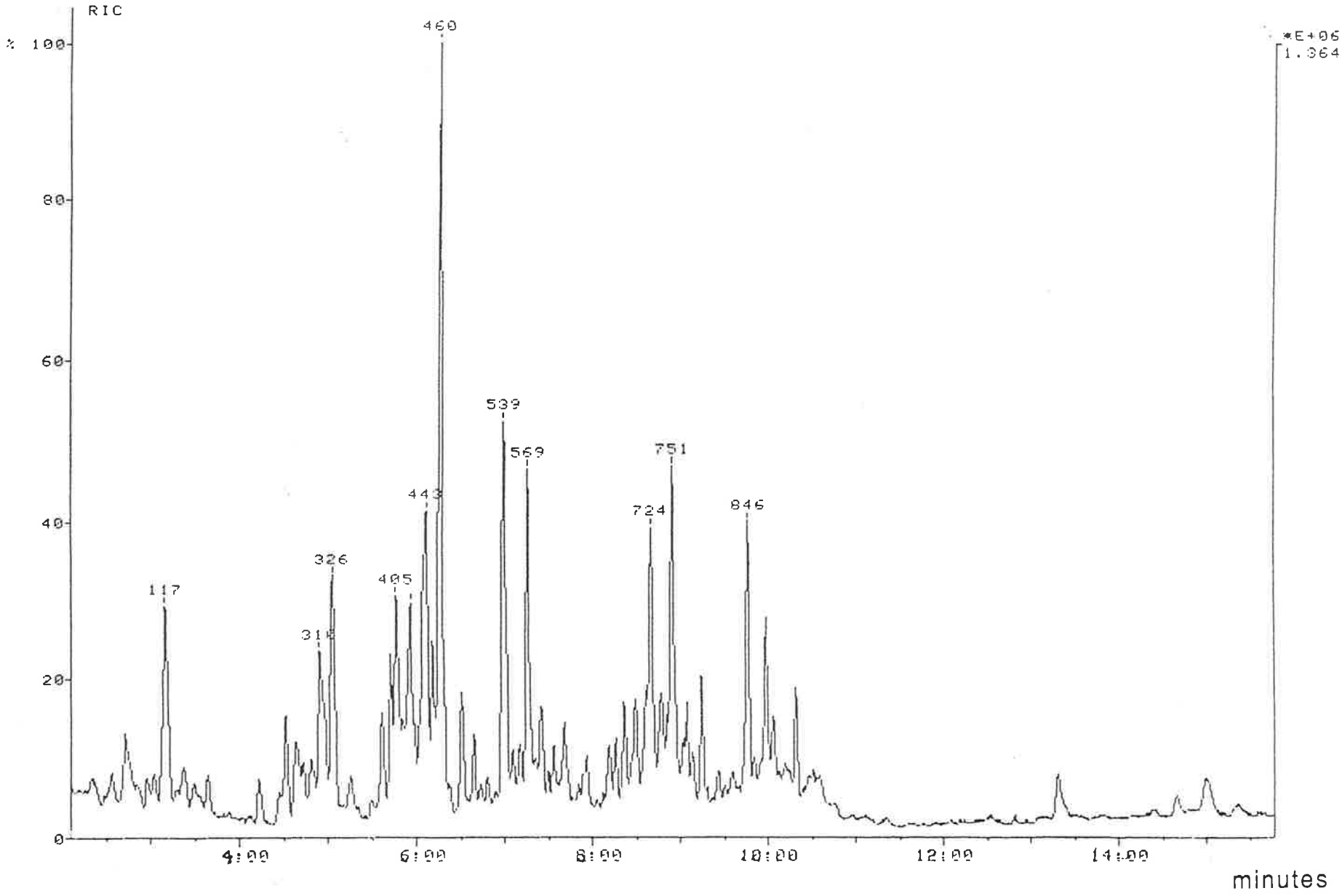


Figure 2. G.C. of Crude Product from Coupling of 6-(4-Butanal)-6-(THP)cyclodecan-1-one (45)

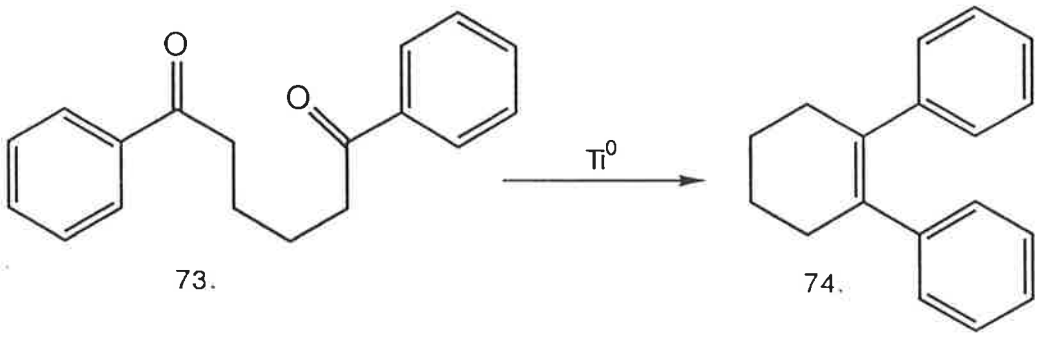
was analysed by TLC and G.C. and then ^1H nmr. Figure 2 is an example of a gas chromatograph from one of the attempted cyclisations of THP-butanalcyclodecanone (45). The ^1H nmr spectrum showed a broad resonance associated with vinylic hydrogens in the olefinic region of 5 to 6 ppm. The lack of resonances in the region 4 to 5 ppm was evidence that the THP group had not remained intact. The G.C. and TLC analyses showed an intractable mixture of products and it became obvious that a gas chromatograph/mass spectrometry analysis of the mixture was going to be vital in order to enable the desired product of the reaction to be identified.

The crude concentrate was analysed by gas chromatographic/mass spectrometric techniques for ions that corresponded to the 6-(tetrahydropyranyloxy)bicyclo[4.4.4]tetradec-1-ene (54) or products that may have arisen from the elimination of the THP group such as the bicyclo[4.4.4]tetradecadienes (7,8,9,10,11). The reaction was worked up under anhydrous conditions and so it was unlikely that the acetal link of the THP ether would have hydrolysed. It has been observed by other workers[31,84] that products may arise from the reduction of aldehydes and ketones to the corresponding methyl and methylenic groups. There were no components observed in the mixture with molecular ions that were consistent with this kind of process taking place.

During the course of some of the zero valent titanium coupling reactions a build up of solids would gather on the walls of the flask, sometimes to such an extent that it would inhibit the action of the magnetic stirrer. This observation, and the lack of success with the intramolecular coupling of the THP-

butanalcyclodecanone (45) suggested that we should test the activity of the zero valent titanium suspension by carrying out a carbonyl coupling reaction on a compound that had already been studied in the literature. Titanium trichloride was clearly a highly reactive compound which required special handling techniques. The products that arise from excessive exposure of the titanium trichloride to oxygen and moisture were reported to have a deleterious effect on the coupling reaction[31,85].

The first model system that was studied was the coupling of 1,4-dibenzoylbutane (73). The coupling reaction to prepare 1,6-diphenylcyclohex-1-ene (74) was carried out according to the procedure of McMurry *et al.*[28]. The product was isolated in 85% yield compared to the literature yield of 95%. The yield dropped to 55% to 65% if a build up of solids occurred during the reaction. There was no obvious reason why the solids occurred only occasionally, but clearly they were indicative of a failure to correctly prepare the zero valent titanium.

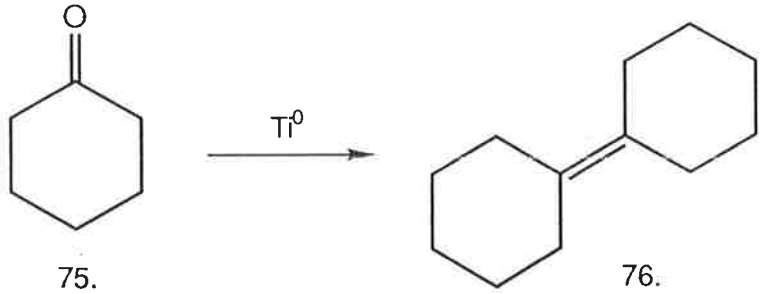


73. 74.

Scheme 30.

A more detailed examination of the literature[83] revealed that benzylic or allylic carbonyl groups are coupled more readily than simple aliphatic carbonyls by the zero valent titanium reagent. This discovery prompted the investigation of a second

model system, the coupling of cyclohexanone (75) to give cyclohexylidenecyclohexane (76) (scheme 31).



75. 76.

Scheme 31.

The cost of dimethoxyethane induced us to study the model systems in THF. The coupling of cyclohexanone (75) was carried out with zero valent titanium formed by the reduction of titanium trichloride with either zinc-copper couple or potassium metal. The reduction of titanium trichloride with potassium metal gave a zero valent titanium suspension that was more black and colloidal than the zero valent titanium suspension that arose by reduction with zinc-copper couple. Even so the yields of 65% to 69% of cyclohexylidenecyclohexane (76) from the latter were consistently better than the yields of 29% or less that were attained from the potassium reduction. The yield from the zinc-copper/titanium trichloride reaction when dimethoxyethane replaced THF as the solvent improved to 80%, compared to 85% reported in the literature[28].

The results from the coupling reactions of the model systems suggested that the zero valent titanium was being prepared in active form, albeit not quite as active as those reported in the literature.

The final model system that we chose to study was 6-(4-butanal)cyclodecan-1-one (32) (scheme 14). McMurry and Hodge[9] had isolated in-bicyclo[4.4.4]tetradec-1-ene (5) in 29% yield from

the intramolecular titanium induced carbonyl coupling of butanalcyclodecanone (32). The degree of success that we achieved with this system would act as a standard against which could be compared the cyclisation of THP-butanalcyclodecanone (45), butanalcyclodecenone (33) and oxobutylidenecyclodecanone (35).

The initial coupling reactions gave the in-alkene (5) in 2% to 3% yields after purification by preparative gas chromatography. The ^{1}H nmr and ^{13}C nmr spectra and mass spectral data were identical to those reported by McMurry and Hodge[9]. The yield increased to 5% when argon was substituted for nitrogen as the carrier gas used in preparative gas chromatography. This avoided the loss of product due to the formation of aerosols, as the column effluent could be condensed in its entirety using traps cooled with liquid nitrogen.

At this stage of the project we communicated with Professor J.E. McMurry with regard to the relatively low yield from the cyclisation of the butanalcyclodecanone (32) and he kindly provided us with the text, prior to publication, of an article[86] that described the preparation and use of titanium trichloride·(dimethoxyethane)$_{1.5}$ complex ($TiCl_3$·$(DME)_{1.5}$) as a means of ensuring pure and active titanium trichloride.

When $TiCl_3$·$(DME)_{1.5}$ was used to generate the zero valent titanium the butanalcyclodecanone (32) underwent intramolecular coupling to give the in-alkene (5) in 18% yield.

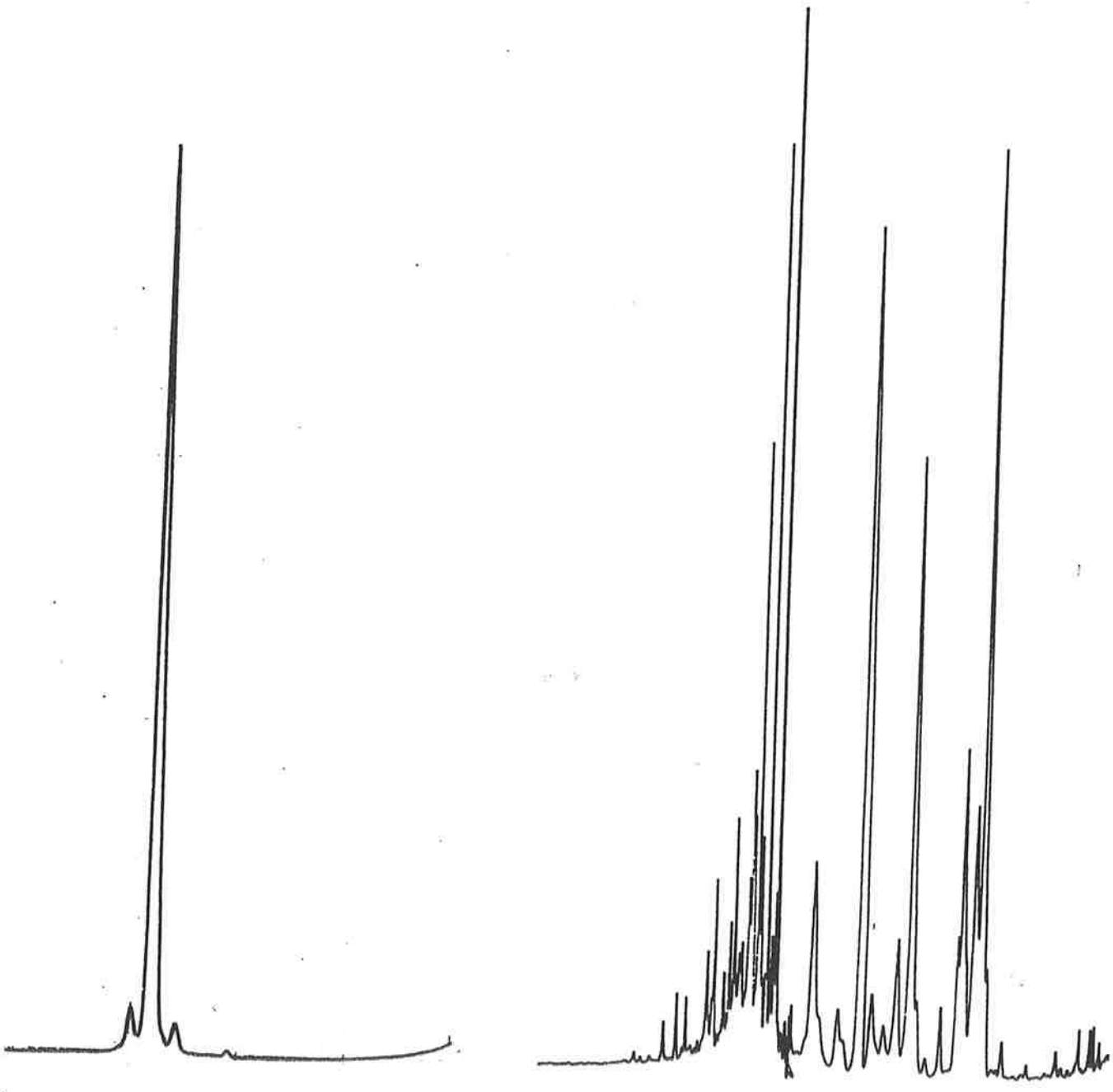
With the use of this complex there has been no observation of solids collecting on the flask walls during the course of zero valent titanium reactions. The improvement in the yield of in-alkene (5) suggested that the titanium trichloride had been partly inactivated by early inadequacies in handling techniques.

Furthermore by the time $TiCl_3 \cdot (DME)_{1.5}$ began to be used other improvements to the reaction procedure had been made: the dimethoxyethane was being twice distilled from potassium, an oxygen trap had been fitted to the argon gas line and specialised glassware had been acquired to enable air sensitive solids to be handled simply under an inert atmosphere.

The cyclisation of THP-butanalcyclodecanone (45) was attempted once more, this time using the $TiCl_3 \cdot (DME)_{1.5}$ complex. The crude product from this reaction proved just as complex and we concluded that the cyclisation process was prevented by intermediates containing too much steric strain. Possibly the carbonyl groups couple in an intermolecular fashion to form oligomeric material even though high dilution techniques had been employed. The attempt to prepare the 6-(tetrahydropyranyloxy)bicyclo[4.4.4]tetradec-1-ene (54) by the intramolecular cyclisation of 6-(tetrahydropyranyloxy)-6-(4-butanal)cyclodecan-1-one (45) was abandoned.

Part 2. The Attempted Cyclisation of 6-(4-Butanal)-5-*E*-cyclodecen-1-one (33).

The intramolecular coupling of the butanalcyclodecenone (33) was carried out with a range of titanium equivalents, see table 2. The concentration of the titanium and equivalents of zinc-copper used to reduce the $TiCl_3 \cdot (DME)_{1.5}$ complex were kept constant. A single component of the mixture of volatile products had a mass spectrum with a molecular ion of *m/z* 190.
The high resolution mass spectrum of this component was consistent with $C_{14}H_{22}$, a molecular formula which corresponds to



purified product *m/z* 190

crude mixture

Figure 3. G.C. of Bicyclic Diene from Coupling of 6-(4-Butanal)-5-*Z*-cyclodecan-1-one (33)

a bicyclic diene. The component was isolated by preparative G.C. in yields of 1% to 3·5%, reaching a maximum when 20 equivalents of titanium per carbonyl group were used in the coupling reaction. The ratio of components that made up the volatile fraction of the crude product was variable even when the reaction conditions were kept constant.

Table 2

Titanium equivalents per carbonyl	Isolated yield (G.C. yield)	Component as % proportion of total eluted in less than 30 min.			
		m/z 178	*m/z* 192	*m/z* 190	*m/z* 206
19 eq.	1% (3%)	27%	30%	23%	20%
20	3·5 (5·5)	17	26	24	33
23	1·5 (3)	22	9	54	15
23	2	17	13	26	27
24	1·3 (2)	30	17	18	35
24	1·6 (2·5)	28	24	33	10
59	(2)	11	59	16	7

The details of the bicyclic diene's structure were investigated using the data contained in the ^{1}H nmr (figure 4) and ^{13}C nmr (figure 5) spectra.

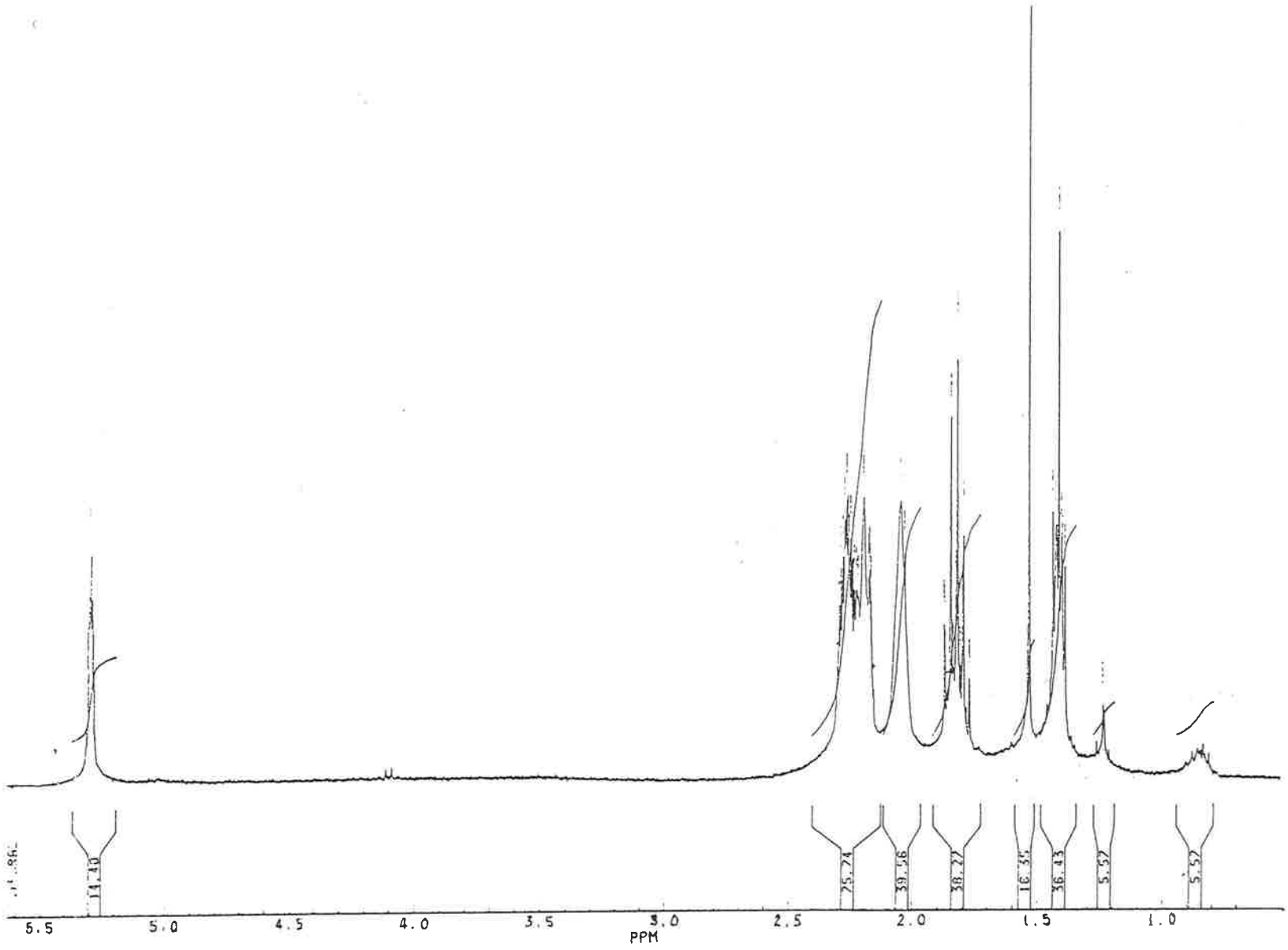


Figure 4. ^{1}H nmr of Bicyclic Diene from Coupling of 6-(4-Butanal)-5-*Z*-cyclodecan-1-one (33)

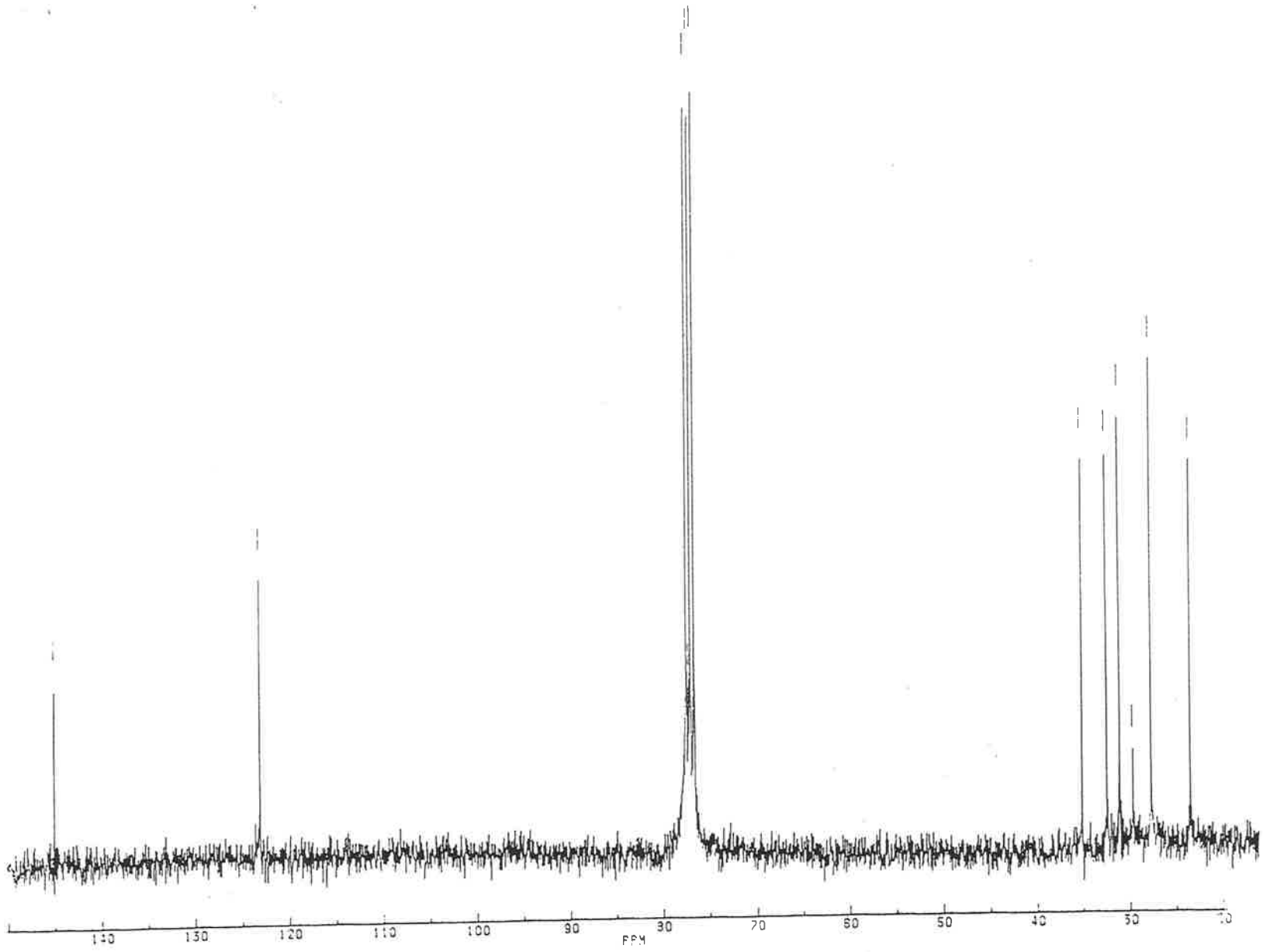
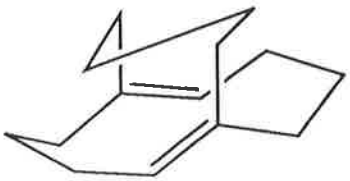
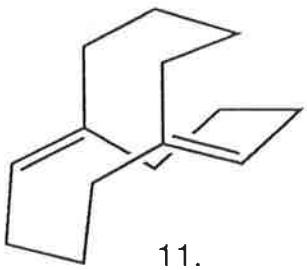


Figure 5. ^{13}C nmr of Bicyclic Diene from Coupling of 6-(4-Butanal)-5-*Z*-cyclodecan-1-one (33)

The precursor for the cyclisation reaction was a single isomer of 6-(4-butanal)-5-cyclodecen-1-one (33), the configuration of the double bond of which had been assigned as cisoid within the cyclodecyl framework on the basis of thermodynamic arguments. Only two bicyclic dienes should arise from the intramolecular coupling of a single alkenyl precursor, and these would be the 1,6-*E,E*-bicyclo[4.4.4]tetradecadiene (9) and 1,6-*E,Z*-bicyclo[4.4.4]tetradecadiene (11). The *E,E*- isomer (9) should possess a C_2 axis of symmetry and so be readily distinguishable from the asymmetric *E,Z*- isomer (11) by ^{13}C nmr spectroscopy. If the stereochemistry of the cycloalkenyl precursor is in fact *trans* then the two possible outcomes of the cyclisation are 1,6-*Z,Z*-bicyclo[4.4.4]tetradecadiene (10) and 1,6-*E,Z*-bicyclo[4.4.4]tetradecadiene (11). The *Z,Z*- isomer (10) would also have a C_2 axis of symmetry.



9.



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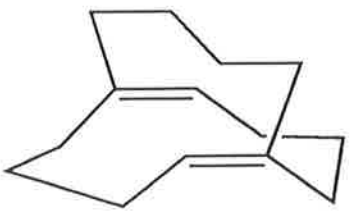
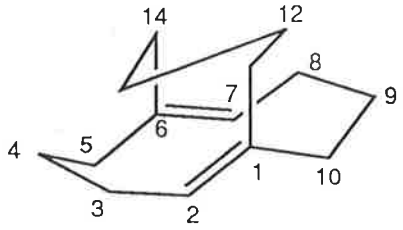


10.

The diene that was isolated by preparative G.C. has seven resonances in the ^{13}C nmr spectrum, two in the olefinic region and five in the aliphatic region, and so the initial structural

assignment of the *E,E-* isomer (9) was made. An experiment which attempted to confirm the *E,E-* (9) over the *Z,Z-* (10) identity is described below.

All of the multiplets in the ^1H nmr spectrum were well resolved except for those at δ 2·26 and 2·19 which partially overlapped and so it was possible to establish the connectivity between the hydrogen resonances with the aid of a "homonuclear shift correlation through J coupling" (^1H COSY) spectrum.



9.

The ^1H COSY spectrum, figure 6, was rationalised in the following manner. The olefinic hydrogens of C2/C7 at δ 5·29 are coupled only to the allylic hydrogens at δ 2·26 which indicates that these hydrogens are located at the C3/C8 position. Both of the allylic resonances at δ 2·26 and 2·19 are coupled to the quintet at δ 1·82 which suggests that this resonance corresponds to the methylenic C4/C9. This establishes all of the hydrogens of the cyclodecadienyl ring, for the methylenic hydrogens at C4/C9 would couple to two different allylic resonances, those of C3/C8 and those of C5/C10. The third allylic resonance at δ 2·04 couples only to the methylenic resonance at δ 1·41. These resonances correspond to the hydrogens of the saturated bridge, respectively C11/C14 and C12/C13, which are isolated from the hydrogens of the rest of the molecule by the interdiction of the bridgehead double bonds.

An experiment was devised to use the assignments that had been made for the allylic hydrogen resonances to provide additional

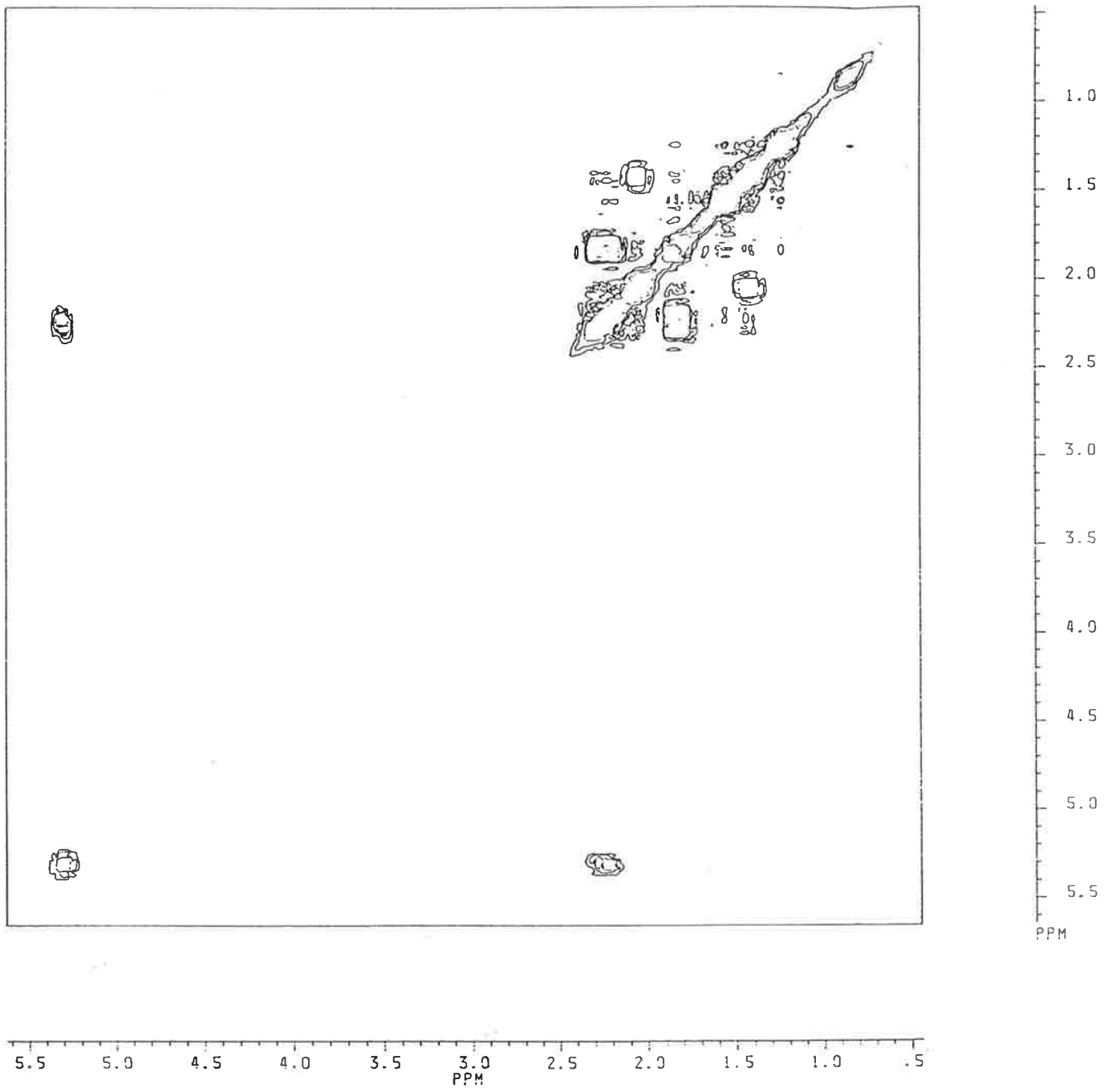


Figure 6. ^{1}H COSY of Bicyclic Diene from Coupling of 6-(4-Butanal)-5-*Z*-cyclodecan-1-one (33)

evidence for the proposed conformation of the bridgehead double bonds.

The steric compression that occurs between the hydrogens of allylic carbons in a cisoid configuration around a double bond can induce carbon-hydrogen bond deformation which increases the electron density on the associated carbons. This gives rise to shielding from what is called the γ effect[87] and is aptly demonstrated by the example of *cis* and *trans* 3-hexene (figure 7)[88]. The γ effect has been used to aid in the assignment of the configuration of trisubstituted double bonds[89], as the steric interaction between the cisoid carbons can result in their resonances occurring upfield from the corresponding *trans* allylic carbon signal. Due caution must be taken to consider all the steric interactions that affect the allylic hydrogens.

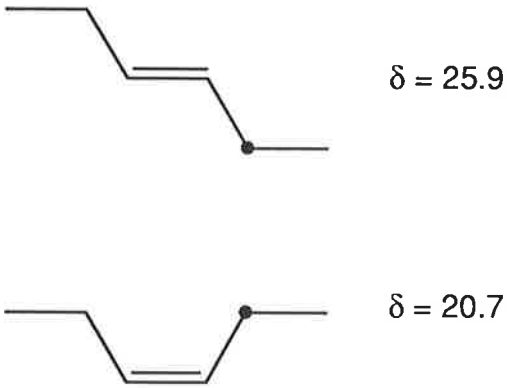
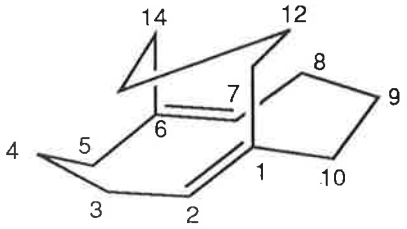


Figure 7.

The carbon resonances associated with each of the allylic hydrogens were determined by the selective application of a low power decoupling irradiation to each of the allylic hydrogen frequencies while observing the effects on the acquired ^{13}C nmr spectrum. With the correct decoupler power the carbon resonance decoupled from the irradiated hydrogen frequency would collapse to a singlet with increased intensity due to nuclear Overhauser

effects, while the remaining carbon signals would still exhibit some residual $^{1}J_{C-H}$ coupling. This experiment is called Single Frequency Off-Resonance Decoupling (SFORD)[78]. It was employed because the small amount of sample and the insensitivity of the available spectrometer precluded the acquisition of a Heteronuclear $^{1}J_{C-H}$ resolved correlation spectrum (HETCOR). The results are presented in table 3.



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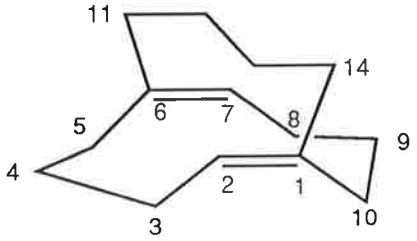


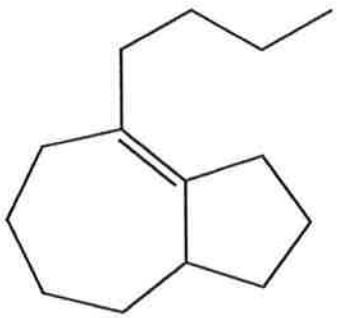
10.

The structures that represent possible *E,E-* (9) and *Z,Z-* (10) geometries of the bicyclo[4.4.4]tetradecadiene (above) show that for the *E,E-* isomer the cisoid allylic carbon pairs are C3 to C11 and C8 to C14, while in the *Z,Z-* isomer it is C3 to C10 and C5 to C8 that are cisoid. The hydrogen resonance at δ 2·04 had been assigned to the C11/C14 carbons of the saturated bridge. The observations from the SFORD experiments show that the resonance at δ 31·01 corresponds to C11/C14 and the resonance at δ 32·42 corresponds to C3/C8. Molecular models suggest that the γ effect discussed above is the dominant steric interaction experienced by the allylic hydrogens in the *E,E-* and *Z,Z-* bicyclo[4.4.4]tetradecadienes (9), (10) and so the chemical shifts of the allylic carbons are consistent with the *E,E-* isomer.

Table 3

^1H decoupling (ppm)	Carbon Resonance (ppm)				
	35·11 (t)	32·45 (t)	31·07 (t)	27·70 (t)	23·47 (t)
2·04	35·01 (t)	32·42 (t)	31·01 (s)	27·63 (t)	23·42 (t)
2·19	35·01 (s)	32·42 (t)	31·02 (t)	27·64 (t)	23·42 (t)
2·26	35·01 (t)	32·42 (s)	31·02 (t)	27·64 (t)	23·39

A second volatile component was isolated from the reaction between the butanalcyclodecenone (33) and zero valent titanium. This compound was a single component by G.C. and was isolated in yields of 1·3% to 2·6%. The mass spectrum of the compound shows a molecular ion of *m/z* 192. The molecule has been tentatively identified as a double bond isomer of 2-butyl-bicyclo[5.3.0]dec-1-ene (77) or (78).



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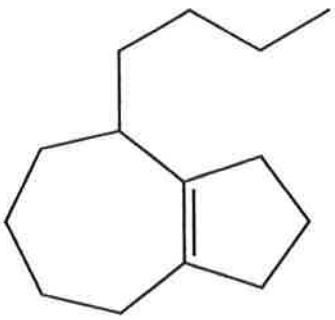
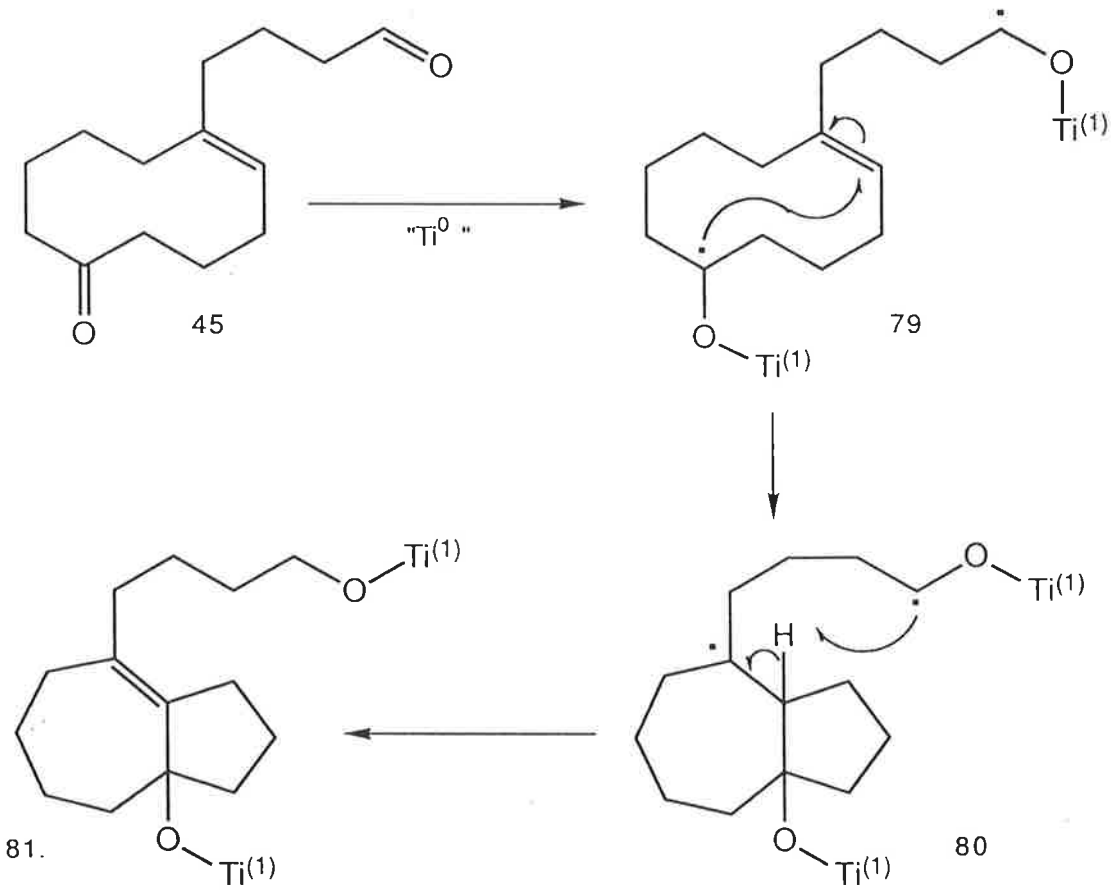


78.

The ^{13}C nmr spectrum of this compound shows fourteen resonances, two of which are in the olefinic region at δ 141·10 and 136·39. The presence of a single double bond and fourteen carbons in combination with a molecular ion of *m/z* 192 indicates a molecular formular of $C_{14}H_{24}$ which is consistent with a bicyclic alkene structure.

The ^1H nmr spectrum contains no resonances in the olefinic region which suggested that the double bond is tetrasubstituted. There are a total of seven hydrogens deshielded by being allylic to the double bond, and this requires that the butyl chain be adjacent to the ring fusion of the bicyclic substructure; a more distal position for the side chain would result in eight allylic hydrogens of a tetrasubstituted double bond. In addition there is a triplet at 0·87 which indicates the presence of an aliphatic methyl group, a feature of the butyl side chain.

81.



Scheme 32.

One possible mechanism by which such a product might arise is detailed in scheme 32. The reaction of the cyclodecyl carbonyl group with zero valent titanium gives rise to a radical (79) which

then undergoes a transannular reaction with the double bond that corresponds to a favourable 1,5 exo cyclisation process. The tertiary hydrogen would then be abstracted, either by the primary alkoxy radical as in (80) or by some other radical species. The formation of the double bond would favour this process. The reaction need not be stepwise, it is illustrated as such only for simplicity. The mechanism by which the alkoxy groups are reduced to methyl and methylenic functions is uncertain. Geise[31] has proposed that the solvent may be acting as a hydrogen atom source.

If the transannular reaction is a facile process it may offer an explanation as to why the yield of cyclised product was not higher. The high proportion of nonvolatile material suggests that there were also intermolecular reactions occurring which formed oligomeric products.

The hydrogenation of the bicyclic diene that had been tentatively identified as 1,6-*E,E*-bicyclo[4.4.4]tetradecadiene (9) was carried out over platinum oxide catalyst under 1 atmosphere of hydrogen pressure. The reaction was complete in less than twelve hours and gave a product that was isolated in 90% yield. This component was shown to be a single component by capillary G.C. analysis and it co-eluted with the bicyclic diene. The mass spectrum of the product shows a molecular ion at *m/z* 194 which is consistent with the hydrogenation of both double bonds to give a saturated bicyclic compound. The high resolution mass spectrum corresponds to $C_{14}H_{26}$, and there are no olefinic hydrogen or carbon resonances in the ^{1}H nmr (figure 8) or ^{13}C nmr (figure 9) spectra

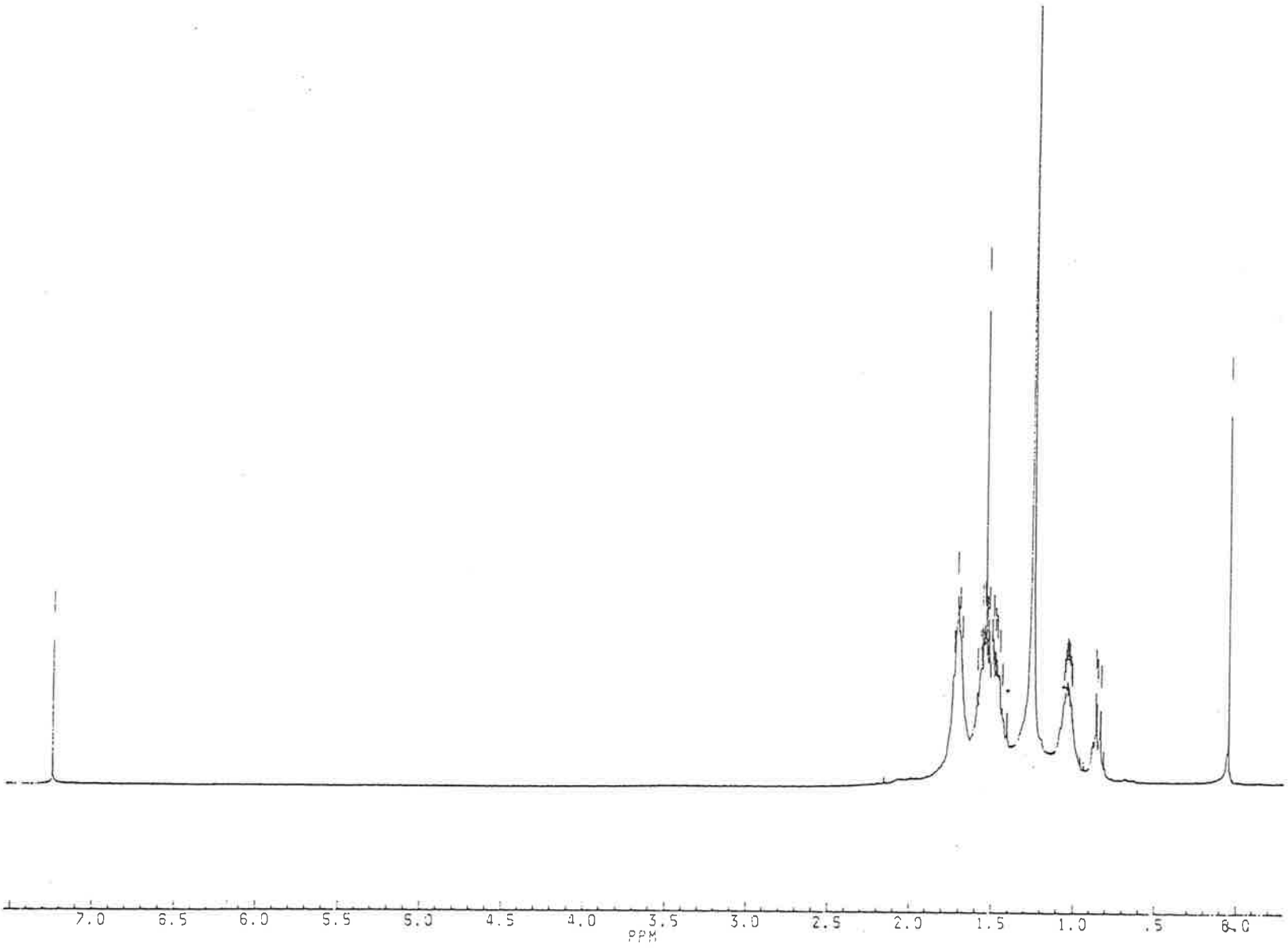


Figure 8. ^{1}H nmr of Saturated Bicyclic Compound

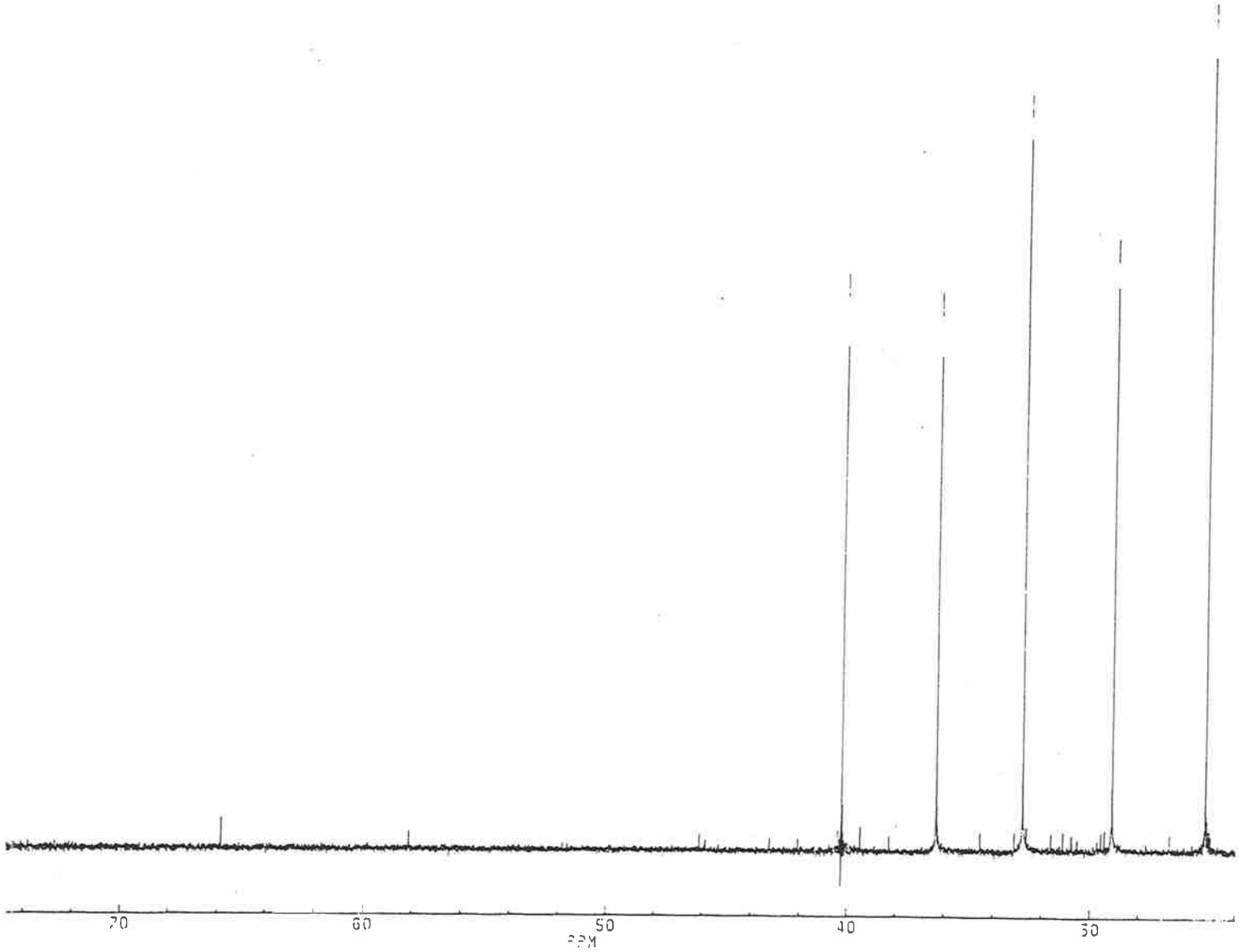


Figure 9. ^{13}C nmr of Saturated Bicyclic Compound

The ease with which the hydrogenation occurred was unexpected. The theoretical predictions regarding the saturation of the *E,E*- diene (9) to give out,out-bicyclo[4.4.4]tetradecane (1) had suggested that the double bonds should resist hydrogenation because of the increase in strain energy that arises upon rehybridisation of the bridgehead carbons from sp^2 to sp^3. Indeed the hydrogenation of the in-alkene (5) required exposure to 50 psi of hydrogen for 24 hours over platinum oxide in order for the reaction to go to completion.In his discussion of the low energy conformations of the out,out-bicyclo[4.4.4]tetradecane (1) Alder[10] predicts that the most stable geometry of the molecule is asymmetric, however he also states that there are many conformations of similar energy available to the molecule and that it might be reasonably expected to exhibit D_3 symmetry. This means that the molecule possesses a C_3 axis of symmetry which passes through the two bridgehead carbons as well as a plane of symmetry which is perpendicular to this axis and which bisects the bridgeheads.

On this basis we expected to observe three aliphatic carbon resonances in the ^{13}C nmr spectrum, and were surprised instead to observe five resonances. One possible explanation is that the out,out-bicyclo[4.4.4]tetradecane (1) lacks a plane of symmetry. This would reduce the overall symmetry of the molecule to C_3 and was suggested by the diagram of out,out-bicyclo[4.4.4]tetradecane (1) included in the paper by Maier and Schleyer[5]. The in,out-bicyclo[4.4.4]tetradecane (3) has C_3 symmetry and shows six resonances in the ^{13}C nmr spectrum[9]. The off resonance spectrum of the saturated bicyclic compound reveals the presence of only one

methine carbon. This indicates that the bridgehead carbons are equivalent and is consistent with C_3 symmetry. The carbon signals were integrated after the spectrum had been acquired with the use of an inverse gated decoupling sequence and a 10 second recycle time to eliminate inconsistencies arising from incomplete relaxation and nuclear Overhauser effects[87]. The ratio between the non bridgehead carbons should be equal for a molecule with C_3 symmetry, as all bridges would be equivalent. Instead the resonances at δ 32·75 and 25·21 were twice the intensity of the resonances at δ 40·20, 36·31 and 29·08, and this observation precludes a C_3 axis.

A ^1H COSY spectrum (figure 10) was acquired in order to establish the connectivity between the multiplets resolved by the one dimensional ^1H nmr spectrum. In addition SFORD experiments were carried out for each of the hydrogen multiplets to assign each to a carbon resonance. The results are shown in table 4.

Table 4

^1H decoupling (ppm)	Carbon Resonance (ppm)				
	40·20 (d 2C)	36·31 (t 2C)	32·75 (t 4C)	29·08 (t 2C)	25·21 (t 4C)
1·03	d	t	d	t	t
1·25	d	s	dd	s	t
1·48	d	t	dd	t	s
1·53	d	t	dd	t	s
1·71	s	t	d	t	t

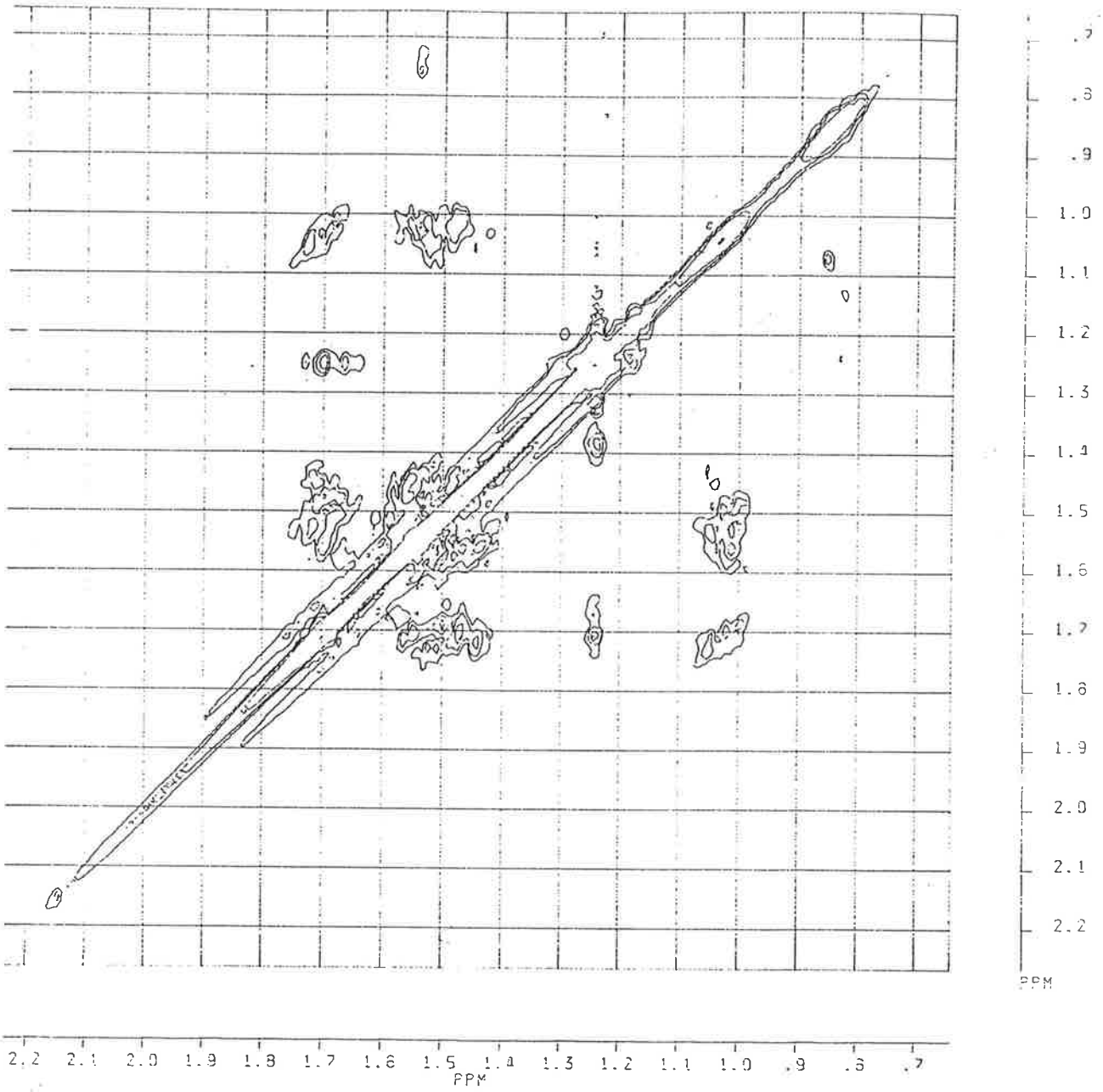
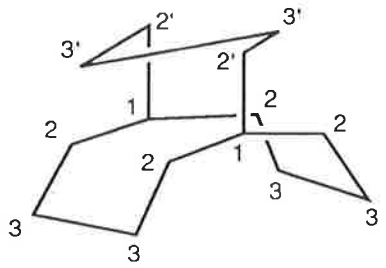


Figure 10. ^{1}H COSY of Saturated Bicyclic compound

The combined data provided by the various ^{1}H and ^{13}C nmr experiments can be interpreted as defining a bicyclic structure that has a unique bridge which does not interconvert with the other two, equivalent bridges on the nmr time scale. Such a structure is represented schematically in figure 11 and the notations are used in the following interpretation.



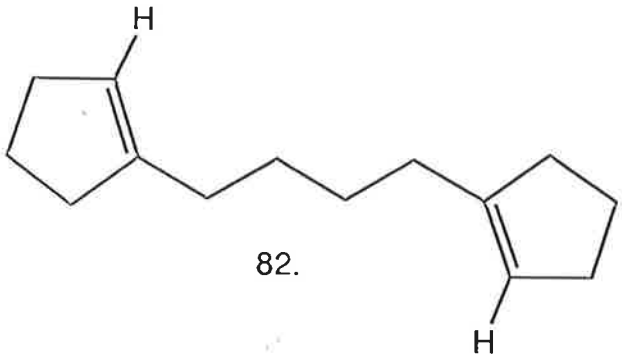
11.

The hydrogens of C2′and C3′ are represented by the eight hydrogen multiplet at δ 1·25. These hydrogens couple only to the bridgehead hydrogens at δ 1·71 and irradiation of the multiplet caused both two carbon triplets at δ 36·31 and 29·08 to collapse to singlets. These carbons then correspond to C2′and C3′. The remainder of the hydrogen resonances all show intercoupling. Irradiation of the multiplet at δ 1·71 showed that the six hydrogens were associated with two carbons; only two hydrogens could be associated with the bridgehead carbons at δ 40·20 and the remaining four hydrogens caused the four carbon triplet at δ 32·75 to collapse to a doublet. This is consistent with the four hydrogens providing half of the total hydrogens required by either C2 or C3. The triplet at δ 32·75 also collapsed to a doublet when the four hydrogen multiplet at 1·03 was irradiated so these hydrogens provide the remaining quota for this carbon. When each of the overlapping multiplets at δ 1·53 and 1·48 were irradiated the four

carbon triplet at δ 25·21 collapsed to a singlet, thus these hydrogens and carbon are associated with the remaining C2 or C3 carbon.

The ^{13}C nmr spectrum did not alter over a temperature range from -70°C to 110°C and the ^{1}H nmr spectrum at 25°C and 70°C were identical.

It is difficult to explain why the bicyclotetradecane structure should be so rigid as to prevent the bridges from interconverting particularly when Alder[10] has suggested that out,out-bicyclo[4.4.4]tetradecane (1) has many low energy conformations in which it may exist. In a private communication with Professor Alder the molecule 1,4-bis(1-cyclopentenyl)butane (82) arose as an alternative identity for the bicyclic diene which was isolated from the reaction of butanalcyclodecenone (45) with zero valent titanium. It is a structure that offers more plausible explanations for the properties exhibited by both the bicyclic diene and the saturated bicyclic molecule.



82.

The bis(cyclopentenyl)butane (82) is isomeric with bicyclo-[4.4.4]tetradecadiene. The double bond of the cyclopentenyl moiety would be expected to hydrogenate more readily as its saturation would lead to an increase in strain energy of 3 $kJmol^{-1}$ compared with the 50 $kJmol^{-1}$ of strain energy per double bond that would be

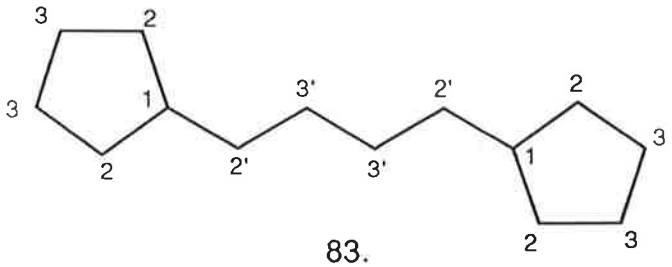
introduced to the bicyclo[4.4.4]tetradecadiene molecule upon saturation[7].

The connectivity between the hydrogen resonances established by the ^1H COSY spectrum (figure 6) of the cyclisation product is also consistent with the bis(cyclopentenyl)butane (82) structure. The vinylic resonance at δ 5·29 couples to the allylic resonance at δ 2·26, and as both δ 2·26 and 2·19 couple to the quintet at δ1·82 these resonances could represent the hydrogens of the cyclopentenyl moiety. The allylic resonance δ 2·04 and the aliphatic resonance δ 1·41 couple only to each other and thus are consistent with the butyl chain.

McMurry observed that for the in-alkene (5) the double bond exhibited characteristics of being distorted from normal geometry. The $^1J_{C-H}$ value of 143·5 Hz for the vinylic carbon-hydrogen coupling was consistent with the loss of s character in the double bond, and he proposed that the U.V. absorption λ_{max} 229 nm (ε 2850) arose from the raised level of the highest occupied molecular orbital relative to the lowest unoccupied molecular orbital; a consequence of double bond deformation. In contrast the $^1J_{C-H}$ value of 157·7 Hz for the bicyclic diene isolated from the cyclisation reaction is more consistent with values of 160 Hz for cyclopentene derivatives[78] and the U.V. spectrum contains only a minor absorption at λ 272 nm. Although the double bonds of the 1,6-*E,E*-bicyclo[4.4.4]tetradecadiene (9) are not expected[7] to be deformed to such an extent as the double bond of the in-alkene (5), the potential for through space interaction of the π orbitals discussed above[15] could well be expected to give rise to significant absorption above 200 nm.

The compound, 1,4-bis(cyclopentyl)butane (83), which would arise from the hydrogenation of the bis(cyclopentenyl)butane (82) is described in the literature[90]; it was obtained by the hydrogenation of a singly bridged ferrocene derivative. The only data provided for the compound was the broad band decoupled and off resonance ^{13}C nmr spectra which are identical to the data for the saturated bicyclic molecule except for a constant upfield shift of 0·7 ppm.

The connectivity observed in the ^{1}H COSY (figure 10) and SFORD spectra (table 4) of the saturated bicyclic compound is also consistent with the bis(cyclopentyl)butane (83) structure which is represented schematically in figure 12. The notations are used in the following interpretation.



83.

Figure 12.

The eight hydrogens of the butyl chain would be expected to have a similar chemical shift, and four of these hydrogens would couple to the methine hydrogens at δ 1·71. This is consistent with the singlet at δ 1·25 that was originally assigned to the unique bridge of the bicyclo[4.4.4]tetradecane (1). The multiplet at δ 1·25 is associated with two carbon resonances, C2' and C3', δ 36·31 and 29·08 which are of equal intensity to the methine carbons, C1, at δ 40·20. The eight hydrogens of the multiplets at δ 1·53 and 1·48 could reside on the four C3 carbons at δ 25·21 and the eight hydrogens of the multiplets at δ 1·71 and 1·03 would then be

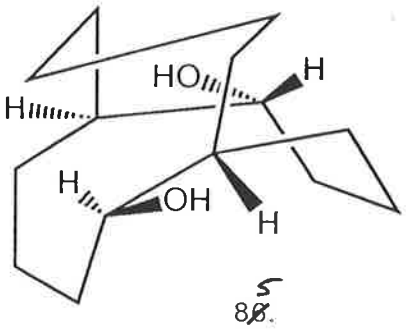
assigned to the four C2 carbons at δ 32·75. The gauche interaction between the butyl sidechain and each of the *cis* C2 hydrogens could then give rise to the shielding effects that result in the marked separation of the C2 hydrogen chemical shifts.

A simple means of determining the size of the ring containing the olefinic moiety would be to introduce a carbonyl group as a substituent to the ring and observe the wavelength of the absorption of the C=O stretch. The absorption of ten membered ring ketones occur around 1700 cm^{-1} while an absorption of 1730cm^{-1} is typical of five membered ring ketones.

It should be possible to transform the olefinic functional groups of the bicyclic diene into carbonyl groups by a two step sequence. The hydroboration of the double bonds followed by an alkaline peroxide workup should provide the anti-Markownikov diol, which could then provide the corresponding dione by a suitable oxidation step. Unfortunately the experimental work was unavoidably interrupted after the diol was isolated, and by the time work resumed both the diol and its bicyclic diene precursor had decomposed to intractable mixtures. Insufficient time remained to allow the work to be repeated. The spectral analysis of the diol does, however, provide some insight into the structure of the bicyclic diene.

When the bicyclic diene was treated with an excess of diborane:THF complex and the crude alkylborane oxidised by alkaline hydrogen peroxide in the usual manner[53], a bicyclic diol was isolated from the product in 81% yield. The chemical ionisation mass spectrum of the diol shows a protonated molecular ion at *m/z* 227 with fragment ions at *m/z* 209 and 191 that correspond to the sequential loss of two molecules of H_2O. The high

resolution mass spectrum of the fragment at *m/z* 209 is consistent with $C_{14}H_{25}O$. The infrared spectrum of the diol has an absorption at 3612 cm^{-1} for the O-H stretch. The ^1H nmr spectrum establishes that the hydrogen of the carbon bearing the hydroxyl group, which occurs at δ 3·79 as a doublet of triplets could be adjacent to both a methine hydrogen and a methylenic pair of hydrogens. There are no resonances consistent with olefinic hydrogens or carbons in either of the appropriate nmr spectra.



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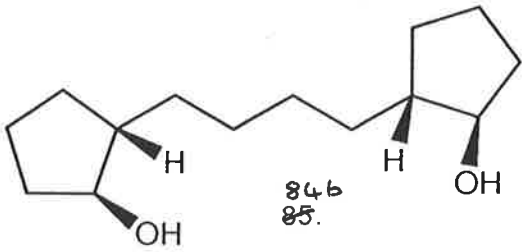
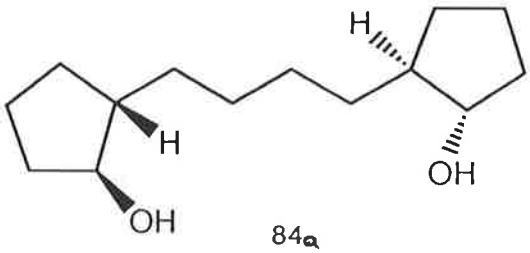


84b
85.



84a

The diol is a single component by TLC and capillary G.C. analyses, however the ^{13}C nmr spectrum reveals seven pairs of very closely shifted resonances that are consistent with the presence of two diastereomers of 1,4-bis(2-cyclopentanol)butane (84a), (85). The double bonds of the 1,6-*E,E*-bicyclo[4.4.4]tetradecadiene (9) can be approached from only one diastereotopic face, and would give rise to only one diastereomeric diol (88), while no such selectivity is expected for the 1,4-bis(cyclopentenyl)butane (82) which should give rise to a meso diol (85) and a pair of enantiomers (84a). All of these diols would be expected to show C_2 symmetry, and each should give rise to seven resonances in their ^{13}C nmr spectra. While the diastereomeric

bis(cyclopentanol) diols (84,85) might be expected to differ slightly and so give rise to the seven pairs of observed resonances in a mixture of the isomers, the only rationale for the 2,7-bicyclo[4.4.4]tetradecanediol (86) having fourteen signals is that it is adopting an asymmetric conformation which does not interconvert with its enantiomeric image on the nmr timescale.

Clearly the spectroscopic data for the products from both the hydrogenation and hydroboration of the bicyclic diene is more consistent with the 1,4-bis(cyclopentenyl)butane (82) identity. The conditions that must be applied with regard to specialised conformations when discussing the bicyclo[4.4.4]tetradecyl derivatives make the bicyclo[4.4.4]tetradecadiene (9) a less logical alternative. The only synthesis of 1,4-bis(1-cyclopentenyl)butane (82) recorded in the literature[90] calls for the homologation of a propyl analogue while it is complexed in a ferrocene configuration. The procedure is not simple and a lack of time prevented the acquisition of this diene (82) which would unambiguously ascertain the structure of the bicyclic diene.

The 1,4-bis(cyclopentenyl)butane structure would arise from some kind of rearrangement of the 1,6-bicyclo-[4.4.4]tetradecadiene. The rearrangement is reminiscent of the metathesis reactions of 1,6-*Z,Z*-cyclodecadiene (17) that have been observed over tungsten and molybdenum catalysts[91]. In these reactions a single equivalent of the diene (17) provides two equivalents of cyclopentene, and elevated temperatures favour the reaction by overcoming the unfavourable energetics of co-ordinating the two cyclodecyl double bonds in a suitable proximity for reaction to take place. While there are no reports of such reactions taking place over titanium catalysts, Geise[31] has

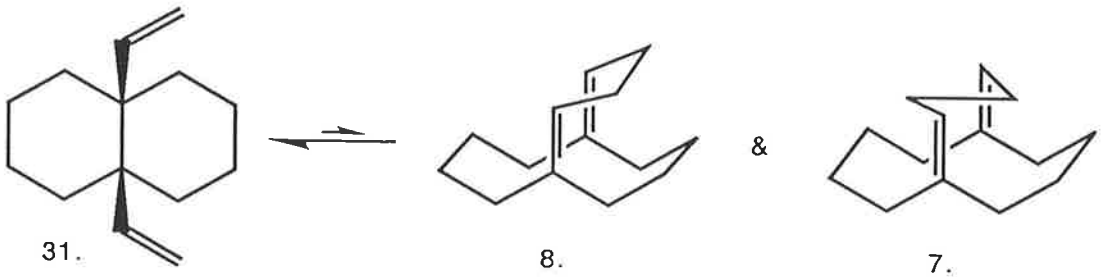
proposed that the olefins which are produced by the titanium induced carbonyl coupling reaction are co-ordinated to a titanium species. The close intrabridgehead relationship of the double bonds of 1,6-bicyclo[4.4.4]tetradecadienes combined with the strain relief that would result from the disruption of the bicyclic skeleton could favour such a rearrangement taking place.

Part 3. The Intramolecular Coupling of 6-(4-Oxobutylidene)cyclodecanone (35).

The volatile compound that was formed from the reaction between the zero valent titanium and butenylcyclodecanone (35) was identified as 1,6-divinyldecalin (31) by comparison of the spectral data, shown in figures 12 and 13, with the data reported by Shea *et al.*[15] The divinyldecalin (31) was isolated in 8% yield, though the internal standard suggested that the actual yield was closer to 15%.

The isolation of the divinyldecalin (31) indicates that the carbonyl coupling reaction had formed meso-1,5-bicyclo[4.4.4]tetradecadiene (8) and/or 1,5-*E,Z*-bicyclo[4.4.4]tetradecadiene (7) as both may undergo the Cope rearrangement through, respectively, either the chair or boat transition state[15]. The crude product from the reaction was subjected to 175°C in order to isolate the divinyldecalin (31). As the crude product was only analysed by G.C./mass spectrometry prior to the purification step, it was not possible to say whether the Cope rearrangement occurred during the reaction, at 80°C or during isolation, at 175°C.

Shea and coworkers had prepared the divinyldecalin (31) in order to use it as a precursor to the meso1,5-bicyclo[4.4.4]-tetradecadiene (8). The two compounds represent valence bond isomers of a Cope equilibrium, scheme 33. The theoretical predictions for the strain energy of the divinyldecalin (31) and the 1,5 diene (8) suggest that an equilibrium would favour the divinyldecalin isomer by approximately 20 kJmol^{-1}. Shea carried out two experiments in an attempt to promote the Cope rearrangement of the divinyldecalin (31) to the 1,5-diene (8). The first was ^{1}H nmr and ^{13}C nmr observations at temperatures up to 100°C which suggested that the divinyldecalin (31) was undergoing only conformational isomerisation. The second was the flash vacuum pyrolysis of divinyldecalin (31) which failed to produce any 1,5-diene (8). These results suggest that even if the activation energy barrier of the rearrangement is high, in conditions where equilibration is possible the equilibrium will favour the divinyl compound.



31. 8. 7.

Scheme 33.

It was unfortunate that the crude product from the cyclisation was not analysed by ^{1}H nmr prior to the purification step as this would have determined whether or not it was exposure to temperatures of 175°C which brought about the Cope rearrangement of the 1,5-diene (8) to the divinyldecalin (31). Given that the metathesis reaction which is thought to have taken place

with the 1,6-bicyclo[4.4.4]tetradecadiene (9 or 11) has also been observed to occur in the form of polymerisation in 1,5-cyclodecadienes[91] which are more strained than the former[7], it is likely that the Cope rearrangement took place as soon as the 1,5-dienes formed. A lack of time prevented the further investigation of this reaction.

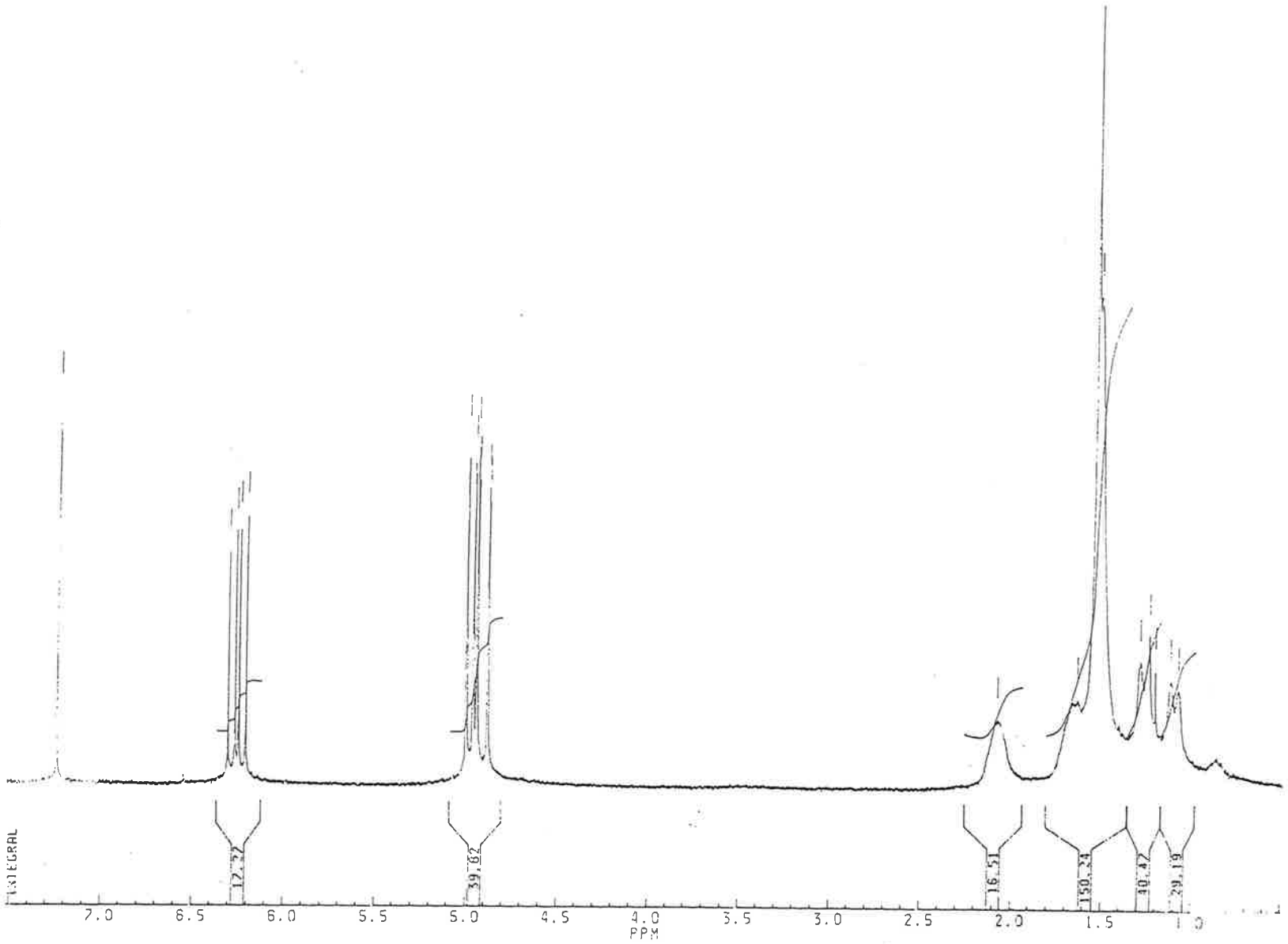

INTEGRAL
12.72
39.62
16.51
150.23
40.42
29.19
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
PPM

Figure 12.

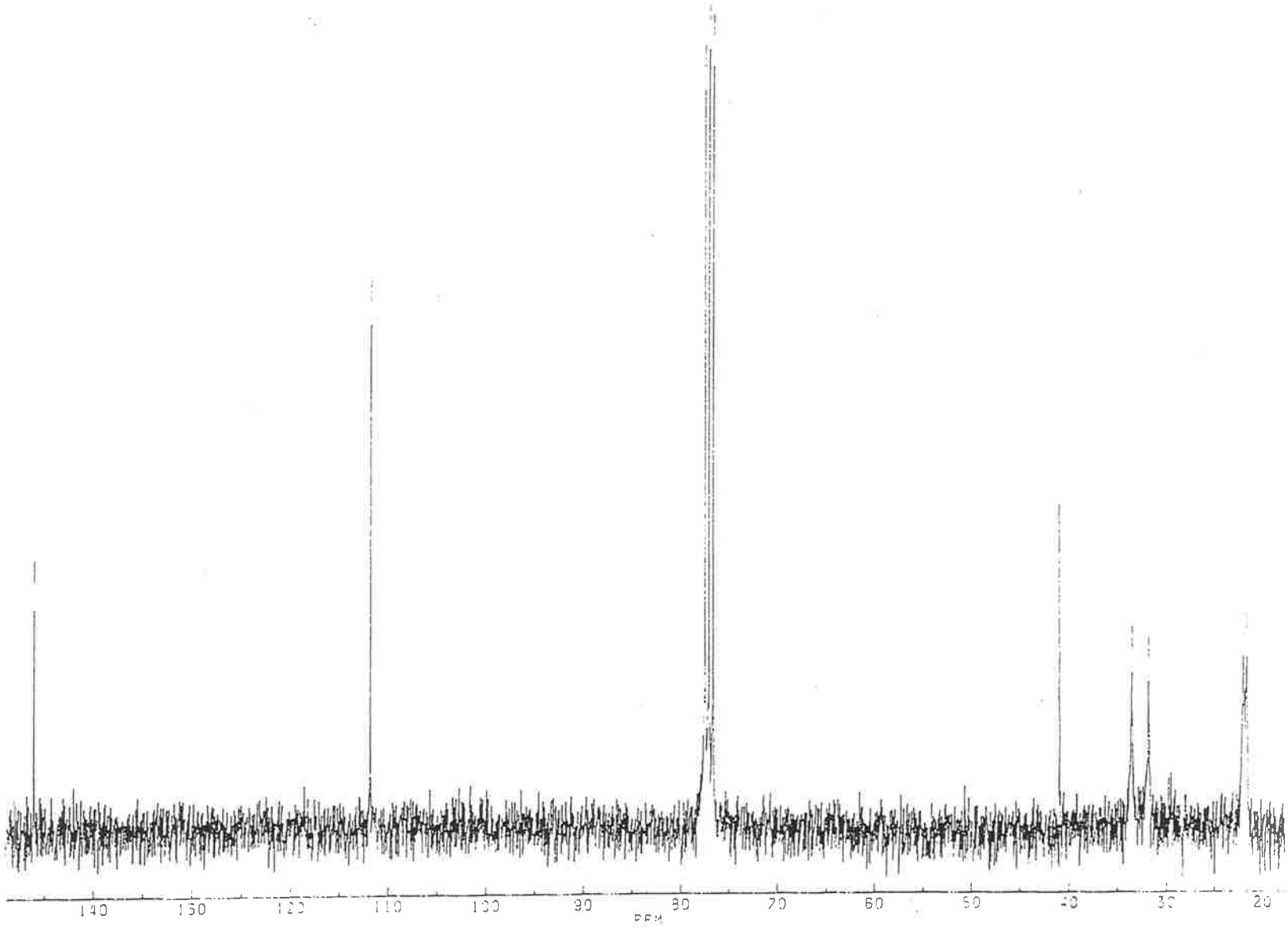
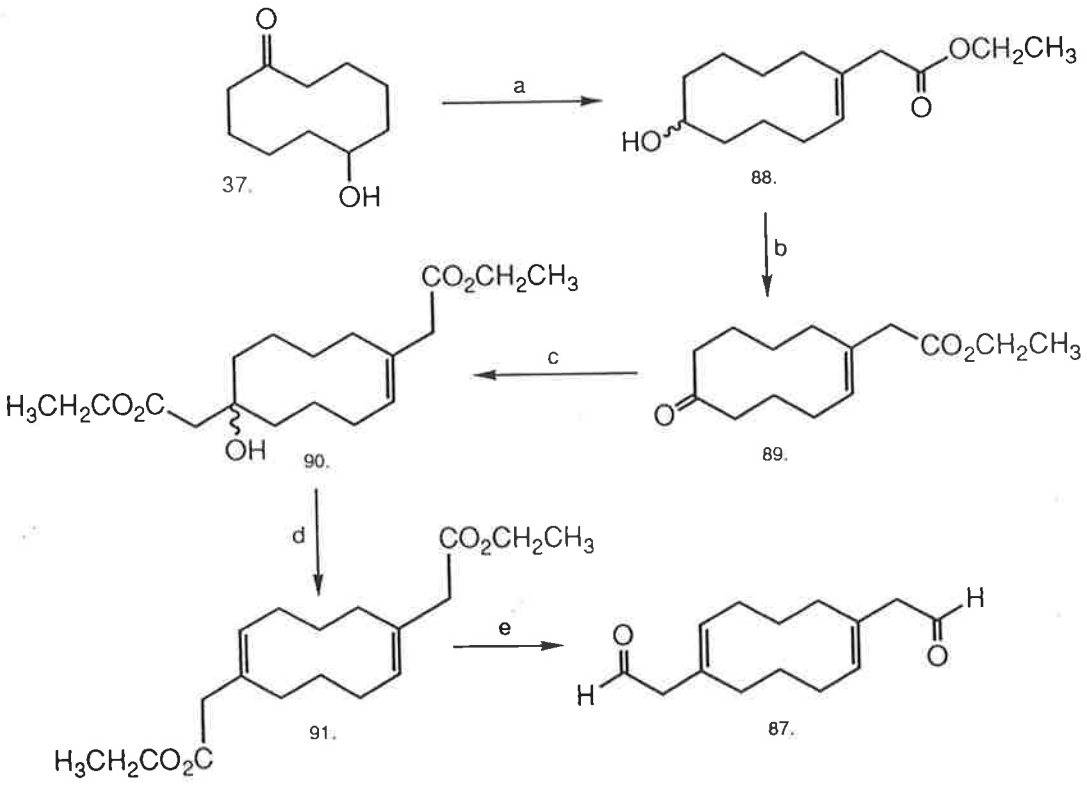


Figure 13.

Chapter 4

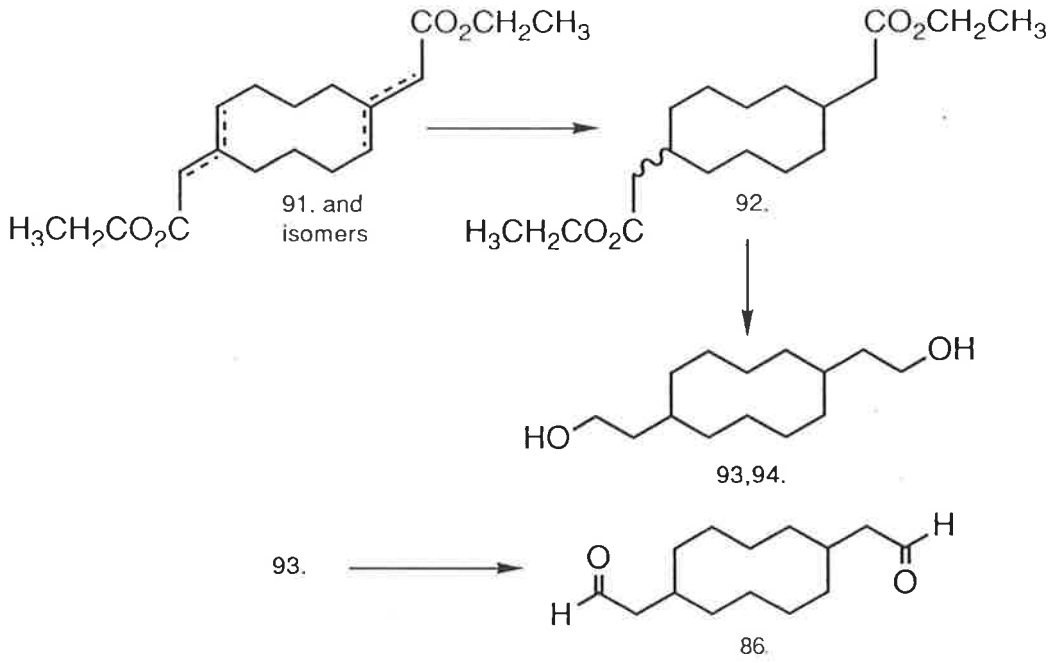
Part 1. Preparation of 1,6-Bis(2-oxoethyl)cyclodecane (86) and 1,6-bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene (87); Type II Key Intermediates.

An alternative approach to the bicyclo[4.4.4]tetradecane skeleton was conceived that has as its key intermediates dialdehydes (86) and (87) with either unsaturated or saturated pro-bridgehead positions, respectivley. The synthetic route by which these compounds were prepared is shown in scheme 34. and 35 The precursor for this sequence is 6-hydroxycyclodecan-1-one (37).



a. $(EtO)_2P(O)CH_2CO_2Et$, EtONa / EtOH; b. PCC; c. EtOAc, LDA, THF;
d. $SOCl_2$, Pyridine, Toluene; e. DIBAL, hexanes.

Scheme 34.



Scheme 35.

Preparation of the Di-unsaturated Key Intermediate (87).

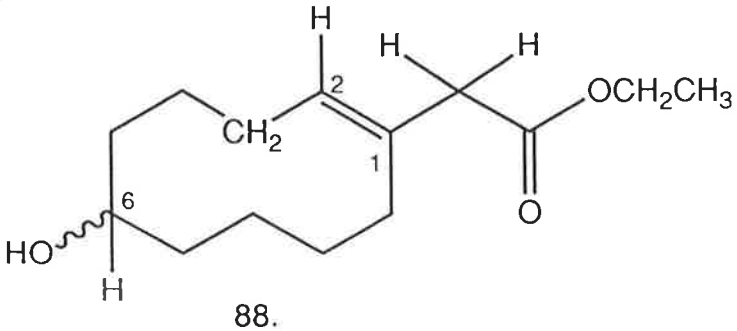
The β,γ-unsaturated hydroxy ester (88) was prepared in 81% yield by the reaction between the hydroxyketone (37) and two equivalents of the anion of triethylphosphonoacetate[92]. The phosphonoacetate was deprotonated by a solution of sodium ethoxide in ethanol and combined with the hydroxy ketone (37) at low temperature. The mixture was then left at room temperature for five days at which time the reaction had gone to 90% completion. That the vinylic hydrogen occurs as a triplet in the ^1H nmr spectrum is clear evidence that the double bond has migrated to an endocyclic position. The configuration of the double bond was assigned as cisoid to the ring based on thermodynamic arguments presented in Chapter 2. Such α,β- to β,γ- migrations have been observed in a number of systems particularly in the presence of an excess of base[93]. There is literature precedence[9] for the

preparation of the α,β-unsaturated hydroxyester (49) from the reaction between the phosphonoacetate anion and the hydroxyketone (37) in THF, where sodium hydride is used as the base. In our hands only starting materials were recovered from this reaction. The reaction between ethyl triphenylphenylphosphorylideneacetate (95) and the hydroxyketone (37) was similarly unsuccessful. The reaction between methylenetriphenylphosphorane and the hydroxyketone (37) is reported[94] to give 6-methylenecyclodecanol in 75% yield, however the stabilised ylid (95) is not as reactive a nucleophile and clearly does not react with the cyclodecyl ketone.

$Ph_3P{=}CHCO_2CH_2CH_3$

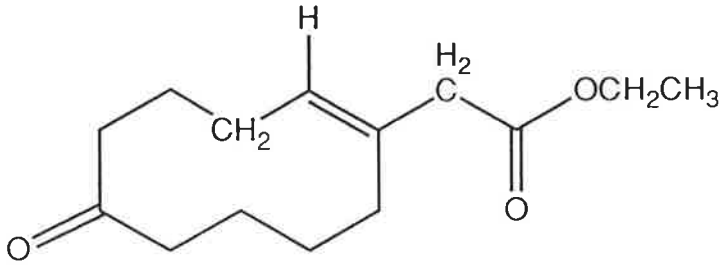
95.

The infrared spectrum of the unsaturated hydroxyester (88) shows a strong O-H stretch at 3412 cm^{-1} but the ketone C=O absorption at 1704 cm^{-1} is absent. It has been replaced by a nonconjugated ester C=O absorption at 1732 cm^{-1}. When a carbonyl system is in conjugation with a double bond this C=O stretch moves to shorter wavelengths, and the C=C stretch has a strong absorption, where as in this spectrum it is a weak band at 1657 cm^{-1}. The unsaturated hydroxyester (88) analyses correctly for $C_{14}H_{24}O_3$.



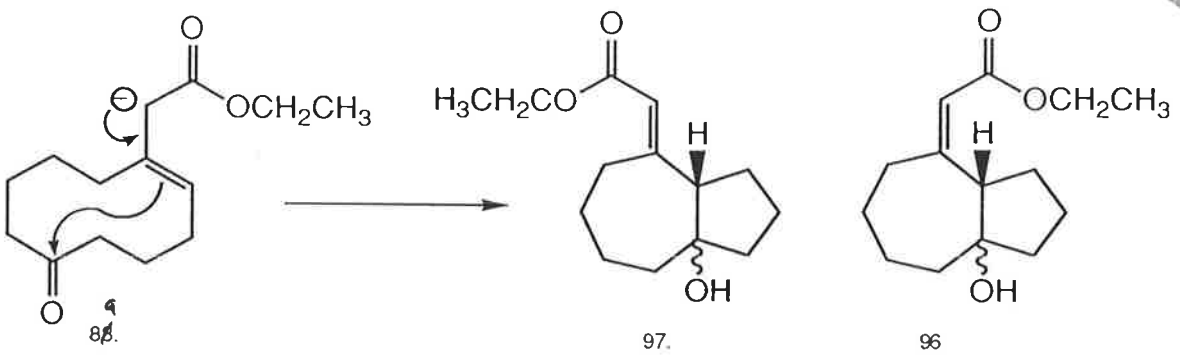
88.

The β,γ- double bond of the unsaturated hydroxyester (88) is characterised by the occurence of a triplet at δ 5·33 in the ^{1}H nmr spectrum, which indicates that the vinylic hydrogen is coupled to a pair of adjacent methylenic hydrogens. The endocyclic double bond makes the C6 cyclodecyl carbon chiral. This asymmetry affects the methylenic hydrogens of the ester side chain which are diastereotopic and occur as a strongly distorted *ab* quartet at δ 3·0 and 2·95 with a geminal coupling of 13·5 Hz. The ^{13}C nmr spectrum contains only 14 resonances which is consistent with the presence of only one, asymmetric, isomer of the trisubstituted double bond.



89.

The β,γ-unsaturated hydroxyester (88) was readily oxidised by pyridinium chlorochromate[72] in the presence of powdered 4Å molecular sieves[73] to give the β,γ-unsaturated keto-ester (89) in 87% yield.The combustion analysis of the keto-ester is consistent with $C_{14}H_{22}O_3$. The infrared spectrum of the keto-ester (89) shows that the hydroxyl absorption at 3412 cm^{-1} is absent and a new carbonyl stretch consistent with a cyclodecyl ketone is present at 1699 cm^{-1}. The ^{13}C nmr spectrum has a new carbonyl resonance at 210·7 for the C1 ketone and the ^{1}H nmr spectrum shows that the *ab* quartet of the methylenic hydrogens α to the ester group have collapsed to a singlet in the absence of the asymmetric hydroxylated C6 carbon.



Scheme 36.

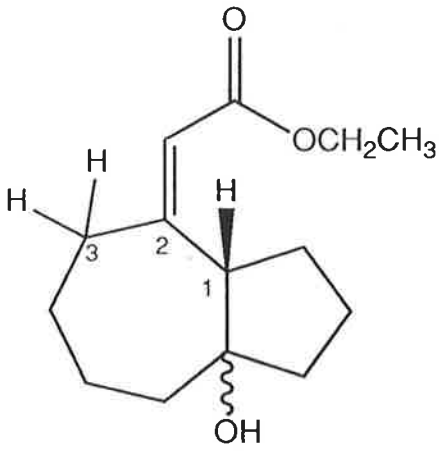
The attempt to alkylate the unsaturated keto-ester (89) with the anion of triethylphosphonoacetate by the method described above was not successful. Instead of alkylating the ketone moiety the phosphonoacetate anion acted as a base (scheme 36) to remove one of the acidic hydrogens α to the ester carbonyl group. The enolate that resulted then underwent an intramolecular aldol type reaction to give a 1:1 ratio of two products that have been tentatively identified as the *Z*- and *E*- isomers of *cis or trans*- fused-2-(ethoxycarbonylmethylene)bicyclo[5.3.0]decan-7-ol (96) and (97), respectively, in an overall yield of 78%. When the reaction was carried out at lower temperatures in an attempt to suppress enolisation the product contained a proportion of unreacted unsaturated keto-ester (89) in addition to the two bicyclic isomers. Table 5 shows the relative proportions of the components in the product as determined by G.C. analysis.

Table 5

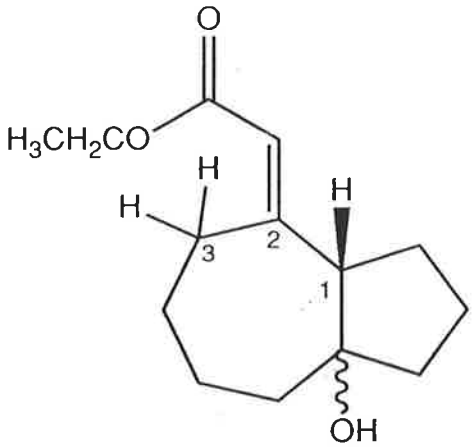
Reaction Temp (°C)	Components in Product (% abundance)		
	Keto-ester (89)	*Z*-[5.3.0] (96)	*E*-[5.3.0] (97)
25	5	44	55
0	52	27	20
-15	100	-	-

The mass spectrum of each of the bicyclic isomers (96) and (97) shows a molecular ion of *m/z* 238 which indicates that both are isomeric with the unsaturated keto-ester (89) and that alkylation did not take place. The ^{13}C nmr spectrum shows that only two olefinic carbons and a single carbonyl are present in each isomer, in keeping with this unsaturation the molecular formula of $C_{14}H_{22}O_3$ indicates that the molecule is bicyclic. The downfield shifts of the hydroxylated carbons at δ 82·97 and 83·09 are consistent with a bridgehead position as tertiary carbons bearing hydroxy functions occur in the range of 77-85 ppm. The infrared spectrum of the *Z*- isomer (96) has a strong O-H stretch at 3492 cm^{-1} and the absorptions associated with the carbonyl and olefinic stretches are consistent with the presence of an α,β-unsaturated ester moiety. The carbonyl stretch of the ester has moved to a lower frequency of 1695 cm^{-1} with a shoulder at 1730 cm^{-1} and the absorption of the olefinic stretch is more intense and at a lower frequency of 1629 cm^{-1}. The spectrum of the *E*- isomer (97)

has similar characteristics which indicate that it, too, is a hydroxy α,β-unsaturated ester.



96.



97.

The *Z*- and *E*- assignments for the double bond are based upon the interpretation of the ^{1}H nmr spectrum. The ^{13}C nmr spectrum of each component contains only 14 signals which indicates that each is a single diastereomer. Thus the transannular reaction selectively forms either a *cis*- or *trans*- fused [5.3.0] bicyclic system. It was not possible to make assignments with regard to the stereochemistry of the ring fusion based upon the available spectral data.

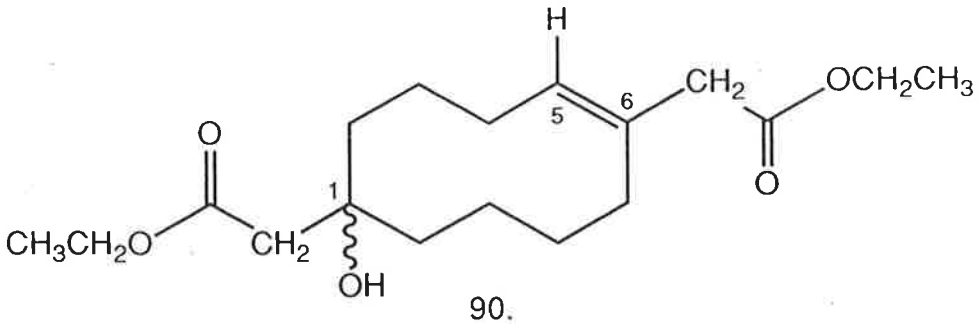
In each of the ^{1}H nmr spectra there are three resonances that correspond to a single hydrogen allylic to a double bond. Two of the resonances appear as complex multiplets and are consistent with the geminal hydrogens of C3, which could be mutually coupled as well as coupling to the vicinal methylenic pair. The remaining resonance appears as a triplet and corresponds to the C1 hydrogen, coupled only to the adjacent methylenic pair. In the isomer (96) assigned the *Z*- double bond configuration the triplet has a chemical shift of δ 3·86 which is downfield by more than 1 ppm from the other allylic resonances. This shift may be due to a

deshielding effect that arises from the close spacial proximity of the C1 hydrogen to the oxygens of the ester moiety which would occur in the *Z*- isomer (96). In the isomer assigned the *E*- double bond configuration (97) the C1 triplet is upfield at 2·64 and one of the C3 multiplets has moved to δ 3·06. This suggests that the ester group is now in close proximity to one of the geminal C3 hydrogens. It is unlikely that the allylic hydrogens on both sides of the double bond would be so markedly affected if the configuration of the double bond was the same in the two isomers.

The second ester side chain was added effectively to the β,γ-unsaturated ester (89) by its reaction with the lithium enolate of ethyl acetate[95] The ethyl acetate anion was generated at -75°C with lithium diisopropylamide, a strong, sterically hindered base. The keto-ester (89) was added to the enolate at -75° in order to discourage the enolisation of the ester moiety which leads to the undesirable transannular reaction described above. The addition of the ethyl acetate anion went to completion in less than one hour to give 1,6-bis(ethoxycarbonylmethyl)-5-*Z*-cyclodecen-1-ol (90) in 90% yield.

The elemental analysis of the β,γ-unsaturated hydroxydiester (90) is consistent with $C_{18}H_{30}O_5$. The mass spectrum does not give a molecular ion but fragment ions at *m/z* 308 and 280 are consistent with the sequential loss from the parent ion of H_2O and ethylene. The loss of water would be a facile fragmentation of a tertiary alcohol, and the loss of ethylene arises from the McLafferty rearrangement of the ethoxy ester. The infrared spectrum shows a strong hydroxyl absorption at 3528 cm^{-1} and a strong broad carbonyl absorption at 1734 cm^{-1} which is

clearly not conjugated to the double bond, which has a weak absorption at 1660 cm^{-1}.



90.

The ^{1}H nmr spectrum shows the presence of two overlapping quartets at δ 4·14 and 4·11 and triplets at δ 1·24 and 1·23 which are consistent with the presence of two unequivalent ethoxycarbonyl moieties in the molecule. The methylenic hydrogens α to the carbonyls occur as broad singlets at δ 2·93 for the pair sandwiched between the ester and the olefinic group and deshielded by both, and at δ 2·37 for the other pair. The ^{13}C nmr spectrum shows two ester carbonyl resonances at δ 172·15 and 171·85, and the tertiary carbon, C1, bearing the hydroxyl group is assigned to the resonance at δ 73·90. This signal is upfield from the region of the spectrum usually associated with tertiary hydroxylated carbons. This may be due to a steric *gauche* interaction[87] between the ester moiety and the hydroxyl group which would increase the shielding experienced by the C1 carbon as a result of bond deformation.

The β,γ-unsaturated hydroxydiester (90) was dehydrated by way of the usual procedure[81] to give an isomeric mixture of three dialkenyl diesters in an overall yield of 78%. The major isomer represented 60% of the mixture by integration of the ^{1}H nmr spectrum, and it was isolated pure in 23% yield by recrystallisation from hexane. The isomer was identified as 1,6-bis(ethoxycarbonylmethyl)-1-*E*-6-*E*-cyclodecadiene (91) on the

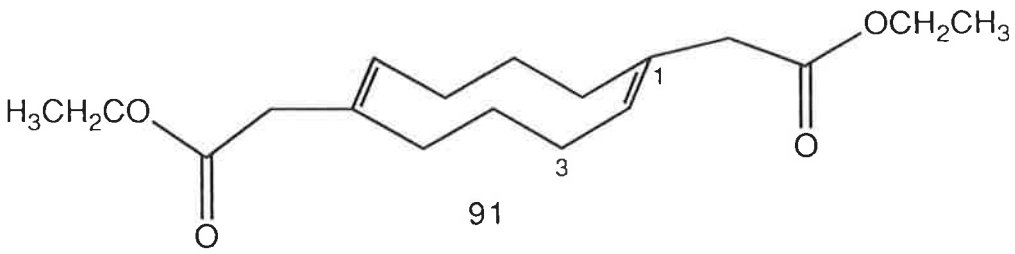
basis of its ^{1}H nmr and ^{13}C nmr spectra as well as previous thermodynamic arguments which favour the cisoid configuration for an endocyclic cyclodecyl double bond.

The isomers that remained in the mother liquor were not readily resolved by analytical TLC and no attempt was made to separate them. The ^{1}H nmr spectrum of the mixture shows a singlet at δ 5·63 and two triplets at δ 5·34 and 5·27 in an approximate ratio of 2:1:1 in addition to the multiplet at δ 5·22 due to the crystalline isomer. The singlet is consistent with an α,β-unsaturated ester moiety, while the triplets represent a β,γ-unsaturated ester group with the double bond in either the *Z*- or *E*- configurations. The ratio between the olefinic signals is consistent with two possibilities for the minor isomers; either the mixture contains a di-α,β-unsaturated diester and an unsymmetrical di-β,γ-unsaturated diester, or it contains two diesters that each contain an α,β-double bond and either of a *Z*- or *E*- double bond. In either case it is clear that the double bond already in existence has been partially isomerised by the reaction conditions. The remainder of the spectrum was too complex to permit further refinement of this assignment to be made.

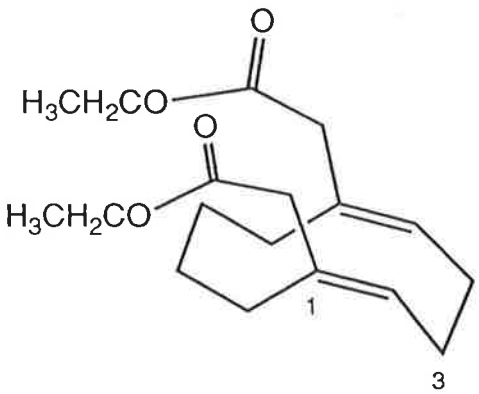
The infrared spectrum of the crystalline diester (91) shows that the hydroxyl absorption at 3528 cm^{-1} of the precursor is absent. The spectrum also indicates that the ester groups are not conjugated to the double bonds, the carbonyl stretches of the ester groups absorb at 1726 cm^{-1} and the C=C stretch is a weak absorption at 1640 cm^{-1}. The high resolution mass spectrum of the dialkenyl diester (91) is consistent with $C_{18}H_{28}O_4$.

The ^{13}C nmr spectrum of the dialkenyl diester (91) shows only 9 signals which include a single ester carbonyl at δ 172·11 and

two olefinic signals at δ 131·80 and 130·63. This indicates that the diester (91) has a two fold element of symmetry and that the configuration of both double bonds is the same. There are two dienes that satisfy these criteria if the predicted *E*-stereochemistry is maintained; 1,6-bis(ethoxycarbonylmethyl)-1-*E*-6-*E*-cyclodecadiene (91) which has a C_2 axis of rotation perpendicular to the plane of the molecule, and 1,6-bis(ethoxycarbonylmethyl)-1-*E*-5-*E*-cyclodecadiene (98) which has a plane of symmetry that bisects the C3-C4 and C8-C9 bonds.



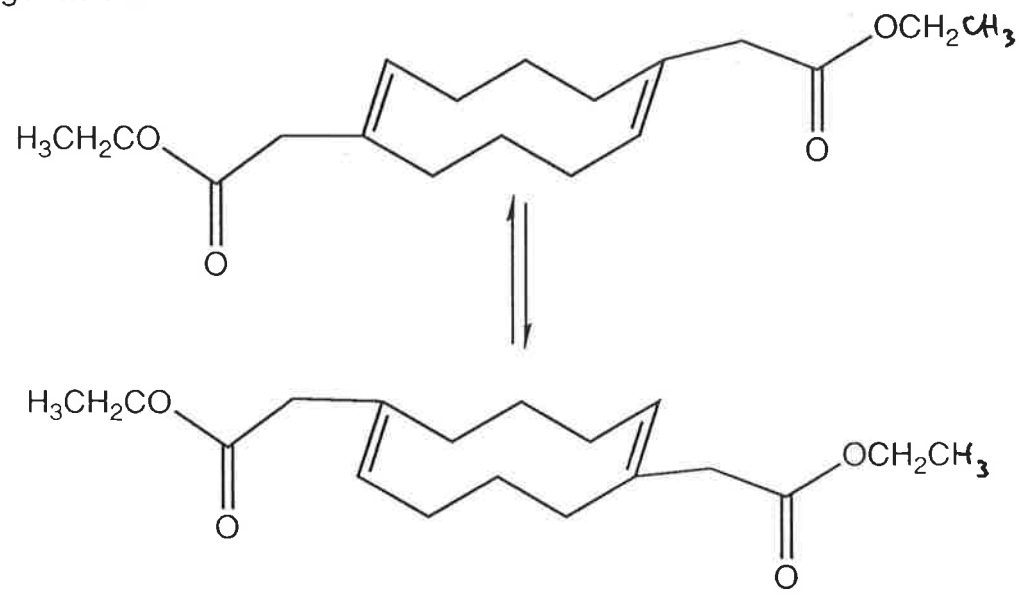
91



98.

An examination of the two possible structures (91) and (98), reveals that the allylic hydrogens of C3 and C4 in the 1,5-diene (98) would only couple to the adjacent vinylic hydrogens of C2 and C5 and possibly between themselves while in the case of the 1,6-diene (91) the allylic hydrogens of C3 and C8 should show coupling not only to the adjacent vinylic hydrogens of C2 and C7 but also to the non-deshielded methylenic hydrogens of C4 and C9.

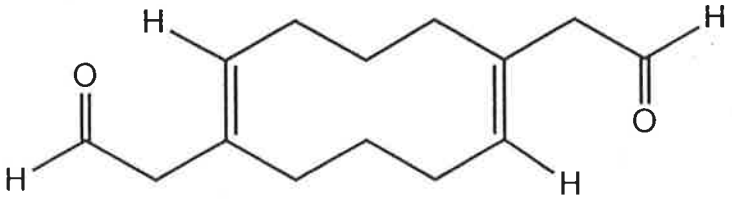
When the vinylic multiplet at δ 5·22 is decoupled, it is only the four hydrogen allylic resonance at δ 2·08 that collapses to a narrow multiplet. The irradiation of this multiplet causes in the aliphatic multiplet at δ 1·44 to simplify to a broad singlet. These observations indicate that the hydrogens of δ 2·08 are adjacent to both vinylic and aliphatic hydrogens which is sufficient to demonstrate that the crystalline diester has the 1,6-diene (91) configuration.



Scheme 37.

An interesting feature of the diester (91) ^1H nmr spectrum is the presence of an *ab* quartet at δ 3·02 and 2·88 with a coupling of 14·16 Hz which is associated with the methylene hydrogens α to the carbonyl groups. The hydrogens are rendered diastereotopic by the substituted cyclodecadienyl ring. The conformers of the substituted cyclodecadiene have a plane of chirality, and even though simple molecular models suggest that these conformers should be interconvertible, scheme 37, the presence of the *ab* coupling pattern suggests that the rate of this interconversion is not appreciable at room temperature on the nmr timescale.

The reduction of the 1,6-diene diester (91) with diisobutylaluminium hydride[96] in hexanes at -78°C gives 1,6-bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene (87) as a crystalline solid in 40% yield after chromatography. In addition to the isolated 1,6-diene dialdehyde (87) the reaction produced a mixture of components that were not identified.



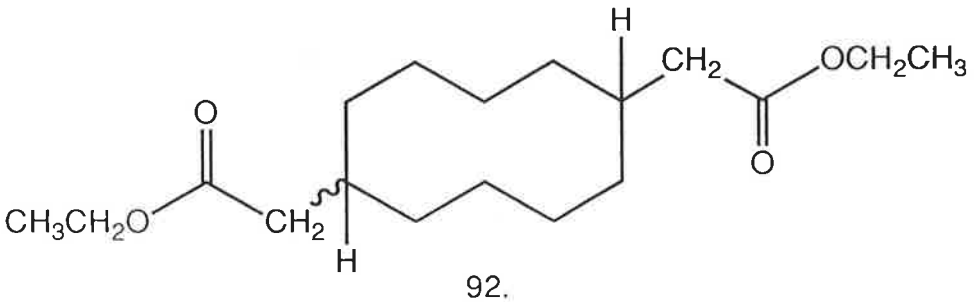
87.

The infrared spectrum of the 1,6-diene dialdehyde (87) shows absorptions at 2736 cm^{-1} and 1712 cm^{-1} which are characteristic of the C(O)-H and C=O stretch of the aldehyde moiety. The quartet at δ 4·1 and triplet at δ 1·2 which characterised the presence of the ethoxy portion of the ester groups are absent from the ^1H nmr spectrum which instead shows a narrow triplet at δ 9·60, a chemical shift typical for hydrogens attached to aldehyde carbonyl carbons. The ^{13}C nmr spectrum shows 7 lines which indicates that the C_2 axis of symmetry is still intact. The carbonyl signal has shifted downfield to δ 200·44 from 172, consistent with its transformation from ester to aldehyde. The high resolution mass spectrum is consistent with $C_{14}H_{20}O_2$.

The diene dialdehyde (87) represents one of the key intermediates of this synthetic strategy. The attempt to cyclise this compound by way of the intramolecular titanium induced dicarbonyl coupling reaction is described below.

The Preparation of the Saturated Key Intermediate (86).

The hydrogenation of the trisubstituted double bonds of the mixture of dialkenyl diesters was carried out over either platinum- or palladium-on-carbon catalysts and in each case the reaction took three days to go to completion. Presumably the hindered nature of the double bond slows the adsorption of the substrate onto the catalyst. The saturated diester (92) was isolated by chromatography in 94% yield. The product was a single component by analytical TLC but ^{13}C nmr indicates that a mixture of diastereomers is present.

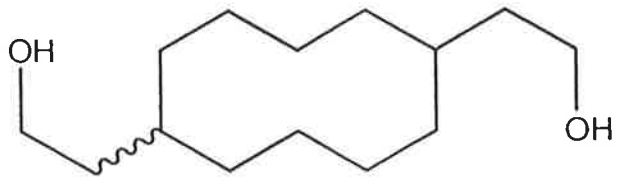


92.

The elemental analysis of the saturated diesters (92) is consistent with $C_{18}H_{32}O_4$. The progress of the hydrogenation was monitored by ^1H nmr with regard to the disappearance of the vinylic resonances at δ 5·2 to 5·6. In the saturated diester (92) the resonances of the hydrogens α to the carbonyl group have moved upfield from δ 3·0 to occur as overlapping doublets at δ 2·18 and 2·15 now that the deshielding effects of the β,γ-double bond have been removed. The hydrogens are no longer diastereotopic but instead reflect the presence of two isomers of the saturated diester (92). The α methylene hydrogens of each isomer have different chemical shifts and couple by different values to the adjacent C1/C6 methine hydrogen to give rise to the two doublets observed.

Each of the isomers has a plane of symmetry passing through C1 and C6. In addition the *trans-* isomer has a C_2 axis that passes through the C3-C4 and C8-C9 bonds, whereas rotation of the *cis-* isomer through 180° around an axis perpendicular to, and passing through the centre of, the plane of the molecule produces its mirror image, indistinguishable from the original structure by nmr. These elements of symmetry should give rise to a simplified ^{13}C nmr spectrum. Each cyclodecyl ring should be represented by three types of carbon as was originally described by Dunitz[22] (see figure 1), with a further four resonances each for the equivalent side chains of both isomers. In fact the ^{13}C nmr spectrum contains only eleven resonances, as the signals at δ 173·18, 59·92 and 14·18 of the ethoxycarbonyl moiety do not distinguish between the *cis-* and *trans-* isomers.

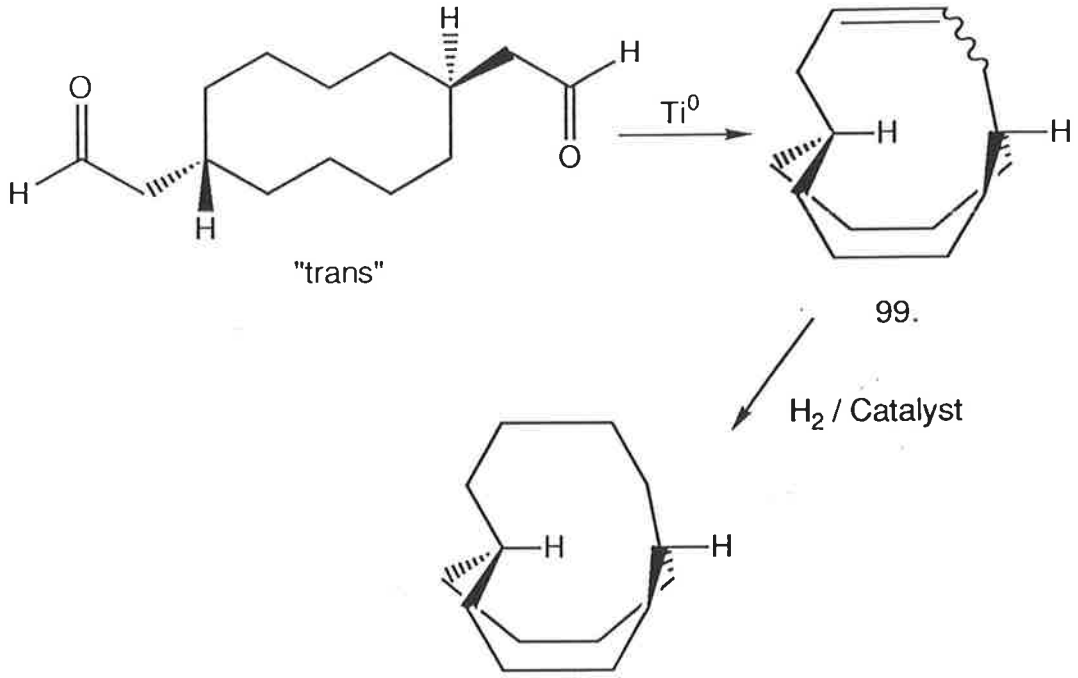
A previous chapter described how it was possible to separate isomeric hydroxybutylidenecyclodecanol (70) from the hydroxybutylcyclodecenol (69) by way of repetitive flash chromatography. This suggested to us that the *cis-* and *trans-* diethylcyclodecanes might also be separable as the dihydroxy derivatives. Indeed the reduction of the saturated diesters (92) with lithium aluminium hydride gave a 90% yield of two diastereomers of 1,6-bis(2-ethanol)cyclodecane (93) and (94) that were separable by repetitive chromatography on silica gel.



93. non polar

94. polar

Scheme 38.

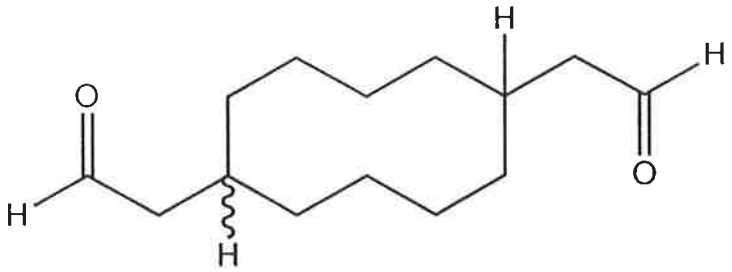


It is not possible to assign *cis*- or *trans*- stereochemistry to the diols (93) and (94) on the basis of their spectral data. It was hoped that the eventual cyclisation of a key intermediate derived from one of the isomers would give rise to in,out-bicyclo[4.4.4]tetradec-3-ene (99) which upon saturation of the double bond could be identified as the in,out-bicyclo[4.4.4]tetradecane (3) (scheme 38) by comparison of its spectral data with that reported in the literature[9,19] This would allow the assignment of the *trans*- stereochemistry to that key intermediate. The attempted cyclisation reactions have so far been unsuccessful and lack of time has prohibited their further investigation, so the problem of stereochemistry has not been resolved. The diols (93) and (94) are labelled as "nonpolar" and "polar" based upon their order of elution from silica gel chromatography.

As might be expected from their similar structure, both diols (93) and (94) exhibited similar spectral characteristics. The infrared spectra show strong hydroxyl absorptions, at 3232 cm^{-1} for (94) and at 3260 cm^{-1} for (93), and in addition the ester carbonyl stretch of 1730 cm^{-1} is absent from both spectra. The ^{1}H nmr spectra shows triplets at δ 3·61 and 3·64 for (94) and (93) respectively, which corresponds to the hydrogens on the carbon bearing the hydroxyl group. The ^{13}C nmr spectrum reveals only five resonances for each isomer. The resonance of the primary hydroxylated carbons occur at δ 60·89 and 61·32 for (94) and (93) respectively. The remaining chemical shifts are in the region associated with saturated hydrocarbons.

The high resolution mass spectrum of the nonpolar diol (93) is consistent with $C_{14}H_{28}O_2$. The mass spectrum shows a weak molecular ion as well as ions at *m/z* 200 and 182 which correspond to the sequential fragmentation of C_2H_4 then H_2O. The polar diol (94) does not give a molecular ion but does show the fragment ions at *m/z* 200 and 182.

The nonpolar diol (93) was oxidised by way of the Swern procedure[79] that uses dimethylsulphoxide activated by reaction with oxalyl chloride. The dialdehyde, 1,6-bis(2-oxoethyl)cyclodecadiene (86) was isolated in 79% yield as a crystalline solid and was stable towards the decomposition of the aldehyde functions for several days at -15°C under oxygen free conditions.



86, single isomer.

The infrared spectrum shows absorptions at 2704 cm^{-1} and 1720 cm^{-1} which characterise the aldeyde functionality. The absorption at 3260 cm^{-1} that corresponded to the OH stretch of the diol (93) is absent. The ^1H nmr spectrum has a narrow two hydrogen triplet at δ 9·73 which is consistent with hydrogens attached to a carbonyl carbon, and there is a narrow singlet at δ 2·29 which corresponds to the hydrogens α to the carbonyl group. The high resolution mass spectrum of the dialdehyde (86) is consistent with $C_{14}H_{22}O_2$.

Part 2. The Attempted Cyclisations of The Type II Key Intermediates.

Two different procedures were used in an attempt to bring about the intramolecular acyloin reaction to cyclise the saturated diesters (92).

In the first method[23,24] a solution of the diesters (92) that contained an excess of trimethylsilyl chloride was perfused into a suspension of sodium sand in refluxing toluene. The product of the reaction was analysed by G.C. which revealed that it contained only unreacted diesters (92). The literature procedure had been modified so that the concentration of the metal in the solvent [0·09 M] and the ratio of metal to carbonyl group (14:1) were approximately

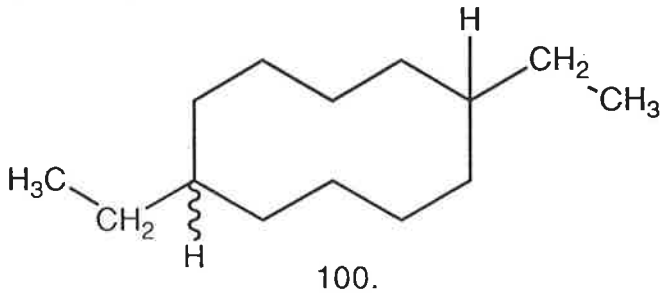
equivalent to the values used in the zero valent titanium carbonyl coupling reaction that was used to prepare the in-alkene (5). The lack of any apparent reaction may have been due to the large dilution factor in conjunction with a relatively poor dispersion of the metal. The titanium metal is produced in a manner similar to Reike type reductions of metal salts[97], it is very finely divided and has a high surface area.

The alternative procedure[98] involved the perfusion of a solution of the diester (92) and trimethylsilyl chloride into a suspension of sodium/potassium alloy in ether at room temperature. This reaction used a metal concentration of [1·4 M] and a metal to carbonyl ratio of 10:1.

The crude product of the reaction distilled at 130°C/0·04 mmHg. The infrared spectrum of the distillate showed the absence of any carbonyl stretch and G.C. analysis confirmed that all the diester (92) had been consumed. The analysis of the distillate by capillary G.C. revealed a mixture of six overlapping components with exceptionally long retention times in comparison to other derivatives of this synthetic sequence and this suggests that the reaction is coupling two or more diester (92) units to form cyclic dimers or oligomers. The results of an attempt to determine the molecular weights of the components of the mixture by G.C./mass spectrometric analysis were too complex to be useful.

An attempt was made to cyclise the saturated dialdehyde (86) by the titanium induced dicarbonyl coupling reaction under the conditions that had proved most efficient with previous key intermediates (see Chapter 3). The volatile fraction of the product was isolated in the usual manner, but analysis of the mixture by

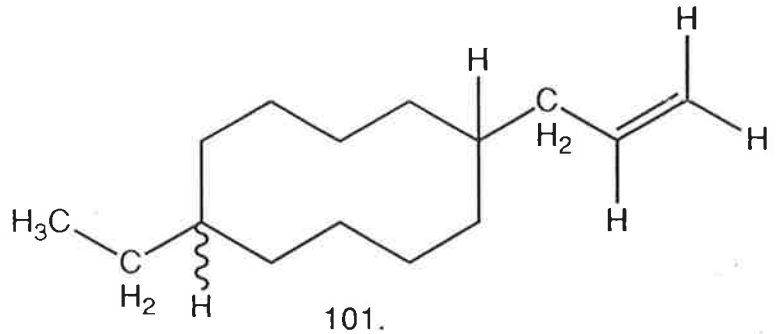
G.C./mass spectrometry revealed that neither of the two major components gave a molecular ion of *m/z* 192, appropriate for *E/Z*-bicyclo[4.4.4]tetradec-3-ene (99). These two volatile components were isolated from the distillate of the crude product by preparative G.C. in yields of 6% and 1·6% and have been identified as 1,6-diethylcyclodecane (100) and 6-ethyl-1-(2-propenyl)cyclodecane (101) respectively on the basis of their spectral characteristics.



100.

The mass spectrum of the diethylcyclodecane (100) shows a molecular ion of 196. This molecular weight could correspond to $C_{14}H_{28}$ which is consistent with a saturated, monocyclic structure. The ethyl side chains of the diethylcylodecane (100), which are equivalent due to previously discussed symmetry considerations, are identified by their distinctive coupling pattern in the ^{1}H nmr spectrum. The spectrum shows a triplet at δ 0·85 of the two equivalent methyl groups coupled to a quintet at δ 1·19 of the adjacent methylenic pairs of hydrogens. The methylenic hydrogens occur as a quintet because they are further coupled to the adjacent C1/C6 methine hydrogens. The ^{13}C nmr spectrum has five resonances which confirms the symmetrical nature of the molecule. All of the resonances occur in the range of δ 12 to 38, a region which is typically associated with saturated hydrocarbon environments.

The identity of 6-ethyl-1-(2-propenyl)cyclodecane (101) is a more tentative assignment which is based upon only mass spectral and ^1H nmr data.



101.

The chemical ionisation mass spectrum shows what is presumed to be a protonated molecular ion at *m/z* 209. This is consistent with a molecular formula of $C_{15}H_{28}$ and could correspond to a monocyclic molecule that contains a single double bond. The G.C. retention time of (101) was similar to (100) and it is unlikely that the molecular ion arises from some fragmentation of a dimeric species. The ^1H nmr spectrum has a quintet at δ 1·19 and triplet at 0·85 which indicates that an ethyl side chain is present, however the integration of the methyl triplet relative to the signals in the vynilic region of the spectrum shows that it contains only three hydrogens, indicating that there is only one ethyl side chain in the structure. The spectrum also contains resonances at δ 4·94 and 4·96 which are both coupled to the remaining vinylic signal at δ 5·77. These are consistent with hydrogens of a terminal olefinic moiety. The resonance at δ 5·77 is further coupled to a triplet at δ 1·94 that corresponds to the allylic pair of hydrogens and completes the assignment of the 2-propenyl side chain.

The occurrence of these kinds of products suggests that the strain involved in the cyclisation of the saturated dialdehyde (86) is too great to permit the formation of an intramolecular bond, and

instead the carbonyl groups undergo alternative reactions, such as reduction. The reduction of carbonyl groups during zero valent titanium induced carbonyl coupling reactions has been observed by both McMurry[84] and Giese[31] , however the formation of (101) is the first observation, albeit tentative, of the addition of a methylene group to an aldehyde carbonyl under these reaction conditions.

The reaction of the 1,6-dialkenyl dialdehyde (87) with zero valent titanium was carried out in manner similar to the saturated dialdehyde (86). An internal standard was added to the distillate of the crude product and the mixture was analysed by G.C. This showed that only micrograms of components with the appropriate retention times observed for previous analogues of tetradecane were present in the mixture. The distillate was analysed by G.C./mass spectrometry. The component observed with a molecular ion of *m/z* 188 which is consistent with an isomer of 1,3,6-bicyclo[4.4.4]tetradecatriene made up only a small fraction of the volatile eluents. An attempt was made to isolate the two major components of the volatile mixture but the preparative G.C. method did not adequately resolve the mixture. Only a trace of material was recovered and further G.C. analysis revealed this to be mixture of components. The products were not identified and the cyclisation was not investigated further.

The lack of volatile materials suggests that perhaps some kind of polymerisation process is taking place.

General Experimental

Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected. Microanalysis were performed by the Canadian Microanalytical Service Ltd, New Westminster, Canada. Flash chromatography was carried out according to the procedure described by Still *et al.*[110] and used Merck Keiselgel 60 (230-400 mesh). Short column chromatography refers to the technique described by Harwood[111] and used Merck Keiselgel HF_{254}. Analytical thin layer chromatography (TLC) was performed using Merck DC-Alufolein Keiselgel $60F_{254}$ and visualised using an ethanolic solution of phosphomolybdic acid (4% w/v). Drying and other purification of organic solvents were accomplished by standard labratory procedures. All organic extracts were dried over anhydrous sodium sulphate. When argon was used as the inert gas it was deoxygenated first by passage through a manganese oxide/vermiculite tower[112].

Analytical gas-liquid chromatography (G.C.) was carried out on a Pye Unicam GCD gas chromatograph which had been fitted with the following columns, using nitrogen as the carrier gas.

Column A — SCOT OV101 0·5mm x 40m, carrier gas flow 2 $ml \cdot min^{-1}$ (pressure in kPa), make-up gas 20 $ml \cdot min^{-1}$.

Column B — 5% OV17 on Varaport 30, 80-100 mesh, 4mm x 1·5m, carrier gas flow 30 $ml \cdot min^{-1}$.

Column C	15% OV101 on varaport 30, 80-100 mesh, 4mm x 1·3m, carrier gas flow 30 $ml \cdot min^{-1}$.
Column D*	20% OV101 on varaport 30, 80-100 mesh, 6mm x 2m, carrier gas flow 50 $ml \cdot min^{-1}$.
Column E**	DB 5 bonded phase microbore

Preparative gas-liquid chromatography (Preparative .G.C.) was carried out using a Pye 104 gas chromatograph fitted with Column D and a gas flow splitter that diverted 90% of the column effluent gas flow out through a heated port in the oven wall. The carrier gas for Preparative .G.C. was argon. Both the Pye 104 and the Pye GCD were fitted with flame ionisation detectors.

Infrared (IR) spectra were recorded on a Hitachi 270-30 or a Jasco IRA-1 grating spectrometer as a neat film for liquids and a nujol mull for solids. The 1602 cm^{-1} band of polystyrene was used to calibrate the spectra from the Jasco spectrometer. The abbreviations: value (ν_{max}), strong (s), medium (m), weak (w), broad (br) and shoulder (sh); are used in reporting the infrared data. Unless otherwise stated ^{1}H and ^{13}C Nuclear magnetic resonance (^{1}H or ^{13}C nmr) spectra were recorded on a Bruker CXP 300 Fourier transform spectrometer operating at 300·1 MHz and 75·4 MHz respectively and were referenced to residual protio solvent with chemical shifts reported as δ ppm. The samples were prepared as dilute solutions in deuterochloroform. Mass spectra were recorded

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*Preparative column.

**Australian Wine Research Institute.

on a number of instruments. Normal fragmentations and high resolution mass spectra were recorded on an AEI MS 3071 spectrometer at 70 eV; Fast atom bombardment spectra were recorded on samples either neat or in a glycerol matrix on a VG ZAB-2HF; Gas Chromatographic/Mass spectrometry observations were made using the Finnegan/Mas TSQ 7000 of the Australian Wine Research Institute (A.W.R.I.) using Electron Impact (E.I.) and Chemical Ionisation (C.I.) techniques.

Chapter 2 Experimental

Part 1. Preparation of 6-Hydroxycyclodecan-1-one (37)

1,2,3,4,5,6,7,8-Octahydronaphthalene (42) from *cis/trans*-Decahydronaphthol

The mixture of octalin isomers was prepared according to the procedure of Campbell and Harris[57]. The crude octalin mixture distilled from sodium, b.p. 114°-118°C / 75 mmHg (Lit.[57] 190°-191°C / 760 mmHg), to give the isomeric octalin mixture in 81% yield.

The distillate was analysed by gas chromatography (column A at 125°C) and was found to contain the following mixture (table 6), the molecular weights were determined by G.C./M.s. analysis at the Australian Wine Research Institute (Column E).

Table 6.

Retention time (minutes)	Percentage of distillate by G.C.	Molecular Weight (*m/z*)
9.4	2	138
9.8	2	136
10.0	3	136
11.0	15	136
11.2	8	138
12.2	70	136

Isomerisation of Octahydronaphthalene Isomers with Phosphorous Pentoxide

The isomerisation of the isomeric octalin mixture was carried out according to the procedure of Campbell and Harris[57].

The crude residue was distilled, b.p. 114°-117°C/ 75 mmHg (Lit.[57]190°-191°C/ 760 mmHg) to give a mixture of octahydronaphthalenes in 70-80% yield.

The distillate was analysed by G.C. (Column C at 125°C) and the results are displayed in table 7.

Table 7.

Retention time (min.)	3.8	4.3	5.0 ($\Delta^{9,10}$)
octalins before isomerisation	14%	50%	36%
octalins after isomerisation	6%	25%	69%

Isomerisation of Octahydronaphthalene Isomers with Amberlite 120-H

Amberlite 120-H resin was activated by washing with aqueous hydrochloric acid (3N) then washing with water until the supernatant was neutral. The resin was then washed with methanol and dried *in vacuo*.

The octalins were isomerised according to the procedure of Doyle and McOsker[99]. A suspension of activated Amberlite 120-H

resin (1.8 g), isomeric octalins (2.25 g, 16.5 mmol) and acetic acid/benzene (2:1, 11.2 ml) was stirred at reflux for 12 hours under an atmosphere of nitrogen at which stage G.C. analysis (Column A at 125°C/75 kPa) showed the ratio of isomers had ceased to change. The solids were removed by filtration and the solvents distilled off at atmospheric pressure under a nitrogen atmosphere. The crude residue was distilled to give the isomeric octalins (table 8) (2.0 g, 14.7 mmol) b.p. 114°-117°C/ 75 mmHg (Lit.[57] 190°-191°C/ 760 mmHg) in 90% yield.

Table 8.

Retention time (min.)	7.0	8.0	8.8 ($\Delta^{9,10}$)
octalins before isomerisation	12%	37%	51%
octalins after isomerisation	3%	12%	85%

The Attempted Isolation of Pure 1,2,3,4,5,6,7,8-Octahydronaphthalene (42) by Application of an Oxymercuration-Demercuration Procedure to an Isomeric Mixture of Octahydronaphthalenes

Method 1. The octalin mixture obtained from the dehydration of the mixed β-decalols was subjected to the oxymercuration procedure of Benkeser, Belmonte and Yang[58]. 1,2,3,4,5,6,7,8-Octahydronaphthalene (42) generally comprised 70% of the starting material according to G.C. analysis (Column A at 125°C/75kPa).

Octahydronaphthalene (42) generally comprised 70% of the starting material according to G.C. analysis (Column A at 125°C/75kPa).

The product 1,2,3,4,5,6,7,8-octahydronaphthalene (42) was recovered by distillation in 50-55% yield, b.p. 116°-118°C/ 75 mmHg (Lit [57]190° 191°C / 760 mmHg). Analysis of the distillate by G.C. (Column A at 125°C/40kPa) revealed that the $\Delta^{9,10}$-octalin (42) Rf 12.2 min., was 90%-95% pure. Two other components, Rf 9·4 and 11·2 min. co-eluted with *cis/trans*-decalins (39) and were not removed by repetitive oxymercuration. ^{1}H nmr δ1.27 to 2.0, mult. **CH_2**.

Method 2. The octalin mixture was subjected to the oxymercuration procedure described in Method 1, however, instead of using alumina to remove the unwanted hydrated isomers of octahydronaphthalenes, the crude concentrate was distilled through a spinning band column. The distillate b.p. 116°-118°C/ 75 mmHg (Lit.[57]190°-191°C / 760 mmHg) was monitored by G.C. (Column A at 125°C/75kPa). 1,2,3,4,5,6,7,8-Octahydronaphthalene (42) was isolated in 33% yield containing less than 3% contaminants.

1,4,5,8-Tetrahydronaphthalene (53)

The procedure of Birch, Murray and Smith[100] was used to prepare 1,4,5,8-tetrahydronaphthalene (53) in 79% yield as white crystalline plates m.p. 54°-55°C (Lit [101] 58°C) recrystallised from methanol.

1,2,3,4,5,6,7,8-Octahydronaphthalene (42) from the Hydrogenation of 1,4,5,8-Tetrahydronaphthalene (53) with Tris(triphenylphosphine)rhodium chloride.

The procedure of Birch and Walker[60] was used to prepare 1,2,3,4,5,6,7,8-octahydronaphthalene (42) in 89% yield, b.p. 108°-110°C/ 47 mmHg (Lit.[57]190°-191°C / 760 mmHg) with purity of 97% when analysed by G.C. (Column A at 125°C/75kPa).

The vigorous exclusion of oxygen from the catalyst solution was essential for a successful hydrogenation to take place. Oxygen contamination caused a cloudy orange suspension to form; very little hydrogen uptake would then occur.

1,6-Cyclodecanediol (41)

Method 1. The 1,2,3,4,5,6,7,8-octahydronaphthalene (42) (10.1 g, 74 mmol) that contained 5-10% of contaminants was dissolved in anhydrous dichloromethane (150 ml) under nitrogen and cooled to -70°C.

A slow stream of ozone was passed through the solution until no $\Delta^{9,10}$-octalin (42) remained. This was determined by the persistence of the blue colour, indicative of an excess of ozone, and also by G.C. (Column C at 125°C); Rf $\Delta^{9,10}$-octalin (42) 4.5 minutes. The solution was then purged with nitrogen to remove traces of ozone while it warmed to 0°C.

A suspension of lithium aluminium hydride (5.63 g, 0.148 mmol) in anhydrous ether (600 ml) stirring under an atmosphere of nitrogen was refluxed for 30 minutes and then cooled with an ice/ water bath. The ozonolysis solution was added dropwise to the

suspension, and when addition was completed the solution was allowed to warm to room temperature and stirred overnight.

The reaction was quenched by the cautious addition of water (5.6 ml), then aqueous sodium hydroxide (15% w/w solution, 5.6 ml) and water (17 ml). The precipitated salts were removed by filtration and washed with hot ethyl acetate (3x100 ml). The organic layers were combined and the solvents removed *in vacuo* to give a crude white solid that was a mixture of 4 components by TLC (70% ethyl acetate/ 30% hexanes).

Repetitive short column chromatography (gradient elution, 100% hexanes to 30% methanol/70% ethyl acetate) separated 1,6-cyclodecanediol (41) (5.7 g, 33.1 mmol) as clear needle-like crystals, m.p.135°-142°C (Lit [102] 145°-147°C). Analysis by TLC (as above) revealed the diol (41) was a mixture of isomers; Rf 0.16, 0.21. IR ϑ_{max} 3350 , s, **OH**; 1295, m; 1090 cm^{-1}.

Method 2. An anhydrous solution of >97% pure 1,2,3,4,5,6,7,8-octahydronaphthalene (42) (9.8 g, 72 mmol) in methanol/ dichloromethane (90 ml, 20 ml) was cooled to 0°C. Ozone/oxygen mixture was bubbled slowly through the mixture until analysis by G.C. (as above) showed no $\Delta^{9,10}$-octalin (42) remained.

The solvent was removed from the mixture *in vacuo*, at room temperature, and traces of methanol were chased off with aliquots of anhydrous THF (2x50 ml). Final drying was achieved with a high vacuum pump (0.5 mmHg) for 2 hours. The resulting white solid was dissolved in anhydrous THF (80 ml) and added slowly to a cold (0°C) ether suspension of lithium aluminium hydride (8.2 g, 0.215 mol) stirring under an atmosphere of nitrogen. Once the addition was

complete the reaction was allowed to warm to room temperature and stirred for a further 12 hours.

The reaction was worked up in the usual manner. Removal of the solvent from the combined organic fractions *in vacuo* gave a crude white solid that was recrystallised from ethyl acetate to give pure 1,6-cyclodecanediol (41) (8.7 g, 50.5 mmol) as clear needle-like crystals m.p. 144°-146°C (Lit.[102] 145°-147°C) in 70% yield. A second crop of crystals was recovered from the mother liquor, 1,6-cyclodecanediol (41) (1.05 g, 6.1 mmol) in 8% yield as a white crystalline solid m.p.138°-140°C.

Method 3. A stream of ozone was bubbled through a solution of pure 1,2,3,4,5,6,7,8-octahydronaphthalene (42) (1.2 g, 8.8 mmol) in methanol/ dichloromethane (4 ml, 16 ml) cooled in an ice/ water bath. The reaction was monitored by G.C. (as above) and when all the $\Delta^{9,10}$-octalin (42) had been consumed the solution was purged with a stream of gaseous nitrogen for 5 minutes. The ozonolysis solution was slowly added to a cold (0°C) solution of sodium borohydride (0.83 g, 22 mmol) in ethanol (15 ml). The reaction was then allowed to warm to room temperature and stirred for 2 hours. Excess borohydride was quenched by the addition of an aliquot of acetone (1 ml) and then the solvents were removed *in vacuo* to give a white powder.

Recrystallisation from ethyl acetate gave pure 1,6-cyclodecanediol (41) (0.75 g, 4.4 mmol) as clear needle-like crystals m.p. 144°-146°C (Lit [102] 145°-147°C) in 50% yield. A second crop of crystals was recovered from the mother liquor, 1,6-cyclodecanediol (41) (0.22 g, 1.3 mmol) in 14% yield as a white crystalline solid m.p.138°-140°C.

6-Hydroxy-cyclodecan-1-one (37)

The silver carbonate on celite was prepared according to the procedure of Fetizon et al.[63] It was found that excessive drying on the rotary evaporator tended to reduce the activity of the reagent. Traces of residual water were more effectively removed as a benzene or toluene azeotrope.

The following reaction was carried out numerous times in an attempt to ascertain the optimum stoichiometry for the oxidation. The exact details are given in the discussion.

The silver carbonate on celite (80 g, 133 mmol) was suspended in toluene (360 ml) and traces of water collected as the toluene azeotrope in a Dean-Stark trap with stirring under an atmosphere of nitrogen. The suspension was cooled to room temperature, then 1,6-cyclodecanediol (41) (6.6 g, 38.3 mmol) was added as a single portion and the suspension brought quickly to reflux. The reaction was monitored by G.C. (Column C at 200°C) which showed the presence of three components; Rf 2.1 min.,2.6 min. and the diol (41) at 3.4 min., identified by coelution with an authentic sample. The reaction was halted when the component at Rf 2.6 min. reached a maximum.

The solid phase was quickly removed by filtration through a pad of celite, and the residue was well washed with warm ethyl acetate (2x200 ml). The solvent was removed from the combined filtrates *in vacuo* to give a crude yellow oil.

The crude product was analysed by TLC (50% ethyl acetate/ 50% hexanes) which showed three components; Rf 0.1, 0.29 and 0.67. The separation of the components by short column

chromatography (gradient elution: 100% hexanes to 100% ethyl acetate by 5% increments) to give, in order of elution; 1,6-cyclodecadione (36) (0.84 g, 4.9 mmol) as prismatic white crystals m.p. 98°-99°C (Lit.[103] m.p. 99°-99.5°C) in 13% yield, 6-hydroxy-decan-1-one (37) (2.23 g, 0.13 mol) in 76% yield as a white crystalline solid m.p. 68°-70°C (Lit.[48] m.p.69°-70°C) and 1,6-cyclodecanediol (41) (0.66 g, 3.8 mmol) in 10% yield m.p. 138°-145°C. ^{13}C nmr δ 214.5 ppm, **C**(O); 103.2, O**C**OH; 75.2, H**C**OC; 69.1, **C**HOH; 41.6, 40.3, 33.5, 24.6, 23.9, 23.1, 22.6.

Chapter 2 Experimental

Part 2. Preparation of 6-(4-Butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45).

6(t-butyldimethylsilyloxy)cyclodecan-1-one (55)

An anhydrous solution of 6-hydroxycyclodecan-1-one (37) (3·33 g, 19·5 mmol), t-butyldimethylsilylchloride (5·01 g, 33·24 mmol) and 4-dimethylaminopyridine (0·85 g, 7·0 mmol) in dichloromethane /triethylamine (4:1, 40 ml) was stirred under an atmosphere of nitrogen for 48 hours.

The reaction was analysed by TLC (40% ethyl acetate/60% hexanes) and contained three components Rf baseline, 0·57 and 0·64. There was no evidence of the hydroxyketone (37) Rf 0·24.

The reaction was diluted with dichloromethane (50 ml) and then washed; first with aqueous hydrochloric acid (10%, 20 ml), then with water (3 x 20 ml) and finally saturated aqueous sodium bicarbonate (1 x 20 ml). The organic fractions were combined and dried then the solvents removed *in vacuo* to give a crude yellow oil.

The crude product distilled at 110°C / 0·01mmHg in a Kugelrohr apparatus to give 6(t-butyldimethylsilyloxy)cyclodecan-1-one (55) (5·28 g, 18·6 mmol) in 95% yield as a clear colourless oil. ν_{max} 2928, s; 2856, s; 1706, s, **C=O**; 1474, m; 1464, m; 1450, m; 1362, m; 1254, s; 1182, w; 1088, s; 1042, s; 1006, m; 974, m;

940, m; 836, s; 774 cm^{-1}, s. ^1H n.m.r. δ 3·64, br mult., 1H, C**H**OSi; 2·27 to 2·57, mult., 4H, $(\mathbf{CH_2})_2CO$; 1·98 to 1·25, mult., 12H, $\mathbf{CH_2}$; 0·83, s, 9H, $(\mathbf{CH_3})_3CSi$; 0·05, s, 6H, Si$\mathbf{CH_3}$. ^{13}C n.m.r. δ 214·07, **C(O)**; 70·1, **CHO**Si; 41·9, 33·4, 25·7, 23·3, 22·3, 17·8; -4·7, $\mathbf{CH_3}$Si. Mass spectrum:*m/z* (F.A.B.) 283 $(M-H)^+$, 227 $(M-C_4H_9)^+$. (E.I.) *m/z* 227 $(M-C_4H_9)^+$(100), 185 (12), 184 (16), 171 (25), 161 (14), 136 (22), 135 (87), 133 (31), 131 (66), 127 (46), 115 (32), 107 (51), 105 (32), 101 (19), 95 (26), 93 (59), 91 (24), 81 (66), 79 (58), 76 (51), 75 (77), 73 (75), 69 (49), 67 (71), 59 (69), 55 (69), found 227.1475, $C_{12}H_{23}O_2Si$ $(M-C_4H_9)$, requires 227.1467.

3-Butenylmagnesium Bromide (57).

The 3-butenylmagnesium bromide (57) was prepared according to the method of Gream *et al.*[70] A typical value from the titration of the reagent with standard aqueous acid and base gave 75% yield based upon starting 4-bromobut-1-ene.

1-(3-Butenyl)-6-(t-butyldimethylsilyloxy)cyclodecan-1-ols (44)

Method 1. According to a general procedure[71] the 3-butenylmagnesium bromide (57) solution was prepared in the usual way by the addition of a solution of 4-bromobut-1-ene (8·18 g, 60·6 mmol) in dry ether (55 ml) to magnesium (2·13 g, 0·091 g atoms) slowly under an atmosphere of nitrogen at a rate which maintained a gentle reflux. The mixture was refluxed for a further hour when addition was completed.

Dry benzene (100 ml) was added to the Grignard solution and the ether was removed by fractional distillation through a short Vigreaux column. A further aliquot of benzene (150 ml) was added.

A solution of 6(t-butyldimethylsilyloxy) cyclodecan-1-one (55) (8·6 g, 30·3 mmol) in benzene (20 ml) was then added slowly to the Grignard solution at room temperature and the reaction was stirred overnight when the addition was completed.

The reaction mixture was poured into saturated aqueous ammonium chloride (300 ml) and then extracted into ether (3 x 150 ml). The combined organic fractions were washed with aqueous sodium bicarbonate (saturated, 50 ml), brine (100 ml) and dried . The solvents were removed *in vacuo* to give a clear colourless oil.

The crude product was analysed by T.L.C. (10% ethyl acetate/90% hexanes) which showed the presence of three components; Rf 0·05, 0·14 and 0·24. Seperation of the crude mixture by flash chromatography (10% ether/90% hexanes) gave, in order of elution; 6(t-butyldimethylsilyloxy)cyclodecan-1-one (55) (3·4 g, 12·1 mmol) in 40% yield and identical to authentic material; an isomeric mixture of1-(3-butenyl)-6-(t-butyldimethylsilyloxy)cyclodecan-1-ols (44) (4·95 g, 14·5 mmol) as a clear colourless oil, in 48% yield and 1-(t-butyldimethyl silyloxy)cyclodecan-6-ol (61) (0·69 g, 2·2 mmol) as a mixture of isomers in 8% yield, a clear colourless liquid that solidified on standing.

6-(t-butyldimethylsilyloxy)-1-(3-butenyl)cyclodecan-1-ols (44) (Found: C, 70.35; H, 11.79. $C_{20}H_{40}O_2Si$ requires C, 70.52; H, 11.84 %). ν_{max} 3375, br s, **OH**; 3060, m; 2910, s; 2840, s; 1640, s; 1482, s; 1469, s; 1460, s; 1441, s; 1386, m; 1372, m; 1359, s; 1252, s; 1080, s; 1055, s; 1002, s; 941, s; 906, s; 833, s; 770 cm^{-}

^{1}, s. ^{1}H n.m.r. δ 5·85, ddt, J 17, 10·6, 6·7 Hz, 1H, **CH**=C; 5·04, dd, J 17, 1·7 Hz, 1H, **trans**, 4·94, dd, J 10·6, 1·7 Hz, 1H, **cis**, C=**CH$_2$**; 3·87, mult., 1H, **CH**OSi; 2·16, dt, J 5·0, 6·7 Hz, 2H, **CH$_2$**C=C; 1·79 to 1·34, mult., 20H, **CH$_2$**; 0·87, s, 9H, (**CH$_3$**)$_3$CSi; 0·05, s, 6H, Si**CH$_3$**. ^{13}C n.m.r. δ 139·25, **CH**=CH$_2$; 114·29 and 114·24, CH=**CH$_2$**; 75·92 and 75·88, **C**OH; 72·14 and 72·07, **CH**OSi; 40·22, 33·49, 33·33, 31·90, 31·34, 27·47, 25·84, 21·97, 21·77, 21·23, 21·03, 18·1; -4·76. **CH$_3$**Si. Mass spectrum *m/z* = 283 (3%, (M-C$_4$H$_9$)$^+$), 267 (1), 265 (2), 227 (1), 181 (2), 171 (3), 153 (13), 149 (10), 135 (40), 109 (22), 95 (50), 93 (15), 81 (31), 75 (100), 73 (37), 69 (15), 67 (40), 55 (34), found 283.2104, C$_{16}$H$_{31}$O$_2$Si (M-C$_4$H$_9$)$^+$, requires 283.2093.

1-(t-butyldimethylsilyloxy)cyclodecan-6-ol (61). ν max 3320, br s, **OH**; 2930, s; 2835, s; 1479, s; 1457, s; 1439, s; 1382, w; 1355, m; 1245, s; 1190, w; 1090, s; 1050, s; 1005, s; 832, s; 765, s. ^{1}H n.m.r. δ 3·92, mult., 1H, **CH**OH; 3·83, mult., 1H, **CH**OSi; 1·55, mult., 16H, **CH$_2$**; 0·85, s, 9H, (**CH$_3$**)CSi; 0·03, s, 6H, Si**CH$_3$**. ^{13}C n.m.r. δ 72·06; 71·76, **CH**OH; 71·31; 71·05, **CH**OSi; 32·75, 32·36, 31·78, 31·65, 25·89, 21·94, 21·75, 18·12, -4·58 and -4·71, **CH$_3$**Si. Mass spectrum *m/z* 269 (3%, (M-OH)$^+$), 230 (14), 229 (100), 137 (21), 135 (19), 133 (18), 131 (15), 115 (16), 105 (40), 101 (13), 95 (86), 93 (22), 81 (77), 75 (71), 73 (64), 69 (74), 67 (74), 55 (61), found 269.2290, C$_{16}$H$_{33}$OSi (M-OH)$^+$, requires 269.2300.

Method 2. The reaction was carried out in a manner similar to that described in Method 1 except that anhydrous toluene was substituted for benzene as the reaction solvent. The toluene solution of 3-butenylmagnesium bromide (57) was cooled to -10°C prior to the slow addition of 6(t-butyldimethylsilyloxy) cyclodecan-1-one (55).

The reaction was worked up in the afore described manner and the crude mixture of components was resolved using flash chromatography to give, in order of elution: 6(t-butyldimethylsilyloxy)cyclodecan-1-one (55) in 30% recovery, 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)cyclodecan-1-ol (44) 60% yield and 1-(t-butyldimethylsilyloxy)cyclodecan-6-ol (61) in 7% yield. All products were identical to authentic materials.

6-(t-butyldimethylsilyloxy)cyclodecan-1-one (55) from 1-(t-butyldimethylsilyloxy)cyclodecan-6-ol (61)

The pyridinium chlorochromate salt was prepared according to the procedure of Corey and Suggs[72]. The bright orange crystals dried to an orange brown *in vacuo* over phosphorous pentoxide, overnight.

Anhydrous dichloromethane (25 ml) was added to pyridinium chlorochromate (1·59 g, 7·4 mmol), powdered 4Å molecular sieves[73] (Aldrich, 1·84 g) and the suspension was stirred for 30 minutes under an atmosphere of nitrogen. A solution of 1-(t-butyldimethylsilyloxy)cyclodecan-6-ol (61) (1·05 g, 3·7 mmol) in dichloromethane (5·5 ml) was added as rapid drops to the suspension, and the reaction was stirred for a further 10 minutes once addition was completed.

Addition of anhydrous ether (40 ml) then caused the solids to clump. The reaction was stirred for 20 minutes then the mixture was filtered through a pad of celite capped Florisil. The residues were well washed with ether. The solvents were removed from the combined filtrates *in vacuo* to give the crude product that was shown by TLC analysis (10% ethyl acetate/90% hexanes) to contain

a single principal component Rf 0·38 with some minor baseline impurities. The crude was distilled using a Kugelrohr apparatus to give 6-(t-butyldimethylsilyloxy) cyclodecan-1-one (55) (0·99 g, 3·5 mmol) b.p. 120°C/0·02 mmHg in 94% yield that was identical to authentic material.

1-(3-Butenyl)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (58).

Method 1. *p*-toluenesulfonic acid (0·02 g, 0·1 mmol) was added to an anhydrous solution of 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)cyclodecan-1-ol (44) (1·87 g, 5·5 mmol) in dihydropyran[77] (1·3 ml, 14 mmol) and the reaction was stirred under nitrogen overnight.

The reaction was diluted with ether (10 ml) and partitioned between an aqueous phase (brine: 10 ml, saturated sodium bicarbonate: 10ml, water: 20ml) and ether (30 ml). The organic phase was separated and dried and the solvent removed *in vacuo* to give the crude product as a light yellow oil.

The crude product was examined by TLC (20% ether/80% hexanes) which revealed a number of components: Rf baseline, 0·14, 0·36,0·42 and 0·58. The least polar component was isolated by flash chromatography (20% ether/80% hexanes) to give a mixture of isomers of 1-(3-butenyl)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (58) (1.93 g, 4.5 mmol) in 82% yield as a clear colourless oil. ν_{max} 3075, m; 2925, s; 2840, s; 2735, w; 2705, w; 1640, s; 1483, s; 1440, s; 1358, s; 1255, s; 1198, m; 1125, s; 1105, s; 1073, s; 1020, s; 990, s; 943, s; 908, s; 868, m; 835, s; 770 cm^{-1}, s. ^1H n.m.r. δ 5·8, ddt, J 17·1, 10·1, 5·9

Hz, 1H, **CH**=CH_2; 4·99, dd, J 17·1, 1·5 Hz, 1H, **trans** and 4·90, dd, j 10·1, 1·5 Hz, 1H, **cis**, CH=**CH_2**; 4·70, mult., 1H, O**CH**(CH_2)O; 3·95, d mult., 1H and 3·44, 1H, **CH_2**O; 3·84, mult., 1H, **CH**OSi; 2·20, mult., 1H and 2·00, mult., 1H, **CH_2**CH=CH_2; 1·87 to 1·33, mult., 24H, **CH_2**; 0·88, s, 9H, (**CH_3**)CSi; 0·03, s, 6H, Si**CH_3**. ^{13}C n.m.r. δ 139·5; 139·4, **CH**=CH_2; 113·75, CH=**CH_2**; 93·17; 92·99, O**CH**(CH_2)O; 81·62, **C**OCH; 72·37; 72·25, **CH**OSi; 63·64; 63·40, **CH_2**O; 36·74, 36·43, 32·52, 32·34, 31·78, 31·69, 31·52, 31·28, 30·69 ,30·58, 27·45, 25·85, 25·70, 25·45, 22·53, 22·44, 22·26, 22·20, 21·06 ,20·96, 20·91, 20·74, 18·09; -4·75, **CH_3**Si. Mass spectrum *m/z* = 424 (<1%, M^+), 367 (4), 349 (3), 324 (19), 323 (67), 285 (8), 283 (10), 267 (6), 265 (12), 191 (7), 159 (75), 135 (18), 109 (17), 95 (22), 85 (100), 75 (71), 73 (27), 67 (21), 55 (16), found 367.2658, $C_{21}H_{39}O_3Si$ ($M-C_4H_9$)$^+$, requires 367.2668 also found 323.2779, $C_{20}H_{39}OSi$ ($M-C_5H_9O_2$)$^+$, requires 323.2770.

Method 2. Pyridinium *p*-toluenesulfonate was prepared according to the procedure of Grieco *et al.*[76] the crude white crystalline residue was recrystallised twice from acetone to give lustrous white crystalline plates in 50% yield, M.p. 114·5°C - 115·5°C (Lit.[76] 120°C).

Pyridinium *p*-toluene sulfonate (0·24 g, 0·95 mmol) was added to an anhydrous solution of 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)cyclodecan-1-ol (44) (3·24 g, 9·5 mmol) in dihydropyran (4·8 g, 57 mmol) under a nitrogen atmosphere and the reaction was stirred for 36 hours.

The reaction was diluted with ether (20 ml) and washed with half saturated brine (15 ml). The aqueous phase was extracted with ether (20 ml) and the combined organic phases dried. The

solvent was removed *in vacuo* to give the crude product as a clear colourless oil.

The crude product was analysed by T.L.C (as above) which revealed a single major component Rf 0·56 contaminated with minor polar impurities. This component was isolated by flash chromatography (20% ether/80% hexanes) to give a mixture of isomers of 1-(3-butenyl)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (58) (3·71 g, 8·7 mmol) in 92% yield as a clear colourless viscous oil, identical to authentic material.

Diborane:THF Complex.

The diborane:THF complex was prepared according to the procedure described by Brown *et al.*[53].

Titration of the gaseous hydrogen released when measured aliquots of the diborane:THF complex were hydrolysed with a 1:1 mixture of water and glycerol showed the concentration to be 1·3M, a yield of 68% based on $NaBH_4$.

1-(4-Butanol)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (59)

Disiamylborane:THF (9·4 mmol) was prepared according to the procedure of Brown *et al.*[53] by the dropwise addition of neat 2-methyl-2-butene (1·32 g, 18·8 mmol) to a solution of diborane:THF complex (1·3 M, 7·25 ml, 9·4 mmol) at -10°C stirred under an atmosphere of nitrogen.

The disiamylborane:THF solution was allowed to stir for 1 hour. A solution of 1-(3-butenyl)-1-(tetrahydropyranyloxy)-6-(t-

butyldimethylsilyloxy)cyclodecane (58) (1·56 g, 3·67 mmol) in THF (5 ml) was added slowly to the disiamylborane mixture and when addition was completed the reaction mixture was allowed to warm to room temperature and stirred for 12 hours.

Excess disiamylborane:THF was quenched by the dropwise addition of water till gas evolution ceased. Aqueous sodium hydroxide solution (3 M, 4·4 ml) was added to the reaction mixture. The mixture was immersed in a water bath at 10°C to aid cooling and aqueous hydrogen peroxide solution (30% w/w, 4·4 ml, 42·4 mmol) was added at a rate to maintain the temperature at or below 50°C. When the addition was completed, the reaction was heated at 50°C for 4 hours.

The reaction was diluted with ether (10 ml) and the aqueous phase was saturated with solid sodium chloride. The organic phase was separated and the aqueous phase was extracted with ether (2 x 15 ml). The combined organic phases were washed with brine (15 ml), dried and then the solvents were removed *in vacuo* to give the crude product as a clear, colourless oil.

The crude product was analysed by T.L.C (40% ether/60% hexanes) which revealed a mixture of a major component Rf 0·16 and two trace components Rf 0·0 and 0·74, the latter co-eluting with starting material (58). Separation of the components by short column chromatography (100% hexanes to 100% ether by 5% increments) gave a mixture of isomers of 1-(4-butanol)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (59) (1·51 g, 3·41 mmol) in 93% yield as a clear, colourless oil.. (Found: C, 67.90; H, 11.36. $C_{25}H_{50}O_4Si$ requires C, 67.82; H, 11.38 %). ν_{max} 3400, br s, **OH**; 2935, s; 2855, s; 2750, w; 2705, w; 1490, s; 1475, s; 1468, s; 1445, s; 1365, m; 1255, s; 1205, m; 1125, s;

1080, s; 1025, s; 992, s; 945, m; 839, s; 778, s; 742 cm^{-1}, s. ^1H n.m.r. δ 4·70 , mult., 1H, O**CH**(CH_2)O; 3·86, mult., 3H, **CH_2**OH and **CH**OSi; 3·76, dt, j 9·6, 6·6 Hz, 0·67H; 3·50, mult., 0·67H; 3·40, dt, j 9·6, 6·5 Hz, 0·67H, all **CH_2**O; 1·86 to 1·23, mult., 26H, **CH_2**; 0·88, s, 9H, (**CH_3**)$_3$CSi; 0·04, s, 6H, Si**CH_3**. ^{13}C n.m.r. δ 93·50 ; 93·37, O**CH**(CH_2)O; 81·99, **C**OCH; 72·34; 72·21, **CH**OSi; 63·86; 63·67, **CH_2**O; 61·93, **CH_2**OH; 36·43, 36·24, 32·62; 32·44, br, 32·29, 31·64, 31·45, 30·74, 30·48, 25·89, 25·44, 22·70, 22·27, 21·04, 20·59, 18·43 18·12; -4·70, **CH_3**Si. Mass spectrum *m/z* (F.A.B.) 425 (8%, {(M+H)-H_2O}$^+$), 341 (14), 265 (3), 227 (9), 209 (24), 191 (17), 159 (22), 135 (69), 109 (67), 101 (78), 95 (100).

1-(4-Butanol)-1-(tetrahydropyranyloxy)cyclodecan-6-ol (60)

A solution of tetrabutyl ammonium flouride in THF (1 M, Aldrich, 3·0 ml, 3·0 mmol) was added to 1-(4-butanol)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (59) (0·47 g, 1·07 mmol) and left to stir under an atmosphere of nitrogen for 5 days.

The reaction mixture was analysed by TLC (100% ethyl acetate) which revealed two mobile components Rf 0·31 and 0·62 as well as considerable baseline material. The mixture was diluted with ethyl acetate/hexane (3:2, 3 ml) and the components of the mixture were separated by gravity chromatography on silica gel (70 g) (gradient elution of 60% to 100% ethyl acetate/hexanes) to give in order of elution: 1-(4-butanol)-1-(tetrahydropyranyloxy)-6-(t-butyldimethylsilyloxy)cyclodecane (59) (60 mg, 0·14 mmol) in 13% recovery, and an isomeric mixture of 1-(4-butanol)-1-

(tetrahydropyranyloxy)cyclodecan-6-ol (60) (289 mg, 0·88 mmol) in 82% as a clear colourless viscous oil that soldified on freezing. ν_{max} 3360, br s, **OH**; 2935, s; 2855, s; 1485, s; 1440, s; 1353, m; 1272, m; 1196, m; 1125, s; 1105, s; 1071, s; 1021, s; 990, s; 865, m; 808, m; 735 cm^{-1}. ^1H n.m.r. δ 4·65, mult., 1H, O**CH**(CH_2)O; 3·92, mult., 1H, {**CH_2**O} overlaps 3·90, mult., 1H, **CH**OH; 3·61, mult., 2H, **CH_2**OH; 3·44, mult., 1H, {**CH_2**O}; 1·23 to 1·89, mult., 30H, **CH_2** includes 1·62, s, **OH**. ^{13}C n.m.r. δ 90·35, O**CH**(CH_2)O; 81·61, **C**OCH; 71·69; 71·63, **CH**OH; 63·72; 61·66, **CH_2**OH; 36·37, 36·12, 32·49, 32·36, 32·23, 31·91, 31·39, 30·74, 30·49, 25·37, 22·71, 22·17, 22·14, 20·89, 20·33, 18·39. Mass spectrum *m/z* (F.A.B.) 329 $(M+H)^+$, 311, 227. (E.I.) *m/z* 227 (16%), 209 (5), 191 (2), 153 (6), 135 (10), 123 (3), 121 (4), 109 (6), 95 (11), 93 (6), 85 (100), 81 (12), 67 (21), 55 (20), found 227.2012, $C_{14}H_{27}O_2$ $(M-C_5H_9O_2)^+$ requires 227.2011.

6-(4-Butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45)

Method 1[72,73]. Anhydrous dichloromethane (15 ml) was added to pyridinium chlorochrochromate (0·5 g, 2·3 mmol), powdered 4Å sieves (Aldrich, 0·59 g) and anhydrous sodium acetate (0·193 g, 2·3 mmol) and the suspension was stirred under an atmosphere of nitrogen for 20 minutes. A solution of 1-(4-butanol)-1-(tetrahydropyranyloxy)cyclodecan-6-ol (60) (0·189 g, 0·57 mmol) in dichloromethane (7 ml) was added slowly to the stirred suspension which promptly turned a dark brown-black colour. The reaction was stirred for 20 minutes then for a further 30 minutes after the addition of anhydrous ether (20 ml).

The reaction mixture was filtered through a pad of Florisil and the residue was well washed with ether. The solvents were removed from the combined filtrates *in vacuo* to give the crude product, a clear orange oil. Analysis of the crude product by TLC (30% ethyl acetate/70% hexanes) revealed a mixture of products with a principal component Rf 0·17. This component was isolated by flash chromatography (20% ethyl acetate/80% hexanes) to give 6-(4-butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45) (0·121 g, 0·37 mmol) in 65% yield as a clear colourless oil. ν_{max} 2932, s; 2868, s; 2724, w; 1725, s; 1707, s; 1478, s; 1453, s; 1440, s; 1364, s; 1256, m; 1199, s; 1124, s; 1073, s; 1025, s; 994, s; 868 cm^{-1}, m. ^1H n.m.r. δ 9·69 , t, J 1·9 Hz, 1H, **C(O)H**; 4·56, mult., 1H, O**CH**(CH_2)O; 3·88, mult., 1H and 3·38, mult., 1H, **CH_2**O; 2·51, mult., 4H, (**CH_2**)$_2$C(O); 2·32, td, J 7·1, 1·9 Hz, 2H, **CH_2**C(O)H; 1·16 to 1·9, mult., 22H, **CH_2**. ^{13}C n.m.r. δ 214·81, (CH_2)**CO**; 202·77, CH_2**CHO**; 93·49, O**CH**(CH_2)O; 80·96, **C**OCH; 63·61, **CH_2**O; 44·01, 42·51, 35·79, 32·10, 31·84, 31·52, 25·23, 23·86, 20·78, 20·13, 20·00, 15·79. Mass spectrum *m/z* = 324 (<1%, M^+), 253 (2), 223 (10), 205 (57), 187 (62), 161 (14), 151 (22), 145 (13), 135 (7), 133 (10), 131 (11), 121 (26), 95 (31), 93 (24), 91 (22), 86 (53), 85 (100), 84 (49), 81 (42), 79 (33), 67 (68), 57 (69), 55 (70), found 324.2299, $C_{19}H_{32}O_4$, requires 324.2301.

Method 2[79]. A solution of anhydrous dimethyl sulfoxide (0·22 ml, 3·1 mmol) in dichloromethane (2 ml) was added slowly to a stirred solution of oxalyl chloride (1·6mmol) in dichloromethane (4 ml) at -50°C under an atmosphere of nitrogen. The mixture was stirred for 2 minutes then to it was slowly added a solution of 1-(4-butanol)-1-(tetrahydropyranyloxy)cyclodecan-6-ol (60) (140

mg, 0·43 mmol) in dichloromethane (1ml) with the concurrent formation of a white precipitate. The reaction was stirred for 15 minutes and then triethylamine (1 ml, 7·03 mmol) was added slowly. The reaction was stirred at -50°C for 5 minutes then warmed to room temperature and stirred for a further 30 minutes.

The reaction was diluted with dichloromethane (5 ml) and poured into water (5 ml). The mixture was extracted into dichloromethane (2 x 5 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate (5 ml) then dried and the solvents removed *in vacuo* to give the crude product as a yellow orange oil with white needle-like crystals. The major component of the crude product was isolated as above to give 6-(4-butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45) (100 mg, 0·31 mmol) in 72% yield with spectral properties identical to the authentic material.

Part 3. Preparation of 6-(4-butanal)-5-*E*-cyclodecen-1-one (33) and 6-(4-oxobutylidene)cyclodecan-1-one (35).

3-Butenyltriphenylphosphonium Bromide

The phosphonium salt was prepared according to the procedure of Gream[104] except that benzene was substituted for nitromethane as solvent. 3-Butenyltriphenylphosphonium bromide was isolated as a white crystalline solid in 46% yield, m.p. 223°-225°C (Lit.[104] m.p. 224°-225°C).

Attempted Reactions of 6-(t-butyldimethylsilyloxy) cyclodecan-1-one (55) with 3-Butenyltriphenyl phosphorane (64)

Sodium methylsulphinylmethide was prepared according to the procedure of Corey *et al.*[80] by heating a suspension of oil free sodium hydride (3·1 mmol) in anhydrous dimethylsulphoxide (1·5 ml) for 40 minutes. A portion of the base (0·15 ml, 0·31 mmol) was transferred to a dry flask and cooled to 0°C under an atmosphere of nitrogen. A solution of 3-butenyltriphenylphosphonium bromide (0·126 g, 0·33 mmol) as a solution in dimethylsulphoxide (0·45 ml) was added slowly to the base and as the reaction warmed to room temperature the reagents mixed and the reaction turned a deep orange colour. A solution of 6-(t-butyldimethylsilyloxy)cyclodecan-1-one (55) (50 mg, 0·18 mmol) in

dimethylsulphoxide (0·05 ml) was added slowly to the mixture after it had stirred at room temperature for 15 minutes.

The reaction was allowed to stir at room temperature for 12 hours, then it was heated at 60°C for 2 hours. The mixture was cooled and diluted with hexanes (5 ml). The organic phase was washed with water, and the aqueous phase further extracted with hexanes (3 x 4 ml). The combined organic fractions were dried and the solvents removed *in vacuo* . The crude product was analysed by TLC (5% ether/95% hexanes) which revealed considerable baseline material as well as two mobile components Rf 0·69 and 0·21. These components were separated using flash chromatography (1% ether/99% hexanes) to give in order of elution; a small amount of what was tentatively assigned as 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65) (2 mg, 6 μmol) in 3% yield as a clear oil; and then 6-(t-butyldimethylsilyloxy)cyclodecan-1-one (55) (24 mg, 0·08 mmol) in 44% yield, identical to authentic material.

1-(3-Butenylidene)-6-(t-butyldimethylsilyloxy) cyclodecane (65). ^{1}H n.m.r. δ 5·83, ddt, j 18, 10, 8 Hz, 1H, **CH**=CH_2; 5·19, t, j 8 Hz, 1H, **CH**=C; 5·03, dd, j 17·8, 1·9 Hz, 1H, **trans** and 4·96, dd, j 10, 1·9 Hz, 1H, **cis** CH=**CH_2**; 3·78, mult., 1H, **CH**OSi; 2·83, t, j 8 Hz, 2H, =CH-**CH_2**-CH=; 2·16, t, j 7 Hz, 4H, (**CH_2**)C=CH; 1·2 to 1·72, mult., 12H, **CH_2**; 0·88, s, 9H, (**CH_3**)$_3$CSi; 0·04, s, 6H, (**CH_3**)$_2$Si.

Method 2. A stirred solution of 3-butenyltriphenyl phosphonium bromide (0·22 g, 0·58 mmol) in anhydrous THF (1 ml) was cooled to -70°C under an atmosphere of nitrogen and to it was added a solution of n-butyllithium (0·95 M, 0·65 ml, 0·61 mmol).

The reaction was allowed to warm to -30°C and stirred for 1 hour during which time the reaction turned a dark orange colour. The reaction was cooled again to -70°C and to it was added a solution of 6-(t-butyldimethylsilyloxy)cyclodecan-1-one (55) (0·19 g, 0·66 mmol) in THF (1 ml).

The reaction was allowed to warm to room temperature overnight. The mixture was then diluted with ether (3 ml) then washed with water (3 x 5 ml). The aqueous phases were extracted with ether (5 ml) then the combined organic phases were dried and the solvents removed *in vacuo.* The crude product was a single component by TLC (as above) with an Rf 0·21 that corresponded to the TBDMS-cyclodecanone (55). The spectral data confirmed that the crude product was simply recovered starting materials.

1-(3-Butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) and 1-(3-Butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65).

Method 1[105]: A solution of the 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)cyclodecan-1-ol (44) (77 mg, 0·23 mmol) in dichloromethane (2 ml) and triethylamine (0·22 ml, 1·6 mmol) was slowly added.to an anhydrous solution of thionyl chloride (83 µl, 1·1 mmol) in dichloromethane (0·4 ml), cooled to -5°C under an atmosphere of nitrogen.

The reaction was analysed by T.L.C. (15% ethyl acetate / 85% hexane) after 3 minutes. All of the tertiary alcohol (44) had been consumed; new components were present at Rf 0·67 and baseline.

The reaction mixture was diluted with dichloromethane (5 ml) and added to water (5 ml). The organic layer was separated and

washed with saturated sodium bicarbonate solution (3 ml), then dried and the solvent was removed *in vacuo*.

The crude residue was separated by flash chromatography (15% ethyl acetate /85% hexane). The non-polar component,1-(3-butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) and 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65) (35 mg, 0·11 mol) were isolated in 48% yield as a clear oil. On a larger scale the yield of the TBDMS-dienes (65,66) decreased to 32% from TBDMS-butenylcycodecanol (44) (2·0g, 5·9 mmol).

The remaining product mixture eluted from the column as an intractable mixture.

1-(3-Butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) and 1-(3-Butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65) (Found: C, 74.39; H, 11.82. $C_{20}H_{38}OSi$ requires C, 74.46; H, 11.87 %). ν_{max} 3060, m; 1640, s; 1250, m; 1245, s; 1075, m; 1070, m; 1040, s; 910, s; 835, s; 770 cm^{-1}, s. ^1H n.m.r. δ 5·83, ddt, J 17·5, 10, 1·9Hz, 1H, **CH** = CH_2; 5·17, t, J 8·4 Hz, 1H, **CH** = C; 5·03, dd, J 17·5, 1·9Hz, 1H, **trans** and 4·94, dd, J 10, 1·9Hz, 1H, **cis, CH_2** = CH; 2·83, t, J 8 Hz, 0·25H, =CH**CH_2**CH=; 3·8, mult., 1H, **CH**OSi; 2·0 to 2·3, mult., 8H, **CH_2 allylic**; 1·2 to 1·8 mult., 10H, **CH_2**; 0·88, s, 9H, **$(CH_3)_3$**CSi; 0·04, s, 6H, **$(CH_3)_2$**Si. ^{13}C n.m.r. δ 138·91, 137·62, 137·29, 125·71, 122·71, 114·24 br, 71·90, 71·56, 35·01, 33·83, 33·67, 32·53, 32·31, 32·21, 31·19, 29·7 br, 26·18, 26·01, 25·92, 25·42, 25·11, 24·36, 23·02 , 22·07, 20·21, 19·28, 18·18, -4·6, -4·7. Mass spectrum *M/z* = 321 (0·8%, $(M-H)^+$), 265 (14, $(M-$ t-butyl$)^+$), 247 (12), 189 (19), 149 (19), 135 (26), 129 (26), 95 (18), 81 (19), 76 (19), 75 (100), 73 (46), 67 (23), found 265.1969, $C_{16}H_{29}OSi$ $(M-C_4H_9)$, requires 265.1988.

Method 2[105]: A stirred solution of the tertiary alcohol (44) (5.22 g, 15·3 mmol) in pyridine was cooled to -10°C under an atmosphere of nitrogen. A solution of thionyl chloride (1·4 ml, 19·1 mmol) in pyridine (7 ml) was slowly added to the cooled solution.

The reaction was monitored by T.L.C. (15% ethyl acetate /85% hexane), all of the tertiary alcohol (44) had been consumed 15 minutes after the addition of thionyl chloride was completed.

The reaction was diluted with ether (100 ml) then poured into saturated sodium bicarbonate solution (65 ml). The aqueous

phase was then extracted with ether (3 x 100 ml). The combined organic phases were washed with brine (50 ml) then dried and the solvent was removed *in vacuo* .

The crude residue was purified by flash chromatography (100% hexane). The product, 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) and 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65); (4·63 g, 14·35 mmol) was isolated in 94% yield with spectral properties identical to authentic material.

Method 3[81]: A solution of the tertiary alcohol (44) (4·5 g, 13·2 mmol) in pyridine (7 ml) and toluene (39 ml) was cooled to -10°C with stirring under an atmosphere of nitrogen. Thionyl chloride (1·25 ml, 17 mmol) in toluene (0·8 ml) was added slowly to the cooled solution during which time the temperature increased to 0°C. The reaction was cooled back down to -10°C, and after 15 minutes TLC (15% ethyl acetate /85% hexanes) analysis showed that the tertiary alcohol (44) had been consumed.

The reaction was quenched by the addition of ice (20 g) then warmed to room temperature and diluted with ether (20 ml). The aqueous phase was extracted with ether (3 x 20 ml), the combined organic phases were washed with brine and then dried and the solvent was removed *in vacuo* .

The product, 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) and 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65). (3·82 g, 11·84 mmol) was isolated in 90% yield by flash chromatography (100% hexanes) with spectral properties identical to authentic material.

1-(4-Butanol)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (67) and 1-(4-Hydroxybutylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (68)

Method 1[53]: Disiamyl borane (6·6 mmol) was prepared under anhydrous conditions and a nitrogen atmosphere by the dropwise addition of 2-methyl-2-butene (1·4 ml, 13·2 mmol) to stirred diborane:THF complex (0·94 M, 7 ml, 6·6 mmol) at 0°C. The solution was used after stirring for a further hour.

A solution of 1-(3-butenyl)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (66) and 1-(3-butenylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (65).(1·56 g, 4·8 mmol) in THF (3 ml) was added rapidly to the stirred disiamyl borane solution at 0°C under an atmosphere of nitrogen. The reaction was analysed by TLC (1% ethyl acetate /99% hexane) after 1 and 3 hours, after which time all the dienes (65),(66), Rf 0·53, had been consumed.

The reaction was quenched by the slow addition of water and then worked up with aqueous sodium hydroxide (3M, 2·18 ml) and then aqueous hydrogen peroxide (30% w/w, 2·18 ml). A cool water bath was used to maintain the temperature below 40°C.

The product was comprised of 1-(4-butanol)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (67) and 1-(4-hydroxybutylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (68) (1·66 g, 4·8 mmol) which were isolated as a mixture by flash chromatography (10% ethyl acetate /90% hexane: Rf 0·4) as a clear oil in 95% yield. ν_{max} 3300, br s; 1645, w; 1255, s; 1080, s; 1050, s; 840, s; 775 cm^{-1}, s. ^1H n.m.r. δ 5·15 , t, J 9·0 Hz, 1H, **CH**=C; 3·78, mult., 1H, **CH**-OSi; 3·62, t, J 6·0 Hz, 2H, **CH_2**-OH; 1·97 and

2·14, mult., 6H, **CH_2 allylic**; 1·19 to 1·78, mult., 14H, **CH_2**; 0·88, s and 0·87, weak s, 9H, $(\mathbf{CH_3})_3CSi$; 0·04, s and 0·03, weak s, 6H, $(\mathbf{CH_3})_2Si$. ^{13}C n.m.r. δ 138·14, 138·39, 125·59, 124·90, 71·86, 71·53, 62·83, 62·68, 35·29, 33·78, 33·70, 33·21, 32·79, 32·58, 31·16, 29·66 br, 26·10, 25·87, 25·78, 25·34, 25·11, 24·31, 24·04, 22·98, 22·40, 20·22, 19·24, 18·12, -4·65, -4·73. Mass spectrum *M/z* = 340 (1%, M^+), 339 (3), 283 (3), 191 (3), 149 (10), 135 (33), 121 (26), 109 (49), 95 (56), 93 (45), 81 (50), 79 (30), 75 (100), 73 (50), 69 (47), 67 (70), 55 (60), found 340.2812, $C_{20}H_{40}O_2Si$, requires 340.2798.

Method 2[53]: For multi-gram preparations: disiamyl borane (18·3 mmol) prepared in the usual manner was taken up in a syringe and added slowly under an atmosphere of nitrogen to a stirred solution of the dienes (65 and 66) (4·32 g, 13·4 mmol) in THF (15 ml). The temperature was maintained at -5°C to -10°C during the addition and then after addition was complete for a total of 4 hours.

The reaction was quenched with water and worked up in the usual manner with alkaline hydroperoxide. The products, 1-(4-butanol)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (67) and 1-(4-hydroxybutylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (68) (4.45 g, 13 mmol) were isolated as a clear oil in 97% yield with identical spectral properties to an authentic sample.

1-(4-Butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-Hydroxybutylidene)cyclodecan-6-ol (70)

A solution of tetrabutyl ammonium fluoride[67,69] in THF (1.0 M, Aldrich, 10 ml, 10 mmol) was added to 1-(4-butanol)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (67) and 1-(4-hydroxybutylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (68) (1·26 g, 3·67 mmol) and the reaction was left to stir under an atmosphere of nitrogen.

The reaction was monitored by TLC (50% ethyl acetate /50% hexanes) which revealed that the silyl ethers (67 and 68) (Rf 0·49) had been almost totally consumed after a period of 5 days.

The reaction mixture was poured into brine (30 ml) then extracted with ethyl acetate (8 x 25 ml) until no product was evident in the organic extract by TLC analysis. The combined organic fractions were washed with brine (15 ml) then dried and the solvent was removed *in vacuo* .

The crude mixture was analysed by TLC (50% ethyl acetate /50% hexane) which revealed two components of Rf 0·11 and 0·49. These were separated by flash chromatography (as for TLC) to give, in order of elution, the silyl ethers (67 and 68) (156 mg, 0·37 mmol) in 10% recovery and 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) as an isomeric mixture (731 mg, 3·23 mmol) as a clear oil in 81% yield.

The isomeric alkenes;1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) could be separated by repeated flash chromatography (45% ethyl acetate

/55% hexane: Rf 0·09 and 0·12) with the major component, 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) eluting first.

1-(4-Butanol)-1-*E*-cyclodecen-6-ol (69). ν_{max} 3345, br s; 2935, s; 2825, s; 1655, w; 1475, m; 1450, m; 1060, s; 1030, m; 1003 cm^{-1} , m. ^1H n.m.r. δ 5·13 , t, J 8·2 Hz, 1H, **CH**=C; 3·84, mult., 1H, **CH**OH; 3·63, t, J 6·2 Hz, 2H, **CH_2**OH; 2·26, mult., 2H, **CH_2 allylic**; 2·07, mult., 2H, **CH_2 allylic**; 1·97, mult., 2H, **CH_2 allylic**; 1.24 to 1·79, mult., 14 H, **CH_2**. ^{13}C n.m.r. δ 138·40, 125·26, 71·24, 62·70, 35·21, 33·40, 32·49, 29·51, 25·77, 24·21, 24·01, 23·10, 18·97. Mass spectrum *M/z* = 226 (0·5%, M^+), 208 (1), 170 (45), 154 (33), 153 (59), 136 (34), 135 (67), 111 (62), 109 (28), 107 (35), 95 (59), 93 (78), 91 (49), 85 (44), 81 (100), 79 (92), 67 (92), 57 (61), 55 (90),found 226.1941, $C_{14}H_{26}O_2$, requires 226.1933.

1-(4-Hydroxybutylidene)cyclodecan-6-ol (70). ν_{max} 3345, br s; 2935, s; 2825, s; 1655, w; 1475, m; 1450, m; 1060, s; 1030, m; 1003 cm^{-1}, m. ^1H n.m.r. δ 5·17, t, J 7·2 Hz, 1H , **CH**=C; 3·84, mult., 1H, **CH**OH; 3·67, t, J 6·9 Hz, 2H, **CH_2**OH; 2·0 to 2·3, mult., 6H, **CH_2 allylic**; 1·38 to 1·83, mult., 14H, **CH_2** ; 1·26, s, 2H, **OH**. ^{13}C n.m.r. δ 137·82 , 125·01, 70·59, 62·14, 33·59, 33·07, 32·68, 32·57, 31·06, 24·94, 24·79, 24·21, 22·59, 19·87. Mass spectrum *M/z* = 168 $(M-C_3H_6O)^+$ (61%), 154 (55), 153 (100), 151 (62), 136 (65), 135 (83), 121 (30), 111 (46), 107 (31), 95 (43), 93 (45), 91 (33), 81 (54), 79 (50), 71 (45), 67 (60), 57 (37), 55 (55), found 168.1507, $C_{11}H_{20}O$ $(M-C_3H_6O)$, requires 168.1515.

Method 2[69]: The 1-(4-butanol)-6-(t-butyldimethylsilyloxy)-1-*E*-cyclodecene (67) and 1-(4-hydroxybutylidene)-6-(t-butyldimethylsilyloxy)cyclodecane (68) (1·85 g, 5·73 mmol) were

dissolved in THF (14 ml) and added to a solution of water (14 ml) and acetic acid (42 ml). The reaction was stirred under nitrogen for 36 hours after which time TLC (50% ethyl acetate/50% hexane) showed that all the starting materials (67 and 68) Rf 0·5, had been consumed.

The reaction mixture was poured into dichloromethane (250 ml) and water (75 ml). The organic layer was washed with water (2 x 75 ml), saturated sodium bicarbonate solution (50 ml) and then dried and the solvent was removed *in vacuo* .

The crude residue was analysed by TLC (50% ethyl acetate/50% hexane) which revealed a major component; Rf 0·2. This component was isolated by flash chromatography (as for TLC) as an isomeric mixture of 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) (1.12 g, 4.95 mmol) as a clear oil in 86% yield. The isomers were resolved as described in Method 1, and were identical to the materials therein described.

6-(4-Butanal)-5-*E*-cyclodecen-1-one (33)

Method 1. Pyridinium chlorochromate[72] (0·827 g, 3·84 mmol), sodium acetate (fused, 84 mg, 1·02 mmol) and powdered 4Å molecular sieves[73] (1·013 g, Aldrich) were added to a dry flask under an atmosphere of nitrogen. Anhydrous dichloromethane (13 ml) was added and the suspension stirred for 90 minutes. A solution of 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) (172 mg, 0·76 mmol) in dichloromethane (5 ml) was added slowly to the suspension which immediately turned black.

The reaction was monitored by TLC (30% ethyl acetate / 70% hexane) which revealed that the butanolcyclodecenol (69), Rf 0·13, had disappeared completely after 10 minutes. The reaction was diluted with anhydrous ether (15 ml) and stirred for 15 minutes before it was filtered through a pad of florisil/HF 254 (1:1, 3 cm x 4 cm). The residue was rinsed with ether (240 ml). and the solvents were removed from the combined filtrates *in vacuo* to leave a viscous brown oil smelling faintly of pyridine.

The crude product was analysed by TLC (as above) which showed a major component Rf 0·39 contaminated with minor products and baseline material. The component was isolated by flash chromatography (30% ethyl acetate /70% hexanes) to give 6-(4-butanal)-5-*E*-cyclodecen-1-one (33) (121 mg, 0·54 mmol) in 70% yield as a clear oil. ν_{max} 2928 , s; 2856, s; 2716, m; 1724, s; 1704, s; 1464, m; 1410, m; 1372, m; 1244, m; 1200, m; 1126, m; 1000, m; 974 cm^{-1}, m. ^1H n.m.r. δ 9·72, t, J 1·95 Hz, 1H, **CHO**; 5·13, t, j 8·5 Hz, 1H, C=**CH**; 2·13, td, J 7·3, 1·95 Hz overlaps 2·4, mult.; 2·29, mult., 6H; 2·0, mult., 6H; 1·67, mult., 8H, $\mathbf{CH_2}$. ^{13}C n.m.r. δ 213·46, **C(O)**; 201·61, **C(O)H**; 138·46, **C**=CH; 124·95, C=**CH**; 45·56, 42·71, 34·11, 33·71, 25·44, 24·60, 23·24, 22·39, 20·59, 19·35. Mass spectrum *M/z* = 222 (2%, M^+), 204 (15), 186 (6), 161 (11), 160 (12), 151 (36), 148 (56), 135 (19), 133 (40), 131 (26), 120 (36), 111 (19), 105 (41), 95 (41), 93 (68), 91 (66), 84 (90), 81 (62), 79 (41), 67 (100), 55 (81), 53 (45), found 222.1613, $C_{14}H_{22}O_2$, requires 222.1620.

Method 2[79]. Oxalyl chloride (freshly distilled, 0·68 ml, 7·8 mmol) was added to dichloromethane (19 ml) and the stirred solution was cooled to - 60°C under an atmosphere of nitrogen.

Dimethylsulphoxide (1·11 ml, 15·6 mmol) dissolved in dichloromethane (3·5 ml) was added to the oxalyl chloride solution slowly, maintaining the temperature of the reaction at - 60°C.

The reaction was stirred for 2 minutes after addition was complete, then a solution of 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) (342 mg, 1·51 mmol) in dichloromethane/DMSO (1:1, 3 ml) was added dropwise. A white precipitate formed after 10 minutes. The reaction was monitored by TLC (as for Method 1), no butanolcyclodecenol (69) remained after 1 hour. Triethylamine (5·5 ml, 39 mmol) was then added to the reaction mixture which was allowed to warm to room temperature after 5 minutes. The white precipitate disappeared and a new white precipitate formed as the reaction warmed to room temperature.

After stirring for 15 minutes the mixture was poured into water (30 ml) then extracted with dichloromethane (3 x 50 ml). The combined organic phases were washed with brine (20 ml) and dried and the solvent was removed *in vacuo* over a water bath <40°C.

The product of the reaction, 6-(4-butanal)-5-*E*-cyclodecen-1-one (33) (274 mg, 1·23 mmol) was isolated pure in 82% yield by flash chromatography (30% ethyl acetate/70% hexanes) with spectral properties identical to authentic material.

6-(4-Oxobutylidene)cyclodecan-1-one (35)

A solution of 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) (150 mg, 0·66 mmol) in dichloromethane/DMSO (1:1, 1·5 ml) was added to the activated dimethyl sulphoxide reagent prepared from

oxalyl chloride (0·29 ml, 3·3 mmol) in dichloromethane (9 ml) and DMSO (0·5 ml, 7·0 mmol) at -60°C in the usual manner.

The reaction was monitored by TLC (30% ethyl acetate/70% hexanes) which revealed the diol (70) of Rf 0·07 had been consumed after 1 hour. Triethylamine (2·3 ml, 16·5 mmol) was added and the reaction worked up in the usual manner.

The crude residue was analysed by TLC (20% ethyl acetate/80% hexanes) which revealed a mixture containing a number of products. The component of Rf 0·12 was separated by flash chromatography (20% ethyl acetate/80% hexanes) to give 6-(4-oxobutylidene)cyclodecan-1-one (35) (77 mg, 0·35 mmol) as a clear oil in 53% yield. ν_{max} (CCl_4) 2928 ; 2884, s; 2716, m; 1730, s; 1706, s; 1456, m; 1416, m; 1374, m; 1344, m; 1278, m; 1198, m; 1110, s; 1048, s; 990 cm^{-1}, m. ^1H n.m.r. δ 9·78, t, j 1·5 Hz, 1H, **CHO**; 5·13, t, j 6·9 Hz, 1H, C=**CH**; 2·51, mult.; 2·44, mult.; 2·35, mult., 6H; 2·14, mult., 2H; 1·8 to 1·98, mult., 4H; 1·48 to 1·8, mult., **CH_2**. ^{13}C n.m.r. δ 214·36, **C(O)**; 202·13, **C(O)H**; 139·63, **C**=CH; 121·71, C=**CH**; 43·81, 43·61, 37·02, 30·81, 30·54, 24·53, 23·30, 23·07, 22·14, 20·52. Mass spectrum *M/z* = 222 $(M)^+$ (1%), 204 (16), 186 (5), 161 (10), 160 (10), 150 (27), 148 (22), 135 (18), 133 (21), 119 (18), 108 (43),105 (22), 95 (40), 93 (48), 91 (61), 81 (73), 79 (92), 77 (53), 67 (90), 55 (100), 53 (90), found 222.1615, $C_{14}H_{22}O_2$, requires 222.1620.

Part 4. Preparation of 6-(4-Butanal)cyclodecan-1-one (32).

6-(4-Butanol)cyclodecan-1-ol (71)

Platinum oxide (245 mg) was added to a solution of 1-(4-butanol)-1-*E*-cyclodecen-6-ol (69) and 1-(4-hydroxybutylidene)cyclodecan-6-ol (70) (1.23 g, 5.4 mmol) in ethyl acetate (10 ml). The stirred suspension was evacuated and flushed three times with hydrogen then left to stir under a hydrogen atmosphere for 3 days. The catalyst was removed by filtration through a short plug of celite; this solid residue was well washed with ethyl acetate and the solvents were removed from the combined organic filtrates *in vacuo* .

The crude product was a mixture of two components by TLC (30% ethyl acetate/70% hexanes; Rf 0·1 and 0·42) and these were separated by flash chromatography (as for TLC) to give, in order of elution, 6-(4-butylacetate)cyclodecan-1-ol (72) (0·242 g, 0·89 mmol) a clear oil in 16% yield as a diastereomeric mixture; and 1-(4-butanol)-cyclodecan-6-ol (71) (0·893 g, 3·9 mmol) a clear oil in 72% yield. The spectral data of 6-(4-butanol)cyclodecan-1-ol (71) was identical to that reported in the literature[19].

6-(4-Butylacetate)cyclodecan-1-ol. ν_{max} 3410, s br; 2925, s; 2860, s; 1738, s; 1725, sh; 1474, m; 1454, m; 1368, s; 1242, s; 1038, s; 788 cm^{-1}, s. ^1H n.m.r. δ 4·07, t, J 6·5 Hz, 2H, C(O)O**CH$_2$**; 3·95, mult., 1H, **CH**OH; 2·88, br s, 1H, **OH**; 2·05, s, 3H, **CH$_3$**C(O); 1·15 to 1·87, mult., 23H, **CH$_2$**.

6-(4-Butanol)cyclodecan-1-ol (71) by Lithium Aluminium Hydride Reduction of 6-(4-Butylacetate)cyclodecan-1-ol (72)

An anhydrous solution of 6-(4-butylacetate)cyclodecan-1-ol (72) (49 mg, 0·18 mmol) in ether (2 ml) was added to a stirred suspension of lithium aluminium hydride (14 mg, 0·37 mmol) in ether (0·5 ml) under a nitrogen atmosphere. The reaction was stirred at room temperature for 1 hour then sodium sulphate decahydrate was added slowly till effervescence ceased. The solids were removed by filtration and the residue was washed with ethyl acetate. The solvent was removed from the filtrate *in vacuo* and 6-(4-butanol)cyclodecan-1-ol (71) (37 mg, 0·16 mmol), with spectral properties identical to those reported in the literature[19], was isolated in 90% yield after separation from minor impurities by flash chromatography (50% ethyl acetate/50% hexanes).

6-(4-Butanal)cyclodecan-1-one (32)

An anhydrous suspension of pyridinium chlorochromate (0·56 g, 2·6 mmol), powdered 4Å molecular sieves (0·65 g) and fused sodium acetate (57 mg, 0·7 mmol) was stirred under a nitrogen atmosphere for 20 minutes. A solution of 6-(4-butanol)cyclodecan-1-ol (71) (0·132 g, 0·58 mmol) in dichloromethane (3 ml) was added slowly to the suspension which was then stirred for 15 minutes. Anhydrous ether was then added to the suspension, and after stirring for a further 20 minutes the mixture was filtered through a pad of Florisil. The residues were washed well with further

portions of ether. The solvents were removed from the combined filtrates *in vacuo* .

The product of the reaction, 6-(4-butanal)cyclodecan-1-one (32) (91 mg, 0·41 mmol) was isolated pure in 71% yield by flash chromatography (30% ethyl acetate/70% hexanes) with spectral properties identical to authentic material[19].

Chapter 3 Experimental.

Part 1. Attempted Cyclisation of 6-(4-Butanal)-6-(tetrahydropyranyloxy)cyclodecan-1-one (45) and Model Systems.

Preparation of the Zinc-Copper couple

The zinc-copper couple was prepared according to the procedure of McMurry and Kees[28] with the following modifications. The zinc was first washed with hexanes, ether, water and methanol and then dried under a vacuum. A solution of hydrated copper sulphate in deoxygenated water (1 M) was substituted for the anhydrous copper sulphate of the literature procedure. The zinc-copper couple was stored in a Schlenck tube sealed under argon to facilitate the exclusion of oxygen and moisture during solids transfers.

1,4–Dibenzoylbutane (73)

1,4–Dibenzoylbutane (73) was prepared according to the method of Fuson and Walker[107].

Recrystallisation of the crude product, a yellow white solid, twice from ethanol gave 1,4–dibenzoylbutane (73) in 70% yield, m.p. 107° -107·5°C. (Lit.[107] m.p.106° - 107°C).

1,2– Diphenylcyclohexene (74)

The reaction was carried out according to the literature procedure of McMurry and Kees[28] except that the dimethoxyethane was dried over the sodium/benzophenone ketyl. The crude product was purified by flash chromatography (5% ethyl acetate/95% hexanes) to give 1,2-diphenylcyclohexene (74) as white crystals in 86% yield, m.p. 47°-48°C (Lit.[108] 48°-48·5°C).

Cyclohexylidenecyclohexane (76)

Cyclohexylidenecyclohexane (76) was prepared according to the procedures described by McMurry *et al.*[28]..

Method 1. The zero valent titanium suspension was prepared from $TiCl_3$ (1·54 g, 10 mmol) and zinc-copper couple (1·5 g, 23 mmol) in anhydrous THF (50 ml; from sodium/benzophenone ketyl) under an argon atmosphere. A solution of cyclohexanone (100 mg, 1·02 mmol) in THF (5 ml) was added to the reaction and the suspension was stirred overnight. The reaction was worked up according to the literature procedure and cyclohexylidenecyclohexane (76) (57 mg, 0·35 mmol) was isolated as a white crystalline solid m.p. 53°-54°C (lit.[108] m.p. 53·5°-54·5°C) in 69% yield.

Method 2. The zero valent titanium suspension was prepared from $TiCl_3$ (0·65 g, 4·16 mmol) and potassium metal (0·55 g, 12·5 mmol) in anhydrous THF (30 ml) under an argon atmosphere. A solution of cyclohexanone (100 mg, 1·02 mmol) in THF (5 ml) was added to the reaction and the suspension was stirred overnight. The reaction was worked up according to the literature procedure and

cyclohexylidenecyclohexane (76) (24 mg, 0·15 mmol) was isolated as a white crystalline solid m.p. 53°-54°C (lit.[108] m.p. 53·5°-54·5°C) in 29% yield.

Method 3. The procedure was as for that described in Method 1 except that anhydrous dimethoxyethane (from potassium/benzophenone ketyl) was used as solvent. The product, cyclohexylidenecyclohexane (76) was isolated as a white crystalline solid, m.p. 53°-54°C (lit [108] m.p. 53·5°-54·5°C) in 80% yield.

In-6*H*- Bicyclo[4.4.4]tetradec-1-ene (5)

Method 1. The in-6*H*- bicyclo[4.4.4]tetradec-1-ene (5) was prepared essentially according to the procedure described by McMurry and Hodge[9], with the modifications described below, to give a white crystalline solid in 5% yield with spectral properties that were identical to those reported in the literature[19]. ^{1}H nmr δ 5·42, mult., 2H. **CH**=C; 3·35, mult., 1H; 2·54, mult., 1H; 2·34, mult., 1H; 0·85 to 2·2, mult., 20H. ^{13}C nmr δ 143·04, **C**=CH; 131·7, C=**CH**; 36·4, 36·06, 35·16, 33·81 br, 32·31, 29·69, 28·94, 27·52, 26·48, 25·85, 23·17. Mass spectrum *m/z* 192 M^{+}.

The following alterations were made to the procedure. The dimethoxyethane was dried over potassium/benzophenone ketyl. The solvent was removed from the filtrate concentrate *in vacuo* with a water bath temperature of 0°C, and the residue was distilled at 120°C/0·2 mmHg prior to the final isolation of the in-alkene (5) by preparative gas chromatography (Column D at 200°C) using argon as the carrier gas and condensing the column effluent with liquid nitrogen.

Preparation of Titanium Trichloride:(Dimethoxyethane)$_{1.5}$ Complex

The $TiCl_3$:$(DME)_{1.5}$ complex was prepared according to details kindly provided by Professor J.E. McMurry[86]. The light blue fluffy crystalline solid was repeatedly obtained in a yield of 73% and stored in a Schlenck tube under argon to enable the exclusion of oxygen and moisture during solids transfer.

Note; the blue precipitate was washed with anhydrous, deoxygenated pentane until the filtrate changed from cloudy-white to clear.

In-6*H*- Bicyclo[4.4.4]tetradec-1-ene (5) using Zero Valent Titanium Prepared from $TiCl_3$:$(DME)_{1.5}$.

A well stirred suspension of $TiCl_3$·$(DME)_{1.5}$ (3·87 g, 13·36 mmol) and zinc-copper couple (2·23 g, 34·1 mmol) in dimethoxyethane (110 ml; twice distilled from potassium) was refluxed under an atmosphere of argon for 4 hours then cooled to 80°C. A solution of 6-(4-butanal)cyclodecan-1-one (32) (87 mg, 0·39 mmol) in dimethoxyethane (12·5 ml) was added to the suspension over a 20 hour period by way of a syringe pump. When the addition was complete the reaction mixture was stirred at 80°C for 18 hours then cooled to room temperature. The suspension was diluted with dry, deoxygenated hexane (120 ml) and worked up in the usual manner. The components of the crude distillate were separated by preparative gas chromatography (as for Method 1) to give in-bicyclo[4.4.4]tetradec-1-ene (5) (12 mg, 62 μmol) in 18%

yield, with spectral properties identical to those reported in the literature[9,19].

Reaction of 6-(tetrahydropyranyloxy)-6-(4-butanal)cyclodecan-1-one (45) with Zero Valent Titanium derived from Titanium Trichloride and Zinc-Copper Couple

Zinc-copper couple (2·4 g, 36·8 mmol) and titanium trichloride (Fluka, 2·13 g, 13·8 mmol) were loaded into seperate Schlenk tubes in a dry box purged with argon. The solids were added to dimethoxyethane (50 ml; dried over sodium/benzophenone ketyl) under anhydrous conditions. The suspenion was refluxed for 4 hours, at which time the reaction had turned a dark yellow-brown-black colour.

A degassed solution of the 6-(tetrahydropyranyloxy)-6-(4-butanal)cyclodecan-1-one (45) (152 mg, 0·46 mmol) in dimethoxyethane (60 ml) was taken up in perfusor syringes and added to the refluxing titanium suspension over 50 hours. When addition was complete, the reaction was refluxed for 2 hours then cooled to room temperature, and diluted with anhydrous, deoxygenated hexanes (40 ml).

The reaction mixture was passed through a pad of Florisil under a positive nitrogen pressure and the residues were washed with hexanes (80 ml) then hexanes/ether (1:1, 200 ml).

The solvent was removed from the combined filtrates by careful distillation under an atmosphere of nitrogen through 15cm Vigreaux column packed with glass helices, to give a concentrate (5ml). The final traces of solvent were removed *in vacuo* using an ice/water bath at aspirator pressure then a brief exposure to a

vacuum of 0·05 mmHg. This gave a viscous, orange-brown, cloudy oil (120 mg).

TLC analysis of the crude product over a range of different polarities of developing solvents revealed a mixture of considerable complexity, with no particular component predominating.

G.C./M.S. (A.W.R.I. Column E) analysis of the crude concentrate showed a complex mixture of volatile components with a wide range of apparent molecular weights.

This reaction was repeated three times under similar conditions with essentially the same intractable mixture as product in each case.

Reaction of 6-(tetrahydropyranyloxy)-6-(4-butanal)cyclodecan-1-one (45) with Zero Valent Titanium derived from Titanium Trichloride:(Dimethoxyethane)$_{1.5}$ Complex and Zinc-Copper Couple

Dimethoxyethane (135 ml, twice distilled from potassium) was added to a well stirred mixture of the $TiCl_3$:(DME)$_{1.5}$ complex (5·22 g, 18·03 mmol) and zinc-copper couple (3·32 g, 50·76 mmol) then the suspension was set at reflux for 4 hours under an atmosphere of argon. The reaction was cooled to 80°C and a solution of 6-(tetrahydropyranyloxy)-6-(4-butanal)cyclodecan-1-one (45) (120 mg, 0·37 mmol) in dimethoxyethane (15 ml) was perfused into the suspension over a period of 20 hours by means of a motor driven syringe pump.

When the addition was completed the reaction was stirred for a further 20 hours at 80°C then cooled to room temperature and diluted with anhydrous, deoxygenated hexanes (150 ml) which caused the solids of the suspension to clump. The reaction mixture was filtered through a pad of celite-capped Florisil under a positive argon pressure. The residues were washed with ether/hexanes (1:1, 160 ml) then the combined filtrates were concentrated at atmospheric pressure to a volume of 2ml. The final traces of solvent were removed *in vacuo* using an ice/water bath at aspirator pressure then a brief exposure to a vacuum of 0·05 mmHg. This gave a pale brown clear oil (112 mg).

TLC analysis of the crude product (as before) revealed a mixture of considerable complexity, with no particular component predominating.

G.C./M.S. (A.W.R.I. Column E) analysis of the crude concentrate showed a complex mixture of volatile components with a wide range of apparent molecular weights.

Part 2. 1,4-Bis(1-cyclopentenyl)butane (82) from the Reaction of 6-(4-butanal)-5-*E*-cyclodecen-1-one (33) with Zero Valent Titanium

A well stirred suspension of $TiCl_3 \cdot (DME)_{1.5}$ (10·37 g, 35·8 mmol) and zinc-copper couple (6·42 g, 98·16 mmol) in dimethoxyethane (280 ml; twice distilled from potassium) was refluxed under an atmosphere of argon for 4 hours then cooled to 80°C. A solution of 6-(4-butanal)-5-*E*-cyclodecen-1-one (33) (200 mg, 0·9 mmol) in dimethoxyethane (26 ml) was added over a period of 20 hours by way of a syringe pump. When the addition was complete the reaction was stirred for a further 12 hours and then cooled to room temperature. The suspension was diluted with degassed, anhydrous pentane (200 ml) then the mixture was filtered through a pad of Florisil under a positive pressure of argon. The residues were washed with pentane (250 ml) then the combined filtrates were concentrated to a volume of 2 ml by distillation at atmospheric pressure. Final traces of solvent were removed *in vacuo* at aspirator pressure with a bath temperature of 0°C.

The crude residue was separated by flash chromatography (100% hexanes to 100% ethyl acetate) into a nonpolar component

(97 mg) and an intractable mixture of polar components (66 mg). The nonpolar component was analysed by G.C. (Column A at170°C/45 kPa) which revealed a mixture of volatile components (table 9).

Table 9.

Retention time (min.)	12·4	16	19·2	29·6
G.C./M.S. $(M)^+$ *m/z* (Flinders University)	178	192	190	206
% proportion of components eluted in < 30 min.	17%	26%	24%	33%

The addition of tetradecane as an internal standard to the crude reaction mixture indicated that the component *m/z* 190 (9·5 mg, 50 μmol) had been produced in 5·5% yield.

The components were separated by preparative gas chromatography (Column D at180°C) using liquid nitrogen cooled traps to collect the column effluent. 1,4-Bis(1-cyclopentenyl)butane (82) (6 mg, 31·5 μmol) was isolated as a clear oil in 3·5% yield. Also isolated was a double bond isomer of 2-butyl-1-bicyclo[5.3.0.]decene (77 or 78) (4·6 mg, 24μmol) in 2·5% yield.

1,4-Bis(1-cyclopentenyl)butane (82) λ_{max} 272 (ε 7). ^1H n.m.r. δ 5·29, m, 2H, C=**CH**; 2·26, m, and 2·19, m, 8H, **allylic CH_2**; 2·04, br s, 4H, **allylic CH_2**; 1·82, quintet, J 7·2 Hz, 4H, **CH_2**; 1·41, m, **CH_2**. ^{13}C n.m.r. δ 144·93 , s, **C**=CH; 123·07, d, $^1J_{C-H}$ 157·7 Hz, C=**CH**; 35·08, t; 32·42, t; 31·07, t; 27·70, t; 23·43, t. Mass spectrum

m/z = 190 ((15%, M^+), 161 (3), 148 (3), 147 (3), 135 (4), 133 (5), 121 (33), 108 (93), 93 (77), 79 (85), 69 (100), 67 (81), 55 (21), 53 (28), found 190.1717, $C_{14}H_{22}$,requires 190.1721.

2-Butyl-1-bicyclo[5.3.0.]decene (77 or 78) ^1H n.m.r. δ 2·29 , m, 4H, **allylic CH_2**; 2·08, m, 3H, **allylic CH, CH_2**: 1·2 to 1·75, m, 14H, **CH_2**; 0·87, t, J 6·9 Hz, 3H, **CH_3**. ^{13}C n.m.r. δ 141·10 , **C**=CH; 136·39, C=**CH**; 40·19, 39·54, 38·64, 31·71, 30·67, 30·29, 29·25, 27·58, 25·95, 22·98, 22·39, 14·12. Mass spectrum *m/z* = 192 (13%, M^+), 135 (100), 121 (5), 107 (10), 93 (28), 79 (26), 67 (27), 55 (11).

1,4-Bis(cyclopentyl)butane (83)

Platinum oxide (16 mg) was added to a solution of 1,4-bis(1-cyclopentenyl)butane (82) (6 mg, 32 μmol) in ether (4 ml) and the stirred suspension was evacuated and flushed three times with hydrogen. The suspension was allowed to stir for 12 hours under an atmosphere of hydrogen then the solids were removed by filtration through a plug of celite and the residues were washed with ether. The solvents were removed from the filtrate *in vacuo* to give 1,4-bis(cyclopentyl)butane (83) (6 mg, 30 μmol) in 94% yield. The crude product was analysed by G.C. (Column A at 170°C/50 kPa). The bis(cyclopentyl)butane (83) was 95% pure and co-eluted with the starting diene (82), Rf 16·4 minutes. The ^{13}C nmr data for bis(cyclopentyl)butane (83) prepared by a different procedure[90] is ^{13}C nmr δ 40·9, d; 37·0, t; 33·4, t; 29·8, t; 25·9, t.

1,4-Bis(cyclopentyl)butane (83) ^1H n.m.r. δ 1·71, m, 6H, **CH, CH_2**; 1·53, m, and 1·48, m, 8H, **CH_2**; 1·25, m, 8H, **CH_2**; 1·03, m, 4H,

CH_2. ^{13}C n.m.r. δ 40·20 , d, 2C; 36·31, t, 2C; 32·75, t, 4C; 29·08, t, 2C; 25·21, t, 4C. Mass spectrum *m/z* = 194 (11%, M^+), 166 (4), 137 (11), 135 (7), 125 (20), 109 (12), 96 (37), 95 (39), 83 (61), 82 (100), 81 (32), 69 (99), 68 (97), 67 (86), 55 (92), found 194.2022, $C_{14}H_{26}$, requires 194.2034.

1,4-bis(2-cyclopentanol)butanes (84) and (~~85~~ 84b)

An anhydrous solution of 1,4-bis(1-cyclopentenyl)butane (82) (2·3 mg, 12 μmol) in THF (0·3 ml) was added dropwise to a stirred solution of diborane:THF complex (0·9 M, 0·13 ml, 0·12 mmol) in THF (0·3 ml) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 2 hours then excess diborane was quenched by cautious addition of water. The reaction was immersed in an ice bath and aqueous sodium hydroxide (3 M, 50 μl) then aqueous hydrogen peroxide (30% w/w, 50 μl) were added slowly. The reaction was allowed to warm to room temperature and stirred for 1·5 hours. The reaction was diluted with brine (1 ml) and then extracted with ether (3 x 1 ml). The combined extracts were dried and the solvents were removed *in vacuo* . The crude product was analysed by TLC (30% ethyl acetate/70% hexanes) which revealed a single major component Rf 0·22 as well as some minor impurities. The component was isolated by flash chromatography (as for TLC) to give 1,4-bis(2-cyclopentanol)butanes (84) and (~~85~~ 84b) (2·2 mg, 10μmol) as a clear colourless oil in 81% yield. Analysis by G.C. (Column A at 250°C/45 kPa) indicated that the diols (84) and (~~85~~ 84b) eluted as a single component.

1,4-bis(2-cyclopentanol)butanes (84a) and (84b) ν_{max} ($CDCl_3$) 3612 , m; 3536, w, **OH**; 2928, s; 2856, s; 2244, m; 1452, m; 1380, m; 1262, m; 1092 cm^{-1}, m. ^1H n.m.r. δ 3·79, dt, J 5·9, 5·5 Hz, 2H, **CH**OH; 1·87, m, 4H; 1·42 to 1·78, m,12H; 1·34, m, 4H; 1·14, m, 4H. ^{13}C n.m.r. δ 79·37, d; 79·36, d, **CHOH**; 48·44, d; 48·34, d, **CH**; 34·77, 34·74, 33·86, 33·85, 30·13, 30·09, 28·51, 28·38, 21·90, 21·87. Mass spectrum (CI at A.W.R.I.) *m/z* = 227 (5%, $(M+H)^+$), 209 (45), 191 (35), 149 (11), 135 (67), 121 (20), 109 (81), 95 (100), 81 (17), 67 (8), found $(M-OH)^+$ 209.1902, $C_{14}H_{25}O$, requires 209.1905.

Part 3. 1,6-Divinylbicyclo[4.4.0]decane (31) from the Reaction of 6-(4-Oxobutylidene)cyclodecan-1-one (35) with Zero Valent Titanium

A well stirred suspension of $TiCl_3 \cdot (DME)_{1.5}$ (4·6 g, 13·6 mmol) and zinc-copper couple (2·89, 44·2 mmol) in dimethoxyethane (115 ml; twice distilled from potassium) was refluxed for 4 hours under an atmosphere of argon and then cooled to 85°C. A solution of the 6-(4-oxobutylidene)cyclodecan-1-one (35) (77 mg, 0·35 mmol) in dimethoxyethane (12 ml) was perfused into the suspension over a 20 hour period by way of a syringe pump. When addition was complete the reaction was stirred for a further 12 hours and then cooled to room temperature. The mixture was diluted with anhydrous, deoxygenated hexanes (100 ml) and filtered through a pad of Florisil. The residues were washed with hexanes (150 ml) then the combined filtrates were concentrated to a volume of 2 ml by distillation at atmospheric pressure. The final traces of solvent were removed *in vacuo* with a bath temperature of 0°C. The crude residue (63 mg) was distilled at 100°C/0·07 mmHg to give a distillate (31 mg) which was analysed by G.C. (Column A at 175°C/41 kPa) and shown to contain a mixture of components (table 10).

Table 10

Retention time (min.)	5·7	12·2	13·3

G.C./M.S. $(M)^+$ *m/z* (Flinders University)	136	176	190
% proportion of components eluted in < 15 min.	17%	15%	68%

The addition of tetradecane as an internal standard indicated that the component *m/z* 190 (9 mg, 48 μmol) had been produced in 15% yield.

The principal component, 1,6-divinylbicyclo[4.4.0]decane (31) (5 mg, 26μmol) was isolated in 8% yield by preparative gas chromatography (Column D at 175°C) using liquid nitrogen cooled traps to collect the column effluent. The spectral characteristics of the divinyldecalin (31) were identical to those reported in the literature[15].

1,6-divinylbicyclo[4.4.0]decane (31) ^{1}H nmr δ 6·25 ,dd, J 17·6, 11·1 Hz, 2H, **CH**=CH_2; 4·98, dd, J 11·1, 1·6 Hz, **cis** and 4·91, dd, J 17·6, 1·6 Hz, **trans**, 4H total, CH=**CH_2**; 2·07, m, impurity; 1·54, m, 10H, **CH_2**; 1·26, m, and 1·09, m, 6H, **CH_2**. ^{13}C nmr δ 145·99, **CH**=CH_2; 111·71, CH=**CH_2**; 40·85; 33·40, br; 31·71, br; 21·93, br; 21·56, br. Mass spectrum *m/z* = 190 (7%, M^+), 161 (27), 147 (42), 133 (49), 121 (90), 108 (26), 107 (25), 105 (31), 95 (63), 93 (57), 91 (81), 81 (51), 79 (100), 77 (37), 67 (85), 55 (37), 53 (30), found 190.1730, $C_{14}H_{22}$, requires 190.1721.

Chapter 4 Experimental

Part 1. Preparation of Unsaturated Key Intermediates.

1-(Ethoxycarbonylmethyl)-6-hydroxy-1-*E*-cyclodecene (88)

Method 1[9,109]. Triethylphosphonoacetate (0·35 ml, 1·76 mmol) in anhydrous THF (0·35 ml) was added dropwise to a suspension of sodium hydride (120 mg, 1·8 mmol, 80% dispersion in oil) in THF (3 ml) stirred in an atmosphere of nitrogen. After stirring for an hour a further aliquot of THF (1·5 ml) was added to dissolve incipient precipitate, then 6-hydroxycyclodecan-1-one (37) (200 mg, 1·17 mmol) dissolved in THF (1·5 ml) was added dropwise to the solution and the reaction was left to stir for 18 hours at room temperature. During this period a white precipitate formed and the solution turned to a clear yellow colour.

The reaction was diluted with ether (5 ml) then quenched with brine (8 ml). The aqueous phase was extracted with ether (3 x 8 ml) then the combined organic phases were dried over sodium sulphate and the solvent was removed *in vacuo* . TLC analysis (50% ethyl acetate/50% hexanes) of the crude product showed a mixture, containing two principal components with Rf values 0·18 and 0·06 that corresponded to the ketol (37) and the phosphonoacetate respectively.

Resonances characteristic of olefinic hydrogens were not observed in an nmr analysis of the crude mixture.

The components were isolated by flash chromatography (50% ethyl acetate/50% hexanes) and identified as 6-hydroxycyclodecan-1-one (37) (160 mg, 0·94mmol), 80% recovery, and the phosphonoacetate, by comparison of spectral data with data of authentic materials.

Method 2[109]. An anhydrous solution of triethylphosphonoacetate (0·35 ml, 1·76 mmol) in THF (0·4 ml) was added dropwise to a stirred suspension of sodium hydride (95 mg, 1·4 mmol, 80% suspension in oil) in THF (3 ml) at room temperature in an atmosphere of nitrogen. The suspension was stirred for an hour during which time the effervescence ceased. A THF (2·2 ml) solution of 6-(t-butyldimethylsilyloxy)cyclodecan-1-one (55) (0·34 g, 1·2 mmol) was added slowly to the mixture and the reaction was stirred for 18 hours.

The reaction changed to a clear orange colour. Brine (5 ml) was added and the organic phase was extracted into ether (3 x 8 ml). The combined organic phases were dried over sodium sulphate and the solvent was removed *in vacuo* . The crude product was analysed by TLC (15% ethyl acetate/85% hexanes). It contained two components with Rf 0·5 and baseline, similar to starting materials. The ^{1}H nmr of the crude mixture revealed no olefinic resonances, only signals corresponding to a mixture of the TBDMS-cyclodecanone (55) and the phosphonoacetate.

Method 3. To a solution of 6-hydroxycyclodecanone (37) (200 mg, 1·17 mmol) in anhydrous ethanol was added ethyl

triphenylphosphorylideneacetate (95) (1·22 g, 3·5mmol). The reaction was left to stir under an atmosphere of nitrogen. The solid had not completely dissolved after 24 hours but had disappeared after 48 hours. The reaction mixture was analysed by TLC (60% ethyl acetate/40% hexanes), the only components present corresponded to starting materials.

Method 4[92]. Sodium (1·4 g, 59 mmol) was added in portions to stirred anhydrous ethanol (60 ml) in an atmosphere of nitrogen. The metal had reacted completely after 30 minutes and the ethoxide solution was cooled to -70°C. A solution of triethylphosphonoacetate (11·9 ml, 60 mmol) in anhydrous ethanol (8 ml) was added dropwise to the sodium ethoxide solution, the mixture was allowed to warm to room temperature for 15 minutes and then cooled again to -70°C. An ethanolic (30 ml) solution of 6-hydroxycyclodecan-1-one (37) (5·0 g, 29·4 mmol) was added dropwise to the mixture and on completion of addition the reaction was allowed to warm to room temperature overnight.

The progress of the reaction was monitored by G.C. analysis (Column C at 230°C), Rf hydroxyketone (37) 1·4 min, product 3·8 min. The hydroxyketone (37) stopped being consumed after 5 days.

The reaction was concentrated to a viscous yellow oil *in vacuo* with a water bath <40°C. The oil was taken up in ether (150 ml) and washed with water (75 ml). The aqueous phase was further washed with ether (3 x 75 ml) then the combined organic phases were dried over sodium sulphate and the solvent was removed *in vacuo* . Analysis of the crude mixture by TLC (60% ethyl acetate/40% hexanes) revealed three components; Rf 0·42, 0·27 and

0·17, the latter two corresponding to the hydroxyketone (37) and phosphonoacetate, respectively.

The components of the crude product were separated by flash chromatography (30% ethyl acetate/70% hexanes) to give in order of elution; 1-(ethoxycarbonylmethyl)-6-hydroxy-1-*E*-cyclodecene (88) (5·75 g, 23·9 mmol), 81% yield as a clear colourless oil, and a mixture that was further resolved by Kugelrohr distillation to give triethylphosphonoacetate (5·5 g, 24·5 mmol) , 41% recovery, and 6-hydroxycyclodecan-1-one (37) (0·5 g, 2·9 mmol) b.p 100°C/0·2 mmHg, 10% recovery. The spectral data for the hydroxyketone (37) and the phosphonoacetate were identical to data for authentic material.

1-(Ethoxycarbonylmethyl)-6-hydroxy-1-*E*-cyclodecene (88).(Found: C, 70·12; H, 10·03. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10·07%). ν_{max} 3412, br s, **OH**; 1732, s, **C=O**; 1657, m, **C=C**; 1367, m; 1301, m; 1262, m; 1161, m; 1031 cm^{-1} ,m. ^1H n.m.r. δ 5·33, t, J 8·3 Hz, 1H, C=**CH**; 4·14, q, J 7·1 Hz, 2H, O**CH$_2$**CH$_3$; 3·85, m, 1H, **CH**OH; 3·00, d, J 13·4 Hz and 2·95, d, J 13·4 Hz, 2H, CH=C**CH$_2$**C(O); 2·35, m, 2H and 2·20, m, 2H, **CH$_2$**CH=C**CH$_2$**; 1·45 to 1· 75, m, 8H, **CH$_2$**; 1·24 to 1·36, m, **CH$_2$**, and 1·26, t, J 7·1 Hz, OCH$_2$**CH$_3$**, superimposed 5H. ^{13}C n.m.r. δ 172·11, **C(O)**; 132·00, **C**=CH; 130·12, C=**CH**; 71·14, **CH**-OH; 60·49, **CH$_2$**O; 41·72, 33·20, 29·52, 26·35, 26·16, 23·88, 22·83, 18·90, 14·18 **CH$_3$**. Mass spectrum *m/z* 240 (4%, M^+), 222 (3), 195 (11), 185 (39), 184 (17), 166 (10), 155 (46), 153 (39), 138 (100), 137 (87), 135 (100), 134 (100), 119 (29), 111 (47), 109 (71), 107 (50), 95 (57), 93 (100), 79 (100), 67 (100), 55 (100), found 240·1733, $C_{14}H_{24}O_3$ requires 240·1725 .

6-(Ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-one (89)

Dichloromethane (83 ml) was added to a dry flask containing pyridinium chlorochromate[72] (5·05 g, 23·4 mmol), powdered anhydrous molecular sieves[73] (4Å, 5·85 g) and fused sodium acetate (0·7 g). The suspension was stirred in an atmosphere of nitrogen for 1 hour then a solution of the 1-(ethoxycarbonylmethyl)-6-hydroxy-1-*E*-cyclodecene (88) (2·5 g, 10·4 mmol) in dichloromethane (10 ml) was added slowly. The reaction turned black from orange almost immediately.

TLC analysis (20% ethyl acetate/80% hexanes; Rf. ester-ol (88) 0·26, product 0·5) showed the complete absence of starting ester-ol (88) after 15 minutes. The reaction was diluted with anhydrous ether (100 ml) then stirred for 20 minutes before decanting onto a pad of Florisil/Hf_{254} (20 g/60 g). The residues were washed with further aliquots of ether (2 x 250 ml). The solvents were removed *in vacuo* to give a white crystalline solid. The crude product was separated from trace impurities by flash chromatography (12% ethyl acetate/88% hexanes) then sublimed using the Kugelrohr apparatus 130°C/0·02 mmHg to give 6-(ethoxycarbonylmethyl)-6-*E*-cyclodecen-1-one (89) (2·17 g, 9·1 mmol) as a white crystalline solid m.p. 45°-46°C (hexanes).

6-(Ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-one (89) (Found: C, 70.44; H, 9.55. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30%).ν_{max} 2974, s; 2934, s; 2868, s; 1728, s, **C=O**; 1699, s, **C=O**; 1655, w, **C=C**; 1453, s; 1411, s; 1373, s; 1266, s; 1228, s; 1209, m; 1189, m; 1115, s; 1047, s; 1029, s; 1001, s; 870, s; 742 cm^{-1}, s. ^1H n.m.r. δ 5·32, t, J 8·5 Hz, 1H, C=**CH**; 4·13, q, J 7·25 H, 2, O**CH_2**CH_3; 3·00, s,

2H, CH=C**CH$_2$**C(O); 2·46, br s, 2H and 2·34, m, 2H, **CH$_2$**CH=C**CH$_2$**; 2·12, m, 4H, **CH$_2$**C(O)**CH$_2$**; 1·73, m, 6H, **CH$_2$**; 1·27, t, J 7·25 Hz, 3H, OCH$_2$**CH$_3$**. ^{13}C n.m.r. δ 210·7 , **C**(O); 171·8, **C**(O)OEt; 133·6, **C**=CH; 129·4, C=**CH**; 60·5, O**CH$_2$**; 46·0, 41·1, 34·8, 26·1, 25·8, 24·0, 22·8, 20·8, 14·4. Mass spectrum *m/z* = 238 (3%, M$^+$), 221 (14), 220 (100), 210 (5), 192 (24), 175 (5), 174 (5), 163 (15), 151 (57), 146 (73), 134 (67), 133 (67), 122 (30), 121 (27), 119 (30), 117 (27), 106 (50), 105 (50), 95 (50), 93 (50), 91 (47), 81 (80), 79 (89), 67 (93), 55 (83); found 238.1556, $C_{14}H_{22}O_3$ requires 238.1569.

The Attempted Alkylation of 6-(Ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-one (89) with Triethylphosphonoacetate

Sodium metal (19 mg, 0·83 mmol) was added to anhydrous ethanol (1·5 ml) and stirred at room temperature under an atmosphere of nitrogen until the metal was consumed. The ethoxide solution was cooled to -70°C and to it was added dropwise a solution of triethylphosphonoacetate (0·18 g, 0·81 mmol) in ethanol (0·6 ml). When addition was complete the mixture was warmed to room temperature for 15 minutes then cooled again to -70°C. A solution of 6-(ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-one (89) (0·123 g, 0·52 mmol) in ethanol (0·5 ml) was added dropwise to the phosphonoacetate anion solution then the reaction was allowed to warm to room temperature slowly overnight. The reaction was allowed to stir at room temperature for 7 days.

The reaction was decanted into water (5 ml) then extracted into dichloromethane (3 x 8 ml). The combined organic phases were dried over sodium sulphate and the solvent was removed *in vacuo*. The crude reaction product was analysed by TLC (10% ethyl

acetate/90% hexanes) which showed two principal components; Rf. 0·11 and 0·05, as well as the absence of the unsaturated keto-ester (89). These components were isolated and separated from other minor impurities by flash chromatography (10% ethyl acetate/90% hexanes) to give in order of elution: *cis or trans*-fused-2-*Z*-(ethoxycarbonylmethylene)bicyclo[5.3.0]decan-7-ol (96) (48 mg, 0·20 mmol) in 39% yield and *cis*-fused-2-*E*-(ethoxycarbonylmethylene)bicyclo[5.3.0]decan-7-ol (97) (47 mg, 0·19 mmol) in 38% yield.

***Cis or trans*-fused-2-*Z*-(ethoxycarbonylmethylene)bicyclo [5.3.0]decan-7-ol (96)**. ν_{max} 3492, br s, **OH**; 2928, s; 2868, s; 1730, sh; 1695, s; 1629, s; 1449, s; 1398, s; 1382, s; 1347, w; 1303, w; 1276, s; 1200, s; 1179, s; 1117, w; 1095, w; 1036, s; 990, s; 941, w; 874 cm^{-1}, m. ^1H n.m.r. δ 5·8 , s, 1H, **CH**=C; 4·12, q, J 7·1 Hz, O**CH$_2$**CH$_3$; 4·03, br s, 1H, **OH**; 3·86, m, 1H, **CH**C=CH; 2·39, m, 1H, **CH**C=CH; 2·18, m, 1H, **CH**C=CH; 1·3 to 1·9, m, 12H, **CH$_2$**; 1·25, t, J 7·1 Hz), 3H, **CH$_3$**.^{13}C n.m.r. δ 167·94, **C**(O)OEt; 163·56, **C**=CH; 118·89, C=**CH**; 82·97, **C**OH; 60·27, O**CH$_2$**CH$_3$; 54·19, 41·02, 40·48, 34·36, 32·45, 30·60, 24·08, 22·30, 14·18. Mass spectrum *m/z* = 238 (7% M^+), 221 (6), 220 (24), 193 (98), 192 (100), 175 (67), 174 (76), 164 (50), 163 (43), 155 (51), 151 (100), 150 (81), 147 (100), 146 (57), 135 (81), 133 (98), 132 (95), 122 (70), 119 (53), 109 (84), 107 (86), 105 (83), 93 (86), 91 (84), 82 (97), 81 (98), 79 (100), 77 (98), 67 (100), 55 (86).

***Cis or trans*-fused-2-*E*- (ethoxycarbonylmethylene)bicyclo [5.3.0]decan-7-ol (97)**. ν_{max} 3480, br s; 2932, s; 2860, s; 1716, s; 1700, s; 1634, s; 1452, s; 1382, s; 1314, m; 1270, m; 1222, m; 1158, s; 1098, m; 1070, w; 1040, s; 986, w; 864 cm^{-1}, s. ^1H n.m.r. δ 5·6, s, 1H, C**H**=C; 4·12, q, J 7·2 Hz, 2H, OC**H$_2$**CH$_3$; 3·06, ddd, J 3·4,

7·4 , 12·1 Hz, 1H, CHC=CH; 2·64, t, J 8·5 Hz, 1H, CHC=CH; 2·41, ddd, J 3·4, 9·3, 12·1 Hz, 1H, CHC=CH; 1·45 to 2·00, m, 13H, CH_2 and OH; 1·26, t, J 7·2Hz. ^{13}C n.m.r. δ 166·34, **C(O)**; 165·13, **C**=CC(O); 114·59, C=**C**C(O); 83·09, **C**OH; 61·18, OCH_2; 59·49, 42·74, 39·28, 31·78, 30·74, 29·62, 28·57, 23·50, 22·89, 14·24. Mass spectrum *m/z* = 238 (4% M^+), 221 (2), 220 (12), 193 (36), 192 (100), 175 (30), 174 (30), 164 (24), 151 (44), 147 (72), 133 (40), 132 (54), 121 (34), 108 (50), 105 (37), 93 (40), 91 (75), 81 (48), 79 (76), 77 (42), 67 (66), 55 (61).

The reaction was carried out as described above except that the temperature at which the reaction was maintained for a five day period was changed to 0°C and -15°C. In these cases the product contained a proportion of unreacted unsaturated keto-ester (89).

1,6-Bis(ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-ol (90)

The reaction follows a general procedure by Rathke[95]. A solution of n-butyllithium in hexanes (Aldrich, 1·4 M, 5·6 ml, 7·8 mmol) was cooled to -10°C in an atmosphere of argon. An anydrous solution of diisopropylamine (1·15 ml, 8·2 mmol) in THF (2·3 ml) was added slowly to this cold stirred solution which was allowed to then warm to room temperature for 15 minutes. The solution of lithium diisopropylamide so formed was cooled to -75°C and to it was slowly added anhydrous ethyl acetate (0·83 ml, 8·5 mmol). After 15 minutes a solution of 6-(ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-one (89) (1·62 g, 6·82 mmol) in THF (5·5 ml) was added slowly and after the reaction had stirred for an hour it was

quenched by the addition of saturated aqueous ammonium chloride (3 ml).

The mixture was diluted with ether (10 ml) and allowed to warm to room temperature before saturating it with sodium chloride. The organic phase was extracted into ether (3 x 15 ml). The combined extracts were dried and the solvents removed *in vacuo*.

The crude residue was analysed by TLC (15% ethyl acetate/85% hexanes) which revealed a trace of keto-ester (89) Rf 0·26 and a single component at Rf 0·15. The mixture was separated by flash chromatography (10% ethyl acetate/ 90% hexanes) to give in order of elution, 6-(ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-one (89) (80 mg, 0·3 mmol) 5% recovery and 1,6-bis(ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-ol (90) (1·99 g, 6·09 mmol) as a clear oil in 90% yield.

1,6-Bis(ethoxycarbonylmethyl)-5-*E*-cyclodecen-1-ol (90) (Found: C, 66·25; H, 9·41. $C_{18}H_{30}O_5$ requires C, 66·23; H, 9·26%). ν_{max} 3528, br s, **OH**; 2980, s; 2932, s; 2856, s; 1734, s, **C=O**; 1476, s; 1450, s; 1406, s; 1370, s; 1302, m; 1261, m; 1212, m; 1156, s; 1096, m; 1034 cm^{-1}, m. ^{13}C nmrδ 172·15, 171·85, **C(O)**OEt; 131·41, **C**=CH; 130·50 C=**CH**; 73·90, **C-O**; 60·31 **CH_2O**; 44·28, 41·69, 34·49, 32·04, 26·59, 25·57, 23·11, 22·7, br; 19·6, br; 14·04 **CH_3**. Mass spectrum *m/z* 308 (<1% M^+), 280 (3), 262 (5), 239 (14), 234 (6), 221 (25), 220 (27), 193 (24), 175 (24), 147 (23), 135 (21), 119 (8), 105 (15), 93 (32), 91 (30), 81 (49), 79 (56), 67 (79), 55 (100) found 308·1991; $C_{18}H_{30}O_5$ requires 308·1989.

1,6-Bis(ethoxycarbonylmethyl)-1-*E*-6-*E*-cyclodecadiene (91)

Pyridine (2·5 ml, 31 mmol) was added to a stirred, anhydrous solution of 1,6-bis(ethoxycarbonylmethyl)-6-*E*- cyclodecen-1-ol (90) (1·99 g, 6·09 mmol) in toluene (18·5 ml) and the mixture was cooled to -10°C under an atmosphere of nitrogen. A solution of thionyl chloride (0·6 ml, 8·22 mmol) in toluene (2·4 ml) was added slowly to the mixture to maintain the temperature at less than -7°C. The reaction was stirred for a further 45 minutes after the addition of the thionyl chloride was complete, then the reaction was poured into cold, saturated aqueous sodium carbonate solution (40 ml). Further portions of solid sodium carbonate were added till effervescence ceased, then the mixture was extracted into ether (2 x 30 ml). The combined extracts were washed with brine (15 ml). The organic phase was dried and the solvents removed *in vacuo*.

The crude product was analysed by TLC (30% ethyl acetate/70% hexanes) which revealed a mixture predominated by two overlapping components at Rf 0·32 and 0·29. These components were isolated by short column chromatography (100% hexanes to 30% ethyl acetate by 2·5% increments)to give a mixture of three isomers of 1,6-bis(ethoxycarbonylmethyl)cyclodecadiene (91) and others (1·47 g, 4·77 mmol) as a colourless liquid in 78% yield. ^{1}H n.m.r. δ 5·63, s, 0·36H, C=**CH**C(O); 5·34, t, J 7·6 Hz, 0·22H, C=**CH**CH_2; 5·27, t, J 7·6 Hz, 0·16H, C=**CH**CH_2; 5·22, mult., 1·26H, C=**CH**CH_2; 4·1, mult. 4H O**CH_2**CH_3; 2·95, mult., **CH_2**C(O); 2·68, mult.; 2·42, mult.; 1·96 to 2·3 mult.; 1·37 to 1·89, mult.; 1·23, mult., OCH_2**CH_3**.

The isomeric mixture was recrystallised twice from hexane to give 1,6-bis(ethoxycarbonylmethyl)-1-*E*-6-*E*-cyclodecadiene (91) (0·43 g, 1·39 mmol) in 23% yield as white crystals, m.p. 56°-57°C (found: C, 70·7; H, 8·9; $C_{18}H_{28}O_4$ requires C, 70·1%;H, 9·1%). ν_{max} (nujol) 2924, s; 2850, s; 1726, s, **C=O**; 1686, w; 1640, w, **C=C**; 1475, s; 1457, s; 1408, s; 1365, s; 1336, s; 1275, m; 1237, m; 1185, s; 1167, s; 1109, m; 1029 cm^{-1}, s. ^1H n.m.r. δ 5·22, mult., 2H, C=**CH**; 4·11, q, J 7·3 Hz, 4H, O**CH_2**CH_3; 3·02, d, J 14·16 Hz, 2H, 2·88, d, J 14·16 Hz, 2H, **CH_2**C(O); 2·42, mult., 2H, **allylic**; 2·08, mult., 2H, **allylic**; 1·6 to 1·9, mult., 6H; 1·44, mult., 2H, **CH_2**; 1·23, t, J 7·3 Hz, 6H, OCH_2**CH_3**. ^{13}C n.m.r. δ 171·11, **C(O)**OEt; 131·80, **C**=CH; 130·63, C=**CH**; 60·37, **OCH_2**CH_3; 41·22, 26·41, 24·72, 23·88, 14·12. Mass spectrum *m/z* 308 (4% M^+), 263 (10), 262 (22), 245 (11), 244 (11), 221 (32), 220 (100), 216 (23), 188 (22), 175 (40), 161 (26), 147 (99), 146 (99), 133 (96), 132 (100), 131 (64), 119 (58), 105 (97), 93 (97), 91 (99), 88 (60), 81 (62), 79 (69), 77 (64), 67 (69), 55 (49) found 308·1976; $C_{18}H_{28}O_4$ requires 308·1988.

1,6-Bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene (87)

A solution of 1,6-bis(ethoxycarbonylmethyl)-1-*E*-6-*E*-cyclodecadiene (91) (0·38 g, 1·24 mmol) in anhydrous hexanes was cooled to -78°C under an atmosphere of nitrogen. Some precipitation took place. A solution of diisobutylaluminium hydride (0·55 ml, 2·97 mmol) in hexanes (3 ml) was added to the stirred suspension at a rate to maintain the low temperature. When addition was complete the mixture was stirred for a further 1·5 hours and then the reaction was quenched by the addition of an aliquot of methanol (1·5 ml). The reaction was warmed to room

temperature and washed with saturated aqueous ammonium chloride (20 ml). The aqueous phase was extracted with ether (3 x 20 ml). The combined extracts were dried and the solvents removed *in vacuo* .

The crude product was analysed by TLC (10% ethyl acetate/90% hexanes) which revealed a mixture of components, Rf 0·27, 0·17, 0·12 and baseline material. The mixture was resolved by flash chromatography (as for TLC) and the component Rf 0·17, identified as 1,6-bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene (87) (0·15 g, 0·69 mmol) was isolated in 40% yield as a white crystalline solid, m.p. 70°-74°C. ν_{max} 2920, s; 2736, m, **C(O)-H**; 1712, s, **C=O**; 1454, s; 1414, m; 1380, s; 1276, w; 1098, s; 1042, s; 1022, m. ^{1}H n.m.r. δ 9·60, t, J 2·9 Hz, 2H, **C(O)H**; 5·24, mult., 2H, C=**CH**; 3·05, dd, J 14·2, 2·9 Hz, 2·94, dd, J 14·2, 2·9 Hz, 4H, **CH$_2$**C(O); 2·49, mult., 2H, **allylic**; 2·13, mult., 2H, **allylic**; 1·91, mult., 2H, **allylic**; 1·71, mult., 4H; 1·53, mult., 2H, **CH$_2$**. ^{13}C n.m.r. δ 200·44, **C(O)H**; 131·93, **C**=CH; 129·99, C=**CH**; 50·08, 27·18, 24·98, 23·56. Mass spectrum *m/z* 220 (10% M$^+$), 202 (11), 184 (5), 176 (99), 147 (99), 134 (99), 131 (62), 119 (70), 117 (55), 107 (86), 105 (91), 95 (94), 93 (99), 91 (99), 81 (99), 79 (99), 77 (94), 67 (100) found 220·1462; $C_{14}H_{20}O_2$ requires 220·1463.

If the ether extract was washed with an aliquot of cold, dilute aqueous hydrochloric acid the organic phase turned immediately turned yellow and the yield of the dialdehyde (87) dropped to 30%.

Saturated Key Intermediates.

cis- and *trans*- 1,6-Bis(ethoxycarbonylmethyl)cyclodecanes (92)

A portion of palladium-on-carbon (10% w/w, 50 mg) was added to a well stirred solution of the dialkenyl diesters (91) and isomers (220 mg, 0·71 mmol) in ethanol (5ml). The suspension was evacuated and flushed three times with hydrogen then left to stir in an atmosphere of hydrogen while the progress of the reaction was monitored by ^{1}H n.m.r. over a period of 72 hours. The solid phase was then removed by filtration through a pad of celite. The residue was washed with ethyl acetate then the solvents removes from the combined filtrate *in vacuo* .

TLC analysis (10% ethyl acetate/90% hexanes) of the crude product revealed a single component, Rf 0·34 indistinguishable from the dialkenyl diesters (91), Rf 0·34. The crude product was separated from trace amounts of polar impurities by passage through a short column of silica (Merck Hf_{254}) to give an isomeric mixture of *cis*- and *trans*- 1,6-bis(ethoxycabonylmethyl)cyclodecanes (92) (210 mg, 0·67 mmol) as a clear oil in 94% yield (found: C, 69·4; H 9·9; $C_{18}H_{32}O_4$ requires C, 69·2; H, 10·3%). ν_{max} 2976, s; 2924, s; 1734, s, **C=O**; 1480, m; 1448, s; 1374, s; 1242, s; 1198, s; 1154, s; 1096, s; 1038 cm^{-1}, s. ^{1}H n.m.r. δ 4·09, q, J 7·1 Hz, 3H, O**CH$_2$**CH$_3$; 2·18, d, J 9·4 Hz, and 2·15, d, J 7·5 Hz, 4H, CH**CH$_2$**C(O); 1·33 to 1·66, br mult., 18H, **CH**, **CH$_2$**; 1·22, t, J 7·2 Hz **CH$_3$**. ^{13}C n.m.r. δ 173·18, **C(O)**OEt; 59·92, **OCH$_2$**CH$_3$; 47·76, 41·48, 33·98, 32·49, 30·72, 29·65, 23·82, 23·49,

14·18, $OCH_2\mathbf{CH_3}$. Mass spectrum *m/z* 312 (2% M^+), 267 (62), 237 (16), 236 (18), 192 (11), 161 (8), 151 (40), 137 (58), 135 (66), 95 (99), 93 (56), 89 (63), 88 (66), 83 (74), 81 (100), 79 (93), 69 (63), 67 (73), 55 (99), found 312·2293; $C_{18}H_{32}O_4$ requires 312·2301.

1,6-bis(2-ethanol)cyclodecanes. Nonpolar (93); Polar (94).

An anhydrous solution of the *cis*- and *trans*- 1,6-bis(ethoxycabonylmethyl)cyclodecanes (92) (3·51 g, 11·23 mmol) in ether (10 ml) was added slowly to a stirred suspension of lithium aluminium hydride (0·58 g, 15·36 mmol) in ether (50 ml) under an atmosphere of nitrogen. The reaction was stirred for 3 hours after addition was complete then quenched by the cautious addition of sodium sulphate decahydrate until gaseous evolution ceased. The suspension was left to stir overnight. The solids were removed by filtration and the residue well washed with warm ethyl acetate. The solvents were removed from the filtrate *in vacuo* to give the crude product as a pasty white solid.

The analysis of the crude product by TLC (50% ethyl acetate/50% hexanes) revealed the presence of two principal components of similar Rf; 0·22 and 0·19. The diester (92) had an Rf of 0·73, the TLC analysis suggested that it had all been consumed.

The two major components of the crude product were separated by repetitive flash chromatography (30% ethyl acetate/70% hexanes) to yield the two stereoisomers of 1,6-bis(2-ethanol)cyclodecane; the nonpolar isomer (93) (1·16 g, 5·6 mmol) as a white crystalline solid, m.p. 84°-85°C (dichloromethane/hexanes) in 45% yield and the polar isomer (94) (1·16 g, 5·6 mmol) as a white

crystalline solid, m.p. 60°-61°C (dichloromethane/hexanes) in 45% yield.

Nonpolar 1,6-bis(2-ethanol)cyclodecane (93). ν_{max} (nujol) 3260, br. s, **OH**; 2922, s; 1489, m; 1377, m; 1083, m; 1065, s; 1040, s; 1019 cm^{-1}, m. ^1H n.m.r. δ 3·64, t, J 6·9 Hz, 4H, $CH_2\mathbf{CH_2}OH$; 1·76, mult., 2H, **CH**; 1·49 to 1·65, br. mult., $\mathbf{CH_2}$, **OH**, superimposed on 1·45, q, J 6·9 Hz, $CH\mathbf{CH_2}CH_2OH$, 22H. ^{13}C n.m.r. δ 61·32, $\mathbf{CH_2}OH$; 40·06, 31·99, 30·87, 24·01. Mass spectrum *m/z* 228 (1% M^+), 200 (6), 182 (6), 181 (4), 165 (22), 163 (49), 137 (82), 136,(35), 135 (32), 123,(18), 121 (19), 109 (43), 95 (63), 81 (68), 69 (69), 67 (76), 55 (100) found 228·2082; $C_{14}H_{28}O_2$ requires 228·2089.

Polar isomer of 1,6-bis(2-ethanol)cyclodecane (94). ν_{max} (nujol) 3232, br. s, **OH**; 2924, s; 2852, s; 1490, m; 1466, s; 1378, m; 1062, s; 1042, m; 1014 cm^{-1}, m. ^1H n.m.r. δ 3·61, t, (J= 6·8 Hz), 4H, $\mathbf{CH_2}OH$; 1·77 to 1·83, mult., 2H, **CH**; 1·36 to 1·6, mult., 22H. ^{13}C n.m.r. δ 60·89, $\mathbf{CH_2}OH$; 39·67, 33·13, 29·96, 24·21. Mass spectrum *m/z* 200 (5% $(M-C_2H_4)^+$), 163 (7), 160 (6), 147 (24), 146 (10), 145 (12), 123 (9), 121 (10), 109 (25), 107,(12), 95 (69), 81 (100), 69 (69), 67 (67), 55 (70).

1,6-Bis(2-oxoethyl)cyclodecane (86) from 1,6-Bis(2-ethanol)cyclodecane (93)

A solution of oxalyl chloride (0·19 ml, 2·19 mmol) in anhydrous dichloromethane (7·3 ml) was cooled under an atmosphere of nitrogen to -60°C. To this stirred solution was added a solution of dimethyl sulphoxide (0·31 ml, 4·83 mmol) in dichloromethane (1 ml) at a rate to maintain the low temperature. After stirring the reaction for 2 minutes a solution of 1,6-bis(2-

ethoxy)cyclodecane (93) (100 mg, 0·44 mmol) in dichloromethane/dimethylsulphoxide (1:1, 1·5 ml) was added dropwise. The reaction was left to stir for 45 minutes during which time a white solid began to precipitate. Triethylamine (1·53 ml, 11mmol) was added slowly to the stirred suspension, bringing about the disappearance of the white solid. After 5 minutes the reaction was warmed to room temperature and 20 minutes later the reaction was diluted with dichloromethane (30 ml) and decanted into saturated aqueous sodium bicarbonate solution (15 ml). The aqueous phase was extracted with dichloromethane (2 x 35 ml). The combined organic phases were washed with brine (20 ml) and dried. The solvent was removed *in vacuo* to give the crude product as a white solid.

Analysis of the crude product by TLC (10% ethyl acetate/90% hexanes) showed a single major component Rf 0·38 with some minor polar impurity. This component was isolated by flash chromatography (5% ethyl acetate/95% hexanes) to give 1,6-bis-(2-oxoethyl)-cyclodecane (86) (78 mg, 0·35 mmol) as a white crystalline solid, m.p. 55°-56°C (hexanes) in 79% yield. ν_{max} (nujol) 2924, s; 2825, s; 2808, w; 2704, m, **C(O)-H**; 1720, s, **C=O**; 1470, s; 1378, m; 1104, w; 1070, w; 960 cm^{-1}, w. ^1H n.m.r. δ 9·73, t, J 1·9 Hz, 2H, CH_2**C(O)H**; 2·29, br. s, 4H, **CH_2**C(O)H; 1·26 to 1·72 br. mult., 18H, **CH_2**. ^{13}C n.m.r. δ 202·75, **C(O)H**; 50·99, **CH_2**C(O); 30·67, 30·32, 23·37. Mass spectrum *m/z* 222 (<1% M^+), 180 (2), 162 (2), 136 (100), 121 (5), 107 (5), 95 (45), 94 (29), 93 (26), 81 (42), 79 (26), 67 (52), 55 (61) found 224·1767; $C_{14}H_{24}O_2$ requires 224·1776.

Attempted Cyclisation Reactions of Key Intermediates

Attempted Acyloin Reaction of *cis*- and *trans*- 1,6-bis(ethoxycabonylmethyl)cyclodecanes (92)

Method 1[23,24]. Anhydrous toluene (350 ml) was added to a dry 500 ml flask fitted with a reflux condenser disconnected from the water supply. Toluene (100 ml) was then distilled from the flask before connecting the water to the condenser and sealing the system under an argon atmosphere. The toluene was cooled and an aliquot was withdrawn in which both trimethylsilyl chloride (1 ml, 7·9 mmol) and the *cis*- and *trans*- 1,6-bis(ethoxycabonylmethyl)cyclodecanes (92) (257 mg, 0·82 mmol) were dissolved.

Pieces of sodium (total 0·533 g, 23·18 mmol) washed first in hexane/ethanol then anhydrous hexane, were added to the toluene. The suspension was brought to reflux and stirred vigorously for 3 hours to form sodium sand; the solution of saturated diester (92) was then added over a period of 14 hours using a syringe pump.

The reaction was cooled and filtered under anhydrous conditions through a pad of celite with a positive argon pressure. The filtrate was concentrated *in vacuo* to a volume of 2 ml and then analysed by G.C. (Column C at 220°C) which showed only two overlapping volatile components with Rf 7·0 and 7·5 minutes. These components were identified as the saturated diesters (92) by co-elution with authentic samples and the reaction was investigated no further.

Method 2[23,98]. Anhydrous toluene (40 ml) was added to a 50 ml flask fitted with a reflux condenser disconnected from the water flow. Toluene (35 ml) was then distilled out of the flask through the condenser to remove traces of water. The system was sealed under an atmosphere of nitrogen and water flow connected to the condenser.

Sodium (0·192 g, 8·35 mmol) and potasium (0·325 g, 8·36 mmol) washed first in hexane/isopropanol then anhydrous hexane were added to the flask and the toluene was brought to reflux with stirring to form the liquid sodium-potassium alloy. The residual toluene was then evaporated by a positive flow of nitrogen down through the flask. A solution of trimethylsilyl chloride (1 ml, 7·88 mmol) in anhydrous ether (12 ml) was added to the alloy. After 1 hour of vigorous stirring at room temperature to disperse the alloy the solution had turned faintly cloudy and had a pale purple colour. The saturated diester (92) (250 mg, 0·8 mmol) was dissolved in ether (10 ml) and added to the alloy suspension by way of a syringe pump over 11 hours. The reaction was stirred for 10 hours once addition was complete, then filtered with a positive nitrogen pressure and anhydrous conditions through a celite pad. The residues were washed with ether and the solvent was removed from the filtrate *in vacuo* .

The crude product distilled at 130°C/0·04 mmHg in a Kugelrohr apparatus to give a clear liquid (0·234 g, 0·63 mmol) in 79% yield. The distillate, when analysed by G.C. (Column A at 250°C/44kpa) was shown to be a mixture of six overlapping components; Rf 27·6 minutes, 28·4 min., 29·4 min., 31·0 min., 31·8 min., 32·8 min.

An attempt was made to ascertain the molecular weights of the components of the mixture by the use of G.C./M.S.with both electron impact and chemical ionisation, however the results were too complex to interpret.

Attempted Titanium Induced Intramolecular Carbonyl Coupling of 1,6-Bis(2-oxoethyl)-cyclodecane (86)

$TiCl_3$:$(DME)_{1.5}$ (5·67 g, 16·8 mmol) and zinc-copper couple (3·62 g, 55·8 mmol) in an oven dried flask fitted with reflux condenser, thermometer and teflon inlet port under an atmosphere of oxygen free argon was set stirring and freshly distilled dimethoxyethane (twice from potassium, 140 ml) was added via cannula. The suspension was refluxed for five hours by which time it had turned a grey-black colour. The suspension was cooled to 81°C. A solution of 1,6-bis(2-oxoethyl)-cyclodecane (86) (78 mg, 0·35 mmol) in dimethoxyethane (14 ml) was added to the well stirred suspension over a period of 20 hours by way of a syringe pump. The reaction was stirred for a further 24 hours when the addition was completed.

The reaction mixture was cooled to room temperature and to it was added alkene free anhydrous hexanes (150 ml) which had been purged with argon. The addition of hexane caused the solids of the suspension to clump. The mixture was filtered through a pad of celite-capped Florisil with a positive pressure of argon. The solid residues were washed with hexane (150 ml). The combined filtrates were concentrated to a volume of 2 ml by distillation at atmospheric pressure; the residual solvent was removed first at

aspirator pressure with an ice/water bath, then by brief exposure to 0·05 mmHg vacuum to give a crude residue (70 mg).

An internal standard (tetradecane; 5 µl, 19·2 µmol) was added.to the crude residue and the mixture was distilled through a short path at 140°C/0·045 mmHg to give a volatile fraction (17 mg). This volatile fraction was analysed by G.C. (Column A at 175°C/40kpa) and by G.C./mass spectrometry (chemical ionisation.) (A.W.R.I.), see table 11..

Table 11.

Retention time (min.)	13·2	17·0	17·3
G.C./M.S. $(M)^+$ *m/z* (A.W.R.I.)	196	209 $(M+H)^+$	
mass as per internal std.	9·5 mg	2·8 mg	
% proportion of components eluted in < 20 min.	77	21	2

The two major components were isolated by way of preparative G.C. (Column D at 175°C) using argon as the carrier gas. The relevant fractions were collected in a trap cooled with a liquid nitrogen to give in order of elution 1,6-diethylcyclodecane (100) (4·1 mg, 2·09 µmol) in 6% yield and 1-(2-propenyl)-6-ethylcyclodecane (101) (1·2 mg, 0·6 µmol) in 1·6% yield.

1,6-diethylcyclodecane (100). ^{1}H n.m.r. δ 1·28 to 1·65, br. mult., **CH_2**; 1·19, quintet, J 7·1 Hz, 2H, **CH**; 0·85, t, J 7·3 Hz. ^{13}C n.m.r. δ 37·27 (d); 30·81, (t); 29·30, (t); 24·34, (t); 12·11, (q). Mass

spectrum (isobutane chemical ionisation A.W.R.I.) *m/z* 196 (14% M^+), 195 (100), 194 (7), 167 (13), 165 (7), 139 (3), 125 (5), 113 (57), 112 (25), 99 (9), 97 (8), 95 (11), 85 (17), 83 (9), 71 (28), 69 (23).

1-(2-propenyl)-6-ethylcyclodecane (101). ^1H n.m.r. δ 5·77, ddt, J 17·0, 10·1, 7·3 Hz, 1H, $CH_2\mathbf{CH}=CH_2$; 4·96, dd, J 2·3, 17·0 Hz, and 4·94, dd, J 2·3, 10·1 Hz, 2H, $CH=\mathbf{CH_2}$; 1·94, t, J 6·9 Hz, 2H, $CH\mathbf{CH_2}CH=$; 1·28 to 1·76, br. mult., 18H, $\mathbf{CH,CH_2}$; 1·19, quintet, (J= 7·0 Hz), 2H $CH\mathbf{CH_2}CH_3$; 0·85, t, (J= 7·3 Hz), 3H, $CH_2\mathbf{CH_3}$. Mass spectrum (isobutane CI, A.W.R.I.) *m/z* 209 (100% $(M+H)^+$), 207 (41), 195 (36), 181 (32), 167 (80), 165 (50), 153 (37), 151 (28), 139 (38), 137 (30), 125 (65), 113 (60), 111 (90), 99 (60), 97 (83), 85 (90), 83 (75), 71 (100), 69 (88).

Attempted Titanium Induced Intramolecular Carbonyl Coupling of 1,6-Bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene (87)

A suspension of zero valent titanium was prepared in the usual manner from $TiCl_3{\cdot}(DME)_{1.5}$ (5·51 g, 16·36 mmol) and zinc-copper couple (3·46 g, 52·9 mmol) in freshly distilled dimethoxyethane (twice from potassium, 140 ml). The suspension was refluxed for 5 hours then cooled to 80°C.

A solution of 1,6-bis(2-oxoethyl)-1-*E*-6-*E*-cyclodecadiene (87) (106 mg, 0·48 mmol) in dimethoxyethane (14 ml) was added to the stirred suspension over a period of 24 hours, and the reaction was stirred at 80°C for a further 12 hours once addition was complete.

The reaction was worked up in the usual way. The crude product was distilled, 100°C /0·04 mmHg to give a distillate (12·5 mg) that was analysed by G.C. (Column A at 170°C/40 kPa) and G.C./Mass spectrometry (A.W.R.I.) see table 12 with tetradecane (1 µl, 3·8 µmol) as an internal standard.

Table 12

Retention time (min.)	5·1	5·5	8·5	8·8
G.C./M.S. $(M)^+$ *m/z* (A.W.R.I.)	190	188		
mass as per internal std.	0·2 mg			0·1 mg
% proportion of components eluted in < 10 min.	54	6	5	25

An attempt was made to isolate the two major components by preparative G.C. (Column D at 200°C) by the procedure described above, but only trace amounts were recovered and further analysis by G.C. (Column A at 170°C/40 kPa) showed that the isolated material was still a mixture of components.

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