APPROACHES TO THE TOTAL SYNTHESIS OF C_{20} GIBBERELLINS

A THESIS

PRESENTED FOR THE DEGREE OF

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AUSTRALIAN NATIONAL UNIVERSITY

by

MARTIN JOSEPH KENNY

Research School of Chemistry,

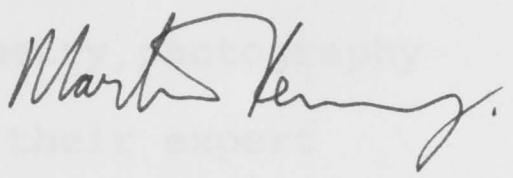
CANBERRA, A.C.T.

July 1981

To Teresa and Peter

DECLARATION

This thesis contains no material previously submitted for a degree in any other University, and to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference is made in the text.



MARTIN J. KENNY

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ABSTRACT

This thesis investigates strategies for the total synthesis of C_{20} gibberellins, and the results are presented in four chapters.

In Chapter 1, an improved synthesis of the versatile tricyclic dienone 23 is described.

In Chapter 2, the selective removal of the $\Delta^{1(9a)}$ olefinic bond in dienone 23 is investigated. Reduction to the desired *cis*-epimer was found to be optimal using lithium aluminium hydride. A rigorous determination of the stereochemical outcome of all the reduction methods studied was also carried out.

Chapter 3 describes the C(1) elaboration of the key tricyclic methoxyenone 49 and also examines the 1,3-transposition of the carbonyl group in the methoxyenone system.

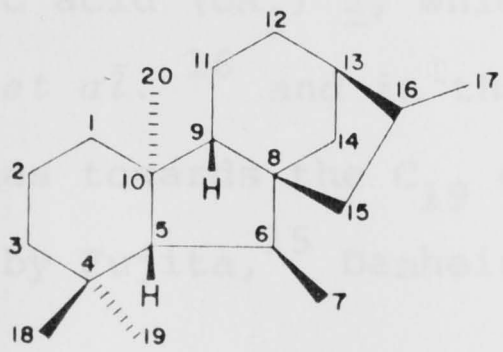
Chapter 4 investigates an alternative strategy to that in Chapter 3, in which the ring-contraction would be effected before the proposed intramolecular Michael reaction. Two approaches are studied: (1) where a potential A-ring fragment is incorporated prior to ring-contraction, and (2) where ring-contraction is carried out before the attachment of the A-ring fragment.

CONTENTS

INTRODUCTION

The gibberellins are an important group of plant-growth hormones which have profound and diverse effects on plant physiology.[1,2] Although the primary role of gibberellins is still obscure,[3] they have found considerable practical use in agriculture[3,4] in the development of seedless fruits (e.g. grapes)[5] and in the improvement of quality or quantity of fruit. They are also used to offset frost damage, to stimulate growth (e.g. sugarcane), and to alter harvest times.[1,3,4] As a consequence of their economic potential, several of the more active gibberellins are produced industrially by fermentation using the fungus *Gibberella fujikuroi*, which was the source of the first isolated gibberellins in 1936.[6]

To date more than sixty different gibberellins have been found in various plants and fungi,[7,8] and they are classified as tetracyclic diterpenoids based on the ent-gibberellane carbocyclic skeleton 1.[9] They can be divided into C_{20} or C_{19} gibberellins, the latter being biogenetically derived from the former by the loss of the C(20) atom.[10]



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Gibberellins originate[11] (Scheme 1) from geranyl-geranyl pyrophosphate 2, which undergoes cyclisation to kaurene 3; then oxidation of the C(19) methyl and C(7) methylene groups to the acid and β-alcohol, respectively, is followed by contraction of the B-ring to give the gibberellin aldehyde 4.[12] This is the immediate precursor of the C_{20} gibberellins which, by loss of C(20) as carbon dioxide, afford C_{19} gibberellins.[13,14,†]

Although much progress has been made in this area, many details of gibberellin biosynthesis have yet to be determined. This is because of the limited availability of suitable compounds from natural sources and also the lack of reliable and flexible methodology suitable for the incorporation of isotopic labels into a range of gibberellin structures.

In these circumstances, total synthesis offers the potential for providing key compounds of biosynthetic interest and, moreover, for generating molecular probes for structure-activity studies. However, the total synthesis of these complex natural products presents a formidable challenge. Nevertheless, this has been readily accepted by several groups, whose efforts have made a sizeable contribution to the reservoir of synthetic methodology and design.[15] Most effort has been directed towards the C_{19} gibberellins, especially towards gibberellic acid (GA_3) 5, which has been recently prepared by Corey *et al.*[16] and in these laboratories.[17] The synthetic approaches towards the C_{19} gibberellins have been reviewed recently by Fujita,[15] Danheiser[18] and Urech.[19]

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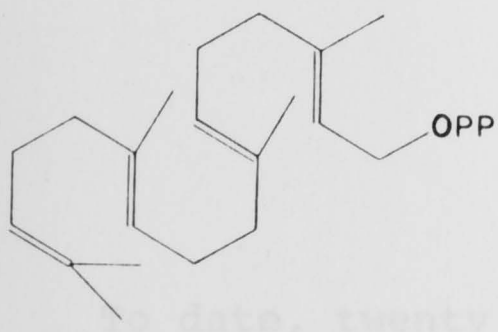
† For a review on gibberellin biosynthesis, see reference 14.



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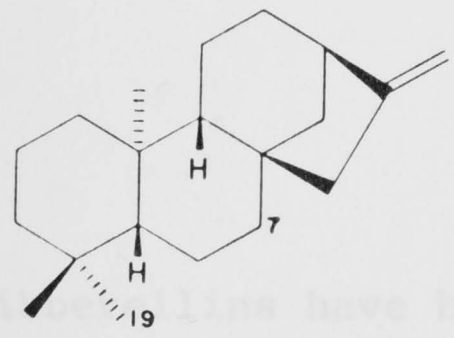

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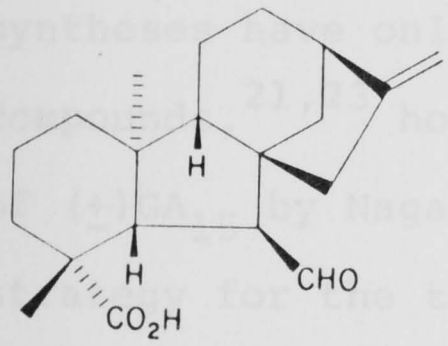
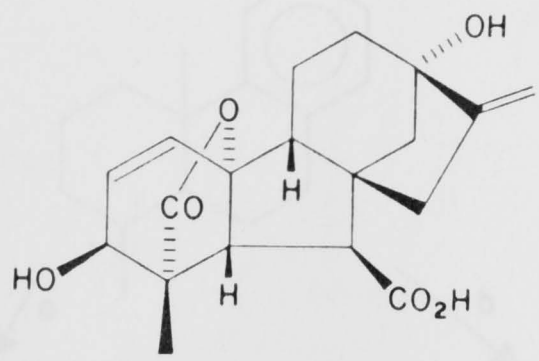


4

C_{20} gibberellins

C_{19} gibberellins

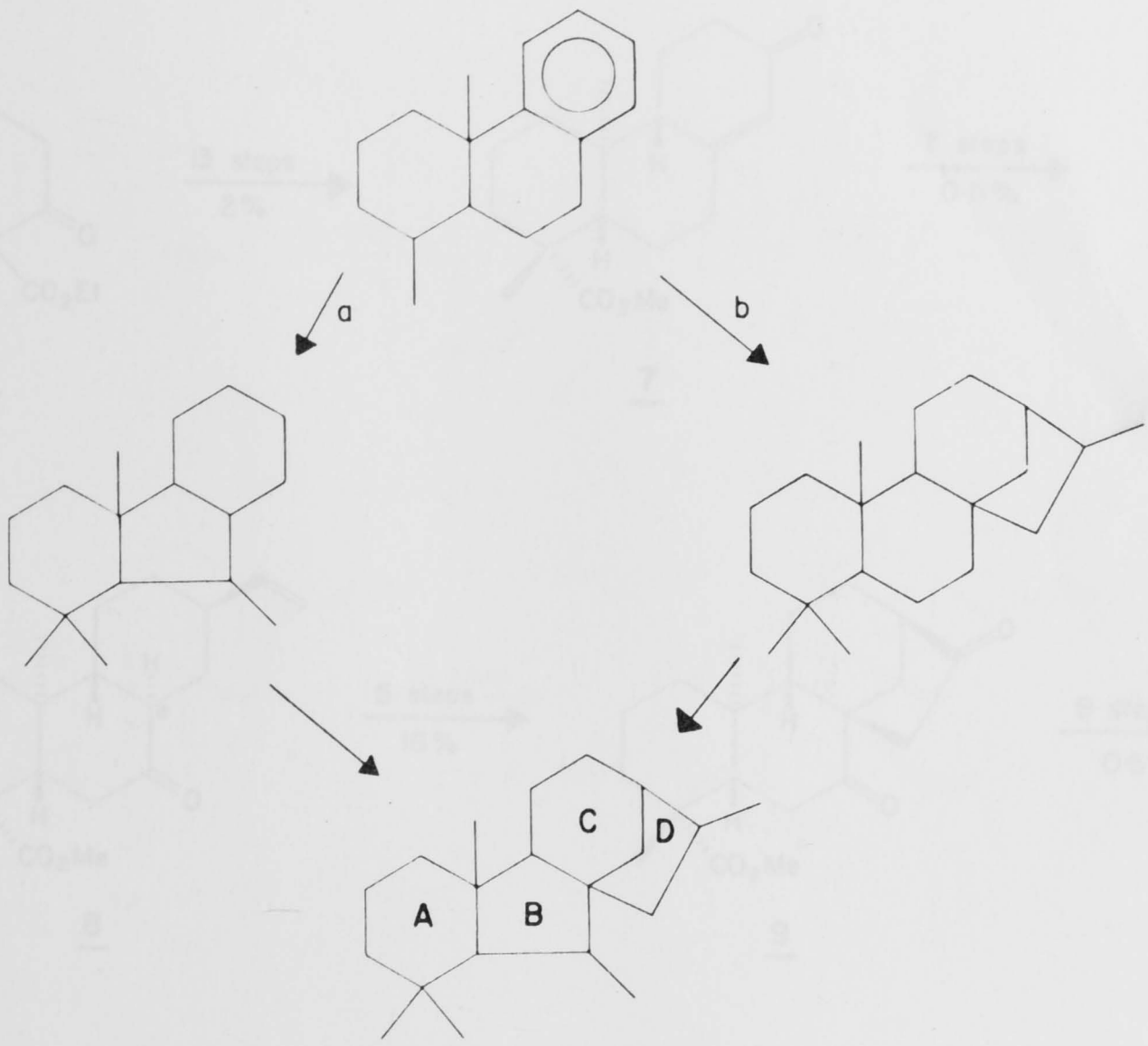
SCHEME 1



5

To date, twenty three C_{20} gibberellins have been isolated and their structures determined,[8,20] but only the syntheses of GA_{12},[21] GA_{15},[22,23] and GA_{37}[23] have been achieved. These syntheses have only been completed through the use of relay compounds,[21,23] however, with the exception of the synthesis of $(\pm)GA_{15}$ by Nagata and co-workers.[22] The most popular strategy for the total synthesis of C_{20} gibberellins has been based on the construction of the phenanthrene skeleton with subsequent contraction of the B-ring and addition of the D-ring as indicated in Scheme 2.[15]

The formal synthesis of GA_{12} by Mori *et al.*[21] (Scheme 3) mimicked the biogenetic route. Enone 7 (prepared from 6[24]) was converted in very low yield into the keto olefin 8, and intramolecular alkylation at C(8) gave the diketone 9. The formal synthesis[25,26] required a total of ∿33 steps with an overall yield of ∿2 x 10^{-5}%. While the strategy is conceptually interesting, in practice the construction of the D-ring is a long and inefficient process, the yield from

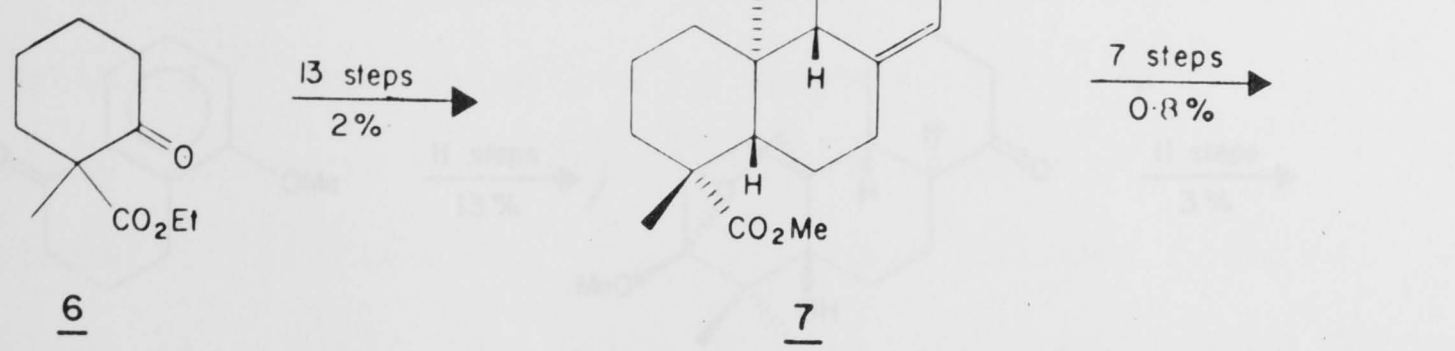


C_{20} gibberellin

SCHEME 2

the B-ring contraction is very poor, and the overall yield minute. Thus, it is not surprising that a relay compound was used.

Fujita and co-workers converted 11, the key intermediate in the total synthesis of enmein,[27] into 12, which was transformed using relay compounds into gibberellins A_{15} and A_{37} (Scheme 4).[23] From this scheme it is evident that the construction of ring D and the contraction of ring B are accomplished by long and inefficient processes. These



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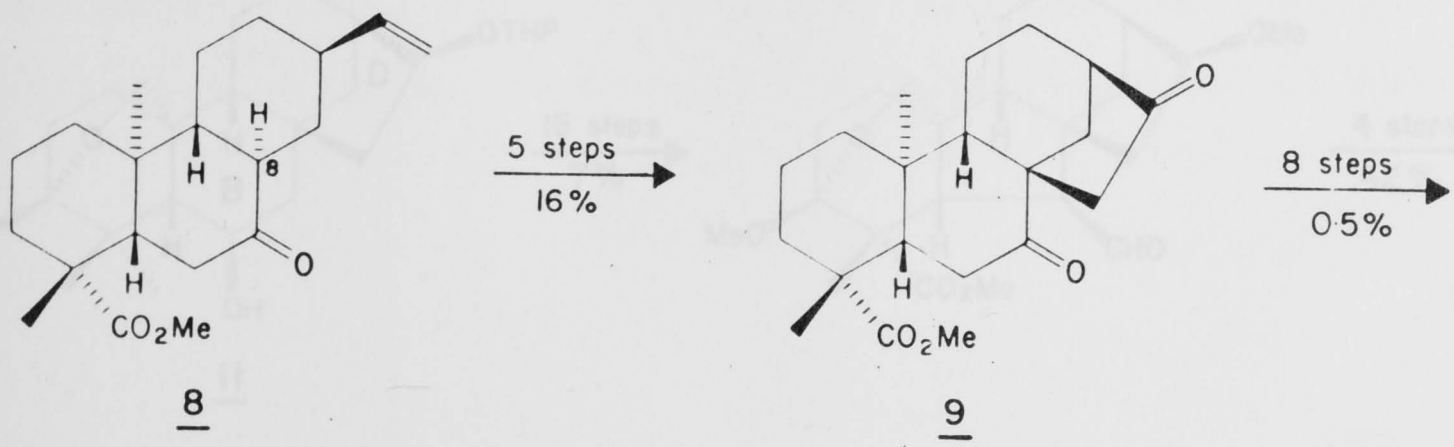
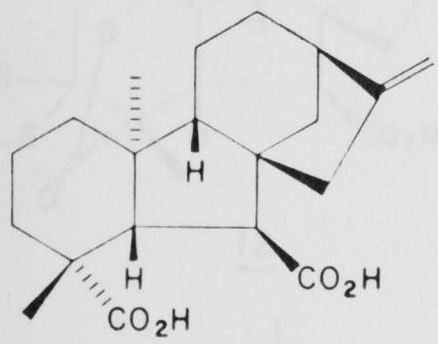
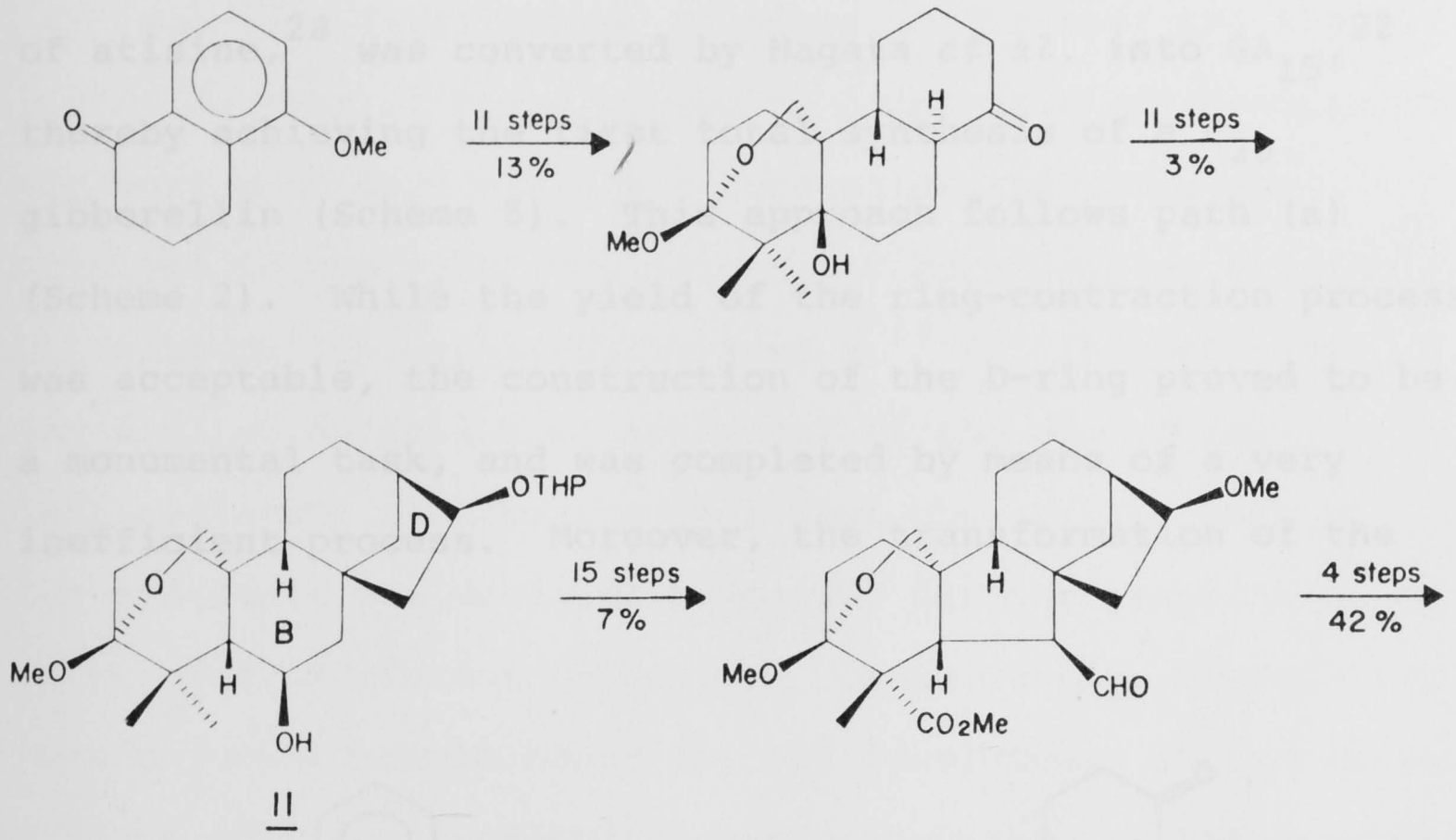


8 9



10 , GA_{12}

SCHEME 3



II

12

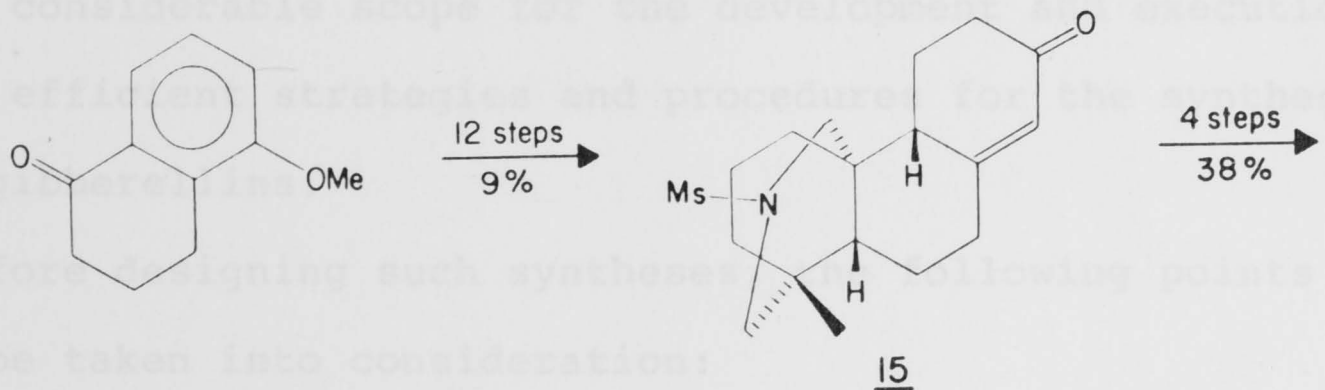
GA_{37}, 14

GA_{15}, 13

SCHEME 4

syntheses afforded an overall yield of ∿2 x 10^{-3}% (GA_{15}) and ∿6.5 x 10^{-4}% (GA_{37}).

Enone 15, an important intermediate in the synthesis of atisine,[28] was converted by Nagata *et al.* into GA_{15},[22] thereby achieving the first total synthesis of a C_{20} gibberellin (Scheme 5). This approach follows path (a) (Scheme 2). While the yield of the ring-contraction process was acceptable, the construction of the D-ring proved to be a monumental task, and was completed by means of a very inefficient process. Moreover, the transformation of the



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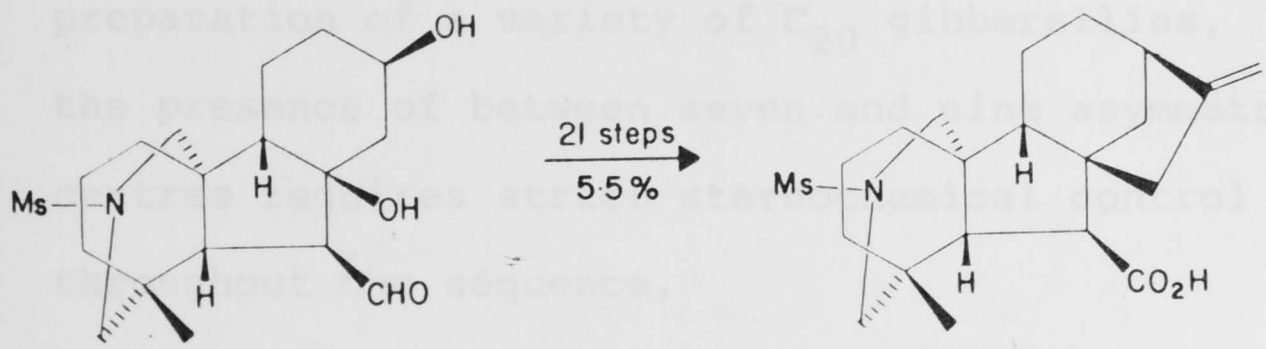


8 steps
3%
GA_{15}, 13

SCHEME 5

piperidine ring into a δ-lactone[29] afforded a low yield. This is also a very long synthesis (∿45 steps) with an overall yield of ∿3 x 10^{-3}%.

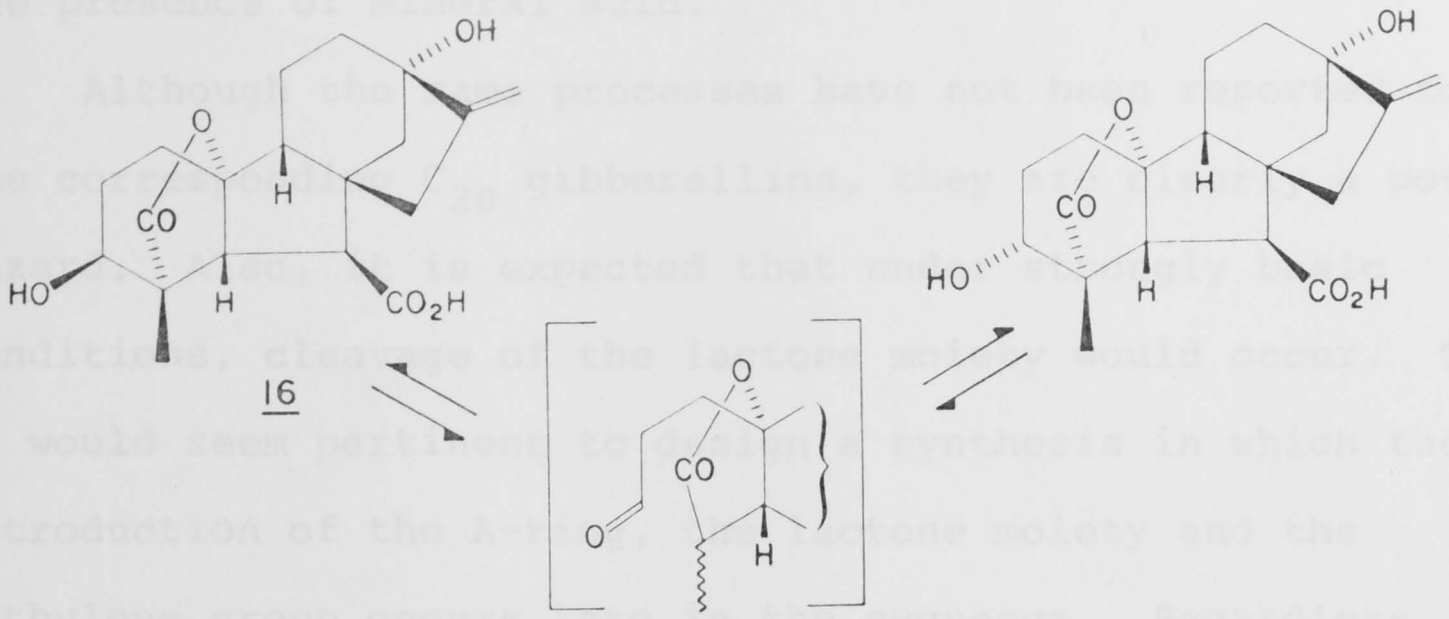
The very large number of steps (∿45 steps) and the low yields in most of these syntheses stand in stark contrast to the very much more efficient strategies and processes involved in the syntheses of the far more complex and labile C_{19} gibberellin, gibberellic acid 5.[16,17] In most cases the earlier deficiencies arise out of the use of relay intermediates, or from the fact that the earlier part of the synthesis was designed primarily for the preparation of an entirely different objective. Consequently, there still remains considerable scope for the development and execution of more efficient strategies and procedures for the synthesis of C_{20} gibberellins.

Before designing such syntheses, the following points should be taken into consideration:

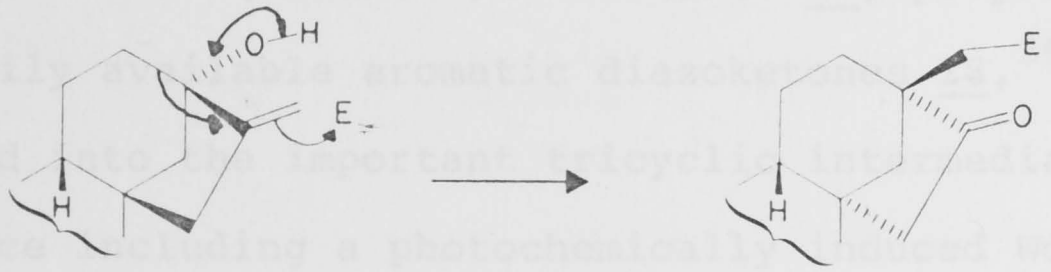
(a) the need for sufficient flexibility to allow the preparation of a variety of C_{20} gibberellins,

(b) the presence of between seven and nine asymmetric centres requires strict stereochemical control throughout the sequence,

(c) the lability of certain regions of gibberellins. For example, the C_{19} gibberellin A_1 16 undergoes epimerisation at C(3) under mildly alkaline conditions.[30,31] The mechanism proceeds by a retro-aldol cleavage of the C(3)-C(4) bond to give the more stable equatorial α-alcohol (Scheme 6). The C/D system of the 13-hydroxy-C_{19} gibberellins rearranges when treated with electrophilic reagents (mineral acids[31,32] or



SCHEME 6



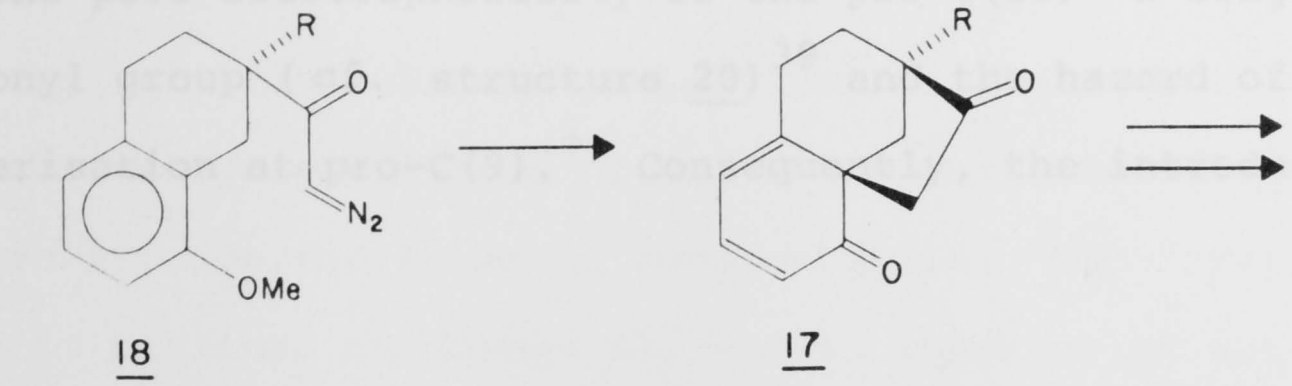
SCHEME 7

Br^{+} [33]) so that the D-ring is inverted (Scheme 7). Gibberellins without a 13-hydroxy group, on the other hand, readily undergo hydration of the exocyclic olefinic bond in the presence of mineral acid.[34]

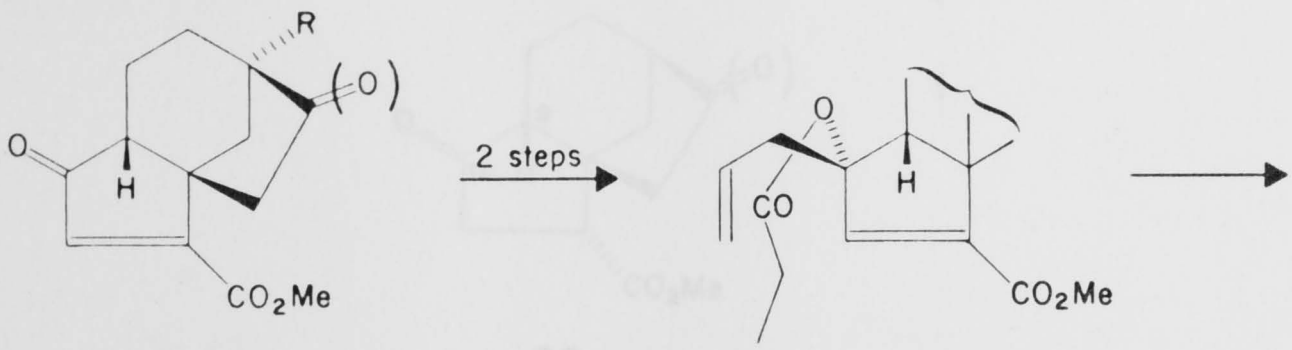
Although the same processes have not been reported for the corresponding C_{20} gibberellins, they are clearly a potential hazard. Also, it is expected that under strongly basic conditions, cleavage of the lactone moiety would occur. Thus, it would seem pertinent to design a synthesis in which the introduction of the A-ring, the lactone moiety and the methylene group occurs late in the sequence. Regardless of these factors, however, the foundation of any successful synthesis must be a short and efficient construction of the main parts of the skeleton.

The recent synthesis of gibberellic acid and related C_{19} gibberellins by groups led by Corey[16] and Mander[17,35] have made very important advances in this area. Of these, the most efficient and versatile strategy for the construction of the gibberellin framework was that pioneered by Lombardo and Mander[17a,35] (Scheme 8). Dienones 17, prepared from the readily available aromatic diazoketones 18,[36-38] were converted into the important tricyclic intermediates 19 by a sequence including a photochemically induced Wolff rearrangement. The stereoselective attachment of the A-ring to 19 through ~~repeated~~ sequential intramolecular carbon-carbon bond formation led to the shortest known synthesis of gibberellins.

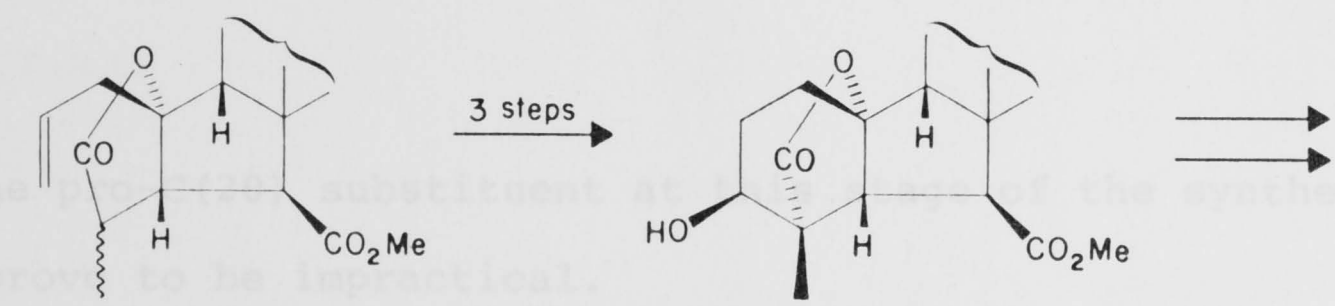
While it seemed that this strategy could be directly adapted to C_{20} gibberellin synthesis, potential limitations

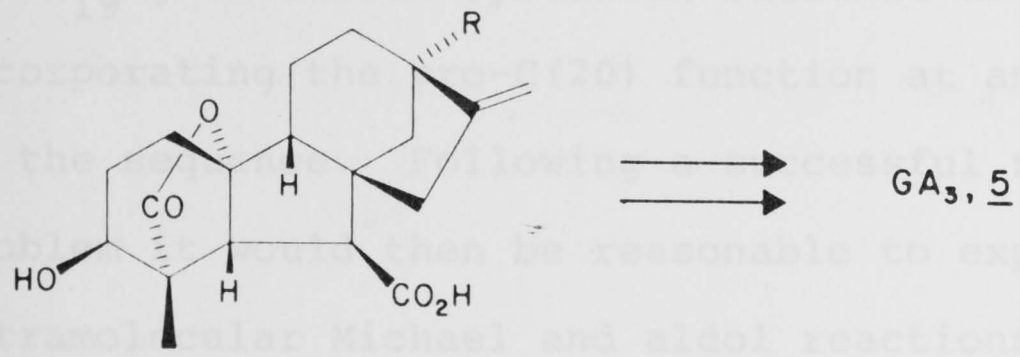


18 17



19



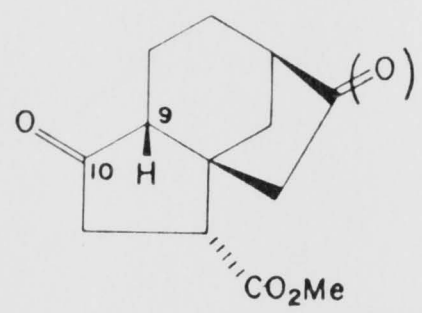


GA4, R=H
GA1, R=OH

GA3, 5

SCHEME 8

are the poor electrophilicity of the pro-C(10)† B-ring carbonyl group (cf. structure 20)[39] and the hazard of epimerisation at pro-C(9).† Consequently, the introduction



20

of the pro-C(20) substituent at this stage of the synthesis may prove to be impractical.

It seemed necessary, therefore, to modify the strategy for C_{19} gibberellin synthesis outlined in Scheme 8 by incorporating the pro-C(20) function at an earlier stage in the sequence. Following a successful resolution of this problem it would then be reasonable to expect that the key intramolecular Michael and aldol reactions in Scheme 8 could be simply adapted to C_{20} gibberellin synthesis as adumbrated in Scheme 9. Gibberellins A_{37} and A_{38} were chosen as targets since it appeared to be possible to transform these compounds into most of the remaining C_{20} derivatives

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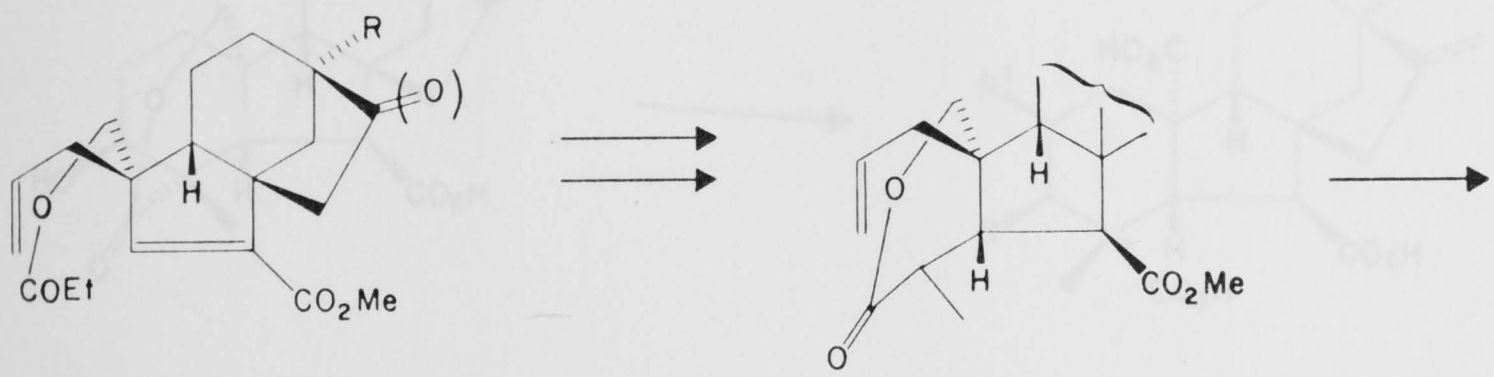
† Gibberellin numbering.

(Scheme 10).[15,40,†]

Two variations on the preparation of a suitable methanobenzocycloheptenone precursor to intermediate 21 (Scheme 9) appeared to merit consideration. The first of these is outlined in Scheme 11, and is based on an adaptation of methodology developed by Masamune[41] and Corey *et al.*[16a] to dienone 22.



SCHEME 9

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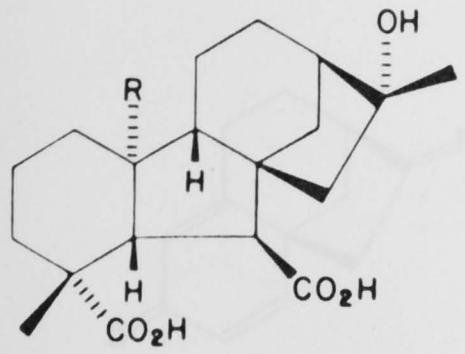
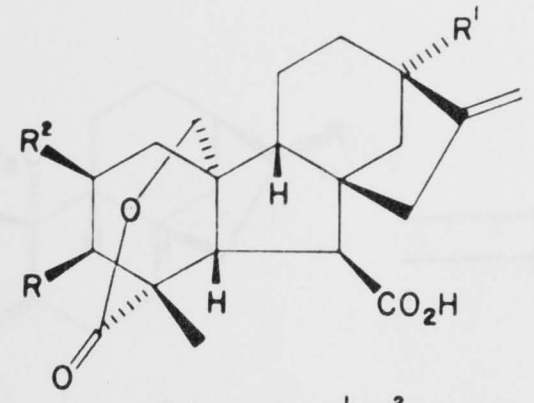
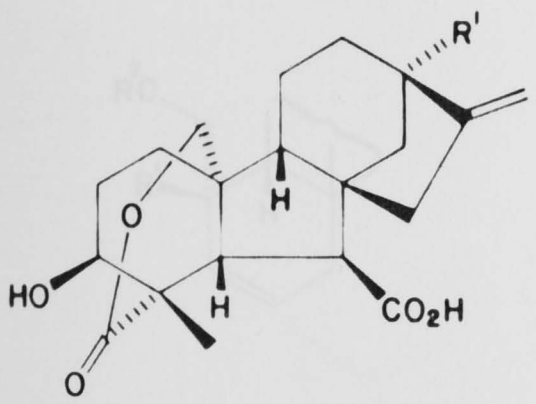
† Gibberellins A_1 and A_4 have been converted into other C_{19} gibberellins[40] and it is assumed that similar procedures could be successfully employed for the C_{20} series.



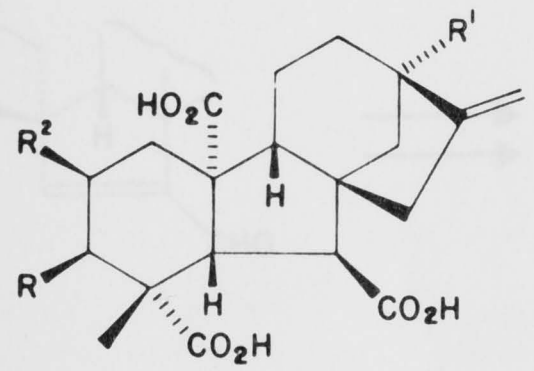
GA_{41}, R = CO_2H
GA_{42}, R = Me



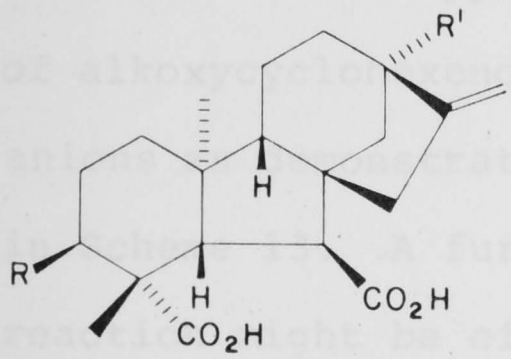
GA_{15}, R = R' = R^2 = H
GA_{27}, R = R^2 = OH, R' = H
GA_{44}, R = R^2 = H, R' = OH



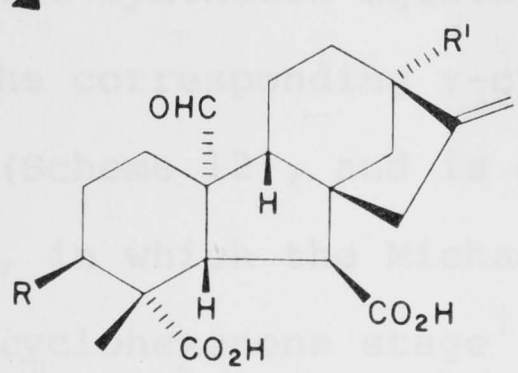
GA_{37}, R' = H
GA_{38}, R' = OH



GA_{13}, R = OH, R' = H = R^2
GA_{28}, R = R' = OH, R^2 = H
GA_{17}, R = R^2 = H, R' = OH
GA_{25}, R = R' = R^2 = H
GA_{43}, R = R^2 = OH, R' = H
GA_{46}, R = R' = H, R^2 = OH

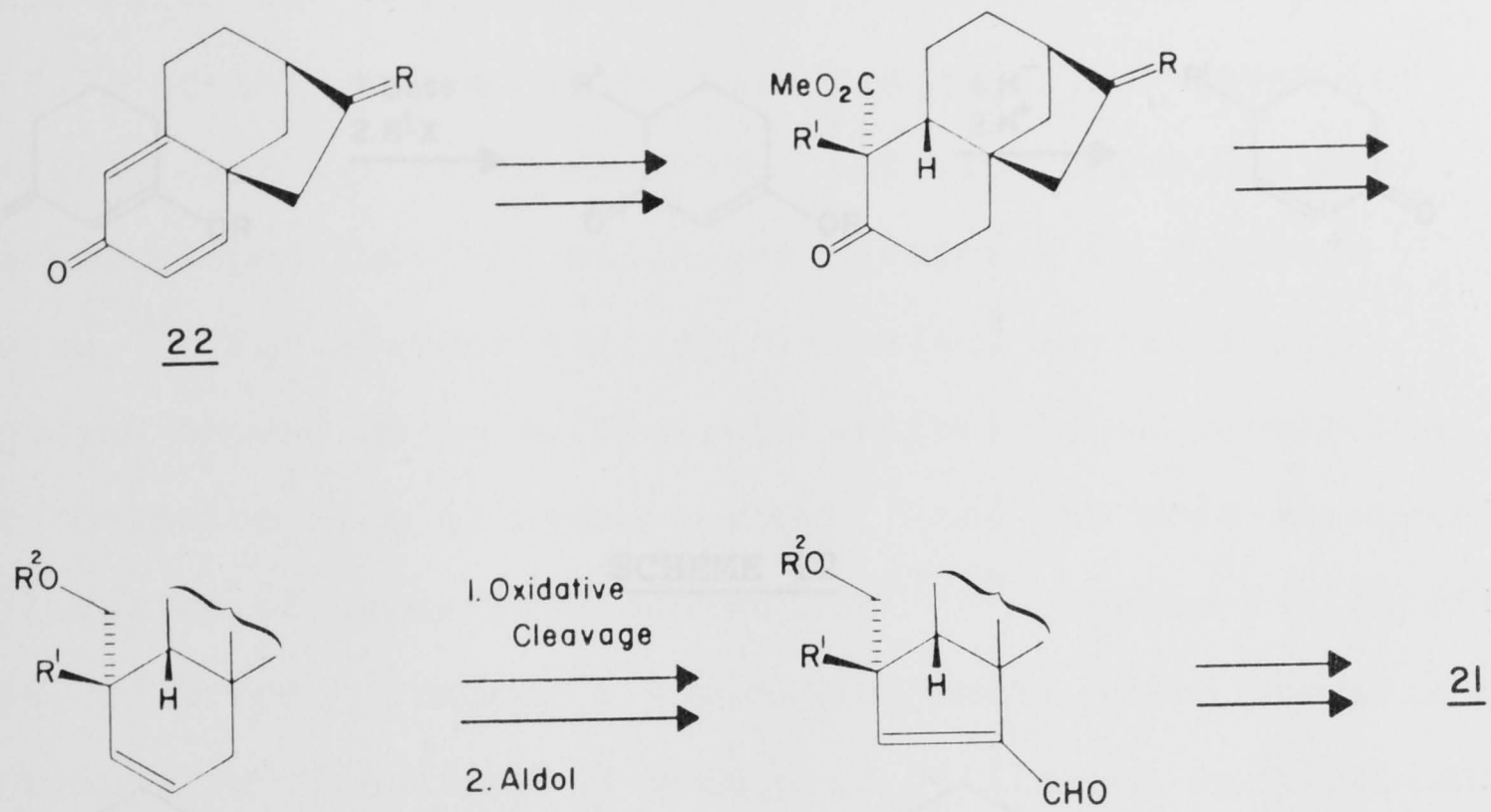


GA_{12}, R = R' = H
GA_{14}, R = OH, R' = H
GA_{53}, R = H, R' = OH
GA_{18}, R = R' = OH



GA_{24}, R = R' = H
GA_{36}, R = OH, R' = H
GA_{19}, R = H, R' = OH
GA_{23}, R = R' = OH

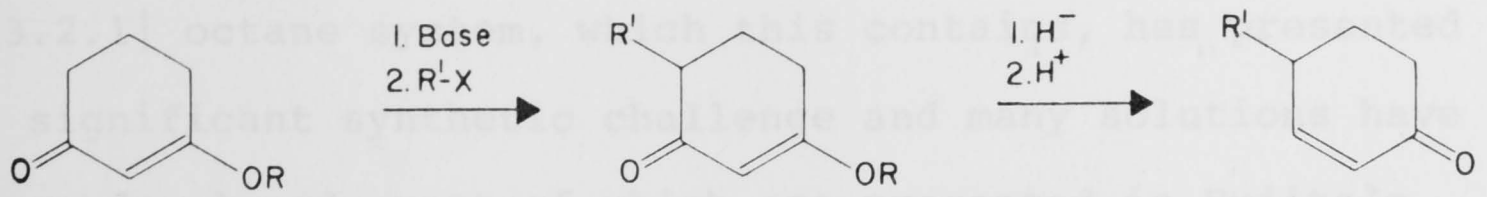
SCHEME 10



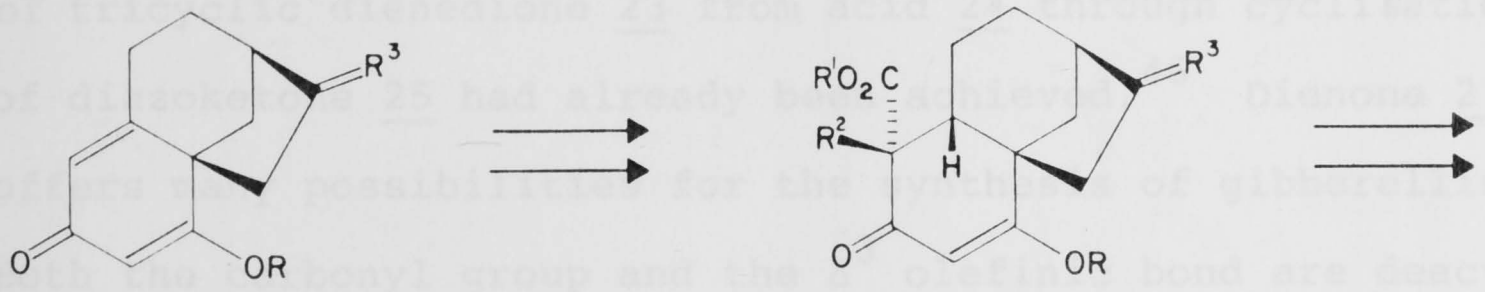
SCHEME 11

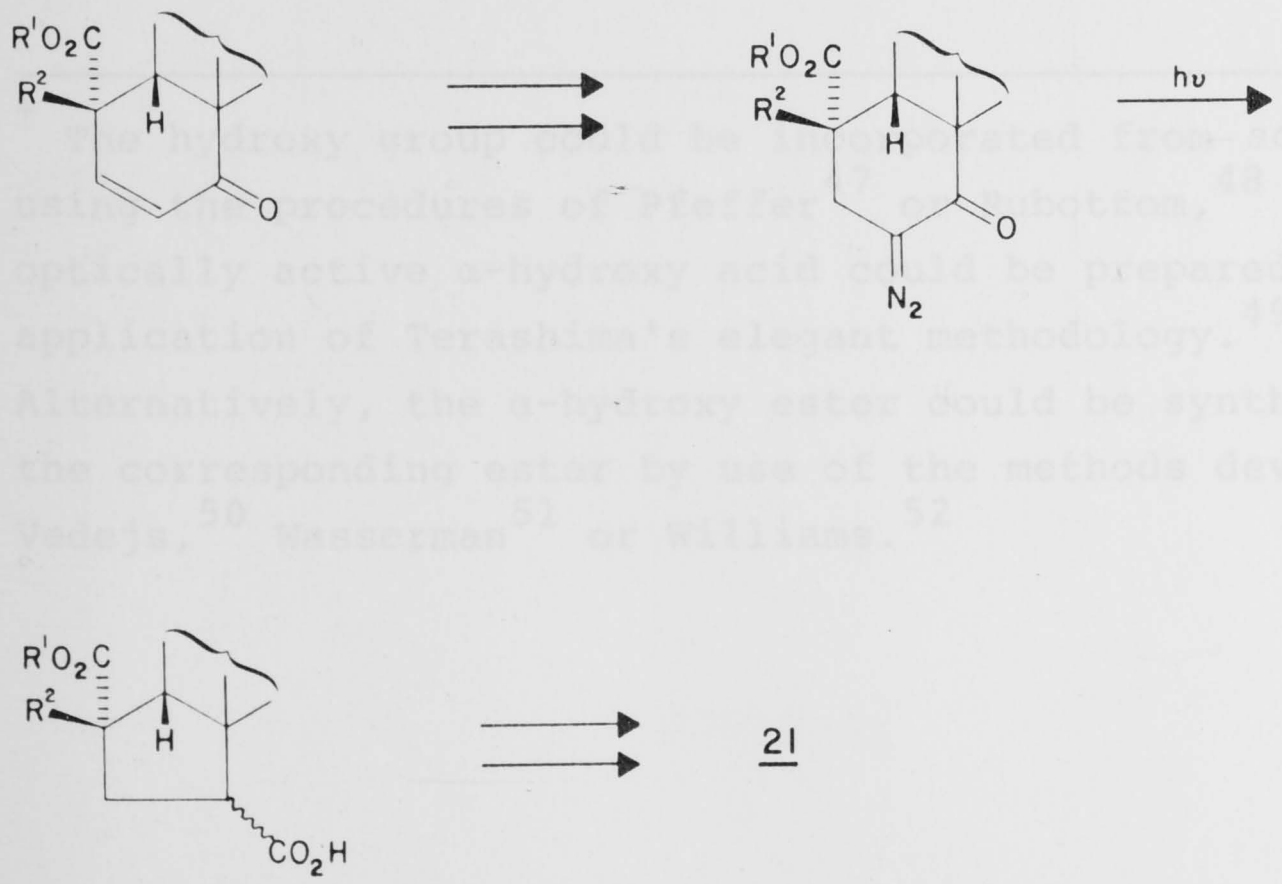
The second approach exploits the synthetic equivalence of alkoxycyclohexenone anions to the corresponding γ-cyclohexenone anions as demonstrated by Stork[42] (Scheme 12), and is outlined in Scheme 13. A further variation, in which the Michael reaction might be effected at the cyclohexenone stage[†] followed by the aldol reaction and then ring contraction (cf. the approach to gibberellin synthesis reported by Mander and Pyne[45]), also bears serious consideration (Scheme 14).

[†] In their approach to C_{19} gibberellin synthesis, Stork's group[43,44] have accomplished intramolecular Michael additions to cyclohexenones using carbanions of β-keto esters.



SCHEME 12





SCHEME 13

Prior to an attempt at any of these routes, an efficient construction of a tricyclic precursor (e.g. 26) for the gibberellin B,C,D-ring moiety is required. The bicyclo |3.2.1| octane system, which this contains, has presented a significant synthetic challenge and many solutions have been developed, most of which are presented in Fujita's review.[15] For reasons already discussed, any strategy employed should be of sufficient flexibility to permit the incorporation of a 13-hydroxy group,† and the acid-catalysed cyclisation of aromatic diazoketones[37,38] (Scheme 15) fulfils this criterion. Indeed, a successful small scale preparation of tricyclic dienedione 23 from acid 24 through cyclisation of diazoketone 25 had already been achieved.[46] Dienone 23 offers many possibilities for the synthesis of gibberellins. Both the carbonyl group and the Δ^3 olefinic bond are deactivated by the 4-methoxy substituent, which should therefore permit the selective reduction of the other olefinic bond to afford methoxyenone 26, envisaged as a key substrate for the execution of Schemes 13 and 14.

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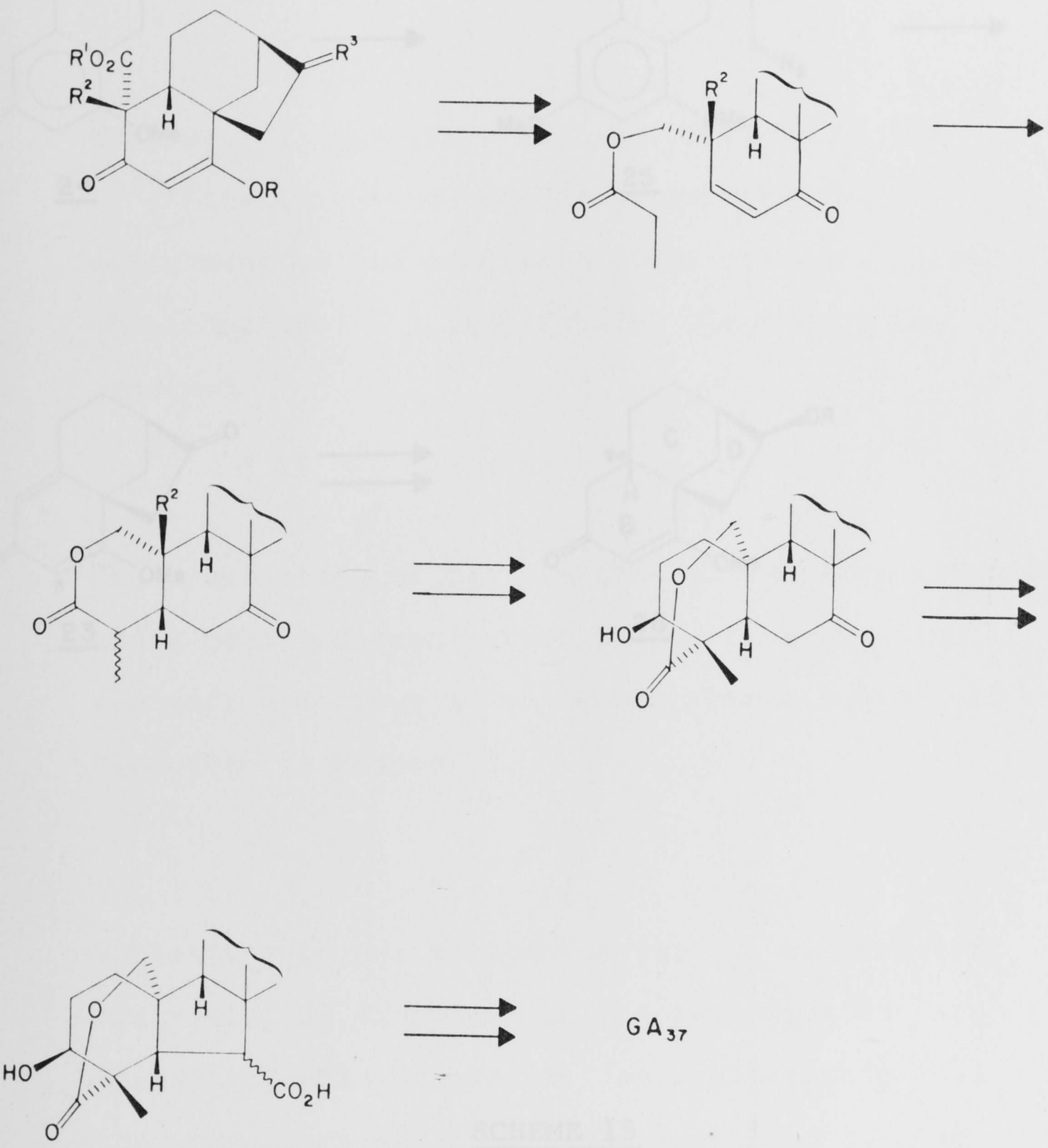
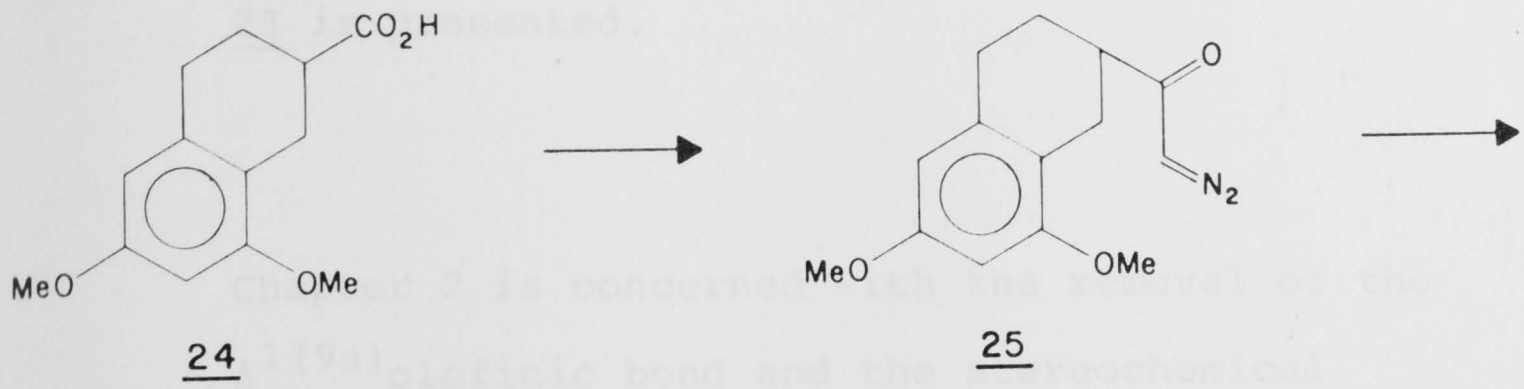
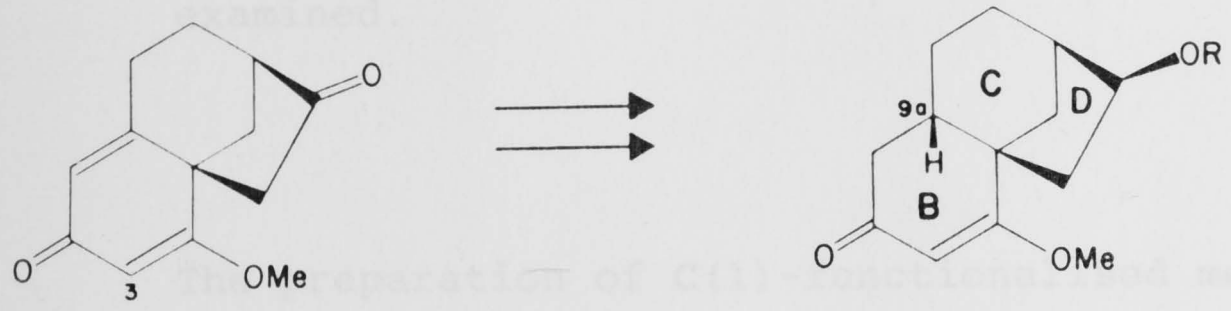
† The hydroxy group could be incorporated from acid 24 using the procedures of Pfeffer[47] or Rubottom,[48] or an optically active α-hydroxy acid could be prepared through application of Terashima's elegant methodology.[49] Alternatively, the α-hydroxy ester could be synthesised from the corresponding ester by use of the methods developed by Vedejs,[50] Wasserman[51] or Williams.[52]



SCHEME 14



24 25



23 26

SCHEME 15

In Chapter 1, an improved synthesis of dienone 23 is presented.

Chapter 2 is concerned with the removal of the $\Delta^{1(9a)}$olefinic bond and the stereochemical assignment of the resulting C9(a)-epimers. Also, the reduction of a less complex dienone 39 is examined.

The preparation of C(1)-functionalised methoxyenones and a detailed examination of the transposition of the carbonyl group in the methoxyenone system are described in Chapter 3.

Variations on our strategies for C_{20} gibberellin synthesis, as discussed in the introduction, are investigated in Chapter 4. An evaluation of all the approaches which we have undertaken is also made in this chapter.

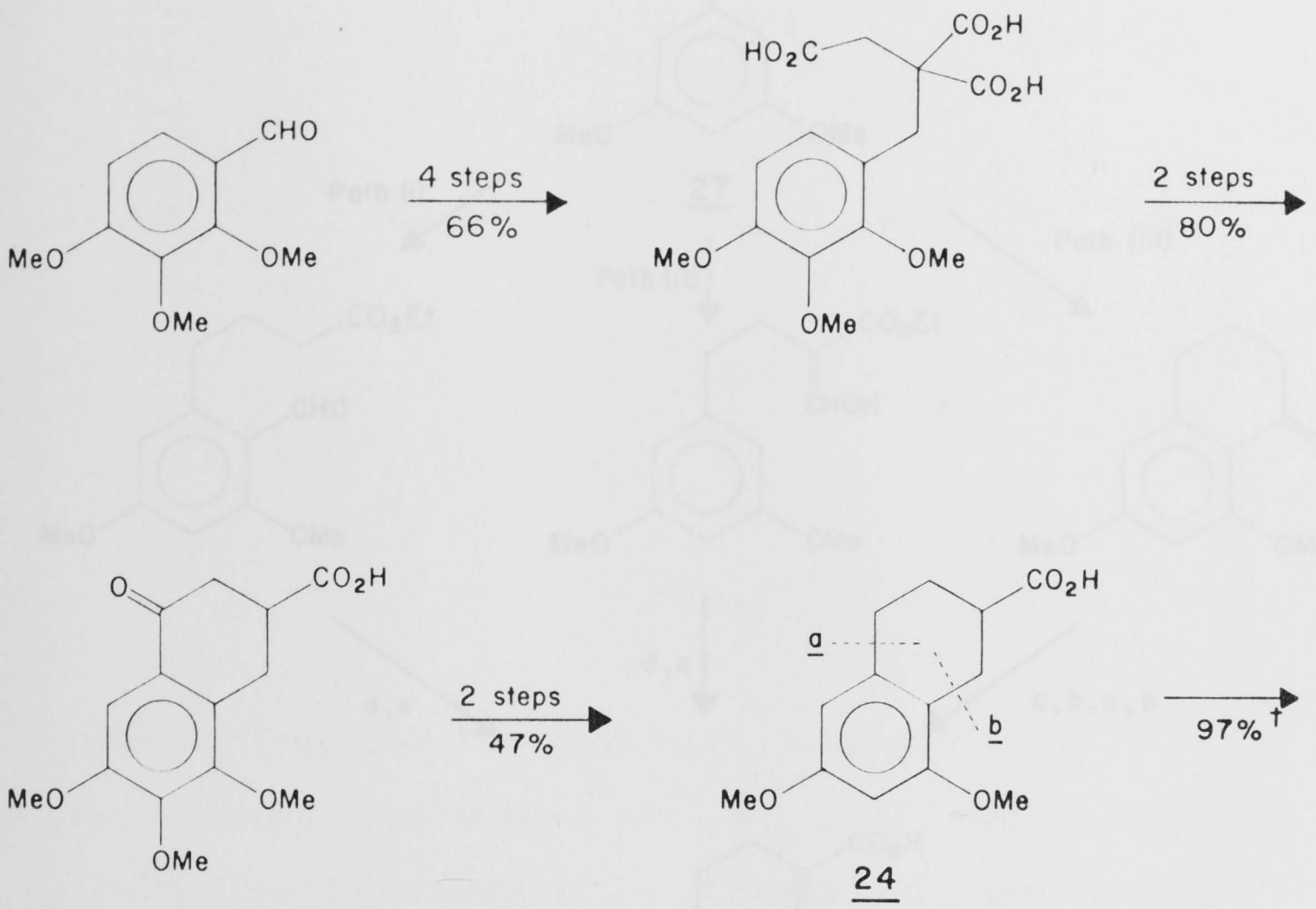
C H A P T E R 1

THE SYNTHESIS OF TRICYCLIC DIENONE 23

An efficient preparation of tricyclic dienone 23 was an important prerequisite for the proposed synthesis of C_{20} gibberellins (Schemes 13 and 14). This compound had been obtained in good crude yield, albeit on a small scale (∿40mg), from 6,8-dimethoxy-2-naphthalene carboxylic acid 24 by an acid-catalysed cyclisation of diazoketone 25 (Scheme 16).[46] However, the route to acid 24 was lengthy. Some transformations had proceeded in only moderate yield and, furthermore, the starting aldehyde was expensive. Clearly a more economical preparation of acid 24 was required for making synthetically useful quantities of tricyclic dienone 23.

In principle, the alicyclic ring in acid 24 may be completed by formation of either bond a or bond b. The earlier synthesis was based on the former pathway, but the cyclisation could be achieved only with the assistance of a para-methoxy substituent, which was then removed by Birch reduction (Scheme 16). The alternative strategy, based on the formation of bond b, appears to have potential for a more direct and efficient synthesis. The initial requirement is a good preparation of a 4-(3,5-dimethoxyphenyl)butanoate ester, e.g. 27, from which it seemed that three possible pathways could be followed to acid 24 (Scheme 17). Acid 28, corresponding to ester 27, had been prepared previously from the acyl chloride 29 by Hardegger[53] and Davies,[54] but in overall yields of only 28%[53] and 20%[54] (Scheme 18). Also, both procedures lack the refinement and brevity required in the early stages of a gibberellin synthesis.

The simple but elegant synthesis of olivetol dimethyl ether 30 by Birch and Slobbe[55] offered the potential for a much more efficient route to ester 27. The olivetol



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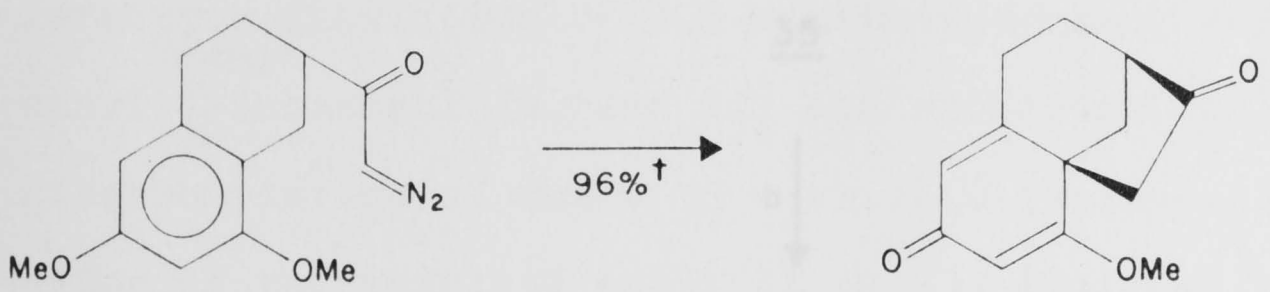

25 23

Overall Yield of Acid 24 = 25%

Overall Crude Yield of Dienone 23 = 23%

SCHEME 16

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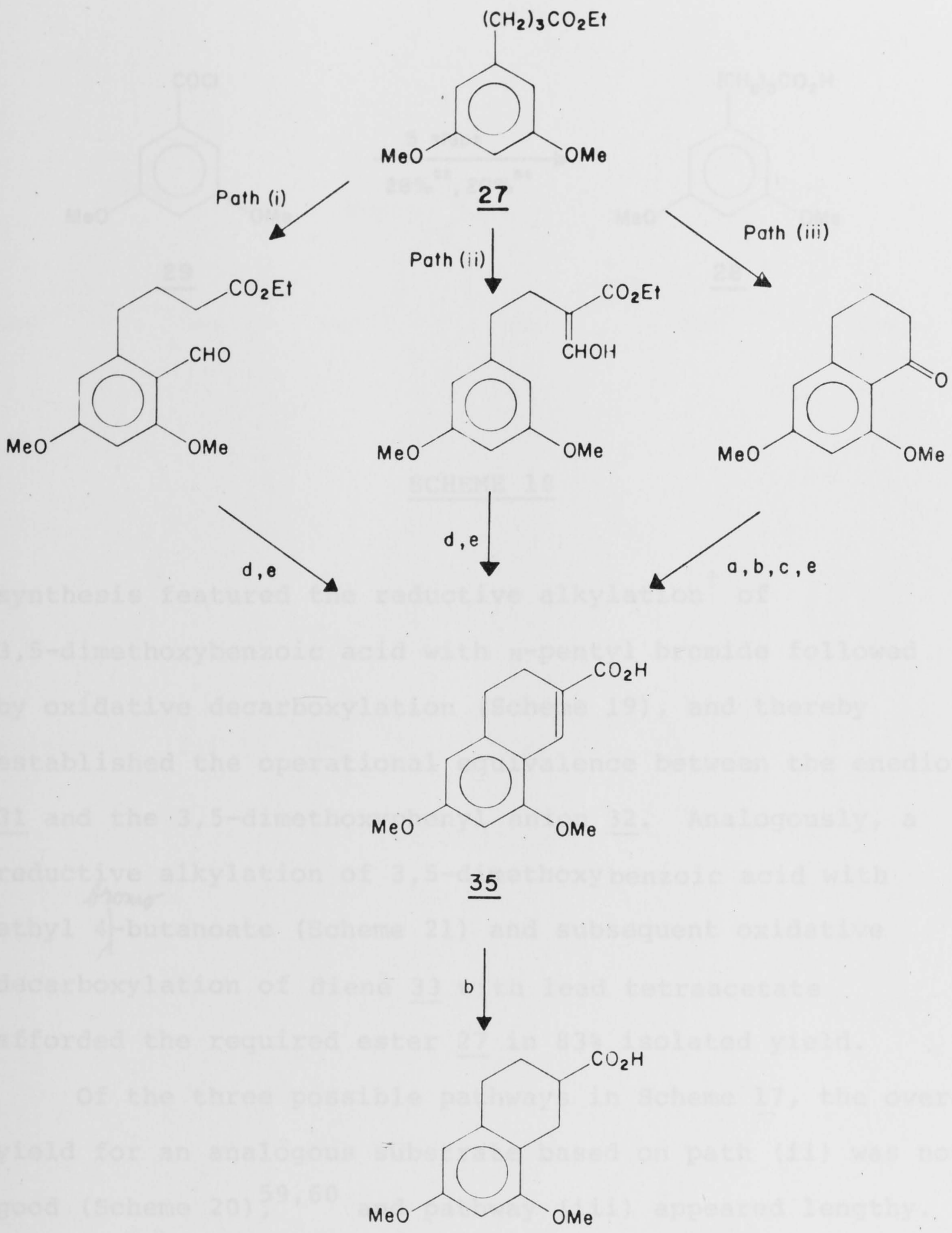
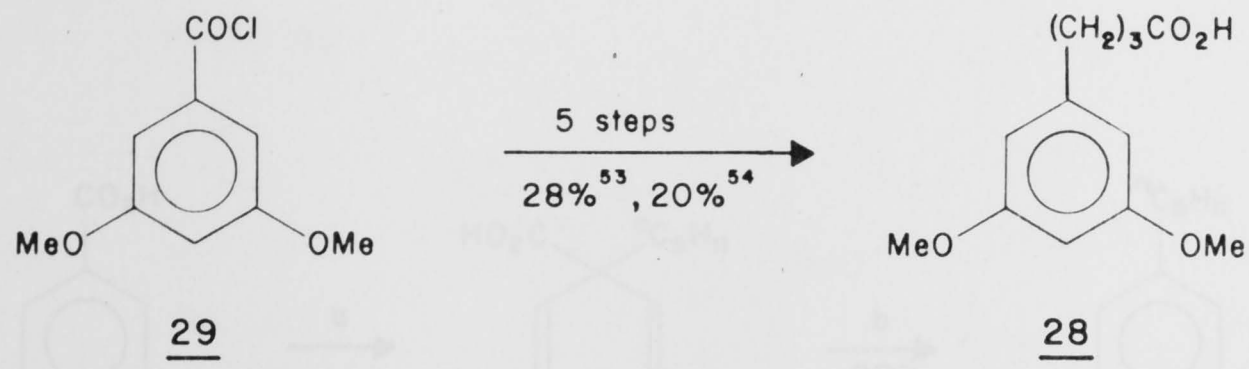
† Crude yield



(a) Acylation; (b) reduction; (c) dehydration; (d) cyclisation; (e) hydrolysis.

SCHEME 17



29 28

SCHEME 18

synthesis featured the reductive alkylation† of 3,5-dimethoxybenzoic acid with *n*-pentyl bromide followed by oxidative decarboxylation (Scheme 19), and thereby established the operational equivalence between the enediolate 31 and the 3,5-dimethoxyphenyl anion 32. Analogously, a reductive alkylation of 3,5-dimethoxybenzoic acid with ethyl 4-bromobutanoate (Scheme 21) and subsequent oxidative decarboxylation of diene 33 with lead tetraacetate afforded the required ester 27 in 83% isolated yield.

Of the three possible pathways in Scheme 17, the overall yield for an analogous substrate based on path (ii) was not good (Scheme 20),[59,60] and pathway (iii) appeared lengthy. Therefore, even though path (i) had not been previously attempted, it was decided to investigate this route, as it seemed to be the most direct.

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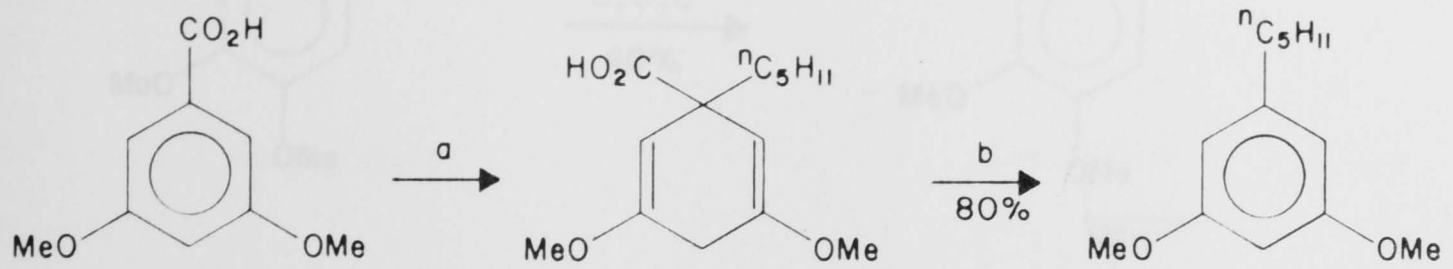
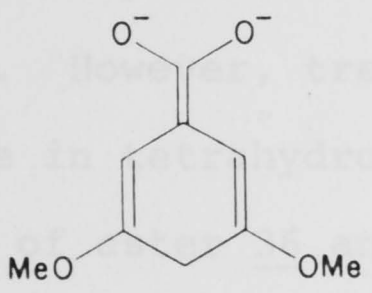
† Since the original reductive alkylation by Birch[56] in 1950, it is surprising to see how few reactions of this type have been produced. Detailed accounts of this process have been recently published.[19,57,58]



30

Reagents: (a) Li, NH_3, $^{n}C_5H_{11}Br$; (b) LTA.

SCHEME 19



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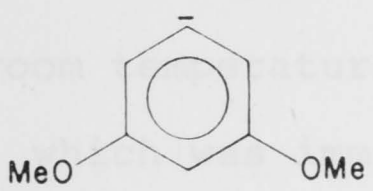

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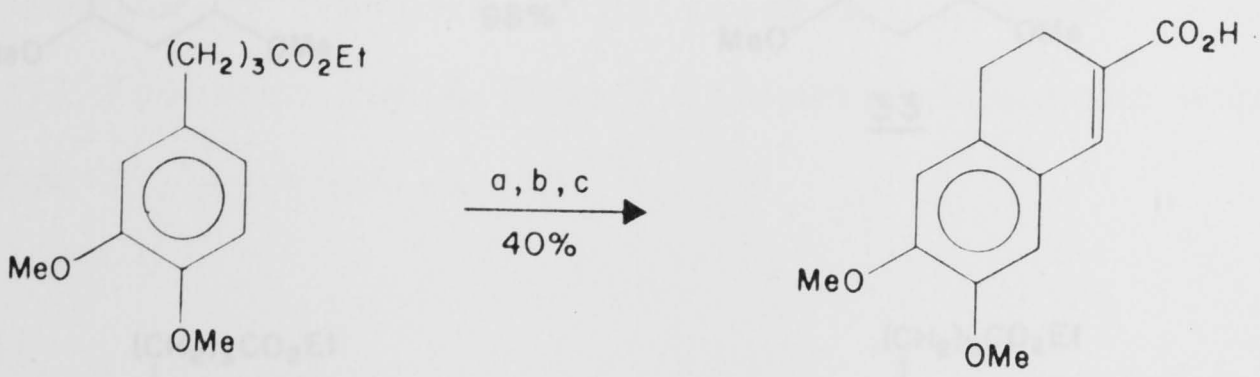
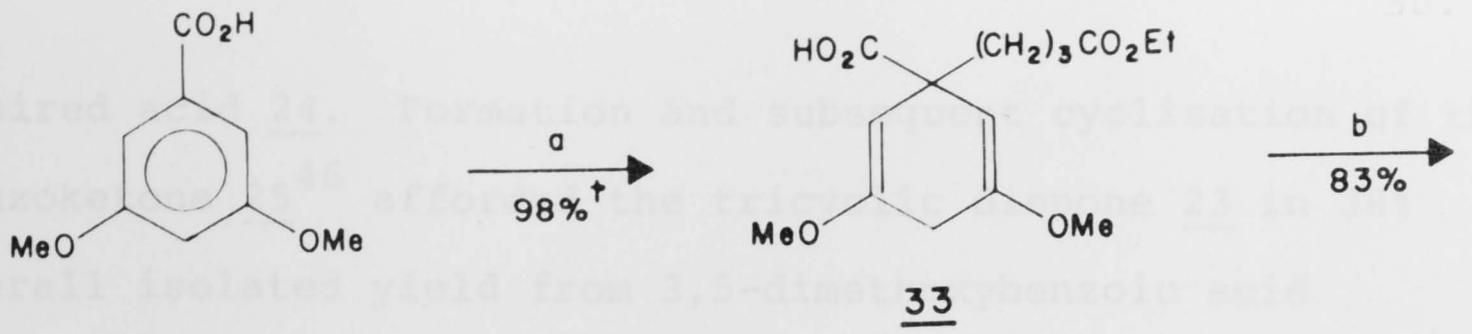


Reagents: (a) $Na^{+}\bar{O}Et$, HCO_2Et; (b) PPA; (c) $\bar{O}H$.

SCHEME 20[59]

Vilsmeier formylation (phosphorus oxychloride, dimethylformamide)[61] of ester 27 was completely regioselective (^1H and ^{13}C n.m.r. analysis) and proceeded smoothly at room temperature to give the desired aldehyde 34. Attempted cyclisation with sodium hydride or potassium *tert*-butoxide in tetrahydrofuran or dimethoxyethane at reflux gave complex mixtures of products with a very low yield of the required acid 35. However, treatment of the aldehyde with sodium ethoxide in tetrahydrofuran at room temperature produced a mixture of ester 36 and acid 35, which was immediately hydrolysed to give 35.

Johnson and Mander[37] had observed that the removal of the olefinic bond in an analogous substrate by catalytic methods was inhibited by the *peri*-methoxy group, but that a successful reduction could be accomplished with sodium in liquid ammonia. Reduction of the unsaturated acid 35 using a modification of the reported conditions[37] afforded the



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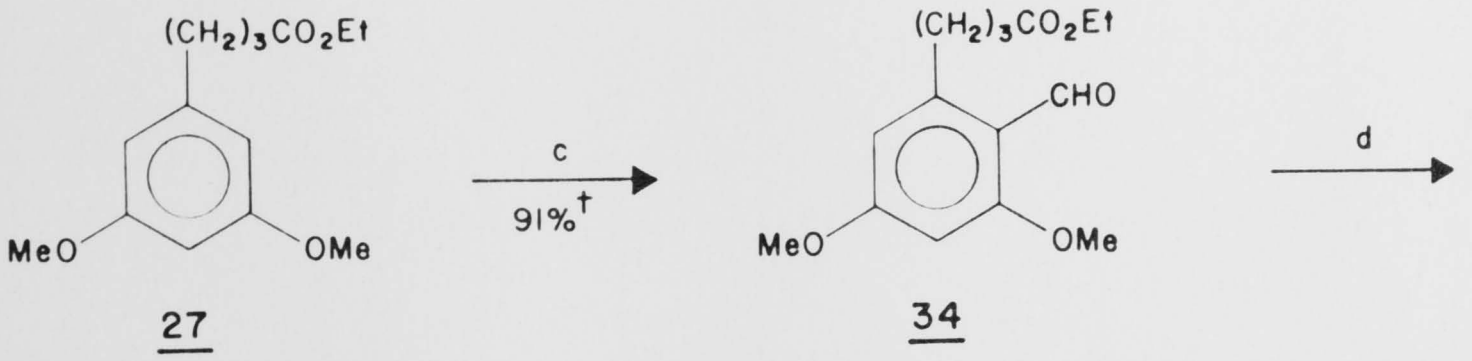
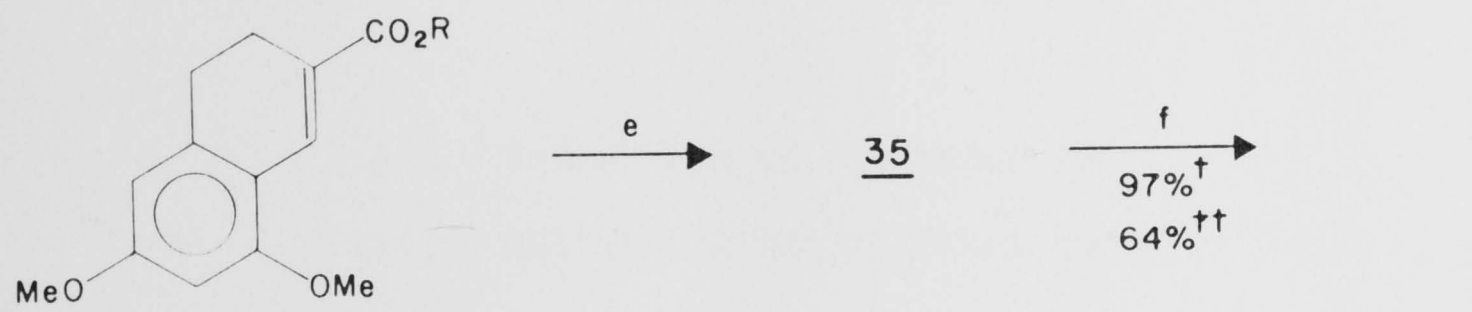
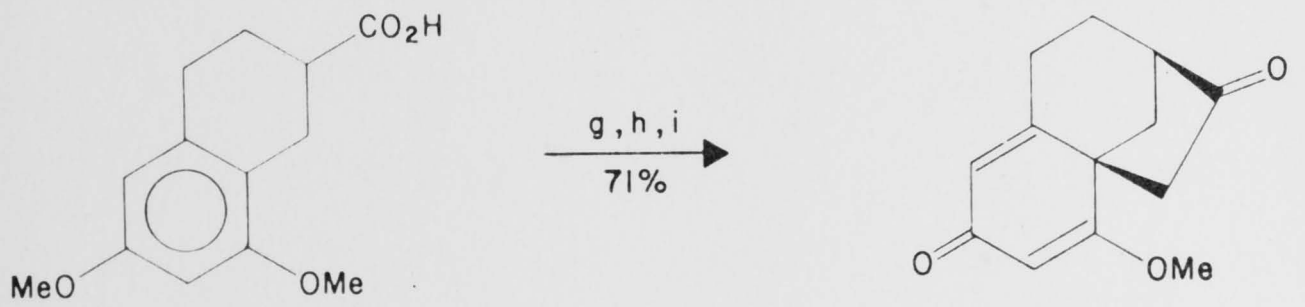


27 34



35, R = H
36, R = Et
37, R = Me



24 23

Reagents: (a) Li,NH_3; $Br(CH_2)_3CO_2Et$; (b) LTA; (c) $POCl_3$, DMF
(d) NaOEt; (e) NaOH; (f) Na, NH_3, ^tBuOH;
(g) $(COCl)_2$; (h) CH_2N_2; (i) TFA.

Overall Yield of Acid 24 = 53% } cf. Scheme 16
Overall Yield of Dienone 23 = 38% }

SCHEME 21

---

† Crude yield

†† Isolated yield of acid 24 from ester 27

desired acid 24. Formation and subsequent cyclisation of the diazoketone 25[46] afforded the tricyclic dienone 23 in 38% overall isolated yield from 3,5-dimethoxybenzoic acid (Scheme 21, cf. Scheme 16).†

---

† While almost quantitative crude yields had been obtained for these two transformations, purification was not straightforward due to the partial decomposition of the dienone upon recrystallisation, even though it had been reported to be thermally stable under both acidic and basic conditions.[46] Flash chromatography of the diazoketone, and then trituration of the dienone with ether was found to be the most successful procedure for purification. The tricyclic dienone was always kept in cold storage because it slowly decomposed at room temperature.

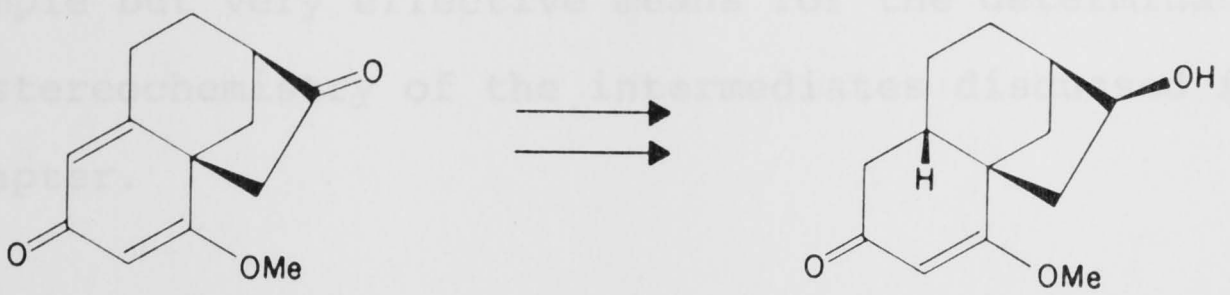
C H A P T E R 2

(i) REDUCTION OF DIENONE 23

(ii) REDUCTION OF DIENONE 39

(iii) CONFIRMATION OF STEREOCHEMISTRY AT THE B,C RING JUNCTION

For the synthesis of C_{20} gibberellins as proposed in Schemes 13 and 14, a reduction of dienone 23 was required, which was chemo-selective for the $\Delta^{1(9a)}$ olefinic bond and which was also stereoselective, leading to a *cis*-fused decalin system as found in methoxyenone 38. It was envisaged



23 38

that regio-control would be possible because the methoxyenone moiety can be regarded as a vinylogous ester and, as such, both the carbonyl group and the olefinic bond have diminished reactivity, thereby permitting the selective reduction of the $\Delta^{1(9a)}$ olefinic bond. It was hoped that polar substituents on the C(5)-C(6) bridge could be exploited to bias a stereoselective attack of reagents towards the β-face of the molecule.

Part (i) of this chapter describes three types of reduction methods:

(a) catalytic hydrogenation;

(b) dissolving metal reduction in liquid ammonia;

(c) hydride reduction;

and each of these will be discussed in turn.

In Section (ii) we briefly examine the possibility of a stereoselective reduction of the simpler dienone 39, using similar methods to those described above.

It was, of course, essential to determine the stereochemistry of each of these reductions, and therefore a rigorous proof of stereochemistry is described in Section (iii). Chemical transformation of the *cis*-fused isomer 38 led to 40, a compound whose stereochemistry had been previously established.[62] This enabled us to use ^{13}C n.m.r. spectroscopy as a simple but very effective means for the determination of the stereochemistry of the intermediates discussed in this chapter.

(i) REDUCTION OF DIENONE 23

(a) Catalytic Hydrogenation

While hydrogenation of the unsubstituted dienone 39 had been reported to afford a 7:3 mixture of *cis*- and *trans*-fused derivatives respectively,[62] hydrogenation of the methoxy substituted dienone 23, using palladium on calcium carbonate as a catalyst, produced a 4:6 mixture of diastereomers 42 and 43, with the *trans*-epimer as the major product (Scheme 22).† Reduction using palladium on carbon resulted in the removal of both olefinic bonds to give ketone 44, which was obtained as a minor product (∿15%) when palladium on calcium carbonate was used as a catalyst.

We considered that the presence of a more polar group in the five-membered ring might improve the stereoselectivity of the hydrogenation. Thus, treatment of 23 with sodium

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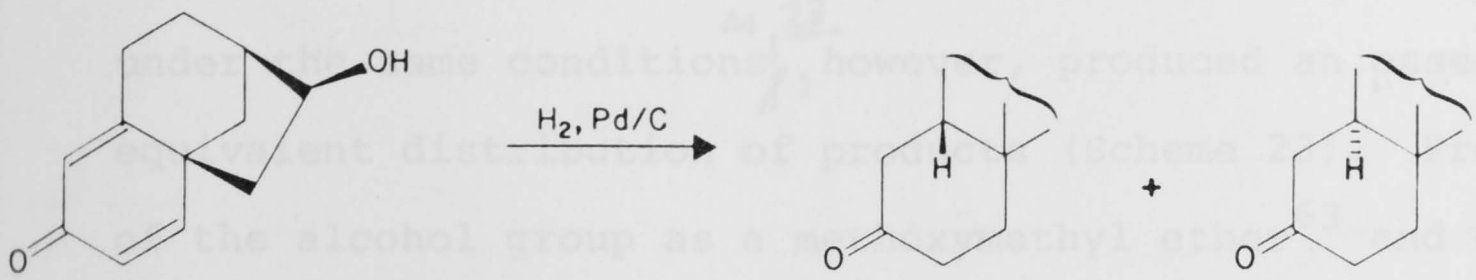
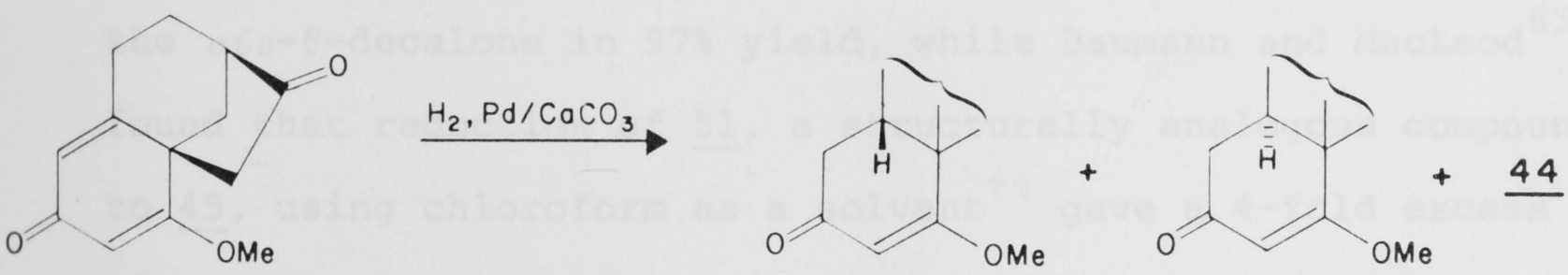
† Determined from ^{13}C n.m.r. spectroscopy and confirmed in Section (iii) of this chapter.



H_2, Pd/C

39 → 40 : 41

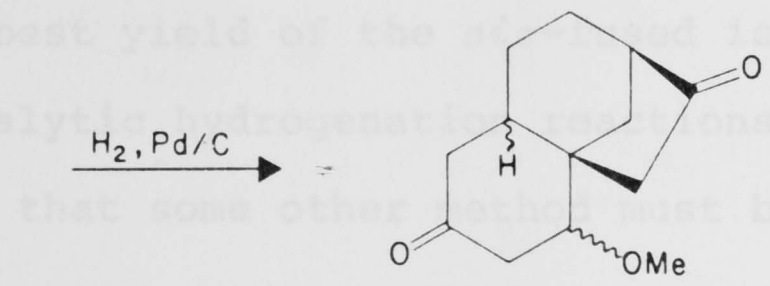
7 : 3



H_2, Pd/$CaCO_3$

23 → 42 + 43 + 44

4 : 6



H_2, Pd/C

23 → 44

SCHEME 22

borohydride afforded the *endo*-alcohol 45 as a discrete diastereomer, the stereochemistry of which was assigned on the expectation of reagent-approach control. Hydrogenation of 45 under the same conditions as 23, however, produced an essentially equivalent distribution of products (Scheme 23). Protection of the alcohol group as a methoxymethyl ether[63] and subsequent hydrogenation resulted in a 1:3 mixture† of *cis*- and *trans*-fused derivatives respectively, but no over-reduced product was obtained.

Hydrogenation of octal-1-en-2-one by Augustine *et al.*[64] with palladium on carbon in carbon tetrachloride produced the *cis*-β-decalone in 97% yield, while Baumann and MacLeod[65] found that reduction of 51, a structurally analogous compound to 45, using chloroform as a solvent†† gave a 4-fold excess of the required *cis*-fused derivative (Scheme 24). Hydrogenation of 45 under similar conditions, however, afforded the desired *cis*-fused intermediate 38 in only 50% isolated yield.†††

(b) Dissolving Metal Reduction

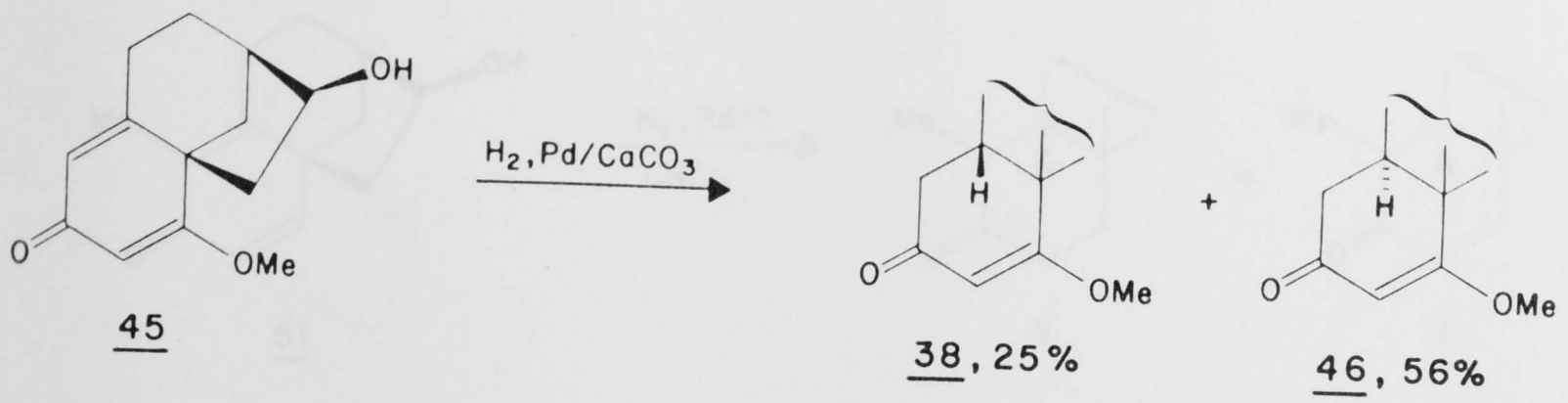
As the best yield of the *cis*-fused isomer 38 obtained from the catalytic hydrogenation reactions was only moderate, it was clear that some other method must be found for the

---

† Determined for ^{13}C n.m.r. spectroscopy and confirmed in Section (iii) of this chapter.

†† The substrate 51 was insoluble in carbon tetrachloride.

††† Under these conditions, deactivation of the catalyst had occurred prior to the completion of the reaction. It was necessary to isolate and treat the mixture further with more catalyst until no dienone remained. This problem, together with some over-reduction to give 47, accounted for the lower yield.

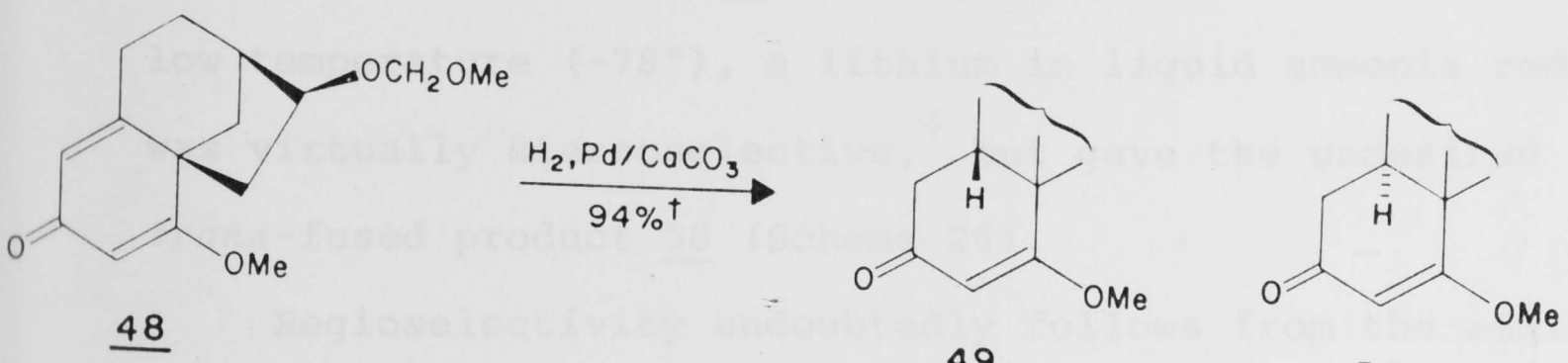


45

38, 25%

46, 56%

47, 11%



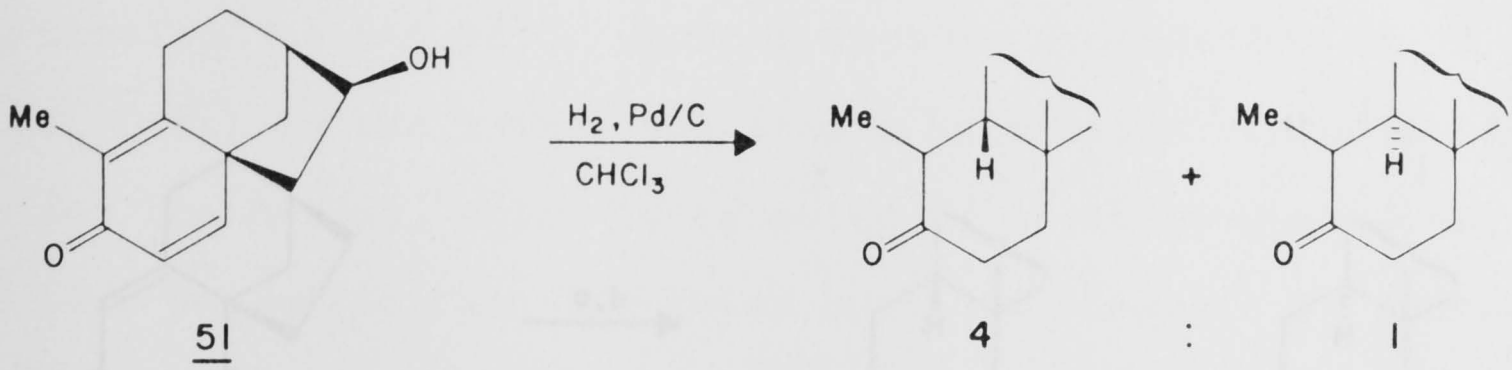
48

49 : 50

1 : 3

SCHEME 23

† Crude yield.



51 4 : 1

SCHEME 24

reduction of the olefinic bond. Although the prognosis for this type of reaction for our purposes was not good,[66-70] the reduction of a structurally analogous compound 52 by Marshall and Brady[71] to give predominantly the *cis*-fused derivative (Scheme 25) prompted us to attempt a similar reaction with dienone 48. Under anhydrous conditions, at low temperature (-78°), a lithium in liquid ammonia reduction was virtually stereoselective,† but gave the undesired *trans*-fused product 50 (Scheme 26).

Regioselectivity undoubtedly follows from the addition of electrons to the more electrophilic olefinic bond. The reported studies of Stork and Darling[67] showed that it was the energies of the stereoelectronically allowed transition states (those in which overlap is maintained between the ß-carbanion and the carbon-carbon olefinic bond of the

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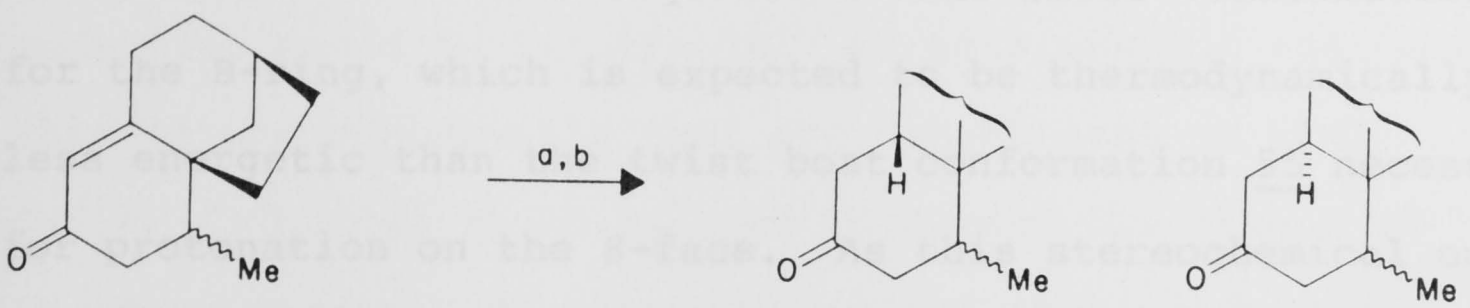
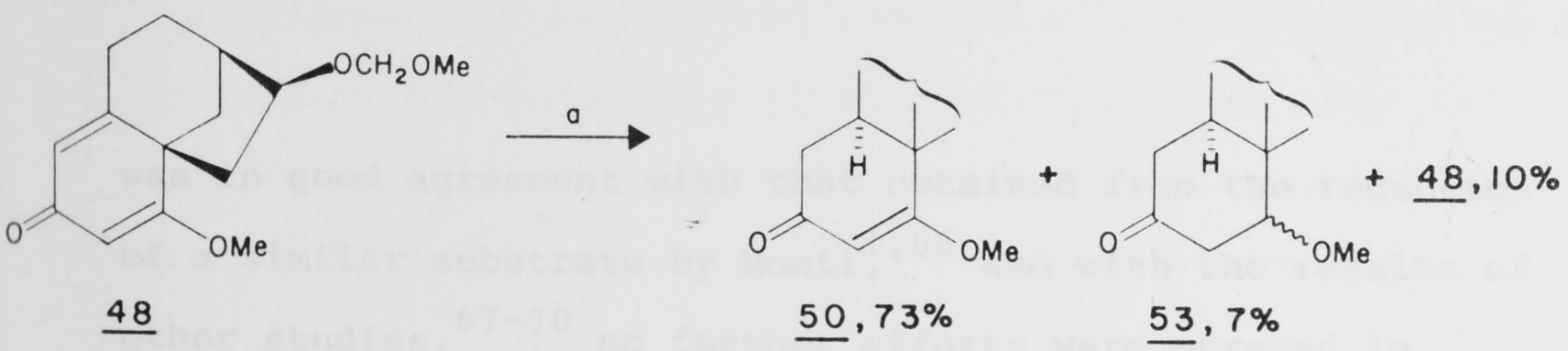
† Less than 10% of the *cis*-fused product was observed by ^{13}C n.m.r. spectroscopy.



52 10 : 1

Reagents: (a) Li, NH_3, EtOH; (b) Jones.

SCHEME 25

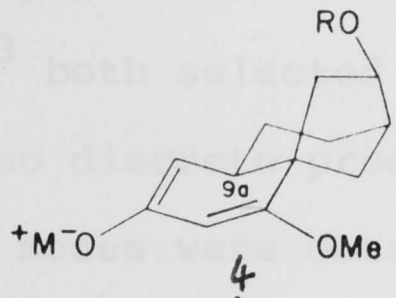


48 50, 73% 53, 7%

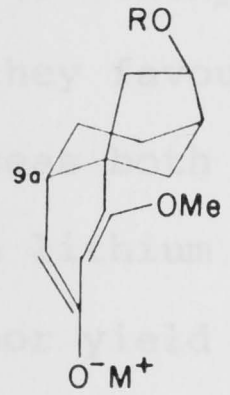
Reagents: (a) Li (2 eqs), NH_3, ^{t}BuOH (1 eq.).

SCHEME 26

enolate system) which determines the stereochemistry of the products. Therefore, the *trans*-fused derivative 50 was obtained as the major product because protonation of an anion at C(9a) on the α-face requires a half-chair conformation 54 for the B-ring, which is expected to be thermodynamically less energetic than the twist boat conformation 55 necessary for protonation on the β-face. As this stereochemical outcome



55



54

was in good agreement with that obtained from the reduction of a similar substrate by Monti,[†,66] and with the results of other studies,[67-70] no further efforts were pursued in this area.

[†] Approximately 5% of the *cis*-fused derivative was produced in this case.

(c) Hydride Reduction

Since the results from the previous attempts at removal of the olefinic bond were not satisfactory, it was hoped that the stereochemical outcome of an intermolecular hydride reduction would be favourable. If this was not the case, then it was conceivable that the substituent on the C(5)-C(6) bridge could be used to direct the attack of the incoming reagent, so that the desired stereochemistry would be obtained.

Treatment of dienone 48 with potassium tri-*sec*-butylborohydride[72] and sodium bis-(2-ethoxymethoxy)aluminium hydride,[73] both selected because they favour 1,4-reduction, produced no discrete product, whereas both 1,2- and 1,4-reduction modes were obtained with lithium triethylborohydride[74] to give the transposed enone in poor yield as the main product (Scheme 27).†

However, the dienone 23 was reduced with lithium aluminium hydride to afford a 2:1 mixture of the diastereomers 38 and 46 (the required *cis*-isomer predominating) as well as the by-product 56 (Scheme 28). This ratio of epimers could not be improved upon, despite the use of a variety of conditions. It appeared possible that this

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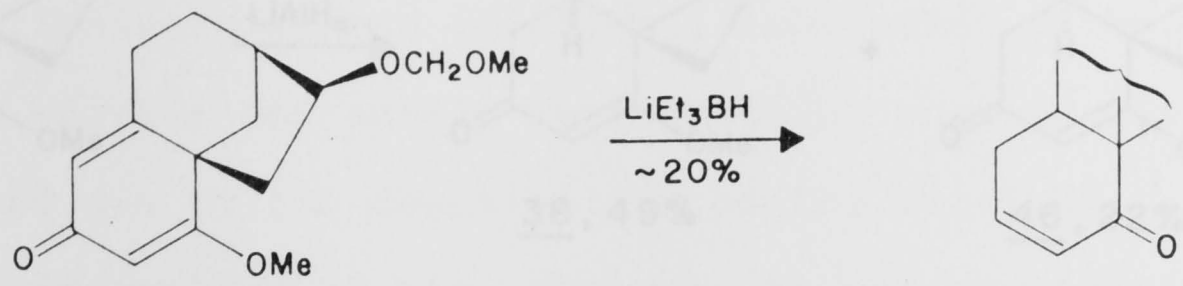
† This over-reduction again occurred for the reduction of 77 (Chapter 3). It appears likely from these results and also from the studies carried out by Brown,[74] that the carbonyl group is reduced first. It is expected that transposition occurred during the work-up. Insufficient material was obtained for the stereochemical outcome of this reaction to be determined.



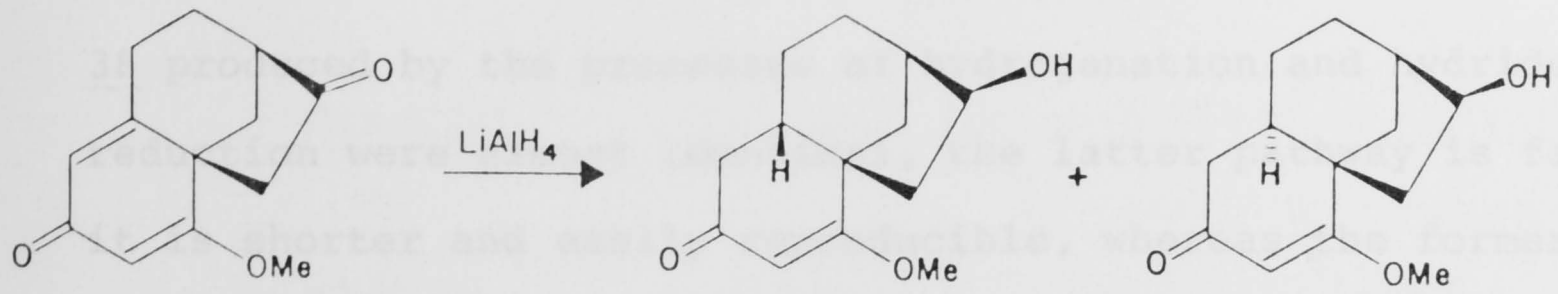
48

SCHEME 27

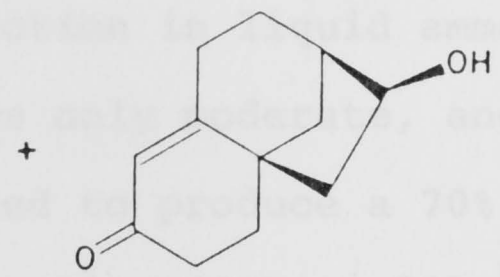
stereochemical result could be explained by an intramolecular process (Scheme 29), as the carbonyl group in the five-membered ring would be expected to undergo reduction first. To test this idea, the dienone alcohol 45 was reduced under the same conditions and an equivalent distribution of products was produced. In contrast, treatment of the protected alcohol derivative 48 afforded an approximate 5.5:4.5 mixture[†] of diastereomers 49 and 50[††] (Scheme 28).

[†] Determined from ^{13}C n.m.r. spectroscopy and confirmed in Section (iii) of this chapter.

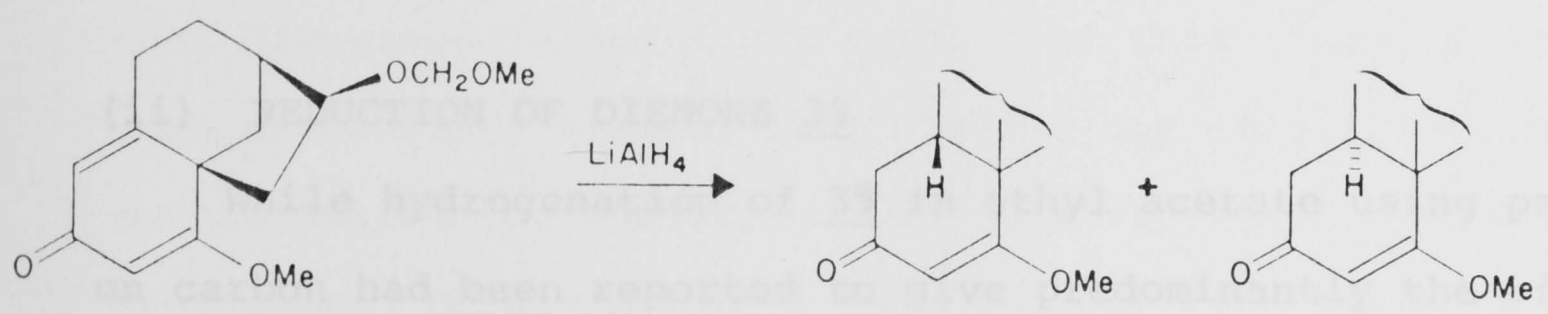
[††] Aluminium can co-ordinate with the oxygen atoms of the methoxymethyl ether group and thereby possibly effect an intramolecular reduction. The possibility that the *endo*-oxygen does not direct reduction, and that this reduced ratio may simply be due to increased steric shielding of the β-face by the *endo*-methoxymethyl ether group, thus resulting in an increased amount of intermolecular hydride attack on the α-face, cannot be discounted.



23 → 38, 49% + 46, 22%

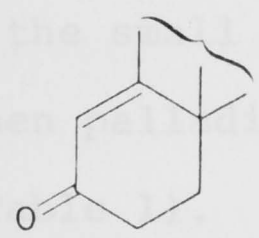


56, 18%



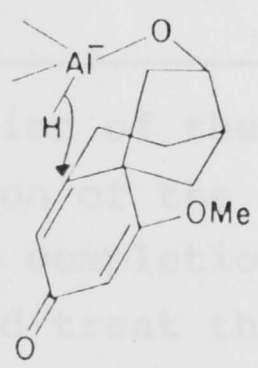
48 → 49 : 50

55 : 45



57

SCHEME 28



SCHEME 29

While the best yields of the required *cis*-fused isomer 38 produced by the processes of hydrogenation and hydride reduction were almost identical, the latter pathway is favoured; it is shorter and easily reproducible, whereas the former is awkward due to the deactivation of the catalyst. If the *trans*-fused derivative 50 was required, it may be efficiently produced by a dissolving metal reduction in liquid ammonia.

As the yield of 38 was only moderate, and the less complex dienone 39 had been reported to produce a 70% yield of the *cis*-epimer 40 upon hydrogenation (Scheme 22),[62] we decided to conduct some exploratory studies with substrate 39.

(ii) REDUCTION OF DIENONE 39

While hydrogenation of 39 in ethyl acetate using palladium on carbon had been reported to give predominantly the *cis*-epimer (Scheme 22),[62] our attempts under equivalent conditions afforded only a slight excess of the required *cis*-isomer 40 (Table 1). This is in contrast to the small excess of the *trans*-fused compound 41 produced when palladium on calcium carbonate was used as a catalyst (Table 1). Treatment with palladium on carbon in chloroform as previously discussed,[64,65] did produce a 4:1 mixture of *cis*- and *trans*-fused epimers respectively, which was in agreement with that previously reported (Scheme 24).[65] The isolated yield, however, was 63% for the required *cis*-compound 40 (Table 1).[†]

[†] As for the hydrogenation of the methoxy-substituted dienone 23, poisoning or deactivation of the catalyst occurred under these conditions prior to the completion of the reaction. It was necessary to isolate and treat the mixture further with more catalyst and, even then, some dienone was not reduced. It was hoped that further studies would overcome the experimental difficulties and produce an improved yield.

HYDROGENATION OF 39

Catalyst	Solvent	Isolated Yield of Epimers	
		40 (*cis*)	41 (*trans*)
Pd/C	EtOAc	52%	42%
$Pd/CaCO_3$	EtOAc	42%	54%
Pd/C	$CHCl_3$	63%	15%

TABLE 1

The intermediate 40 can be regarded as part of an alternative plan for gibberellin synthesis (Scheme 11) to that discussed in the first section of this chapter, and thus some exploratory studies were carried out to examine the possibilities for utilising this strategy for C_{20} gibberellin synthesis. Possible routes were evident from Masamune's work,[41] but no yields and very little experimental information was reported. While a regioselective acylation of an analogous substrate to 58 was implied in this work, our attempts did not result in complete regioselectivity. Enolate generation under kinetically controlled conditions followed by silylation afforded a 2:1 mixture of enol ethers 59 and 60 (Scheme 30).†

Attempts to generate the thermodynamic enolate 60 (potassium hydride, trimethylsilyl chloride[75]; triethylamine, dimethylformamide, trimethylsilyl chloride[76]) were unsuccessful.

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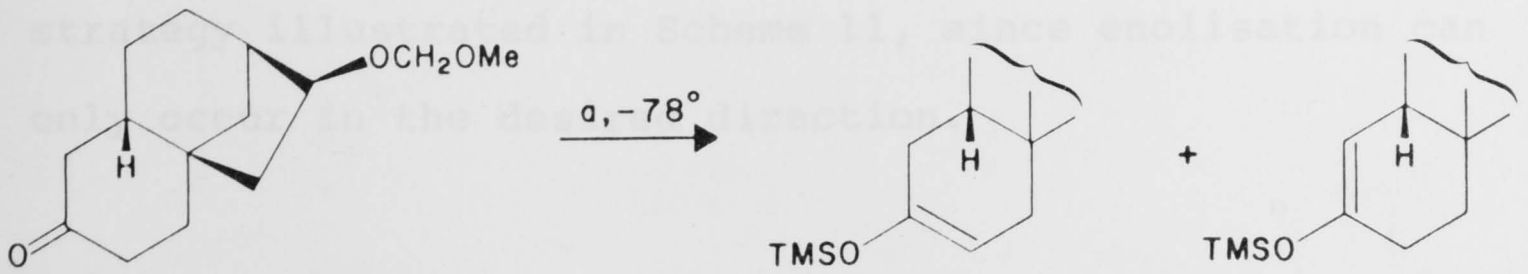
† This ratio was determined from ^{13}C n.m.r. spectroscopy.

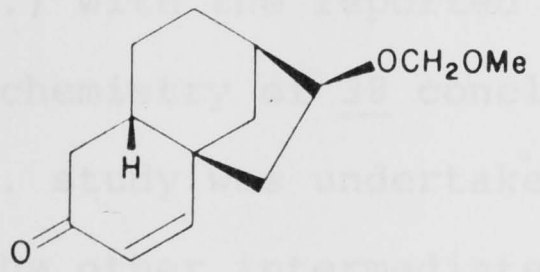


58 59 60

2 : 1

Reagents: (a) LDA, TMS-Cl.

SCHEME 30



61

While these results are not especially encouraging, possibilities for gibberellin synthesis still remain. It may be possible, by conducting the kinetic enolisation at a temperature below -78°, to obtain a higher percentage of 59. Selenenylation of the derived enolate and subsequent oxidation would give the α,β-unsaturated ketone 61.[77,78] This could

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† This ratio was determined from ^{13}C n.m.r. spectroscopy.

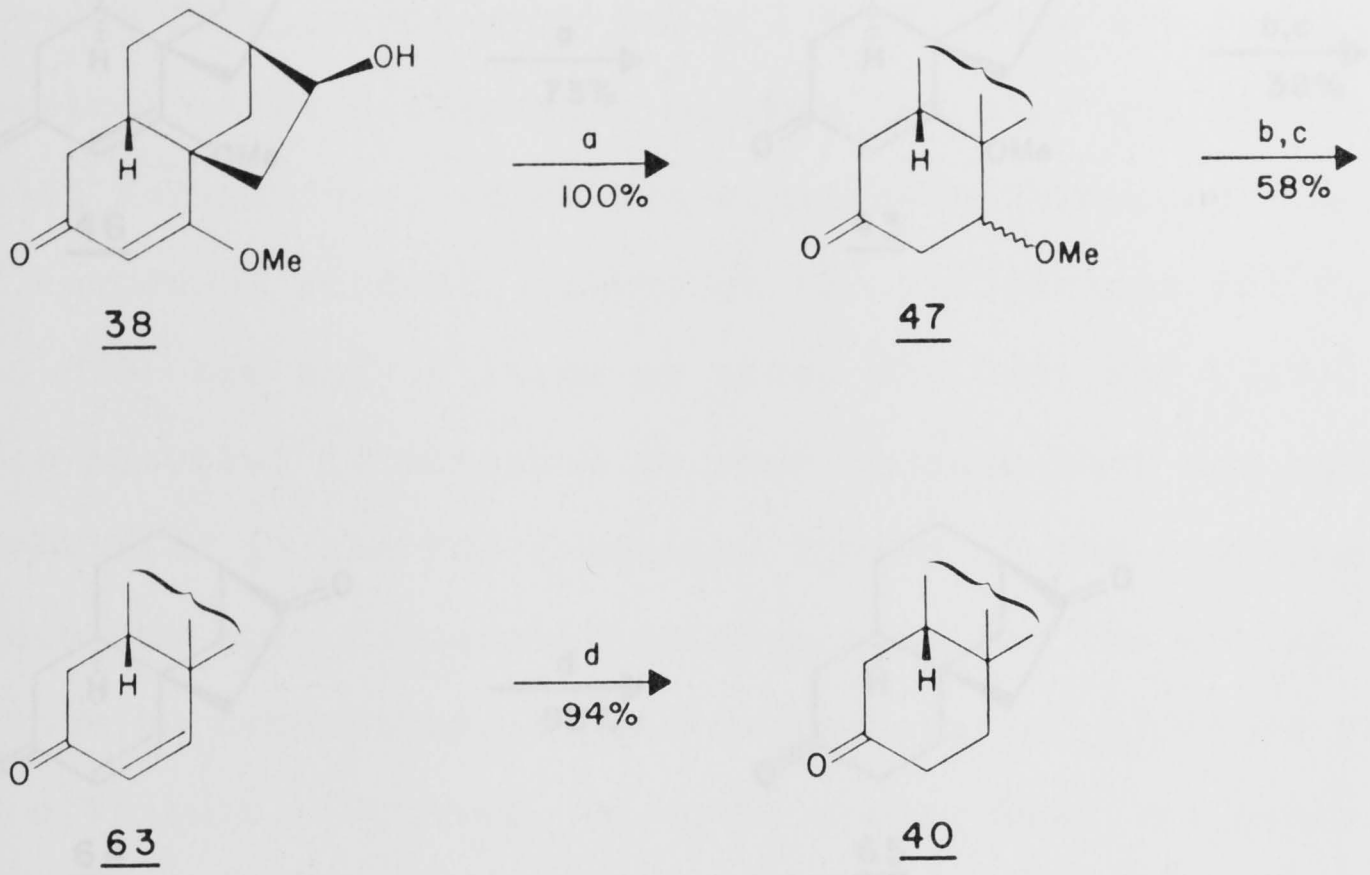
be an important intermediate for the development of the strategy illustrated in Scheme 11, since enolisation can only occur in the desired direction.

(iii) CONFIRMATION OF STEREOCHEMISTRY AT THE B,C RING JUNCTION

In the first two sections of this chapter, the stereochemistry of the intermediates had been assigned on the basis of ^{13}C n.m.r. chemical shifts. It seemed prudent, however, to seek a more rigorous proof of structure before continuing the sequence. Thus, the methoxyenone 38 was converted into the known *cis*-fused ketone 40[62] according to Scheme 31. Hydrogenation of 38 proceeded smoothly and elimination was accomplished under acidic conditions to give enone 63 in moderate yield. Further catalytic hydrogenation afforded a ketone which was recrystallised to provide a sample identical m.p., ^{1}H n.m.r., i.r.) with the reported compound.[62]

With the stereochemistry of 38 conclusively assigned, a detailed ^{13}C n.m.r. study was undertaken to establish the stereochemistry of the other intermediates reported in Section (i) of this chapter. Unfortunately, attempts to reproduce the above scheme using the *trans*-fused methoxyenone 46 were unsuccessful, as the olefinic bond could not be removed by catalytic hydrogenation, despite the use of a variety of pressures and temperatures. However, treatment of the alcohol 46 with Jones' reagent gave the ketone 43, and subsequent hydrogenation, elimination and hydrogenation as above afforded the diketone 65 (Scheme 32).

Duplication of this route for the *cis*-fused epimer 38 produced the required intermediates 42, 66 and 67 (Scheme 33).



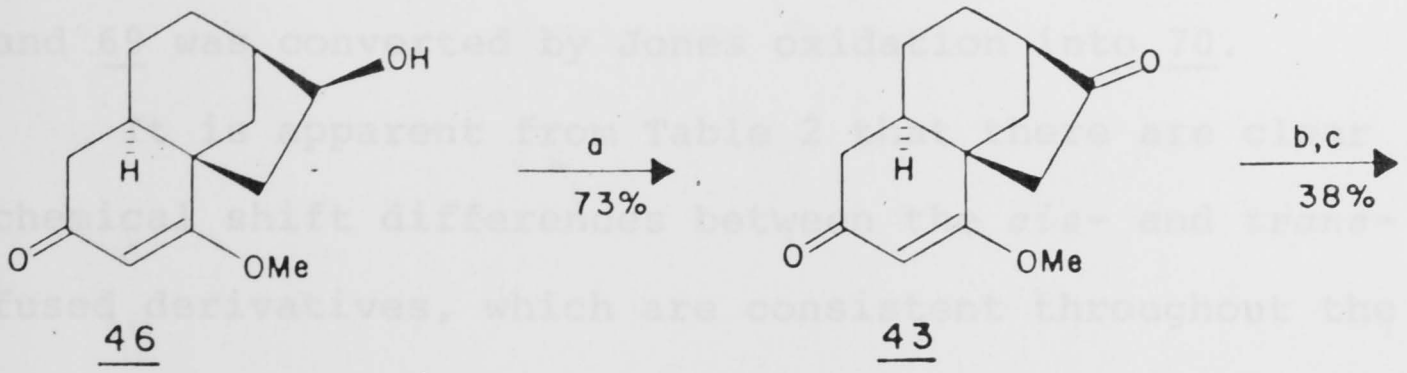
38 47 63 40

Reagents: (a) H_2, Pd/C; (b) TFA; (c) $NaHCO_3$; (d) H_2,Pd/$CaCO_3$.

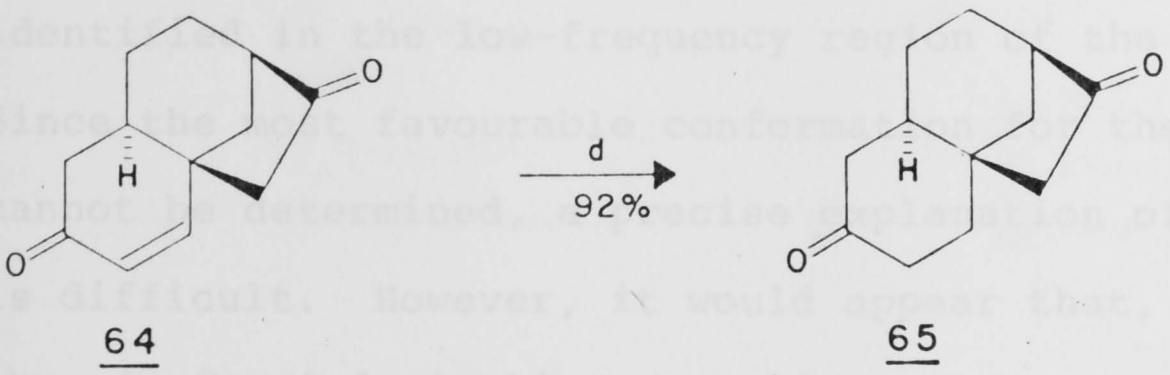
SCHEME 31

The methoxymethyl ethers 49, 50, 58 and 68 were prepared from the alcohols 38, 46, 40 and 41 respectively in the usual way (diisopropylethylamine, chloromethyl methyl ether).[63] To assist in the assignment of the various carbon atoms in compounds 38, 39, 64 and 66, the ^{13}C n.m.r. spectra of the known analogous compounds 68[79] and 69[62] were obtained,†

† Samples were provided by Cossey and Mander,[62,79] but no ^{13}C n.m.r. data had been previously obtained.



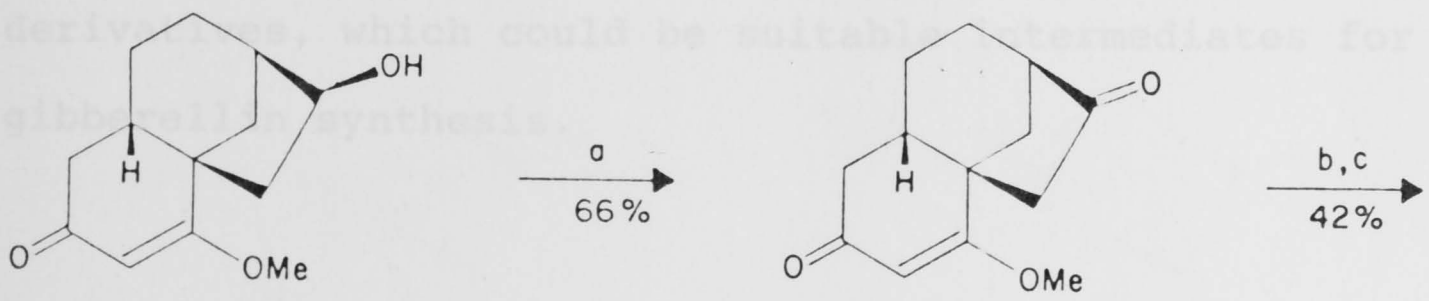
46 43



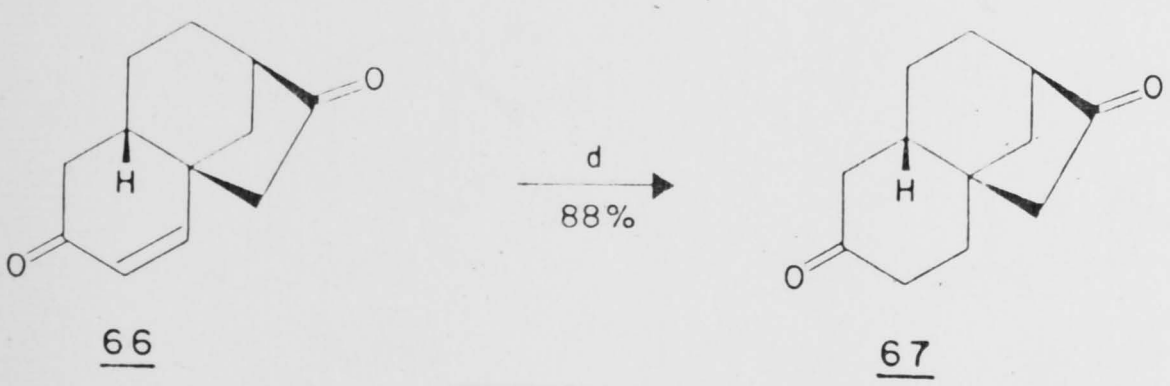
64 65

Reagents: (a) Jones; (b) H_2, Pd/C; (c) TFA;
(d) H_2, $Pd/CaCO_3$.

SCHEME 32



38 42



66 67

Reagents: (a) Jones; (b) H_2, Pd/C; (c) TFA;
(d) H_2, $Pd/CaCO_3$.

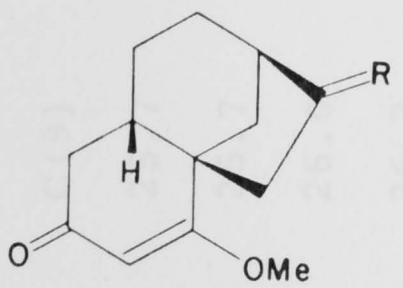
SCHEME 33

and 69 was converted by Jones oxidation into 70.

It is apparent from Table 2 that there are clear chemical shift differences between the *cis*- and *trans*-fused derivatives, which are consistent throughout the range of compounds studied. Although the differences for C(8) and C(9) are not as large as those for C(5) and C(10), more interest is attached to them because they may be readily identified in the low-frequency region of the spectrum. Since the most favourable conformation for the C-ring cannot be determined, a precise explanation of these results is difficult. However, it would appear that, *in general*, the *cis*-fused derivatives experience greater steric interactions, and this may account for their more upfield chemical shifts.

Thus, ^{13}C n.m.r. spectroscopy provides a simple but effective method for the stereochemical identification of functionalised *cis*- and *trans*-fused methanobenzocycloheptenone derivatives, which could be suitable intermediates for gibberellin synthesis.

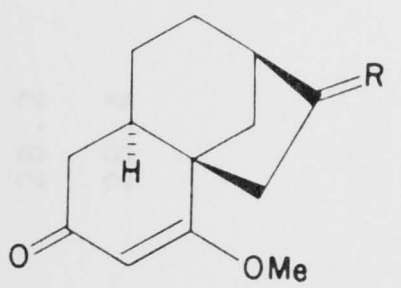
COMPOUNDS IN TABLE 2



42, R=O

38, R=αH, βOH

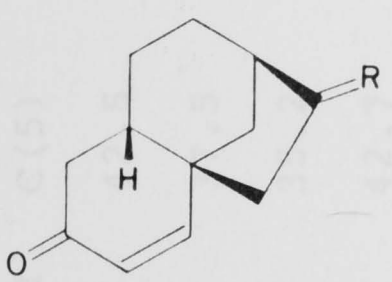
49, R=αH, βOCH$_2$OMe



43, R=O

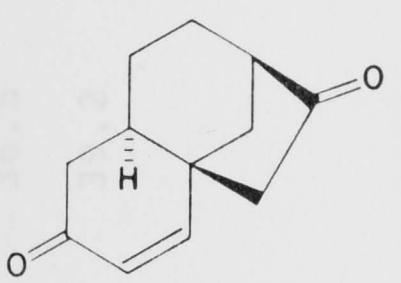
46, R=αH, βOH

50, R=αH, βOCH$_2$OMe

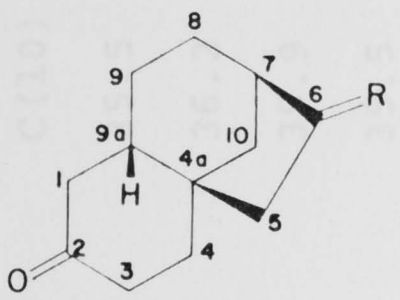


66, R=O

63, R=αH, βOH



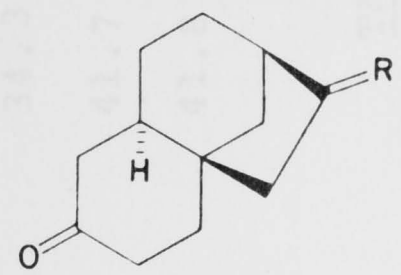
64



67, R=O

40, R=αH, βOH

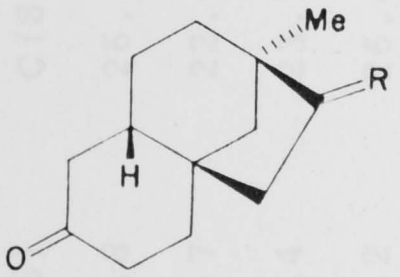
58, R=αH, βOCH$_2$OMe



65, R=O

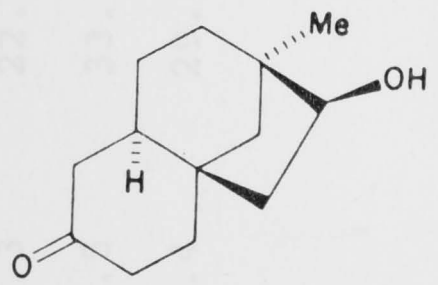
41, R=αH, βOH

68, R=αH, βOCH$_2$OMe



71, R=O

70, R=αH, βOH



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^{13}C n.m.r. CHEMICAL SHIFTS FOR CERTAIN CARBON ATOMS OF SOME METHANOBENZOCYCLOHEPTENONE INTERMEDIATES

CIS-FUSED					*TRANS*-FUSED				
Compound	C(5)	C(8)	C(9)	C(10)	Compound	C(5)	C(8)	C(9)	C(10)
42	45.8	26.5	24.2	35.5	43	42.5	29.1	25.7	37.8
38	39.7	22.6	24.2	36.2	46	37.5	26.5	25.7	39.0
49	37.4	23.1	24.2	35.9	50	35.2	26.2	26.0	38.2
66	51.2	26.4	25.6	35.5	64	42.7	29.0	26.2	42.7
63	46.5	22.5	24.4	36.0					
67†	51.3	26.0	25.2	34.6	65†	44.4	29.1	27.7	43.0
40†	45.8	22.2	25.5	34.7	41†	39.4	25.6	28.2	43.8
58	43.3	22.7	25.5	34.3	68	36.5	26.1	28.2	43.4
71†	51.5	33.7	25.9	41.7	69†	39.2	32.7	28.4	50.9
70†	46.4	29.5	25.5	41.8					

TABLE 2

† Deuterium exchange (NaOD, D_2O, Dioxan)[80] was necessary for the unambiguous assignment of some carbon atoms.

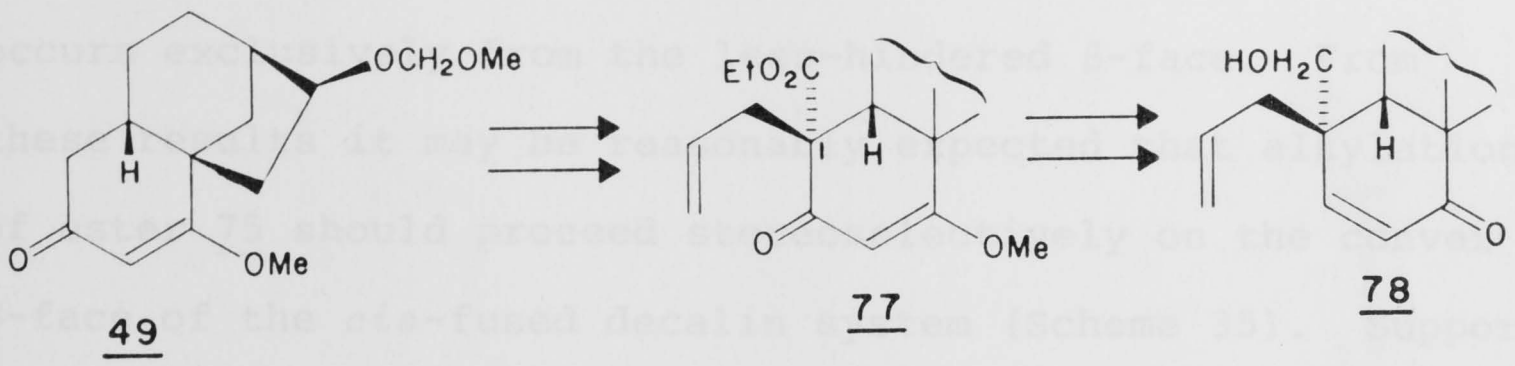
C H A P T E R 3

(i) C(1) ELABORATION OF METHOXYENONE 49

(ii) TRANSPOSITION OF THE CARBONYL GROUP IN THE METHOXYENONE SYSTEM

(iii) A STUDY OF FURTHER APPROACHES TO INTERMEDIATE 78

In this chapter a detailed study is made of the conversion of methoxyenone 49 into enone 78, a potentially key intermediate for C_{20} gibberellin synthesis. Regio-controlled introduction of the C(1) substituents was assured, while it was expected



49 77 78

that ethoxycarbonylation *followed* by C-allylation would establish the required stereochemistry at C(1). Reduction of the ester group and of the methoxyenone system in the 1,2-mode, followed by acid treatment, was then expected to furnish 78. The acylation/alkylation sequence (49 → 77) is described in Section (i) and the reduction studies in Section (ii). Because considerable difficulty was experienced in the reduction sequence (77 → 78) other precursors to the C(1) hydroxymethyl group were examined, and these are discussed in Section (iii).

(i) C(1) ELABORATION OF METHOXYENONE 49

The efficient introduction of two synthons for the construction of the A-ring and lactone moieties of gibberellins was crucial to the success of the synthetic strategies outlined in Schemes 13 and 14. From the studies carried out by

Afonso[81] (Scheme 34), alkylation is stereoelectronically controlled in the saturated compound and occurs on the more hindered α-face. The presence of the olefinic bond, however, makes a pseudo-boat conformation of ring A more accessible in the transition state, thus allowing good orbital overlap on both faces. ~~Alkylation~~ Alk ylation is now sterically controlled and occurs exclusively from the less-hindered β-face. From these results it may be reasonably expected that alkylation of ester 75 should proceed stereoselectively on the convex β-face of the *cis*-fused decalin system (Scheme 35). Support for this prediction comes also from the work of Orsini *et al.*,[82] where only one alkylated product was obtained under all conditions tested (Scheme 36).

In his original study of alkylation at C(1) of enol ethers of β-diketones, Stork[42] had reported that, although the lithium enolates possessed low reactivity in tetrahydrofuran, alkylation was achieved when a highly reactive alkylating agent was utilised, or when alkyl iodides were employed in the presence of some hexamethylphosphorictriamide.† In order to determine whether C(1) elaboration of methoxyenone 49†† was feasible, 49 was

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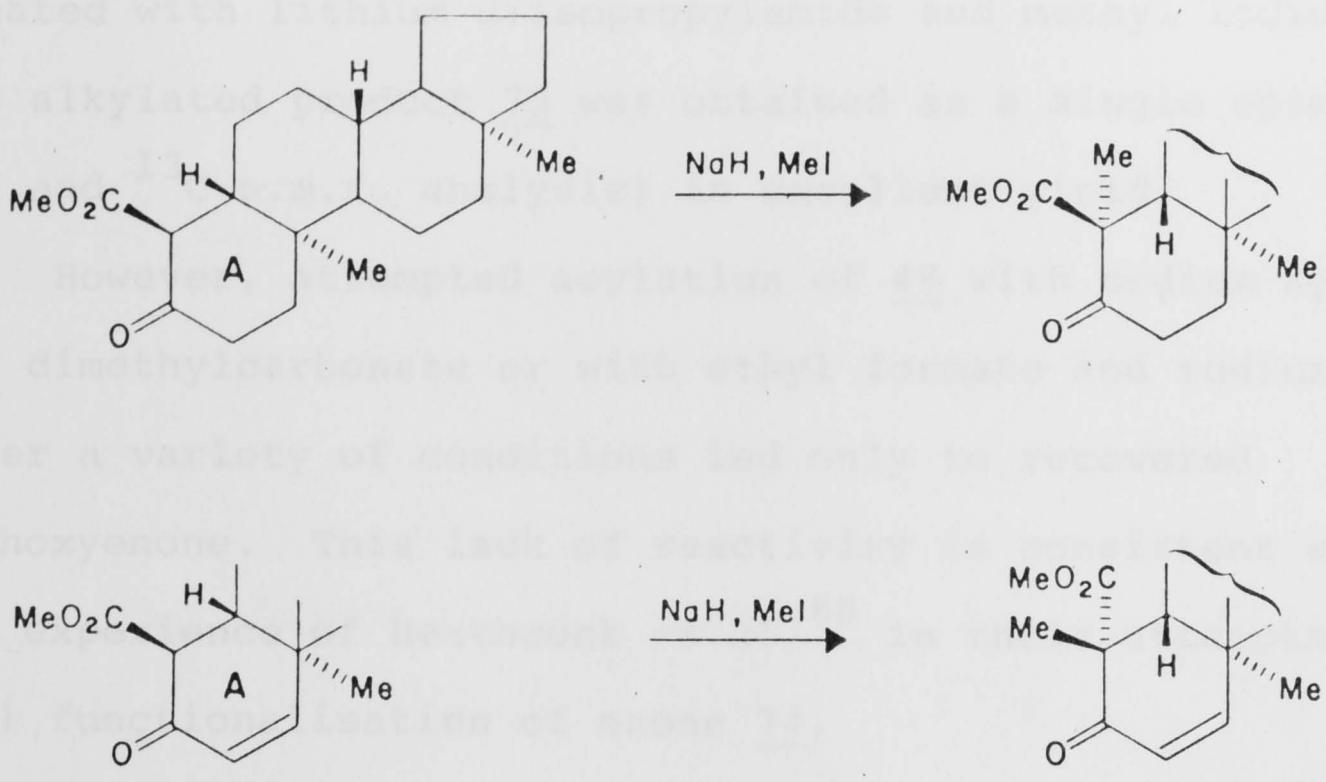
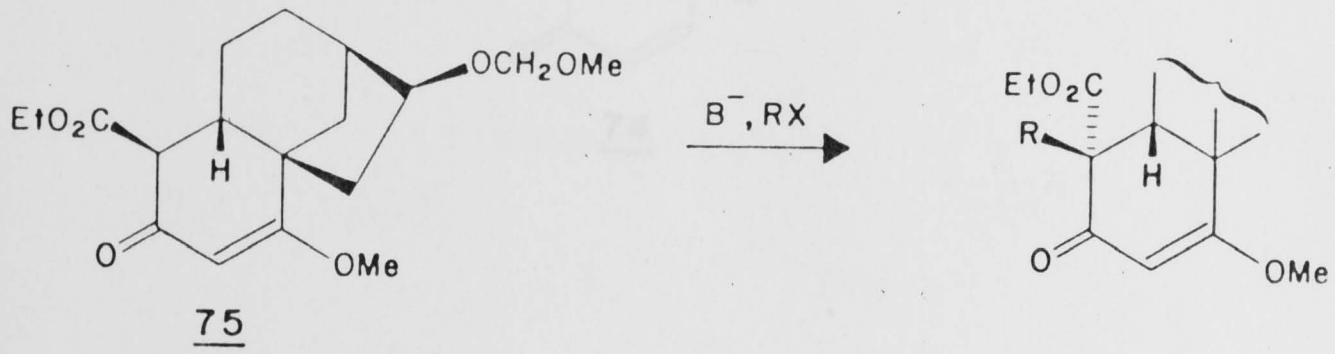
† Following Stork's report, this type of alkylation has been used by a variety of research groups.[83-87]

†† Attempted selective ketalisation[17a] of 42 using the acidic resin Dowex W 50 gave the tris-acetal compound 72. A methoxymethyl ether moiety was therefore chosen as a protecting group for the C(6) function, since it appeared to be suitable

[*continued on p.57*]



SCHEME 34



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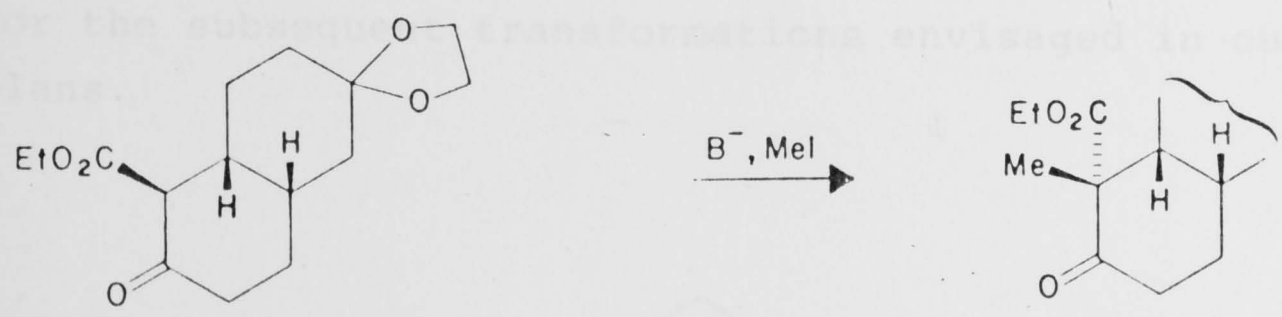
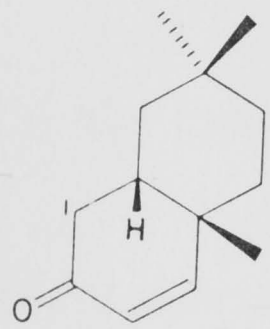
SCHEME 35



SCHEME 36

treated with lithium diisopropylamide and methyl iodide. The alkylated product 73 was obtained as a single epimer (^{1}H and ^{13}C n.m.r. analysis) in excellent yield.

However, attempted acylation of 49 with sodium hydride and dimethylcarbonate or with ethyl formate and sodium hydride under a variety of conditions led only to recovered methoxyenone. This lack of reactivity is consistent with the experience of Heathcock *et al.*[88] in their attempts at C(1) functionalisation of enone 74.



74

Acylation of 49 using lithium diisopropylamide and ethyl chloroformate was then examined, and we were delighted when 75 was formed as a discrete diastereomer (^{1}H and ^{13}C n.m.r.

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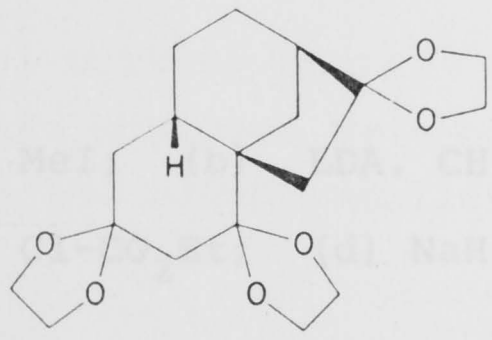
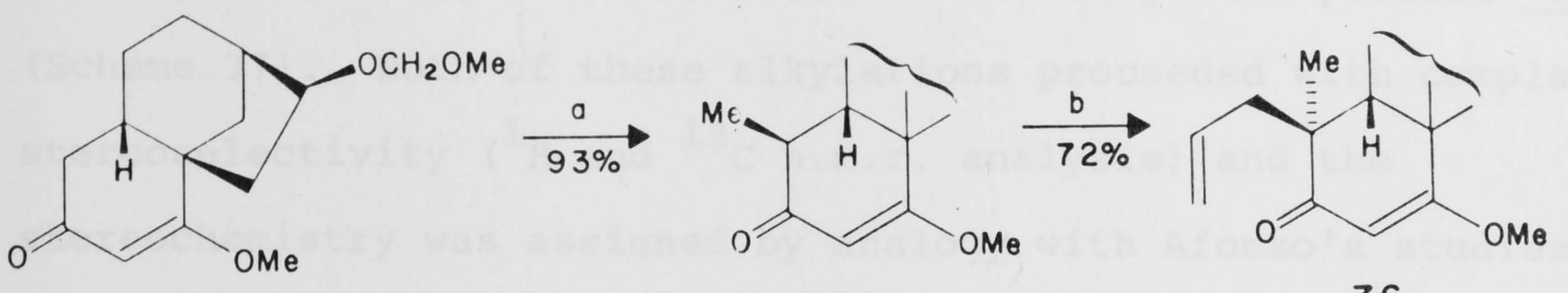
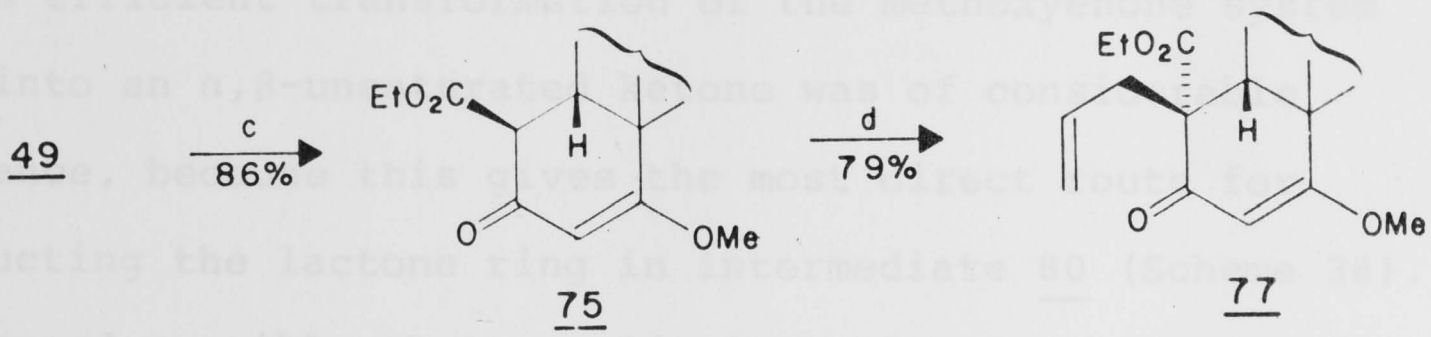
for the subsequent transformations envisaged in our synthetic plans.



72



49 73 76



75 77

Reagents: (a) LDA, MeI; (b) LDA, $CH_2=CH-CH_2Br$;
(c) LDA, $Cl-CO_2Et$; (d) NaH, $CH_2=CH-CH_2Br$.

SCHEME 37

analysis) in 86% isolated yield (Scheme 37).† Although 73 was smoothly converted into 76 with lithium diisopropylamide and allyl bromide, alkylation of the β-keto ester 75 under equivalent conditions was very sluggish, and gave a mixture of starting material and the required product 77. Treatment of 75 with sodium hydride and allyl bromide in dimethylformanide, however, afforded the alkylated product 77 (Scheme 37). Both of these alkylations proceeded with complete stereoselectivity (^{1}H and ^{13}C n.m.r. analysis) and the stereochemistry was assigned by analogy with Afonso's studies,[81] which have been previously described in this chapter.

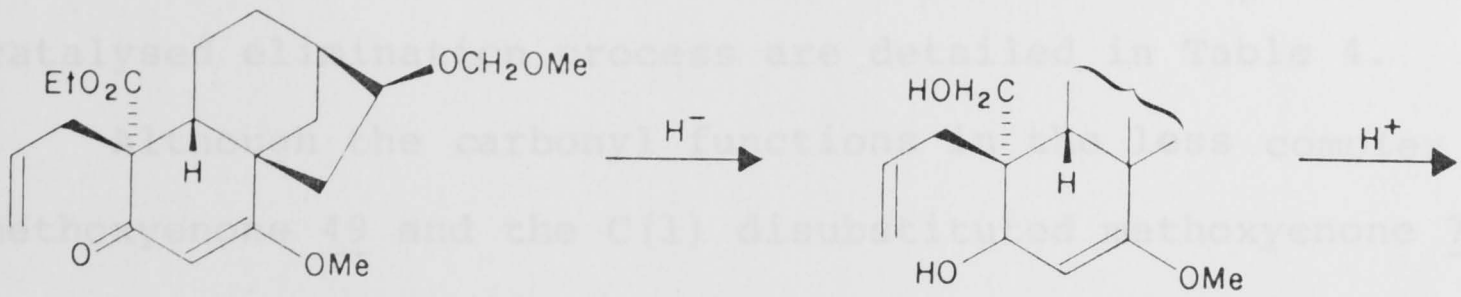
(ii) TRANSPOSITION OF THE CARBONYL GROUP IN THE METHOXYENONE SYSTEM

An efficient transformation of the methoxyenone system in 76 into an α,β-unsaturated ketone was of considerable importance, because this gives the most direct route for constructing the lactone ring in intermediate 80 (Scheme 38). It appeared possible that a selective reduction of the carbonyl group with concomitant reduction of the ester moiety could be accomplished; subsequent acid-catalysed elimination would then produce the required Michael acceptor system.††

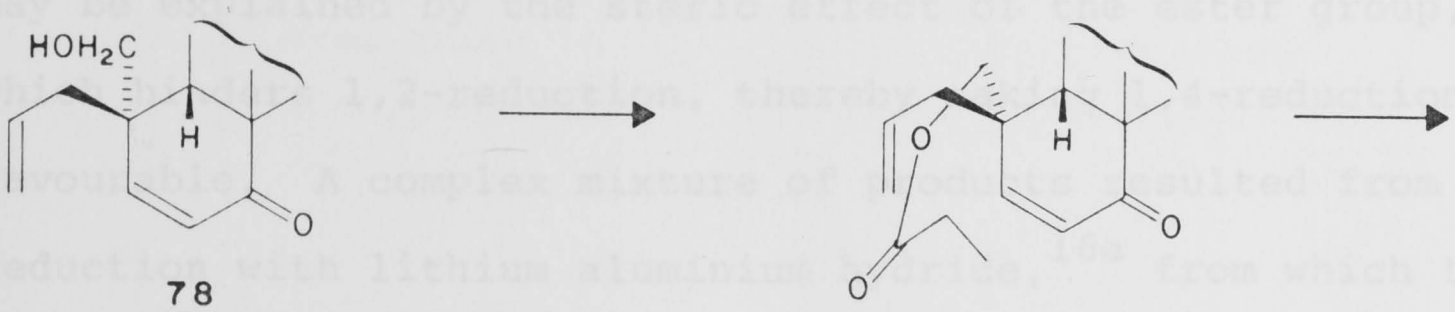
---

† The methoxyenone system directs acylation onto carbon. Acylation occurred on oxygen with the ketone 58 under equivalent reaction conditions.

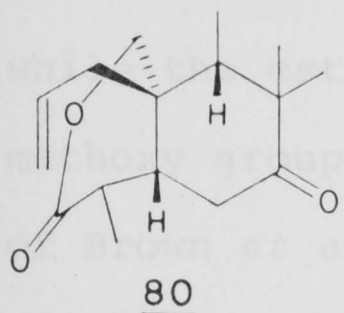
†† Since the original work by Stork,[42] this type of transposition has been employed by a number of groups,[16a,83-87,89] but all were without the added complication of ester reduction.



77



78 79



80

SCHEME 38

In order the find the most suitable conditions for the transposition, model studies were undertaken using a variety of substrates. The results from the reduction stage are presented in Table 3 and subsequent studies of the acid-catalysed elimination process are detailed in Table 4.

Although the carbonyl functions in the less complex methoxyenone 49 and the C(1) disubstituted methoxyenone 76 could be transposed efficiently using diisobutylaluminium hydride (Dibal)[90-92] and trifluoroacetic acid, the transposition in 77 under equivalent conditions produced a mixture of products with a very poor yield (21%) of the desired enone 78. This may be explained by the steric effect of the ester group, which hinders 1,2-reduction, thereby making 1,4-reduction more favourable. A complex mixture of products resulted from reduction with lithium aluminium hydride,[16a] from which the 1,4-reduced compound 84 was the only discrete product observed (^{1}H n.m.r. analysis).† Treatment of 77 with an excess of lithium triethylborohydride (Superhydride, 4 eqs.)[74] afforded reduction in both the 1,2- and 1,4-modes to give alcohol 85, while the ester group remained unaffected. Because the methoxy group is retained in 85, and in the light of the work of Brown *et al.*,[74] it is likely that the carbonyl group is reduced first. Attempted reduction with one equivalent of superhydride, however, led to a mixture of starting material and alcohol 85. Therefore, the second reduction must occur at a faster rate than the first. Accordingly, no further reduction attempts were made using this reagent. Reduction of

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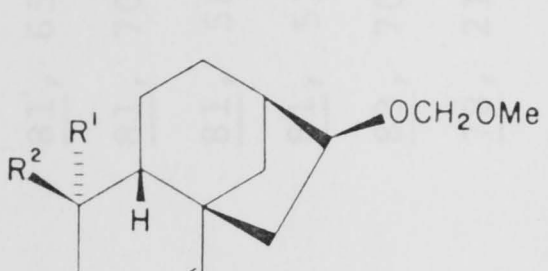
† No reduction in the 1,2-mode was observed in this case.

COMPOUNDS IN TABLES 3 AND 4

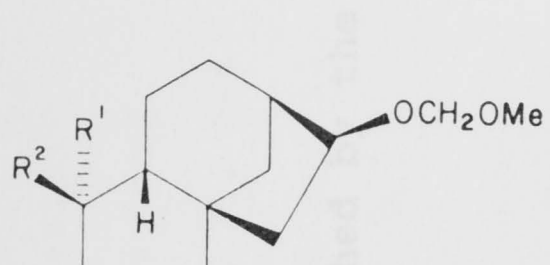


49, $R^1 = R^2 = H$

75, $R^1 = H$, $R^2 = CO_2Et$

76, $R^1 = Me$, $R^2 = allyl$

77, $R^1 = CO_2Et$, $R^2 = allyl$

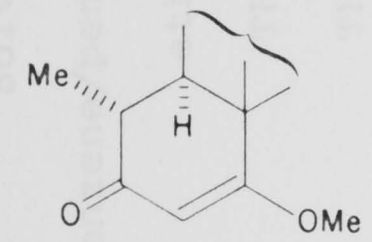


81, $R^1 = R^2 = H$

82, $R^1 = H$, $R^2 = CO_2Et$

83, $R^1 = Me$, $R^2 = allyl$

78, $R^1 = CH_2OH$, $R^2 = allyl$



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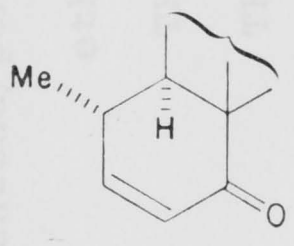

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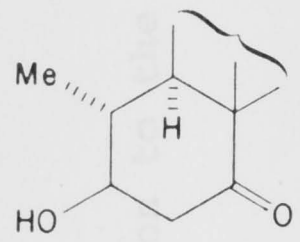

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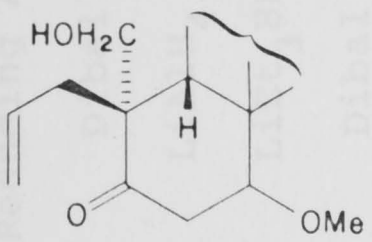

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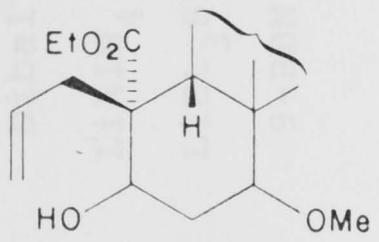

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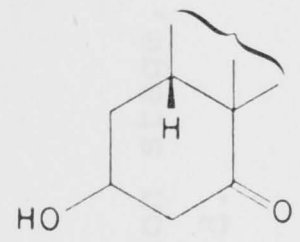

89

REDUCTION OF THE METHOXYENONE SYSTEM

Substrate	Reducing Agent	Solvent	Products and Yields[†]
49	Dibal	benzene/pentane (2:1)	81, 65%
49	$LiAlH_4$	ether	81, 70%
49	$LiEt_3BH$	THF	81, 58%
49	Dibal	THF	81, 51%
76	Dibal	benzene/pentane (2:1)	83, 70%
77	Dibal	benzene/pentane (2:1)	78, 21%
77	$LiAlH_4$	ether	complex mixture
77	$LiEt_3BH$	THF	85, 47%
77	9-BBN	THF	starting material

TABLE 3

[†] After the reduction stage, transposition to the enones was accomplished by the use of trifluoroacetic acid.

Substate†	Elimination Conditions	Products and Yields
49	TFA, CH_2Cl_2	81, 65%
49	6% HCl, THF	81, 68% and 89, 9%
49	*p*TsOH, benzene	81, 91%
86	6% HCl, THF	87, 49% and 88, 20%
86	*p*TsOH, benzene	87, 90%
75	TFA, CH_2Cl_2	82, 35-46%
75	6% HCl, THF	82, 52%
75	(1) Py, MsCl; (2) $KHCO_3$[16a]	complex mixture
75	Dowex W 50	complex mixture
75	*p*TsOH, benzene	82, 60% and 75, 26%
77	*p*TsOH, benzene	78, 24%, 93, 17% and 94, 29%

TABLE 4

† All substrates were reduced with Dibal in benzene/pentane (2:1) at 0° for 1 min., and then isolated prior to elimination.

77 with Dibal in tetrahydrofuran occurred predominantly in the 1,4-mode, and starting material was returned when 9-borabicyclo [3,3,1] nonane[92] was employed as a reducing agent.

While there are difficulties with the reduction of 77, the importance of the elimination stage is apparent from the model studies carried out on 49, 86† and 75 (Table 4). The β-hydroxy ketones 88 and 89 were formed as by-products when the elimination was attempted under aqueous conditions. Both 88 and 89 were obtained as discrete diastereomers (^{13}C n.m.r. analysis), and were presumably formed from hydrolysis of the enol ether without elimination, or from hydration of enones 81 and 87. Therefore, it seemed advisable to perform this reaction and its work-up under anhydrous conditions to ensure the attainment of maximum yields. This was accomplished by the use of a catalytic amount of *p*-toluenesulphonic acid, which smoothly effected the required transformation in

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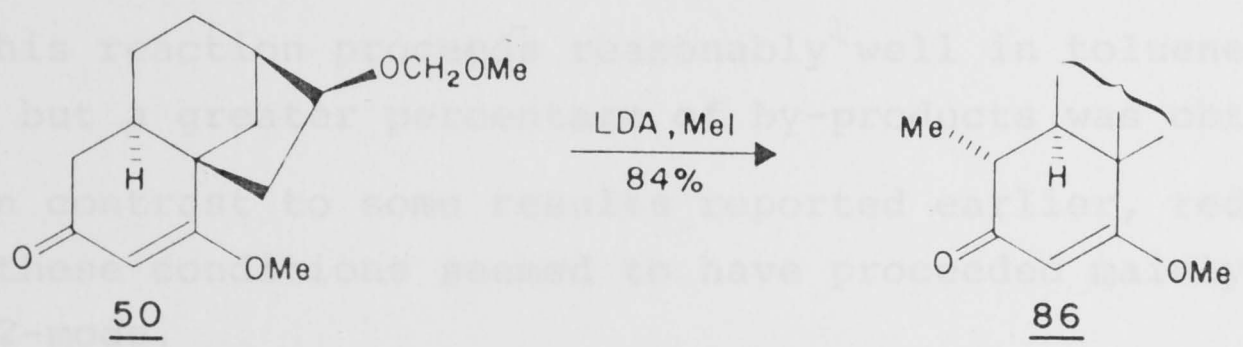
† This compound is an intermediate in the synthesis of a helminthosporin analogue,[93] and was prepared from 50 using the same procedure as for the synthesis of 73 from 49.



50 86

anhydrous benzene under very mild conditions.[†]

Transposition of the β-keto ester 75 using the above eliminating conditions gave a much cleaner product with an improved yield, but problems still existed in the reduction step, as small amounts of minor products were present.[††] Optimum results were eventually obtained when Dibal (0.9 eqs.) was used in a 2:1 mixture of benzene/pentane at 0°,[†††] with the product 82 easily separated by medium pressure liquid chromatography from 75, which was subsequently recycled.

The transposition of the carbonyl group in 76 was then reattempted using Dibal and tosic acid as above, and although an improved yield of the desired α,β-unsaturated ketone was observed (^{1}H n.m.r. analysis), the ester group was only partially reduced, even with the considerable excess of reagent present in the reaction medium. Thus, three α,β-unsaturated ketones were obtained (Scheme 39).[††††] Further reduction of the isolated mixture of alcohols 90, 91 and 92 with both Dibal and lithium aluminium hydride resulted in a loss of

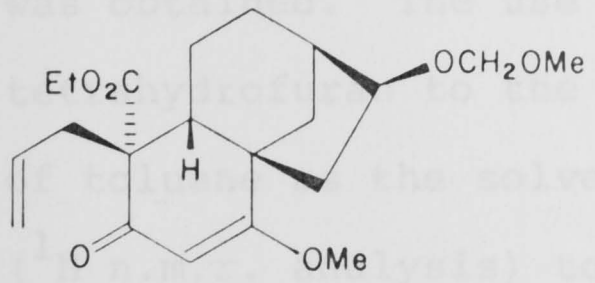
---

[†] Removal of the benzene under reduced pressure and purification of the residue by flash chromatography afforded a very mild procedure for product isolation.

[††] These minor products could be due to partial reduction of the ester group.

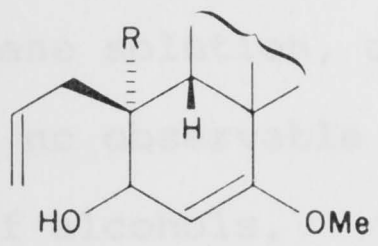
[†††] This reaction proceeds reasonably well in toluene at -78°[94] but a greater percentage of by-products was obtained.

[††††] In contrast to some results reported earlier, reduction under these conditions seemed to have proceeded mainly in the 1,2-mode.



77

a

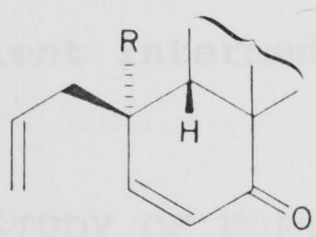


b

90, R = CH_2OH

91, R = CHO

92, R = CO_2Et



78, R = CH_2OH, 24%

93, R = CHO , 17%

94, R = CO_2Et , 29%

Reagents: (a) Dibal; (b) *p*TsOH.

SCHEME 39

the enol ether methoxy group.† Therefore, efforts to complete the reduction of the ester group must be attempted *in situ*. Thus, 77 was reduced with Dibal under the above conditions, and a solution of lithium aluminium hydride in tetrahydrofuran was added to the medium, but a complex mixture of products was obtained. The use of excess Dibal, or the addition of tetrahydrofuran to the benzene/pentane solution, or the use of toluene as the solvent, produced no observable difference (^{1}H n.m.r. analysis) to the ratio of alcohols.

This difficulty of ester reduction, presumably a solubility problem caused by aggregation, did not seem to have a readily accessible and efficient solution. We therefore examined other pathways in an attempt to find a viable route to 78, or an equivalent intermediate.

(iii) A STUDY OF FURTHER APPROACHES TO INTERMEDIATE 78

After our attempts to produce a satisfactory reduction of 77 were unsuccessful, it became apparent that a different pathway must be developed to set up the required functionality

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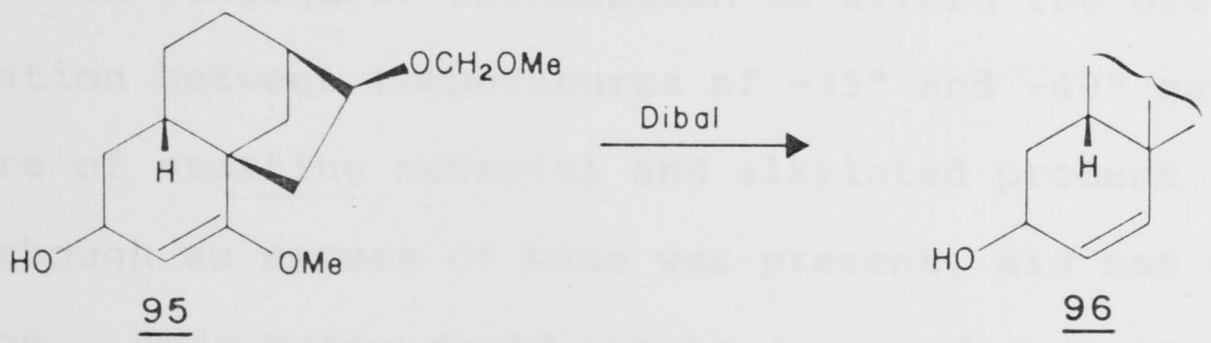
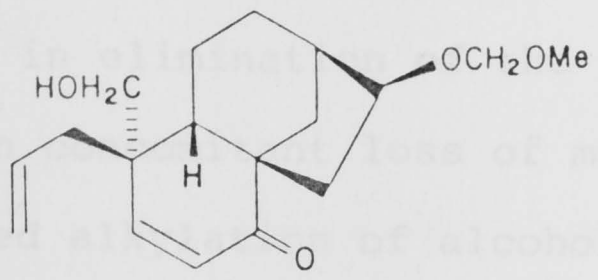
† The cleavage of enol ethers to allylic alcohols by Dibal has been reported.[95] Treatment of the enol ether 95 with Dibal afforded the allylic alcohol 96, in which the olefinic bond had not undergone migration, as determined by ^{1}H n.m.r. spectroscopy.



95 96

for the intramolecular Michael addition (Scheme 38). Our initial target was the key intermediate 78; stereochemical considerations demand that the first group introduced to the C(1) position of methoxyenone 47 must be either a hydroxymethyl group, or a potential hydroxymethyl group. This section is



78

composed of two routes, the first of which is based on the direct introduction of a hydroxymethyl group, and the second on the incorporation of an allyl moiety as a precursor to the desired hydroxymethyl group.

(a) Introduction of a Hydroxymethyl group.

As our efforts to reduce the ester function in 77 to a hydroxymethyl moiety were unsuccessful, it seemed that a direct incorporation of the hydroxymethyl group was worth examination. While alkylation of 49 with lithium diisopropylamide and paraformaldehyde[96] at room temperature proceeded with subsequent elimination to afford the olefin 97, alkylation between temperatures of -35° and -40° gave a 1:1 mixture of starting material and alkylated product 98, which, although an excess of base was present, did not undergo elimination. This ratio could not be improved upon by the

use of paraformaldehyde, but treatment of the lithium enolate of 49 with gaseous formaldehyde[97,98] at -40° afforded an excellent crude yield of 98 (Scheme 43).†

A problem is presented by the alkylation of 98 (or a derivative) because of the likelihood of β-elimination. Treatment of the bis-methoxymethyl ether 100 with lithium diisopropylamide at -78° with subsequent addition of allyl bromide resulted in elimination of the primary methoxymethyl ether group, with concomitant loss of most of the methoxyenone system. Attempted alkylation of alcohol 98 under similar conditions gave only starting material, even when hexamethylphosphorictriamide was present. Starting material was again returned when alkylation was attempted at temperatures between -78° and -25°,†† but a complex mixture of products, of

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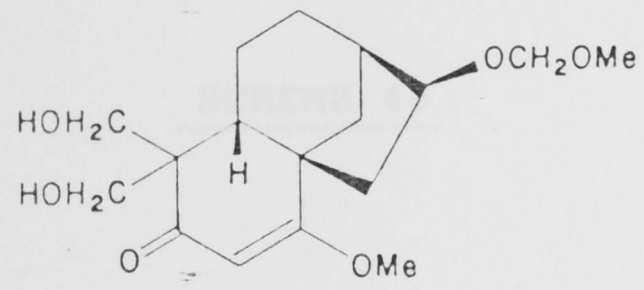
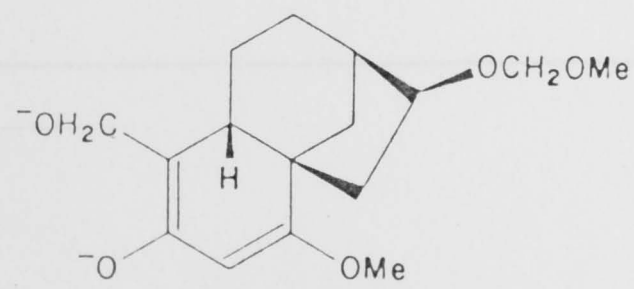
† A mixture of 98 and the bis-alkylated product 99 in an approximate 3:1 ratio was obtained on one occasion.

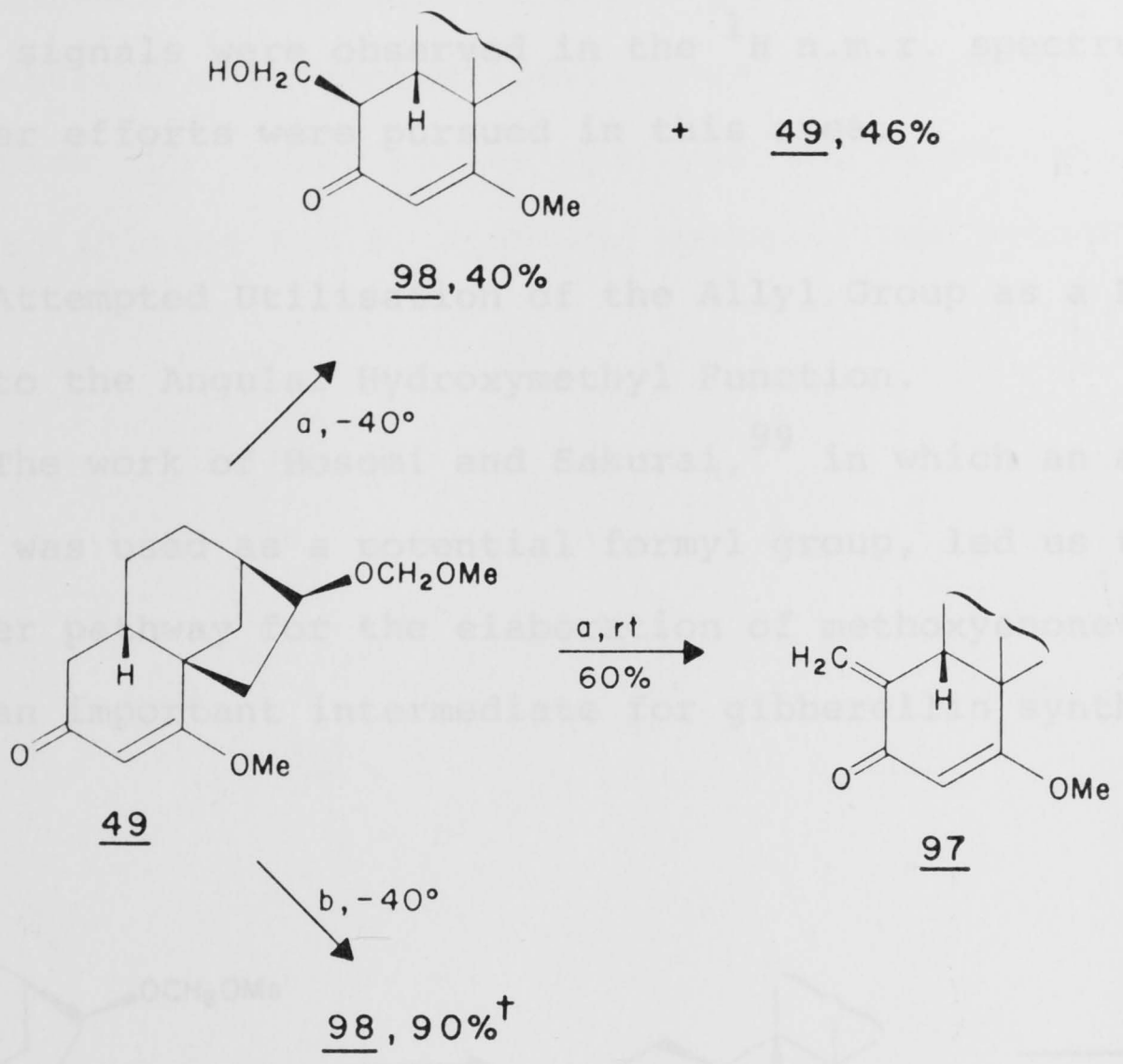


99

†† Under these conditions, the dianion 101 must be at least partially formed, otherwise the dialkylated product 99 would not have been produced.

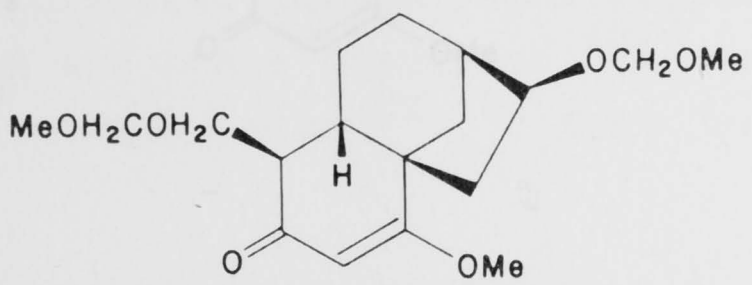


101



Reagents: (a) LDA, *p*-HCHO; (b) LDA, HCHO(g).

SCHEME 40



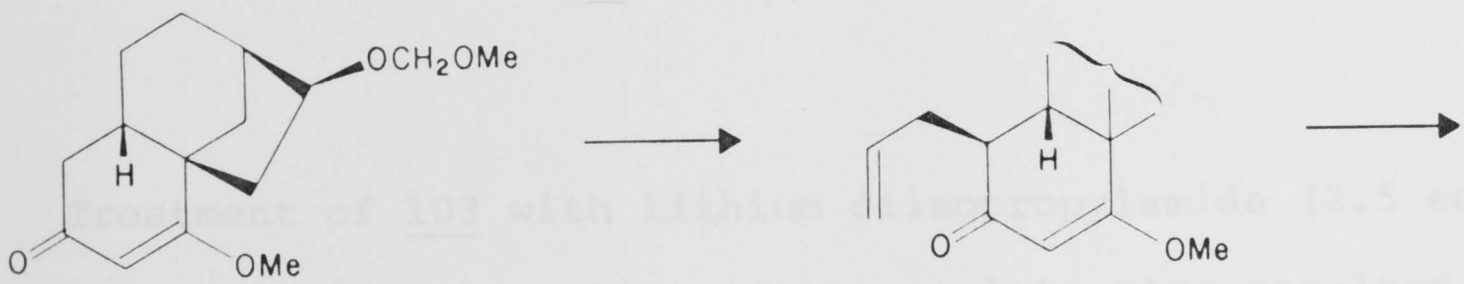
100

† Crude yield.

which the olefin 97 was the major product, was obtained when this reaction was carried out between -20° and 0°. As no allyl signals were observed in the ^{1}H n.m.r. spectrum, no further efforts were pursued in this area.

(b) Attempted Utilisation of the Allyl Group as a Precursor to the Angular Hydroxymethyl Function.

The work of Hosomi and Sakurai,[99] in which an allylic group was used as a potential formyl group, led us to devise another pathway for the elaboration of methoxyenone 49 to 102, an important intermediate for gibberellin synthesis



SCHEME 41

(Scheme 41).† While alkylation of 49 with lithium diisopropylamide and allyl bromide proceeded smoothly to give 103, subsequent attempted alkylations with bromide 104[100] and iodide 105†† were not successful; the isomerised olefin 106 was isolated and no starting material was present.

104

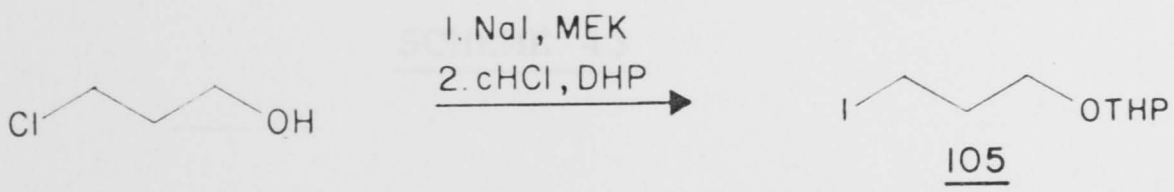
105

Treatment of 103 with lithium diisopropylamide (2.5 eqs.) and an aqueous quenching of the enolate also resulted in

---

† Obviously a second allyl group cannot be employed in this case, and consequently this plan requires the use of a more suitable three carbon synthon as a precursor to the A-ring.

†† This iodide was prepared from 3-chloropropan-1-ol by iodide substitution and ether formation.[101] Attempts to prepare the methoxymethyl ether[63,102] from 3-chloropropan-1-ol were unsuccessful.



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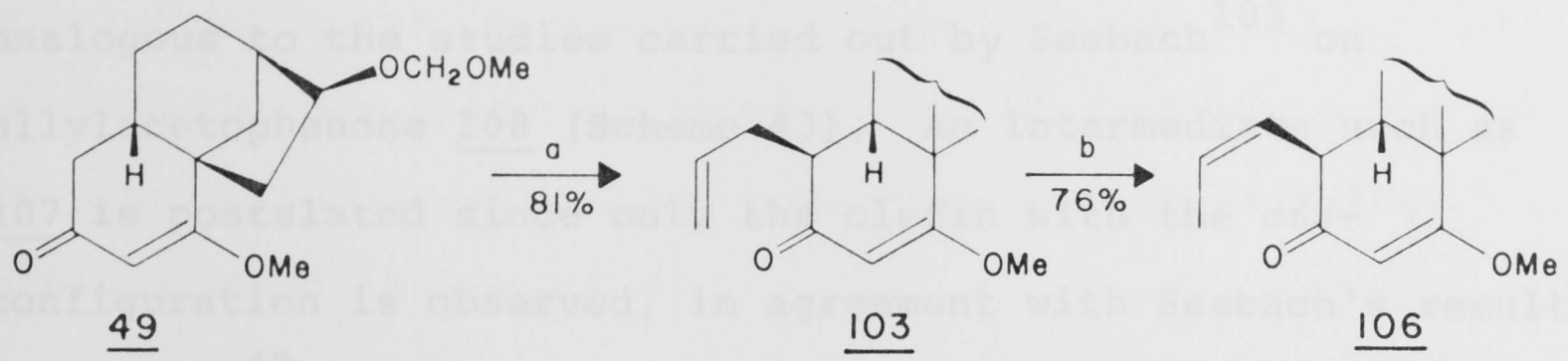
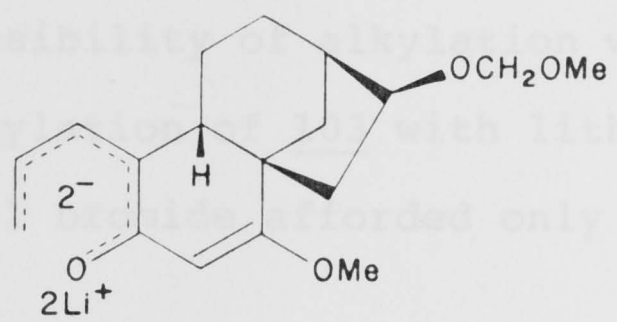


49 103 106

Reagents: (a) LDA, $H_2C{=}CH{-}CH_2Br$; (b) LDA, H_2O.

SCHEME 42



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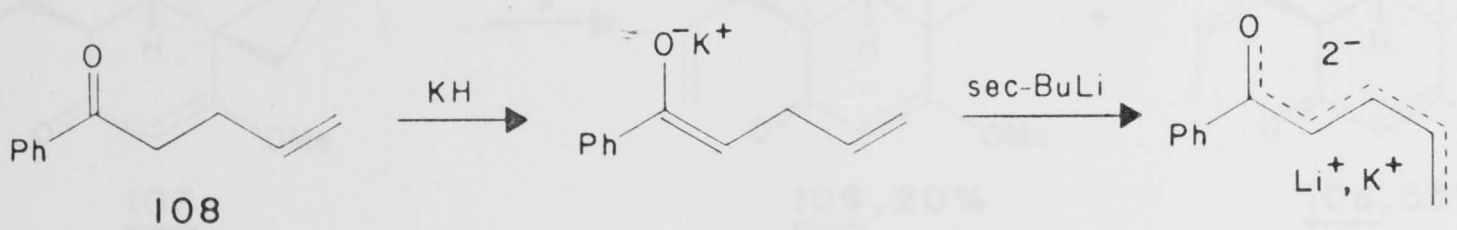
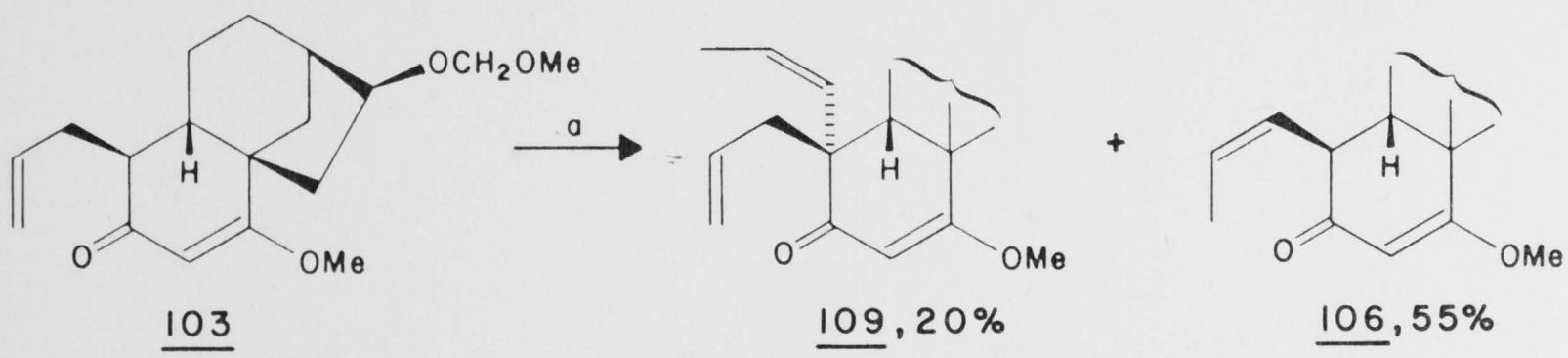


108

SCHEME 43

isomerisation to give 106 as the sole product (Scheme 42). This appears to be a consequence of double deprotonation, analogous to the studies carried out by Seebach[103] on allylacetophenone 108 (Scheme 43). An intermediate such as 107 is postulated since only the olefin with the *cis*-configuration is observed, in agreement with Seebach's results.

Stork[42] had reported that the lithium enolates of enol ethers of β-diketones possessed low reactivity in tetrahydrofuran, presumably due to aggregation. Alkylation proceeded smoothly for a highly reactive alkyl halide such as allyl bromide, but the addition of some hexamethylphosphorictriamide was necessary for alkylation to be successful with alkyl iodides. Therefore, it seemed prudent to undertake a model study in order to evaluate the feasibility of alkylation with 103 as a substrate. Attempted alkylation of 103 with lithium diisopropylamide and allyl bromide afforded only a poor yield



103 109, 20% 106, 55%

Reagents: (a) LDA, $H_2C{=}CH{-}CH_2Br$.

SCHEME 44

of 109, with the isomerised olefin 106 as the major product (Scheme 44). Therefore, it was considered that an efficient alkylation of this system with a less reactive alkyl halide would be a very difficult process, and we decided to turn our investigations towards other more promising areas: these are described in Chapter 4.

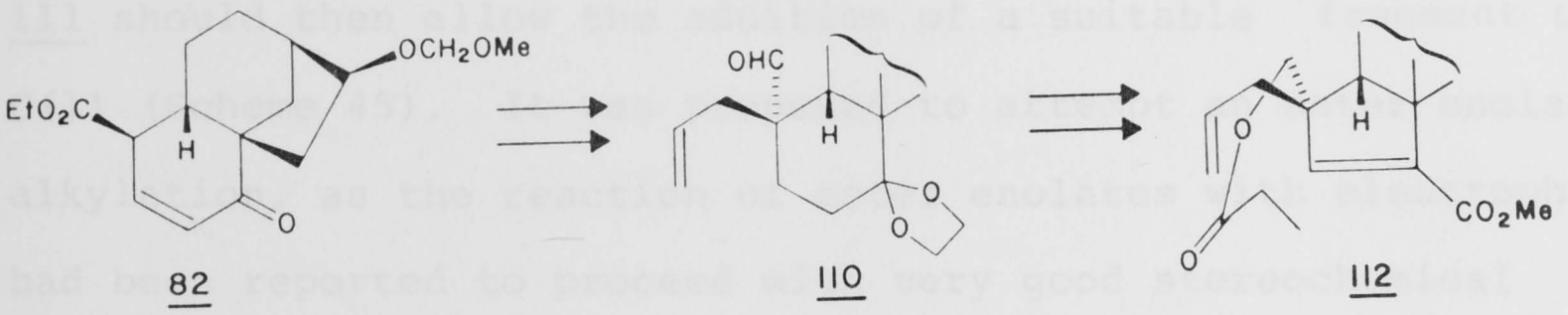
C H A P T E R 4

(i) PREPARATION OF TRICYCLIC ACETAL 110

(ii) PREPARATION OF METHANOAZULENE INTERMEDIATES FOR GIBBERELLIN SYNTHESIS

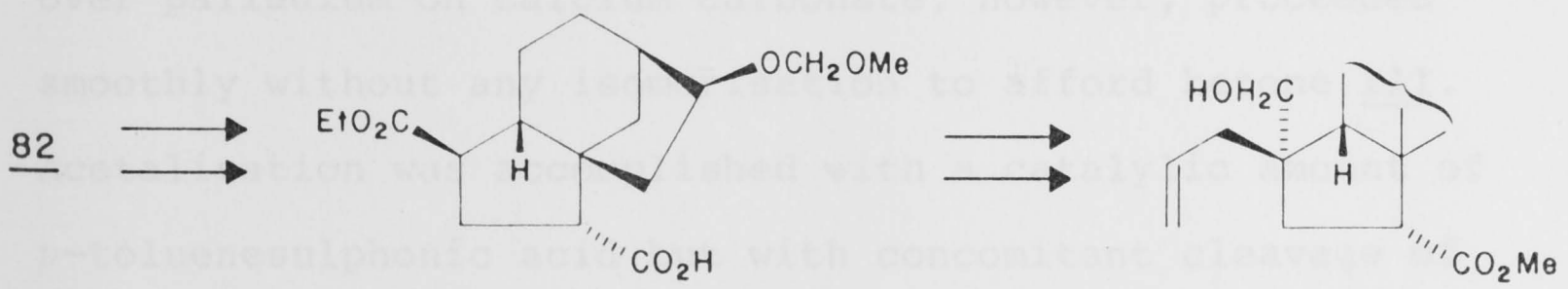
(iii) FUTURE DIRECTIONS

Since difficulties were encountered in our previous approaches, variations on these are examined in this chapter. It was not considered practical to attempt a radically different strategy, but rather to alter the order of our projected transformations. The carbonyl group of the methoxyenone system in the β-keto ester 75 could be efficiently transposed to give 82. The transformation of 82 into 110 and attempts to convert it into 112 are discussed in Section (i).



82 110 112

Because unforeseen difficulties were experienced in attempts to carry out the ring contraction process, 82 was also converted into methanoazulene 124. This sequence,



124 147a

together with the elaboration of 124 to the potential C_{20} gibberellin precursor 147a is detailed in Section (ii).

(i) PREPARATION OF TRICYCLIC ACETAL 110

Although the removal of the olefinic bond in 82 might seem to be contrary to our objectives, this operation increases the flexibility of our general strategy, and provides opportunities for an earlier ring contraction with extrusion of the future carboxyl group prior to the intramolecular Michael addition (Scheme 45). The blocking of the ketone group of 111 should then allow the addition of a suitable fragment to C(1) (Scheme 45). It was proposed to attempt an ester enolate alkylation, as the reaction of ester enolates with electrophiles had been reported to proceed with very good stereochemical control.[104] Also, it was expected that at a later stage in the sequence, a selective reduction of an ester function in the presence of a carboxylic acid moiety would be feasible.[74,105] A practical synthesis of the key compound 112 should then be possible (Scheme 45).

While hydrogenation of the olefinic bond in 82 was accomplished using a palladium on carbon catalyst,[106] a mixture of C(1)-epimers was produced.[106] Catalytic hydrogenation over palladium on calcium carbonate, however, proceeded smoothly without any isomerisation to afford ketone 111. Acetalisation was accomplished with a catalylic amount of *p*-toluenesulphonic acid but with concomitant cleavage of the methoxymethyl ether.† An attempt to avoid this complication

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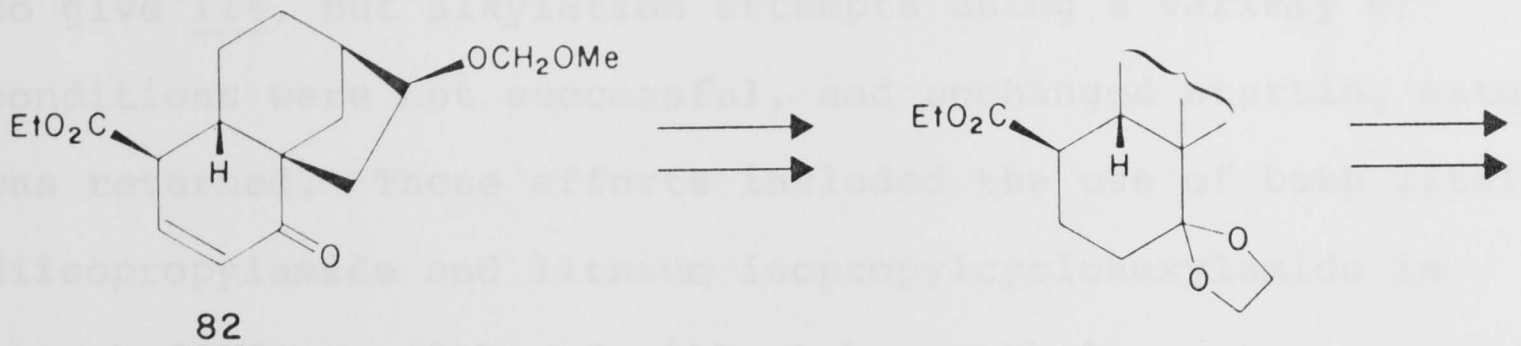
† The alcohol 113 was usually the major product obtained from this reaction. However, on one occasion, the ethereal

[*continued on p.81*]



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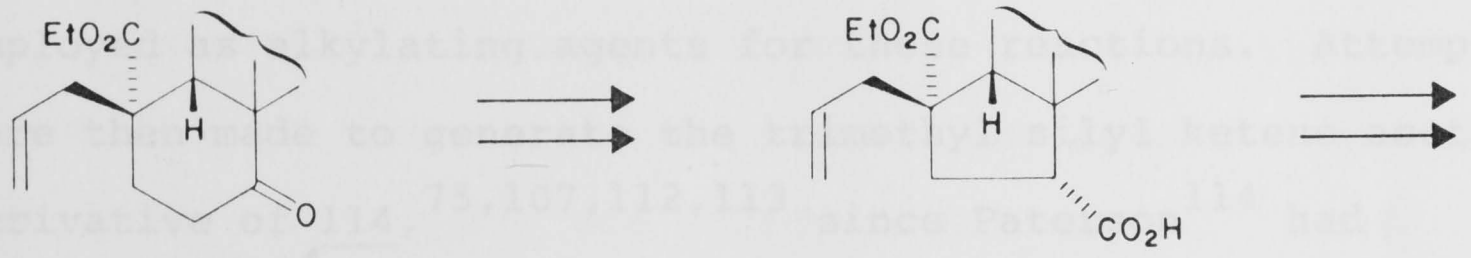

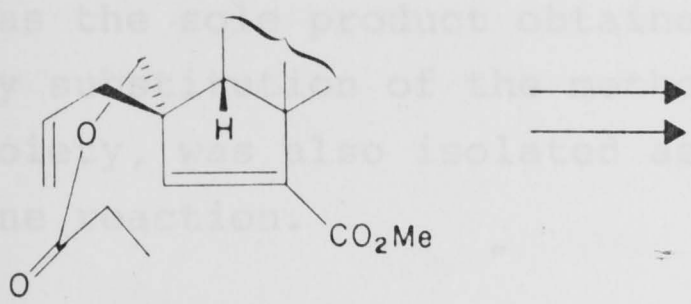

112

GA_{37} (Scheme 9)

SCHEME 45

through the use of Dowex 50 W resin as a catalyst was unsuccessful.

Alcohol 113 was reprotected under the usual conditions[63] to give 114, but alkylation attempts using a variety of conditions were not successful, and unchanged starting material was returned. These efforts included the use of both lithium diisopropylamide and lithium isopropylcyclohexylamide in tetrahydrofuran with and without hexamethyl-phosphorictriamide,[107-110] sodium hydride in dimethylformamide and potassium hydride in tetrahydrofuran with and without dimethylformamide.[75] Methyl iodide and allyl bromide were employed as alkylating agents for these reactions. Attempts were then made to generate the trimethyl silyl ketene acetal derivative of 114,[75,107,112,113] since Paterson[114] had alkylated ~~these~~ such compounds, but unchanged starting material was recovered.

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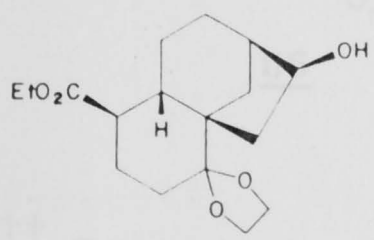
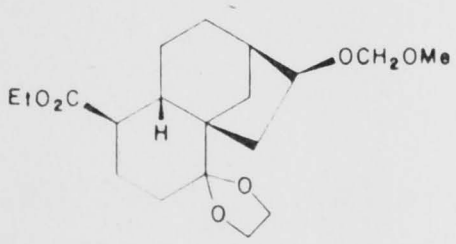
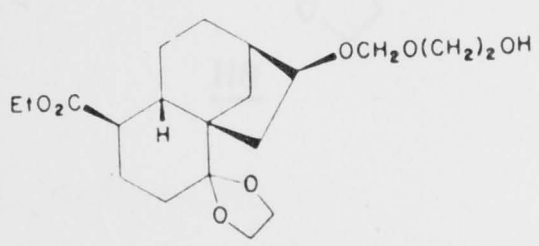
protecting group was intact after acetalisation so that 114 was the sole product obtained. Acetal 115, which is formed by substitution of the methoxy group by an ethylene glycol moiety, was also isolated as a minor product (11%) from one reaction.



113



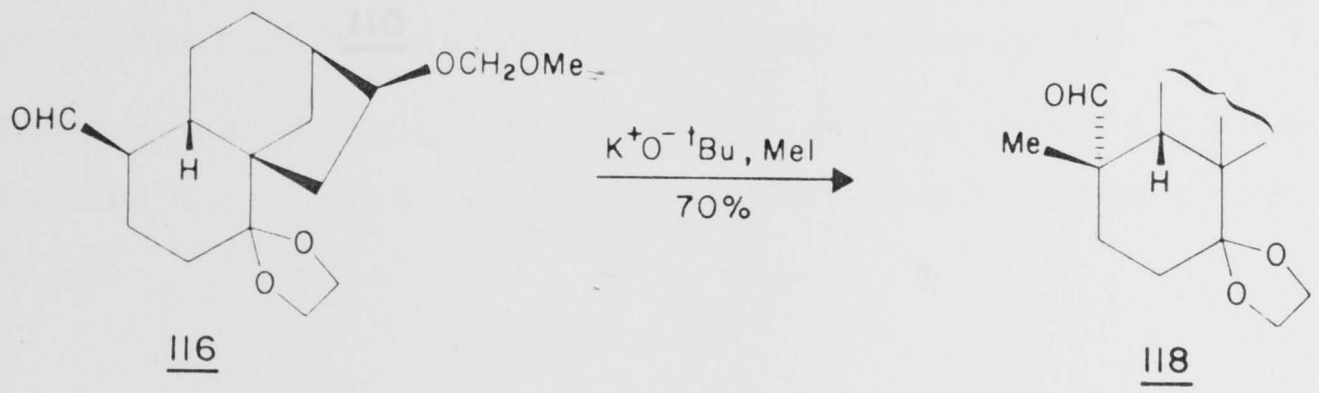
114



115

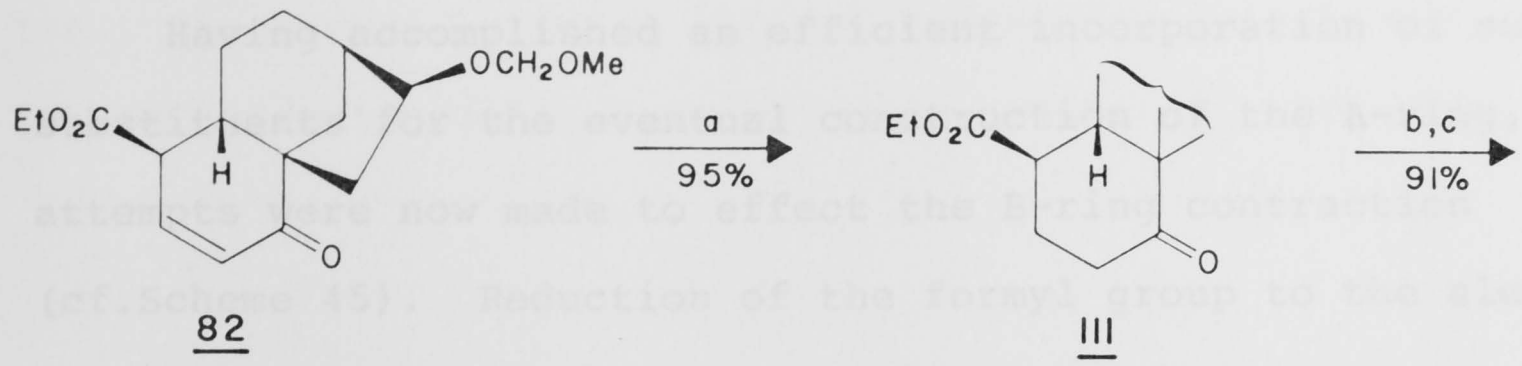
It was presumed that steric hindrance of the ester group was responsible for the failure of 114 to undergo alkylation, and therefore it seemed logical to attempt an alkylation on the corresponding aldehyde. Thus, reduction of 114 with a small excess of Dibal[94] gave predominantly the aldehyde 116 with the alcohol 117 as a minor product. This presented no great difficulty as these compounds were easily separable by flash chromatography, and alcohol 117 was readily re-oxidised to 116. Although starting aldehyde was returned on treatment of 116 with lithium diisopropylamide and methyl iodide in tetrahydrofuran, the important intermediate 110[†] was isolated as a discrete diastereomer (^{1}H and ^{13}C n.m.r. analysis) when a solution of potassium *tert*-butoxide and allyl bromide in anhydrous *tert*-butanol was employed (Scheme 46).[††] The stereoselective equatorial alkylation of aldehyde 116 was expected on the basis of previous studies,[28,115-117]

[†] In a preliminary experiment the C(1)-methyl substituted acetal 118 was prepared using the same procedure as for 110, but with methyl iodide as the alkylating agent.



116 118

[††] Treatment of ester 114 with these reagents under equivalent conditions gave a mixture of products as well as a major quantity of starting material, but no alkylation was observed (^{1}H n.m.r. analysis).



82 111 114 117, 20% 116, 74% 110

Reagents: (a) H_2, $Pd/CaCO_3$; (b) *p*-TsOH, $HOCH_2CH_2OH$; (c) $(\text{>—})_2NEt$, $MeOCH_2$-Cl; (d) Dibal; (e) PDC; (f) $K^{+-}O^tBu$, $H_2C{=}CH_2Br$.

SCHEME 46

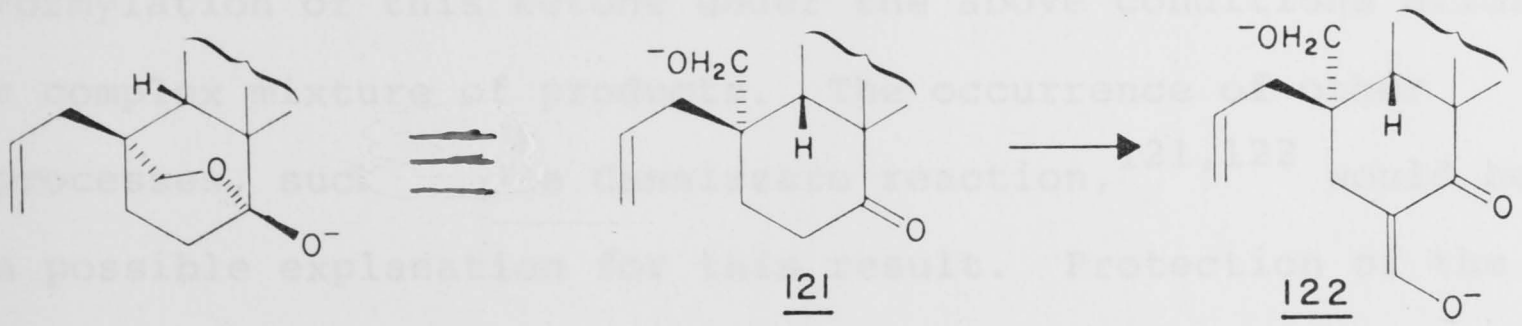
as the stereochemistry of alkylation for exocyclic enolate anions appears to be sterically controlled.

Having accomplished an efficient incorporation of suitable substituents for the eventual construction of the A-ring, attempts were now made to effect the B-ring contraction (cf.Scheme 45). Reduction of the formyl group to the alcohol 119 with sodium borohydride proceeded smoothly, but an intramolecular cyclisation to the hemi-acetal 120 occurred on hydrolysis of the acetal group with dilute hydrochloric acid in acetone (Scheme 47).† It was proposed to effect the ring-contraction process by a photolytically induced Wolff rearrangement[118] of the corresponding diazoketone,[119] by use of the procedures which Cossey and Mander had efficiently employed for the ring-contraction of analogous compounds.[120] Attempted formylation of the hemi-acetal 120,†† a necessary prelude to the introduction of the diazo group, was

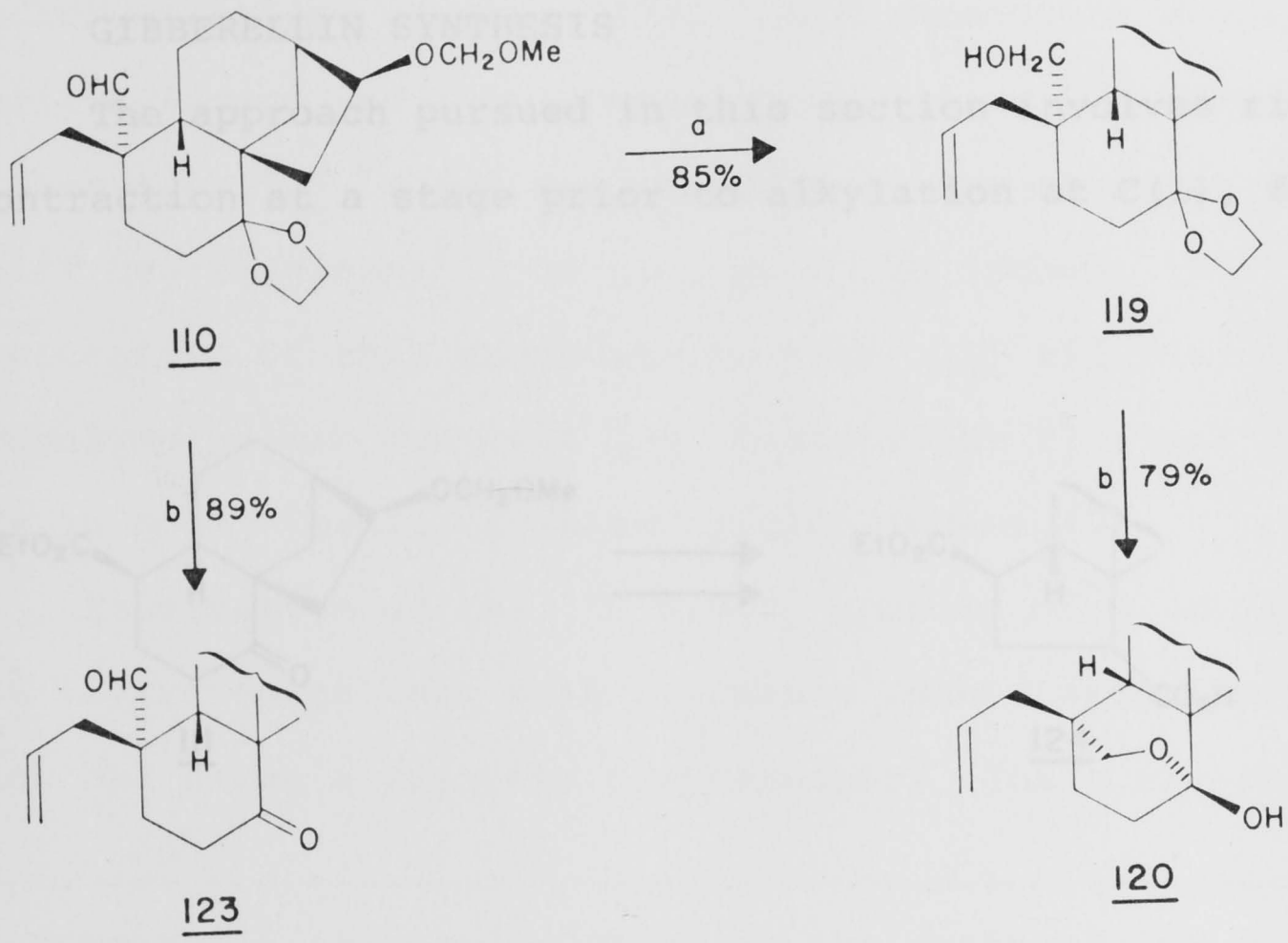
---

† This reaction was complete in 9 hours, whereas the hydrolysis of the acetal group in 110 under equivalent conditions took 36 hours, and even then, a small percentage of starting material remained. Thus the hydroxy group must be providing some assistance to the hydrolysis.

†† It was hoped that the alkoxide derivative of 120 would be in equilibrium with ketone 121 which would then react to give 122.



unsuccessful, however. Treatment with sodium hydride and ethyl formate in both benzene and tetrahydrofuran returned 120. The acetal group of 110 was hydrolysed selectively with dilute hydrochloric acid to give the ketone 123, but attempted



Reagents: (a) $NaBH_4$; (b) 6% HCl.

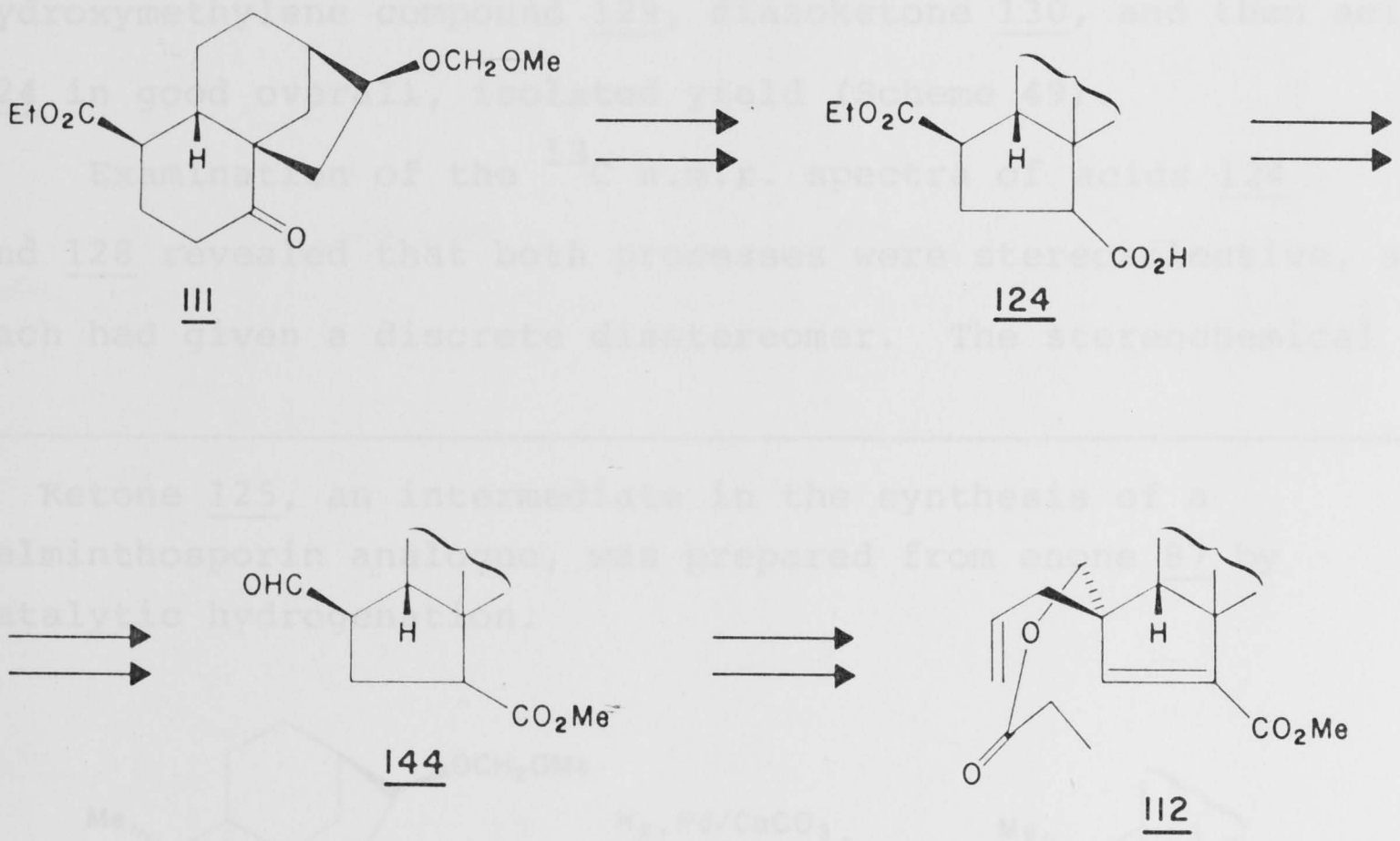
SCHEME 47

formylation of this ketone under the above conditions afforded a complex mixture of products. The occurrence of other processes, such as the Cannizzaro reaction,[121,122] would be a possible explanation for this result. Protection of the hydroxymethyl group would clearly provide a satisfactory

solution to our difficulties, but the choice of a suitable function was not clear and introduces yet two more steps into the sequence. Accordingly, we decided to examine an alternative approach (Section (ii)), prior to any further efforts to elaborate 110.

(ii) PREPARATION OF METHANOAZULENE INTERMEDIATES FOR GIBBERELLIN SYNTHESIS

The approach pursued in this section involves ring-contraction at a stage prior to alkylation at C(1), followed



SCHEME 48

by the attempted elaboration of acid 124 into the critical intermediate 112 (Scheme 48). As our substrate 111 was precious (due to the advanced stage of the synthesis), a model compound for the ring-contraction was examined initially. The B,C *trans*-fused ketone 125[†] was available from other studies.[95] Formylation (sodium hydride, ethyl formate, benzene) proceeded smoothly at room temperature to afford the unstable hydroxymethylene compound 126,[††] and subsequent azide transfer (triethylamine and *p*-toluenesulphonyl azide)[119] gave the diazoketone 127, which was immediately subjected to a photo-Wolff rearrangement[118] to give acid 128 (Scheme 49). Application of this procedure to ester 111 afforded the hydroxymethylene compound 129, diazoketone 130, and then acid 124 in good overall, isolated yield (Scheme 49).

Examination of the ^{13}C n.m.r. spectra of acids 124 and 128 revealed that both processes were stereoselective, and each had given a discrete diastereomer. The stereochemical

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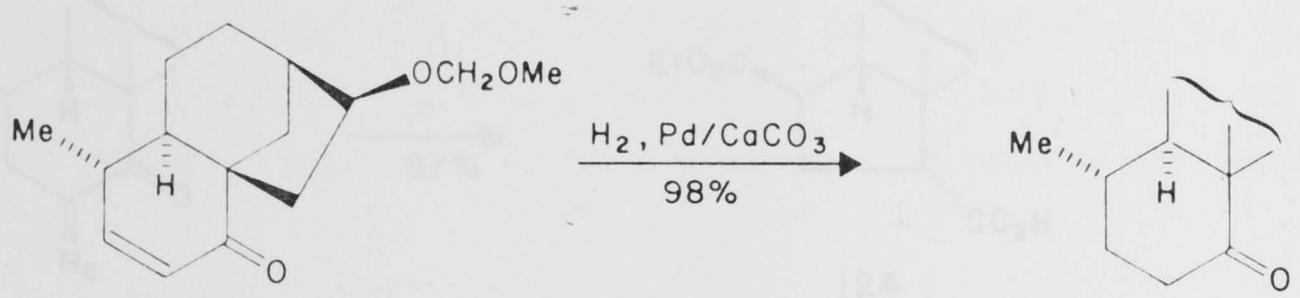
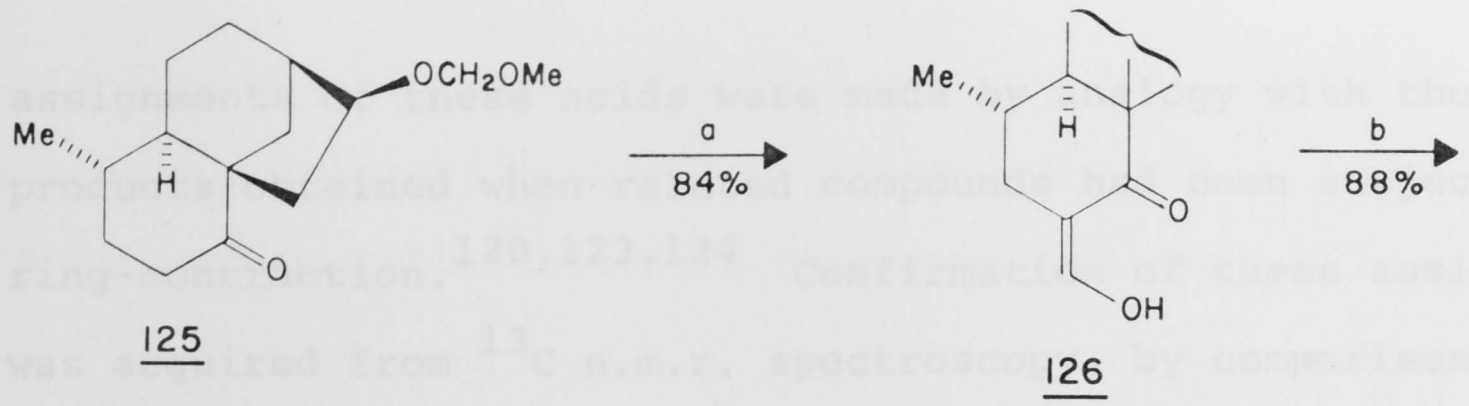
[†] Ketone 125, an intermediate in the synthesis of a helminthosporin analogue, was prepared from enone 87 by catalytic hydrogenation.

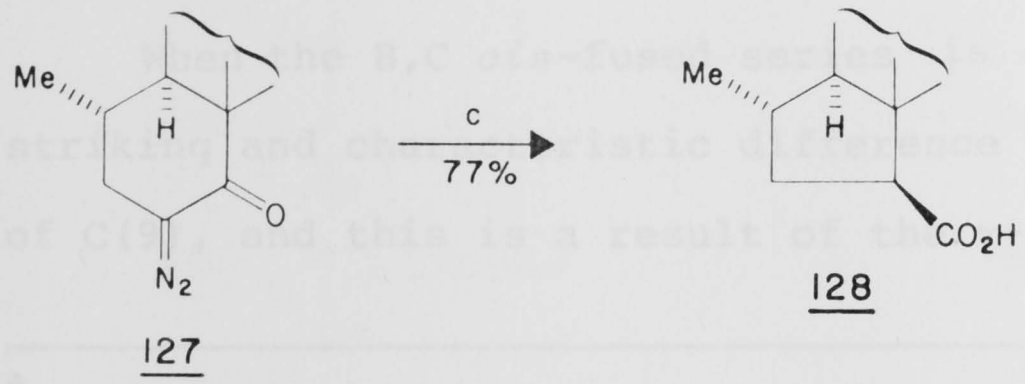


87 125

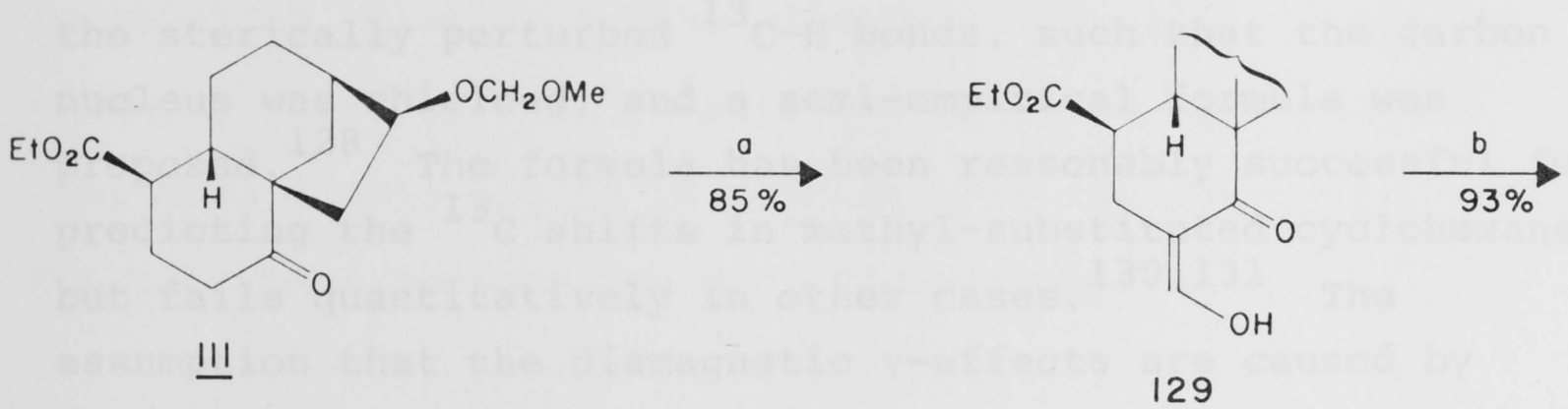
[††] This compound was found to decompose, even with cold storage (t.l.c. and ^{1}H n.m.r. analysis), and so α-hydroxymethylene ketones and diazoketones were immediately used for the next reaction in each case.



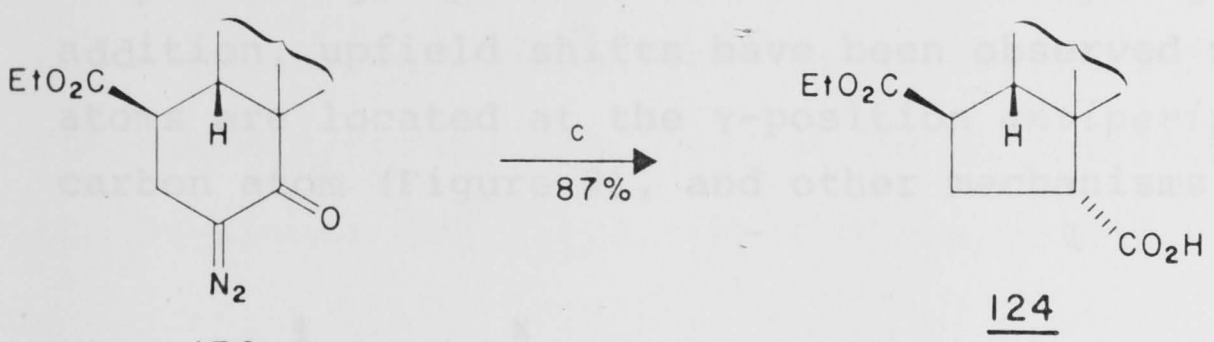
125 126



127 128



111 129



130 124

Reagents: (a) NaH, HCO_2Et; (b) Et_3N, TsN_3;
(c) hν, $NaHCO_3$.

SCHEME 49

assignments of these acids were made by analogy with the products obtained when related compounds had been subjected to ring-contraction.[120,123,124] Confirmation of these assignments was acquired from ^{13}C n.m.r. spectroscopy, by comparison of the chemical shifts of acids 124 and 128 with the previously characterised compounds, 131-136[123] (Table 5).

When the B,C *cis*-fused series is considered, the most striking and characteristic difference is the chemical shift of C(9), and this is a result of the γ-gauche effect.† In

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† The γ-gauche effect is an explanation for the well-documented upfield shift observed[125-127] for the resonance of a carbon nucleus which is gauche to another carbon or heteroatom at the γ-position (Figure 1). This diamagnetic shift was initially attributed to induced polarisation of charge along the sterically perturbed ^{13}C-H bonds, such that the carbon nucleus was shielded, and a semi-empirical formula was proposed.[128] The formula has been reasonably successful for predicting the ^{13}C shifts in methyl-substituted cyclohexanes,[129] but fails quantitatively in other cases.[130,131] The assumption that the diamagnetic γ-effects are caused by repulsive hydrogen-hydrogen interaction is clearly insufficient, since similar diamagnetic shifts are caused by many other groups that do not contain hydrogen.[130,131] In addition, upfield shifts have been observed when N, O or F atoms are located at the γ-position *antiperiplanar* to a carbon atom (Figure 2), and other mechanisms have been proposed

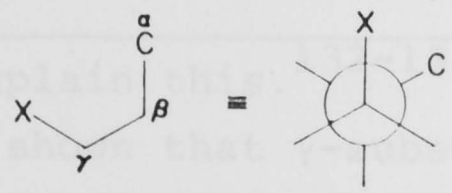


Figure 1

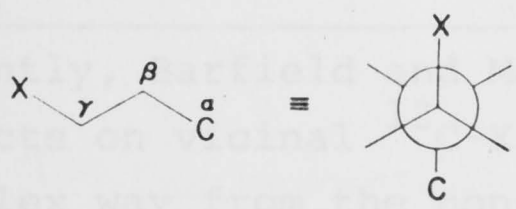
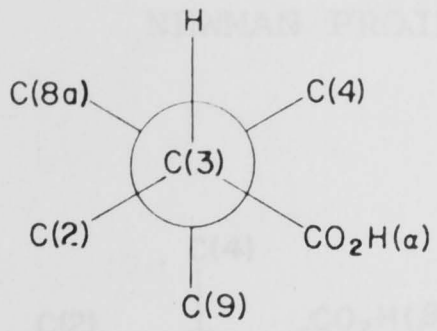


Figure 2

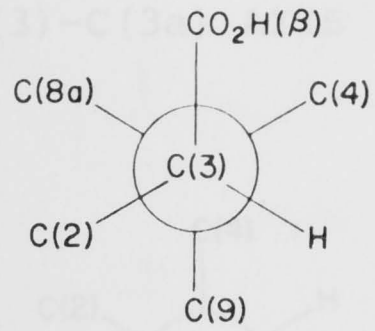
[*continued p.90*]

acid 124 (cf. 137) the carboxyl group and C(9) are in a γ-gauche relationship when the carboxyl group has the α-configuration, and it is therefore expected that C(9) would

NEWMAN PROJECTION ALONG C(3)-C(3a) AXIS



137



138

be shielded relative to the 3β-epimer (cf. 138). From the chemical shift of C(9) in acid 124 relative to analogous compounds (Table 5), it is evident that the carboxylic acid function must possess the α-configuration.

For the B,C *trans*-fused derivatives, the most characteristic difference is for C(4). In acid 128 (cf. 139) the carboxyl group and C(4) are in a γ-gauche relationship when the carboxyl group has the β-configuration, and it is therefore expected that C(4) would be shielded relative to the 3α-epimer (cf. 140). From a comparison of the chemical

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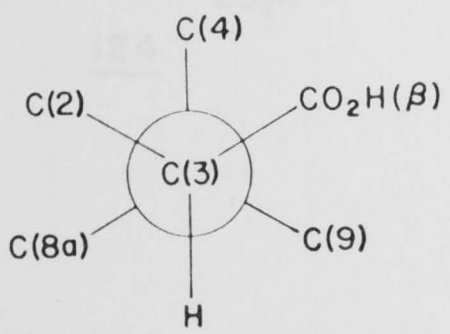
to explain this.[132-134] More recently, Barfield and Marshall have shown that γ-substituent effects on vicinal ^{13}C-X coupling constants arise in a complex way from the non-bonded interactions associated with groups bonded to the γ-carbon atom.[135] These studies suggest that the mechanism(s) is more complex than initially envisaged, and is likely to be a combination of several factors.

shift of C(4) in acid 128 with analogous compounds (Table 5), it is clear that the carboxylic acid function must possess the β-configuration. The shielding of C(4) and C(9) of methanoazulenes by means of a γ-gauche effect from a C(3) carboxyl group has been well documented.[17a,120,123,124]

NEWMAN PROJECTION ALONG C(3)-C(3a) AXIS



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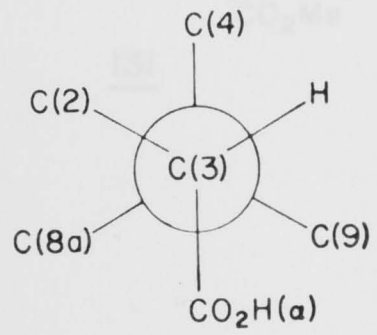
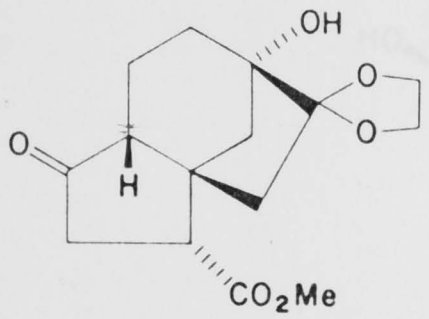


140

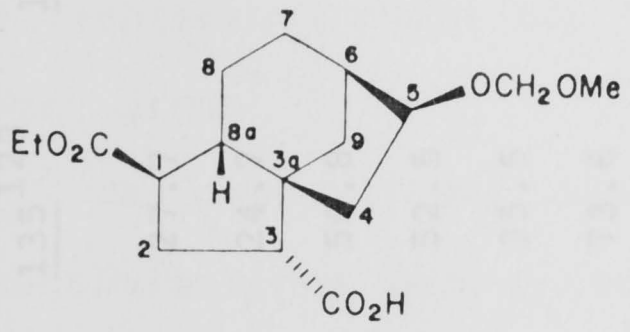
The α-C(3)-epimer 124 was expected to undergo C(1)-alkylation on the less hindered β-face, ~~in~~ by analogy with the



141

reaction of triallyl alane with 141.[17a] Before attempting alkylation, however, a selective reduction of the ester group was necessary. Although starting material was returned unchanged with lithium borohydride,[105] the ester group was

COMPOUNDS IN TABLE 5



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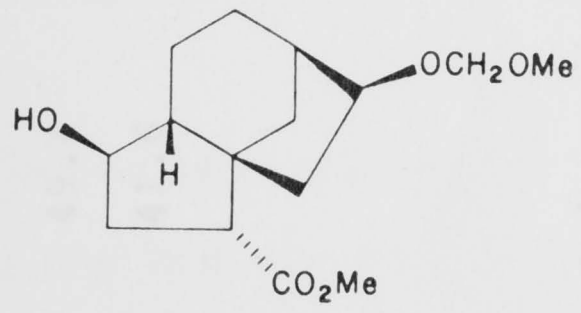

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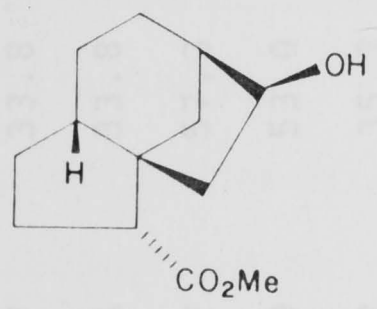

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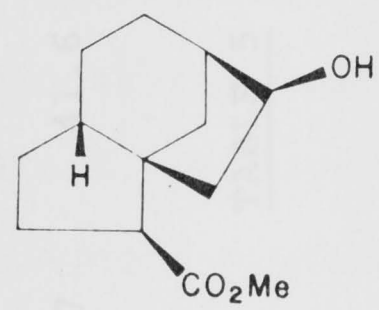

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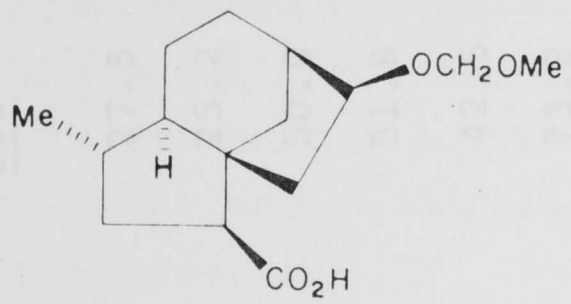

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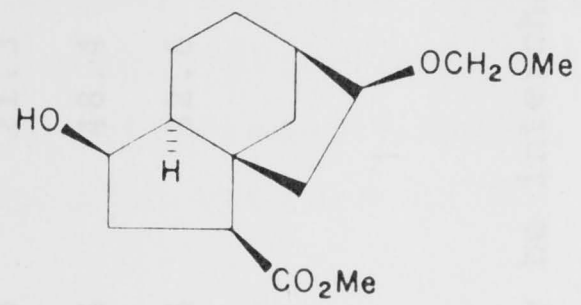

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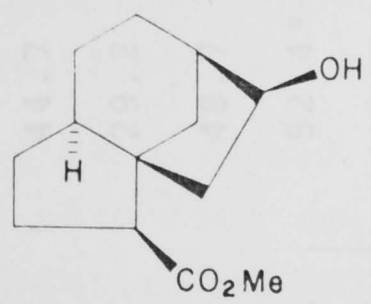

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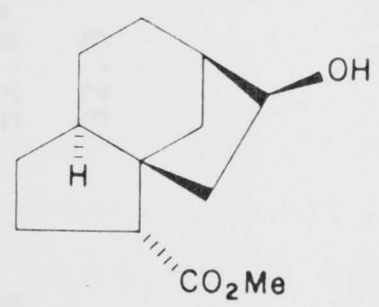


136

^{13}C n.m.r. CHEMICAL SHIFTS FOR THE SKELETAL CARBONS OF SOME METHANOAZULENE INTERMEDIATES†

Carbon Atom	124	131[123]	132[123]	133[123]	128	134[123]	135[123]	136[123]
1	44.7	73.5	27.5	28.7	33.8	75.2	27.7	29.2
2	29.2	35.3	25.2	26.4	33.8	35.1	24.7	26.0
3	48.7	47.6	50.0	51.7	57.3	48.3	50.8	52.2
3a	52.4*	50.5	51.8	51.9	53.0	51.6	52.5	53.1
4	39.4	40.5	42.5	41.7	35.7	35.8	35.5	43.2
5	77.2	77.1	73.8	73.1	78.2	83.1	73.6	73.8
6	36.9	36.9	38.4	38.7	38.1	43.0	39.7	39.7
7	23.4	23.2	22.7	22.6	26.4	33.6	26.4	26.0
8	19.9	19.0	21.3	20.8	24.7	23.9	25.8	26.0
8a	52.6*	56.6	48.4	44.8	49.5	56.9	49.4	45.5
9	32.9	33.5	32.6	38.7	41.6	48.7	41.6	40.3

TABLE 5

* These assignments may be interchanged.

† The remainder of the ^{13}C n.m.r. data is detailed in the experimental section.

reduced selectively using lithium triethylborohydride[74] to give alcohol 142 (Scheme 50). Methylation with diazomethane[136] and subsequent oxidation with pyridinium dichromate afforded the important intermediate 144. Alkylation using the same conditions as for acetal 110, however, gave a 7:3 mixture of C(1)-epimers (Scheme 50),[†] with concomitant cleavage of the ester group.[††]

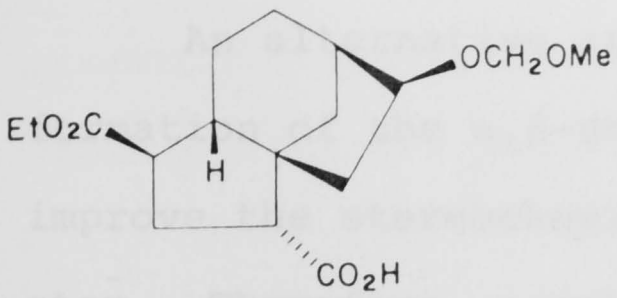
As material was scarce, the planned subsequent transformations were attempted using the mixture of diastereomeric acids. A sodium borohydride reduction gave the alcohols 146a-b which were methylated with diazomethane,[136] as above, to afford esters 147a-b in good isolated yields. Attempted selenenylation with potassium hydride and diphenyldiselenide,[17a] however, was unsuccessful, resulting in cleavage of the methyl ester.[†††] Therefore, protection of the hydroxy group may be necessary for an adequate preparation of 112.

[†] From previous studies, it was assumed that the epimer 145a was the major compound; the stereochemical dichotomy in this case is presumably due to the smaller difference between the *quasi*-axial and *quasi*-equatorial approach vectors in the cyclopentane ring.

[††] This cleavage could not be averted, despite the use of freshly-prepared potassium *tert*-butoxide from potassium metal and anhydrous *tert*-butanol. In his studies in other areas, Mander has found that methyl esters are often cleaved in the presence of potassium *tert*-butoxide.[137]

[†††] This is a result of a preliminary study, and it should be treated with caution. It is notable, however, that α-selenenylation of 143 under equivalent conditions did not lead to a loss of the methyl ester, perhaps suggesting that

[*continued p.96*]



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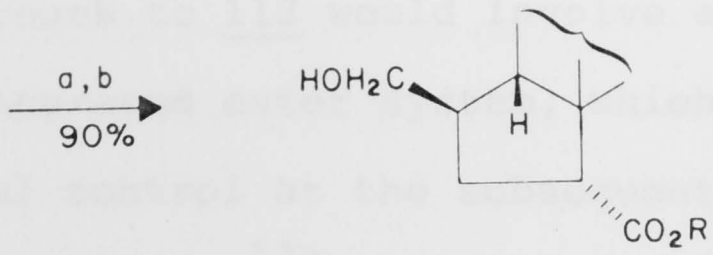
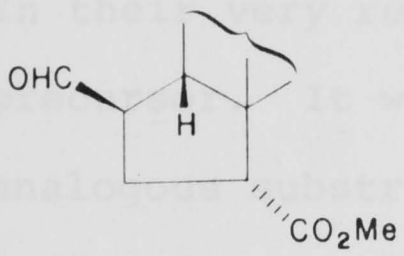


142, R = H

143, R = Me



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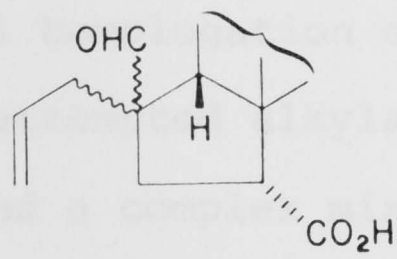
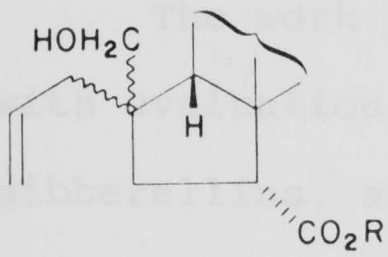


145 a-b

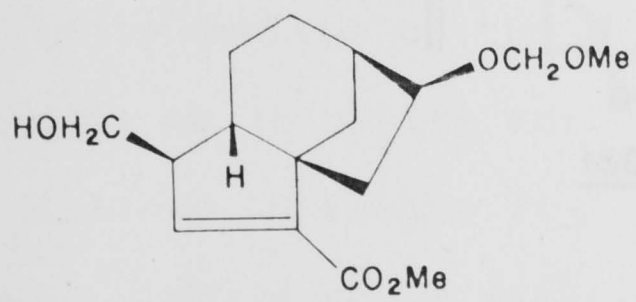


146 a-b, R = H

147 a-b, R = Me

Reagents: (a) $LiEt_3BH$; (b) CH_2N_2; (c) PDC;
(d) $K^{+-}O^tBu$, $H_2C{=}CH{-}CH_2Br$; (e) $NaBH_4$.

SCHEME 50



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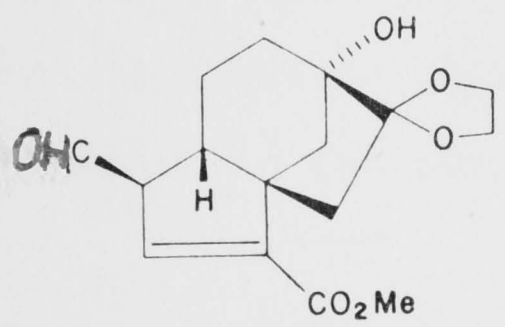

149

An alternative approach to 112 would involve an earlier formation of the α,β-unsaturated ester system, which might also improve the stereochemical control at the subsequent alkylation step. Therefore, α-selenenylation[17a] of 143 and oxidation of the intermediate selenide gave mainly 148.† This approach converges on the pathway developed by Lombardo and Mander[143] in their very recent successful homologation of a C_{19} gibberellin precursor. It was found that attempted alkylation of an analogous substrate 149 produced a complex mixture of products,[138] and studies are continuing in this area by other workers.

(iii) FUTURE DIRECTIONS

The work presented in this dissertation has been concerned with evaluation of strategies for the total synthesis of C_{20} gibberellins, and a variety of approaches has been rigorously investigated. Preliminary studies, discussed in Section (ii) of this chapter, have shown that the methanoazulene derivative 145a, a potential precursor for C_{20} gibberellins, is reasonably

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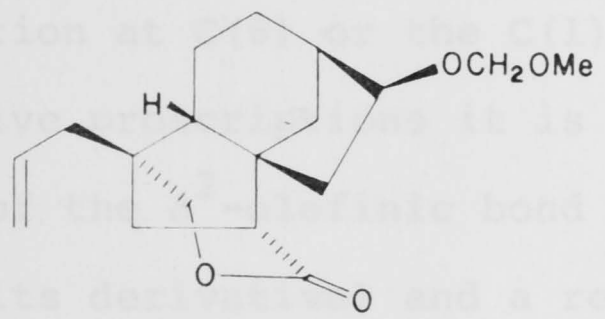
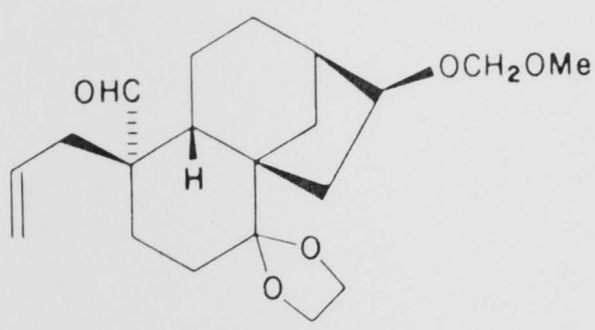
cleavage occurs via an intramolecular displacement, with subsequent opening of the lactone 150 on work-up.



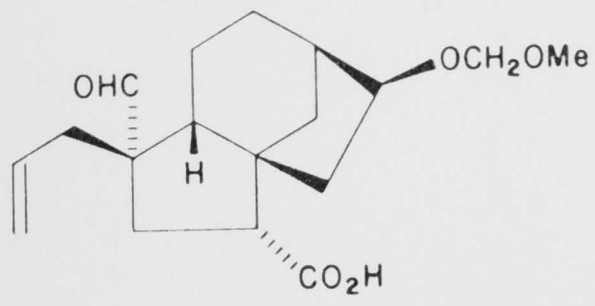
150

† This is a result of a preliminary study and it should be treated with caution. A mixture of 143 and 148 was obtained (t.l.c. and ^1H n.m.r. analysis).

accessible, and further studies for the development of this intermediate are continuing in this laboratory.



110



145a

While our initial attempts to elaborate acetal 110 were unsuccessful, it is proposed to examine alternative pathways which were postponed while the approach described in Section (ii) could be investigated. In the light of our initial results, it is clear that the angular hydroxymethyl group in 119 must be suitably protected so that it does not interfere with subsequent manipulations. It must survive the acidic conditions necessary for removal of the acetal protecting function and the basic conditions involved subsequently in the preparation of the diazoketone and α,β-unsaturated ester groups. Although not essential, it seems desirable also that it can be eventually removed without disturbing the methoxymethyl protecting function at C(6) or the C(1) allyl moiety. In view of these extensive proscriptions it is worth contemplating the reintroduction of the Δ^2-olefinic bond (i.e. as an alternative route to 78 or its derivative) and a return to the strategy outlined in Scheme 14.

While scope still exists for further efforts to be directed towards the approaches discussed in Chapter 3, it is

apparent from our studies that the strategies described in Chapter 4 are the most advanced, and accordingly, future efforts are probably best concentrated in these areas.

E X P E R I M E N T A L

GENERAL TOPICS

(i) Melting points were determined with a Reichert hot-stage apparatus. Melting points (m.p.) and boiling points (b.p.) are uncorrected.

(ii) Microanalyses were performed by the Australian National University Analytical Services Unit, Canberra.

(iii) Infrared spectra were recorded on a Jasco IRA-1 spectrophotometer in chloroform solution (1.00mm cells) unless otherwise stated.

(iv) ^1H n.m.r. spectra were recorded on a Jeol Minimar 100 spectrometer operating at 100MHz. The spectra were measured in deuterochloroform, unless otherwise stated, using tetramethylsilane (TMS) as an internal standard (δ 0.00ppm). Data are presented in the following order: chemical shift relative to TMS; multiplicity; intensity as the number of protons; coupling constant (Hz); assignment. The following abbreviations are used: S, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; exch., signal disappears on addition of D_2O; $W_{\frac{1}{2}}$ = half-width of peak; app., apparent; e, envelope; br., broad.

(v) Low resolution mass spectra were recorded on AEI 902 and V.G.-Micromass 7070F double-focussing mass spectrometers. High-resolution mass data were recorded on the AEI 902 using heptacosafluorotributylamine as a reference. Data are presented in the following order: m/z value; relative intensity as a percentage of the base peak; assignment where possible. Peaks of low mass and high intensity (e.g. m/z = 45, CH_2OMe) are not assigned as base peaks. Where possible, an accurate intensity is

presented, but when off-scale, they are represented as >100%.

(vi) Ultra-violet spectra were recorded on a Unicam S.P. 800 spectrophotometer using methanol as a solvent unless otherwise stated. Data are presented in the following order: wavelength at maximum absorption; extinction coefficient.

(vii) ^{13}C n.m.r. spectra were recorded on a Jeol FX60 spectrometer operating at 15.04 MHz. The spectra were measured in deuterochloroform solution, using tetramethylsilane (TMS) as an internal standard (δ 0.00ppm). Data are presented in the following order: chemical shift relative to TMS; assignment. ^{13}C n.m.r. assignments were based on multiplicity and correlations of chemical shifts in closely related compounds. Deuterium exchange was employed when necessary. Similar frequencies (<2ppm) may be interchanged in some cases.

(viii) Column chromatography was carried out using Merck Kieselgel 60 (70-230 mesh, 63-200μm) as the adsorbent,[139] and Merck Kieselgel 60 (40-63μm) was used for flash chromatography.[140] Lobar LiChroprep Si 60 (40-63μm) pre-packed size B Merck columns were employed for medium pressure liquid chromatography. Preparative thick layer chromatography (p.l.c.) was carried out on glass-backed plates (20 x 20cm; 0.5mm - 2mm thick) coated with Merck Kieselgel KGF_{254}. Analytical t.l.c. was performed on micro-slides coated with a layer of Merck Kieselgel KGF_{254}. The microslides were visualised using first an ultra-violet light and then by spraying with a solution of 5% (w/v) vanillin in concentrated sulphuric acid and heating at 180°. The eluant used for all of these

operations is denoted in brackets. Solvent mixtures are expressed as v/v percentages. Light petroleum refers to the fraction which boils between 40° and 60°.

(ix) Organic extracts were dried over anhydrous sodium sulphate unless otherwise indicated. After filtration the bulk of the solvent was evaporated on a Büchi rotary evaporator (water aspirator pressure), and the last traces of solvent removed under high vacuum (∿0.1mm).

(x) When anhydrous conditions were required, the glassware was flame-dried under a positive pressure of nitrogen.

(xi) Anhydrous solvents were prepared using standard procedures.[141-143] In particular, tetrahydrofuran (THF) and diethyl ether (ether) were distilled from the ketyl formed by the reaction of sodium with benzophenone. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored over 4Å sieves.[144] Dimethylformamide (DMF) was passed through a column of alumina and stored over 4Å sieves.[144]

(xii) Ethereal diazomethane was prepared from *N*-nitroso-*N*-methylurea[145,146] (small amounts) or *p*-toluenesulphonyl-methylnitrosamide (Diazald, large scale).[146,147] For the preparation of methyl esters it was used directly, and for the preparation of diazoketones it was dried over potassium hydroxide pellets (5 hr) before use.[136]

GENERAL PROCEDURE

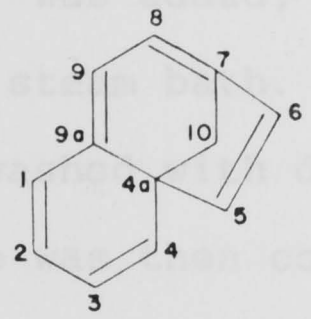
Preparation of Lithium Diisopropylamide.

A solution of *n*-butyllithium in hexane (0.65ml, 1mmol, 1.53M solution standardised according to ref. 148) was added dropwise to a solution of dry diisopropylamine[149,150] (0.14ml, 1mmol) in dry THF (2ml) at 0° under an atmosphere of nitrogen.

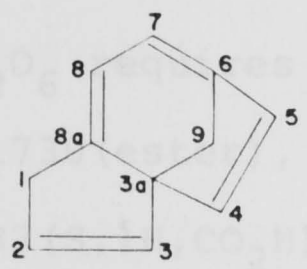
Stirring was continued at 0° for 30 min. to afford a solution of lithium diisopropylamide ready for use.

NOTES ON NOMENCLATURE

Compounds described in the Experimental have been named, where appropriate, as derivatives of the following:



4a,7-Methano-4a*H*-benzocycloheptene (Ref. 151)



1*H*-3a,6-Methanoazulene (Ref. 152)

CHAPTER 1

1-(4'-Ethoxycarbonylbutyl)-3,5-dimethoxycyclohexa-2,5-dienoic acid 33

Lithium metal (800mg, 114mg atom) was added piecewise to a stirred solution of 3,5-dimethoxybenzoic acid (9.1g, 50mmol) in liquid ammonia (500ml) at -33° under an atmosphere of nitrogen until a deep blue colour persisted. After 15 min. ethyl 4-bromobutyrate (8.6ml, 60mmol) was added dropwise. Stirring was continued for 1 hr at -33°, ammonium chloride (30g) was added, and the ammonia was removed by careful boiling on a steam bath. The residue was dissolved in water (300ml), and washed with dichloromethane (2 x 100ml). The basic aqueous phase was then cooled to 0°, saturated with sodium chloride, layered with chloroform (300ml), and acidified carefully to pH 4 with 5N hydrochloric acid. The layers were separated and the aqueous phase was re-extracted with chloroform (2 x 100ml). The extracts were successively washed with water (1 x 100ml), brine (1 x 100ml) and dried. Removal of the solvent gave acid 33 (14.6g, 98%) as a pale yellow solid. Recrystallisation from dichloromethane-light petroleum gave colourless crystals, m.p.129-130°. (Found: C, 60.21; H, 7.42. $C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43%.)

ν_{max} 1730(ester), 1700(CO_2H), 1660(HC=COMe) cm^{-1}.

δ 11.87(S,1H,CO_2H), 4.69(S,2H,2xC=CH), 4.15(q,2H,J=7Hz,$CO_2CH_2CH_3$), 3.62(S,6H,2xOMe), 2.79(S,2H,C=CCH_2C=C), 2.31(t,2H,J=7Hz, CH_2CO_2), 1.32-1.96(e,4H,CH_2CH_2), 1.26(t,3H,J=7Hz,Me).

MS 253(51%,M-CO_2H), 207(69%), 187(51%), 139(100%).

Ethyl 4-(3',5'-dimethoxybenzene)butanoate 27

Acid 33 (14.6g, 49mmol) was added portionwise to a stirred suspension of lead tetraacetate (26g, 59mmol) and copper (II) acetate (20mg) in dry benzene (150ml) under an atmosphere of nitrogen at 25°. Vigorous effervescence was immediately observed. When the bubbling had ceased, ethylene glycol was added to destroy the excess reagent. Water (200ml) and ether (200ml) were added, the layers separated, and the aqueous phase was re-extracted with ether (2 x 100ml). The organic extracts were washed with water (1 x 100ml), aqueous 10% sodium hydrogen carbonate solution (2 x 100ml), brine (1 x 100ml) and dried. Removal of the solvents gave ester 27 as a red oil. Purification by column chromatography (120g, 70-230 mesh, dichloromethane) afforded 27 (10.5g, 83% from 3,5-dimethoxybenzoic acid) as a pale yellow oil. A portion was distilled b.p.(Kugelrohr) 78°(.1mm) to provide an analytical sample. (Found: C, 66.38; H, 8.00. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.99%.)

$\nu_{max(film)}$ 1730(ester), 1605, 1600(aromatic C=C) cm^{-1}.

δ 6.38(S,2H,ArH), 4.15(q,2H,J=7Hz,$CO_2\underline{CH_2}CH_3$), 3.77(S,3H,OMe), 3.76(S,3H,OMe), 2.62(t,2H,J=7Hz,CH_2Ar), 2.34(t,2H,J=7Hz, CH_2CO_2), 1.99(app.q,J=7Hz,$\underline{CH_2}CH_2CO_2$), 1.25(t,3H,J=7Hz,Me).

MS 252(78%,M^+), 207(39%,M-OEt), 165(81%,M-CH_2CO_2Et), 164(49%), 152(100%).

Ethyl 4-(2'-formyl-3',5'-dimethoxybenzene)butanoate 34

Phosphorus oxychloride (7.3ml), 80mmol) was added dropwise to dry DMF (10ml) at 0° under an atmosphere of nitrogen. Stirring was continued at 0° for 5 min. and then the solution was allowed to warm up to room temperature. A solution of

ester 27 (10g, 40mmol) in dry DMF (15ml) was added slowly and the solution was stirred at 25° for 5 hr and at 40° for 1 hr. The reaction mixture was cooled to 0° and poured onto a mixture of crushed ice and aqueous 50% sodium acetate solution (100ml). It was then cooled at 0° for 30 min. followed by stirring at room temperature for 1 hr. Ether (200ml) was added, the layers separated, and the aqueous phase was extracted further with ether (2 x 100ml). The organic extracts were successively washed with water (3 x 100ml), aqueous 10% sodium hydrogen carbonate solution (1 x 100ml), brine (1 x 100ml) and dried. Removal of the solvent then gave the aldehyde 34 (10.14g, 91%) as a yellow oil. A portion was purified by column chromatography (5g, 70-230 mesh, 5% ethyl acetate-dichloromethane) and distilled b.p.(Kugelrohr) 74°(.2mm) to afford an analytical sample. (Found: C, 64.36; H, 7.38. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19%.)

$\nu_{max(film)}$ 1730(ester), 1675(CHO), 1600, 1570(aromatic C=C) cm^{-1}.

δ 10.45(S,1H,CHO), 6.30(S,2H,ArH), 4.11(q,2H,J=7Hz,$CO_2CH_2CH_3$), 3.82(S,6H,2xOMe), 3.00(t,2H,J=7Hz,CH_2Ar), 2.37(t,3H,J=7Hz, CH_2CO_2), 2.91(app.q,J=7Hz,$CH_2CH_2CO_2$), 1.24(t,3H,J=7Hz,Me).

MS 280(59%,M^+), 252(33%,M-CO), 207(60%,M-CO_2Et), 193(100%), 192(34%), 165(58%), 162(43%).

6,8-Dimethoxy-3,4-dihydronaphthalene-2-carboxylic acid 35

A solution of aldehyde 34 (9.8g, 35mmol) in dry THF (15ml) was added to a stirred suspension of freshly prepared sodium ethoxide (70mmol) in dry THF (100ml) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 hr, cooled to 0° and poured onto a mixture of ice-water

(100ml). The basic aqueous phase was acidified to pH 1 with 12% hydrochloric acid, saturated with sodium chloride and extracted with ethyl acetate (3 x 100ml). The organic extracts were washed with brine (1 x 100ml), dried and removal of the solvents gave a mixture of ester 36 and acid 35 as a black gum (9.1g). Ethanol (100ml) and a solution of sodium hydroxide (16g, 0.4mmol) in water (150ml) were added, and the mixture was stirred for 1 hr at room temperature. The ethanol was removed carefully under reduced pressure and the residue was dissolved in water and washed with dichloromethane (2 x 50ml). The aqueous phase was cooled to 0°, acidified slowly to pH 1 with 5N hydrochloric acid, and the resulting brown precipitate collected to give acid 35 (8.0g, 98%). A sample was recrystallised from dichloromethane-light petroleum as a pale yellow solid m.p.310-314°(dec.). (Accurate mass: Found 234.0896. $C_{13}H_{14}O_4$ requires 234.0892.)

ν_{max} 1695(CO_2H), 1605(C=C), 1580(aromatic C=C) cm^{-1}.

$\delta_{CDCl_3/DMSO}$† 7.86(S,1H,CH=C), 6.33(S,2H,ArH), 3.83(S,6H,2xOMe), 2.65-1.98(m,4H).

MS 234(100%,M^+), 233(14%), 189(75%,M-CO_2H), 174(16%), 158(12%).

36: δ 7.85(S,1H,CH=C), 6.29(S,2H,ArH), 4.25(q,2H,J=7Hz, $CO_2CH_2CH_3$), 3.79(S,3H,OMe), 3.77(S,3H,OMe), 2.93-2.43 (M,4H), 1.32(t,3H,J=7Hz,Me).

Methyl 6,8-dimethoxy-3,4-dihydronaphthalene-2-carboxylate 37

Anhydrous potassium carbonate (6.9g, 70mmol) was added to a stirred suspension/solution of crude acid 35 (8.2g, 35mmol)

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† This spectrum was recorded on a Jeol JNM-PMX60 spectrometer operating at 60MHz.

in dry DMF (50ml) under a nitrogen atmosphere at room temperature. Methyl iodide (5.47ml, 87.5mmol) was added and the reaction mixture was stirred for 20 hr. The reaction mixture was poured slowly onto a mixture of ice-water (100ml) and ethyl acetate (100ml) at 0°. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 75ml). The organic extracts were successively washed with water (2 x 100ml), brine (1 x 75ml) and dried. Removal of the solvents gave ester 37 (8.3g) as a black oil. Purification by column chromatography (90g, 70-230 mesh), dichloromethane-light petroleum 1:1) gave 37 (5.6g, 64%) as a pale yellow solid. A portion was recrystallised as granular colourless crystals from acetone to afford an analytical sample, m.p.88-89°. (Found: C, 67.56; H, 6.46. $C_{14}H_{16}O_4$ requires C, 67.76; H, 6.50%.)

ν_{max} 1705(CO_2Me), 1610(C=C), 1580(aromatic C=C) cm^{-1}.

δ 7.80(S,1H,CH=C), 6.25(S,2H,ArH), 3.77(S,3H,OMe), 3.75(S,3H, OMe), 3.74(S,3H,CO_2Me), 2.90-2.41(m,4H).

MS 248(100%,M^+), 217(27%,M-OMe), 189(66%,M-59).

6,8-Dimethoxy-3,4-dihydronaphthalene-2-carboxylic acid 35

A suspension of ester 37 (10.7g, 43mmol) in methanol (30ml) was added to a solution of sodium hydroxide (10.5g, 0.26mol) in water (30ml). The mixture was heated under reflux for 1 hr, cooled to 0° and acidified to pH 1 with 5N hydrochloric acid. The resulting precipitate was collected to afford acid 35 (9.75g, 97%) as a pale yellow solid which was identical (i.r., ^1H n.m.r.) to the previously prepared material.

6,8-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid 24

Liquid ammonia (300ml) was added to a suspension of acid 35 (9.75g, 42mmol) in dry THF (150ml) and anhydrous *tert*-butanol (19.7ml, 0.21mol) under a nitrogen atmosphere . Sodium metal (2.9g, 0.13g atom) was added portionwise. The reaction mixture was stirred for 45 minutes at -33°, ammonium chloride (22g) added and the ammonia removed by careful heating on a steam bath. The residue was poured onto a mixture of crushed ice and concentrated hydrochloric acid (100ml). Water (250ml) and ethyl acetate (300ml) were added and the layers separated. Further extraction (ethyl acetate 2 x 200ml), sequential washing of the extracts (brine 2 x 200ml), drying and solvent removal left acid 24 as a black gum. Purification by column chromatography (75g, 70-230 mesh, 10% ether-benzene) gave acid 24 (9.5g, 97%), which was identical (i.r., ^{1}H n.m.r.) with the product in the literature. Recrystallisation of a sample from dichloromethane-light petroleum gave colourless crystals, m.p. 131.5-133° (sweats from 125°). An authentic sample afforded the identical melting point.[153] An analogous Birch reduction of the crude acid 35 and purification by column chromatography as above afforded acid 24 in 64% overall yield from ester 27.

2-Diazo-1-(6,8-dimethoxy-1,2'3'4'-tetrahydro-1-naphthalenyl)-ethanone 25

A solution of acid 24 (4.7g, 20mmol) in dry dichloromethane (30ml) was added dropwise to a stirred solution of oxalyl chloride (5.4ml, 60mmol) in dry dichloromethane (15ml) at 25° under a nitrogen atmosphere. The mixture was stirred for 45 min.

and then heated under reflux for 1 hr. The volatiles were evaporated, and the residual oxalyl chloride was removed by the addition of dry benzene (3 x 30ml) to the residue, and then separate re-evaporation to give the acid chloride (5.0g, 100%) as a colourless solid with some green impurity. The hydrogen chloride was then removed under high vacuum (∿0.2mm, 15 min).

The crude acid chloride (5.0g, 20mmol) in dry benzene (75ml) was added dropwise to a stirred dried solution of ethereal diazomethane at -30° (prepared from Diazald (21.5g, 100mmol)).[147] The reaction mixture was allowed to warm up slowly and stirred overnight. The filtered solution (celite) was concentrated *in vacuo*, and the residue purified by column chromatography (40g, 70-230 mesh, 12½% ether-dichloromethane) to afford diazoketone 25 (4.6g, 88%, 83% pure by ^{1}H n.m.r.) which was identical (i.r., ^{1}H n.m.r.) with the product in the literature.[154] Recrystallisation from dichloromethane-ether gave yellow crystals, m.p. 94-95° dec.(lit.84-85° dec.).[154]

4-Methoxy-8,9-dihydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(5*H*,7*H*)-dione 23

A solution of diazoketone 25 (4.6g, 17.7mmol) in dry dichloromethane (50ml) was added dropwise with rapid stirring to a mixture of trifluoroacetic acid (120ml) and dry dichloromethane (60ml) at -25° under a nitrogen atmosphere. When the addition was complete, a mixture of ice and water (500ml) and dichloromethane (300ml) was added. The layers were separated and the aqueous phase was re-extracted with dichloromethane (2 x 200ml). Sequential washing of the organic

extracts (aqueous 10% sodium hydrogen carbonate solution 2 x 150ml, brine 1 x 150ml), drying, solvent removal and trituration with ether gave tricyclic dienone 23 (3.1g, 71% from acid 24) as a pale yellow solid. A sample was recrystallised from acetone as pale yellow rhombohedral crystals, m.p. 184.5-185.5° (lit. 181-182°).[155] This product was identical (i.r., ^{1}H n.m.r.) with the product in the literature.[155]

δ 216.0, C(6); 186.9, C(2); 174.3, C(4); 158.4, C(9a); 123.0, C(1); 103.1, C(3); 56.0, OMe; 47.9, C(4a); 47.1 (C(5); 46.6, C(7); 41.4, C(10); 29.4, C(9); 28.4, C(8).

CHAPTER 2

(4aα,7α)-4-Methoxy-hexahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,3*H*)-diones 44

Dienone 23 (109mg, 0.5mmol) in ethyl acetate (10ml) was hydrogenated at atmospheric pressure at 25° for 4 hr over 5% palladium on carbon (11mg). The filtered solution (celite) was concentrated *in vacuo* to give 44 (106mg, 96%) as a colourless solid which was comprised of 4 diastereomers (^{13}C n.m.r. analysis). Recrystallisation from ether-light petroleum gave colourless crystals, m.p.87-97°. (Found: C, 70.22; H, 8.07. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%.)

ν_{max} 1740 (cyclopentanone), 1720(C=O) cm^{-1}.

δ 3.34,3.32(2xS,3H,OMe), 3.22-1.18(m,15H).

MS 222(100%,M^+), 207(10%,M-Me), 190(40%,M-MeOH), 180(58%), 163(23%), 149(45%), 148(88%), 122(45%), 121(44%), 120 (36%), 107(44%), 106(40%), 105(39%), 93(55%), 91(50%), 79(76%).

42 and 43

Dienone 23 (109mg, 0.5mmol) in ethyl acetate (10ml) was hydrogenated at atmospheric pressure at 25° for 4 hr using 10% palladium on calcium carbonate (11mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* to afford a pale yellow solid (110mg, 100%). This residue was comprised (^{1}H n.m.r. analysis) of a mixture of diastereomers 42 and 43 (85%) and the saturated ketone (15%). Separation by t.l.c.

(30% ethyl acetate-dichloromethane) afforded a 4:6 mixture (^{13}C n.m.r. analysis) of diastereomers (R_f~0.3, 83mg, 75%). (Both 42 and 43 have been individually prepared and characterised.)

(4aα,6β,7α)-6-Hydroxy-4-methoxy-6,7,8,9-tetrahydro-4a,7-methano-4a*H*-benzocyclohepten-2(5*H*)-one 45

Sodium borohydride (114mg, 3mmol) was added to a solution of dienone 23 (654mg, 3mmol) in ethanol (75ml) at 0° under a nitrogen atmosphere. Stirring was continued for 1 hr at 0°. The ethanol was evaporated carefully under reduced pressure and the residue partitioned between water (50ml) and ethyl acetate (50ml). The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 50ml). Sequential washing of the organic extracts (water 1 x 50ml), brine 1 x 50ml) drying and removal of the solvent gave alcohol 45 (633mg, 96%). A portion was recrystallised from acetone-light petroleum as colourless needles, m.p.202-204°. Found: C, 70.71; H, 7.33. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%.)

ν_{max} 3390(OH), 1655(C=O), 1610(C=C), 1595(C=COMe) cm^{-1}.

δ 5.93(S,1H,CH=C), 5.58(d,1H,J=1.5Hz,CH COMe), 4.72(m,1H, $W_{\frac{1}{2}}$=14Hz,CHOH), 3.71(S,3H,OMe), 3.58(S,1H,exch.,OH), 3.05-2.10(m,6H), 1.85-1.38(m,3H).

MS 220(91%,M^+), 202(24%,M-H_2O), 174(100%).

λ_{max} 250(12,400), 211(8,600) nm.

δ 188.7, C(2); 177.1, C(4); 164.3, C(9a); 120.9, C(1); 102.9, C(3); 74.0, C(6); 56.1, OMe; 50.5, C(4a); 43.6*, C(5); 43.0*, C(10); 41.0, C(7); 29.7, C(9); 28.2, C(8).

* may be interchanged.

38, 46 and 47

Dienone 45 (660mg, 3mmol) in ethyl acetate (25ml) was hydrogenated at atmospheric pressure at 25° for 1 hr using 10% palladium on calcium carbonate (66mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* to afford a mixture of the diastereomers 38 and 46, and the saturated alcohol 47. These were separated using medium pressure liquid chromatography (50% ethyl acetate-dichloromethane) to give, in order of increasing retention, 47 (72mg, 11%), 38 (164mg, 25%) and 46 (370mg, 56%).

47: (4aα,6β,7α,9aβ)-6-Hydroxy-4-methoxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-ones

Recrystallisation from ether-light petroleum gave a colourless solid, m.p.52-54°, which was comprised of virtually one diastereomer (∿90%, ^{13}C n.m.r. analysis). (Found: C, 69.55; H, 8.95. $C_{13}H_{20}O_3$ requires C,69.61; H, 8.99%.)

ν_{max} 3420(OH), 1700(C=O) cm^{-1}.

δ 4.45(m,1H,W½=13Hz,CHOH), 3.35(S,3H,OMe), 3.13(dd,1H,J=5Hz, J=10Hz,CHOMe), 2.94-1.12(m,15H).

MS 224(100%,M^+), 206(17%,M-H_2O), 192(22%,M-MeOH), 174(25%), 135(99%)

38: (4aα,6β,7α,9aβ)-6-Hydroxy-4-methoxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one

Recrystallisation from ether gave a colourless solid, m.p.162-163°. (Found: C, 70.10; H, 8.07 . $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%).

ν_{max} 3390(OH), 1630(C=O), 1585(C=C) cm^{-1}.

δ 5.30(S,1H,CH=C), 4.47(m,1H,W½=13Hz,CHOH), 3.91(br.S,1H,exch., OH), 3.71(S,3H,OMe), 2.93(dd,1H,J=10Hz,J=14Hz,H5α), 2.68-1.12(m,11H).

MS 222(100%,M^+), 204(11%,M-H_2O), 125(29%), 124(20%).

λ_{max}† 252(12,700) nm.

δ 199.9, C(2); 181.9, C(4); 102.1, C(3); 72.6, C(6); 56.1, OMe; 47.4, C(4a); 40.6, C(1); 40.0, C(9a); 39.7, C(5) and C(7); 36.2, C(10); 24.2, C(9); 22.6, C(8).

46: (4aα,6β,7α,9aα)-6-Hydroxy-4-methoxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one

A portion was recrystallised from ether-pentane as a colourless solid, m.p.95.5-96.5°. (Found: C, 70.37; H, 8.01. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%.)

ν_{max} 3420(OH), 1640(C=O), 1590(C=C) cm^{-1}.

δ 5.46(S,1H,CH=C), 4.45(m,1H,W½=13Hz,CHOH), 3.91(br.S,1H,exch., OH), 3.69(S,3H,OMe), 2.44-1.24(m,12H).

MS 222(100%,M^+), 125(24%), 124(18%).

λ_{max} 253(13,600) nm.

δ 199.1, C(2); 180.5, C(4); 102.2, C(3); 73.2, C(6); 56.0, OMe; 47.0, C(4a); 41.2, C(9a); 40.9, C(1); 40.0, C(7); 39.0, C(10); 37.5, C(5); 26.5, C(8); 25.7, C(9).

38 and 46

Dienone 45 (110mg, 0.5mmol) in chloroform (8ml) was hydrogenated at atmospheric pressure at 25° for 2 hr over 10% palladium on calcium carbonate (11mg). The filtered solution

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† This spectrum was recorded using ethanol as a solvent.

(celite) was concentrated *in vacuo* to give a mixture of epimers 38 and 46 and some starting dienone 45. The above process was repeated twice and the residue was separated as above by medium pressure liquid chromatography to afford 38 (55mg, 50%), which was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

(4aα,7α,9aβ)-4-Methoxy-7,8,9,9a-tetrahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,5*H*)-dione 42

A solution of Jones reagent in acetone was added to a solution of alcohol 38 (110mg, 0.5mmol) in acetone (10ml) at 0° until an orange colour persisted for 5 min. The excess reagent was then quenched by the addition of isopropanol. Water (10ml) was added and the acetone was carefully removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 25ml),and the extracts were washed with brine (2 x 15ml) and dried. Removal of the solvent and purification of the product by preparative t.l.c. (R_f∿0.1, ether) afforded 42 (73mg, 66%) as a colourless solid. Recrystallisation from ether gave colourless crystals, m.p.152-154°. (Found: C, 70.79; H, 7.30. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%.)

ν_{max} 1740(cyclopentanone), 1640(C=O), 1595(C=C) cm^{-1}.

δ 5.42(S,1H,CH=C), 3.74(S,3H,OMe), 2.97(d,1H,J=18Hz,H5α), 2.94-1.43(m,12H).

MS 220(100%,M^+), 138(70%), 125(29%).

λ_{max} 250(12,400), 211(8,600) nm.

δ 218.3, C(6); 198.2, C(2); 179.1, C(4); 102.5, C(3); 56.4, OMe; 46.4, C(7); 45.8, C(4a) and C(5); 40.0, C(1); 38.3, C(9a); 35.5, C(10); 26.5, C(8); 24.2, C(9).

(4aα,7α,9aα)-4-Methoxy-7,8,9,9a-tetrahydro-4a7-methano-4a*H*-benzocycloheptene-2,6(1*H*,5*H*)-dione 43

Alcohol 46 (222mg, 1mmol) was oxidised using the same procedure employed for the preparation of 42. The product was purified by column chromatography (10g, 70-230 mesh, 10% ethyl acetate-dichloromethane) to give 43 (160mg, 73%) as a colourless solid. A portion was recrystallised from ether to afford an analytical sample, m.p. 133-135°. (Found: C, 70.72; H, 7.47. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%.)

ν_{max} 1740(cyclopentanone), 1640(C=O), 1595(C=C) cm^{-1}.

δ 5.40(S,1H,CH=C), 3.76(S,3H,OMe), 2.79-1.17(m,12H).

MS 220(100%,M^+), 138(100%), 125(39%).

λ_{max} 249(15,400) nm.

δ 217.4, C(6); 197.3, C(2); 177.8, C(4); 102.9, C(3); 56.2, OMe; 46.5, C(7); 44.9, C(4a); 42.5, C(5); 40.8, C(1); 40.1, C(9a); 37.8, C(10); 29.1, C(8); 25.7, C(9).

(4aα,6β,7α)-4-Methoxy-6-methoxymethyloxy-6,7,8,9-tetrahydro-4a,7-methano-4a*H*-benzocyclohepten-2(5*H*)-one 48

Chloromethyl methyl ether (0.34ml, 4.5mmol) was added dropwise to a solution of alcohol 45 (660mg, 3mmol) and diisopropylethylamine (1.30ml, 7.5mmol) in dry dichloromethane (20ml) at 0° under a nitrogen atmosphere. After 1 hr at 0°, stirring was continued at 25° for 16 hr. The solution was cooled to 0°, and ice-water (30ml), and dichloromethane (20ml) were added. The layers were separated, and the aqueous phase was re-extracted with dichloromethane (2 x 25ml). The organic extracts were washed with 6% hydrochloric acid (1 x 20ml), aqueous 10% sodium hydrogen carbonate (1 x 20ml), brine

1 x 20ml) and dried. The solvent was removed and the product purified by column chromatography (20g, 70-230 mesh, 15% ethyl acetate-dichloromethane) to give 48 (649mg, 82%), of a colourless oil. A portion was distilled to afford an analytical sample, b.p.(Kugelrohr) 80°(.15mm). (Found: C, 68.22; H, 7.51. $C_{15}H_{20}O_4$ requires C,68.16; H, 7.63%.)

ν_{max} 1655(C=O), 1605(C=C), 1595(C=COMe) cm^{-1}.

δ 5.89(br.S,1H,CH=C), 5.54(d,1H,J=1.5Hz,CH=COMe), 4.67(S,2H, OCH_2O), 4.50(m,1H,$W_{\frac{1}{2}}$=14Hz,CHOCH_2O), 3.72(S,3H,C=COMe), 3.38(S,3H,OMe), 2.96-2.06(m,6H), 1.84-1.40(m,3H).

MS 264(100%,M^+), 232(25%, M-MeOH), 205(27%), 195(33%), 175(26%), 174(24%), 15(125%).

λ_{max} 273(sh.,6,000), 244(18,000), 208(5,900) nm.

δ 188.0, C(2); 176.3, C(4); 163.3, C(9a); 120.7, C(1); 102.5, C(3); 96.3, OCH_2O; 78.6, C(6); 55.6, 2 x OMe; 49.5, C(4a); 42.6, C(4); 40.4, C(5); 39.0, C(7); 29.2, C(9); 28.2, C(8).

49 and 50

Dienone 48 (264mg, 1mmol) in ethyl acetate (20ml) was hydrogenated at atmospheric pressure at 25° for 3 hr using 10% palladium on calcium carbonate (27mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* and the residue purified by column chromatography (8g, 70-230 mesh, 15% ethyl acetate-dichloromethane) to afford a 1:3 mixture (^{13}C n.m.r. analysis) of diastereomers 49 and 50 (242mg, 91%), which were identical (t.l.c., i.r., ^1H n.m.r.) to authentic samples.

(4aα,6β,7α,9aβ)-4-Methoxy-6-methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 49

Chloromethyl methyl ether (0.57ml, 7.5mmol) was added dropwise to a solution of alcohol 38 (91.1g, 5mmol) and diisopropylethylamine (2.18ml, 12.5mmol) in dry dichloromethane (30ml) at 0° under a nitrogen atmosphere. After 1 hr at 0°, stirring was continued at 25° for 15 hr. The solution was cooled to 0° and ice-water (30ml) and ether (60ml) were added. The layers were separated and the aqueous phase was re-extracted with ether (2 x 30ml). The organic extracts were washed with 6% hydrochloric acid (1 x 30ml), 10% aqueous sodium hydrogen carbonate (1 x 30ml), brine (1 x 30ml) and dried. The solvent was evaporated and the product purified by flash chromatography (30g, 10% ether-dichloromethane), to give 49 (1.1g, 81%) as a colourless oil. Recrystallisation from ether-light petroleum gave colourless crystals, m.p.66-67°. A portion was distilled, b.p.(Kugelrohr), 65°(0.3mm), to afford an analytical sample. (Found: C, 67.55; H, 8.11. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.33%.)

ν_{max} 1640(C=O), 1595(C=C) cm^{-1}.

δ 5.31(S,1H,CH=C), 4.65(S,2H,OCH_2O), 4.31(m,1H,$W_{½}$=13Hz,C$\underline{H}$$OCH_2O$), 3.66(S,3H,C=COMe), 3.37(S,3H,OMe), 2.92(dd,1H,J=11Hz, J=15Hz,H5α), 2.65-2.01(m,5H), 1.87-1.18(m,6H).

MS 266(100%,M^+), 238(49%), 237(57%), 222(26%), 179(52%), 45(56%).

λ_{max} 253(14,500) nm.

δ 199.5, C(2); 181.5, C(4); 102.1, C(3); 96.3, OCH_2O; 77.6, C(6); 56.0, C=CO$\underline{C}$$H_3$; 55.5, OMe; 46.9, C(4a); 40.7, C(1); 40.0, C(9a); 38.2, C(7); 37.4, C(5); 35.9, C(10); 24.2, C(9); 23.1, C(8).

(4aα,6β,7α,9aα)-4-Methoxy-6-methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 50

Methoxyenone 50 was prepared from alcohol 46 (444mg, 2mmol) using the same procedure employed for the synthesis of 49. Purification by column chromatography (10g, 70-230 mesh, 15% ethyl acetate-dichloromethane) gave 50 (400mg, 76%) as a colourless oil. A portion was distilled, b.p.(Kugelrohr) 78°(.15mm) to afford an analytical sample. (Found: C,67.58; H, 8.29. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.33%).

ν_{max} 1640(C=O), 1595(C=C) cm^{-1}.

δ 5.32(S,1H,CH=C), 4.65(S,2H,OCH_2O), 4.32(m,1H,W½=14Hz, $CHOCH_2O$), 3.69(S,3H,C=C-OMe), 3.40(S,3H,OMe), 2.56-1.18(m,12H).

λ_{max} 253(17,000) nm.

MS 266(100%), 238(43%), 237(41%), 179(36%), 45(73%).

δ 199.0, C(2); 180.2, C(4); 102.3, C(3); 96.0, OCH_2O; 78.0, C(6); 56.0, C=CO$\underline{C}H_3$; 55.5, OMe; 46.4, C(4a); 41.1, C(9a); 40.8, C(1); 38.5*,C(7) ; 38.2*, C(10); 35.2, C(5); 26.2**, C(8); 26.0**, C(9).

*,** may be interchanged

(4aα,6β,7α,9aα)-4-Methoxy-6-methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 50

Lithium metal (74mg, 10.5mg atom) was added piecewise to a solution of dienone 48 (1.32g, 5mmol) and *tert*-butanol in dry THF (10ml) and anhydrous liquid ammonia (100ml, dried with sodium and a catalytic amount of ferric (III) chloride) at -78° under a nitrogen atmosphere. Pentadiene was added after 5 min. (the blue colour disappeared on the addition of the diene).

Ammonium chloride (1.0g, 20mmol) was then added and the ammonia removed under a stream of nitrogen. The residue was partitioned between water (50ml) and ethyl acetate (100ml), the layers were separated and the aqueous phase was extracted further with ethyl acetate (2 x 50ml). The organic extracts were washed with brine (2 x 50ml) and dried. Removal of the solvents afforded a mixture of compounds which were separated by medium pressure liquid chromatography (35% ethyl acetate-dichloromethane) to give, in order of increasing retention 53 (93mg, 7%), 50 (971mg, 73%) and 48 (133mg, 10%). Both 48 and 50 were identical (t.l.c., i.r., ^{1}H n.m.r.) with previously prepared authentic samples.

53: (4aα,6β,7α,9aα)-4-Methoxy-6-methylmethyloxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-ones

Distillation afforded a colourless oil, b.p.(Kugelrohr) 78°(.15mm). (Accurate Mass: Found 268.1670. $C_{15}H_{24}O_4$ requires 268.1674.)

ν_{max} 1700 cm^{-1}.

δ 4.65(S,2H,OCH_2O), 4.29(m,1H,W½=15Hz,C<u>H</u>OCH_2O), 3.74(m,1H, W½=13Hz,C<u>H</u>OMe), 3.40(S,3H,$OCH_2OC\underline{H}_3$), 3.37(S,3H,OMe), 3.10(m,1H,W½=11Hz,H5α), 2.86-0.98(m,13H).

MS 268(41%,M^+), 236(58%), 207(27%), 206(76%), 176(100%), 168 (42%), 145(32%), 105(43%), 93(41%), 91(46%), 79(48%), 45(>100%).

(4aα,6β,7α)-6-methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one

A solution of lithium triethylborohydride in THF (0.35ml, 0.35mmol) was added dropwise to a solution of dienone 48

(53mg, 0.2mmol) in dry THF (3.5ml) at 0° under an atmosphere of nitrogen. Stirring was continued for 1 hr at 0°. A 2% aqueous solution of disodium hydrogen phosphate (pH∿9.1, 1ml) and 30% hydrogen peroxide (0.5ml) were added and the mixture was stirred overnight at 25°. Ice-water (10ml) was added, and the mixture was extracted with ethyl acetate (3 x 10ml). The organic extracts were washed with water (1 x 10ml), brine (1 x 10ml) and dried. Removal of the solvents and purification of the residue by preparative t.l.c. (20% ethyl acetate-dichloromethane) gave a small amount of enone (R_f∿0.4, 9mg, 20%). This compound was identical (t.l.c., i.r., ^{1}H n.m.r.) with an authentic sample of 81, but the small amount of material did not permit the stereochemistry of the B,C-ring junction to be determined.

(4aα,6β,7α,9aβ)-6-Hydroxy-4-methoxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 38

A solution of lithium aluminium hydride in ether (1ml, 4.4mmol) was added to dry THF (50ml) at 0° under an atmosphere of nitrogen. A solution of dienone 23 (880mg, 4mmol) in dry THF (36ml) was slowly added to the stirred solution. Stirring was continued at 0° for 1 hr and acetone (∿5ml) was added to quench the excess reagent. A saturated aqueous solution of sodium sulphate (∿1ml) was added, and the mixture was stirred until the aluminium salts had precipitated. Ethyl acetate (150ml) was added and the mixture dried. The filtered solution (celite) was concentrated *in vacuo* to afford a mixture of the diastereomers 38 and 46, and enone 56. These were separated using medium pressure liquid chromatography (50% ethyl acetate-

dichloromethane) to give, in order of increasing retention, 56 (136mg, 18%), 38 (439mg, 49%) and 46 (195mg, 21%).

56: (4aα,6β,7α)-6-Hydroxy-4,5,6,7,8,9-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(3*H*)-one

Distillation afforded a colourless oil, b.p.(Kugelrohr) 70°(.15mm). (Accurate mass: Found 192.1149. $C_{12}H_{16}O_2$ requires 192.1150.)

ν_{max} 3440(OH), 1665(C=O), 1625(C=C) cm^{-1}.

δ 5.73(S,1H,CH=C), 4.61(m,1H,$W_{\frac{1}{2}}$=13Hz,CHOH), 3.10-1.38(m,14H).

MS 192(17%,M^+), 174(100%,M-H_2O), 146(72%), 132(28%), 118(46%), 117(26%), 104(35%), 91(30%).

λ_{max} 243(15,000) nm.

(4aα,6β,7α)-6-Methoxymethyloxy-4,5,6,7,8,9-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(3*H*)-one 57

Chloromethyl methyl ether (0.15ml, 2mmol) was added dropwise to a solution of alcohol 56 (192mg, 1mmol) and diisopropylethylamine (3mmol) in dry dichloromethane (10ml) at 0° under an atmosphere of nitrogen. After 1 hr at 0°, stirring was continued at 25° for 12 hr. The solution was cooled to 0°, and ice-water (20ml) added. Ether (30ml) was added and the layers were separated. The aqueous phase was re-extracted with ether (2 x 20ml), and the organic extracts were washed with 6% aqueous hydrochloric acid (1 x 20ml), 10% aqueous sodium hydrogen carbonate (1 x 20ml), brine (1 x 20ml) and dried. The solvent was removed and the product purified by column chromatography (10g, 70-230 mesh, 5% ether-dichloromethane) to give 57 (191mg, 81%) as a colourless oil. A portion was

distilled to afford an analytical sample, b.p.(Kugelrohr) 60°(.25mm). (Found: C, 71.16; H, 8.30. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%.)

ν_{max} 1660(C=O), 1620(C=C) cm^{-1}.

δ 5.72(S,1H,CH=C), 4.65(S,2H,OCH_2O),4.41(m,1H,$W_{\frac{1}{2}}$=12Hz,C<u>H</u>OCH_2O), 3.39(S,3H,OMe), 3.04-1.36(m,13H).

MS 236(100%,M^+), 191(25%, M-CH_2OMe), 45(120%),

λ_{max} 242(17,600) nm.

<u>49 and 50</u>

Dienone <u>48</u> (53mg, 0.2mmol) in THF (4ml) was treated with lithium aluminium hydride (0.22mmol) using the same procedure employed for the preparation of <u>38</u>. Removal of the solvents afforded a mixture of products. Separation by preparative t.l.c. (ether) gave: <u>57</u> (R_f~0.3, 9mg, 19%) which was identical (t.l.c., i.r., ^{1}H n.m.r.) to a previously prepared authentic sample; and a 5.5:4.5 mixture (^{13}C n.m.r. analysis) of diastereomers <u>49</u> and <u>50</u> (R_f~0.2, 35mg, 66%), which were also identical (t.l.c., ^{1}H and ^{13}C n.m.r.) to previously prepared authentic samples.

<u>40 and 41</u>

Dienone <u>39</u>[156] (380mg, 2mmol) in ethyl acetate (20ml) was hydrogenated at atmospheric pressure at 25° for 1 hr using 5% palladium on carbon (38mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* and the epimers were separated using medium pressure liquid chromatography

(40% ether-dichloromethane) to give, in order of increasing retention, 40 (202mg, 52%), and 41 (163mg, 42%).

40: (4aα,6β,7α,9aβ)-6-Hydroxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one

Recrystallisation from ether-light petroleum gave colourless crystals, m.p.92-93° (lit.92-93°).[62] This product was identical (i.r., ^{1}H n.m.r.) to an authentic sample.[62]

δ 212.1, C(2); 73.0, C(6); 45.8, C(5); 44.3†,C(1); 43.1, C(9a); 42.3, C(4a); 40.0, C(7); 39.1†,C(3); 37.4, C(4); 34.7, C(10); 25.5, C(9); 22.2, C(8).

†Peak absent after NaOD/D_2O/Dioxan exchange.

41: (4aα,6β,7α,9aα)-6-Hydroxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one

Recrystallisation from ether-light petroleum gave colourless needles, m.p.72-73°. (Found: C, 74.16; H, 9.41. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%.)

$\nu_{max(nujol)}$ 1700(C=O) cm^{-1}.

δ 4.60(m,1H,$W_{½}$=13Hz, CHOH), 2.41(S,1H,exch.,OH), 2.51-1.18 (m,16H).

MS 194(100%,M^+), 176(24%, M-H_2O), 165(18%), 150(17%), 147(17%), 134(24%), 124(39%).

δ 211.8, C(2); 73.9, C(6); 45.2†,C(1); 44.7, C(9a); 43.8, C(10); 42.4, C(4a); 39.8†,C(3); 39.4*,C(5) ; 38.9*, C(7); 38.3, C(4); 28.2, C(9); 25.6, C(8).

*may be interchanged

†Peak absent after NaOD/D_2O/Dioxan exchange.

Dienone 39[156] (380mg, 2mmol) in ethyl acetate was hydrogenated at atmospheric pressure at 25° for 2½ hr over palladium on calcium carbonate (38mg). The filtered solution (celite) was concentrated *in vacuo* and the epimers were separated as above to give 40 (163mg, 42%) and 41 (209mg, 54%).

Dienone 39[156] (228mg, 1.2mmol) in chloroform (15ml) was hydrogenated at atmospheric pressure at 25° for 2 hr over 5% palladium on carbon (23mg). The filtered solution (celite) was concentrated *in vacuo* to give epimers 40 and 41, and some starting material or enone 56. The above process was repeated twice and the epimers were separated as above to afford 40 (147mg, 63%) and 41 (35mg, 15%).

(4aα,6β,7α,9aβ)-6-Methoxymethyloxy-2-trimethylsilyloxy-octahydro-4a,7-methano-4a*H*-benzocyclohept-2-ene 59 and (4aα,6β,7α,9aβ)-6-methoxymethyloxy-2-trimethylsilyloxy-octahydro-4a,7-methano-4a*H*-benzocyclohept-1-ene 60

A solution of ketone 58 (95mg, 0.4mmol) in dry THF (2.5ml) was added dropwise to a solution of lithium diisopropylamide (1.2mmol) in dry THF (2ml) at -78° under a nitrogen atmosphere. Stirring was continued for 1 hr at -78° and trimethylsilyl chloride (0.2ml, 1.6mmol) was added slowly dropwise. The solution was stirred for a further 30 min. at -78°, and the volatiles were removed. Dry *n*-pentane (3 x 20ml) was added to the residue, and the filtered solution (celite) was concentrated *in vacuo* to give a 2:1 mixture (^{13}C n.m.r. analysis) of isomers 59 and 60 as a colourless oil (119mg, 96%). (Accurate mass: Found 310.1964. $C_{17}H_{30}O_3Si$

requires 310.1964.)

ν_{max} 1660,1620(C=C-OSiMe$_3$) cm^{-1}.

δ 4.78(m,1H,CH=C), 4.62(S,2H,OCH$_2$O), 4.21(m,1H,CHOCH$_2$O),
3.38(S,3H,OMe), 2.34-0.82(m,14H), 0.26-0.02(m,9H,SiMe$_3$).

MS 310(100%,M^+), 265(82%), 73(44%).

δ 103.5(Me$_3$SiO-C=C-CH$_2$), 110.5(Me$_3$SiO-C=C-CH).

(4aα,6β,7α,9aβ)-6-Hydroxy-4-methoxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-ones 47

Methoxyenone 38 (67mg, 0.3mmol) in ethyl acetate (10ml) was hydrogenated at atmospheric pressure at 25° for 1 hr using 5% palladium on carbon (7mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* to give ketone 47 (63mg, 100%) as a colourless solid. The product was identical (t.l.c., i.r., ^{1}H n.m.r.) to a previously prepared authentic sample.

(4aα,6β,7α,9aβ)-6-Hydroxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 63

Trifluoroacetic acid (1ml) was added to a solution of ketone 47 (67mg, 0.3mmol) in dry dichloromethane (4ml) under an atmosphere of nitrogen. Stirring was continued at room temperature for 10 hr. The solution was cooled to 0°, and a 10% aqueous solution of sodium hydrogen carbonate was added until the mixture was alkaline. Ethyl acetate (15ml) was added and the layers were separated. The aqueous phase was re-extracted with ethyl acetate (2 x 10ml) and the organic extracts were washed with brine (1 x 10ml), and dried.

Removal of the solvent gave a mixture of 63 and its trifluoroacetate ester.

ν_{max} 1775(F_3CCO_2), 1680(C=O) cm^{-1}.

10% aqueous sodium bicarbonate (2ml) was added to a solution of the mixture in THF (5ml). Stirring was continued for 12 hr at room temperature. Ethyl acetate (10ml) was added, the layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 5ml). The organic extracts were washed with brine (2 x 5ml) and dried. Removal of the solvent and purification of the residue by preparative t.l.c. (ether) afforded enone 63 (R_f~0.2, 33mg, 58%) as a colourless solid. Recrystallisation from ether-light petroleum gave colourless crystals, m.p.99.5-100.5°. (Found: C, 75.11; H, 8.28. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%.)

ν_{max} 3440(OH), 1670(C=O) cm^{-1}.

δ 6.80(d,1H,J=10Hz,CH=CHCO), 5.92(d,1H,J=10Hz,CH=CHCO), 4.56 (m,1H,W½=15Hz,CHOH), 2.96(br.S,1H,exch.,OH), 2.76-1.12 (m,12H).

MS 192(100%,M^+), 174(26%, M-H_2O), 107(88%).

λ_{max} 230(9,000) nm.

δ 201.2, C(2); 159.6, C(4); 128.3, C(3); 73.0, C(6); 46.5, C(5); 44.5, C(4a); 41.2, C(1); 40.1, C(9a); 39.3, C(7); 36.0, C(10); 24.4, C(9); 22.5, C(8).

(4aα,6β,7α,9aβ)-6-Hydroxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 40

Enone 63 (58mg, 0.3mmol), in ethyl acetate (10ml) was hydrogenated at atmospheric pressure at 25° for 1 hr using palladium on calcium carbonate (6mg) as a catalyst.

The filtered solution (celite) was concentrated *in vacuo* to give 40 (55mg, 94%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p.92-93°, (lit.92-93°).[62] This product was identical (i.r., ^{1}H n.m.r.) to an authentic sample.[62]

(4aα,7α,9aβ)-7,8,9,9a-Tetrahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,5*H*)-dione 66

Methoxyenone 42 (77mg, 0.35mmol) in ethyl acetate (8ml) was hydrogenated over 5% palladium on carbon (16mg) at atmospheric pressure at 25° for 2 hr. The filtered solution (celite) was concentrated *in vacuo* to give the saturated ketone (75mg). δ 3.36(S,3H,OMe), 3.19(m,1H,W½=10Hz, CHOMe), 3.00-1.29(m,14H). This product was identical (t.l.c., i.r.) to the mixture of C(9a)-epimers, 44.

The above product was dissolved in dry dichloromethane (5ml). Trifluoroacetic acid (1ml) was added to this solution at 0° under a nitrogen atmosphere. After 10 min., the cooling bath was removed and the solution was stirred for 16 hr at room temperature. The reaction mixture was cooled to 0° and ice-water (10ml) and dichloromethane (8ml) were added. The layers were separated and the aqueous phase was re-extracted with dichloromethane (2 x 10ml). The organic extracts were washed with water (1 x 10ml), a 10% aqueous solution of sodium hydrogen carbonate (1 x 10ml), brine (1 x 10ml) and dried. The solvent was removed and the residue purified by preparative t.l.c. (ether) to afford enone 66 (28mg, 42%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p. 101.5-102.5°. (Found: C, 75.74; H, 7.26. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%.)

ν_{max} 1740(cyclopentanone), 1680(C=O) cm^{-1}.

δ 6.83(d,1H,J=10Hz,CH=CHCO), 5.99(d,1H,J=10Hz,CH=CHCO), 2.95-1.21(m,12H).

MS 190(100%,M^+), 150(28%), 148(24%), 147(29%), 146(32%), 137(35%), 91(50%), 79(41%).

λ_{max} 229(8,000) nm.

δ 218.4, C(6); 199.3, C(2); 155.9, C(4); 129.4, C(3); 51.2, C(5); 46.1, C(7); 43.1, C(4a); 40.5, C(1); 38.7, C(9a); 35.5, C(10); 26.4, C(8); 25.6, C(9).

(4aα,7α,9aβ)-Hexahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,3*H*)-dione 67

Enone 66 (38mg, 0.2mmol) in ethyl acetate (5ml) was hydrogenated at atmospheric pressure at 25° for 2 hr over 10% palladium on calcium carbonate (6mg). The filtered solution (celite) was concentrated *in vacuo* and the residue purified by column chromatography (3g, 70-230 mesh, 10% ethyl acetate-dichloromethane) to give 67 (34mg, 88%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p.66-67.5°. (Found: C, 74.93; H, 8.59. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%.)

ν_{max} 1740(cyclopentanone), 1705(C=O) cm^{-1}.

δ 2.78-1.21(m,16H).

MS 192(80%,M^+), 148(100%), 108(30%), 107(28%), 106(29%), 93(35%),91(29%), 79(41%).

δ 219.6, C(6); 210.5, C(2); 51.3†,C(5); 47.7, C(7); 43.8†, C(1); 41.7, C(9a); 41.1, C(4a); 38.5†,C(3); 36.9, C(4); 34.6, C(10); 26.0, C(8); 25.2, C(9).

†Peak absent after $NaOD/D_2O$/Dioxan exchange.

Alcohol 40 (58mg, 0.3mmol) was oxidised using the same procedure employed for the preparation of 42. Purification of the product by flash chromatography (3g, 8% ether-dichloromethane) afforded 67 (53mg, 93%) which was identical (t.l.c., i.r., ^{1}H n.m.r.) to a previously prepared authentic sample.

(4aα,7α,9aα)-7,8,9,9a-tetrahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,5*H*)-dione 64

Methoxyenone 43 (77mg, 0.35mmol) in ethyl acetate (8ml) was hydrogenated over 5% palladium on carbon (16mg) at atmospheric pressure at 25° for 4 hr. The filtered solution (celite) was concentrated *in vacuo* to give the saturated ketone (77mg). δ 3.38(S,3H,OMe), 3.19(m,1H,W½=10Hz, CHOMe), 2.95-1.15(m,14H). This product was identical (t.l.c., i.r.) to the mixture of C(9a)-epimers, 44.

The above product was treated with trifluoroacetic acid in a similar manner to that described for the preparation of 66. The residue was purified by preparative t.l.c. (ether) to afford enone 64 (R_f∿0.3, 25mg, 38%) as a colourless oil. A sample was distilled, b.p.(Kugelrohr) 95°(.003mm).
(Accurate Mass: Found 190.0994. $C_{12}H_{14}O_2$ requires 190.0994.)
ν_{max} 1740(cyclopentanone), 1680(C=O) cm^{-1}.
δ 6.74(d,1H,J=10Hz,CH=CHCO), 5.96(d,1H,J=10Hz,CH=CHCO), 2.68-1.16(m,12H).
MS 190(100%,M^+), 148(24%), 147(20%), 108(26%).

217.4, C(6); 198.6, C(2); 154.7, C(4); 129.2, C(3); 46.8, C(7); 42.7, C(5) and C(10); 41.3*, C(1) and C(4a); 41.0*, C(9a); 29.0, C(8); 26.2, C(9).

(4aα,7α,9aα)-Hexahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,3H)-dione 65

Enone 64 (95mg, 0.5mmol) in ethyl acetate (8ml) was hydrogenated at atmospheric pressure at 25° for 2 hr using 10% palladium on calcium carbonate (19mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* and the residue purified by column chromatography (5g, 70-230 mesh, 10% ethyl-acetate dichloromethane) to give 65 (88mg, 92%) as a colourless oil. Distillation of a portion, b.p.(Kugelrohr) 74°(.15mm), afforded an analytical sample. (Found: C, 74.99; H, 8.13. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%.)

ν_{max} 1700(C=O) cm^{-1}.

δ 2.78-1.21(m,16H).

MS 192(100%,M^+), 164(16%), 144(19%), 143(24%), 142(26%), 130(31%), 108(18%), 107(25%), 93(28%), 91(22%), 79(34%).

δ 219.2, C(10); 209.6, C(2); 46.9, C(7); 45.2*†, C(1); 44.4†,C(5); 43.5, C(9a); 43.0, C(10); 40.9, C(4a); 39.4*†, C(3); 37.9, C(5); 29.1, C(8); 27.7, C(9).

†Peak absent after NaOD/D_2O/Dioxan exchange.

*Peak absent when alcohol 41 was subjected to a deuterium exchange (NaOD/D_2O/Dioxan) and then carefully oxidised with pyridinium dichromate.[157]

Alcohol 41 (96mg, 0.5mmol) was oxidised using the same procedure employed for the preparation of 42. The product was purified by flash chromatography (3g, 8% ether-dichloromethane) to give 65 (77mg, 81%), which was identical (t.l.c., i.r., ^1H n.m.r.) to a previously prepared authentic sample.

(4aα,6β,7α,9aβ)-6-Methoxymethyloxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 58

Alcohol 40 (388mg, 2mmol) was treated with diisopropylethylamine (1.0ml, 6mmol) and chloromethyl methyl ether (0.3ml, 4mmol) in dry dichloromethane (20ml) using the same procedure employed for the preparation of 49. Purification by column chromatography (10g, 70-230 mesh, 20% ether-dichloromethane) afforded 58 (400mg, 84%). Recrystallisation from light-petroleum gave colourless crystals, m.p.47.5-48.5°. (Found: C, 70.70; H, 9.66. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30%.)

ν_{max} 1700(C=O) cm^{-1}.

δ 4.63(S,2H,OCH_2O), 4.25(m,1H,W½=13Hz,C<u>H</u>OCH_2O), 3.37(S,3H,OMe), 2.81-1.05(m,16H).

MS 238(43%,M^+), 206(25%,M-MeOH), 194(100%), 164(22%), 149(33%), 45(135%).

δ 212.2, C(2); 96.0, OCH_2O; 77.6, C(6); 55.5, OMe; 44.4, C(1); 43.5*, C(9a); 43.3*, C(5); 42.0, C(4a); 39.2, C(3); 38.6, C(7); 37.6, C(4); 34.3, C(10); 25.5, C(9); 22.7, C(8).

*may be interchanged

(4aα,6β,7α,9aα)-6-Methoxymethyloxy-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 68

Alcohol 41 (97mg, 0.5mmol) was treated with diisopropylethylamine (0.26ml, 1.5mmol) and chloromethyl methyl ether (0.08ml, 1mmol) in dry dichloromethane (7ml) using the same procedure employed for the preparation of 49. Purification by flash chromatography (3½g, 5% ether-dichloromethane) afforded

68 (89mg, 75%). A sample was distilled, b.p.(Kugelrohr) 67° (.005mm) to give a colourless oil. (Found: C, 70.29; H, 9.28. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30%.)

ν_{max} 1700(C=O) cm^{-1}.

δ* 4.62(S,2H,OCH_2O), 4.32(m,1H,$W_{½}$=12Hz,C<u>H</u>OCH_2O), 3.37(S,3H,OMe), 2.37-1.12(m,16H).

MS 238(16%,M^+), 209(26%), 206(100%, M-MeOH), 181(30%), 178 (52%), 177(30%), 176(89%), 149(51%).

δ 211.6, C(2); 95.9, OCH_2O; 78.5, C(6); 55.5, OMe; 45.4, C(1); 44.7, C(9a); 43.4, C(10); 42.0, C(4a); 39.8, C(3); 38.3, C(4); 37.6, C(7); 36.5, C(5); 28.2, C(9); 26.1, C(8).

69:[158] δ 212.3, C(2); 78.8, C(6); 50.9, C(10); 44.8†, C(1); 44.0, C(9a); 42.6, C(7); 41.6, C(4a); 39.5†, C(3); 39.2, C(5); 38.2, C(4); 32.7, C(8); 28.4, C(9); 24.9, Me.

70:[158] δ 212.8, C(2); 77.8, C(6); 46.4, C(5); 44.2†, C(1); 43.5, C(7); 42.5, C(9a); 41.8, C(10); 41.6, C(4a); 39.1†, C(3); 37.4, C(4); 29.5, C(8); 25.5, C(9); 25.5, Me.

† Peak absent after NaOD/D_2O/Dioxan exchange.

* This spectrum was recorded on a Varian HA-100 spectrometer operating at 100MHz.

(4aα,7α,9aβ)-7-Methyl-hexahydro-4a,7-methano-4a*H*-benzocycloheptene-2,6(1*H*,3*H*)-dione 71

Alcohol 70 (62mg, 0.3mmol) was oxidised using the same procedure employed for the preparation of 42 to give 71 (59mg, 96%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p.131-132°. (Found: C, 75.76; H, 8.70. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%.)

ν_{max} 1740(cyclopentanone), 1710(C=O) cm^{-1}.

δ 2.54-1.24(m,15H), 1.09(S,3H,Me).

MS 206(79%,M^+), 163(66%), 162(100%), 107(39%), 105(37%), 79(38%).

δ 220.3, C(6); 210.5, C(2); 51.5, C(5); 49.9, C(7); 43.7†,C(1); 41.7, C(10); 40.9, C(9a); 39.2, C(4a); 38.5†,C(3); 36.8, C(4); 33.7, C(8); 25.9, C(9); 20.3, Me.

† Peak absent when alcohol 70 was subjected to a deuterium exchange ($NaOH/D_2O$/Dioxan) and then carefully oxidised with pyridinium dichromate.[157]

CHAPTER 3

(4aα,7α,9aβ)-2,4,6-Triethylenedioxy-decahydro-4a,7-methano 4a*H*-benzocycloheptene 72

Dowex 50W (3mg) was added to a solution of 42 (22mg, 0.1mmol) and ethylene glycol (0.06ml, 1mmol) in dry benzene (10ml), and the mixture was heated at reflux under an atmosphere of nitrogen for 18 hr, with azeotropic removal of water (side-arm with test tube filled with 4Å sieves). The benzene was carefully evaporated under reduced pressure, the residue dissolved in dichloromethane and filtered through a small amount of silica gel (2g, 70-230 mesh, 30% ethyl acetate-dichloromethane) to afford 72 (24mg, 70%) as a colourless solid. Recrystallisation from ether-light petroleum afforded an analytical sample, m.p.137-139°. (Found: C, 64.09; H, 7.63. $C_{18}H_{26}O_6$ requires C, 63.89; H, 7.74%.)

δ 3.99, 3.97. 3.92, 3.89, 3.86(singlets, 12H, acetal H's),
2.38-1.15(m,14H).

MS 338(53%, M^+), 252(30%), 166(100%), 157(55%).

(1α,4aβ,6α,7β,9aα)-4-Methoxy-6-methoxymethyloxy-1-methyl-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 73

A solution of methoxyenone 49 (53mg, 0.2mmol) in dry THF (2.5ml) was added dropwise to a solution of lithium diisopropylamide (0.5mmol) in dry THF (2ml) at 25° under an atmosphere of nitrogen. Stirring was continued for 30 min.

at 25°. The solution was cooled to 0° and methyl iodide (0.04ml, 0.6mmol) was added slowly dropwise. The mixture was stirred at 0° for 30 min. and ice-water (10ml) and ethyl acetate (15ml) were added. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 10ml). The organic extracts were washed with 6% hydrochloric acid (1 x 10ml),10% aqueous sodium hydrogen carbonate (1 x 10ml), brine (1 x 10ml) and dried. Removal of the solvents and purification of the product by column chromatography (5g, 70-230 mesh, 15% ethyl acetate-dichloromethane) gave 73 (52mg, 93%). A sample was sublimed, b.p.(Kugelrohr) 65°(0.01mm) to give colourless crystals, m.p.99-101° (sub). (Found: C, 68.78; H, 8.48. $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.63%.)

ν_{max} 1640(C=O), 1600(C=C) cm^{-1}.

δ 5.31(S,1H,CH=C), 4.66(S,2H,OCH_2O), 4.30(m,1H,$W_{½}$=12Hz, $CHOCH_2O$), 3.67(S,3H,C=COMe), 3.39(S,3H,OMe), 2.93(dd, 1H,J=10Hz,J=14Hz, H5α), 1.58-1.05(m,10H), 1.20(d,3H, J=7Hz,Me).

MS 280(100%, M^+), 251(32%), 235(37,M-CH_2OCH_3), 219(42%), 218 (52%), 193(37%), 112(44%), 45(248%).

λ_{max} 252(13,500) nm.

δ 201.3, C(2); 180.4, C(4); 101.6, C(3); 96.4, OCH_2O; 77.8, C(6); 56.0, C=COCH_3; 55.5, OMe; 47.4, C(4a); 46.9*,C(9a); 41.0*,C(1); 38.0, C(7); 37.5, C(5); 36.6, C(10); 23.1, C(8); 21.0, C(9); 13.4, Me.

*may be interchanged.

Ethyl (1α,4aβ,6α,7β,9aα)-4-methoxy-6-methoxymethyloxy-2-oxo-1,2,5,6,7,8,9,9a-octahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 75

A solution of methoxyenone 49 (530mg, 2mmol) in dry THF (5ml) was added slowly to a solution of lithium diisopropylamide (5mmol) in dry THF (5ml) at 25° under an atmosphere of nitrogen. Stirring was continued at 25° for 30 min. The solution was cooled to -78° and ethyl chloroformate (0.57ml, 6mmol) was added dropwise. The mixture was stirred at -78° for 5 min. and ice-water (20ml) and ethyl acetate (40ml) were added. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 20ml). The organic extracts were washed with 6% hydrochloric acid (1 x 20ml), 10% aqueous sodium hydrogen carbonate (1 x 20ml), brine (1 x 20ml) and dried. Removal of the solvents and purification of the product by medium pressure liquid chromatography (20% ethyl acetate-dichloromethane) gave 75 (579mg, 86%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p.101-102°. (Found: C, 63.75; H, 7.38. $C_{18}H_{26}O_6$ requires C, 63.89; H, 7.74%.)

ν_{max} 1735(ester), 1650(C=O), 1600(C=C) cm^{-1}.

δ 5.33(d,1H,J=2Hz,CH=C), 4.64(S,2H,OCH_2O), 4.27(m,1H, $W_{\frac{1}{2}}$=14Hz, C<u>H</u>OCH_2O), 4.24(q,2H,J=7Hz, CO_2CH_2), 3.69(S,3H,C=COMe), 3.52(d,1H,J=14Hz,$CHCO_2$), 3.38(S,3H,OMe), 2.94(dd,1H, J=10Hz,J=14Hz,H5α), 2.64-1.12(m,9H), 1.30(t,3H,J=7Hz,Me).

MS 338(34%,M^+), 309(33%,M-Et), 293(52%), 2.77(40%), 276(100%), 265(56%), 247(71%), 45(220%).

λ_{max} 254(17,000) nm

δ 194.0, C(2); 181.2, C(4); 170.6, <u>C</u>O_2Et; 101.3, C(3); 96.2, OCH_2O; 77.0, C(6); 61.0, CO_2<u>C</u>H_2; 56.4, C(1) and C=CO<u>C</u>H_3;

55.5, OMe; 46.6, C(4a); 42.3, C(9a); 38.6, C(7); 37.4, C(5); 26.6, C(10); 23.1, C(8); 22.5, C(9); 14.3, Me.

(1α,4aβ,6α,7β,9aα)-4-Methoxy-6-methoxymethyloxy-1-methyl-1-(2'-propenyl)-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 76

A solution of methoxyenone 73 (56mg, 0.2mmol) in dry THF (4ml) was added dropwise to a solution of lithium diisopropylamide (0.5mmol) in dry THF (2ml) at 25° under an atmosphere of nitrogen. Stirring was continued for 30 min. at 25°. The solution was cooled to 0° and allyl bromide (0.05ml, 0.6mmol) was added dropwise. The mixture was stirred at 0° for 1 hr and ice-water (10ml) and ethyl acetate (15ml) were added. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 10ml). The organic extracts were washed with 6% hydrochloric acid (1 x 10ml), 10% aqueous sodium hydrogen carbonate (1 x 10ml), brine (1 x 10ml) and dried. Removal of the solvents and purification of the product by p.l.c. (25% ethyl acetate-dichloromethane) gave 76 (R_f∿0.5, 46mg, 72%). Sublimation b.p.(Kugelrohr) 80°(.008mm) afforded a colourless solid, m.p.97-99°(sub). (Found: C, 71.14; H, 8.81. $C_{19}H_{28}O_4$ requires C, 71.22; H, 8.81%.)

ν_{max} 1630(C=O), 1600(2 x C=C) cm^{-1}.

δ 5.55(m,1H,W½=20Hz, CH_2=C<u>H</u>), 5.34(S,1H,C<u>H</u>=COMe), 4.96(m,2H, W½=12Hz,C<u>H</u>$_2$=CH), 4.66(S,2H,OCH_2O), 4.25(m,1H,W½=13Hz, C<u>H</u>OCH_2O), 3.68(S,3H,C=COMe), 3.40(S,3H,OMe), 2.91(dd,1H, J=10Hz,J=14Hz,H5α), 2.80(m,1H,W½=16Hz,CH_2=CHC<u>H</u>), 2.48-1.30(m,10H), 1.24(t,3H,J=7Hz,Me).

MS 320(100%,M^+), 305(56%,M-Me), 275(26%,M-CH_2OCH_3), 260(34%),

259(46%), 232(100%), 152(45%), 151(27%), 45(94%).

λ_{max} 254(17,000) nm.

δ 203.5, C(2); 179.6, C(4); 135.3, CH_2=C<u>H</u>; 117.5, <u>CH_2</u>=CH; 101.7, C(3); 96.2, OCH_2O; 77.1, C(6); 55.7, 2 x OCH_3; 46.8, C(4a); 42.9, C(1) and C(9a); 41.1, CH_2=CH<u>CH_2</u>; 38.1, C(7); 37.2, C(9) and C(10); 25.6, C(8); 23.7, Me; 18.3, C(9).

<u>Ethyl (1α,4aα,6β,7α,9aβ)-4-methoxy-6-methoxymethyloxy-2-oxo-1-(2'-propenyl)-1,2,5,6,7,8,9,9a-octahydro-4a,7-methano 4a*H*-benzocycloheptene-1-carboxylate 77</u>

A solution of ester 75 (131mg, 0.4mmol) in dry DMF (3ml) was added slowly dropwise to a stirred suspension of sodium hydride (24mg, 1mmol) in dry DMF (3ml) at 25° under an atmosphere of nitrogen. After 15 min., allyl bromide (0.1ml, 1.2mmol) was added dropwise. Stirring was continued for 3 hr, and ice-water (15ml) and ethyl acetate (15ml) were added. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 15ml). The organic extracts were washed with water (2 x 15ml), brine (1 x 15ml) and dried. Removal of the solvent and purification of the product by column chromatography (3g, 5% ethyl acetate-dichloromethane) gave <u>77</u> (115mg, 79%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p.102-103°. (Found: C, 66.44; H, 7.84. $C_{21}H_{30}O_6$ requires C, 66.65; H, 7.99%.)

ν_{max} 1720(ester), 1640(C=O), 1600(2 x C=C) cm^{-1}.

δ 5.51(S,1H,C<u>H</u>=COMe), 5.48(m,1H,$W_{½}$=20Hz,CH_2=C<u>H</u>), 5.22(m,2H, $W_{½}$=27Hz, C<u>H_2</u>=CH), 4.65(S,2H,OCH_2O), 4.15(q,2H,J=7Hz, CO_2CH_2), 4.23(m,1H,$W_{½}$=15Hz,C<u>H</u>OCH_2O), 3.71(S,3H,C=COMe), 3.39(S,3H,OCH_3), 3.03(m,2H,$W_{½}$=15Hz,H5α and CH_2=CHC<u>H</u>),

2.71(dd,1H,J=5Hz,J=14Hz,CH_2=CHCH), 2.41-1.14(m,9H), 1.26 (t,3H,J=7Hz,Me).

MS 378(39%,M^+), 334(12%), 316(10%), 306(25%), 305(100%, M-CO_2Et), 163(21%), 149(18%), 45(>100%).

λ_{max} 256(17,000) nm.

δ 196.1, C(2); 179.9, C(4); 173.4, $\underline{C}O_2Et$; 133.6, CH_2=$\underline{C}H$; 119.3, $\underline{C}H_2$=CH; 103.2, C(3); 96.1, OCH_2O; 77.1, C(6); 61.4, $CO_2\underline{C}H_2$; 58.3, C(1); 56.0, C=CO$\underline{C}H_3$; 55.6, OMe; 46.8, C(4a); 43.8, C(9a); 40.5,CH_2=CH$\underline{C}H_2$; 38.2, C(7); 37.7, C(5); 35.7, C(10); 23.6, C(8); 18.4, C(9); 13.9,Me.

(1α,4aα,6β,7α,9aα)-4-Methoxy-6-methoxymethyloxy-1-methyl-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 86

A solution of methoxyenone 50 (266mg, 1mmol) in dry THF (6ml) was added dropwise to a solution of lithium diisopropylamide (2.5mmol) in dry THF (4ml) at 0° under an atmosphere of nitrogen. The reaction mixture was stirred at 25° for 30 min., cooled to 0° and methyl iodide (0.19ml, 3mmol) was added dropwise. Stirring was continued at 0° for 30 min., ice-water (30ml) added and the mixture extracted with ethyl acetate (3 x 30ml). Sequential washing of the extracts (6% hydrochloric acid 1 x 20ml, water 1 x 20ml, brine 1 x 20ml), drying and solvent removal left a red oil. Purification by medium pressure liquid chromatography (22% ethyl acetate-dichloromethane) gave methoxyenone 86 (235mg, 84%). A sample was distilled, b.p.(Kugelrohr) 79°(.13mm), to afford a colourless oil. (Found: C, 68.36; H, 8.61. $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.63%.)

ν_{max} 1645(C=O), 1605(C=C) cm^{-1}.

δ 5.30(S,1H,CH=C), 4.64(S,2H,OCH_2O), 4.30(m,1H,$W_{½}$=14Hz, C<u>H</u>OCH_2O), 3.68(S,3H,C=COMe), 3.39(S,3H,Me), 2.50-1.14 m,11H),1.07(d,3H,J=7Hz,Me).

MS 280(100%,M^+), 235 (18%, M-CH_2OMe), 219(23%), 218(27%), 45(36%).

λ_{max} 252(16,800) nm.

δ 200.8, C(2); 178.9, C(4); 101.7, C(3); 96.2, OCH_2O; 78.1, C(6); 56.0, C=CO<u>C</u>H_3; 55.6, OMe; 47.3, C(4a) and C(9a); 42.6, C(1); 38.6*,C(7); 38.1*.C(10); 35.7, C(5); 26.2, C(8); 24.0, C(1); 11.2, Me.

*may be interchanged.

<u>(4aα,6β,7α,9aβ)-6-Methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one</u> <u>81</u>

(a) <u>With Dibal and trifluoroacetic acid (TFA)</u>

A solution of Dibal in benzene (0.15ml, 0.25mmol) was added dropwise to a solution of methoxyenone <u>49</u> (53mg, 0.2mmol) in dry benzene (3ml) and dry *n*-pentane (1.5ml) at 0° under an atmosphere of nitrogen. After 1 min. at 0°, acetone (0.5ml) was added. A saturated aqueous sodium sulphate solution (0.25ml), and ethyl acetate (10ml) were added. The solution was stirred rapidly at 25° for 30 min., by which time the aluminium salts had precipitated. The dried and filtered solution (celite) was concentrated *in vacuo* to give the alcohol (51 mg, 96%).

ν_{max} 3440(OH), 1650(C=C) cm^{-1}

δ 4.62(S,2H,OCH_2O), 4.55(d,1H,J=2Hz,CH=C), 4.58-4.09(m,2H, C<u>H</u>OH and C<u>H</u>OCH_2O), 3.47(S,3H,C=COMe), 3.36(S,3H,OMe), 2.73(dd,1H,J=11Hz,J=14Hz,H5α), 1.94(br.S,1H,exch.,OH), 2.41-1.09(m,11H).

The alcohol (51mg) was dissolved in dry dichloromethane (5ml), cooled to 0° and TFA (1 drop) was added.† After 1 min. at 0°, 10% aqueous sodium hydrogen carbonate solution was added until the solution was alkaline. Ether (15ml) was added, the layers were separated and the aqueous phase was re-extracted with ether (2 x 10ml). The organic extracts were washed with brine (2 x 10ml) and dried. Removal of the solvents and purification of the product by p.l.c. (ether) gave enone 81 (R_f~0.5, 31mg, 65%) as a colourless oil. Distillation, b.p.(Kugelrohr)55°(.2mm) afforded an analytical sample. (Found: C, 70.99; H, 8.56. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%.)

ν_{max} 1660(C=O) cm^{-1}.

δ 6.86(m,1H,$W_{½}$=11Hz,CH=CHCO), 5.95(dd,1H,J=3Hz,J=10Hz, CH=CHCO), 4.63(S,2H,OCH_2O), 4.29(m,1H,$W_{½}$=16Hz,CHOCH_2O), 3.37(S,3H,OMe), 3.04(dd,1H,J=10Hz,J=14Hz,H5α), 2.65-1.09 (m,11H).

MS 236(49%,M^+), 193(21%, 192(91%), 191(58%), 181(24%), 176 (29%), 175(32%), 174(25%), 161(31%), 160(56%), 129(23%), 127(32%), 115(26%), 121(34%), 120(27%), 119(100%), 107 (27%), 95(31%), 93(30%), 91(49%), 79(53%, 45(>100%), 44(>100%).

λ_{max} 226 (7,000) nm.

δ 202.4, C(4); 149.1, C(2); 129.2, C(3); 96.2, OCH_2O; 77.2, C(6); 55.6, OMe; 53.1, C(4a); 39.5, C(9a); 38.5, C(7); 36.3, C(10); 34.4, C(5); 29.9, C(1); 24.4, C(9); 23.1, C(8).

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†Because of their lack of stability, alcohols of this type were immediately subjected to the elimination process.

(b) With Lithium aluminium hydride and TFA

A solution of lithium aluminium hydride in ether (0.05ml, 0.2mmol) was added dropwise to a solution of methoxyenone 49 (53mg, 0.2mmol) in dry ether (4ml) at 0° under an atmosphere of nitrogen. Stirring was continued at 0° for 1 hr and the excess reagent was then quenched by the addition of acetone (0.5ml). The reaction mixture was worked up as described for 38. Elimination and purification as in (a) afforded enone 81 (33mg, 70%), which was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

(c) With lithium triethylborohydride and TFA

A solution of lithium triethylborohydride in THF (0.15ml, 0.15mmol) was added dropwise to a solution of methoxyenone 49 (27mg, 0.1mmol) in dry THF (3ml) at -78° under an atmosphere of nitrogen. The reaction temperature was allowed to warm up slowly to 0° over a period of 3 hr. An aqueous solution of 2% disodium hydrogen phosphate (pH∿9.1, 1ml) and 30% hydrogen peroxide (0.5ml) were added and stirring was continued overnight at 25°. The mixture was extracted with ethyl acetate (3 x 15ml) and the extracts were washed with water (1 x 15ml), brine (1 x 15ml) and dried. Removal of the solvent left 26mg. Reduction had occurred mainly in the 1,2-mode but some 1,4-reduced product was present (∿25%, ^{1}H n.m.r. analysis). Elimination and purification as in (a) afforded enone 81 (12mg, 51%), which was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

(d) With Dibal in THF and TFA

A solution of Dibal in benzene (0.09ml, 0.15mmol) was added dropwise to a solution of methoxyenone 49 (27mg, 0.1mmol)

in dry THF (3ml) at -78° under an atmosphere of nitrogen. Stirring was continued at -78° for 30 min., acetone (0.5ml) was added and the reaction was worked up as described for (a). Elimination and purification as in (a) afforded enone 81 (14mg, 58%), which was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

(e) With Dibal and 6% hydrochloric acid

Methoxyenone 49 (53mg, 0.2mmol) was reduced as in (a) with Dibal (0.15ml, 0.25mmol). 6% Hydrochloric acid (1ml) was added to a solution of the product in THF (4ml) at 0°. Stirring was continued at 0° for 5 min., and then ice-water (10ml) and ethyl acetate (10ml) were added. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 10ml). The organic extracts were washed with water (1 x 10ml), brine (1 x 10ml) and dried. Removal of the solvent and purification of the product by p.l.c. (ether) afforded 81 (32mg, 68%) and 89 (5 mg, 9 %). Enone 81 was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

89: (2ξ,4aα,6β,7α,9aβ)-2-Hydroxy-6-methoxymethyloxy-octahydro 4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one

Distillation, b.p.(Kugelrohr) 62°(.05mm) gave a colourless oil. (Accurate mass: Found 254.1514. $C_{14}H_{22}O_4$ requires 254.1518.)

ν_{max} 1705(C=O) cm^{-1}.

δ 4.63(S,2H,OCH_2O), 4.22(m,1H,W½=15HHz,C<u>H</u>OCH_2O), 3.37(S,4H, OMe and C<u>H</u>OH), 2.72-1.12(m,15H).

MS 254(51%, M^+), 210(30%), 209(100%,M-CH_2OMe), 192(38%), 191(30%), 127(34%), 45(>100%).

(f) With Dibal and *p*-toluenesulphonic acid

Methoxyenone 49 (53mg, 0.2mmol) was reduced as in (a) with Dibal (0.15ml, 0.25mmol). *p*-Toluenesulphonic acid (1 crystal) was added to a solution of the product in dry benzene (2ml) at 25°. Stirring was continued for 5 min., the solvent carefully removed under reduced pressure (no heating) and the residue was purified by flash chromatography (2½g, 10% ether-dichloromethane) to give enone 81 (43mg, 91%), which was identical (t.l.c., ^1H n.m.r.) to a previously prepared authentic sample.

(1α,4aβ,6α,7β,9aα)-6-Methoxymethyloxy-1-methyl-1-(2'-propenyl)-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one 83

Methoxyenone 76 (64mg, 0.2mmol) was reduced with Dibal (0.15ml, 0.25mmol) as described for 81 (a) to afford the required alcohol (63mg, 98%).

ν_{max} 3450(OH), 1660(C COMe) cm^{-1}.

δ 5.85(m,1H,W½=20Hz,CH_2=C<u>H</u>), 5.14(m,2H,W½=9Hz,C<u>H</u>$_2$=CH), 4.62 (S,2H,OCH_2O), 4.44(S,1H,CH=C), 4.24(S,1H,C<u>H</u>OH), 4.08 (m,1H,W½=14Hz,C<u>H</u>OCH_2O), 3.49(S,3H,C=COMe), 3.36(S,3H,OMe), 2.60(dd,1H,J=10Hz,J=13Hz,H5α), 2.46-0.78(m,12H), 0.92 (S,3H,Me).

The above alcohol (63mg) was treated with TFA as described for 81(a) and the residue was purified by p.l.c. (15% ethyl acetate-dichloromethane) to give enone 83 (R_f~0.4, 41mg, 70%). Distillation, b.p.(Kugelrohr) 72°(0.1mm) afforded a colourless oil. (Found: C,74.25; H, 8.96. $C_{18}H_{26}O_3$ requires C, 74.45; H, 9.02%.)

ν_{max} 1665(C=O) cm^{-1}.

δ 6.55(d,1H,J=10Hz,C<u>H</u>=CHCO), 5.93(d,1H,J=10Hz,CH=C<u>H</u>CO), 5.59 (m,1H,$W_{½}$=19Hz,CH_2=C<u>H</u>), 5.01(m,2H,$W_{½}$=14Hz,C<u>H</u>$_2$=CH), 4.64 (S,2H,OCH_2O), 4.25(m,1H,$W_{½}$=13Hz,C<u>H</u>OCH_2O), 3.37(S,3H,OMe), 3.05(dd,1H,J=10Hz,J=13Hz,H5α), 2.53-1.16(m,11H), 1.31 (S,3H,Me).

MS 290(29%,M^+), 258(15%), 249(42%), 245(30%), 217(78%), 216 (57%), 199(34%), 187(99%), 173(32%), 159(100%), 145(67%), 45(>100%).

δ 202.5, C(4); 157.1, C(2); 134.1, CH_2=<u>C</u>H; 126.8, C(3); 118.6, <u>C</u>H_2=CH; 96.2, OCH_2O; 77.2, C(6); 55.5, OMe; 52.8, C(4a); 47.2, C(9a); 43.4*,C(7); 40.5, C(1); 39.6*,CH_2=CH<u>C</u>H_2; 39.1*, C(5); 37.4*, C(10); 24.8, C(8); 23.4, Me; 19.1, C(9).

*may be interchanged.

<u>(1α,4aα,6β,7α,9aβ)-1-Hydroxymethyl-6-methoxymethyloxy-1-(2'-propenyl)-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one</u> <u>78</u>

A solution of Dibal in benzene (0.23ml, 0.4mmol) was added dropwise to a solution of methoxyenone <u>77</u> (38mg, 0.1mmol) at 0° in dry benzene (3ml) and dry *n*-pentane (1.5ml) under an atmosphere of nitrogen. Stirring was continued for 15 min. at 0°. The reaction was worked up and the carbonyl group

transposed as described for 81(a) to give a mixture of products (t.l.c., ^{1}H n.m.r.). Separation by p.l.c. (30% ethyl acetate-dichloromethane) gave enone 78 (R_f~0.35, 6mg, 21%). Distillation, b.p.(Kugelrohr) 86°(.005mm), afforded a colourless oil. (Accurate mass: Found 306.1829. $C_{18}H_{26}O_4$ requires 306.1831.)

ν_{max} 3450(OH), 1600(C=O) cm^{-1}.

δ 6.78(d,1H,J=10Hz,C<u>H</u>=CHCO), 6.06(d,1H,J=10Hz,CH=C<u>H</u>CO), 5.63 (m,1H,W½=23Hz,CH_2=C<u>H</u>), 5.06(m,2H,W½=18Hz,C<u>H$_2$</u>=CH), 4.64 (S,2H,O<u>CH$_2$</u>O), 4.28(m,1H,W½=16Hz,C<u>H</u>O<u>CH$_2$</u>O), 4.08 and 3.78 (ABq†,J_{AB}=10Hz,C<u>H$_2$</u>OH), 3.38(S,3H,OMe), 3.02(dd,1H,J=11Hz, J=13Hz,H5α), 1.90(br.S,1H,exch.,OH), 2.82-1.06(m,11H).

MS 306(10%,M^+), 261(24%), 244(26%), 243(20%), 233(34%), 215 (50%), 214(68%), 213(28%), 203(80%), 189(44%), 185(86%), 175(48%), 173(98%), 171(44%), 161(48%), 159(100%), 157 (76%), 145(92%), 131(94%), 129(44%), 119(54%), 107(40%), 105(48%), 93(56%), 91(96%), 79(76%).

Attempted reduction of 77 with lithium aluminium hydride

A solution of methoxyenone 77 (38mg, 0.1mmol) in ether (3ml) was added dropwise to a solution of lithium aluminium hydride (0.3mmol) in dry ether (2ml) at 0° under an atmosphere of nitrogen. Stirring was continued at 0° for 1½ hr and the reaction was worked up as described for 81(b) to afford a complex mixture of products (t.l.c., ^{1}H n.m.r.). Reduction had proceeded in the 1,4-mode and no 1,2-reduction was observed (^{1}H n.m.r. analysis).

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† AB quartets have been analysed using the formula described by Jackman and Sternhell.[159]

Ethyl (1α,2ξ,4ξ,4aα,6β,7α,9aβ)-2-hydroxy-4-methoxy-6-methoxymethyloxy-1-(2'-propenyl)-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 85

A solution of lithium triethylborohydride in THF (0.2ml, 0.2mmol) was added to a solution of methoxyenone 77 (19mg, 0.05mmol) in dry THF (2.5ml) at -78° under an atmosphere of nitrogen. The reaction temperature was allowed to warm up slowly to 0° over a period of 3 hr and the reaction was worked up as described for 81(c). Purification of the residue by p.l.c. (20% ethyl acetate-dichloromethane) gave 85 (R_f~0.4, 9mg, 47%). Distillation, b.p.(Kugelrohr) 98°(.005mm) afforded a colourless oil. (Accurate mass: Found 382.2370. $C_{21}H_{34}O_6$ requires 382.2355.)

ν_{max} 3530(OH), 1705(ester) cm^{-1}.

δ 5.76(m,1H,$W_{½}$=20Hz,CH_2=C<u>H</u>), 5.10(m,2H,$W_{½}$=13Hz,C<u>H</u>$_2$=CH), 4.63 (S,2H,OCH_2O), 4.48-3.96(m,3H,CO_2CH_2 and C<u>H</u>OCH_2O), 3.37 (S,3H,OCH_2OCH_3), 3.34(S,3H,OMe), 2.96-1.03(m,17H), 1.32(t,3H,J=7Hz,Me).

MS 382(16%,M^+), 367(19%,M-CH_3), 350(64%,M-MeOH), 337(32%), 324(100%), 322(76%), 292(30%), 291(31%), 288(46%), 157 (51%), 129(48%), 117(43%), 105(40%), 93(36%), 91(68%), 79(49%), 69(55%), 41(48%).

(1α,4aα,6β,7α,9aα)-6-Methoxymethyloxy-1-methyl-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one 87

(a) With Dibal and 6% hydrochloric acid

Methoxyenone 86 (84mg, 0.3mmol) was reduced with Dibal (0.25ml, 0.45mmol) as described for 81(a) to afford the

required alcohol (81mg, 96%).

ν_{max} 3450(OH), 1650(C=C) cm^{-1}.

δ 4.62(S,3H,CH=C and OCH_2O), 4.19(m,1H,W½=12Hz,C<u>H</u>OCH_2O), 3.81 (m,1H,W½=9Hz,C<u>H</u>OH), 3.50(S,3H,C=COMe), 3.37(S,3H,OMe), 2.38-0.86(m,15H).

The above alcohol was treated with 6% hydrochloric acid as described for <u>81</u>(e) and the residue was purified by p.l.c. (ether) to afford enone <u>87</u> (R_f∿0.5, 37mg, 49%) and <u>88</u> (R_f∿0.25, 16mg, 20%).

<u>87</u>: Distillation, b.p.(Kugelrohr) 73°(.1mm) gave a colourless oil. (Found: C, 72.02; H, 8.78. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%.)

ν_{max} 1660(C=O) cm^{-1}.

δ 6.64(dd,1H,J=2Hz,J=10Hz,C<u>H</u>=CHCO), 5.92(dd,1H,J=2Hz,J=10Hz, CH=C<u>H</u>CO), 4.63(S,2H,OCH_2O), 4.31(m,1H,W½=15Hz,C<u>H</u>OCH_2O), 3.37(S,3H,OMe), 2.52(m,11H), 1.12(d,3H,J=7Hz,Me).

MS 250(56%,M^+), 206(58%),205(40%), 190(100%), 160(35%), 133 (74%), 45(124%).

λ_{max} 228(8,000) nm.

δ 202.7, C(4); 155.2, C(2); 127.7, C(3); 96.2, OCH_2O; 78.4, C(6); 55.5, OMe; 51.5, C(4a); 47.8, C(9a); 37.8, C(7) and C(10); 35.6, C(1); 34.7, C(5); 26.8, C(8); 24.8, C(9); 18.1, Me.

<u>88</u>: <u>(1α,2ξ,4aα,6β,7α,9aα)-2-Hydroxy-6-methoxymethyloxy-4-methyl-octahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one</u>

Distillation, b.p.(Kugelrohr) 78°(0.3mm), gave a colourless oil. (Accurate mass: Found 268.1671. $C_{15}H_{24}O_4$ requires 268.1674.)

$\nu_{max}^{\dagger}$ 1710(C=O) cm^{-1}.

δ 4.63(S,2H,OCH_2O), 4.19(m,1H,C<u>H</u>OCH_2O), 3.38(S,4H,OMe and C<u>H</u>OH), 2.81-1.05(m,14H), 1.04(d,3H,J=6Hz,Me).

MS 268(42%,M^+), 248(17%), 224(34%), 223(100%), 213(35%), 208 (40%), 206(40%), 151(55%), 45(148%).

δ 210.6, C(4); 96.2, OCH_2O; 77.7, C(6); 73.9, C(2); 55.5, OMe; 54.8, C(4a); 49.3, C(9a); 46.3, C(1); 41.7, C(3); 37.3*, C(7); 36.6*, C(5) and C(10); 26.4, C(8); 24.4, C(9); 14.0, Me.

*may be interchanged.

(b) <u>With Dibal and *p*-toleunesulphonic acid</u>

Methoxyenone <u>86</u> (420mg, 1.5mmol) was reduced with Dibal (1.1ml, 1.9mmol) as described for <u>81</u>(a) to afford the required alcohol (411mg, 97%).

p-Toleunesulphonic acid (1 crystal) was added to a solution of the above alcohol (411mg) in dry benzene (8ml) at 25°. Stirring was continued for 5 min. at 25°. The solvent was carefully removed under reduced pressure (no heating) and the residue purified by column chromatography (10g, 70-230 mesh, 10% ether-dichloromethane) to afford enone <u>87</u> (337mg, 90%), which was identical (t.l.c., ^1H n.m.r.) to a previously prepared authentic sample.

<u>Ethyl (1α,4aβ,6α,7β,9aα)-6-methoxymethyloxy-4-oxo-1,4,5,6,7,8,9,9a-octahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate</u> <u>82</u>

(a) <u>With Dibal and TFA</u>

Methoxyenone <u>75</u> (51mg, 0.15mmol) was reduced with Dibal

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† This spectrum has been recorded on a Perkin-Elmer 683 spectrometer.

(0.09ml, 0.15mmol) as described for 81(a) to afford the required alcohol (49mg, 96%).

ν_{max} 3450(OH), 1720(ester), 1650(C=O) cm^{-1}.

δ 4.61(S,2H,OCH_2O), 4.86-4.04(m,3H,CH=C,CHOH and $CHOCH_2O$), 4.19(q,2H,J=7Hz,CO_2CH_2), 3.49(S,3H,C=COMe), 3.36(S,3H,OMe), 3.00-1.04(m,12H),1.30(t,3H,J=7Hz,Me).

The above alcohol was treated with TFA as described for 81(a) and the residue was purified by p.l.c. (75% ether-light petroleum) to give enone 82 (R_f∿0.35, 18mg, 39%). Distillation, b.p.(Kugelrohr) 80°(.25mm) gave a colourless oil. (Found: C, 66.26; H, 7.97. $C_{17}H_{24}O_5$ requires C, 66.21; H, 7.84%.)

ν_{max} 1730(ester),1670(C=O) cm^{-1}.

δ 6.68(dd,1H,J=2Hz,J=10Hz,CH=CHCO), 5.98(dd,1H,J=2Hz,J=10Hz, CH=CHCO), 4.60(S,2H,OCH_2O), 4.25(m,1H,W½=14Hz,$CHOCH_2O$), 4.17(q,2H,J=7Hz,CO_2CH_2), 3.51(m,1H,W½=19Hz,$CHCO_2$), 3.37 (S,3H,OMe), 3.05(dd,1H,J=10Hz,J=14Hz,H5α), 2.51 -2.23 (m,2H), 2.23-1.14(m,7H), 1.28(t,3H,J=7Hz,Me).

MS 308(93%,M^+), 264(66%), 263(72%), 248(31%) 247(38%), 246 (100%), 173(62%), 131(44%), 119(37%), 45(>100%).

λ_{max} 221(6,600) nm.

δ 200.6, C(4); 172.3, CO_2Et; 144.9, C(2); 129.7, C(3); 96.2, OCH_2O; 77.2, C(6); 61.5, CO_2CH_2; 55.5, OMe; 52.8, C(4a); 46.0, C(1); 41.6, C(9a); 38.5, C(7); 36.3, C(10); 35.5, C(5); 23.1, C(8); 22.4, C(9); 14.3, Me.

(b) With Dibal and 6% hydrochloric acid

Methoxyenone 75 (51mg, 0.15mmol) was reduced with Dibal (0.09ml, 0.15mmol) as described for 81(a), and the alcohol treated with 6% hydrochloric acid as described for 81(e). Purification of the product by column chromatography (4g, 70-

230 mesh, 5% ethyl acetate-dichloromethane) afforded enone 82 (24mg, 52%) which was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

(c) With Dibal and *p*-toluenesulphonic acid

Methoxyenone 75 (1.0g, 3mmol) was reduced with Dibal (1.5ml, 2.7mmol) as described for 81(a), and the alcohol treated with *p*-toluensulphonic acid (1 crystal) as described for 81(f) to afford a mixture of enone 82 and starting methoxyenone 75. Separation by medium pressure liquid chromatography (20% ethyl acetate-dichloromethane) gave, in order of increasing retention, 82 (554mg, 60%) and 75 (260mg, 26%). These compounds were identical (t.l.c., ^{1}H n.m.r.) to previously prepared authentic samples.

78, 93 and 94

A solution of Dibal in benzene (0.71ml, 1.25mmol) was added dropwise to a solution of methoxyenone 77 (95mg, 0.25mmol) in dry benzene (3.5ml) and dry *n*-pentane (1.5ml) at 0° under an atmosphere of nitrogen. Stirring was continued for 10 min. at 0°, and the reaction was worked up as described for 81(a) to give a mixture of products (t.l.c.).
δ 3.55, 3.52 and 3.49(3 singlets, 3H, CH=C).

The mixture was treated with *p*-toluensulphonic acid (1 crystal) as described for 81(f). The residue was purified by p.l.c. (ether) to give alcohol 78 (R_f~0.35, 18mg, 24%), aldehyde 93 (R_f~0.5, 13mg, 17%) and ester 94 (R_f~0.6, 25mg, 29%). Alcohol 78 was identical (t.l.c., ^{1}H n.m.r.) to a previously prepared authentic sample.

93: (1α,4aα,6β,7α,9aβ)-6-Methoxymethyloxy-4-oxo-1-(2'-propenyl)-1,4,5,6,7,8,9,9a-octahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carbaldehyde

Distillation, b.p.(Kugelrohr) 77°(.005mm), afforded a colourless oil. (Accurate mass: Found 304.1677. $C_{18}H_{24}O_4$ requires 304.1674.)

ν_{max} 1705(CHO), 1665(C=O) cm^{-1}.

δ 9.92(S,1H,CHO), 6.69(d,1H,J=10Hz,C<u>H</u>=CHCO), 6.20(d,1H,J=10Hz,CH=C<u>H</u>CO), 5.62(m,1H,W½=21Hz,CH_2=C<u>H</u>), 5.14(m,2H,W½=14Hz,C<u>H_2</u>=CH), 4.65(S,2H,OCH_2O), 4.28(m,1H,W½=17Hz,C<u>H</u>OCH_2O), 3.39(S,3H,OMe), 3.11(dd,1H,J=10Hz,J=14Hz,H5α), 2.83-1.15(m,11H).

MS 304(7%,M^+), 260(17%), 231(19%), 185(30%), 173(33%), 171(40%), 161(31%), 159(57%), 131(37%), 105(38%), 93(40%), 91(100%), 79(71%), 77(64%).

λ_{max} 221(6,300) nm.

94: Ethyl (1α,4aα,6β,7α,9aβ)-6-methoxymethyloxy-4-oxo-1-(2'-propenyl)-1,4,5,6,7,8,9,9a-octahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate

Distillation, b.p.(Kugelrohr) 86°(.01mm) afforded a colourless oil. (Accurate mass: Found 348.1944. $C_{20}H_{28}O_5$ requires 348.1937.)

ν_{max} 1710(ester), 1665(C=O) cm^{-1}.

δ 6.75(d,1H,J=10Hz,C<u>H</u>=CHCO), 6.09(d,1H,J=10Hz,CH=C<u>H</u>CO), 5.69(m,1H,W½=27Hz,CH_2=C<u>H</u>), 5.15(m,2H,W½=15Hz,C<u>H_2</u>=CH), 4.65(S,2H,OCH_2O), 4.27(m,1H,W½=18Hz,C<u>H</u>OCH_2O), 4.22(q,2H,J=7Hz,CO_2CH_2), 3.38(S,3H,OMe), 3.09(dd,1H,J=11Hz,J=14Hz,H5α), 2.92-1.07(m,11H), 1.22(t,3H,J=7Hz,Me).

MS 348(100%,M^+), 307(65%), 303(51%), 288(42%), 286(55%), 231 (41%), 217(40%), 213(42%), 168(40%), 145(41%), 45(>100%).

λ_{max} 220(5,900) nm.

δ 201.7, C(4): 173.2, $\underline{C}O_2Et$; 149.1, C(2); 132.3, $CH_2{=}\underline{C}H$; 128.1, C(3); 120.1, $\underline{C}H_2{=}CH$; 96.2, OCH_2O; 77.1, C(6); 61.7, $CO_2\underline{C}H_2$; 55.6, OMe; 52.9, C(4a); 49.8, C(1); 46.4*, C(9a); 43.9*, $CH_2{=}CH\underline{C}H_2$; 39.1*, C(5); 38.6*, C(7); 36.5*, C(10); 23.5, C(8); 18.8, C(9); 14.0, Me.

* may be interchanged.

(4aα,6β,7α,9aβ)-4-Methoxy-6-methoxymethyloxy-1-methylene-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 97

Paraformaldehyde (12mg, 0.4mmol) was added to a solution of the enolate anion of 49 (27mg, 0.1mmol, prepared as for the synthesis of 73) in dry THF (4ml) at 25°. Stirring was continued for 10 min., the mixture cooled to 0°, and ice-water (10ml) was added. The mixture was acidified to pH 1 with 6% hydrochloric acid and extracted with ethyl acetate (3 x 15ml). The extracts were washed with water (1 x 15ml), brine (1 x 15ml) and dried. Removal of the solvents and purification of the product by p.l.c. (25% ethyl acetate - dichloromethane) gave 97 (R_f~0.4, 18mg, 65%). Recrystallisation from ether-light petroleum gave colourless crystals, m.p. 120.5-122°. An analytical sample was obtained by sublimation, b.p.(Kugelrohr) 85°(.15mm). (Found: C, 68.92; H, 7.91. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97%.)

ν_{max} 1660(C=O), 1600(2 x C=C) cm^{-1}.

δ 6.19(d,1H,J=2Hz,$C{=}CH_2$,syn), 5.40(S,1H,$C\underline{H}{=}COMe$), 5.33(d,1H, J=2Hz,$C{=}CH_2$,anti), 4.65(S,2H,OCH_2O), 4.28(m,1H,$W_{½}$=15Hz,

CHOCH$_2$O), 3.69(S,3H,C=COMe), 3.38(S,3H,OMe), 3.12-2.67 (m,2H), 2.42-1.24(m,8H).

MS 278(100%,M$^+$), 263(42%), 233(53%,M-CH$_2$OMe), 223(99%), 217 (45%), 45(>100%).

λ_{max} 274(8,000) nm.

(1α,4aβ,6α,7β,9aα)-1-Hydroxymethyl-4-methoxy-6-methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 98

METHOD A:

Paraformaldehyde (12mg, 0.4mmol) was added to a solution of the enolate anion of 49 (27mg, 0.1mmol, prepared as for the synthesis of 73) at -40°. Stirring was continued for 2 hr at -40°, ice-water (10ml) added, and work up as described for 97 gave a mixture of starting material and alcohol 98. Separation by p.l.c. (35% ethyl acetate-dichloromethane) gave 97 (R_f∿0.25, 13mg, 48%), and 98 (R_f∿0.15, 11mg, 44%). Distillation of 98, b.p.(Kugelrohr) 90°(0.9mm) afforded a colourless oil. (Found: C, 64.65; H, 8.11. $C_{16}H_{24}O_5$ requires C, 64.84; H, 8.16%.)

ν_{max} 3460(OH), 1630(C=O), 1600(C=C) cm^{-1}.

δ 5.31(S,1H,CH=C), 4.64(S,2H,OCH$_2$O), 4.38-3.59(m,3H,CHOCH$_2$O and CH$_2$OH), 3.69(S,3H,C=COMe), 3.38(S,3H,OMe), 2.93(dd,1H, J=10Hz,J=14Hz,H5α), 2.68-1.21(m,11H).

MS 296(100%,M$^+$), 278(15%,M-H$_2$O), 266(67%,M-CH$_2$O), 234(27%), 233(37%), 232(30%),221(31%), 216(28%),205(43%), 204(31%), 178(34%), 45(125%).

λ_{max} 253(16,000) nm.

METHOD B:

Gaseous formaldehyde (90mg, 3mmol) was bubbled in a stream of nitrogen into a solution of the enolate anion of 49 (80mg, 0.3mmol, prepared as for the synthesis of 73) at -40°. Stirring was continued for 30 min. when it was established (t.l.c.) that no starting material remained. Ice-water (10ml) was added, and the reaction mixture was worked up as described for 97 to give a mixture of products (80mg) Separation by p.l.c. (35% ethyl acetate-dichloromethane) gave 98 (34mg, 43%) and 99 (11mg, 11%).

99: (4aα,6β,7α,9aβ)-1,1-Dihydroxymethyl-4-methoxy-6-methoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one.

Distillation, b.p.(Kugelrohr) 83°(.01mm), afforded a colourless oil. (Accurate mass: Found 326.1730. $C_{17}H_{26}O_6$ requires 326.1729.)

ν_{max} 3445(OH), 1600(C=O,C=C) cm^{-1}.

δ 5.37(S,1H,CH=C), 4.63(S,2H,OCH_2O), 3.70(S,3H,C=COMe), 3.37 (S,3H,OMe), 4.36-1.14(m,17H).

MS 326(11%), 296(49%,M-CH_2O), 295(100%),M-CH_2OH), 278(72%), 233(36%), 223(44%), 158(49%), 45(130%).

λ_{max} 255(16,500) nm.

(1α,4aβ,6α,7β,9aα)-4-Methoxy-1,6-dimethoxymethyloxy-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 100

Methoxyenone 100 was prepared from alcohol 98 (44mg, 0.15mmol) using the same procedure employed for the synthesis of 57. Purification by p.l.c. (ether) afforded 100 (R_f~0.25,

36mg, 71%) as a colourless oil. Distillation, b.p.(Kugelrohr) 93°(.2mm), provided an analytical sample. (Found: C, 63.60; H, 8.07. $C_{18}H_{28}O_6$ requires C, 63.51; H, 8.29%.)

ν_{max} 1640(C=O), 1600(C=C) cm^{-1}.

δ 5.36(S,1H,CH=C), 4.65(S,2H,CHOC$\underline{H}_2$O), 4.54(app.d,2H,J=2Hz, $CH_2OC\underline{H}_2O$), 4.26(m,1H,W½=12Hz,C$\underline{H}$OCH_2O), 4.23 and 3.76 (ABq†, J_{AB}=13Hz,J=2Hz,C$\underline{H}_2$OCH_2O), 3.66(S,3H,C=COMe), 3.39(S,3H,OMe), 3.32(S,3H,$CH_2OCH_2O\underline{CH}_3$), 2.96(dd,1H, J=11Hz,J=13Hz,H5α), 2.63-1.15(m,1OH).

MS 340(4%,M^+), 325(2%,M-Me), 309(10%,M-OMe), 296(28%), 295 (100%,M-CH_2OMe), 45(35%).

λ_{max} 253(15,400) nm.

Attempted Alkylation of 100

A solution of 100 (27mg, 0.08mmol) in dry THF (3ml) was added slowly dropwise to a solution of lithium diisopropylamide (0.2mmol) in dry THF (2ml) under a nitrogen atmosphere. Stirring was continued at -78° for 3 hr, and allyl bromide (0.03ml, 0.32mmol) was added dropwise. The solution was stirred for 1 hr at -78° and then allowed to warm up slowly to room temperature over a period of 1 hr. Ice-water (10ml) was added and the mixture was extracted with ethyl acetate (3 x 15ml). The extracts were washed with 6% hydrochloric acid (1 x 10ml), brine (1 x 10ml) and dried. The solvents were removed to afford 13mg. It was clear from ^{1}H n.m.r. analysis that the primary methoxymethyl ether group had been eliminated, with concomitant loss of most of the methoxyenone system.

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† Analysed using the formula described by Jackman and Sternhell.

Attempted Alkylation of 98

(a) A solution of alcohol 98 (59mg, 0.2mmol) in dry THF (3ml) was added dropwise to a solution of lithium diisopropylamide (0.6mmol) in dry THF (6ml) and dry HMPA (4ml) at -78° under a nitrogen atmosphere. The temperature of the solution was increased gradually to -35°, and the reaction mixture was stirred between -35° and -25° for 3 hr. Allyl bromide (0.06ml, 0.7mmol) was added dropwise and stirring was continued for 1 hr between -35° and -25°. Ice-water (15ml) and ethyl acetate (20ml) were added and the aqueous phase was acidified to pH 1 with 6% hydrochloric acid. The layers were separated and the aqueous phase was extracted further with ethyl acetate (2 x 20ml). Sequential washing of the organic extracts (water 2 x 20ml, brine 1 x 20ml), drying and removal of the solvents afforded a complex mixture (t.l.c., ^{1}H n.m.r.) of products (50mg). Separation by p.l.c. (ether) gave starting alcohol 98 (R_f~0.1, 14mg, 24%). No discrete product was obtained.

(b) A solution of alcohol 98 (30mg, 0.1mmol) in dry THF (2ml) was added dropwise to a solution of lithium diisopropylamide (0.3mmol) in dry THF (2ml) and dry HMPA (1ml) at -78° under a nitrogen atmosphere. The reaction mixture was stirred at -78° for 30 min. and the temperature was increased to 0° over a period of 30 min. Stirring was continued at 0° for 3 hr, and allyl bromide (0.04ml, 0.4mmol) was added dropwise. The reaction mixture was further stirred at 0° for 2½ hr and then worked up as described for (a). A complex mixture of products was obtained (t.l.c., ^{1}H n.m.r.) and separation by p.l.c. (ether) gave olefin 97 (R_f~0.4, 10mg, 33%) as the only discrete product.

(1α,4aβ,6α,7β,9aα)-4-Methoxy-6-methoxymethyloxy-1-(2'-propenyl)-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 103

Allyl bromide (0.05ml, 0.6mmol) was added slowly dropwise to a solution of the enolate anion of 49 (53mg, 0.2mmol, prepared as for the synthesis of 73) at 0°. Stirring was continued at 0° for 1 hr and the reaction mixture was worked up as described for 73. The product was purified by column chromatography (4g, 10% ethyl acetate-dichloromethane) to give 103 (49mg, 81%) as a colourless oil. Distillation of a sample, b.p.(Kugelrohr) 70°(.15mm) provided an analytical sample. (Found: C, 70.58; H, 8.46. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55%.)

ν_{max} 1640(C=O), 1605(2 x C=C) cm^{-1}.

δ 5.66(m,1H,W½=19Hz,CH_2=C<u>H</u>), 5.34(S,1H,C<u>H</u>=COMe), 5.06(m,2H, W½=14Hz,C<u>H</u>$_2$=CH), 4.65(S,2H,OCH_2O), 4.31(m,1H,W½=13Hz, C<u>H</u>OCH_2O), 3.64(S,3H,C=COMe), 3.37(S,3H,OMe), 2.95(dd, 1H,J=11Hz,J=14Hz,H5α), 2.93(m,1H,W½=13Hz,CH_2=CHC<u>H</u>), 2.72-1.24(m,11H).

MS 306(100%, M^+), 261(19%, M-CH_2OMe), 245(23%), 244(15%), 177(18%), 45(38%).

λ_{max} 254(13,000) nm.

δ 200.1, C(2); 180.6, C(4); 135.5, CH_2=<u>C</u>H; 116.8, <u>C</u>H$_2$=CH; 102.1, C(3); 96.2, OCH_2O; 77.6, C(6); 56.0, C=CO<u>C</u>H$_3$; 55.6, OMe; 47.2, C(4a); 45.4*, C(9a); 42.4*, C(1); 37.9, C(7); 37.4, C(5); 36.6, C(10); 31.1, CH_2=CH<u>C</u>H$_2$; 23.1, C(8); 20.3, C(9).

*may be interchanged.

(1α,4aβ,6α,7β,9aα)-4-Methoxy-6-methoxymethyloxy-1-(1'*Z*-propenyl)-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 106

A solution of methoxyenone 103 (46mg, 0.15mmol) in dry THF (2ml) was added to a solution of lithium diisopropylamide (0.45mmol) in dry THF(2ml) at 25° under a nitrogen atmosphere. The reaction mixture was stirred at 25° for 2½ hr and then cooled to 0°. Ice water (10ml) and ethyl acetate (15ml) were added, the layers separated and the aqueous phase was extracted further with ethyl acetate. The organic extracts were washed with 6% hydrochloric acid (1 x 10ml), water (1 x 10ml), brine (1 x 10ml) and dried. Removal of the solvent and purification of the residue by p.l.c. (ether) afforded 106 (R_f∿0.25, 35mg, 76%). Recrystallisation from ether-light petroleum gave colourless needles, m.p.118-119°. (Found: C, 70.49; H, 8.39. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55%.)

ν_{max} 1640(C=O), 1600(2 x C=C) cm^{-1}.

δ 5.78(m,1H,W½=24Hz,MeCH=CH), 5.35(S,1H,C<u>H</u>=COMe), 5.18(m,1H, W½=17Hz, MeCH=CH), 4.64(S,2H,OCH_2O), 4.29(m,1H,W½=14Hz, C<u>H</u>OCH_2O), 3.66(S,3H,C=COMe), 3.38(S,3H,OMe), 2.92(dd,1H, J=11Hz,J=13Hz,H5α), 2.69(d,3H,J=6Hz,Me), 2.50-1.16(m,10H).

MS 306(100%,M^+), 245(28%), 45(70%).

λ_{max} 253(14,800) nm.

δ 199.7, C(2); 180.6, C(4); 128.4 and 128.0, CH=CH; 101.7, C(3); 96.2, OCH_2O; 77.6, C(6); 56.0, C=CO<u>C</u>H_3; 55.5, OMe; 47.0, C(4a); 45.9*, C(9a); 45.0*, C(1); 37.9, C(7); 37.6, C(5); 36.5, C(10); 23.7, C(8); 21.2, C(9); 13.4, Me.

*may be interchanged.

(1α,4aα,6β,7α,9aβ)-4-Methoxy-6-methoxymethyloxy-1-(1'Z-propenyl)-1-(2'-propenyl)-5,6,7,8,9,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one 109

A solution of methoxyenone 103 (30mg, 0.1mmol) in dry THF (2ml) was added to a solution of lithium diisopropylamide (0.3mmol) in dry THF (1ml) at 25° under an atmosphere of nitrogen. Stirring was continued at 25° for 1½ hr and the mixture was cooled to 0°. Allyl bromide (35ml, 0.4mmol) was added dropwise. The reaction mixture was further stirred for 1½ hr at 0° and worked up as described for the preparation of 106. Purification by p.l.c. (ether) gave 109 (R_f~0.45, 7mg, 20%) and 106 (R_f~0.25,17mg, 57%). Methoxyenone 106 was identical (t.l.c., ^{1}H n.m.r.) to an authentic sample.

109: Distillation, b.p.(Kugelrohr) 76°(.008mm), afforded a colourless oil. (Accurate mass: Found 346.2149. $C_{21}H_{30}O_4$ requires 346.2144.)

ν_{max} 1640(C=O), 1600(3 x C=C) cm^{-1}

δ 5.95-4.79(m,5H), 5.33(S,1H,C<u>H</u>=COMe), 4.64(S,2H,OCH_2O), 4.27 (m,1H,W½=13Hz, C<u>H</u>OCH_2O), 3.66(S,3H,C=COMe), 3.37(S,3H,OMe), 3.11-1.07(m,15H).

MS 346(100%,M^+), 305(88%,M-CH_2=$CHCH_2$), 285(27%), 45(133%).

CHAPTER 4

Ethyl (1α,4aβ,6α,7β,9aα)-6-methoxymethyloxy-4-oxo-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 111

Enone 82 (308mg, 1mmol) in ethyl acetate (20ml) was hydrogenated at atmospheric pressure at 25° for 1½ hr using 10% palladium on calcium carbonate (31mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* and the residue purified by flash chromatography (4g, 5% ether-dichloromethane) to give 111 (295mg, 95%) as a colourless oil. Distillation, b.p.(Kugelrohr) 70°(0.5mm) afforded an analytical sample. (Found: C, 66.16; H, 8.65. $C_{17}H_{26}O_5$ requires C, 65.78; H, 8.44%.)

ν_{max} 1705(C=O and ester) cm^{-1}.

δ 4.64(S,2H,OCH_2O), 4.21(m,1H,W½=14Hz,C<u>H</u>OCH_2O), 4.17(q,2H,J=7Hz, CO_2CH_2), 3.37(S,3H,OMe), 3.05(dd,1H,J=11Hz,J=15Hz,H5α), 3.08(m 1H,W½=13Hz,$CHCO_2$), 2.60-1.31(m,14H), 1.27(t,3H,J=7Hz,Me).

MS 310(21%, M^+), 266(27%), 265(79%), 250(25%), 249(35%), 248 (100%), 223(24%), 207(53%), 175(26%), 133(21%), 45(100%).

δ 210.9, C(4); 174.9, <u>C</u>O_2Et; 96.2, OCH_2O; 77.1, C(6); 60.7, $CO_2\underline{C}H_2$; 56.1, C(4a); 55.5, OMe; 45.2, C(1); 43.7, C(9a); 38.5, C(7); 37.6, C(5); 36.1, C(10); 29.8*, C(3); 29.1*, C(2); 23.4, C(8); 22.7, C(9); 14.3, Me.

*may be interchanged.

Ethyl (1α,4aβ,6α,7β,9aα)-4-ethylenedioxy-6-hydroxy-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 113

A solution of ketone 111 (310mg, 1mmol), ethylene glycol (0.56ml, 10mmol), and *p*-toluensulphonic acid (1 crystal) in dry benzene (40ml) was heated under reflux for 17hr under an atmosphere of nitrogen with water removal via a Dean and Stark apparatus. The volatiles were carefully removed under reduced pressure and the residue was purified by flash chromatography (4g, 20% ether-dichloromethane) to give 113 (300mg, 97%). Distillation, b.p.(Kugelrohr) 92°(.02mm), gave 113 as a viscous gum. (Found: C, 65.89; H, 8.31. $C_{17}H_{26}O_5$ requires C, 65.78; H, 8.44.)

ν_{max} 1705(ester) cm^{-1}.

δ 4.34(m,1H,$W_{½}$=15Hz, CHOH), 4.10(q,2H,J=7Hz,CO_2CH_2), 3.93 (S,4H,OCH_2CH_2O), 2.83-1.03(m,16H), 1.24(t,3H,J=7Hz,Me).

MS 310(26%,M^+), 265(16%,M-OEt), 248(10%), 237(12%), 195(43%), 186(22%), 100(27%), 99(100%), 43(86%).

Ethyl (1α,4aβ,6α,7β,9aα)-4-ethylenedioxy-6-methoxymethyloxy-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 114

Alcohol 113 (300mg, 0.97mmol) was treated with diisopropylethylamine (0.5ml, 2.9mmol) and chloromethyl methyl ether (0.15ml, 1.9mmol) using the same procedure employed for the preparation of 49. Purification by flash chromatography (3g, 7% ether-dichloromethane) gave 322mg (91% from ester 111) of a colourless oil. A portion was distilled, b.p.(Kugelrohr) 98°(.2mm), to afford an analytical sample. (Found: C, 64.46; H, 8.62. $C_{19}H_{30}O_6$ requires C, 64.39; H, 8.53%.)

ν_{max} 1715(ester) cm^{-1}.

δ 4.61(S,2H,OCH_2O), 4.14(m,1H,W½=14Hz,C<u>H</u>OCH_2O), 4.11(q,2H, J=7Hz,CO_2CH_2), 3.93(S,4H,OCH_2CH_2O), 3.36(S,3H,OMe), 2.74 (m,1H,W½=21Hz,$CHCO_2$), 2.43-1.08(m,14H), 1.23(t,3H, J=7Hz,Me).

MS 354(3%,M^+), 239(10%), 186(7%), 100(10%), 99(100%), 86(22%).

δ 175.8, <u>C</u>O_2Et; 110.6m C(4); 96.0, OCH_2O; 77.7, C(6); 65.1 and 64.6, OCH_2CH_2O; 60.2, $CO_2\underline{C}H_2$; 55.5, OMe; 50.3, C(4a); 43.9*, C(1); 42.4*, C(9a); 38.2, C(7); 36.4, C(10); 32.6, C(5); 30.3, C(3); 26.8, C(2); 23.9, C(8); 22.9, C(9); 14.3, Me.

*may be interchanged.

<u>Ethyl (1α,4aβ,6α,7β,9aα)-4-ethylenedioxy-6-hydroxyethyloxy-methyloxy-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 115</u>

A solution of ketone <u>111</u> (500mg, 1.6mmol), ethylene glycol (0.9ml, 16mmol) and *p*-toluensulphonic acid (1 crystal) in dry benzene (50ml) was heated under reflux for 28 hr under an atmosphere of nitrogen with water removal via a Dean and Stark apparatus. The volatiles were carefully removed under reduced pressure and the residue was filtered through a small amount of silica gel to give a mixture of 3 products. These were separated using medium pressure liquid chromatography (20% ether-dichloromethane) to give, in order of increasing retention, <u>114</u> (60mg, 10%) and <u>113</u> (354mg, 71%). The column was reverse flushed with ethyl acetate to give <u>115</u>, which was then purified by flash chromatography (3g, 10% ether-dichloromethane) to afford 72mg (11%).

115:

A portion was distilled, b.p.(Kugelrohr) 103°(.06mm). (Accurate Mass: Found 384.2158. $C_{20}H_{32}O_7$ requires 384.2148.)

ν_{max} 3415(OH), 1705(ester) cm^{-1}.

δ 4.70(S,2H,OCH_2O), 4.20(m,1H,W½=15Hz,C<u>H</u>OCH_2O), 4.11(q,2H,J=7Hz,CO_2CH_2), 3.92(S,4H,OCH_2CH_2O), 3.69(S,4H,$OC\underline{H}_2C\underline{H}_2OH$), 2.75(br.S,1H,exch.,OH), 2.83-1.12(m,15H), 1.23(t,3H,J=7Hz, Me).

MS 384(3%,M^+), 356(1%), 339(4%), 309(12%), 293(25%), 269(47%), 186(23%), 100(39%), 99(100%), 86(59%), 45(24%).

δ 175.8,<u>C</u>O_2Et; 110.5, C(4); 95.3, OCH_2O; 77.4, C(6); 71.0, $O\underline{C}H_2CH_2OH$; 64.6 and 65.1, OCH_2CH_2O; 62.4, CH_2OH; 60.2, $CO_2\underline{C}H_2$; 50.3, C(4a); 43.9*, C(1); 42.4*, C(9a); 38.1, C(7); 36.1, C(10); 32.6, C(5); 30.1, C(3); 26.8, C(2); 23.8, C(8); 22.9, C(9); 14.3, Me.

*may be interchanged.

Attempted alkylation of ester 114

(a) With lithium diisopropylamide and allyl bromide

A solution of ester 114 (35mg, 0.1mmol) in dry THF (2ml) was added dropwise to a solution of lithium diisopropylamide (0.2mmol) and HMPA (0.03ml, 0.2mmol) in dry THF (2ml) at -78° under an atmosphere of nitrogen. The reaction mixture was stirred at -78° for 1 hr and allyl bromide (20µl, 0.25mmol) added. After 30 min. at -78°, the temperature was allowed to increase slowly to 25° over a period of 3 hr. The mixture was further stirred for 1 hr at 25°, cooled to 0° and ice-water (10ml) added. The reaction was worked up as described for 73 to return unchanged ester (t.l.c., ^1H n.m.r.).

(b) With potassium hydride and allyl bromide

Potassium hydride (8mg, 0.2mmol) was added to a solution of 114 (35mg, 0.1mmol) and allyl bromide (20µl, 0.25mmol) in dry THF (2ml) at 25° under a nitrogen atmosphere. The reaction mixture was stirred for 2 hr at 25°, cooled to 0° and *tert*-butanol (0.5ml) added. Water (10ml) was added and the mixture was extracted with ethyl acetate (3 x 10ml). Sequential washing of the organic extracts (water 1 x 10ml, brine 1 x 10ml), drying and removal of the solvents afforded unchanged ester (t.l.c., ^{1}H n.m.r.).

(c) With lithium cyclohexylisopropylamide and methyl iodide

A solution of ester 114 (35mg, 0.1mmol) in dry THF (2ml) was added dropwise to a solution of lithium cyclohexylisopropylamide[†] (0.2mmol) in THF (2ml) at 0° under a nitrogen atmosphere. The reaction mixture was stirred at 25° for 2 hr, cooled to 0° and methyl iodide (20µl, 0.3mmol) added. Stirring was continued for 2 hr at 0°. The reaction was worked up as described for 73 to return unchanged ester (t.l.c., ^{1}H n.m.r.).

116 and 117

A solution of diisobutylaluminium hydride in benzene (0.62ml, 1.1mmol) was added dropwise to a solution of ester 114 (354mg, 1mmol) in dry toluene (6ml) at -78° under a nitrogen atmosphere. Stirring was continued for 1 hr at -78°,

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[†] A solution of lithium cyclohexylisopropylamide was prepared from *N*,*N*-cyclohexylisopropylamine and *n*-butyl lithium as described for lithium diisopropylamide.

acetone (1ml) was added and the solution was allowed to warm up to 25°. A saturated aqueous sodium sulphate solution (0.2ml) and ethyl acetate (10ml) were added, and the reaction was worked up as described for 81(a). Separation by flash chromatography (4g, 10% and 50% ether-dichloromethane) gave 116 (229mg, 74%) and 117 (62mg, 20%).

116: (1α,4aβ,6α,7β,9aα)-4-Ethylenedioxy-6-methoxymethyloxy-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carbaldehyde

Distillation, b.p.(Kugelrohr) 81°(.005mm), afforded a colourless oil. (Found: C, 65.64; H, 8.59. $C_{17}H_{26}O_5$ requires C, 65.78; H, 8.44%.)

ν_{max} 1710(C=O) cm^{-1}

δ 9.40(d,1H,J=4Hz,CHO), 4.62(S,2H,OCH_2O), 4.16(m,1H,W½=15Hz, C<u>H</u>OCH_2O), 3.95(S,4H,OCH_2CH_2O), 3.36(S,3H,OMe), 2.94-1.10(m,15H).

MS 310(1%,M^+), 282(17%,M-CO), 142(12%), 99(78%), 87(95%), 86(100%).

δ 205.1, CHO; 110.5, C(4); 96.0, OCH_2O; 77.6, C(6); 65.1 and 64.7, OCH_2CH_2O; 55.5, OMe; 49.9, C(4a); 49.4, C(1); 40.0, C(9a); 37.9, C(7); 36.3, C(10); 32.9, C(5); 29.5*, C(3); 23.7*, C(8); 23.3*, C(2); 22.1, C(9).

*may be interchanged.

117: 1-[(1α,4aβ,6α,7β,9aα)-4-ethylenedioxy-6-methoxymethyloxy-decahydro-4a,7-methano-4a*H*-benzocycloheptenyl]-methanol

Distillation, b.p.(Kugelrohr) 82°(.1mm), afforded a colourless oil. (Found: C, 65.32; H, 9.24. $C_{17}H_{28}O_5$ requires C, 65.36; H, 9.03%.)

ν_{max} 3530(OH) cm^{-1}.

δ 4.63(S,2H,OCH_2O), 4.29-3.43(m,3H,C<u>H</u>OCH_2O and C<u>H_2</u>OH), 3.93 (S,4H,OCH_2CH_2O), 3.37(S,3H,OMe), 2.02(br.S,1H,exch.,OH), 2.45-1.12(m,15H).

MS 312(16%,M^+), 239(25%), 99(100%).

δ 111.2, C(4); 96.0, OCH_2O; 78.0, C(6); 66.1, CH_2OH; 65.0 and 64.6, OCH_2CH_2O; 55.5, OMe; 50.5, C(4a); 42.4, C(9a); 38.3, C(7); 36.9, C(1); 36.5, C(10); 33.0, C(5); 30.7*, C(3); 26.8*, C(2); 23.9, C(8); 20.5, C(9).

*may be interchanged.

Pyridinium dichromate (376mg, 1mmol) was added to a solution of alcohol <u>117</u> (156mg, 0.5mmol) in dry dichloromethane (10ml) under an atmosphere of nitrogen. Stirring was continued for 16 hr at 25°. Ether (40ml) was added slowly from a pipette with continuous stirring. The resulting precipitate was removed by filtration (celite) and removal of the solvents gave an orange oil. Purification by flash chromatography (3g, 10% ether-dichloromethane) afforded aldehyde <u>116</u> (136mg, 88%) as a colourless oil, which was identical (t.l.c., ^1H n.m.r.) to the previously characterised material.

<u>(1α,4aα,6β,7α,9aβ)-4-Ethylenedioxy-6-methoxymethyloxy-1-methyl-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carbaldehyde 118</u>

A solution of aldehyde <u>116</u> (31mg, 0.1mmol) in dry *tert*-butanol (3.5ml) was added dropwise to a solution of potassium

tert-butoxide (0.3mmol)[†] in dry *tert*-butanol (2.3ml) at 25° under a nitrogen atmosphere. The solution was stirred for 90 min., methyl iodide (25µl, 0.4mmol) was added dropwise and stirring was continued for 1 hr. Water (10ml) was added and the mixture extracted with ether (3 x 10ml). Sequential washing of the extracts (water 1 x 10ml, brine 1 x 10ml), drying, solvent removal and purification by flash chromatography (3g, 10% ether-dichloromethane) gave 118 (23mg, 70%). Distillation, b.p.(Kugelrohr) 74°(.005mm), afforded a colourless oil. (Found: C, 66.60; H, 8.47. $C_{18}H_{28}O_5$ requires C, 66.64; H, 8.70%.)

ν_{max} 1705(C=O) cm^{-1}.

δ 9.90(S,1H,CHO), 4.62(S,2H,OCH_2O), 4.13(m,1H,$W_{½}$=14Hz,C<u>H</u>OCH_2O), 3.94(S,4H,OCH_2CH_2O), 3.36(S,3H,OMe), 2.43-1.01(m,14H), 1.08(S,3H,Me).

MS 324(1%,M^+), 296(3%), 155(6%), 99(100%), 87(37%), 86(52%).

δ 206.2, CHO; 110.5, C(4); 95.9, OCH_2O; 77.6, C(6); 64.5, 2 x OCH_2; 55.4, OMe; 50.9*, C(1); 50.7*, C(4a); 49.4, C(9a); 37.9, C(7); 37.4, C(10); 32.7, C(5); 29.9**, C(3); 28.3**, C(2); 26.5, C(8); 24.2, Me; 19.2, C(9).

*, ** may be interchanged.

[†] A 1M solution of potassium *tert*-butoxide was prepared by adding clean potassium metal (391mg) to anhydrous *tert*-butanol (10ml) under an atmosphere of nitrogen and stirring overnight at 25°.

(1α,4aα,6β,7α,9aβ)-4-Ethylenedioxy-6-methoxymethyloxy-1-(2'-propenyl)-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carbaldehyde 110

Aldehyde 116 (62mg, 0.2mmol), in dry *tert*-butanol (7ml), was treated with potassium *tert*-butoxide (0.6mmol) and allyl bromide (70µl, 0.8mmol) using the same procedure employed for the preparation of 118. Purification of the residue by flash chromatography (3g, 10% ether-dichloromethane) gave 110 (52mg, 74%). Distillation, b.p.(Kugelrohr) 65°(.05mm), afforded a colourless oil. (Found: C, 68.58; H, 8.72. $C_{20}H_{30}O_5$ requires C, 68.55; H, 8.63%.)

ν_{max} 1710(C=O) cm^{-1}.

δ 9.91(S,1H,CHO), 5.60(m,1H,W½=24Hz,CH_2=C<u>H</u>), 5.06(m,2H,W½=15Hz,C<u>H</u>$_2$=CH), 4.63(S,2H,OCH_2O), 4.17(m,1H,W½=15Hz,C<u>H</u>OCH_2O), 3.93(S,4H,OCH_2CH_2O), 3.35(S,3H,OMe), 2.71-1.05(m,16H).

MS 350(9%,M^+), 322(10%), 318(9%), 309(8%), 305(7%), 182(7%), 141(8%), 126(33%), 99(100%), 87(43%), 86(60%), 45(26%).

δ 206.1, CHO; 132.2, CH_2=<u>C</u>H; 118.9, <u>C</u>H_2=CH; 110.8, C(4); 95.9, OCH_2O; 77.6, C(6); 64.7 and 64.5, OCH_2CH_2O; 55.4, OMe; 52.5, C(1); 50.6, C(4a); 48.5, C(9a); 40.7, CH_2 CH<u>C</u>H_2; 37.9, C(7); 37.4, C(4); 32.7, C(5); 27.9*, C(3); 26.6*, C(8); 26.4*, C(2); 18.6, C(1).

* may be interchanged.

1-[(1α,4aα,6β,7α,9aβ)-1-Ethylenedioxy-6-methoxymethyloxy-1-(2'-propenyl)-decahydro-4a,7-methano-4a*H*-benzocycloheptenyl]-methanol 119

Sodium borohydride (11mg, 0.3mmol) was added to a solution of 110 (105mg, 0.3mmol) in ethanol (10ml) at 0° under an

atmosphere of nitrogen. Stirring was continued at 0° for 1 hr, the ethanol carefully removed and the residue partitioned between water (15ml) and ether (15ml). The layers were separated and the aqueous phase was re-extracted with ether (2 x 15ml). The organic extracts were washed with water (1 x 15ml), brine (1 x 15ml) and dried. Removal of the solvents and purification of the residue by flash chromatography (3g, 10% and 30% ether-dichloromethane) gave alcohol 119 (89mg, 85%). Distillation, b.p.(Kugelrohr) 77°(.01mm), afforded a colourless oil. (Found: C, 67.93; H, 9.24. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15%.)

ν_{max} 3500(OH) cm^{-1}.

δ 5.88(m,1H,$W_{\frac{1}{2}}$=23Hz,CH_2=C<u>H</u>), 5.01(m,2H,$W_{\frac{1}{2}}$=18Hz,C<u>H</u>$_2$=CH), 4.61 (S,2H,OCH_2O), 4.09(m,1H,$W_{\frac{1}{2}}$=15Hz,C<u>H</u>OCH_2O), 4.05 and 3.65 (AB_q[†],J_{AB}=11Hz,C<u>H</u>$_2$OH), 3.91(S,4H,OCH_2CH_2O), 3.34(S,3H,OMe), 2.52-1.05(m,17H).

δ 135.7, CH_2=<u>C</u>H; 117.5, <u>C</u>H_2=CH; 111.2, C(4); 96.0, OCH_2O; 77.4, C(6); 65.8, CH_2OH; 64.6, 2 x OCH_2; 55.5, OMe; 50.5, C(4a); 45.7*, C(1); 42.8*, C(9a); 42.8, CH_2=CH<u>C</u>H_2; 38.9, C(10); 37.9, C(7); 34.0, C(5); 27.9**, C(3); 27.3**, C(2); 26.1, C(8); 18.6, C(1).

*,** may be interchanged.

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† Analysed using the formula described by Jackman and Sternhell.[159]

(1α,4β,4aα,6β,7α,9aβ)-6-Methoxymethyloxy-1-(2'-propenyl)-decahydro-4,1-epoxymethane-4a,7-methano-4a*H*-benzocyclohepten-4-ol 120

6% Hydrochloric acid (2.5ml) was added to a solution of acetal 119 (35mg, 0.1mmol) in acetone (5ml) at 0°. Stirring was continued for 9 hr at 4°, and water (15ml) and ethyl acetate (15ml) were added. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 10ml). The organic extracts were washed with water (1 x 10ml), brine (1 x 10ml) and dried. Removal of the solvents and purification of the residue by flash chromatography (2g, 10% ether-dichloromethane) gave 120 (24mg, 79%). Distillation, b.p. (Kugelrohr) 91°(.1mm), afforded a colourless oil. (Found: C, 69.95; H, 9.23. $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15%.)

ν_{max} 3500(OH) cm^{-1}.

δ 5.71(m,1H,$W_{½}$=23Hz,CH_2=C<u>H</u>), 5.03(m,2H,$W_{½}$=16Hz,C<u>H</u>$_2$=CH), 4.61 (S,2H,OCH_2O), 4.06(m,1H,$W_{½}$=15Hz,C<u>H</u>OCH_2O), 4.07 and 3.63 (ABq†,J_{AB}=10Hz,CH_2O), 3.36(S,3H,OMe), 2.84(br.S,1H,exch.,OH), 2.61-2.29(m,2H), 2.12-0.98(m,14H).

MS 308(55%,M^+), 276(11%), 263(21%), 246(43%), 245(32%), 217 34%), 205(43%), 107(68%), 95(62%), 93(79%), 91(68%), 79(100%).

δ 133.3, CH_2=C<u>H</u>; 117.7, C<u>H</u>$_2$=CH; 96.3, C(4); 95.6, OCH_2O; 78.1, C(6); 70.8, CH_2O; 55.5, OMe; 51.1, C(1) and C(9a); 49.4, C(4a); 43.7, CH_2=CHC<u>H</u>$_2$; 37.7, C(7); 34.7, C(5); 31.5, C(10); 30.5, C(3); 26.5, C(2); 18.7, C(8); 16.1, C(9).

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† Analysed using the formula described by Jackman and Sternhell.[159]

(1α,4aα,6β,7α,9aβ)-6-Methoxymethyloxy-4-oxo-1-(2'-propenyl)-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carbaldehyde 123

6% Hydrochloric acid (2ml) was added to a solution of acetal 110 (21mg, 0.06mmol) in acetone (4ml) at 0°. Stirring was continued for 36 hr at 4°, and water (10ml) and ether (10ml) were added. The layers were separated and the aqueous phase was re-extracted with ether (2 x 10ml). The organic extracts were washed with brine (1 x 10ml) and dried. Removal of the solvents gave 123 (^{1}H n.m.r. analysis established the presence of a small amount of starting material). Purification by flash chromatography (2g, 5% ether-dichloromethane) afforded 123 (16mg, 89%) as a colourless oil. Distillation, b.p. (Kugelrohr) 77°(.01mm), provided an analytical sample. (Found: C, 70.52; H, 8.79. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55%.)

$\nu_{max.}$ 1700(2 x C=O) cm^{-1}.

δ 9.97(S,1H,CHO), 5.52(m,1H,W½=20Hz,CH_2=C<u>H</u>), 5.06(m,2H,W½=14Hz, C<u>H</u>$_2$=CH), 4.61(S,2H,OCH_2O), 4.16(m,1H,W½=14Hz,C<u>H</u>OCH_2O), 3.36(S,3H,OMe), 3.01(dd,1H,J=11Hz,J=15Hz,H5α), 2.79-1.04(m,15H).

MS 306(14%, M^+), 274(10%), 261(35%), 99(100%).

Ethyl (1α,4aβ,6α,7β,9aα)-3-hydroxymethylene-6-methoxymethyloxy-4-oxo-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate 129

A solution of 111 (620mg, 2mmol) in dry benzene (9ml) was added to a stirred mixture of sodium hydride (216mg, 9mmol), dry ethanol (0.01ml) and dry ethyl formate (0.8ml, 10mmol) in dry benzene (5ml) under an atmosphere of nitrogen. Stirring

was continued for 16 hr at 25°. Water (20ml) and ether (30ml) were added and the mixture was acidified to pH 1 with 6% hydrochloric acid. The layers were separated and the aqueous phase was re-extracted with ether (2 x 20ml). The organic extracts were washed with brine (1 x 20ml) and dried. The solvents were removed and the product was purified by flash chromatography (5g, 5% ether-dichloromethane) to afford 129 (575mg, 85%) as a pale yellow oil. (Accurate mass: Found 338.1718. $C_{18}H_{26}O_6$ requires 338.1729.)

ν_{max} 1725(sh. ester), 1715(C=O) cm^{-1}.

δ 14.45(e,1H,W½=14Hz,OH), 8.44(S,1H,C=CH), 4.64(S,2H,OCH_2O), 4.32(m,1H,W½=14Hz,C<u>H</u>OCH_2O), 4.17(q,2H,J=7Hz,CO_2CH_2), 3.38(S,3H,OMe), 2.96(dd,1H,J=10Hz,J=14Hz,H5α), 3.18-1.12(m,12H), 1.28(t,3H,J=7Hz,Me).

MS 338(12%,M^+), 308(20%), 293(31%), 276(100%), 264(37%), 251(33%), 248(36%), 219(38%), 203(33%), 189(35%), 91(49%).

<u>Ethyl (1α,4aβ,6α,7β,9aα)-3-diazo-6-methoxymethyloxy-4-oxo-decahydro-4a,7-methano-4a*H*-benzocycloheptene-1-carboxylate</u> <u>130</u>

A solution of *p*-toluenesulphonyl azide (400mg, 2mmol) in dry acetonitrile (3ml) was added slowly dropwise over a period of 10 min. to a solution of <u>129</u> (575mg, 1.7mmol) and triethylamine (0.71ml, 5.1mmol) in dry acetonitrile (15ml) at -15° (ice-acetone) under a nitrogen atmosphere. The reaction mixture was stirred at -15° for 30 min., and an aqueous 0.25M solution of potassium hydroxide (20ml) was added. Stirring was continued for 5 min. and the product extracted with dichloromethane (3 x 30ml). Sequential washing of the

extracts (0.25M potassium hydroxide 3 x 20ml, brine 1 x 20ml), drying and solvent removal left a yellow oil. Purification by flash chromatography (5g, dichloromethane and 10% ether-dichloromethane) gave 130 (532mg, 93%) as a yellow oil. [Accurate mass ($M-N_2$ peak): Found 308.1627. $C_{17}H_{24}O_5$ requires 308.1624.]

ν_{max} 2070,1705($COCN_2$), 1720(ester) cm^{-1}.

δ 4.63(S,2H,OCH_2O), 4.29(m,1H,$W_{\frac{1}{2}}$=14Hz,C<u>H</u>OCH_2O), 4.18(q,2H, J=7Hz,CO_2CH_2), 3.39(S,3H,OMe), 3.20-2.72(m,4H), 2.45-1.17(m,9H), 1.28(t,3H,J=7Hz,Me).

MS 308(42%,$M-N_2$), 246(79%), 219(35%), 173(93%), 155(80%), 119 (60%), 117(100%), 91(93%).

(1α,3β,3aβ,5α,6β,8aα)-1-Ethoxycarbonyl-5-methoxymethyloxy-octahydro-1*H*-3a,6-methanoazulene-3-carboxylic acid 124

A solution of diazoketone 130 (256mg, 0.7mmol) and sodium hydrogen carbonate (1.2g, 14mmol) in THF (40ml) and water (115ml) was photolysed (450W Hanovia lamp, pyrex filter, nitrogen bubbled through solution) for 1 hr at 0°. Ethyl acetate (100ml) was added and the solution was acidified slowly to pH 1 with 12% hydrochloric acid. The layers were separated, and the aqueous phase was re-extracted with ethyl acetate (2 x 50ml). The extracts were washed with brine (1 x 50ml), dried and the solvents removed. The residue was dissolved in dichloromethane (50ml) and washed with a 10% aqueous sodium carbonate solution (2 x 50ml). The alkaline washings were acidified to pH 1 with 12% hydrochloric acid and extracted with ethyl acetate (3 x 50ml). The extracts were washed with brine (1 x 50ml), dried and the solvent was removed to give acid 124 (216mg, 87%) as a discrete diastereomer. A sample

was purified by flash chromatography (2.5g, 10% ether-dichloromethane) and distilled, b.p.(Kugelrohr) 82°(.007mm) to afford a colourless oil. (Found: C, 62.27; H, 7.79. $C_{17}H_{26}O_6$ requires C, 62.58; H, 8.03%.) Recrystallisation from ether-light petroleum gave colourless crystals, m.p. 201-203° (sweats from 162°).

ν_{max} 3510(OH), 1725(ester and acid) cm^{-1}.

δ 8.14(e,1H,$W_{½}$=38Hz,exch.,OH), 4.65(S,2H,OCH_2O), 4.16(q,2H, J=7Hz,CO_2CH_2), 4.18(m,1H,$W_{½}$=14Hz,C<u>H</u>OCH_2O), 3.39(S,3H,OMe), 3.04-1.07(m,14H),1.27(t,3H,J=7Hz,Me).

MS 326(7%,M^+), 308(6%,M-H_2O), 294(16%), 281(47%), 266(34%), 264(84%), 248(43%), 219(63%) 191(75%) 119(56%), 117(100%), 91(69%).

δ 178.5, CO_2H; 176.2, <u>C</u>O_2Et; 96.0, OCH_2O; 77.2, C(5); 60.7 CO_2<u>C</u>H_2; 55.5, OMe; 52.6*, C(8a); 52.4*,C(3a); 48.7, C(3); 44.7*, C(1); 39.4, C(4); 36.9, C(6); 32.9, C(9); 29.2, C(2); 23.4, C(7); 19.9, C(8); 14.4, Me.

* may be interchanged.

<u>(1α,4aα,6β,7α,9aα)-6-Methoxymethyloxy-1-methyl-octahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one 125</u>

Enone <u>87</u> (330mg, 1.3mmol) in ethyl acetate (20ml) was hydrogenated at atmospheric pressure at 25° for 2 hr using 10% palladium on calcium carbonate (33mg) as a catalyst. The filtered solution (celite) was concentrated *in vacuo* to give ketone <u>125</u> (326mg, 98%). Distillation of a sample, b.p. (Kugelrohr) 55°(.005mm) afforded a colourless oil. (Found: C, 71.32; H, 9.50. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%.)

ν_{max} 1695(C=O) cm^{-1}.

δ 4.63(S,2H,OCH_2O), 4.18(m,1H,$W_{½}$=14Hz,C<u>H</u>OCH_2O), 3.37(S,3H, OMe), 2.48-1.03(m,15H), 0.91(d,3H,J=7Hz,OMe).

MS 252(60%,M^+), 220(15%,M-MeOH), 207(100%, M-CH_2OMe), 197 (54%), 192(57%), 165(38%).

δ 214.0, C(4); 96.2,OCH_2O; 78.0, C(6); 55.5, OMe; 55.1, C(4a); 51.7, C(9a); 40.2, C(2); 37.4*, C(7); 36.8*, C(5) and C(10); 35.1, C(1); 33.9, C(3); 26.4, C(8); 25.1, C(9); 18.5, Me.

* may be interchanged.

<u>(1α,4aα,6β,7α,9aα)-3-Hydroxymethylene-6-methoxymethyloxy-1-methyl-octahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one 126</u>

Ketone <u>125</u> (326mg, 1.3mmol), in dry benzene (20ml) was treated with sodium hydride (94mg, 3.9mmol), dry ethanol (10μl) and dry ethyl formate (0.42ml, 5.2mmol), using the same procedure employed for the preparation of <u>129</u>. Purification of the residue by flash chromatography (4g, 5% ether-dichloromethane) gave <u>126</u> (304mg, 84%) as a pale yellow oil. (Accurate mass: Found 280.1672. $C_{16}H_{24}O_4$ requires 280.1674.)

ν_{max} 3130(OH), 1715(C=O) cm^{-1}.

δ 8.77(S,1H,C=CH), 4.64(S,2H,OCH_2O), 4.32(m,1H,$W_{½}$=14Hz, C<u>H</u>OCH_2O), 3.38(S,3H,OMe), 2.53-1.08(m,13H), 0.95(d,3H, J=7Hz,Me).

MS 280(52%,M^+), 252(34%), 234(45%), 218(56%), 206(59%), 205 (53%), 204(100%), 45(>100%).

(1α,4aα,6β,7α,9aα)-3-Diazo-6-methoxymethyloxy-1-methyl-octahydro-4a,7-methano-4a*H*-benzocyclohepten-4(1*H*)-one 127

Compound 126 (304mg, 1.1mmol) in dry acetonitrile (18ml), was treated with triethylamine (0.46ml, 3.3mmol) and *p*-toluenesulphonyl azide (250mg, 1.27mmol), using the same procedure employed for the preparation of 130. Purification of the residue by flash chromatography (5g, dichloromethane and 10% ether-dichloromethane) gave 127 (265mg, 88%) as a yellow oil. [Accurate mass ($M-N_2$ peak): Found 250.1565. $C_{15}H_{22}O_3$ requires 250.1569.]

ν_{max} 2075,1595($COCHN_2$) cm^{-1}.

δ 4.57(S,2H,OCH_2O), 4.27(S,1H,C<u>H</u>OCH_2O), 3.39(S,3H,OMe), 3.08-0.92(m,13H), 1.02(d,3H,J=7Hz,Me).

MS 250(70%,$M-N_2$), 220(51%), 189(55%), 161(100%), 45(67%).

(1α,3β,3aα,5β,6α,8aα)-5-Methoxymethyloxy-1-methyl-octahydro-1*H*-3a,6-methanoazulene-3-carboxylic acid 128

Diazoketone 127 (265mg, 0.95mmol) in THF (50ml) and water (105ml) was photolysed as described for the preparation of 124 to give acid 128. Purification by flash chromatography (5g, 5% and 15% ether-dichloromethane) afforded 197mg (77%) of a colourless oil. Distillation, b.p.(Kugelrohr) 78°(.1mm), provided an analytical sample. (Found: C, 66.91; H, 8.88. $C_{15}H_{24}O_4$ requires C, 67.14; H, 9.01%.) Recrystallisation from light petroleum gave colourless crystals, m.p.98-100° (sweats from 81°).

ν_{max} 1710(CO_2H) cm^{-1}.

$\delta^{\dagger}$ 4.62(S,2H,OCH_2O), 4.19(m,1H,$W_{\frac{1}{2}}$=15Hz,C<u>H</u>OCH_2O), 3.35(S,3H, OMe), 2.88-1.06(m,14H), 0.94(d,3H,J=7Hz,Me).

MS 268(3%,M^+), 236(9%), 223(8%), 206(100%), 45(86%).

δ 180.0, CO_2H; 95.9, OCH_2O; 78.2, C(5); 57.3, C(3); 55.5, OMe; 53.0*, C(3a); 49.5*, C(8a); 41.6, C(9); 38.1, C(6); 35.7, C(4); 33.8, C(1) and C(2); 26.4, C(7); 24.7, C(8); 19.2, Me.

* may be interchanged.

<u>(1α,3β,3aβ,5α,6β,8aα)-1-Hydroxymethyl-5-methoxymethyloxy-octahydro-1*H*-3a,6-methanoazuluene-3-carboxylic acid 142</u>

A solution of lithium triethylborohydride in THF (2.5ml, 2.5mmol) was added dropwise to a solution of <u>124</u> (163mg, 0.5mmol) in dry THF (4ml) at 25° under an atmosphere of nitrogen. Stirring was continued for 10 min., aqueous solutions of 2% disodium hydrogen phosphate solution (2ml, pH∿9.1) and 30% hydrogen peroxide (0.75ml) were added, and the mixture was heated between 40° and 50° for 1 hr. Water (10ml) and ethyl acetate (20ml) were added, and the solution was acidified to pH 1 with 12% hydrochloric acid. The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 15ml). Sequential washing of the extracts (water 1 x 10ml, brine 1 x 10ml), drying and removal of the solvents left acid <u>142</u> (140mg, 99%). A sample was purified by flash chromatography (3g, 20% and 50% ether-dichloromethane) and distilled, b.p.(Kugelrohr) 92°(.008mm), to provide an analytical

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† This spectrum was recorded on a Varian HA-100 operating at 100MHz.

sample. (Found: C, 63.25; H, 8.69. $C_{15}H_{24}O_5$ requires C, 63.36; H, 8.51%.) Recrystallisation from ether-light petroleum gave colourless crystals, m.p.109.5-111.5°.

ν_{max} 3500(OH), 1705(CO_2H) cm^{-1}.

δ 6.55(e,1H,W½=45Hz,exch.,CO_2H), 4.62(S,2H,OCH_2O), 4.18(m,1H, W½=14Hz,C<u>H</u>OCH_2O), 3.71(m,2H,W½=19Hz,CH_2OH), 3.35(S,3H,OMe), 2.82-1.08(m,15Hz).

MS 266(9%,M-H_2O), 252(30%), 234(33%), 222(71%), 221(45%), 206 (47%), 204(44%), 177(60%), 161(33%), 149(32%), 147(33%), 145(33%), 133(53%), 131(100%), 119(41%), 105(41%), 91 (70%), 79(40%).

<u>Methyl (1α,3β,3aβ,5α,6β,8aα)-1-hydroxymethyl-5-methoxymethyloxy-octahydro-1*H*-3a,6-methanoazulene-3-carboxylate</u> <u>143</u>

An ethereal solution of diazomethane was added to a solution of acid <u>142</u> (140mg, 0.49mmol) in methanol† (16ml) and dichloromethane (4ml) at 0° until a yellow colour persisted. Stirring was continued at 0° for 15 min., and the excess diazomethane was removed by boiling gently on a steam bath. The filtered solution (celite) was concentrated *in vacuo* and the residue purified by flash chromatography (5g, 10% and 30% ether-dichloromethane) to give <u>143</u> (132mg, 90%) as a colourless oil. Distillation, b.p.(Kugelrohr) 70°(.006mm), afforded an analytical sample. (Found: C,64.65; H,8.96. $C_{16}H_{26}O_5$ requires C, 64.71; H, 8.78%.)

ν_{max} 3500(OH), 1720(ester) cm^{-1}.

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† It was necessary to use methanol as a solvent so that methylation would proceed at a faster rate than the polymerisation of diazomethane, which predominated in ethereal solvents.

δ 4.63(S,2H,OCH_2O), 4.19(m,1H,W½=15Hz,C<u>H</u>OCH_2O), 3.66(S,3H, CO_2Me), 3.56(m,2H,W½=19Hz,C<u>H_2</u>OH), 3.37(S,3H,OMe), 2.47 (br.S,1H,exch.,OH), 2.84-0.93(m,14H).

MS 266(15%), 249(13%), 236(21%), 221(20%), 218(19%), 204(20%), 191(23%), 176(24%), 158(28%), 147(28%), 145(27%), 133 (38%), 131(100%), 91(59%).

δ 174.3, <u>C</u>O_2Me; 96.0, OCH_2O; 77.4, C(5); 66.1, CH_2OH; 55.5, OMe; 52.2, C(3a); 51.3, CO_2<u>C</u>H_3; 50.5*, C(8a); 48.9, C(3); 41.8*, C(1); 39.8, C(4); 36.9, C(6); 33.1, C(9); 29.4, C(2); 23.5, C(7); 20.0, C(8).

* may be interchanged.

<u>Methyl (1α,3β,3aβ,5α,6β,8aα)-1-formyl-5-methoxymethyloxy-octahydro-1*H*-3a,6-methanoazulene-3-carboxylate 144</u>

Pyridinium dichromate (300mg, 0.8mmol) was added to a solution of alcohol <u>143</u> (119mg, 0.4mmol) in dry dichloromethane (10ml) under an atmosphere of nitrogen. The suspension was stirred for 16 hr at 25° and ether (40ml) was added slowly with rapid stirring. The filtered solution (celite) was concentrated *in vacuo*, and the residue purified by flash chromatography (4g, 5% ether-dichloromethane) to give aldehyde <u>144</u> (103mg, 87%) as a colourless oil. A sample was distilled, b.p.(Kugelrohr) 68°(.008mm). [Accurate mass (M-1 peak): Found 295.1542. $C_{16}H_{23}O_5$ requires 295.1545.]

ν_{max} 1720(CHO and ester) cm^{-1}.

δ 9.60(d,1H,J=3Hz,CHO), 4.62(S,2H,OCH_2O), 4.19(m,1H,W½=14Hz, C<u>H</u>OCH_2O), 3.68(S,3H,CO_2Me), 3.36(S,3H,OMe), 2.90-0.92(m,14H).

MS 295(12%,M-H), 266(23%), 252(39%), 250(39%), 222(36%), 220 (52%), 218(33%), 206(44%), 205(45%), 204(39%), 193(46%),

191(49%), 177(32%), 161(36%), 147(46%), 145(39%), 135 (41%), 133(55%), 131(56%), 119(66%), 117(78%), 105(59%), 91(100%), 79(67%).

δ 203.2, CHO; 173.2, $\underline{C}O_2Me$; 96.0, OCH_2O; 77.2, C(5); 55.5, OMe; 52.2*, C(8a) and C(3a); 51.6, $CO_2\underline{C}H_3$; 49.5*, C(1); 49.0, C(3); 39.5, C(4); 36.6, C(6); 33.1, C(9); 26.0, C(2); 23.3, C(7); 19.6, C(8).

* may be interchanged.

(1α,3α,3aα,5β,6α,8aβ)-1-Formyl-5-methoxymethyloxy-1-(2'-propenyl)-octahydro-1*H*-3a,6-methanoazulene-3-carboxylic acid 145a and (1α,3β,3aβ,5α,6β,8aα)-1-formyl-5-methoxymethyloxy-1-(2'-propenyl)-octahydro-1*H*-3a,6-methanoazulene-3-cabroxylic acid 145b

Aldehyde 144 (45mg, 0.15mmol), in dry *tert*-butanol (4ml) was treated with potassium *tert*-butoxide (0.45mmol) and allyl bromide (50µl, 0.6mmol) using the same procedure employed for the preparation of 118. Purification of the residue by flash chromatography (2g, 20% ether-dichloromethane) afforded a 7:3 mixture (^{13}C n.m.r. analysis) of C(1)-epimers 145a-b (36mg, 71%). Distillation, b.p.(Kugelrohr) 83°(.007mm) gave a colourless oil. (Accurate mass: Found 322.1779. $C_{18}H_{26}O_5$ requires 322.1780.)

ν_{max} 3500(OH), 1705(CHO and CO_2H) cm^{-1}.

δ 9.77 and 9.72(2 x S,1H,CHO), 5.58(m,1H,W½=22Hz,$CH_2{=}C\underline{H}$), 5.07 (m,2H,W½=14Hz,$C\underline{H}_2{=}CH$), 4.20(m,1H,W½=15Hz,$C\underline{H}OCH_2O$), 3.36 (S,3H,OMe), 2.88-0.94(m,17H).

MS 322(3%,M^+), 252(100%), 236(55%), 220(31%), 206(36%), 191 (49%), 149(90%), 147(53%), 119(61%), 117(58%), 91(88%).

(1α,3α,3aα,5β,6α,8aβ)-1-Hydroxymethyl-5-methoxymethyloxy-1-(2'-propenyl)-octahydro-1*H*-3a,6-methanoazulene-3-carboxylic acid 146a and
(1α,3β,3aβ,5α,6β,8aα)-1-hydroxymethyl-5-methoxymethyloxy-1-(2'-propenyl)-octahydro-1*H*-3a,6-methanoazulene-3-carboxylic acid 146b

Sodium borohydride (5mg, 0.14mmol) was added to a solution of diastereomeric aldehydes 145a-b (23mg, 0.07mmol) in ethanol (5ml) at 0° under an atmosphere of nitrogen. Stirring was continued at 0° for 1 hr and the ethanol was carefully removed under reduced pressure. The residue was dissolved in water (5ml), acidified with 6% hydrochloric acid and extracted with ethyl acetate (3 x 15ml). The extracts were washed with brine (1 x 15ml), dried and the solvent was removed to give a mixture of the diastereomeric alcohols 145a-b (18mg, 78%). Distillation of a sample, b.p.(Kugelrohr) 91°(.005mm) afforded a colourless oil. [Accurate Mass (M-H_2O peak): Found 306.1830. $C_{18}H_{26}O_4$ requires 306.1831.]

ν_{max} 3480(OH), 1705(CO_2H) cm^{-1}.

δ 6.40-5.66(m,2H,CO_2H and $CH_2=CH$), 5.09(m,2H,$W_{½}$=14Hz,$CH_2=CH$), 4.62 and 4.58(2 x S,2H,OCH_2O), 4.11(m,1H,$W_{½}$=14Hz,$CHOCH_2O$), 3.63(m,2H,$W_{½}$=14Hz,CH_2OH), 3.38(S,3H,OMe), 2.96-1.06(m,14H).

MS 306(13%,M-H_2O), 278(11%), 261(30%), 259(23%), 232(27%), 203(25%), 191(28%), 145(40%), 131(60%), 117(60%), 105(48%), 93(45%), 91(100%).

Methyl (1α,3α,3aα,5β,6α,8aβ)-1-hydroxymethyl-5-methoxymethyloxy-1-(2'-propenyl)-octahydro-1*H*-3a,6-methanoazulene-3-carboxylate 147a and

methyl (1α,3β,3aβ,5α,6β,8aα)-1-hydroxymethyl-5-methoxymethyloxy-1-(2'-propenyl)-octahydro-1*H*-3a,6-methanoazulene-3-carboxylate 147b

An ethereal solution of diazomethane was added to a solution of the diastereomers 145a-b (32mg, 0.1mmol) in methanol (16ml) and dichloromethane (4ml) at 0° until a yellow colour persisted. Stirring was continued at 0° for 15 min., and the excess diazomethane was removed by careful boiling on a steam bath. The filtered solution (celite) was concentrated *in vacuo* and the residue purified by flash chromatography to give a mixture of the diastereomers 147a-b (31mg, 92%) as a colourless oil. An analytical sample was obtained by distillation, b.p.(Kugelrohr) 83°(.006mm). (Found: C, 67.26; H, 9.00. $C_{19}H_{30}O_5$ requires C, 67.43; H, 8.93%.)

ν_{max} 3440(OH), 1725(C=O) cm^{-1}.

δ 5.84(m,1H,$W_{½}$=25Hz,CH_2=C<u>H</u>), 5.08(m,2H,$W_{½}$=14Hz,C<u>H</u>$_2$=CH), 4.60 and 4.58(2 x S,2H,OCH_2O), 3.81(m,2H,$W_{½}$=15Hz,C<u>H</u>OCH_2O and C<u>H</u>OH), 3.63(m,1H,$W_{½}$=14Hz,C<u>H</u>OH), 3.67(S,3H,CO_2Me), 3.36 (S,3H,OMe), 2.89-0.91(m,16H).

MS 306(18%,M-MeOH), 261(25%), 247(29%), 246(40%), 245(42%), 235(40%), 217(100%), 205(40%), 145(41%), 131(62%), 129 (78%), 117(60%), 105(46%), 91(94%).

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