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Full Name of Author — Nom complet de l'auteur

DAVID BRUCE MOIR

Date of Birth — Date de naissance

APRIL 26, 1952

Country of Birth — Lieu de naissance

CANADA

Permanent Address — Résidence fixe

2 - 7 MONK ST
OTTAWA, ONTARIO, CANADA
K1S 3Y5

Title of Thesis — Titre de la thèse

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J.W. APSIMON

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D. Moir

Approaches to the Total Synthesis

of Pentacyclic Triterpenes.

© David B. Moir B.Sc.

A thesis submitted to the Faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry
Carleton University

July 1985.

The undersigned hereby recommend to
the Faculty of Graduate Studies the acceptance of
this thesis submitted by David Bruce Moir, B. Sc.,
in partial fulfilment of the requirements for
the degree of Doctor of Philosophy.

Supervisor

Chairman of the
Chemistry Department

External Examiner

For Sherry,

ABSTRACT

Three approaches to the synthesis of an intermediate suitable for use as the CDE rings of some pentacyclic triterpenes such as friedelin (10) are described. Each of these approaches attempts to establish the anti-cis relationship between the C-13 α -methyl group and the DE ring junction with the C-20 geminal methyl groups in place.

The first approach involved the use of the directed Simmons-Smith reaction on the homoallylic alcohols 3,3,10a β -trimethyl-1,2,3,4,4a β ,5,6,7,8,9,10,10a-dodecahydrophenanthren-7-ol (117). This reaction was unsuccessful presumably for steric reasons.

The second approach was an attempted intramolecular cyclopropanation. The catalytic decomposition of 2-acetoxy-4a β -diazoacetoxymethyl-1,7,7-trimethyl-3,4,4a,5,6,7,8,8a β -octahydronaphthalene (155) was to have generated a carbene that would add to the double bond from the β -face, forcing the methyl group (future C-13) into the α -configuration. Various conditions failed to effect the desired transformation.

The third approach involved an intramolecular Diels-Alder reaction to establish the desired stereochemistry. The triene 3-benzyloxy-5-(1,4,4-trimethyl-3-vinyl-cyclohex-2-enyl)-2-methylene

pentanal (205) was synthesized and underwent a thermal Diels-Alder reaction giving a mixture of three isomeric aldehydes. The synthesis of 205 was marked by an unusual diastereofacial selectivity in the addition of an acrolein equivalent to 3-(1,4,4-trimethyl-3-vinylcyclohex-2-enyl) propionaldehyde (189).

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INTRODUCTION

Terpenes are natural products that are classified together on the basis of their biogenesis from a common precursor, isopentenyl pyrophosphate (1). The Biogenetic Isoprene Rule propounded by Ruzicka successfully accounts for the formation of all terpenes from geranyl pyrophosphate (2), farnesyl pyrophosphate (3) and geranyl geranyl pyrophosphate (4) ^{1,2} (Scheme 1 ³). Each condensation of isopentenyl pyrophosphate takes place in a head to tail fashion, while the dimerization of both farnesyl pyrophosphate and geranyl geranyl pyrophosphate take place in a head to head fashion.

The dimerization of farnesyl pyrophosphate results in the formation of hexaene all-trans squalene (5) which is the precursor of all triterpenes². Eschenmoser *et al.*⁴ and Ruzicka² have described how all triterpene ring systems can arise from cyclization of the different conformations available to squalene. In fact, the precursor to the many 3-oxygenated triterpenes is a 3-(S)-squalene-2,3-epoxide.⁵

The triterpenes can be subdivided into three groups. Acyclic triterpenes are the smallest group of triterpenes and include squalene in their number; tetracyclic triterpenes include lanosterol (6), the immediate precursor of cholesterol in mammals and cycloartenol (7), the initial tetracyclic triterpene formed in plants;

pentacyclic triterpenes are the largest group and include lupeol (8), β -amyrin (9) and friedelin (10).

The triterpenes shown above are merely representative of the complexity and diversity that characterize this class of compounds. An excellent review of triterpenoids was published some years ago⁷.

The biosynthesis of the oleanane (β -amyrin) and friedelane groups of pentacyclic triterpenes begins with squalene-

2,3-epoxide folded into a chair-chair-chair-boat conformation as shown in Scheme 2. Cyclization leads to the intermediate cation 11 which is the progenitor of a number of tetracyclic triterpenes; 11 undergoes a ring expansion by migration of the C-16 methylene to provide the tetracyclic cation 12 which itself can isomerize to 13. This cation can lose a proton to provide lupeol 8 or can ring-expand to provide the six-membered E-ring as shown in 14.

Intermediate 14 is a remarkable cation in that it possesses a flat backbone skeleton punctuated by a series of axial substituents arranged in a trans-diaxial sense (Figure 1). This means that it is possible that a shift of a substituent can easily be succeeded by one or more subsequent shifts.

Figure 1

Cation 14 can be quenched by the elimination of the C-18 α -hydrogen to generate germanicol (15) or a hydride shift can occur from C-18 to C-19 and so generate a new cation at C-18. This in turn can lose the C-13 hydrogen to account for δ -amyrin (16) or can isomerize by a shift of the methyl from C-14 to C-13. In this manner, friedelin (10) is eventually produced after nine hydrogen or methyl 1,2-shifts; fewer shifts and an elimination produce β -amyrin (9), taraxerol (17), multiflorenol (18) or alnusenol (19).

Compounds 17 through 19 and friedelin (10) all contain a cis DE ring junction and an α -methyl group at C-13. This causes some severe non-bonded interactions between this methyl group and

one of the methyls on C-20. This is shown in Figure 2 for friedelin in an all chair conformation.⁸

Figure 2

Another possibility, not shown, is the chair-chair-chair-boat-boat conformer which also has a severe interaction. It is this strain which has been suggested as the reason for the famous acid-catalyzed backbone rearrangement of friedelin-3 β -ol (20) and similar friedelanes⁹ to δ -amyrin skeletons such as olean-13(18)-ene (21) (Scheme 3)¹⁰.

Scheme 3

This remarkable reaction is in effect a reverse recapitulation of the biogenesis of friedelin (10) from δ -amyrin (16).

Synthetic Approaches to Pentacyclic Triterpenes

Pentacyclic triterpenes have been attractive synthetic targets for some years, offering as they do, the challenges of a large number of chiral centres, complex stereochemical relationships caused by the angular methyl groups and the assemblage of the pentacyclic backbone itself. A recent review by ApSimon and co-workers¹¹ has served to complement an earlier review out of the same laboratory¹².

A retrosynthetic analysis of a pentacyclic triterpene must necessarily lead eventually to a determination of the order of ring formation and so approaches to synthesis of these compounds are often termed an "AB plus DE Approach" etc. (Figure 3).

Figure 3

Figure 3 depicts the idea that a pentacycle can be synthesized from the condensation of two suitably functionalized bicycles. This terminology will be used in this thesis where convenient.

Several total syntheses have been published which are germane to this thesis and will be summarized in this introduction, along with some recent approaches to the total synthesis of pentacyclic triterpenes.

Alnusenone

Ireland and his co-workers have published two total syntheses of alnusenone as well as a variation on one of the approaches. The first synthesis¹³ represented an $A + DE \rightarrow A-CDE \longrightarrow ABCDE$ approach and featured the differential reduction of an aromatic E-ring over an aromatic A-ring as well as the use of the Nagata hydrocyanation reaction to generate the trans-CD ring junction having two angular methyl groups¹⁴. The carbons for the ring system were assembled by the Michael addition of the β -tetralone 22 to the vinyl ketone 23, providing the A-CDE tetracycle 24 (Scheme 4). It was realized that compound 24 would be amenable to the introduction of the trans-CD ring junction by use of Nagata's procedure¹⁴, probably by use of his thermodynamic conditions. It was surprising that use of diethyl aluminium cyanide in benzene generated the anti-cis compound 28, implying that the intermediate cis enolate is more stable than the enolate containing the trans-fused ring junction.

Scheme 4

(i) KOH (aq.), CH_3OH ; (ii) $(\text{C}_2\text{H}_5)_3\text{Al}$, HCN, THF; (iii) CH_3MgI ; SOCl_2 , pyr; (iv) DIBALH; $\text{N}_2\text{H}_4 \cdot \text{HCl}$, $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, TEG, KOH; (v) pTSA, C_6H_5 .

The use of kinetically controlled conditions (triethyl aluminium and hydrogen cyanide) generated compound 25 possessing the desired anti-trans arrangement in a yield of 86%. Several routine steps allowed the conversion of 25 to the diether 27. The viability of this A-E diaromatic approach depends upon the ability to differentiate the A ring from the E ring. It is known that a phenoxide has a higher reduction potential than an alkoxy aromatic,¹⁵ so the problem became a matter of selective cleavage of a methoxy over an ethoxy. By a modification of a known procedure¹⁶ Ireland and co-workers were able to selectively cleave the methoxy group cleanly (90%) without touching the ethoxy group. The phenol (29) so formed was sufficiently differentiated that Birch reduction conditions resulted in the reduction of the E ring only; methylation of the phenol provided compound 30. A moderate yield of 42% in the reduction could not be improved (Scheme 5). The introduction of the 8a angular methyl group presented some problems. Lithium dimethyl cuprate failed to add, probably due to the steric effect of the C-12b-angular methyl group. It was decided that the directed Simmons-

Smith reaction would be a viable alternative¹⁷. Reduction of 30 using the bulky lithium tri-*t*-butoxy aluminium hydride provided the β -alcohol 31, which, when treated with the Simmons-Smith reagent provided the β -cyclopropyl- β -alcohol 32.

Scheme 5

(i) LiPPh_2 , THF; (ii) Li , NH_3 , glyme; CH_3I ; (iii) $\text{Li}(\text{O}^t\text{Bu})_3\text{AlH}$, THF, C_6H_6 ; (iv) $\text{CH}_2\text{I}_2\text{Zn}(\text{Cu})$, DME- Et_2O

The cyclopropyl group acted not only as the latent angular methyl group, but subsequent to the oxidation of 32 to 33, it also served to assist in directing the enolization of compound 33 to the desired α -side to allow the introduction of the geminal methyl groups at C-9. Reductive ring opening of the cyclopropyl provided compound 34 which has the desired trans-anti-cis arrangement of the CDE rings. The attempted Woff-Kishner reduction of 34 to 35 gave disappointing yields at best, providing an insight into the congestion in the E ring caused by the geminal methyl groups and C-8a angular methyl group. Better results were obtained by reducing the ketone to a mixture of alcohols and subsequently forming the N,N,N',N'-tetramethyl phosphorodiamide derivative. This group was reductively removed by treatment with lithium in ammonia which also served to reduce the A ring to the α,β -unsaturated ketone 36. The introduction of the geminal methyl groups using potassium t-butoxide and methyl iodide completed the total synthesis of dl-alnusenone (19) (Scheme 6).

The alternate synthesis of alnusenone by Ireland's group¹⁸ involved a polyene cyclization approach to polycycles similar to that pioneered by Johnson¹⁹, van Tamelen²⁰ and Corey²¹. The synthesis leads to the pentacycle 30 and so constitutes a formal total synthesis of alnusenone. This alternative synthesis was undertaken partly because of the difficulties encountered in the initial synthesis with regard to differentiation of the aromatic rings and partly because of the availability in good yield of the aldehyde 37, prepared as an intermediate in the synthesis of the

Scheme 6

- (i) $\text{CrO}_3 \cdot 2\text{Pyr}$, CH_2Cl_2 ; (ii) $\text{KO}-t\text{-Bu}$, THF, CH_3I ; (iii) Li , NH_3 , THF; NH_4Cl ; (iv) N_2H_4 , $\text{N}_2\text{H}_4 \cdot 2\text{HCl}$, TEG; (v) Li , NH_3 , THF-EtOH; H_3O^+ ; (vi) LiAlH_4 , THF-Et₂O; (vii) $n\text{-BuLi}$, DME; $\text{HMPA}-\text{NEt}_3$, $\text{ClPO}(\text{NMe}_2)_2$; (viii) $\text{KO}-t\text{-Bu}$, $t\text{-BuOH}$, CH_3I .

tetracycle shionone²². This compound was not well behaved under the conditions of cyclization (stannic chloride, benzene, room temperature, 75 seconds) due to the lability of the aldehyde function and a moiety was sought which would be an effective source of cationic character without being as sensitive as the aldehyde.

The 3-methyl-2-cyclopentenol group has been shown to be efficacious in reactions of this type²³.

The aldehyde was converted into the desired 3-cyclopentenol moiety by the series of reactions shown in Scheme 7; these were initially developed in a model study. Grignard reaction of 37 with 4-trimethylsilylhomopropargyl magnesium chloride was followed with hydration, desilylation and oxidation to provide a dione which underwent an intramolecular aldol condensation to provide an α,β -unsaturated cyclopentenone. Reduction with lithium aluminium hydride provide the cyclopentenol 38 in an overall yield of 25% from 37.

Scheme 7

- (i) $(\text{CH}_3)_3\text{SiC}\equiv\text{CCH}_2\text{CH}_2\text{MgCl}$; (ii) $\text{HgSO}_4, \text{H}_2\text{SO}_4 (\text{aq.})$; (iii) H_2CrO_4 ;
 (iv) $2\% \text{ NaOH} (\text{aq.})$; EtOH ; (v) LiAlH_4

The results of cyclization of a model system had been encouraging but **38** proved to be not so well behaved. It developed that the best conditions for cyclization were stannic chloride in dichloromethane at -78°C or silica gel chromatography. The optimum yield of the desired pentacycle **39** was 83% and was always accompanied by the formation of the isomeric **39a**. Oxidative ring enlargement²³ of **39** provided the desired enone **30** and so completes a formal total synthesis of alnusenone (Scheme 8).

Scheme 8

- (i) SnCl_4 , CH_2Cl_2 , -78°C ; (ii) OsO_4 , dioxane, H_2S , CH_2Cl_2 ;
 (iii) $\text{Pb}(\text{OAc})_4$; (iv). 10% NaOH (aq.), MeOH .

Concurrent with the above approach, Ireland *et al.*

investigated the possibility of employing a preformed 6-membered E-ring already containing the C-17 methyl group²⁴. Successful cyclization would provide a pentacycle requiring only the introduction of the geminal methyl groups to furnish a compound which overlaps a previous synthesis¹³. Using the aldehyde 37 as starting material, the 4-methyl cyclohexenol 40 was synthesized in an excellent yield

of 70%. Subsequent cyclization with stannic chloride in dichloromethane-ethylene carbonate gave a complex mixture of products, containing only 12% of the desired pentacycle (41). This yield could not be improved (Scheme 9).

Scheme 9

- (i) AgNO_3 , NaOH (aq.), EtOH ; (ii) LDA , THF , HMPA , CH_3I ; (iii) LiAlH_4 ;
 (iv) $\text{CrO}_3 \cdot 2\text{Py}$, CH_2Cl_2 ; (v) $\text{C}_4\text{H}_9\text{N}$, MVK ; (vi) SnCl_4 , $(\text{CH}_2\text{O})_2\text{CO}$,
 CH_2Cl_2 ; (vii) BH_3 , THF , THF , H_2O_2 , NaOH ; (viii) H_2CrO_4

The introduction of geminal methyl groups at C-20 compound 41 would complete a formal total synthesis of alnusenone. Hydroboration/oxidation provided the ketone 42 in acceptable yield but this ketone resisted all attempts at introduction of the geminal methyls. This was attributed to steric interference by the 14a α -methyl group.

Friedelin

Ireland and Walba reported the first total synthesis of friedelin 10 ²⁵. Their scheme took advantage of Ireland's previous synthesis of alnusenone ¹³ as well as his approach to shionone ²⁶. Drawing on the experience of the alnusenone synthesis, it was decided to reduce the A ring of the diaromatic pentacycle (43) before reducing the E ring. It was hoped that this could improve the rather poor yield of 14% for modification of the E ring in the alnusenone synthesis; it was also felt that initial A ring reduction would circumvent the possibility of backbone rearrangement during a cationic cyclization step caused by the strain inherent in the cis-D-E ring junction had the E ring been previously modified. This would allow the introduction of the strained cis-DE ring junction at a less sensitive point.

By use of a slight modification of a known procedure ¹³, the key diaromatic pentacycle (43) was obtained in 25% yield; the switching of the ethyl and methyl ethers relative to 27 allowed the

differentiation of the A-ring over the E-ring to provide the ketone 44. Eschenmoser cleavage of the derived epoxide and treatment with methyl lithium afforded the tertiary acetylenic alcohol (45) which cyclized and was trapped as its enol trifluoroacetate (46). This sequence had been devised during the total synthesis of shionone ²⁶. The enolate of 46 was cycloproponated to provide 47, which was submitted to Birch reduction conditions and opening of the cyclopropyl to give 48. The E ring was modified in the fashion of the earlier alnusenone synthesis ¹³ to afford racemic friedelin (10) (Scheme 10).

Kametani and co-workers have also achieved the total synthesis of alnusenone and friedelin by intercepting Ireland's routes at the pentacyclic diether stage, compounds 27 and 43 respectively ²⁷. Kametani *et al.* devised two approaches to these molecules. The first hinged upon the double cycloaddition of an isoprene unit to a bis-o-quinodimethane to generate the pentacyclic ring system containing the correct stereochemistry. Unfortunately, 2 moles of isoprene reacted per mole of bis-o-quinodimethane (Scheme 11). The second approach involved the construction of the AB rings by a cycloaddition of a benzocyclobutene to isoprene followed by the introduction of another benzocyclobutene and a subsequent intramolecular cycloaddition to form the pentacycle.

The CDE portion of the pentacycle will arise from the iodide, 53 (Scheme 12) ²⁸. Knoevenagel condensation of the aldehyde 49 with cyanoacetic acid yielded the α -cyanocinnamic acid which was reduced and decarboxylated to give the o-bromophenylpropionitrile (50). Cyclization to the benzocyclobutane 51

Scheme 10

- (i) $(C_6H_5)_2PLi$, THF; (ii) Li , NH_3 , DME, EtOH; (iii) CH_3I , DME;
 (iv) 5 N HCl, EtOH, C_6H_6 ; (v) H_2O_2 , NaOH, MeOH; (vi) $pTsNHNH_2$,
 HOAc, CH_2Cl_2 ; (vii) CH_3Li , Et_2O ; (viii) CF_3CO_2H , $(CF_3CO)_2O$;
 (ix) LDA, THF; (x) Zn-Ag, CH_2I_2 , THF; (xi) $Li(O^tBu)_3AlH$, THF,
 C_6H_6 , $0^\circ C$; (xii) DHP, $POCl_3$, CH_2Cl_2 ; (xiii) $Li(O^tBu)_3AlH$,
 THF, C_6H_6 , Δ ; (xiv) $CrO_3 \cdot 2Py$, CH_2Cl_2 ; (xv) KO^tBu , CH_3I , THF;
 (xvi) Li , NH_3 , THF, tBuOH ; (xvii) $ClPO(NMe_2)_2$, DME, HMPA,
 $n-BuLi$; (xviii) Li , $EtNH_2$, tBuOH ; (xix) $pTsOH$, CH_3OH , THF.

Scheme 11

Scheme 12

was accomplished using sodium amide, in liquid ammonia. Treatment of **51** with LDA and condensation with the THP ether of ethylene bromohydrin provided **52**. The desired iodide **53** was formed by cleavage of the THP ether followed by formation of the tosylate and treatment with sodium iodide.

The synthesis of the precursor of the AB portion of the pentacycle is delineated in Scheme 13. Treatment of the 1-cyano-4-methoxybenzocyclobutene with an excess of isoprene in a sealed tube at 180°C provided a 1:1 mixture of the bicycles **54** and **55** in a combined yield of 84%. **55** was condensed with the iodide **53** using sodium amide in ammonia to give **56**. It was expected that this condensation would proceed with addition from the less

Scheme 13

hindered face, generating a syn relationship between the cyano and isopropenyl groups. 56 was heated in toluene in a sealed tube at 210°C for 3 h and the desired pentacycle 57 was obtained in 58% yield. Diisobutyl aluminium hydride reduction of 57 gave the diimine which was treated with Wolff-Kishner conditions to give the diether 27, Ireland's intermediate to alnusenone (Scheme 14).

Scheme 14

Switching the methoxy group to ethoxy and vice-versa provided Ireland's diaromatic friedelin intermediate 43.

The stereochemical selectivity observed in the above intramolecular cyclization was explained as a function of the relative stability of the possible conformers of the intermediate 58 (Figure 4). The exo chair conformer shown is favoured over the possible endo chair conformer, which has some steric repulsion, as well as over the boat conformer.

Figure 4

Approaches to the Synthesis of Pentacyclic Triterpenes

As pentacyclic triterpenes arise from a common biogenetic precursor it is not unusual that they bear structural features common to one another. A number of pentacyclic triterpenes are isomeric with one another, differing only in the position of a methyl group or a hydrogen. This means that large portions of these molecules are identical. For example, the disposition of the methyls and the ring junction stereochemistry of the A-B rings of lupeol (8), β -amyrin (9), germanicol (15), δ -amyrin (16) and taraxerol (17) are the same (Figure 5). Similarly, multi-

Figure 5

florenol (18), alnusenone (19) and friedelin (10) all have the same CD and DE ring junction stereochemistry and substitution (Figure 6). Partial structural identities have always been popular synthetic targets because a facile synthesis to a key intermediate can lead to the synthesis of a number of molecules with a great saving of effort. Several such approaches are presented below.

Figure 6

Heathcock *et al.*²⁹ have prepared the AB rings synthons 73 and 80 from the previously prepared keto alcohol 59³⁰. However, in their hands, Heathcock and co-workers found that the hydrogenation step generating the ring junction stereochemistry leading to 59 was

capricious, so they designed their own route to 59 as detailed in Scheme 15. Robinson annelation of 2-methyl-1,3-cyclohexadione with ethyl vinyl ketone gave the bicyclic dione 60 which was selectively reduced to afford the keto alcohol 61. The enantiomers can be resolved at this stage by forming the brucine salt of the hydrogen phthalate derivative.

Scheme 15

- (i) KOH, CH₃OH; (ii) Pyrrolidine, benzene; (iii) NaBH₄, EtOH;
 (iv) Li, NH₃, CH₃I.

(-)-61 leads to optically pure (+) 80 which has the absolute configuration found in pentacyclic triterpenes. Reductive methylation of 61 gives the keto alcohol 59 along with small amounts of reduced, unalkylated keto alcohol and dialkylated material.

Standard protection and oxidation of 59 gave the ketone 62 which was alkylated with methyl lithium to provide a 3:2 mixture of the tertiary alcohols 63 and 64 (Scheme 16). Dehydration of this mixture optimally afforded the desired ketone 65 in 89% yield along with the exocyclic ketone 66 (6%) and the rearranged ketone 67 (5%). The product ratios were quite sensitive to the acid concentration and the organic solvent that was employed. Standard ketalizations of 65 gave the desired 68 and 69 in 54% and 58% recrystallized yields, respectively. These were converted into the desired enones by two different methods. Scheme 17 delineates the route from 68 to 73. Reaction of 68

Scheme 16

(i) $HOCH_2CH_2OH$, β -naphthalenesulfonic acid; (ii) bispyridine chromium (VI) oxide, (iii) CH_3Li , (iv) H_2SO_4/H_2O , pentane;
 (v) to 68 (i); to 69 2,2-methyl-1,3-propanediol, β -naphthalenesulfonic acid

with singlet oxygen gave a mixture

of the allylic alcohols 70 (55%), 71 (24%) and 72 (21%) in a

yield of 89%. Oxidation of a mixture of these alcohols gave the

enones 73 and 74 in a ratio of 3:1.

Scheme 17

(i) $h\nu$, rose bengal, O_2 (ii) $CrO_3 \cdot Py_2$

69 was converted to the other desired enone (80) by the route shown in Scheme 18. Epoxidation of 69 with *m*-chloroperoxybenzoic acid was quantitative, giving a 1:1 mixture of 75 and 76. When separated and treated with lithium diisopropylamine, the α -epoxide gives 3:2 mixture of the desired allylic alcohol (77) to the undesirable tertiary alcohol (78). The β -epoxide reacts under the same conditions to give only the secondary

Scheme 18

(i) m CPBA; (ii) LiNPr_2 , THF; (iii) $\text{CrO}_3 \cdot \text{Py}_2$.

alcohol in 89% yield. Treatment of the 1:1 mixture of epoxides with the same base and subsequent oxidation gives the desired enone **80** and the enone resulting from the allylic rearrangement of the tertiary alcohol **78**. **80** is obtained in 58% yield from **69**.

In 73 and 80, Heathcock and co-workers have synthetic intermediates containing the functionality found in A and B rings of many pentacyclic triterpenes as well as the capacity within the B ring for coupling with a suitably functionalized DE fragment.

The same laboratory has reported the synthesis of an intermediate (82) which is suitable for use as the DE rings of 6 -amyrin ³¹.

The synthesis began with the known ³² trimethyl octalone 85. As Halsall's method was not amenable to large scale preparation, 85 was prepared as outlined in Scheme 19. Standard transformations from 83 provided 85 in 28% yield. Carbonation of the derived anion of 85 produced the keto acid 86 which was esterified with diazomethane to give 87 (Scheme 20). The ethyl ester (89) can be prepared in one step from the trimethylcyclohexanone 84 by acid catalyzed condensation with the keto diester 88 (Scheme 21).

Catalytic hydrogenation of 89 gave a single stereoisomer 90 which was shown to have the desired cis ring junction by

Scheme 19

(i) LiAlH_4 ; (ii) H_2CrO_4 ; (iii) H_2 , Pd/C; (iv) MVK

Scheme 20

(i) $\text{CH}_3\text{SOCH}_2^-\text{Na}^+$; (ii) CO_2 ; (iii) CH_2N_2

Scheme 21

hydrolysis and decarboxylation to a known compound. Reduction of 90 with lithium aluminium hydride provided the allylic alcohol 91 having the alcohol equatorial which resulted from an unusual axial hydride attack. Oxidation and treatment of the resulting enone with methyl lithium resulted in a mixture of 1,4 and 1,2 addition products 92 and 93 in 65% and 30% yields respectively. 82 was obtained quantitatively when 93 was treated with phosphorous tribromide (Scheme 22).

The preponderance of 1,4-addition product in Scheme 22 led Heathcock *et al.* to explore an alternate route to compound 82 (Scheme 23). Epoxidation of 91 gave a 3:1 mixture of β -addition product (94) to α -addition product (95). Treatment of the mixture with Jones reagent led to the isolation of 96 as the only oxidized product in 60% yield. Methylenation and reduction provided the alcohol 97 which was readily converted into the target molecule.

Scheme 22

- (i) H_2 , Pd/C ; (ii) LiAlH_4 ; (iii) Jones reagent; (iv) CH_3Li ;
 (v) PBr_3

Scheme 23

- (i) m CPBA; (ii) Jones reagent; (iii) $(C_6H_5)_3P=CH_2$, Me_2SO ;
 (iv) Li , $C_2H_5NH_2$; (v) PBr_3

ApSimon *et al.*³³ have also recognized the advantage to be gained by synthesizing an intermediate amenable to the synthesis of several molecules. Their intermediate, **98**, contains the *cis* DE ring junction found in friedelin (**10**), alnusenol (**19**), multi-florenol (**18**) and taraxerol (**17**). The key intermediate towards **98** was the carbomethoxy octalone **100**. Scheme 24 outlines its synthesis from ethylacetoacetate. Carboxymethylation of 3,3-dimethyl-

Scheme 24

- (i) HCHO , piperidine; (ii) H_2SO_4 ; (iii) MeMgI , CuI ;
 (iv) $\text{CO}(\text{OMe})_2$, NaH ; (v) EVK , NaOMe .

cyclohexanone provided the keto ester 99. Robinson annelation of 99 with ethyl vinyl ketone gave the octalone in 35% yield from ethyl acetoacetate. Literature precedent seemed to favour generation of the cis decalone via catalytic hydrogenation ^{31,32} although Dauben and Rogan obtained the trans decalinol upon hydrogenation of the keto ester 101 ³⁴. Catalytic hydrogenation of 100 by several

catalysts and conditions gave only the undesirable trans stereochemistry as was shown by x-ray analysis ³⁵. The desired cis decalone was obtained by reduction of the corresponding hydroxymethyl compound (105) (Scheme 25). Lithium aluminium hydride reduction of 100 provided the diol 102 (60%) as well as some mono-reduced product (15%). Activated manganese dioxide effected the allylic oxidation of 102 to the desired keto alcohol (105) but the large amounts of manganese dioxide necessary precluded the use of this route for any large scale preparations.

Scheme 25

(i) LiAlH_4 ; (ii) MnO_2 ; (iii) $\text{HOCH}_2\text{CH}_2\text{OH}$, pTSA; (iv) 10% HCl ;
 (v) 10% Pd/C , H_2 .

Ketalization of 100 proceeded smoothly, although some double bond isomerization occurred. Reduction of 103 to 104 and subsequent deprotection provided the keto alcohol (105). Catalytic hydrogenation provided the cis decalone 98 along with some hydrogenolysis product.

ApSimon *et al.*³⁶ have also described the synthesis of a pentacyclic precursor of triterpenes, specifically towards friedelin (10). The strategy employed the coupling of a tricyclic ABC ring precursor with an E ring precursor. The tricyclic ketone 110 has been described³⁷. The synthesis of the E ring precursor (109) is presented in Scheme 26.

Scheme 26

- (i) $\text{CH}_2(\text{CN})_2$, KF; (ii) $\text{HOCH}_2\text{CH}_2\text{OH}$, pTSA, (iii) KOH;
 (iv) 140-145°C; (v) LiAlH_4 ; (vi) pTsCl, pyr.

Potassium fluoride catalyzed Michael addition of malonitrile to 3,6,6-trimethylcyclohexenone provided the ketone 106 which after protection was hydrolyzed to the diacid 107. Thermal decarboxylation afforded 108 which was reduced and tosylated to give the E-ring precursor 109. Alkylation of 110 was accomplished using the dienolate ion generated using potassium *tert*-amylate to form 111 as a mixture of diastereomers (Scheme 27). Hydrolysis of the ketal

Scheme 27

provided the diketone 112 which was subjected to a variety of conditions designed to effect cyclization. Although it was expected that the condensation of 109 and 110 would give a mixture of diastereoisomers, it was hoped that one of these isomers would cyclize preferentially over the other; it was felt that the desired isomer would demonstrate a greater proclivity toward cyclization.

A number of bases failed to give the desired intramolecular aldol-like condensation. Tert-butyl magnesium chloride did selectively effect the reaction of one diastereomer, but not in the desired sense; hydride transfer from the Grignard reagent had reduced the E-ring carbonyl. Acid catalysis was attempted; p-toluene sulfonic acid in boiling xylene yielded a crystalline material which x-ray analysis showed to be 113.

In order to minimize rearrangement products derivable from intermediate cations during cyclization, the double bond in 112 was catalytically reduced with predictable stereochemistry to give compound 114 (Scheme 28). Both diastereoisomers of 114 reacted in boiling xylene in the presence of *p*-toluene sulfonic acid; one product was crystalline (45%) and was shown by x-ray to be the pentacycle 115. The other isomer was difficult to purify and has defied characterization.

Scheme 28

RESULTS & DISCUSSION

The various total syntheses of pentacyclic triterpenes and approaches thereto, described in the introduction of this thesis, speak eloquently of the complexity of these molecules and of the ingenuity shown by the synthetic chemist in meeting the challenge of the complexity. This ingenuity notwithstanding, there is yet a perceived need for the development of syntheses that are more efficient, perhaps by virtue of their employment of more modern ideas and techniques, or perhaps by the synthesis of intermediates suitable to the total synthesis of several different natural products. This thesis investigates three approaches to the synthesis of an intermediate suitable for use as the CDE-ring fragment in an A + CDE approach to the total synthesis of friedelid (10), taraxerol (17), multiflorenol (18) and alnusenol (19).

Friedelin (10), multiflorenol (18) and alnusenol (19) have identical CD and DE ring junction stereochemistry and substitution:

Taraxerol lacks the C-14 β -methyl group but does have the remaining structural features. The trans-anti-cis arrangement of substituents

around the ring junctions is not unstable per se. However, the cis-DE-ring junction forces the C-20 α -methyl group into a 1,4-diaxial interaction with the C-13 α -methyl group. This is the apparent reason for the susceptibility of friedelanes to backbone rearrangement⁹. Ireland had some difficulty introducing the C-20 methyl groups as the ultimate step in one of his syntheses towards alnusenone²⁴, because the C-13 α -methyl group was hindering the approach of the reagent.

It was felt that it would be worthwhile investigating the construction of a synthetic intermediate having the above characteristics. Three different routes were explored; it developed that each route had initial introduction of the geminal methyls and the C-17 β -methyl group, followed by the attempted introduction of the C-13 α -methyl group. The first route described utilized a hydroxy-directed Simmons-Smith reaction on a tricyclic intermediate; the second involved an intramolecular carbene addition via a diazo ester on a bicyclic intermediate; the last route capitalized on an intramolecular Diels-Alder reaction of a monocyclic material bearing a sidechain.

The CDE Route

The initial approach to the desired tricycle represented a C + E $\longrightarrow$ CE $\longrightarrow$ CDE ring construction strategy. It appeared that it would be possible to introduce the crucial C-13 α -methyl group stereospecifically, after the cis DE ring junction has been established, possibly by employing a hydroxy-directed³⁸ Simmons-Smith reaction on the alcohol 117 (Figure 7).

Figure 7

This strategy was employed by Ginsig and Cross³⁹ in their synthesis towards 10 α -testosterone (Scheme 29).

Scheme 29

The resulting cyclopropyl alcohol could then be converted into the desired allylic alcohol by acid catalysis.

Scheme 30 depicts a possible retrosynthetic route leading to 116; the α hydroxy compound 117a would be available from the corresponding ketone by taking advantage of the concave morphology caused by the cis DE ring junction.

Scheme 30

Daum et al.⁴⁰ synthesized the tricyclic 119 by alkylating

the ketoester 120 with *m*-methoxyphenylethyl bromide. Treatment of the resulting pendant bicycle with sulfuric acid cyclized and decarboxylated the bicycle to afford 119 (scheme 31).

Scheme 31

Several years ago this laboratory developed a synthesis of aketoester analagous to 120, bearing geminal methyls in the 5 position and lacking the ketal³³. This ketoester (99) is eminently suitable as an E ring precursor and is available in 35% overall yield from ethyl acetoacetate in several steps. Treatment of 99 with potassium-*tert*-butoxide followed by *m*-methoxyphenylethyl bromide afforded the alkylated ketoester 121 in a disappointing yield of 31% (Scheme 32). Mild acid catalysis with concomitant removal of

Scheme. 32

(i) KO^tBu, ^tBuOH; (ii) pTSA, benzene.

water gave the ester 122 in 83% yield. Transformation of 122 to the immediate goal (118) requires the introduction of the cis ring-junction stereochemistry and the reduction of the angular carbomethoxy group to the desired methyl group.

In order to effect the generation of the desired cis DE ring junction, it was felt that advantage could be taken of the known directing influence of hydroxymethyl groups on the stereochemical course of catalytic hydrogenations ⁴¹. ApSimon et al. ³³ demonstrated this quite effectively in their synthesis of the cis decalin 98 from the ester 100 via the intermediacy of the hydroxy ketone 105 (see Scheme 25). Hydrogenation of the ester itself gave only the

undesirable transring junction (123); hydrogenation of 105 gave exclusively the cis compound (Figure 8).

Figure 8

Thompson *et al.*⁴² have investigated the stereochemical course of reduction in a system remarkably similar to the tricycle 122 (Scheme 34). They found that the catalytic reduction of the ester 124 (R = Et) gave the expected trans compound 125, which was reduced to the alcohol 126. Dissolving metal reduction of the acid 124 (R = H) provided a material which was assigned a cis stereochemistry (127) on the basis of a comparison of its lithium aluminum hydride reduction product (128) with that from the hydrogenation and reduction of the ester (126). Initial reduction of the ester 124 to the alcohol 129 and subsequent hydrogenation provided a somewhat anomalous result. It was expected that the directed influence of the angular hydroxymethyl would result in hydrogenation from the β -face of the molecule, producing a cis

ring junction. In fact, the ratio of cis product to trans product proved to be extremely solvent dependent, varying from 80:20 in hexane to 9:91 in DMF (cis:trans).

Scheme 34

(i) Li, NH₃; (ii) LiAlH₄; (iii) 5% Pd/C, H₂.

Scheme 35 depicts the course of investigation of the reduction of the ester 122. Catalytic hydrogenation of 122 provided a single ester (130) in 98% yield which was further reduced with lithium aluminum hydride to afford the alcohol 131⁴³. Initial

reduction of 122 with hydride afforded the unsaturated alcohol (132) in 97% yield which, when subjected to catalytic hydrogenation, gave a mixture of cis (133) and trans (131) alcohols (36:64 cis:trans). Although the conversion of the angular substituent from ester to hydroxymethyl did allow for the production of a relatively greater amount of the cis product (36% compared to 0%), it did not effect the desired reversal of stereochemistry.

Scheme 35

(i) 10% Pd/C, H₂; (ii) LiAlH₄

Thompson et al.⁴² were able to reduce the unsaturated

124 to the cis compound 127 (Scheme 34) by using lithium in liquid ammonia. To this end, the ester 122 was hydrolyzed with potassium hydroxide in refluxing methoxyethanol and afforded the required acid 134 in a yield of 71% (Scheme 36). Reduction of 134 by lithium in liquid ammonia gave a single saturated carboxylic acid 135, which was reduced by lithium aluminium hydride to provide a saturated alcohol 133 which was not identical to the alcohol obtained by lithium aluminium hydride reduction of 130 (131)⁴³.

Scheme 36

(i) KOH, CH₃OCH₂CH₂OH; (ii) Li, NH₃; (iii) LiAlH₄

The relative stereochemistries of the alcohols 133 and 131 were assigned on the basis of literature precedent for the

crucial reduction steps ^{42,44} and on the basis of their ¹³C and ¹H NMR spectra. The ¹³C-shift of the hydroxymethyl carbon in 131 appears at 59.2 ppm; the analogous carbon in 133 resonates at 69.2 ppm. In methyl decalin systems it is known that the angular methyl group in the trans-decalin is shielded significantly relative to the corresponding cis-decalin (Figure 9).

Figure 9

The C-10 hydroxymethyl protons of 131 appear as a pair of doublets at δ 3.20 and 3.61 ($J = 11$ Hz.) while in 133 they show up at δ 3.30 and 3.42 ($J = 11$ Hz.). The chemical shift separation of the doublets in the trans isomer is substantially greater than the cis isomer ($0.41 > 0.12$). This can be explained by considering the probable conformers 131 and 133 (Figure 10) (Note that only one rotamer is shown). In 131 the preferred configuration allows one of the protons to experience the anisotropic effect of the phenyl ring causing this proton to be shielded relative to the other proton. No such effect is apparent in the preferred conformer of 133.

Figure 10

These stereochemical assignments are further supported by spectra of subsequent intermediates in the synthetic sequence.

McMurry *et al.*⁴⁴ have considered the participation of an angular carboxyl group in the reduction of a nearby reducible double bond and have postulated that the carboxylic acid function acts to direct the approach of a proton donor from the syn-face, so providing the cis-stereochemistry. Alternatively, the carboxyl function might serve to stabilize the cis-anionic intermediate over the analogous trans intermediate (Figure 11).

Lithium in ammonia reductions were carried out on the ester 122 and the alcohol 132 and the results support the contention that an acidic functional group can be effective in deciding the stereochemical course of such reductions. The ester 122, upon reduction,

provided essentially an 1:1 mixture of cis:trans (47:53) while the alcohol functionality in 132 displayed a significant directing ability, producing a mixture which heavily favoured the cis isomer (82:18). The greatest stereoselection was predictably shown by the carboxylic acid function itself, producing the cis isomer almost stereoselectively (>98%).

Thompson has continued to investigate the hydroxymethyl group as a director or chelator of reducing agents and has shown significant stereoselection in reductions using lithium aluminium hydride and diimide ⁴⁶ as well as with the ethylenediamine complex of chromium (II) sulfate ⁴⁷.

Figure 11

With the cis alcohol 133 in hand, several routine steps led to the production of the tricyclic ether 118 (Scheme 37). Treatment of 133 with pyridinium chlorochromate in methylene chloride efficiently provided the aldehyde 136, which was subjected to

Wolff-Kishner reduction conditions to provide the desired ether 118. The harsh conditions employed also caused some demethylation of the ether, producing the phenol 137. The reaction mixture was treated with sodium hydride and methyl iodide to provide 118 in good yield (75%) from the aldehyde (136). A comparison of the ^{13}C NMR spectra of 118 and the trans ether derived from 131 further support the stereochemical assignments made on the alcohols 131 and 133.

Scheme 37

(i) PCC; (ii) Wolff-Kishner reduction; (iii) NaH, CH₃I, THF

Following the strategy outlined in Scheme 30, the tricyclic ether 118 was subjected to reduction by lithium in liquid ammonia to afford the α,γ -enone 138 in 89% yield (Scheme 38).⁴⁸

Scheme 38

(i) Li, NH₃

Molecular models of 138 indicate that of the two possible chair conformers of the E-ring, one has a very severe non-bonded interaction between the α -geminal methyl and C-1 and C-2 α -hydrogens (Figure 12). The other E-ring chair conformer has no such interactions.

Figure 12.

Assuming the D-ring can be depicted as a half-chair conformer, it remains to consider the two half-chairs that can be conceived for the C-ring (Figure 13). The relative inflexibility of the E-ring

Figure 13

coupled with the 4b-8a unsaturation serve to restrict the conformational mobility of the D-ring. A more usual depiction of the two C-ring conformers is shown in Figure 14.

Figure 14

In conformer A, the carbonyl seems accessible from either face with equal facility. The only steric constraint which might be involved would arise from the C-4 carbon which is sitting axial to the plane of the CD rings; this could serve to make approach from the β -face slightly more attractive. A similar situation exists for conformer B. Either face of the carbonyl seems to be available to ready approach by a reducing agent. However, the 10a-axial methyl group might exert some influence on an attacking group, especially if that group were very large.

Some years ago Hartman⁴⁹ reported that the lithium aluminium hydride reduction of 17 β -hydroxyestrene-3-one (139) gave a single epimeric alcohol to which he assigned the β -configuration (Scheme 39). Further investigations by Levine *et al.*⁵⁰ showed that in fact the α -hydroxy compound is obtained. They used lithium tri-*tert*-butoxy aluminium hydride to effect the reduction of 17 β -hydroxy- $\Delta^5(10)$ -estrene-3-one propionate and found that two alcohols were obtained. The major isomer (81-83%) (140) was

saponified to give a diol which was identical to that obtained by Hartman. Both 140 and the minor isomer were treated with osmium tetroxide to provide separable mixtures of triols which corresponded to the syn addition of 2 moles of hydroxyl across the double bond
Scheme 40

Scheme 40

1. OsO_4 , benzene.

The NMR spectra of the two triols arising from 140 displayed the C-3 proton resonance at δ 4.08 and δ 3.70 with peak width at half-height of 20 and 22 Hz, respectively. The two triols from 141 presented the C-3 hydrogen at δ 4.01 and δ 4.12 with $W_{1/2}$ of 8 Hz, each. This narrow band at half height is characteristic

of equatorial protons, while the broad band is characteristic of protons sitting axially⁵¹. Steroid models indicated that with the AB cis ring system in a chair/chair conformation a C-3 axial proton will have the β -configuration. It follows then that the major reduction product of the 17 β -hydroxy- $\Delta^{5(10)}$ -estrene-3-one is the α -hydroxy compound 140.

It has long been known that hydride reduction of unhindered ketones generally gives the equatorial alcohol as the major if not the only product⁵². The reduction product of 5(10)-unsaturated 3-keto steroids should be an equal mixture of the two epimeric alcohols as both the α - and β -hydroxy can adopt a conformation having the alcohol equatorial (Figure 15). Levine et al.⁵³

Figure 15

attribute the unusual stereoselectivity to a large non-bonded interaction between the C-11 α -H and C-1 β -H which forces the A-ring to adopt that conformation which will allow for the formation of the equatorial α alcohol (Figure 16).

Figure 16

Models suggest that the ketone 138 has no such interaction and both C-ring conformers appear to be equally favoured. Any stereochemical preference in reduction will result from the steric effect exerted on the α -face by the C-10a angular methyl group and on the β -face by the C-4 carbon and its hydrogens.

The initial reductions were carried out using sodium borohydride in ethanol at 0°C and provided an 88% yield after purification of an alcohol that was homogenous by thin layer chromatography (tlc). The IR spectrum displayed the expected broad absorption centred at 3325 cm^{-1} . The NMR showed a 3H singlet at δ 0.95 ppm and a 6H singlet at δ 0.97 ppm along with some unresolved multiplets from 1.1-2.2 ppm. The C-7 hydrogen (phenanthrene numbering) appeared as a broad absorption centred at 3.95 ppm. The peak width at half-height was measured to be 21 Hz, which is characteristic of an axial proton; this is not surprising as the equatorial alcohol was predicted. It was expected that the relatively small reducing agent would provide a mixture of epimers and that the employment of bulkier reducing groups would allow for the enhancement of one

epimer over the other. ^{13}C NMR showed that in fact a mixture had been obtained; the carbinol resonances appeared at: 67.99 and 67.57 ppm. Gas chromatographic analysis of the mixture of derivided trimethylsilyl ethers failed to provide any insight into the proportion of α -epimer to β -epimer as no resolution could be effected. This was not surprising as a packed column was used and the conformational differences between the α -equatorial alcohol and the β -equatorial alcohol are slight indeed. It was felt that ^{13}C NMR would be a satisfactory probe in that when the bulkier reducing agents were employed, a change in the α/β ratio would be reflected in the relative intensities of the two carbinol carbon resonances.

To this end, various reducing agents were used including Red-Al ⁵⁵, L-selectride ⁵⁶ and lithium tri-tert-butoxy aluminium hydride ⁵⁷. These reagents were singular in their failure to stereoselectively reduce the ketone functionality in compound 138 as judged by ^{13}C NMR. This was somewhat surprising as lithium tri-tert-butoxy aluminium hydride has been shown to provide greater

than 80% stereoselection in the reduction of some steroids ^{50,53,58}

and lithium tri-sec-butyl borohydride ⁵⁶ (L-Selectride) is known to be extremely sensitive to even remote steric encumbrances.

As it is known that tetrasubstituted double bonds are often reluctant to undergo catalytic hydrogenation, it was felt that it might be possible to hydrogenate the ketone functionality in 138 and use the bulk of the catalyst surface to facially discriminate the molecule. Hydrogenation of 138 in aqueous ethanol in the presence of pre-hydrogenated 5% ruthenium on carbon at 1 atmosphere and room temperature for an extended period of time (72 hours) produced no detectable reduction products ⁵⁸.

Faced with this disappointing inability to generate some stereoselection in the reduction step and with the epimeric alcohols in hand, it was felt that a worthwhile course of investigation would be the Simmons-Smith methylenation of the mixture of alcohols. Although the faces of ketone 136 proved to be sterically indistinguishable towards reduction, it is possible that the epimeric alcohols might display differential reactivity towards the Simmons-Smith reaction. After all, the reactive site in the form of the 4b-8a double bond has been moved ~~closer~~ to the perceived steric contributors: the 10a--methyl and the C-4 carbon. If models of the epimers are considered, with each having the E and D rings in a chair and half chair conformation respectively, and the C-ring in the half chair conformation carrying the alcohol axially (to deliver the Simmons-Smith reagent) it is possible to expect that one side is more encumbered than the other (Figure 17).

Figure 17

Interestingly, Chan and Rickborn⁵⁹ suggested that 2-cyclohexenols undergo Simmons-Smith methylenation through a quasi-equatorial conformation, while the homoallylic 3-cyclohexenols effect methylenation only with the alcohol in an axial conformation⁶⁰.

Both the C-10a methyl group and C-4 carbon sit axially relative to the plane of the C-4b-8a double bond, but the C-10a methyl group forms an angle of $< 90^\circ$ to this plane while the C-4 carbon forms an angle $> 90^\circ$ (Figure 17); the methyl group is leaning towards the double bond. It was hoped that this might differentiate the faces sufficiently.

In the event, there were no conditions found that effected the methylenation of the 4b-8a unsaturation. Generally the method followed was adapted from Rawson and Harrison⁶¹ with the zinc portion of the reagent being activated by stoichiometric amount of cuprous chloride rather than by the presence of copper metal (For a comprehensive review of the Simmons-Smith reaction see ref. 62).

The stoichiometry of Simmons-Smith reagent to unsaturated alcohol ranged from 1.1 to 30 equivalents and diethyl ether and THF were employed as solvents.

In a typical procedure, zinc dust (35 mg, 0.6 mmol) and cuprous chloride (67 mg, 0.5 mmol) in 8 mL of anhydrous ether were refluxed under argon for 1 h. The alcohol 117 (35 mg, 0.1 mmol) in 1 mL of anhydrous ether was added dropwise, followed by the addition of methylene iodide (50 mg, 0.2 mmol). The mixture was refluxed for 18 h. The order of addition of the alcohol and methylene iodide can be reversed with no deleterious effect⁶²; after cooling, the mixture was poured into 25 mL of saturated aqueous ammonium chloride and filtered. The filtrate was extracted with ether (2 X 25 mL) and the combined organics were washed with saturated ammonium chloride (aq) (25 mL), and saturated sodium chloride (aq) (25 mL) and dried over anhydrous magnesium sulfate.

Invariably, a good yield of starting material was realized in each attempted methylenation. Ginsig and Cross³⁹ reported that estr-5(10)-ene-3, 17-diol (See Scheme 29) was inert to the usual Simmons-Smith conditions and that a good yield of cyclopropanated material was obtained when the reaction was done at a very high concentration in ether in a stainless steel tube at 92°C. Forcing conditions were tried on the alcohols 117; preformed Simmons-Smith reagent was added to the alcohol in ether in a sealable vial. After sealing under argon, the vial was heated to 80-90°C for up to 18 h. Starting material was recovered. Ginsig and Cross reported a substantial amount of etherification

of the hydroxyl group caused by reaction with methyl and ethyl iodide, by-products of the reaction. No etherification was encountered.

In consideration of the failure of numerous cyclopropanations, it was concluded that the 4b-8a double bond was too sterically congested to allow for the approach of the organometallic Simmons-Smith reagent. This is not surprising as the susceptibility of this reaction to steric interference is known⁶². Faced with this disappointing lack of reactivity, this once-promising route was abandoned in favour of those routes whose descriptions follow.

The DE Route

The disappointing failure of the above-described tricyclic route led to a re-evaluation of the synthetic strategy towards the desired intermediate 116. From a synthetic point of view, the key features of this compound are the anti-cis arrangement of the 4b α -methyl group, the 4a β -hydrogen and 10a β -methyl as well as the C-3 geminal methyl groups. As its ultimate stereochemical step, the above route was to have had the introduction of the 4b α -methyl to a system already containing the cis-ring junction and the geminal methyl groups. It was felt that the rationale behind this approach was sound in that it seemingly offered a greater chance of success than the alternatives: introduction of the geminal methyl groups or introduction of the cis DE ring junction as a last stereochemically-significant step.

The establishment of stereochemistry at C-4b can be considered in two ways: the introduction of the methyl group from the α -face or the introduction of the nascent C-ring carbons from the β -face. The lack of success with the Simmons-Smith reaction on compound 117 was due in large part to the steric congestion at the reactive site. This steric congestion could be side-stepped by alkylating a suitably functionalized intermediate containing a C-4b methyl group from the β -face and so persuade the methyl group to adopt the α -configuration. Several such ideas have been previously investigated in these laboratories.

The bicyclic ketone (143) was available in six steps from dimedone⁴³ and was considered to be a suitable substrate for

intermolecular alkylation as the cis-ring junction causes the molecule to adopt a hinged shape; this creates a differential accessibility to the two faces, with the β -face being more available (Figure 18). It had been planned to perform the alkylation

Figure 18

on the trimethylsilylenol ether 144 but this proved to be not readily available from 143. The enol ester 145 was available quantitatively from 143 by treatment with acetic anhydride and a catalytic amount of perchloric acid (Scheme 41). The lithium enolate of 145 failed to react with allyl bromide in a number of solvents such as ether, THF and DME, but when hexamethylphosphoramide was used as solvent, and allyl bromide again, as alkylating agent, a good yield of O-alkylated product 146 was obtained. This material is able to undergo a Claisen rearrangement and it was hoped that it would proceed by the stereoelectronically-favoured axial attack ⁶³ to give the α -methyl group. A moderate yield of 45% of rearranged product (147) was obtained by refluxing 146 in diglyme ⁴³ (Scheme 42).

Scheme 41

(i) Ac_2O , HClO_4 ; (ii) $\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$, HMPA ; (iii) $\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$, TiCl_4 , -78°C .

Scheme 42

The stereochemistry at the alkylation site was in question until a lanthanide shift study of the derived isomeric alcohol showed that the C-4b methyl group had the α -configuration⁶⁴.

The trimethylsilylenol ether 144 is derivable from 145 via the lithium enolate and this type of enol ether has been shown to be susceptible to Lewis acid promoted alkylations⁶⁵.

Addition of 144 to a mixture of titanium tetrachloride and allyl bromide at -78°C led only to the recovery of the ketone 143.

At this point, the intermolecular alkylation of an enolate in this system was considered to be of little synthetic value.

Consideration was then given to an intramolecular approach wherein the alkylating agent and the enolate are in the same molecule. This strategy offers several advantages over the intermolecular route in that a substituent of known relative stereochemistry can be used as a point of attachment for the alkylating group and so ensure the stereochemical outcome of the alkylation; and intermolecular side reactions such as dimerization and polymerization, common in the usual alkylation reactions, are minimized. On the other hand, the setting-up of an intramolecular alkylation generally adds steps to a synthesis and that which is gained in one sense might well be lost in another.

As it had been decided to have the ring junction stereochemistry in place, a functionalized 10a β -methyl group could be used as the attachment point for the intramolecular alkylating agent (Figure 19). The R and R₁ groups must be of a nature to allow for further functionalization to 116.

Figure 19

It is known that diazoacetic esters decompose in the presence of certain metals to give carbenes or carbenoid species, which are capable of adding to olefins to form cyclopropanes⁶⁶. House and Blankley took advantage of this in their preparation of some perhydroindan derivatives in an intermolecular sense⁶⁷ and less successfully in an intramolecular sense⁶⁸. It was felt that such an intramolecular carbenoid addition might find application in this synthesis. To this end, compound 98 was considered to be eminently suitable as a starting point in the envisioned synthesis. A retrosynthetic scheme is presented in Figure 20 and depicts the use of the γ -hydroxymethyl group as the internal director of carbenoid addition.

The original synthesis of compound 98 is described in Scheme 25³³ but this route was found to be somewhat capricious and an alternative method was developed by Dr. K. Fyfe⁶⁴. The bicyclic alcohol 98 was derivable from the ester 100 via either a ketalization-reduction process or a double reduction-allylic

Figure 20

oxidation process (Figure 21). The latter required a large excess of manganese dioxide and was unsuitable for large scale work.

The former also had a serious flaw in that the mixture of ketals 103 was extremely unstable, requiring that the reduction be performed immediately on the crude mixture from the ketalization. On larger scale reactions, the yields dropped to unacceptable levels.

The problem of instability of the ketal mixture 103 was overcome by the use of the thioketal protecting group. Treatment of enone 100 in methanol with 1,3-propanedithiol in the presence of gaseous hydrochloric acid provided 148 in 83% recrystallized yield (Scheme 43). Routine reduction of this ester with lithium aluminium hydride afforded the hydroxythioketal 149 in 91% yield. The initial removal of the thioketal protecting group was effected using 1,3-diiodo-5,5-dimethylhydantoin⁶⁹; although a good yield of enone was obtained, residual sulfur compounds poisoned the subsequent catalytic hydrogenation. The mercuric chloride-mercuric oxide

Figure 21

method of thioketal removal ⁷⁰ forms insoluble complexes with sulfur compounds and so allows for their removal by filtration. This technique provided an excellent yield (95%) of the enone **105** which was essentially free of sulfur-containing contaminants.

A more direct route to **105** was developed by Dr. Fyfe involving the DIBALH reduction of the ester functionality of **100** while the ketone functionality was protected as the enolate (Scheme 44) ⁶⁴.

Scheme 43

- (i) 1,3-propanedithiol, HCl; (ii) LiAlH_4 ; (iii) HgCl_2 , HgO ;
 (iv) 10% Pd/C, H_2

Scheme 44

- (i) LDA; (ii) DIBALH

The work-up of this reaction was plagued with emulsions; this contributed heavily to the reported low yield of 51, which would not be unacceptable given that this reaction is replacing three others: protection, reduction and deprotection. In our hands, however, the maximum yield obtained was only 29, which represented too great a loss of material. Consequently, the dithiane route was employed in the production of 105 and represented an improvement over the previously reported synthesis (Scheme 25).

With the acquisition of 105, the modified synthesis merges with that depicted in Scheme 25; all that remains is the catalytic hydrogenation of the enone to the cis-ketone 98. When 105 is hydrogenated in ethyl acetate over 50% by weight of 10% palladium on charcoal, a yield of 88% of ketone 98 is obtained if the scale of the reaction is relatively small (< 2 g). Attempts to scale-up the reaction resulted in a rapid decline in the yield and on a synthetically useful scale of 10 g, the reduction failed totally, even with prolonged reaction times. This unfortunate dependence on scale remains a major problem in this synthesis; large quantities of 98 were obtained by performing a number of small-scale reductions as described. These reductions are quite clean and essentially complete after 14 h.

The reactions of diazo carbonyl compounds with various metals have been the subject of several reviews^{66,71}. Recently, Anciaux *et al.* have postulated that there are two possible mechanisms which might be in operation in cyclopropanations, depending upon the metal catalyst⁷². A mechanism which they describe as a carbenoid

mechanism involves the reaction of the olefin substrate (S) with the carbenoid-metal complex (Figure 22). Rhodium carboxylates

Figure 22

probably act in this fashion, being only mildly affected by strain, coordinating ability and steric hinderance. Palladium catalysts are quite sensitive to these factors and usually will only cyclopropanate activated or strained double bonds. Palladium has an additional coordination site available and the mechanism shown in Figure 23 presents an initial complexation of the metal and olefins followed by a coordination with the diazo compound. Loss of nitrogen provides

Figure 23

a complex containing the olefin and carbenoid associated with the same metal. Obviously such an intermediate would be extremely sensitive to steric considerations. The advantage that palladium catalysts offer is in their selectivity in intramolecular competition reactions, with the less substituted bond being the more reactive.

Copper seems to be intermediate relative to rhodium and palladium; depending upon the ligands, copper can act in a purely carbenoid sense as with copper acetylacetonate or it can display the selectivity shown for the coordination mechanism as with copper triflate.

The initial substrate for attempted intramolecular cyclopropanation was the diazo diester 150 (Scheme 45)⁶⁴. This material was readily available from the keto alcohol 98; treatment of 98 with carboethoxyacetyl chloride in the presence of 4-dimethylamino pyridine provided the diester 151 in 70% yield. The enol acetate was readily formed using acetic anhydride and perchloric acid and treatment of 152 with triethylamine and *p*-toluene sulfonylazide in acetonitrile gave the diazo-ester 150 in 95% yield.

Scheme 45

As palladium catalysts involve olefin coordination and considering the hindered nature of the double bond in 150, it was felt that copper and rhodium catalysts would be more successful in effecting cyclopropanation. Copper (II) sulfate failed to decompose the diazo function; copper bronze in refluxing toluene gave rise to a plethora of products. The rhodium (II) acetate dimer is known to be an excellent catalyst for cyclopropanation ⁷². Treatment of 150 in hexane with this catalyst led to the disappearance of the diazo

functionality as shown by IR spectroscopy and work up allowed for the isolation of one major product which showed itself to be the hydrolysis product 153 (Scheme 46).

Scheme 46

The reaction was performed under anhydrous conditions; this addition of water occurred during the work up, indicating that the intermediate carbene has an unusual stability. This could arise as a function of the carbene being situated between two esters or it could be a manifestation of a lack of reactivity of the tetrasubstituted double bond.

The last catalyst used on 150 was copper acetylacetonate which has the advantage of solubility in some ether solvents such as dioxane. The slow addition of 150 to a refluxing solution of copper acetylacetonate in dioxane resulted in the rapid decomposition

of the starting material and production of a major, more polar product. The mass spectrum of this product indicated that addition of $-\text{CH}_2\text{CH}_2\text{O}-$ had occurred and the structure 154 was tentatively assigned.

The failure of 150 to undergo the desired cyclopropanation under a variety of conditions prompted the investigation in this thesis of a slightly simpler system. The diazoacetic ester 155 has

a substantially smaller pendant side chain which will help to minimize the congestion during cyclopropanation; the carbene derived from 155

might well be more reactive than that from 150. The diazoacetic ester 155 was synthesized according to the method of House and Blankley ⁶⁸.

The benzene sulfonylhydrazone of glyoxylic acid was converted into the acid chloride (156) by treatment with thionyl chloride (Scheme 47). Condensation of this acid chloride with an alcohol

Scheme 47

156

in the presence of one equivalent of a mild base yields a stereoisomeric mixture of hydrazone esters. Thus, coupling of 156 with 98 provided the esters 157, which were not isolated, but were treated with a second equivalent of triethylamine to provide the keto-diazoester 158 (Scheme 48). House and Blankley reported that their diazoacetic esters were most efficiently prepared by the initial use of two equivalents of triethylamine. Application of this method to the synthesis in Scheme 48 provided the diazoester 158 in a yield of 43%. This disappointing yield might well be a function of a side reaction which has recently been investigated by

Schème 46

Corey and Myers⁷³. They report that the tosyl hydrazone of the acid chloride of glyoxylic acid can react with triethylamine to form a ketenyl species capable of rearranging to a diazoester. This, in turn, can react with the added alcohol to form a *p*-toluene-sulfinate ester (Figure 24).

Figure 24

2

This problem is circumvented by the use of a base which is not strong enough to form the proposed ketenyl intermediate.

Dimethylaniline allowed for a general increase in yields of approximately 50%.

As an alternative to the use of two equivalents of triethylamine, sodium bicarbonate in dichloromethane provided 157 in 56% yield, which when treated with triethylamine gave 158 in good yield (72% from 157). However, the overall yield of this two-step process was actually lower than the one-step process: 40% compared to 43%. It is quite possible that the sodium bicarbonate was strong enough to effect the reaction shown in Figure 24 and hence lower the yield of 157 appreciably.

With 158 in hand, it remained to introduce the enol acetate function. Treatment of the keto diazoester with acetic anhydride and a catalytic amount of perchloric acid in the usual fashion failed to introduce the desired functionality. The reactions were monitored by thin layer chromatography which showed the slow consumption of starting material and the appearance of a poorly resolved streak. Infrared analysis showed the complete absence of the extremely strong diazo absorption at 2110 cm^{-1} . The reactions were run under an inert atmosphere and in the absence of light in an effort to minimize decomposition of the starting material; the keto diazoester is not compatible with the conditions employed.

As it was apparent that the enol acetate could not be readily introduced with the diazo function already in place a rather circuitous route of protection, enol acetate formation, deprotection

and diazoacetic ester formation was undertaken (Scheme 49). It was found that initial protection of the alcohol allowed for reproducible results in the sometimes capricious enol acetate formation.

Scheme 49

- (i) ClCH_2COCl , pyr.; (ii) Ac_2O , HClO_4 ; (iii) thiourea, NaHCO_3 ;
 (iv) **156**, NaHCO_3 ; (v) Et_3N .

Accordingly, treatment of the keto alcohol **98** with chloroacetyl chloride and pyridine provided the chloroacetate **159** in an adequate yield of 73%⁷⁴. This particular protecting group was chosen because of the particularly mild conditions which can be employed to effect its removal. Enol acetate formation proceeded uneventfully giving **160** in 71% isolated yield. Initially, removal of the chloroacetyl

protecting group was attempted using sodium hydride in dimethyl formamide. This resulted in a great number of products which is not surprising given the strength of the base. However, stirring 160 for 18 h at room temperature in ethanol with a stoichiometric amount of thiourea and a slight excess of base allows the isolation of the alcohol 161 in 62% yield. Elevated temperatures cause production of the keto alcohol 98 and a concomitant reduction in the yield of desired hydroxyenol acetate. The thiourea not only removes the protecting group but forms the water-soluble pseudothiohydantoin which helps to clean up the reaction appreciably (Figure 25).

Figure 25

When 161 was treated in the stepwise manner described in Scheme 48, the diazo ketone 155 was isolable in 84% yield.

A consideration of the types of catalysts available led to the initial use of rhodium acetate dimer ⁷². The catalyst was suspended in cyclohexane and the diazo ketone was added. The reaction was stirred at room temperature under an inert atmosphere and protected from light and its progress was monitored by tlc. After

12 h the starting material was consumed, producing a large number of products. One higher R_f material was isolable in very small quantity which provided a mass spectrum showing a presumed molecular ion of 348 and prominent fragmentation ions at 248, 220, 206 and 178 (100%). The diazo ketone has a molecular weight of 334 and the intermediate carbene a weight of 306, indicating that the product has incorporated an additional 42 mass units. C_3H_6 satisfies nicely except that there is no reasonable explanation as to why it should be incorporated as opposed to C_4H_8 or even the whole cyclohexane molecule. It does appear that the new mass is carried in the angular side chain. A comparison with the mass spectrum of the starting material shows essentially the same fragmentation from a mass of 248 and lower, implying that the basic ring structure including enol acetate is intact. 248 can be envisioned arising in the following fashion:

Faced with the disappointing results obtained with the rhodium catalyst, it was decided to use copper acetylacetonate. Unhappily, this catalyst fared no better than the rhodium acetate dimer. Stirring for prolonged periods (> 72 h) at room temperature

resulted in the loss of the starting material as judged by tlc, producing an apparently homogenous, higher R_f material. The infrared spectrum showed the lack of diazo absorption at 2110 cm^{-1} and displayed two carbonyl resonances at 1725 and 1748 cm^{-1} with the latter being assigned to the acetyl group. Proton NMR confirmed the presence of the enol acetate: three-hydrogen singlets at δ 2.1 ppm ($\text{CH}_3\overset{\text{O}}{\parallel}\text{C}-\text{O}$) and 1.45 ppm ($\text{CH}_3-\text{C}=\text{O}$). The geminal methyls appeared as a 6-hydrogen singlet and the 2-hydrogen doublet of doublets in the starting material at δ 4.2 ppm ($-\text{CH}_2-\text{O}-$) has become an unresolved 2-hydrogen multiplet centred around 4.1 ppm. The vinyl region of the spectrum displays what appears to be three singlets, integrating for a total of one hydrogen at δ 6.2, 6.8 and 7.3 ppm. The resonance at 6.8 is approximately twice the size of the other resonances. These three resonances could be a doublet of doublets with a coincidence of peaks or they could represent two singlets at 6.2 and 6.8 and the third resonance could arise from residual chloroform in the sample. Discounting the region from 5-8 ppm, the proton NMR of the material differs little from that of the starting material.

In the intermolecular cyclopropanation reactions, such as the catalyzed addition of ethyl diazoacetate to olefins, often-major side products are the "dimers" of the carbene species. In the case of ethyl diazoacetate, these are diethyl fumarate and diethyl maleate. They probably arise from attack of a carbene on a diazo compound rather than by condensation of two carbene molecules. The extent of this type of reaction obviously depends upon the stoichiometry of the reaction and generally is not an important side

Diethyl maleate

Diethyl fumarate

reaction because the carbene species are usually so reactive that dimerization becomes statistically unfavoured. However, this type of reaction does occur. House and Blankley⁶⁸ reacted the diazoester 162 with cuprous oxide in hexane and obtained the desired cyclopropanated product in 6% yield, while the fumarate (163) and maleate (164) esters were obtained in 11 and 22% yields respectively (Scheme 50). Presumably, the yields of these types of products would increase if the lifetime of the intermediate carbene increased.

The possibility of dimer formation leads to a consideration of 165 and 166. The infrared spectrum of the product has a carbonyl absorption at 1725 cm^{-1} which is quite acceptable for fumarate and/or maleate esters. The proton NMR supports the possibility of a mixture of 165 and 166 if the singlet at 7.3 ppm arises from chloroform. The peak at 6.8 ppm would represent the fumarate ester (165) while that at 6.2 would correspond to the vinyl proton

Scheme 50

in 166, indicating that the E-isomer (165) was preferentially formed over the Z-isomer (2:1).

The ^{13}C NMR spectrum displays 19 peaks, which is quite acceptable if the 16-carbon bicycles of the two diesters 165 and 166 are identical and if there is a coincidence of peaks of the maleate and fumarate carbonyls. The ^{13}C spectrum was obtained using a technique known as the Attached Proton Test (APT) which differentiates methyl and methine carbons from methylene and fully substituted carbons. The vinyl region shows 4 peaks, two fully substituted at 122 and 139 ppm and two methine at 128 and 132. The peak at 128 is of a lesser intensity. Only two carboxyl peaks are present which means that the

unsaturated ester carboxyl for the Z-isomer is coincident with the E-isomer carbonyl. The carboxyl carbons in Z- and E-3-chloro-acrylic acid are coincident and the corresponding methyl esters are only slightly differentiated (0.2 ppm)⁷⁵. As 165 and 166 each represents a dl pair and a meso isomer, more carbon resonances should be seen, unless one of the diastereoisomeric pairs was removed during chromatography.

The mass spectrum of the material is inconclusive. The electron impact mass spectrum showed what appeared to be a mixture of three materials having very similar fragmentation patterns from

a mass of 248 and below. They displayed highest ion masses of 472, 300 and 294, none of which are readily explained given the starting material, solvent and other spectral data. The isomers 165 and 166 have a mass of 612 and it is known that EI techniques do not give consistent results for higher molecular weight materials.

An alternative method of carbene generation from diazo ketones is exposure of the substrate to radiation. These photochemically-induced carbenes are often in the singlet state and so can be of a higher energy than their counterparts arising from transition metal catalysis. This higher energy carries the corollary of higher reactivity which in turn means less selectivity. On the other hand, the absence of the large transition metal catalyst might allow the olefin greater access to the carbene.

Compound 155 was dissolved in dioxane and stirred under argon while being irradiated at 254 nm in a Rayonet photochemical reactor for 5 days by which time the starting material had been replaced by a uniform streak on tlc. The crude mixture was treated with potassium hydroxide in order to hydrolyze the esters and make characterization possible. Basic treatment for 20 h at room temperature caused the uniform streak to coalesce into two resolvable materials, the more polar being the keto alcohol 98 which was recovered in a

yield of 24% based on the diazo ketone. The mass recovery in the hydrolysis step was consistently poor. The higher R_f material displayed an absorption in the IR at 3380 cm^{-1} but did not have a carbonyl absorption. The proton NMR displayed two three-hydrogen singlets at 0.87 and 0.92 ppm (geminal methyls) along with a three-hydrogen doublet centred at 1.1 ppm ($\text{CH}_3\text{-CH}$, $J = 8\text{ Hz.}$). A pair of doublets integrating for one hydrogen each having $J = 8\text{ Hz.}$ appeared at 3.82 and 3.47 ppm with the latter being split by a 2 Hz. coupling.

The ^{13}C NMR spectrum shows 14 peaks, 12 under 44 ppm as well as peaks at 78.4 and 96.5 ppm. The mass spectrum shows the molecular ion at 224 along with a fragmentation pattern consistent with the hemiacetal 167. The white solid was recrystallized from

hexane and has a melting point of $95\text{-}97^{\circ}\text{C.}$ High resolution mass spectrometry provided an observed mass of 224.1773. This compound has been reported in this laboratory previously ⁷⁶ and the physical and spectral characteristics are consistent with those described above for 167.

The acquisition of 167 and 98 as the only isolable

products from the photolysis/hydrolysis sequence provides little information about the initial photolysis step. Treatment of 98 itself with base will generate the hemiacetal 167 as will the hydroxy enol acetate 161. In fact any ester of 161 will also be hydrolyzed. All that can be said of the photolysis/hydrolysis sequence is that none of the desired product, 168, was obtained.

In retrospect, the failure of the intramolecular carbene addition might be due in part to the transition state not favouring the formation of the desired seven-membered ring (fused to the cyclopropyl). Previous successful cyclopropanations have resulted in the formation of six-membered species ⁶⁸.

Rather than abandon totally what had seemed to be a most promising synthetic route, it was decided to investigate the possibility of intermolecular cyclopropanation on the protected enol acetate 160. This compound possesses a cis ring junction and so should be preferentially accessible from the β -face. Treatment of 160 with ethyl diazoacetate in either cyclohexane or diethyl ether

in the presence of either cupric sulfate or 10% palladium on charcoal resulted in no discernable reaction whatsoever. These reactions were characterized by a good recovery of the starting material contaminated with large amounts of diethyl fumarate and maleate. The lack of cyclopropanation is probably due to a combination of low reactivity of the double bond and a lack of accessibility to the double bond caused by the rather large protecting group.

It was demonstrated a number of years ago that copper-catalyzed insertion of carbenes in hydroxylic bonds was a useful reaction ⁷⁷. Rhodium acetate dimer was also shown to be effective, giving the insertion products in moderate to good yields ⁷⁸:

More recently, Noels et al. ⁷⁹ investigated the relative yields of O-H insertion products to multiple bond addition products for a number of unsaturated alcohols using a variety of catalysts and several alkyl diazoesters. In each case, insertion into the O-H bond dominated olefin addition, with the percent of cyclopropinol formed varying from 6 to 28% depending upon the substrate alcohol, the catalyst and the alkyl diazoester. In the hope of generating some olefin addition product, the hydroxyenol acetate 161 was treated with ethyl diazoacetate in cyclohexane in the presence of cupric sulfate. The absence ^{by} of the chloroacetyl protection group would possibly allow easier access of the carbene/carbenoid species to the

olefin. This perceived increase in accessibility was, in this case, a moot point, as a 78% isolated yield of the O-H insertion product (169) was realized (Scheme 51). There was no trace of an addition product.

Scheme 51

The olefin in this bicyclic series has been persistent in its unreactivity towards cyclopropanation. Both intra- and intermolecular attempts have been singular in their failure to effect addition to this double bond. Enol acetates have been used as substrates in carbenoid additions⁶⁷ so there is nothing inherently wrong with the idea per se. It seems obvious however, that the idea and the system are not compatible and this particular approach to a functionalized DE ring intermediate for triterpene synthesis has been abandoned.

The Diels-Alder Route

During the course of the investigations described above, a third route was developed which featured the use of an intramolecular Diels-Alder reaction to introduce the desired stereochemistry. This type of reaction is a tremendously powerful synthetic tool because it allows the introduction of up to four new asymmetric centres; the relative stereochemistry at these centres is generally predictable and judicious selection of substituents can sometimes serve to reverse this stereochemistry. It was felt that it would be possible to capitalize on these features of the intramolecular Diels-Alder reaction in an approach to the synthesis of the target enone, 116.

Figure 26

Figure 26 depicts how the tricycle 116 could arise via the intermediacy of the decahydrophenalene 170; the triene precursor for 170 was considered to be not only fairly easily available, but also amenable to extension to more complex systems. For example, a suitable R group could allow for the production of a system containing the basic framework of the pentacyclic system (Figure 27):

Figure 27

The first example of an intramolecular Diels-Alder reaction was reported by Alder and Schumacher in 1953⁸⁰ and was followed by a hiatus of a decade at which time Klemm and Gopinath described a route to apopicrodophyllin⁸¹ and Brieger⁸² reported an attempted synthesis of longifolene via an intramolecular Diels-Alder reaction. Shortly thereafter, House and Cronin⁸³ reported the stereospecific synthesis of cis- and trans-fused tetrahydroindanes by intramolecular Diels-Alder reactions of cis, trans- and trans, trans-2,7,9-

decatrienoates (171, 172) respectively (Figure 28).

Figure 28

The above work demonstrated the utility of this type of reaction and heralded a period of investigation into the predictability of stereochemistry and applicability to total synthesis of the intramolecular Diels-Alder reaction. A number of reviews have appeared recently ⁸⁴.

Both cis- and trans-dienes can give either cis- or trans-fused products depending upon the orientation of the dienophile to the diene in the transition state. Figure 29 shows the two possible orientations of the dienophile to diene for a trans-diene. The anti and syn designations refer to the orientation of the side chain relative to the diene. The length of the connecting chain is crucial:

less than three atoms in the chain prevents the reaction from occurring as the transition states are too strained. Three or more atoms in the chain will allow the molecule to cyclize by either transition state depending upon the substituents present, the types of diene and dienophile and catalysts.

Figure 29

Cis-dienes can also cyclize via one of two transition states (Figure 30). With connecting chains of four atoms or less, these substrates are constrained to react only via the anti transition state as the syn transition states are too strained.

Figure 30

In the intermolecular Diels-Alder reaction, electron withdrawing substituents on the dienophile favour the formation of the endo-addition product due to secondary orbital interactions between that substituent and the diene. However, Roush *et al.*⁸⁵ have shown that this is not true for the uncatalyzed intramolecular Diels-Alder reaction. In their investigations of trienes 175 and 176, they found that both molecules preferred to cyclize via the anti transition state which for 176 represents a violation of the endo rule (Scheme 52). The results of the cyclization of 175 partially refutes the stereospecificity reported by House and Cronin⁸³ who indicated that this trans, trans-triene cyclized to give only the

trans-fused tetrahydroindene.

Scheme 52

The preference for the anti transition state is rationalized as being a result of strain and non-bonded interactions that are found in the syn transition state. The most severe interaction

occurs between the allylic methylene hydrogens and the hydrogen on C-8; this interaction is absent in the anti transition state.

The other rationale for preferential anti orientation is based on frontier molecular orbital theory. Boeckman and Ko⁸⁶ and White and Sheldon⁸⁷ have independently cited the possibility of concerted but non-synchronous bond formation⁸⁸ in which the two σ bonds begin forming simultaneously but form at different rates. The coefficient of the LUMO at C-3 is larger than at C-2, causing bond formation between C-3 and C-7 to be more advanced than between C-2 and C-10. The development of the five-membered ring has progressed significantly, allowing the non-bonded interactions within the connecting chain to dominate the stereochemical course of the reaction.

In intermolecular Diels-Alder reactions, Lewis acid catalysis increases the endo selectivity by increasing the secondary orbital interactions between the electron withdrawing group and diene⁸⁹. This is true for the triene 175 as well, but the increase in secondary orbital interactions is not large enough to overcome the anti-preference in 176.

It is possible to reverse the dienophile's preferred orientation by placing an activating group within the connecting chain and α to the dienophile. Taber *et al.*⁹⁰ obtained a ratio of 69:31 (cis:trans) in their cyclization of the enone 177.

The same general considerations apply to systems in which the diene and dienophile are linked by a four carbon chain; cyclizations of such systems lead to decahydronaphthalenes. Trienes with all trans double bonds generally give mixtures of cis and trans products; the trans products can predominate if a Lewis acid is present⁹¹ or if substituents cause some non-bonded interactions in the syn transition state⁹².

Trans-fused products can be obtained almost exclusively if there is carbonyl α to the diene. Roush and Hall⁹³ obtained none of the isomeric cis product in their cyclization of **178**.

The anti transition state allows the carbonyl and the diene to remain coplanar; the syn transition state causes the carbonyl to be twisted out of the plane of the diene, so this state is disfavoured.

In contrast to these results and in keeping with those described above for the tetrahydroindanes, a carbonyl α to the dienophile can cause an almost exclusive production of the cis-fused product. An excellent example of this was recently described by Stock, Clark and Shiver⁹³ in their novel approach to the synthesis of 11-oxygenated steroids (Scheme 53). The cis-fused product was obtained in 66% yield as compared to 4% for the trans-product.

Scheme 53

It is apparent that the stereochemical outcome of these reactions depends on a combination of steric and electronic effects. It is also apparent that the desired stereochemistry can be selected by varying substituents or by the inclusion or exclusion of catalysts; this makes the intramolecular Diels-Alder reaction an

extremely versatile tool for the synthesis of complex molecules.

The initial approach to the use of this type of reaction in a stereorational synthesis of a suitable DE-ring intermediate for triterpene synthesis was undertaken by Dr. K. Fyfe⁶⁴. The target triene was compound 179 and was selected on its availability and with the hope that the quite-bulky dithianyl group would constrain the dienophile to adopt the desired anti orientation and so lead to the desired stereochemistry (180)

The synthesis of 179 is illustrated in Scheme 54. Condensation of methyl vinyl ketone with the enolate of 3-methyl-2-butanone provided 3,6,6-trimethyl-2-cyclohexenone in a modest yield of 31%⁹⁴. Addition of vinyl magnesium bromide to the cyclohexenone in the presence of tetrakis iodo (tri-*n*-butylphosphine)-copper (I) afforded the 1,4-addition product exclusively. Ketalization was followed by hydroboration with 9-BBN and oxidation to provide the primary alcohol, 180. Treatment of the derived mesylate with LiBr⁹ formed the bromide, but also cleaved the ketal; this was reintroduced in the standard fashion to give 181. The thioacetal

Scheme 54

- (i) KOH; (ii) (*n*-Bu)₃P-CuI, CH₂=CHMgBr; (iii) HOCH₂CH₂OH, pTsOH, benzene; (iv) 9-BBN; H₂O₂, NaOH; (v) MsCl, pyr; (vi) LiBr, acetone; (vii) oxalic acid, acetone; (viii) CH₂=CHMgBr; (ix) pTsOH, benzene

of 2-methyl acrolein was treated with methyl lithium and hexamethyl phosphoramide (HMPA) in THF; this anion served to displace bromide from 181 in an acceptable yield of 69%. With the dienophile now present in the molecule, it remained to introduce the diene. Deprotection of the ketone was followed by addition of vinyl magnesium bromide to provide the tertiary alcohol 182. The dehydration of 182 was effected by use of *p*-toluene sulphonic acid in benzene and gave a mixture of two isomers, 183 and 184 in a ratio of 1.3:1. 184 most likely arises as a result of internal nucleophilic attack by a sulfur atom on the intermediate allyl cation.

184

The triene 183 was dissolved in degassed xylene and sealed in a Carius tube under an inert atmosphere. Heating at 200°C for several days caused a small amount of decomposition but none of the desired Diels-Alder product(s) was in evidence. This disappointment was undoubtedly due to the unactivated nature of the

dienophile and the large steric requirements of the dithiane group.

The intramolecular Diels-Alder route undertaken as part of this thesis capitalized on several features of the above-described route. Ultimate failure of the triene 183 to undergo the Diels-Alder reaction prompted the inclusion of a dienophile activating group in the form of an aldehyde. Compound 185 was the desired target molecule. There are two examples in the literature of intramolecular

185 R = H

186 R = Bz

Diels-Alder reactions of compounds carrying an aldehyde on the non-terminal carbon of the dienophile and both of these cases give a preponderance of the cis-fused product. Roush and Peseckis⁹⁵ reported that the thermal cyclization of 187 gave the cis-tetrahydroindane in a yield of 63%. The trans was present in 19% yield (Scheme 55). In an extremely similar study, Taber *et al.*⁹⁰ found that aldehyde 188 cyclized to give a 4.5:1 ratio of cis:trans products.

Scheme 55

These results are somewhat anomalous. The preference for the formation of the cis-fused product represents another violation of the endo "rule". More startling is the realization that this preference is a manifestation of a lower energy syn transition state, which conflicts with the previously seen predilection for the anti transition state (Scheme 52). In the intermolecular Diels-Alder reaction, it is known that α -alkylated acrylates, such as methyl

methacrylate, show a preference for exo addition⁹⁶. In this intramolecular case, Roush and Peseckis offer a frontier molecular orbital explanation. The LUMO coefficient at C-1 (Scheme 55) is larger than at C-2; according to the concerted but non-synchronous bond formation model, this means that bonding between C-1 and C-9 will be more advanced than between C-2 and C-6. Molecular models indicate that a C-1 to C-9 bond is able to form most easily if a syn transition state is considered; this seems to minimize the non-bonded interactions between the reacting moieties.

On the basis of this rather limited evidence, triene 185 would be expected to cyclize to the undesired cis-fused product. However, 185 will react to form a decahydrophenalene, not a tetrahydroindane; the energetics of the transition state will necessarily be different. 185 is also more heavily substituted than the above examples; the α -geminal methyl group is in a position to influence the orientation of the dienophile. The chain connecting diene to dienophile consists of four carbons as opposed to three. This could influence predicted product ratios as well. Roush and Gillis⁹⁷ have shown that all-trans trienes undergo exclusive cyclization to the trans-fused products in the presence of certain Lewis acids (Scheme 56). The aldehyde carbonyl in 185 is capable of interacting with a Lewis acid in a similar fashion. The above rationale led to the selection of 185 as the intermediate synthetic objective.

Scheme 56

It was felt that 185 would be available from the condensation of an acrylate equivalent with the aldehyde 189 (Figure 31).

Figure 31

Fortuitously, compound 189 is derivable from the primary alcohol 180,

an intermediate in Dr. Fyfe's synthesis of the triene 183. The transformation of 180 to 189 requires the deprotection of the ketone, followed by addition of vinyl magnesium bromide and dehydration. The third carbon atom in the chain must also be added. These routine transformations are depicted in Scheme 57. Hydrolysis of the ketal followed by protection of the alcohol as the tetrahydropyranyl ether gave 190 in a yield of 73%. The addition of vinyl magnesium bromide to the ketone 190 provided the mixture of isomeric alcohols, 191, which were separable by chromatography. However, as both isomers were readily dehydrated in the presence of *p*-toluene sulfonic acid, separation proved to be unnecessary; the diene 192 was available in excellent yield (> 90%) from the allylic alcohols 191. The removal of the tetrahydropyranyl group from 192 was effected using aqueous oxalic acid. Unfortunately, the yield of purified alcohol 193, after silica gel chromatography, was only 25%. It appears that it is the alcohol itself which is not stable; this step remains a problem in this synthesis. Mesylation of the crude hydrolysis product might circumvent this substantial loss of material.

Treatment of 193 with mesyl chloride in the presence of pyridine afforded the mesylate (194) in 88% yield and the molecule was set up for the introduction of the required third carbon in the pendant side chain. The mesyl group was displaced by cyanide in refluxing aqueous ethanol, giving the nitrile 195 in 60% yield. The proton NMR of 195 showed the absence of the methane sulfonyl methyl singlet at 3.0 ppm; the IR spectrum displayed the characteristic nitrile absorption at 2250 cm^{-1} . The reduction of the nitrile to

Scheme 57

(i) oxalic acid, H_2O ; (ii) dihydropyran, PTSA; (iii) $CH_2=CHMgBr$, THF; (iv) PTSA, benzene; (v) oxalic acid; (vi) $MsCl$, pyr.; (vii) KCN , ethanol/water; (viii) DIBALH

the aldehyde (189) was accomplished using diisobutylaluminum hydride (DIBALH) in benzene and was invariably accompanied by the formation of some side products which necessitated chromatography. The poor yields obtained ($< 50\%$) were undoubtedly a function of the inherent instability of the aldehyde; 189 could not be stored at -15°C under an inert atmosphere for more than a few days before appreciable decomposition was apparent. Consequently, the aldehyde was prepared in small amounts immediately before use.

This synthetic route to 189 arose, in part, due to the availability of compound 180. An alternative synthesis was briefly investigated which would have introduced the three carbon side chain in one step (Figure 32). Hydroboration/oxidation would provide the

Figure 32

alcohol which could be protected before introduction of the vinyl group and dehydration to diene. Deprotection and oxidation would provide the aldehyde. Unfortunately, the conjugate addition of

allyl magnesium bromide was not successful, invariably giving large numbers of products regardless of variations in the experimental conditions.

Concurrent with the above studies, Dr. Claude Luttmann investigated the conjugate addition of trimethylallylsilane to 3,6,6-trimethylcyclohex-2-enone in the presence of titanium tetrachloride ⁹⁸ (Scheme 58). The reaction proceeded readily enough on a small scale (< 500 mg) but was not amenable to scaling-up to synthetically useful quantities.

Scheme 58

In an effort to shorten the synthetic route to the aldehyde 189, Dr. Luttmann developed a synthesis involving the conjugate addition of a three carbon Grignard reagent having the desired oxidation state on the third carbon (Scheme 59). Great difficulty was encountered in the formation of the Grignard reagent due to the known propensity of β -halo ketals to undergo intramolecular

Scheme 59

(i) Mg, THF; (ii) CuI·Me₂S; (iii) 3,6,6-trimethyl-2-cyclohexenone;
 (iv) CH₂=CHMgBr; (v) pTSA.

attack when the Grignard is forming⁹⁹. Careful attention to temperature allowed for the formation of the Grignard reagent¹⁰⁰ and subsequent reaction with the cyclohexenone provided the alkylated ketone in an excellent yield of 92%. The usual vinyl

magnesium bromide addition and dehydration gave 198 in 40% yield from 197. Unfortunately, this diene ketal 198 was extremely

resistant to a wide range of hydrolytic agents and conditions; consequently, a three carbon bromo dioxolane (199) was employed instead (Scheme 60). In the event, the formation of dioxolane

Scheme 60

- (i) Mg; (ii) CuI·Me₂S; (iii) 3,6,6-trimethylcyclohexenone
(iv) CH₂=CHMgBr; (v) pTSA

was as efficient as that of the dioxane over the three steps to the diene; 200 was obtained in a yield of 49% from 3,6,6-trimethyl cyclohex-2-enone. Remarkably, this dioxolane was also reluctant to undergo clean hydrolysis to the desired aldehyde. Mixtures were obtained in every case and the situation was complicated by coincident R_f values for 200 and 189, rendering tlc useless for monitoring the progress of the reactions. Silica gel chromatography was not efficient in purification of 189 and in fact, the aldehyde obtained through this synthetic route was never free of contaminants. Although plagued by a multitude of reactions and a poor yield in the ultimate step, the synthesis to 189 presented in Scheme 57 is the method of choice for acquisition of this compound.

The acrylate equivalent used to condense with 189 was 1,1-diethoxy-2-lithio-2-propene (201)¹⁰¹. Acrolein was brominated, then dehydrobrominated with triethylamine to give α -bromoacrolein, which was treated with triethylorthoformate and ammonium nitrate in ethanol to provide 1,1-diethoxy-2-bromo-2-propene. Metallation with *n*-butyl lithium gave 201.

The triene 202 was synthesized according to the method of Roush and Peseckis⁹⁵ (Scheme 61). The vinyl lithium 201, was

Scheme 61

generated in situ at -78°C prior to the addition of the aldehyde.

Normal work-up, followed by silica gel chromatography, provided extremely poor yields of a material subsequently identified as 202; variation of the stoichiometry in later experiments allowed the desired triene to be acquired free of contaminants (according to tlc) and so obviate the need for chromatography. This also served to increase the yields to a respectable 72%; the sensitivity of 202

to silica gel is undoubtedly due to the presence of the acetal group.

The infrared spectrum of 202 displayed the characteristic, broad OH absorption centred at 3440 cm^{-1} as well as a weak absorption at 3080 cm^{-1} from vinylic C-H stretching. There was no absorption in the carbonyl region.

Figure 33

To facilitate analysis of the proton NMR the arbitrary numbering system depicted in Figure 33 will be employed. The three methyl groups appear as singlets at 0.99, 1.05 and 1.07 ppm. The ethyl groups of the acetal are seen to be non-equivalent as evidenced by the two 3H triplets from 1.2 to 1.3 ppm and two 2H multiplets from 3.45 to 3.8 ppm. This non-equivalence arises because the methylenes of the ethyl groups are diastereotopic. The spectrum also contains an 8H multiplet between 1.3 and 1.75 ppm.

The vinyl group provided the expected ABX system. The C-2 hydrogen appears as an octet centred at 6.29 ppm. It is coupled to the two C-1 hydrogens: H_A (cis, $J = 10$ Hz) and H_B (trans, $J = 18$ Hz). There is a further long range coupling of 2 Hz between the C-2 hydrogen and C-4 hydrogen. H_A and H_B display a geminal coupling of 2 Hz in addition to the couplings mentioned above and so each appears as a quartet: H_A at 4.90 and H_B at 5.26 ppm. The C-4 hydrogen resonates at 5.44 ppm and shows as a doublet due to the four bond coupling ($J = 2$ Hz) to the C-2 hydrogen. The C-10 hydrogens appear as broadened singlets at 5.27 and 5.23 ppm. The remaining resonances are the carbinol hydrogen (C-8) at 4.2 (1H, m) and the acetal hydrogen at 4.89 (1H, s); the hydroxy proton resonates at 2.72 ppm (1H, d).

The ^{13}C NMR spectrum confirms the structure of 202 and shows that only one of the possible alcohols is present. The peak assignments are shown in Figure 34. The vinyl and cyclohexenyl carbons were assigned using the spectra of β -ionone, vitamin A acetate and β -carotene¹⁰² as guides. The two methylenes of the acetal are seen to be non-equivalent, resonating at 62.167 and 62.592 ppm; the adjacent methyls appear coincidentally at 15.12 ppm.

Figure 34

The most interesting feature of the ^{13}C NMR spectrum of 202 is the singularity of the carbinol carbon resonance at 72 ppm. The aldehyde 189 is a racemic mixture and generation of a second chiral centre will cause the production of diastereomers; four compounds should be produced, two pairs of enantiomers: RS and SR and RR and SS.⁵ Each pair of enantiomers should have different proton- and carbon- ^{13}C -NMR spectra. In fact, the spectra of 202 indicate the presence of only one pair of enantiomers. After work-up and prior to any purification, the crude reaction mixture from this alkylation was subjected to ^{13}C NMR analysis and showed the presence of a single carbinol carbon along with a remarkably clean olefinic region. This indicates that only one racemic diastereomer was produced and means that the reaction is diastereofacially selective.

The induction of asymmetry at a nascent chiral centre by an adjacent chiral centre was systematically studied by Cram and Abd Elhafez¹⁰⁴ with respect to additions to carbonyl compounds containing an α chiral centre. This study led to Cram's Rule; a modified cyclic model could be used if the α -carbon carried a heteroatom capable of chelating with organometallic reagent¹⁰⁵. The asymmetric induction arises from reagent approach from the least hindered face of the carbonyl and so the amount of induction varies with the size of the approaching reagent as well as with the relative amounts of hinderance offered by the two faces of the carbonyl. This type of 1,2-asymmetric induction can be essentially diastereospecific¹⁰⁶.

1,3-Asymmetric induction is known as well but generally suffers from a much-reduced degree of selectivity. Leitereg and Cram¹⁰⁷ obtained a maximum ratio of 4.8:1 of A:B when the ketone 203 was reacted with phenyl magnesium bromide (Figure 35).

Figure 35

Fukuyama et al.¹⁰⁸ have reported an 11-fold excess of one diastereomer in a 1,4-asymmetrically inductive reduction of the epoxy ketone 204 in the presence of dl-2-(o-2-toluidinomethyl)-pyrrolidine (Figure 36). This stereospecificity was demonstrated

Figure 36

only by various aluminium hydrides; reaction with borohydride failed to effect the desired induction. This implies that in the aluminium case there is some kind of coordination between the metal and the oxygens of the ketone and epoxide.

Compound 189 has no heteroatoms to chelate the incoming organometallic reagent; it does have a chiral centre four carbons removed which could be expected to have little influence at best on the stereochemical cause of the addition in a purely acyclic case. The seemingly high degree of diastereoselection must be related to the presence of the dienyl functionality. Secondary orbital interactions between the carbonyl and the diene cause a large differential facial accessibility. Drieding models seem to indicate the preferred conformations shown in Figure 37,

Figure 37

but as the method and extent of carbonyl/diene association is not certain, it is quite possible that the other pair of enantiomers form instead.

The above observation opens up a whole area of potential research. The diastereoselection is quite high but must be quantified. The effect of chain length between the established and incipient chiral centres should be investigated as should the carbonyl-diene interaction. In fact, the generality of the reaction must be determined; the minimum requirements for diastereoselection should be delineated.

The observed stereoselection in the formation of 202 is, in this case, superfluous, as the newly formed chiral centre is destined to eventually lose its asymmetry through transformation to a carbonyl.

Compound 202 was the triene used for the initial Diels-Alder attempts even though the dienophile was inactivated. 202 was

dissolved in carbon tetrachloride and sealed under argon in a Carius tube⁹⁵ and heated for 20 h at 100 or 150°C. These thermolyses were characterized by the production of large numbers of products, some of which seem to correspond to cyclized materials, but which were available in very limited quantities. The mass spectra of these products were characterized by prominent peaks at m/e 259, 215 and 103 (especially) (Figure 38). The triene

Figure 38

202, on the other hand, shows a most abundant peak at 149, which has been assigned the structure:

The presence of a large peak at m/e 149 might be useful as an indicator

of lack of cyclization.

202 was also treated at room temperature for 16 h. in the presence of ethyl aluminium dichloride with similar results to the thermal attempts. Lewis acids are known to not only accelerate Diels-Alder reactions but also can increase the stereoselectivity⁸⁵. The presence of the diethyl acetal and the allylic alcohol in 202 undoubtedly contributed to the low mass recovery in both sets of reactions so it was decided to protect the alcohol as the benzyl ether and deprotect the aldehyde in order to activate the dienophile. Accordingly, 202 was dissolved in dry DME and added to a suspension of sodium hydride in the same solvent. Benzyl bromide was added and the mixture was heated to 85°C for 4 h. then allowed to stand overnight at room temperature. Normal work-up with dichloromethane provided an oil which was treated with 1 N HCl (aq) and acetone for 2 h. at room temperature. Work-up and silica gel chromatography provided the aldehyde 205 in a yield of 68% for the two steps (Scheme 62).

Scheme 62

(i) BzBr, NaH, DME; (ii) HCl, acetone.

The infrared spectrum of 205 showed the expected unsaturated carbonyl absorption at 1690 cm^{-1} as well as an aldehyde overtone at 2700 cm^{-1} and displayed an absence of absorption in the OH region of $3200\text{--}3600\text{ cm}^{-1}$. The proton NMR shows the same ABX-pattern displayed by 202 along with benzylic protons (dd 4.47 and 4.36), the aldehydic proton (s, 9.6 ppm) and the carbinol proton at 4.32 (1 H, m).

This triene (205) was dissolved in carbon tetrachloride and a small amount of 2,6-di-tert-butyl-4-methyl phenol (BHT) was added to minimize polymerization⁹⁵. The mixture was sealed under argon in a Carius tube and heated at 150°C for 18 h. by which time there was no starting material remaining according to tlc and IR. The mixture was flash chromatographed on silica gel and provided a colourless oil which proved to be a mixture of 3 aldehydes. The infrared spectrum showed saturated carbonyl at 1712 cm^{-1} and was transparent in the conjugated carbonyl region. An aldehyde overtone was visible at 2710 cm^{-1} . The proton NMR shows three aldehydic singlets at 10.34, 9.72 and 9.53 ppm and a broad singlet at 5.5 ppm assignable to the one vinyl proton. The benzylic protons appear as a complicated multiplet (4.79–4.43 ppm) integrating for 2 H and the carbinol hydrogen is assigned to the 1H multiplet centred at 3.88 ppm.

The Diels-Alder reaction of 205 could be expected to provide 4 possible cycloadducts (Figure 39). If the addition of the organolithium to aldehyde 189 was diastereospecific then it would be reasonable to expect only two of the above possibilities:

Figure 39

206 and 208 or 207 and 209. The proton NMR clearly shows at least three aldehydes indicating that this diastereoselection was not total.

The limited amount of material available, coupled with the complexity of the mixture, prompted a rapid attempt at estimating the relative quantities of *cis* and *trans* ring fusion. Consequently, the mixture was hydrogenated over 10% Pd/C for 48 h. to remove the benzyl group; this also partially hydrogenated the double bond. Oxidation of the resulting alcohols provided a mixture of two aldehydes (Scheme 63). The infrared spectrum showed ketone and aldehyde absorptions at 1700 and 1725 cm^{-1} . The proton NMR indicated the

Scheme 63

(i) H_2 , Pd/C; (ii) PCC, CH_2Cl_2

presence of two aldehydes in a ratio of 64:36. Literature suggests that this ratio will favour the *cis*-fused compound 210^{90, 95}; isolation and characterization of 210 and 211 will establish which mode of cyclization predominates. Subsequently, efforts can be made to enhance or reverse the displayed selectivity. Work is continuing in these laboratories towards this end.

CONCLUSIONS AND SUGGESTIONS FOR FURTHER WORK

The CDE Route

A method of introducing the desired cis-ring junction stereochemistry between the DE rings was developed by employing lithium in ammonia to effect the reduction of the unsaturated acid 134.

All attempts at introducing the desired C-13 (triterpene numbering) α -methyl group on the isomeric alcohols (117) met with failure, presumably due to steric encumbrances. However, the Simmons-Smith reaction is known to have a concentration dependence⁶²; it might be worthwhile attempting the cyclopropanation on a multigram scale. Larger quantities might also permit the separation of 117a and 117b, by HPLC for example.

The DE Route

Both intra- and intermolecular carbene addition attempts failed to effect addition to the double bond. It is felt that further

investigations along these lines would not be worthwhile. However, rather than waste the nice array of functionality present in 161 it might be possible to take advantage of it in another fashion. Enol acetates have been known to undergo intramolecular Diels-Alder reactions and 161 is set up such that a properly functionalized group would be constrained to react only from the β -face:

Studies have begun towards a suitable dienyl functionality.

The Diels-Alder, Route

An efficient route to the triene 202 was developed marked by the very interesting diastereoselective addition to the aldehyde 189.

This diastereoselectivity will be investigated further as 1,4 asymmetric induction is rare. The extent and generality of this diastereoselectivity will be explored.

Studies are continuing in this laboratory on the cyclization of 202 and 205. The product ratios must be determined and yields optimized.

EXPERIMENTAL

General

All melting points were obtained on a Fisher-Johns hot stage apparatus and are uncorrected. Boiling points are uncorrected. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 UV-Vis spectrometer. Infrared spectra were recorded on a Perkin-Elmer 683 Spectrometer and frequencies are reported in cm^{-1} . Mass spectra were obtained on a VG 707E instrument located at the University of Ottawa. Routine proton NMR spectra were acquired on a Varian EM 360 spectrometer while high resolution ^1H and ^{13}C NMR spectra were recorded on a Varian XL 200 instrument. Chemical shifts are reported in ppm (δ from tetramethyl silane). Abbreviations used in the NMR descriptions are: s- singlet; d- doublet; t- triplet; q- quartet; m- multiplet; br- broad. Combustion analyses were performed at Guelph Chemical Laboratories Ltd., Guelph, Ontario.

Thin layer chromatography (tlc) was used to monitor all reactions; pre-coated silica gel plates from E.M. Merck (Merck 60 PF0254, 0.25 mm) were used. Plates were examined under UV irradiation followed by exposure to a solution of 1% ceric ammonium nitrate in 50% sulphuric acid (aq.). Preparative TLC was carried out on Merck 60 F-254 plates (2.0 mm). Column chromatography employed silica gel (Grace, Davison Chemical Co. 100-200 mesh).

Flash chromatography was carried out using Merck 60 H silica gel. Preparative HPLC was done on a Waters Prep-500 HPLC.

Dry tetrahydrofuran (THF), benzene, toluene and dimethoxyethane (DME) were obtained by drying over sodium and were distilled from sodium.

2-Methoxycarbonyl-5,5-dimethyl-2-(m-methoxyphenethyl)-cyclohexanone (121)

Freshly purified potassium ¹⁰⁹ (5.5 g, 0.14 mol) was dissolved in 100 mL of dry tert-butanol under argon. The solution was mechanically stirred during the dropwise addition of the keto ester (99) (25.7 g, 0.14 mol) in 50 mL of tert-butanol; a further 100 mL of tert-butanol was added. 2-(m-methoxyphenyl)-ethyl bromide (30.0 g, 0.14 mol) in 50 mL of tert-butanol was added and the mixture was refluxed for 80 h. After cooling, the reaction mixture was poured into ice-water and ether (200 mL) was added. The organic layer was washed with 100 mL of dilute (3 N) hydrochloric acid, saturated sodium bicarbonate (100 mL) and brine (100 mL). The mixture was dried over sodium sulfate (anh.) and concentrated to afford a viscous oil which was distilled at high vacuum (0.75 mm Hg) to give 17.1 g of 121 (175-190°C) 38.6%; IR (neat): 1734 (ester) and 1712 (carbonyl) cm⁻¹; NMR (CDCl₃): δ : 0.89 (s, 3H), 1.03 (s, 3H), 3.70 (s, 3H, ester), 3.76 (s, 3H, methoxy), 6.62-7.3 (m, 4H, aromatics); MS m/e (rel. int.): 318 (M⁺, 6), 184 (33), 152 (21), 135 (27), 134 (100) and 121 (23). Anal. calcd. for C₁₉H₂₆O₄: C 75.46, H 8.67; found: C 75.32, H 8.58.

7-methoxy-10a-methoxycarbonyl-3,3-dimethyl-1,2,3,9,10,10a-hexahydro-phenanthrene (122)

Ketoester (121) (17.13 g, 0.05 mol) and 4.0 g of p-toluene-sulphonic acid in 600 mL of dry benzene were refluxed under argon for 12 h. After cooling the mixture was passed through a short column of alumina and concentrated to give 12.8g (79%) of 122 as a yellow solid. An analytical sample was recrystallized from hexane, mp 74-75°C; IR (KBr): 1712(ester) cm^{-1} ; NMR (CDCl_3) δ : 1.05 (s, 3H), 1.10 (s, 3H), 3.54 (s, 3H, ester), 3.72 (s, 3H, methoxy), 5.94 (s, 1H, olefinic) and 6.50-7.57 (m, 3H, aromatics); MS m/e (rel. intensity): 300 (M^+ , 100), 285 (100), 241 (31) and 225 (42).
Anal. calcd. for $\text{C}_{19}\text{H}_{24}\text{O}_3$: C 75.97, H 8.05; found C 75.98, H 8.08.

10a-Hydroxymethyl-7-methoxy-3,3-dimethyl-1,2,3,9,10,10a-hexahydro-phenanthrene (132)

Lithium aluminium hydride (352 mg, 8.8 mmol) was suspended in 50 mL of dry ether and stirred under argon during the dropwise addition of the ester 122 (2.80 g, 9.3 mmol) in 50 mL of dry ether. The mixture was refluxed for 4 h. and stirred for 16 h. at room temperature. The reaction was quenched by the addition of several mL of saturated sodium sulfate solution. The suspension was diluted with dilute hydrochloric acid (3 N) (100 mL) and the organics were separated and washed with saturated sodium bicarbonate and brine.

The solution was dried (anh. sodium sulfate) and concentrated to give a semi-solid which was chromatographed on silica gel to afford 2.49 g (97%) of 132. Recrystallization from hexane gave a sample for analysis, mp 55-56 °C; IR (KBr): 3400 cm^{-1} ; NMR (CDCl_3) δ : 1.03 (s, 3H), 3.46 (s, 2H, hydroxymethyl), 3.76 (s, 3H, methoxy), 5.84 (s, 1H, olefinic) and 6.50-7.42 (m, 3H, aromatics). Anal. calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_2$: C 79.37, H 8.88; found C 79.41, H 8.90.

10a-Carboxy-7-methoxy-3,3-dimethyl-1,2,3,9,10,10a-hexahydrophenanthrene (134)

The ester 122 (26.0 g 0.09 mol) in 1600 mL of methoxy ethanol was refluxed with 40 g of potassium hydroxide for 72 h. Upon cooling, the reaction mixture was acidified with hydrochloric acid (3 N) and extracted with ether (3 X 300 mL). The combined organics were washed with water (2 X 400 mL) and brine, and dried over anhydrous sodium sulfate. Concentration provided 18.9 g (73%) of the acid 134 as a yellow solid. A sample was recrystallized from ethanol to give a white powder, mp 180 °C (dec); IR (KBr): 3300-2400, 1735 and 1690 cm^{-1} ; NMR (CDCl_3) δ : 1.03 (s, 3H), 1.1 (s, 3H), 3.75 (s, 3H, methoxy), 5.90 (s, 1H, olefinic), 6.45-7.50 (m, 3H, aromatics) 7.91 (s, 1H, COOH); MS m/e (rel. intensity): 286 (M^+ , 64), 271 (100) and 241 (15).

10a β -Carboxy-7-methoxy-3,3-dimethyl-1,2,3,4,4a β ,9,10,10a-octahydrophenanthrene (135).

A solution of the acid (134) (8.90 g, 0.03 mol) in 400 mL of dry 1:1 ether:tetrahydrofuran was added to a stirred solution of lithium (3.60 g, 0.52 mol) in 1200 mL of distilled liquid ammonia. The reaction was stirred for 30 min. after the addition was complete and was quenched by the addition of solid ammonium chloride. The ammonia was allowed to evaporate and dilute (3 N) hydrochloric acid (500 mL) was added and the organics were extracted with ether (2 X 500 mL). The ether extract was washed with water (2 X 500 mL) and brine and dried over sodium sulfate (anh.). Concentration gave 8.48 g (89%) of crude 135. A sample was recrystallized from ethanol mp 175-182°C: IR (KBr): 3450, 3200 and 1723 cm⁻¹; NMR (CDCl₃).

δ : 0.90 (s, 3H), 1.03 (s, 3H), 3.74 (s, 3H, methoxy) and 6.50-7.06 (m, 3H, aromatics); MS m/e: 288 (M⁺, 100), 242 (63) and 186 (11).
Anal. calcd. for C₁₈H₂₄O₃: C 74.97, H 8.39; found: C 74.79, H 8.46.

10a β -Hydroxymethyl-7-methoxy-3,3-dimethyl-1,2,3,4,4a β ,9,10,10a-octahydrophenanthrene (133)

(i) By reduction of acid 135

To a slurry of 1.8 g (0.05 mol) of lithium aluminium hydride in 300 mL of dry THF under argon was added, dropwise, a solution of the acid 135 (18.0 g, 0.06 mol) in 800 mL of dry THF. The suspension was refluxed for 4 h. and allowed to cool. The reaction was worked-up by the sequential slow addition of 1.8 mL of water, 1.8 mL of 15% NaOH (aq) and 5.4 mL of water. The mixture was

stirred at room temperature for 2 h. then filtered through a pad of Celite. After drying (anh. sodium sulfate), concentration afforded 15.8 g of 133 (89%) as a yellow solid. A sample was recrystallized from hexane, mp 97-98°C; IR (KBr): 3350 cm^{-1} ; NMR (CDCl_3) δ : 0.87 (s, 3H), 1.00 (s, 3H), 3.30 (d, 1H, $J = 11$ Hz, hydroxymethyl), 3.42 (d, 1H, $J = 11$ Hz, hydroxymethyl), 3.74 (s, 3H, methoxy) and 6.54-6.96 (m, 3H, aromatics); MS m/e (rel. int.): 274 (M^+ , 100), 256 (22) and 243 (22). Anal. calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_2$: C 78.79, H 9.55; found: C 78.80, H 9.59.

(ii) By Birch reduction of alcohol 132

A solution of the alcohol 132 (923 mg, 3.4 mmol) in 30 mL of dry 1:1 ether:tetrahydrofuran was added to a stirred solution of lithium (444 mg, 64 mg-atoms) in ca. 100 mL of distilled liquid ammonia. The reaction was stirred for 30 min. after the addition was complete and was quenched by the addition of solid ammonium chloride. The ammonia was allowed to evaporate and the residue was treated with dilute (3 N) hydrochloric acid (50 mL). The organics were extracted with ether (2 X 50 mL) and washed with saturated sodium bicarbonate solution (50 mL) and brine. After drying, concentration afforded 720 mg (77%) of reduced products, a sample of which was submitted to gas chromatography as the trimethylsilyl ether ⁵⁴: To 10 mg of the reaction product in 1 mL of anh. pyridine was added 0.2 mL of hexamethyldisilazane and 0.1 mL of trimethylchlorosilane. The mixture was shaken for 30 sec. and let stand for 5 min. 1.2 μL was injected onto an OV-17 column at 200°C and the reaction mixture was

shown, by comparison to authentic samples, to be composed of a mixture of 82% cis and 18% trans.

10a β -Formyl-7-methoxy-3,3-dimethyl-1,2,3,4,4a β ,9,10,10a-octahydrophenanthrene (136)

Pyridinium chlorochromate (2.70 g, 13 mmol) was suspended in 150 mL of dry dichloromethane with vigorous mechanical stirring. The alcohol 133 (2.31 g, 8.4 mmol) dissolved in 10 mL of dichloromethane was added rapidly and the mixture was stirred at room temperature for 5 h. The solution was diluted with ether (100 mL) and the solvent was decanted; the residue was triturated with ether (2 X 150 mL) and the combined ether solutions were filtered through a Florisil pad. Concentration gave 1.95 g of 136 (85%); a sample was recrystallized from methanol/water, mp 100-102°C; IR (CCl₄): 2710, 1718 cm⁻¹; NMR (CDCl₃) δ : 0.93 (s, 3H), 1.03 (s, 3H), 3.74 (s, 3H, methoxy), 6.50-7.10 (m, 3H, aromatics) and 9.40 (s, 1H, aldehyde). Anal. calcd. for C₁₈H₂₄O₂: C 79.37, H 8.88; found: C 79.30, H 8.86.

7-Methoxy-3,3,10a β -trimethyl-1,2,3,4,4a β ,9,10,10a-octahydrophenanthrene (118)

The aldehyde 136 (2.88 g, 10 mmol), 70 mL of distilled diethylene glycol and 25 mL (0.49 mol) of 100% hydrazine hydrate

were warmed to 100°C over a two hour period and maintained at this temperature for a further 2 h. The mixture was cooled, potassium hydroxide (5.6 g, 0.10 mol) was added and water was distilled from the reaction mixture over a 3 h. period. The solution was refluxed for a further 12 h, then cooled, acidified with dilute (3 N) hydrochloric acid and extracted with ether. The organics were washed with water and brine and dried over magnesium sulfate (anh.). Concentration gave 2.38 g of a solid which was methylated in 50 mL of dry THF using sodium hydride (200 mg, 8.3 mmol) and methyl iodide (4.00 g, 16.5 mmol). Work-up with ether gave 2.02 g of 118 (75%). A sample was twice recrystallized from methanol to provide colourless needles, mp 65-66°C; IR(KBr): 1600 and 1510 cm^{-1} ; UV_{max} (CH₃OH): 220 (ϵ = 5210), 280 (1740) and 285 (1610) nm; NMR (CDCl₃) δ : 0.89 (s, 6H, gem-methyls), 1.00 (s, 3H), 3.76 (s, 3H, methoxy) and 6.57-7.06 (m, 3H, aromatics); MS m/e (rel. int.): 258 (M⁺, 100). Anal. calcd for C₁₈H₂₆O: C 83.67, H 10.14; found: C 83.55, H 10.15.

3,3,10a ϵ -Trimethyl-1,2,3,4,4a ϵ ,5,8,9,10,10a-decahydrophenanthren-7(6H)-one (138)

A solution of 118 (1.14 g, 4.4 mmol) in 75 mL of dry 1:1 tetrahydrofuran: tert-butanol was added to a stirred solution of lithium (600 mg, 87 mg-atoms) in 150 mL of distilled ammonia. The mixture was stirred at -78°C for 1 h, then quenched by the addition

of absolute methanol. The ammonia was allowed to evaporate and the residue was dissolved in water (150 mL) and extracted with ether (4 X 100 mL). The combined ether extracts were passed through a pad of anhydrous magnesium sulfate and concentrated to give a colourless oil. This oil was dissolved in 100 mL of cold absolute ethanol and treated with 30 mL of 1 M aqueous oxalic acid solution for 30 min. at 0°C. The mixture was neutralized with saturated sodium carbonate solution and extracted with ether (4 X 100 mL). The combined organics were washed with water (2 X 200 mL) and brine (200 mL) and dried over magnesium sulfate (anh.). Concentration gave 1.02 g (94%). Distillation at 1.0 Torr gave 138 as a colourless oil bp 95-100°C; IR (neat): 1718 cm^{-1} ; NMR (CDCl_3) δ : 0.87 (s, 3H), 0.90 (s, 6H, geminal methyls); MS m/e (rel. int.): 246 (M^+ , 100), 231 (100), 217 (86), 105 (38). Anal. calcd. for $\text{C}_{17}\text{H}_{26}\text{O}$: C 82.87, H 10.64, found: C 82.90, H 10.68.

3,3,10a-trimethyl-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydro-phenanthren-7-ol (117a and 117b)

(i) Reduction of 138 using sodium borohydride

To a stirred solution of 8 mg of sodium borohydride (0.2 mmol) in 5 mL of absolute ethanol at 0°C under argon was added dropwise, the ketone 138 (156 mg, 0.5 mmol) in 10 mL of absolute ethanol. The mixture was stirred at 0°C for 2 h. and quenched by the slow addition of 2 mL of 5 M acetic acid (aq.). The mixture was partitioned between ether (25 mL) and water (25 mL) and the aqueous phase was extracted with ether (25 mL). The combined ether extracts were washed with water (2 X 25 mL) and brine (25 mL) and dried

over magnesium sulfate. Concentration afforded 163 mg of a colourless oil which after chromatography yielded 138 mg (88%) of 117 as an oil, IR (neat): 3325 cm^{-1} ; NMR (CDCl_3) δ : 0.95 (s, 3H, c-10a methyl), 0.97 (s, 6H, geminal methyls), 3.95 (br.s., 1H, C-7 H). ^{13}C NMR (CDCl_3) δ : 67.99 and 67.57 ($-\text{C}(\text{H})\text{OH}-$). MS m/e (rel. int.): 248 (M^+ , 18), 230 (44) and 215 (100). Anal. calcd. for $\text{C}_{17}\text{H}_{28}\text{O}$: C 82.19, H 11.28; found: C 82.49, H 11.50.

(ii) Reduction of 138 using RedAl (sodium bis-(2-methoxyethoxy) aluminium hydride)

A solution of 0.03 mL of RedAl (50% in benzene, 0.08 mmol) in 5 mL of dry THF was slowly added to a stirred solution of 138 (20 mg, 0.08 mmol) in 5 mL of dry THF at 0°C under argon. The solution was stirred for 3 h. and quenched by the dropwise addition of 2 mL of 5% sodium hydroxide (aq.). The mixture was extracted with ether (2 X 20 mL) and the organics were washed with saturated sodium bicarbonate (30 mL) and brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration afforded 15 mg (74%) of a mixture of 117a and 117b.

(iii). Reduction of 138 using L-Selectride (Lithium tri-sec-butyl borohydride).

1.64 mL of 1 M L-Selectride in THF (1.64 mmol) was diluted with 5 mL of dry THF and cooled to -78°C under argon. The ketone 138 (200 mg, 0.82 mmol) in 2 mL dry THF was added dropwise and the mixture was stirred at -78°C for 2 h. After warming to room temperature, 1.5 mL of 15% aqueous sodium hydroxide solution was added, followed

by 1 mL of 30% hydrogen peroxide (aq.) solution. The mixture was extracted with ether (2 X 25 mL) and the organics were washed with water (50 mL) and brine (50 mL) and dried over anhydrous magnesium sulfate. Concentration gave 150 mg of an oil which was subjected to preparative thin layer chromatography (20% ethyl acetate/hexane) to provide 60 mg (30%) of the alcohols 117a and 117b.

(iv) Reduction of 138 using lithium tri-tert-butoxy-aluminium hydride

The method of Ireland et al.¹³ was followed. Lithium tri-tert-butoxy-aluminium hydride (1.07 g, 4.2 mmol) was dissolved in 20 mL of dry THF under argon. A solution of the ketone 138 (273 mg, 1.1 mmol) in 17 mL of dry THF and 4 mL of dry benzene was added over 10 min. to the aluminium hydride solution. The mixture was refluxed for 4 h. then cooled in an ice bath during the addition of 1.9 mL of 10% sodium hydroxide solution (aq.). The mixture was stirred for 15 h. at room temperature and filtered through a pad of Celite. The Celite was washed with 100 mL of THF and 150 mL of 1:1 ether:chloroform. Concentration gave an oil which was flash chromatographed on silica gel (20 g) eluting with 10% ethyl acetate in hexane to provide 153 mg (56%) of 117a and 117b.

(v) Attempted reduction of 138 by 10% Ruthenium on charcoal

10 mg of 10% ruthenium on charcoal was suspended in 5 mL of 80% ethanol (aq.) and hydrogenated for 1.5 h. The ketone 138 (45 mg, 0.2 mmol) in 2 mL of 80% ethanol (aq.) was added and the mixture was hydrogenated for 72 h. The reaction mixture showed only

starting material by tlc (50% ethyl acetate/hexane). The suspension was filtered and partitioned between ether and water. The aqueous phase was extracted with ether (2 X 25 mL) and the combined ether extracts were washed with water (50 mL) and brine (50 mL) and dried over magnesium sulfate (anh.). Concentration afforded 42 mg of 138 as shown by ^{13}C NMR.

Typical procedure for the attempted Simmons-Smith Methylenation of 117

A stirred mixture of zinc dust (33 mg, 0.5 mmol) and cupric chloride (67 mg, 0.5 mmol) in 8 mL of anhydrous ether was refluxed under argon for 1 h. The alcohol 117 (35 mg, 0.14 mmol) in 1 mL of anhydrous ether was added dropwise, followed by the dropwise addition of methylene iodide (49 mg, 0.2 mmol). The mixture was refluxed for 18 h., cooled and poured into 25 mL of saturated ammonium chloride (aq.) (25 mL) and filtered. The filtrate was extracted with ether (2 X 25 mL) and the combined organics were washed with saturated ammonium chloride (aq.) (25 mL) and dried over MgSO_4 (anh.). Concentration gave 33 mg of the alcohols 117.

4a β -Methoxycarbonyl-1,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalene-2(3H)-spiro-2'-(1',3'-dithiane) (148)

4a β -Methoxycarbonyl-1,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalene-2(3H)one (100) (15.0 g, 60 mmol) was dissolved in 250 mL of dry methanol and cooled to 0°C. Argon was bubbled through the solution for 0.5 h. and 1,3-propanedithiol (7.0 mL, 70 mmol) was added neat. Anhydrous hydrogen chloride was bubbled into the solution for 0.5 h. and the resulting suspension was stirred for a further 2 h. The reaction was cooled to -10°C and product was collected by filtration, providing a white powder (15.1 g, 74%) mp 100-103°C. IR (CHCl₃): 1725 (ester) cm⁻¹; NMR (CDCl₃) δ : 0.80 (s, 3H), 0.91 (s, 3H), 2.0 (s, 3H, methyl), 2.1-3.2 (m, 6H), 3.68 (s, 3H, methoxy) ppm.

4a β -Hydroxymethyl-1,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalene-2(3H)-spiro-2'-(1',3'-dithiane) (149)

To lithium aluminium hydride (2.4 g, 63 mmol) in 300 mL of anhydrous ether was added the ester 148 (15.1 g, 44 mmol) in 120 mL of ether, dropwise. The suspension was stirred for 14 h. at room temperature then saturated aqueous ammonium chloride was added to

quench the reaction. The organics were separated and the aqueous phase was extracted with ether (2 X 50 mL). The combined organics were washed with water (250 mL) and saturated aqueous sodium chloride solution (250 mL) and dried over anhydrous MgSO_4 . Concentration gave 11.1 g of 149 as a white solid (80%), mp 112-114°C. IR (CHCl_3): 3500 cm^{-1} (-OH); NMR δ : 3.85 (br.s., 2H) ppm.

4a ϵ -Hydroxymethyl-1,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalene-2(3H)-one (105)

To mercuric chloride (21.2 g, 0.078 mol) and mercuric oxide (8.4 g, 0.039 mol) in 400 mL of acetonitrile: water (3:1) was added the thioketal (149) (11.1 g, 35.5 mmol) in 90 mL of the same solvent. The mixture was refluxed for 2h., cooled and filtered through a Celite pad. The Celite pad was washed with 500 mL of 1:1 dichloromethane:hexane. The combined organics were washed with ammonium acetate (5 M) (2 X 250 mL), water (2 X 250 mL) and brine (250 mL) and dried over anh. MgSO_4 . Concentration gave 6.4 g of 105 as an oil (89%). IR (neat): 3410 (-OH) and 1670 (ketone) cm^{-1} .

Formation of 105 by direct reduction of 100

The keto ester (100) (5.0 g, 20 mmol) was dissolved in 200 mL of benzene:pentane 1:1 and cooled to -15°C. To this solution was added dropwise a solution of 40 mmol of lithium diisopropylamide in 50 mL of benzene:pentane (1:1). The reaction was allowed to come room temperature and was stirred for (16 h.). Diisobutylaluminum

hydride (51 mL of 25.2 % solution in toluene, 90 mmol) was added dropwise and the mixture was stirred for 3h. Methanol (11 mL) was added dropwise, followed by the addition of glacial acetic acid until the mixture was acidic. The solvent was removed and the resulting gum was partitioned between ethyl acetate (200 mL) and 3N H_2SO_4 (200 mL). The organics were washed with 3N H_2SO_4 (200 mL), saturated NaHCO_3 (aq.) (200 mL) and brine (200 mL). Dried over MgSO_4 . Concentration gave a viscous oil which was purified to give 1.3 g of 105 (29%).

4a β -Hydroxymethyl-1,7,7-trimethyl-1,4,4a,5,6,7,8,8a β -octahydronaphthalene-2(3H)one (98)

10% palladium on charcoal (1.0 g) was suspended in ethyl acetate (30 mL) and the enone (105) (2.0 g, 9 mmol) in 5 mL of ethyl acetate was added. The mixture was hydrogenated for 48 h. then filtered and concentrated. The mixtures from several reactions were combined for purification by HPLC which gave the hydroxy ketone (98) (= 90%) mp 95-97°C. IR (CHCl_3): 3400 (br., -OH) and 1710 cm^{-1} ; NMR (CDCl_3) δ : 0.82 (s, 6H, geminal methyls), 0.95 (s, 3H, methyl), 3.80 (d, 2H, $-\text{CH}_2-\text{OH}$) ppm.

Glyoxalic acid chloride benzene sulphonylhydrazone (156)

Glyoxalic acid (9.3 g, 0.13 mol) was dissolved in water (50 mL) and the solution was warmed to 40°C. Benzene sulphonylhydrazide (10.6 g 0.06 mol) dissolved in 250 mL of 2.5 M HCl (aq.) was added to the warm solution of glyoxalic acid and the temperature was maintained

at 40°C for 2 h. The mixture was cooled and the crystals were filtered and washed with water, and dried to provide 12.7 g of glyoxalic acid benzene sulphonylhydrazone. This acid was suspended in benzene (75 mL) and thionyl chloride (8.1 mL, 0.11 mol) was added. The mixture was refluxed for 1.5 h. and after cooling, 10 g of Florisil was added and the mixture was stirred. The suspension was filtered and the Florisil was washed with benzene (5 X 20 mL). The combined organics were concentrated to provide 156 (16.2 g, 48 %).

4a ϵ -Diazoacetoxymethyl-1,7,7-trimethyl-1,4,4a,5,6,7,8,8a ϵ -octahydronaphthalene-2(3H)-one (158)

Method A: Directly from 98

The keto alcohol (98) (100 mg, 0.4 mmol) was dissolved in 5 mL of CH_2Cl_2 under argon and cooled to 0°C. The acid chloride (156) (123 mg, 0.5 mmol) was added and mixture was stirred for 15 min. Triethylamine (0.15 mL, 1.0 mmol) in 1 mL of CH_2Cl_2 was slowly added and the reaction was stirred at 0°C for 1h. The ice bath was removed and Florisil (1 g) was added and the suspension was stirred for 20 min. before filtering. The Florisil was washed with benzene (4 X 20 mL) and the organics were concentrated to give a yellow solid. Preparative tlc (1:1 ethyl acetate:hexane) gave 158 as a yellow oil (57 mg, 43%). IR (neat) 2100 (diazo), 1740-1680 (br., both carbonyls); NMR (CDCl_3) δ : 0.84 (s, 3H, geminal methyl), 0.89 (s, 3H, geminal methyl), 0.99 (s, methyl), 4.40 (s, 2H, $-\text{CH}_2-\text{O}-$) and 4.80 (s, 1H, $-\text{COCH}=\text{N}-$) ppm.

Method B: Stepwise from 98

The keto alcohol 98 (500 mg, 2.3 mmol) was dissolved in 5 mL of CH_2Cl_2 and the acid chloride (156) (620 mg, 2.5 mmol) was added. The mixture was stirred for 10 min. then NaHCO_3 (380 mg, 4.5 mmol) was added and the suspension was stirred under argon for 3 h. at room temperature. The mixture was filtered through Celite and concentrated to give a light brown oil which was dissolved in 5 mL of CH_2Cl_2 and treated with triethylamine (0.32 mL, 2.3 mmol). After stirring for 2 h., 0.5 g of Florisil was added and suspension was stirred for 15 min. prior to filtering. The Florisil was washed with CH_2Cl_2 and the combined organics were concentrated to provide a light brown oil which was chromatographed on silica gel to give 158 as a yellow oil (274 mg, 40%).

Attempted enol acetate formation on 158

Diazoketone 158 (20 mg, 0.07 mmol) was dissolved in 1 mL of CCl_4 . Acetic anhydride (0.1 mL) was added, followed by 1 drop of perchloric acid. The reaction was stirred under argon for 13 h. Tlc (1:1 ethyl acetate:hexane) showed no change. Another drop of perchloric acid was added and the mixture was stirred for 18 h. Tlc showed no starting material. The reaction was diluted with CCl_4 and filtered through a short Celite pad. Concentration afforded a brown oil which had no diazo absorption in the IR spectrum.

4a : -Chloroacetyloxymethyl-1,7,7-trimethyl-1,4,4a,5,6,7,8,8a : -
octahydronaphthalene-2(3H)-one (159)

The keto alcohol 98 (2.52 g, 11 mmol) was dissolved in dry CH_2Cl_2 (25 mL) under argon. Pyridine (1.0 mL, 12 mmol) was added and the mixture was stirred for 20 min. Ice was packed around the flask and chloroacetyl chloride (1.4 g, 12 mmol) was added neat, dropwise. The reaction was slowly allowed to come to room temperature while stirring for 16 h. under argon by which time pyridine hydrochloride had precipitated. The mixture was poured into water and the organics were removed. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organics were washed with 2 N HCl (2 X 30 mL) and saturated NaHCO_3 (aq.) (1 X 30 mL). Dried over anhydrous MgSO_4 . Concentration gave 159 (2.47 g, 73 %). IR (neat): 1760-1700 cm^{-1} (br., ketone and ester); NMR (CDCl_3) δ : 4.20 (s, 2H, $-\text{CO}-\text{CH}_2-\text{Cl}$), 4.45 (s, 2H, $-\text{CH}_2-\text{O}-$) ppm.

2-Acetoxy-4a : -chloroacetyloxymethyl-1,7,7-trimethyl-3,4,4a,
8,8a : -octahydronaphthalene (160)

The keto ester 159 (948 mg, 3 mmol) was dissolved in 10 mL of CCl_4 and freshly distilled acetic anhydride (2 mL) was added. One drop of perchloric acid was added and the reaction was stirred at room temperature under argon for 19 h. The reaction was cooled in an ice bath and sodium bicarbonate (sat'd. aq.) (5 mL) was added and mixture was stirred for 0.5 h. The organics were separated

and dried over anhydrous MgSO_4 . Concentration gave 983 mg (97 %) of a light oil. ^1NMR (CDCl_3) δ : 0.90 (s, 6H, geminal methyls), 1.40 (s, 3H, $=\text{C}-\text{CH}_3$), 2.20 (s, 3H, $\text{CH}_3\text{CO}-$), 4.11 (s, 2H, $-\text{COCH}_2\text{Cl}$) and 4.22 (d, 2H, $-\text{CH}_2-\text{O}$) ppm.

2-Acetoxy-4a β -hydroxymethyl-1,7,7-trimethyl-3,4,4a,5,6,7,8,8a β -octahydronaphthalene (161)

The α -chloroester (160) (205 mg, 0.6 mmol) was dissolved in 5 mL of ethanol and sodium bicarbonate (84 mg, 1 mmol) and thiourea (50 mg, 0.7 mmol) were added. The reaction was stirred for 17 h. under argon then acidified with dilute HCl (aq.). The mixture was partitioned between ether (20 mL) and water (20 mL) and the organics were washed with water (20 mL) and brine (20 mL). After drying over MgSO_4 (anh.), concentration gave 93 mg of 161. IR (neat): 3480 (br., OH) and 1740 (acetyl) cm^{-1} ; ^1NMR (CDCl_3) δ : 0.98 (s, 6H, geminal methyls), 1.55 (s, 3H, $=\text{C}-\text{CH}_3$), 2.15 (s, 3H, $\text{CH}_3\text{CO}-$) and 3.56 (d, 2H, $-\text{CH}_2-\text{OH}$) ppm.

2-Acetoxy-4a β -diazoacetoxymethyl-1,7,7-trimethyl-3,4,4a,5,6,7,8,8a β -octahydronaphthalene (155)

The enol acetate (161) (319 mg, 1.2 mmol) and the acid chloride (156) (326 mg, 1.3 mmol) were dissolved in 10 mL of dry dichloromethane under argon. Sodium bicarbonate (202 mg, 2.4 mmol) was added and the mixture was stirred at room temperature for 24 h.

The suspension was filtered through Celite and concentrated to give a light brown oil. This oil was redissolved in 10 mL of dry CH_2Cl_2 and triethylamine (0.18 mL, 1.3 mmol) was added. The reaction was put under argon, protected from light and stirred for 14 h. at room temperature. Florisil (0.2 g) was added and the suspension was stirred for 15 min. then filtered. The filtrate was concentrated to afford a dark brown oil which was flash chromatographed on silica gel (5% ethyl acetate/hexane) to give 336 mg (84%) of 155. IR (neat): 2095 (dialzo), 1740 (acetyl) and 1685 (diazo ester) cm^{-1} ; NMR (CDCl_3): δ : 0.95 (br. s., 6H, geminal methyls), 1.45 (s, 3H, vinyl methyl), 2.10 (s, 3H, acetyl methyl), 4.20 (d, 2H, $-\text{CH}_2-\text{O}-$) and 4.90 (s, 1H, $-\text{CO}-\text{CH}=\text{N}-$), ppm MS m/e (rel.int.): 264 (9), 248 (22), 220 (27), 206 (42), 191 (30), 178 (97) and 43 (100).

Catalytic Decomposition of 155

A. Rhodium acetate dimer

Rhodium (II) tetracetate (3 mg) was suspended in 0.5 mL of dry cyclohexane under argon. The diazoester 155 (12 mg, 0.04 mmol) in 1 mL of dry cyclohexane was added dropwise and the reaction was protected from light. The mixture was stirred for 12 h. at room temperature. Tlc showed the absence of starting material and the mixture was filtered and concentrated. Preparative tlc (20% ethyl acetate/hexane) allowed the isolation of only one material (3 mg). MS m/e (rel. int.) 348 (3), 248 (14), 220 (20), 206 (37), 178 (100).

B. Copper acetylacetonate

Copper acetylacetonate (1 mg) was suspended in hexane (1 mL) and placed under argon. The diazoester (155) (50 mg, 0.15 mmol) in hexane (1 mL) was added dropwise and the mixture was protected from light. The reaction was stirred at room temperature until tlc showed the disappearance of the starting material (24 h.). The mixture was filtered through a small pad of Celite and concentrated to give 47 mg of an apparently homogenous glassy oil. IR (CHCl_3); 1748 and 1725 cm^{-1} ; NMR (CDCl_3) δ : 0.95 (s, 6H, geminal methyls), 1.45 (s, 3H, $=\text{C}-\text{CH}_3$), 2.1 (s, 3H, acetyl methyl), 4.2 (m, 2H, $-\text{CH}_2-\text{O}-$ and 6.2, 6.8, 7.3 (3s, 1H). ^{13}C NMR (CDCl_3) δ : 167.9, 164, 139, 132, 128, 122, 69.8, 40.7, 37.99, 37.90, 34.3, 34.1, 32.7, 31.6, 29.6, 23.0, 22.8, 19.7, 13.9 ppm.

C. Photochemical Catalysis

The diazoester 155 (183 mg, 0.6 mmol) was dissolved in 25 mL of dioxane and placed in a quartz reaction vessel inside a Rayonet photochemical reactor. The reaction was maintained under argon during irradiation at 254 nm for 5 days at which time, tlc showed a uniform streak. Concentration gave 175 mg of a yellow oil which was dissolved in ethanol (5 mL) and added to a solution of potassium hydroxide (544 mg, 9.7 mmol) in ethanol (5 mL). The reaction was stirred at room temperature for 21 h. and partitioned between ether (50 mL) and water (50 mL). The aqueous phase was re-extracted with ether (50 mL) and the combined organics were washed with water (75 mL) and brine (75 mL) and dried over MgSO_4 .

The aqueous phase was acidified with 3 N HCl and extracted with ether (2 x 50 mL). This acid extract was washed with water and brine (75 mL), and dried. Tlc in ethyl acetate showed only baseline material. The basic extract was concentrated to give 92 mg of a glassy oil. Chromatography allowed the isolation of the keto alcohol 198 (29 mg, 24 %) and the hemiacetal 167 (36 mg, 29 %). A sample was recrystallized from hexane, mp 95-97°C. IR (CHCl₃): 3280 (-OH) cm⁻¹; NMR (CDCl₃) δ: 0.87 and 0.92 (each s, 3H, geminal methyls), 1.1 (d, 3H, CH₃-CH), 3.47 and 3.82 (each d, 1H, -CH₂-O-) ppm. ¹³C NMR (CDCl₃): 96.5, 78.3, 43.4, 43.1, 42.0, 33.9, 33.2, 33.1, 31.8, 30.5, 28.7, 24.6, 24.3 and 13.8 ppm. MS m/e (rel. int.): 224 (17, M⁺), 194 (28), 109 (51) and 95 (100). High resolution: calculated mass 224.1776, observed mass 224.1773.

Representative procedure for attempted intermolecular cyclopropanation of 160.

The enol acetate, 160 (97 mg, 0.3 mmol), was dissolved in cyclohexane (3 mL) and cupric sulphate (5 mg) was added. The mixture was brought to reflux under argon and ethyl diazoacetate (0.10 mL, 1.0 mmol) in cyclohexane (4 mL) was added slowly. The mixture was refluxed for 2 h. after the addition was complete, then cooled and stirred overnight (14 h.). Tlc showed only starting material (160) bracketed by diethyl fumarate and diethyl maleate.

Attempted intermolecular cyclopropanation of 161

The hydroxy enol acetate 161 (65 mg, 0.2 mmol) was dissolved in cyclohexane (3 mL) and cupric sulphate (3 mg) was added. The mixture was brought to reflux under argon and ethyl diazoacetate (0.07 mL, 0.7 mmol) in 4 mL of cyclohexane was added slowly. The reaction was refluxed for 2 h., then stirred for 19 h. at room temperature. The solution was diluted with cyclohexane and filtered through Florisil. Concentration gave 84 mg which was chromatographed by preparative tic (25% ethyl acetate/hexane) to give 67 mg of a white solid (mp ~~47-48~~⁴⁸ °C) (169) (78%). IR (CHCl₃): 1750-1730 (br., both esters); NMR (CDCl₃): 0.90 (s, 6H, geminal methyls), 1.22 (t, 3H, -O-CH₂-CH₃), 2.10 (s, 3H, acetyl), 3.40 (q, 2H, -O-CH₂-CH₃), 4.05 (s, 2H, -O-CH₂-CO-) and 4.18 (d, 2H, -CH₂-O-CH₂-CO-) ppm. ¹³C NMR (CDCl₃): 170.8, 169.9, 140.8, 123.3, 78.1, 69.1, 60.6, 41.7, 38.8, 36.0, 34.0, 32.8, 30.7, 30.4, 24.1, 24.0, 22.8, 20.7, 14.9, 14 ppm. MS m/e (rel. int.): 310 (44), 206 (28), 193 (63), 178 (100). Anal. calcd. for C₂₀H₃₂O₅: C 66.15, H 9.15; found., C 68.23, H 9.18.

3-(2-Hydroxyethyl)-3,6,6-trimethyl cyclohexanone

The ketal 180 (56.3 g, 0.25 mol) was dissolved in acetone (400 mL) and 5% aqueous oxalic acid was added until the mixture remained cloudy. The reaction was refluxed for 25 h., cooled and concentrated. The residue was extracted with ether (2 X 200 mL) and

the organics were washed with saturated NaHCO_3 (aq.) (300 mL) and brine (800 mL) and dried over anhydrous MgSO_4 . Concentration gave 38.2 g of the title compound (67%) as a colourless liquid. IR (neat): 3400 (OH) and 1705 (CO) cm^{-1} ; NMR (CDCl_3) δ : 0.93 (s, 3H, C-3 methyl), 1.05 (s, 6H, geminal methyls), 1.5-1.9 (m, 4H, methylenes), 2.18, 2.40 (dd, each 1H, $J = 14$ Hz, C-2 methylene) and 3.70 (t, 2H, $J = 6$ Hz, $-\text{CH}_2-\text{OH}$).

3- (2-Tetrahydropyranyloxyethyl) -3,6,6-trimethyl cyclonexanone (190)

3- (2-Hydroxyethyl) -3,6,6-trimethyl cyclonexanone (38.2 g, 208 mmol) was dissolved in freshly distilled dihydropyran (180 mL). A few crystals of *p*-toluene sulphonic acid were added and the reaction was stirred under argon at room temperature for 20 h. The mixture was diluted with ether (200 mL) and washed with water (250 mL). The aqueous phase was extracted with ether (200 mL) and the combined organics were washed with saturated NaHCO_3 (aq.) (350 mL) and dried over MgSO_4 anhyd. Concentration gave 50 mL of an oil which was purified by HPLC (25% ethyl acetate hexane) to give 48.5 g (87% of 190) as a light yellow oil. IR (neat): 1700 (CO); NMR (CDCl_3) δ : 0.90-1.10, 1.12 (each s, 3H, methyls), 1.2-1.8 (m, 12H), 2.18, 2.40 (dd, 1H each, $J = 14$ Hz), 3.1-4.0 (m, 4H, $-\text{CH}_2-\text{O}-$), and 4.50 (br.s., 1H, acetal) ppm.

3-(2-Tetrahydropyranyloxyethyl)-3,6,6-trimethyl-1-vinyl-cyclo-
hexanol (191)

The ketone (190) (47.2 g, 176 mmol) was dissolved in dry THF (300 mL) and added dropwise to a stirring solution of vinyl magnesium bromide (190 mL of 1.3 M in THF, 247 mmol) under argon. Stirring was continued for 16 h and a further 50 mL of vinyl magnesium bromide (1.3 M) was added. The reaction was stirred for 12 h. then the excess vinyl magnesium bromide was destroyed with aqueous ammonium chloride (saturated). The mixture was extracted with ether (400 mL) and the organics were washed with brine and dried over $MgSO_4$. Concentration gave an oil which was purified by HPLC (2% ethyl acetate/hexane) to give the isomeric alcohols (44.3 g, 85 %). IR (neat): 3460 (OH) and 3080 ($CH=C$) cm^{-1} ; NMR ($CDCl_3$) δ : 0.85, 0.90 and 1.12 (each s, 3H, methyl), 1.2-2.0 (m, 14 H), 3.2-3.9 (m, 4H, CH_2-O-), 4.50 (br. s., 1H, acetal), 4.80-5.40 (m, 2H, $CH_2=C$) and 5.60-6.20 (1H, 2 sets of quartets, $-CH=$) ppm.

2-(2-(1,4,4-Trimethyl-3-vinylcyclohex-2-enyl)ethoxy) tetrahydro-
pyran (192)

The alcohols 191 (15.8 g, 55 mmol) were dissolved in benzene (200 mL) and p-toluene sulphonic acid (1.0 g) was added. The mixture was refluxed for 3 h. with concurrent removal of water, then cooled and filtered through a Florisil pad. Concentration gave 14.2 g of a dark brown oil which was immediately treated with oxalic acid.

2-(1,4,4-Trimethyl-3-vinyl cyclohex-2-enyl) ethanol (193)

Crude 192 (14.2 g) was dissolved in acetone (120 mL) and aqueous oxalic acid (5%) was added until the mixture was turbid. The reaction was refluxed for 18 h. then cooled and the acetone was removed. Ether (200 mL) was added and the small aqueous layer was removed. The organics were washed with saturated NaHCO_3 (aq.) and brine and dried over Na_2SO_4 (anh.). Concentration gave 12.7 g of a dark brown oil which was chromatographed on silica gel (10 % ethyl acetate/hexane) to give 2.45 g (24 % from 191) of 193. IR (neat): 3340 (OH), 3080 (C=C) cm^{-1} ; NMR (CDCl_3) δ : 1.03 (s, 3H, methyl), 1.05 (s, 6H, geminal methyls), 1.5-1.8 (m, 6H), 3.70 (t, J = 8 Hz, $-\text{CH}_2-\text{OH}$), 4.90 (1H, dd, J = 2, 10 Hz), 5.20 (1H, dd, J = 2, 18 Hz), 5.45 (1H, br. s.; C-2 vinyl H) and 6.20 (1H, dd, J = 10, 18 Hz, $\text{CH}=\text{CH}_2$). MS m/e (rel. int.): 194 (M^+ , 15), 179 (16), 149 (100).

2-(1,4,4-Trimethyl-3-vinyl cyclohex-2-enyl)-1-methanesulphonyloxyethane (194)

The alcohol 193 (2.45 g, 13 mmol) was dissolved in dry dichloromethane (10 mL) and dry pyridine (1.2 g, 15 mmol) and methanesulphonylchloride (1.6 g, 14 mmol) were added. The reaction was stirred under argon at room temperature for (15 h.). The reaction was diluted with dichloromethane (20 mL) and washed with water (25 mL), 1 N hydrochloric acid (25 mL) and brine and dried over

MgSO₄. Concentration gave 3.12 g of 194 (88%). NMR (CDCl₃) : 3.0 (s, 3H, CH₃-SO₃-), 4.3 (t, 2H, J = 8 Hz, -CH₂-O-).

3-(1,4,4-Trimethyl-3-vinylcyclohex-2-enyl)-propiononitrile (195)

The mesylate 194 (3.10 g, 11 mmol) was dissolved in 15% aqueous ethanol (15 mL) and potassium cyanide (1.47 g, 27 mmol) was added. The reaction was refluxed for 21 h., then cooled and partitioned between ether (25 mL) and water (25 mL). The aqueous phase was extracted with ether (25 mL) and the combined organics were washed with water (50 mL) and brine (50 mL). Concentration gave 195 as an oil (1.41 g, 60%). IR (neat): 3080 (C=C), 2250 (C≡N) cm⁻¹. NMR (CDCl₃) : 2.1-2.3 (m, 2H, -CH₂-CN).

3-(1,4,4-Trimethyl-3-vinyl-cyclohex-2-enyl)-propionaldehyde (189)

The nitrile 195 (221 mg, 1.1 mmol) was dissolved in benzene (10 mL) under argon and diisobutylaluminum hydride (3.3 mL of 1 M in hexane, 3.3 mmol) was added dropwise. The reaction was stirred at room temperature for 17 h. Saturated aq. ammonium chloride (2 mL) was added and the mixture was cooled to 0°C. Cold 50% H₂SO₄ (aq.) (2 mL) was added and the mixture was allowed to come to room temperature, then partitioned between ether (25 mL) and water (25 mL). The aqueous phase was extracted with ether (25 mL) and the combined organics were washed with saturated NaHCO₃ (aq.) (50 mL) and brine (50 mL). After drying over MgSO₄, concentration gave an oil which was

chromatographed on silica gel (10% ethyl acetate/hexane) to give the aldehyde 189 as an oil (110 mg, 49%). IR (neat): 3095 (C=C), 2710 and 1730 (CHO). cm^{-1} ; NMR (CDCl_3) δ : 9.75 (br.s., 1H, CHO). MS m/e (rel. int.): 206 (M^+ , 13), 191 (10), 162 (24) and 149 (100).

α -Bromoacrolein

Acrolein was distilled (50-53°C) under argon into a receiver containing a small amount of hydroquinone. 35.6 g (0.64 mol) was transferred via stainless steel cannula into a round bottom flask containing ether (250 mL). Bromine (101.5 g, 0.64 mol) was added dropwise with ice-bath cooling, then a further 250 mL of ether was added. The reaction was cooled to 0°C then triethylamine (88.5 mL, 0.64 mol) was added dropwise. After the addition was complete, the reaction was allowed to come to room temperature and stirred for 19 h. The suspension was filtered through two short Celite pads and concentrated to a volume of approximately 200 mL. The organics were washed with 3 N HCl (aq.) (200 mL) and brine (200 mL) and dried over anhydrous MgSO_4 . Concentration gave an oil which was distilled at aspirator pressure to give the title compound (34.2 g, 40%).

α -Bromoacrolein diethyl acetal

α -Bromoacrolein (26.3 g, 195 mmol) was mixed with triethylorthoformate (40 mL) and a warm solution of ammonium nitrate (740 mg) in 13 mL of ethanol was added. The mixture was put under an inert atmosphere and stirred for 20 h. at room temperature.

The mixture was filtered, and 980 mg of NaHCO_3 was added. Distillation at aspirator pressure provided the title compound at 50°C (21.5 g, 53%). NMR (CDCl_3) δ : 1.15 (t, 6H, CH_3CH_2), 3.5 (q, 4H, $\text{O-CH}_2\text{CH}_3$), 4.82 (s, 1H, acetal H), 5.65, 6.12 (br.s., 1H each, $\text{H}_2\text{C=}$) ppm.

3-Hydroxy-5-(1,4,4-trimethyl-3-vinyl-cyclohex-2-enyl)-2-methylene-pentanal diethyl acetal (202)

α -Bromoacrolein diethyl acetal (160 mg, 0.8 mmol) was dissolved in dry THF (2 mL) and cooled to -78°C under argon. *n*-Butyllithium (0.44 mL of 1.6 M, 0.7 mmol) was added and the solution was stirred for 0.5 h. The aldehyde 189 (112 mg, 0.5 mmol) in dry THF (1.5 mL) was added dropwise and the reaction was stirred for 1 h. The temperature was then brought to 0°C and saturated ammonium chloride solution (aq.) (2 mL) was added. The mixture was partitioned between ether (25 mL) and water (25 mL). The aqueous phase was extracted with ether (25 mL) and the combined organics were washed with water (50 mL) and brine (50 mL) and dried over MgSO_4 . Concentration gave 131 mg of 202 (72%). IR (neat): 3440 (OH) and 3080 (C=C-H) cm^{-1} . NMR (CDCl_3) δ : 0.99, 1.05 and 1.07 (3H each, s, ring methyls), 1.2-1.3 (3H each, dt, $\text{CH}_3\text{CH}_2\text{-O}$), 1.3-1.75 (8H, m), 2.72 (1H, d, -OH), 3.45-3.8 (4H, m, OCH_2CH_3), 4.2 (1H, m, CH-OH), 4.89 (1H, s, acetal), 4.90 (1H, dd, $^2J = 2 \text{ Hz}$, $^3J = 10 \text{ Hz}$ (cis), $\text{H}-\text{C}=\text{C}-\text{H}$), 5.23 and 5.27 (each 1H, s, $\text{H}_2\text{C}=\text{C}$), 5.26 (1H, dd, $^2J = 10 \text{ Hz}$, $^3J = 18 \text{ Hz}$ (trans), $\text{H}-\text{C}=\text{C}-\text{H}$), 5.44 (1H, d, $^4J = 2 \text{ Hz}$, ring vinyl proton) and 6.29 (1H, octet, $^3J = 10 \text{ Hz}$ (cis), $^3J = 18 \text{ Hz}$ (trans), $^4J = 2 \text{ Hz}$, ($\text{H}_2\text{C}=\text{C}-\text{H}$)). MS m/e (rel.int.):

291 (43), 273 (100), 245 (66), 227 (72) and 149 (99).

Diels-Alder Reactions of 202

A. Thermal

The triene 202 (12 mg, 0.04 mmol) was dissolved in carbon tetrachloride (2 mL) and sealed in a Carius tube under argon. The solution was heated at 150°C for 21 h., cooled and chromatographed (prep. tlc, 30% ethyl acetate/hexane) to yield 5 mg of a high R_f (0.84) material. MS m/e (rel. int.): 308 (8), 259 (48), 215 (30), 103 (100).

B Lewis Acid catalyzed

The triene 202 (67 mg, 0.2 mmol) was dissolved in dichloromethane (3 mL) and put under argon for the addition of ethyl aluminium dichloride (0.09 mL of 25% in dichloromethane, 0.2 mmol) and stirred for 16 h. at room temperature. Several drops of water were added and the mixture was partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous phase was extracted with a further 10 mL of CH_2Cl_2 and the combined organics were washed with water (20 mL) and brine (20 mL) and dried over Na_2SO_4 (anh.). Concentration gave 63 mg of an oil which was chromatographed to yield 2 mg (3%) of a high R_f (0.80) material. MS m/e (rel. int.): 336 (0.9), 305 (5), 259 (29), 246 (28), 201 (32), 103 (100).

3-Benzyloxy-5-(1,4,4-trimethyl-3-vinyl-cyclohex-2-enyl)-2-methylene-pentanal (205)

The triene 202 (680 mg, 2 mmol) in dry DME (7 mL) was added to a pre-washed suspension of 200 mg of 60% dispersion of NaH in oil (2.5 eq.). The suspension was stirred for 5 min. and benzyl bromide (0.6 mL, 5 mmol) was added. The reaction was heated to 85°C for 4 h., then allowed to stand at room temperature for 12 h. The mixture was diluted with brine (40 mL) and extracted with dichloromethane (4 x 20 mL) and dried over Na₂SO₄. Concentration gave an oil which was dissolved in a mixture of 5 mL of 1 N HCl and 15 mL of acetone. The reaction was stirred for 2 h. at room temperature and then diluted with 40 mL of water. The solution was extracted (4 x 20 mL) and the organics were dried (Na₂SO₄) and concentrated to give an oil which was flash chromatographed on silica gel (5% ethyl acetate/hexane) to give 205 as an oil (460 mg, 68%). IR (neat): 2700 (CHO) and 1690 (C=C-CHO) cm⁻¹. NMR (CDCl₃): 4.47 and 4.36 (2H, dd, benzylics), 7.3 (5H, s, aromatics) and 9.64 (1H, s, aldehyde proton). MS m/e (rel. int.): 261 (2), 233 (3), 215 (4), 149 (38), 91 (100).

Diels-Alder Reaction of 205

The aldehyde 205 (200 mg, 0.6 mmol) was dissolved in carbon tetrachloride (5 mL) that had been degassed and 2,6-di-tert-butyl-4-methylphenol (2 mg) was added. The solution was sealed in a Carius tube and heated at 150°C for 18 h. After cooling and concentration, the mixture was flash chromatographed on silica gel (1% ethyl acetate/hexane) to provide 100 mg of a colourless oil. IR (neat): 2710 and

1712 (CHO) cm^{-1} ; NMR (CDCl_3) δ : 3.88 (1H, m, -CH-O-), 4.43-4.79 (2H, m, benzylic), 5.5 (1H, br.s., H-C=C), 9.53, 9.72 and 10.34 (1H total, s, aldehydes).

The above oil was dissolved in ethanol (3 mg) and hydrogenated over 10% Pd/C (100 mg) for 48 h. The mixture was filtered and concentrated to give an oil which was dissolved in dichloromethane (10 mL).

Celite (1g) and pyridinium chlorochromate (95 mg) were added and the suspension was stirred at room temperature for 12 h. The mixture was filtered through a small silica gel pad and concentrated to give an oil (35 mg) which was subjected to spectral analysis. IR (neat): 1730, 1700 (CHO, CO) cm^{-1} ; NMR (CDCl_3) δ : 9.52 and 9.53 (aldehydes) ppm.

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Appendix I

Selected NMR Spectra

^1H Spectrum of 167

^{13}C Spectrum of 167

179

0

50

100

^1H Spectrum of 155

180

^{13}C Spectrum of 138

^{13}C Spectrum 117

3 3

OF / DE

¹H Spectrum of 202

^{13}C Spectrum of 202

¹H Spectrum of 205

¹H Spectrum of 206-209

¹H Spectrum of 210 and 211

Appendix 2

Flow Charts

Flow Chart 3

191

END

1	0	0	4	8	6
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FIN