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SYNTHETIC PLANT GROWTH-REGULATORS RELATED TO GIBBERELLINS AND HELMINTHOSPORINS

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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by

JOHN V. TURNER, B.Sc(Hons.)

Department of Organic Chemistry

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CONTENTS

SUMMARY

Through a systematic synthesis of model compounds, a new approach has been initiated towards solving the structure-function enigma of the plant growth-regulators, gibberellins and helminthosporins.

Chapter 1 contains the rationale behind this undertaking.

Chapter 2 describes the syntheses of $\Delta^{6,7}$- and $\Delta^{7,12}$-14-norhelminthosporin analogues *via* a new and efficient method for the synthesis of β,γ-unsaturated aldehydes employing a base induced [2,3]-sigmatropic rearrangement of allylic α-cyanomethylpyrrolidinium salts.

Chapter 3 details the synthesis of tricyclic model compounds to probe the structure-function problem. In this chapter are discussed the factors controlling regiospecificity of cyclopropyl bond-fission in the Birch reduction of cyclopropyl-ketones; the stereochemistry at the β-carbon atom on ring-scission has been shown to undergo inversion.

Chapter 4 extends the structure-function investigation through the synthesis of a tetracyclic-acid *84* from (+)phyllocladene.

Chapter 5 contains the results of bio-assays and discusses the significance of finding growth-promoting effects with some synthetic compounds. In particular, the results obtained are

consistent with the gibberellin C/D-ring being the effector region of the molecule and the A-ring region being responsible for binding.

Chapter 6 describes the synthesis of a tetracyclic gibberellin analogue 100 having a C/D-ring bridgehead hydroxyl group.

Chapter 7 examines the stereochemical requirements, a side reaction, and the potential of the approach to β,γ-unsaturated aldehyde synthesis developed in Chapter 2.

STATEMENT

Compounds 49 to 54 (50 and 52 not fully characterised, C6 stereochemistry undefined) were made in preliminary investigations directed to objectives separate from those of this thesis as part of the Honours degree of B.Sc. (1970). Apart from the above, this thesis contains no material previously submitted for a degree in any 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.

J. V. TURNER

ACKNOWLEDGEMENTS

I am sincerely grateful for the opportunity of having worked under the supervision of Dr. L.N. Mander, whose teaching, guidance and enthusiastic encouragement have been invaluable.

I am thankful for the help of other members of the department through the years. In particular I am indebted to Dr. R.H. Prager for stimulating discussions and advice during 1972.

The biological testing of synthetic compounds has been conducted by Dr. B.G. Coombe of the Waite Institute, University of Adelaide, South Australia, and I am happy to acknowledge this help and the useful discussions held with him and Professor L.G. Paleg of the Institute.

This work was conducted during the tenure of a Commonwealth Post-Graduate Award, for which I am grateful.

Finally, the unfailing interest and understanding of my parents and my wife throughout the course of this work is deeply appreciated.

CHAPTER 1

INTRODUCTION

It is a matter for regret that, unlike their animal counterparts, the fundamental cellular function of the principal plant growth-regulators - the auxins, the cytokinins, and the gibberellins - is poorly understood.[1] A better understanding could furnish a potential for alleviating the food shortage experienced by millions today and which threatens the future of human civilisation.[2] It is ironical that the gibberellins, whose primary effect is the least defined, have so far found greatest use in agriculture and horticulture, by increasing the height of plants, or the number or size of leaves, by improving the set of fruit and yield from a tree, by offsetting frost damage, by delaying senescence,and effecting other spectacular changes in plant physiology.[3-5] It is these astounding properties of the gibberellins which stir the imagination as to the possibilities of even better exploitation with a deeper knowledge of the fundamental processes involved.

Ever since a mixture of gibberellins was extracted from the fungus Gibberella fujikuroi in 1938,[6] investigations have been intensive. So far, more than 36 gibberellins* have been isolated, constituting a class of C19 and C20 tetracyclic diterpenoids based

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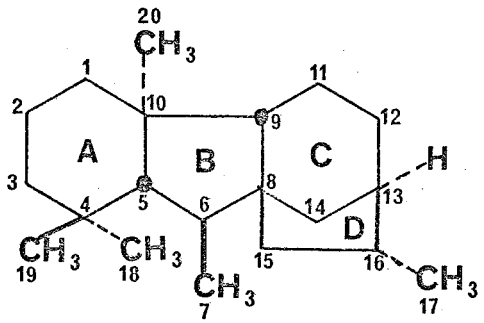
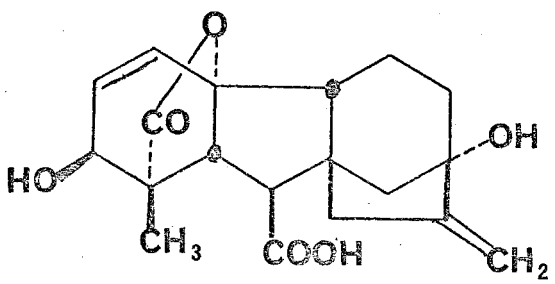
* Four representative gibberellins are illustrated on the fold-out Appendix, together with their respective GA number.

on the ent-gibberellane skeleton 1, and their occurrence in plants now seems ubiquitous.[1,7]



1

Only the absolute configuration of the best known and first isolated[8] gibberellin, gibberellic acid (GA3) 2, has been rigorously determined, by X-ray crystallographic[9-11] and circular-dichroism[12] studies, the others have been related either chemically or through analogy.



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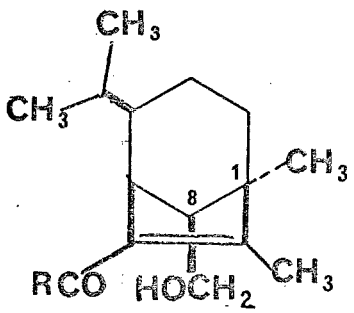
Nevertheless, despite prolific information on the chemistry of gibberellins, the precise mode of physiological action in the cell in relation to structure remains a mystery.[7,13] Much effort has been expended on this problem, testing the relative biological activities of gibberellins and structurally related molecules, usually derived through chemical modification of gibberellins themselves,[14,15] but these approaches are confused by a diverse functional array and by the difficulty of effecting desired structural changes without altering simultaneously other regions of a gibberellin molecule. So far, the only functional group found essential for activity is the B-ring β-carboxylic acid,[14] although the more active gibberellins also possess an A-ring γ-lactone trans-fused to the B-ring.[16]

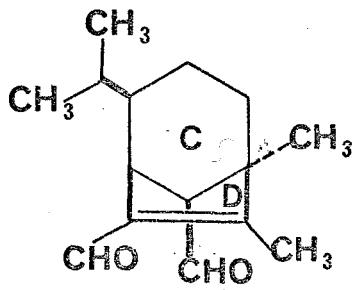
Flexible syntheses of gibberellins, which could provide isotopic labels,[17] could be invaluable in unravelling the structure-function enigma, but such an approach seems restricted by molecular complexity. The problem would be simplified enormously if the moiety essential for growth activity (the effector part) could be delineated and synthesised; then, a systematic elaboration of substituent groups about this basic skeleton, should enable the growth-promoting effects of each to be evaluated.

A clue to the composition of the effector might lie in the

known gibberellin-like activity of the sesquiterpenes, helminthosporic acid 3 and helminthosporol 4.[18] These helminthosporins* have been related chemically[19] to helminthosporal 5, a plant toxin first isolated from the fungus Helminthosporium sativum,[20,21] whose absolute configuration[22] corresponds to the C/D-rings of gibberellins.



3R=OH, 4R=H



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Briggs has suggested[18] that helminthosporins may possess the minimum growth-effector requirement and a number of helminthosporin derivatives have been prepared and subjected to bio-assay.[23,24]

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* "Helminthosporin" is the family name suggested for these compounds and "helminthosporane" proposed for the carbon network numbered, for consistency with the literature,[26] as in the Appendix diagram 1. For example, the name of helminthosporic acid 3 formally becomes 14-hydroxyhelminthospor-6-en-13-oic acid, but for simplicity the established name of this acid and of helminthosporol and helminthosporal will be retained. In this thesis the helminthosporane-rings are labelled C and D, as shown, to facilitate the discussion and avoid confusion.

Nevertheless, these investigations are also limited by the available natural material.[25]

By comparing gibberellin and helminthosporin structures, it becomes apparent that the minimum effector part may be smaller than the natural helminthosporane skeleton itself. Obviously, helminthosporins differ from gibberellins by the absence of both a B-ring and a highly oxygenated, hydrophilic A-ring. Nevertheless, studies of molecular models reveal that the most energetically favourable conformation for the helminthosporane skeleton is that with the isopropyl group equatorially disposed, and so oriented with respect to the C/D-rings as to lie approximately in the region occupied by the C1, C5 atoms of a gibberellin A-ring (Fig.1).

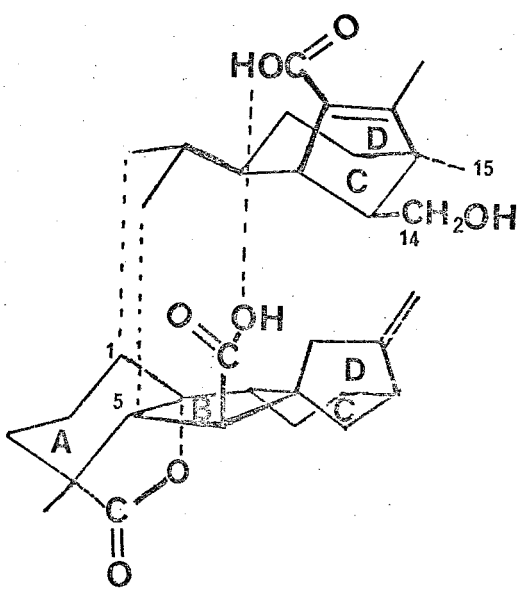

Figure 1

Other differences include the absence in gibberellins of both an angular C/D-ring methyl group and, more interestingly, the C-ring hydroxymethyl (or formyl) group (C14) found in helminthosporins. Particularly striking is the steric relationship between a gibberellin D-ring, which usually bears an exocyclic methylene group, and the B-ring β-carboxyl group, the hydroxyl of which, in molecular models, can occupy the same relative position in space as the hydroxyl of the carboxyl group in helminthosporic acid 3, which has the olefinic bond endocyclic and conjugated.

If helminthosporic acid 3 is mimicking gibberellin activity, then loss of the C8 substituent (C14) and deconjugation of the olefinic bond should be inconsequential (e.g. 44); so, too, should removal of the C1-methyl group (C15) and the introduction onto bicyclo-octane framework of a non-polar B-ring, approximating to a gibberellin B-ring (e.g. 75). A non-polar, hydrophobic A-ring (e.g. 84), however, should reduce or prevent activity if this portion of a gibberellin molecule is responsible for binding to a polar site within the cell, close to the effector site, thereby enhancing activity.*

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* Helminthosporic acid 3 shows activity $\sim 10^3$ times lower than GA3,[4] but more than half the gibberellins known show this level of activity or less.[15]

The syntheses* of compounds, designed to investigate the above hypotheses, present many interesting and challenging problems. These have been undertaken, and the results are described in Chapters 2, 3 and 4 of this thesis.

The implications of bio-assays, carried out on relevant synthetic compounds, are discussed in Chapter 5.

Chapter 6 describes an approach to the synthesis of a tetracyclic gibberellin analogue having an hydroxyl group at the C/D-ring bridgehead.

Chapter 7 is devoted to the study of a new method for the synthesis of β,γ-unsaturated aldehydes via the [2,3]-sigmatropic rearrangement of allylic ammonium ylides, which was invented to solve the difficulty of elaborating the groups present on the helminthosporin bridge.

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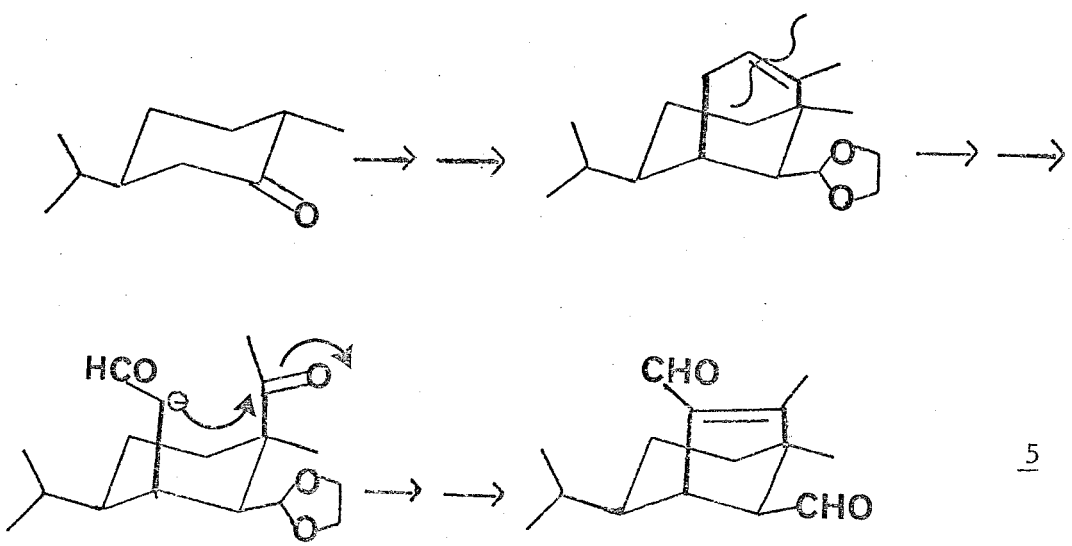
* Although racemic mixtures would result from non-chiral starting material, it is considered unlikely that both antipodes would induce a growth effect. Work in this area is proposed.

CHAPTER 2

SYNTHESIS OF 14-NOR ANALOGUES OF HELMINTHOSPORINS

In designing syntheses of 14-norhelminthospor-6-enoic aldehyde 43 and acid 47, and the $\Delta^{7,12}$-analogues 42 and 44* (page 28), it was essential to devise a route which, for maximum efficiency, would involve a common intermediate late in the sequence, and which would also provide compounds early in the sequence with a bicyclo[3,2,1]octane skeleton, suitable for biological testing.

Clearly, it would have been incompatible with our requirements to modify Corey and Nozoe's synthesis of helminthosporal 5[22] from (-)carvomenthone, as abridged in Scheme 1, via a bicyclo-[3,3,1]nonene derivative.



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Scheme 1

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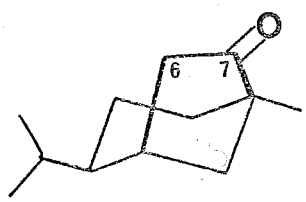
* From model-studies the hydroxyl of the $\Delta^{7,12}$-acid 44 aligns well with the hydroxyl of the β-carboxylic acid group on the gibberellin B-ring.

Only the pertinent enantiomer is drawn for racemic mixtures.

A more appropriate and potentially versatile intermediate seemed to be the bicyclo[3,2,1]octanone 19, not only for introducing a variety of functional groups on the C6,C7 bridge, but also for a projected total synthesis of helminthosporins themselves.*



19

Thus, our synthetic strategy became: first to derive the ketone 19; then to elaborate the helminthosporin-like bridge functionality.

The crucial step to the bicyclic-ketone 19 was a proposed intramolecular nucleophilic displacement of nitrogen, from the protonated diazoketone 17 by the $\Delta^{3,4}$-olefinic bond, simply depicted with an α-keto-diazonium ion in Figure 2.

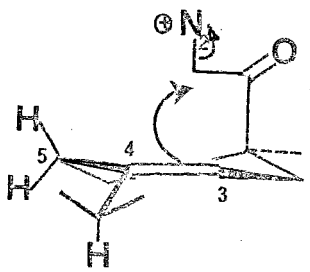


Figure 2

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* This proposal involves two deep-seated rearrangements.

There are excellent precedents for this reaction which, in analogous cyclisations, has been used with participating aryl, styryl,[27] and also isolated olefinic[28] π-bonds. We anticipated that cyclisation would be directed to C3, rather than C4, by the greater stability of the incipient C4 tertiary carbenium ion,[29] which would then collapse to give two olefins 18 (A and B), although the possibility of further rearrangement was not ruled out (see page 17). Catalytic hydrogenation of the olefins, from the less hindered face, would then afford the desired ketone 19.

Scheme 2 outlines the realisation of these proposals, which are now discussed in detail.

p-Cuminic acid 12 was obtained, initially, by an electrophilic bromination of cumene 9, giving o-bromo- and p-bromocumene 10 (11:39 respectively) as a mixture which was metallated with lithium in ether, and subsequently carboxylated.[30] Fractional recrystallisation afforded the acid 12 in 15% overall yield from cumene, and greater than 99% purity by G.C. analysis (methyl ester).* In later preparations cuminic acid 12 was made more easily, by a Jones' oxidation[31] of commercially available cuminic aldehyde 11. This oxidation is much more convenient than the old, laborious procedure using alkaline hydrogen peroxide.[32]

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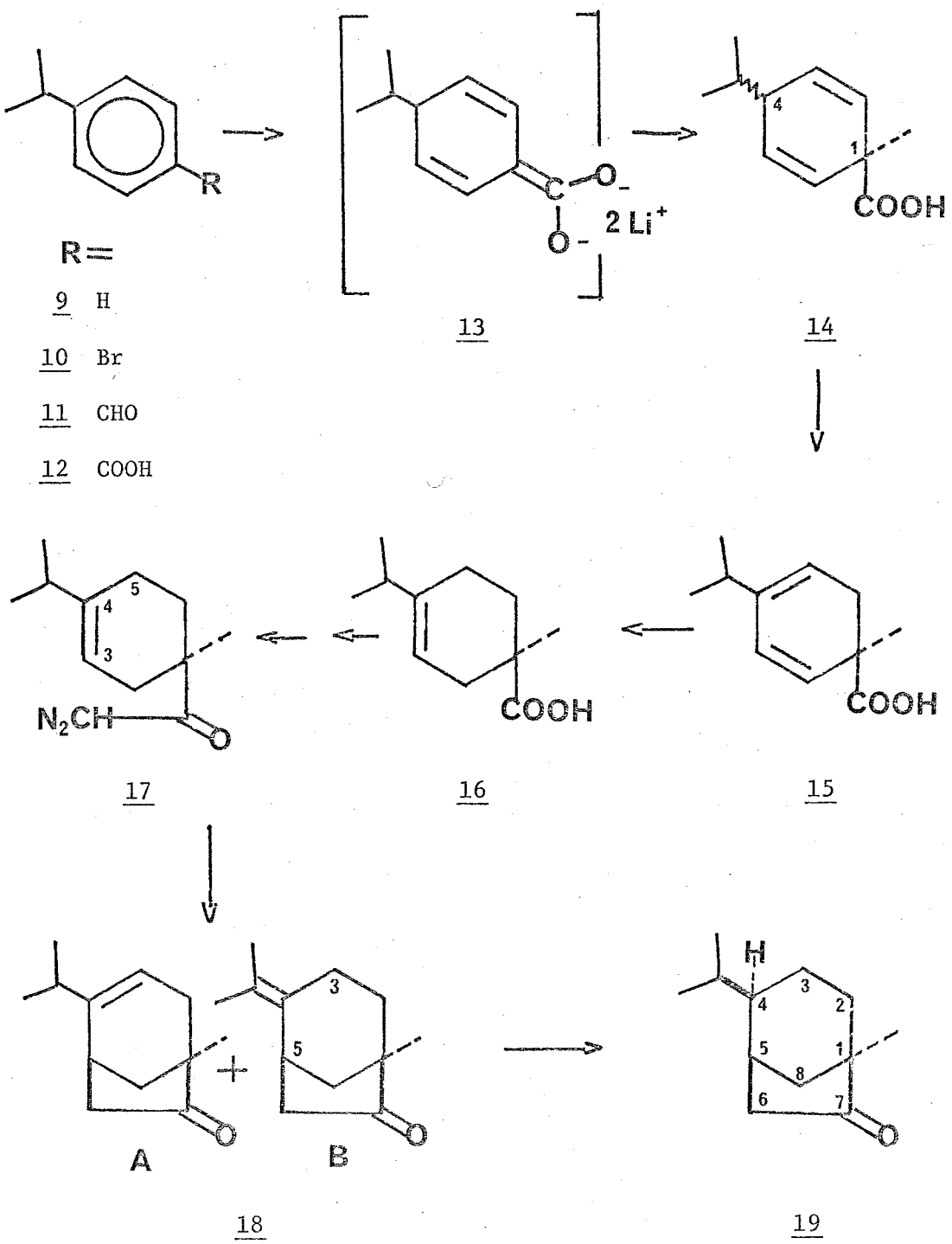
* All methyl esters for G.C. analysis were prepared from a small sample of acid with an excess of ethereal diazomethane (see Experimental).



Scheme 2

Introduction of the C1 methyl group was achieved by reducing, with lithium, cuminic acid 12 in dry liquid ammonia and ether to the, expected, di-anionic intermediate 13;[33] this was methylated *in situ* at -70° with methyl iodide,[34] to furnish the diene-acid 14, epimeric at C4. It was important to avoid a large excess of lithium, and a rapid addition of methyl iodide to the blue solution, otherwise a violent reaction ensued, presumably between the solvated electrons and methyl iodide.

Conversion of the acids 14 to the conjugated diene-acid 15 proved unexpectedly troublesome. Normal acidic methods, for example: p-toluene sulphonic acid-catalyst in benzene under reflux,[35] dry hydrogen chloride in chloroform,[36] trifluoroacetic acid at 40°,[37] with the acid 14, failed to effect conjugation.

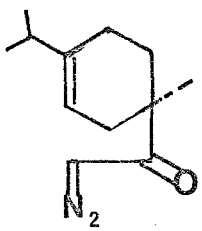
Stronger acidic media such as BF_3-etherate:benzene:sulpholane[38] were not investigated because of the likely decarboxylation in such β,γ-olefinic-acids.[39] Since protection and regeneration of the carboxyl group would have added at least two steps to the sequence, neutral and basic conditions were examined.[40]

Heating the acids 14 with tris(triphenylphosphine)rhodium chloride in chloroform[41] was unsuccessful, as was using lithium amide in liquid ammonia.[42] Although lithium ethylamide in tetrahydrofuran[43] afforded the desired acid 15, these conditions also produced some unidentified material.

Eventually, by boiling the diene-acids 14 in a strong solution of potassium hydroxide and ethylene glycol[44] under nitrogen for 20 hr, the required acid 15 was obtained in high yield and sufficient purity for immediate use.

A Birch reduction[45] of the crude diene-acid 15 proceeded without incident to the olefinic acid 16, which was formed in 86% overall yield from cuminic acid.

The oily diazo-ketone 17, which was obtained in almost quantitative yield from the derived acid chloride (16 plus pyridine and oxalyl chloride) and ethereal diazomethane,[46] gave consistent spectral data and a satisfactory elemental analysis after simple bulb-to-bulb distillation and was therefore used without purification in subsequent reactions.



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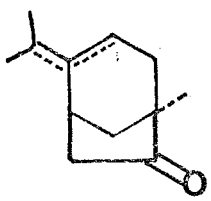


18

For the crucial acid-catalysed intramolecular C-alkylation of the diazo-ketone 17 to the olefinic ketones 18 we considered that, for maximum cyclisation, the acidic catalyst should have a conjugate base of low nucleophilicity and that the ideal medium

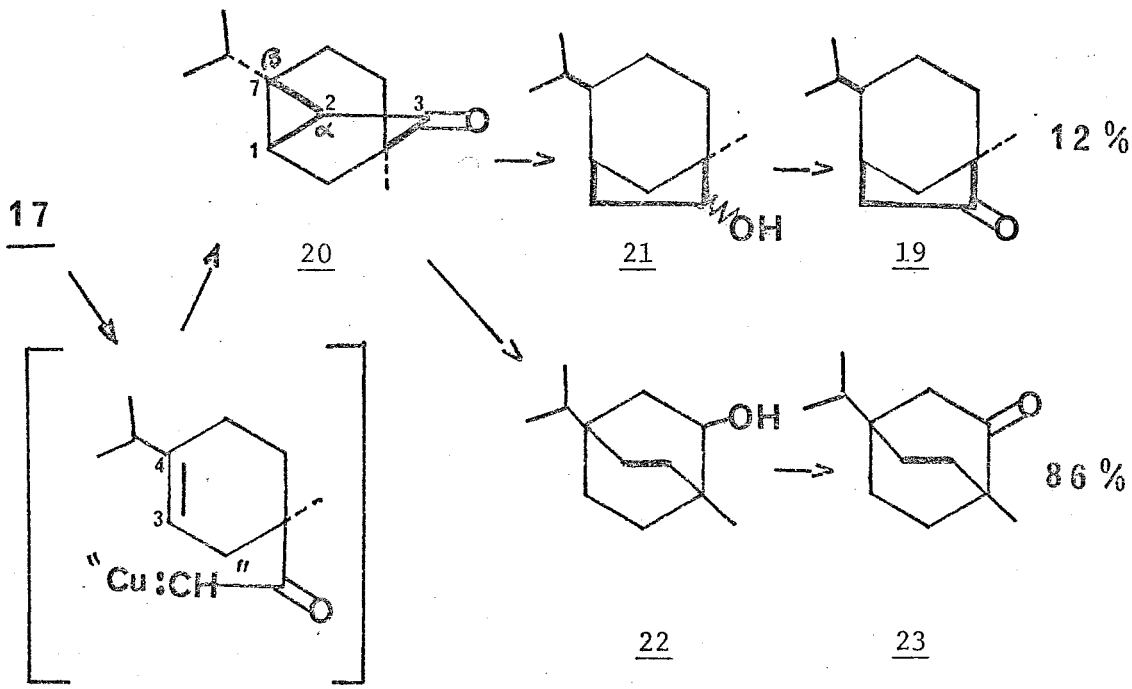
should be a dipolar, aprotic, weakly nucleophilic solvent, since this should assist ionisation without itself reacting. We found that the combination of BF_3-etherate with the diazo-ketone 17 in nitromethane,[47] afforded an excellent yield (>98%) of olefinic-ketones 18.

Interestingly, the cyclisation may proceed with kinetically controlled olefin formation, since the initial ratio, 1:4 respectively, of olefins 18A:18B slowly increases to 9:11 if the reaction mixture is examined over a period of 48 hr. It is clear from a molecular model 17, that the tertiary isopropyl-hydrogen bond can align with the C3,C4 π-bond orbitals in the transition state, thereby facilitating proton-loss,[48] whereas the C5 hydrogen-carbon bonds make an angle of about 45° with the π-system (see Figure 2). Undoubtedly, relief of steric interactions in 18B, particularly between the vinylic methyl groups and the ring members C3 and C5 ($A^{1,3}$ strain), accounts for the observed thermodynamic equilibration.

Catalytic hydrogenation of the olefinic mixture gave the saturated ketone 19 in 91% overall yield from the diazo-ketone 17.

The stereochemistry of the isopropyl group at C4 follows, not only from analogous hydrogenations,[26,49,50] but also from G.C. comparison with the same bicyclo[3,2,1]octanone 19 derived from the cyclopropyl-ketone 20 via a Birch reduction,[45] which is

expected to proceed with stereochemical inversion at the β-carbon atom (see Chapter 3, page 43).



Scheme 3

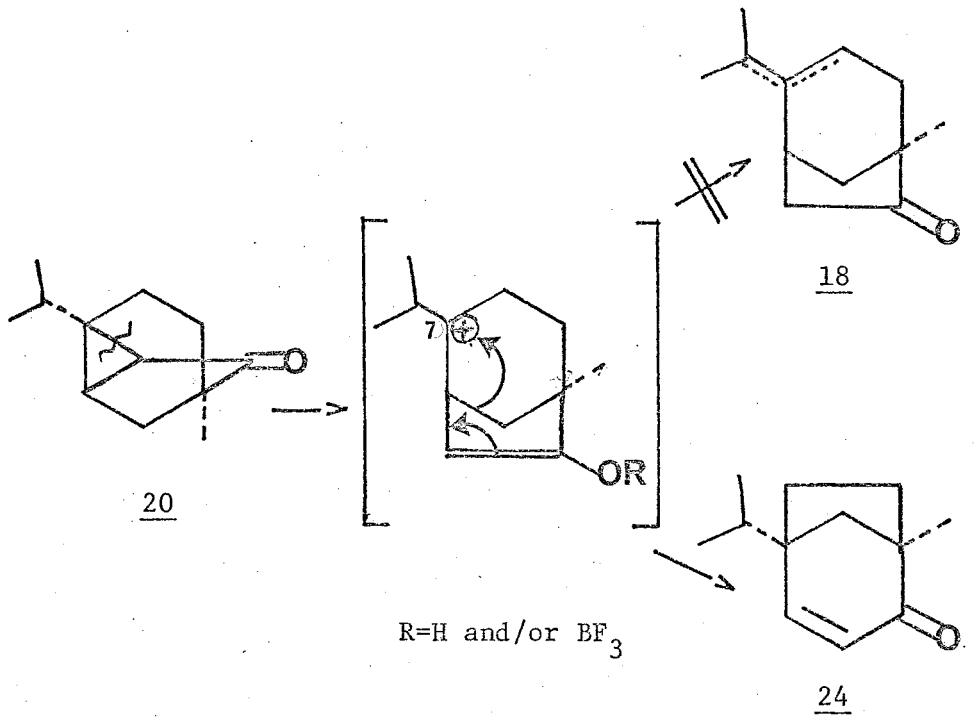
The cyclopropyl-ketone 20 was prepared in 98% yield by copper-catalysed decomposition of the diazo-ketone 17, in boiling cyclohexane, to generate a transient copper-carbenoid moiety[51-53] which added intramolecularly into the $\Delta^{3,4}$-olefinic bond[54-56] as outlined in Scheme 3 above.

We had originally thought that reductive cleavage of the cyclopropyl-ketone 20 would be a synthetically useful procedure for obtaining the key intermediate ketone 19. Unfortunately,

the bicyclo[2,2,2]octanone derivative 23 predominated (86%), after Jones oxidation[31] of the initially formed mixture of alcohols 21 and 22. This is not expected from the rule formulated by Dauben and Deviny which dictates that the C2,C7 bond of 20 should cleave since, in models, this has better overlap with the π-system of the C3 carbonyl group.[57,58] Here, presumably, the greater stability of an incipient secondary carbanion at C1 in the transition state, outweighs the marginally better overlap of the C2,C7 bond, which on breaking leads to a less stable[58,59] incipient tertiary carbanion at C7. A more detailed discussion of this type of reductive cyclopropyl bond-fission is given in Chapter 3, with particular emphasis on the regiospecificity[60] of cleavage and the stereochemical fate of the β-carbon atom.

Since the intramolecular alkylation step to the cyclopropyl-ketone 20 was efficient, and a quantity of ketone was in hand, we investigated the prospects of an acid catalysed cyclopropyl-ring opening[61-64] which, intuitively, might be expected to afford the olefins 18 through collapse of an incipient tertiary[62] carbenium ion[29] at C7 (Scheme 4).

Heating the ketone 20 with trifluoroacetic acid (TFA) did not effect ring cleavage, but after 4.5 hr at 94° in TFA:BF_3-etherate (2:1) a homogeneous oil was obtained quantitatively which was



Scheme 4

neither of the olefins 18 (A and B), from G.C. analysis, but was clearly structurally isomeric, having a mass spectrum with M^+ 178 and analysing for $C_{12}H_{18}O$. The infra-red spectrum (film) suggested an α,β-unsaturated ketone, probably in a 6-membered ring [1680 (C=O), 1610 cm^{-1} (C=C)], an interpretation which was supported by an absorbance at 223 nm in the ultra-violet spectrum (ethanol).*

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* λ_{max}^{EtOH} calc. for cyclohexenone 227 nm.

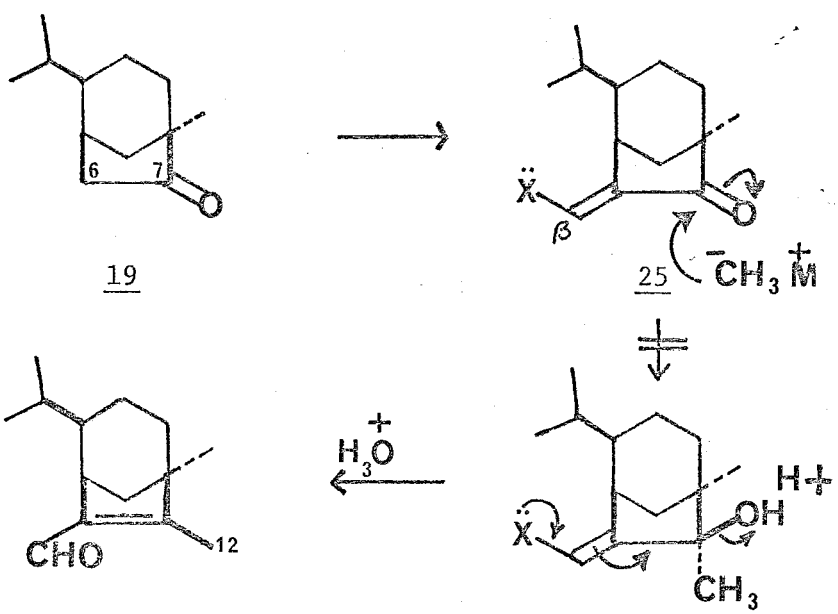
Fortunately, nmr spectral analysis, which incorporated double resonance techniques, was highly diagnostic (see Experimental, page 111) and left no doubt as to the correct structure as depicted 24.

Doubtless, the forcing conditions required to break the cyclopropyl bond are sufficient to induce rearrangement of the initially formed carbenium ion, in a manner frequently encountered with bicyclo-octenone derivatives[65] and related systems.[66-68]

It is unlikely that the olefins 18 are intermediates in the process, because when subjected to the medium used to rearrange the cyclopropyl-ketone 20 they failed to give the olefinic-ketone 24 (G.C. analysis). Perhaps cyclisation of the protonated diazo-ketone 17, described earlier, occurs with concerted proton loss leading to the observed kinetic olefinic-products 18.

Having established an efficient sequence (Scheme 2) to the bicyclo[3,2,1]octanone 19, we directed our efforts next to elaborating helminthosporin-like functionality on the C6,C7 bridge. This proved to be surprisingly difficult, and eventually the problem was surmounted by the development of a new reaction.

Our initial endeavours, however, were concentrated on introducing first a potential C6 carboxyl group, then adding the C7 methyl group (C12) along the lines indicated in Scheme 5.



X= OH, OiPr, SnBu

M= Li, MgI

Scheme 5

Hydroxymethylation 25 (X=OH) of ketone 19 was straightforward,[69] as was generation of the enol ethers 25 (X=isopropoxy,[70,71] n-butane

thio[72,73]), but despite numerous solvent systems (ether, THF, DME,[74] THF-TMED,[75,76] THF-HMPTA[77,78]) with methyl lithium and methyl magnesium iodide on both enol ethers, over a range of temperatures (-78° - reflux), predominantly starting material was recovered. Only in one instance [CH_3MgI, THF under reflux with 25 (X=nBuS)] an extensive reaction occurred and this gave a gross mixture (tlc) containing presumably 1,4-addition product [ir 1738 (st C=O), 1600 cm^{-1} (wk, C=CHSnBu)], and very little 1,2-addition [3450 cm^{-1} (wk, OH)] product.

Steric congestion in the neopentylic environment of the C7 carbonyl carbon,[79,80] and the tendency for β-hetero-atoms to direct organometallic addition 1,4 to α,β-unsaturated carbonyl systems,[81-84] both militate against this approach and so it was relinquished in favour of attempting to position first the prospective C7 methyl group, and to add an oxygenated group at C6 later.

Furthermore, it was apparent that steric problems would be largely circumvented if a group at C6 could be introduced by some intramolecular process emanating from a C7 substituent as exemplified by the type A and B processes in Figure 3.

Such [2,3]-sigmatropic rearrangements[85] are particularly attractive in that the initial products would have C7 exocyclic methylene groups, required in the synthesis of 14-norhelminthospor-7(12)-ene

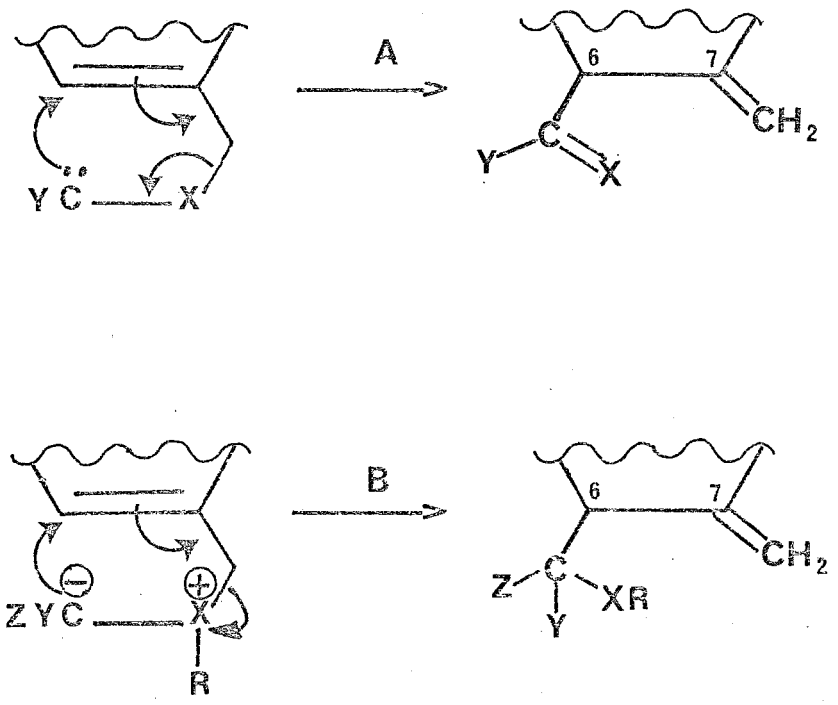
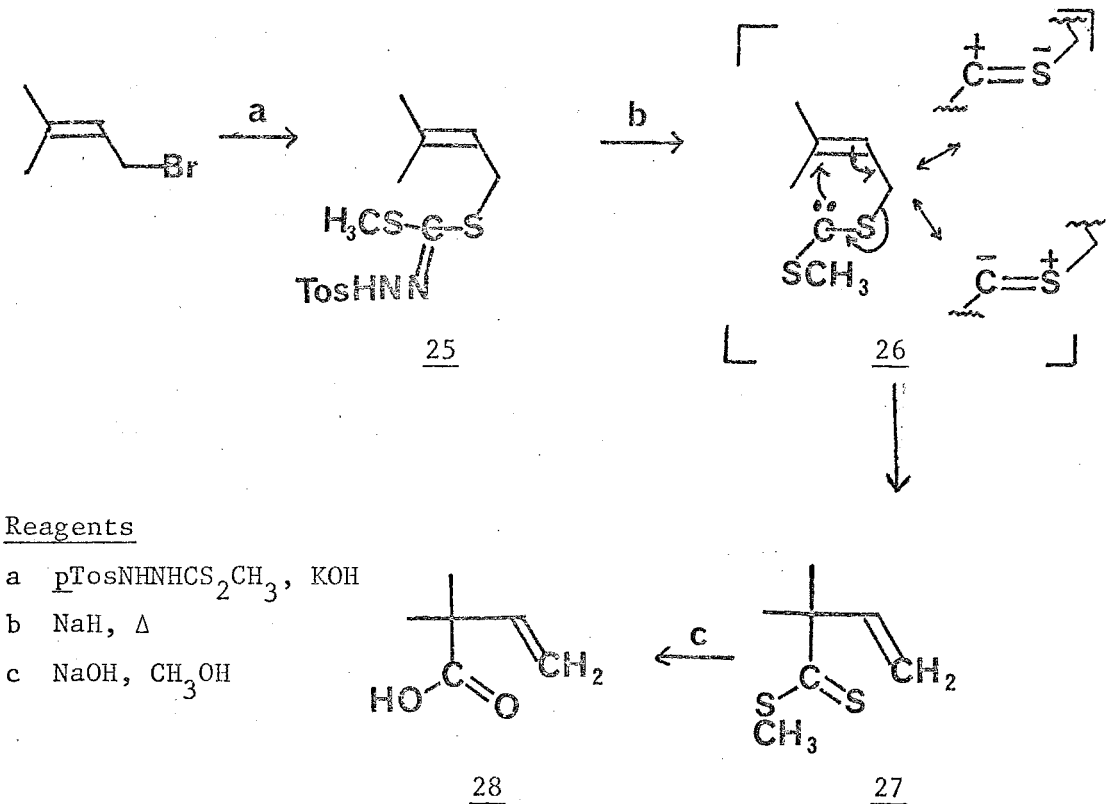


Figure 3

derivatives (e.g. 42), which on isomerisation of the olefinic bond to the endocyclic position, should afford 14-norhelminthospor-6-ene derivatives (e.g. 43). A number of interesting syntheses of β,γ-unsaturated carbonyl compounds utilising [2,3]-sigmatropic rearrangements of sulphonium ylides, e.g. Fig. 3 (X=S), have been published already.[86-88] Of these, a carbene type (A, Scheme 6), developed by Baldwin and Walker[86] appeared the best in terms of

the reported overall yield after ylide-precursor formation 25, rearrangement 26, and hydrolysis of the dithiomethylester 27 to a carboxylic acid 28.



25 26 27 28

Reagents

a pTosNHNHCS$_2$CH$_3$, KOH
b NaH, Δ
c NaOH, CH$_3$OH

Scheme 6

In order to apply their methods, we required either of the allylic bromides 30 (A and B)*, which seemed accessible through allylic radical-bromination of the methylene bicyclo-octane 29 obtainable, in principle, from the key intermediate ketone 19.

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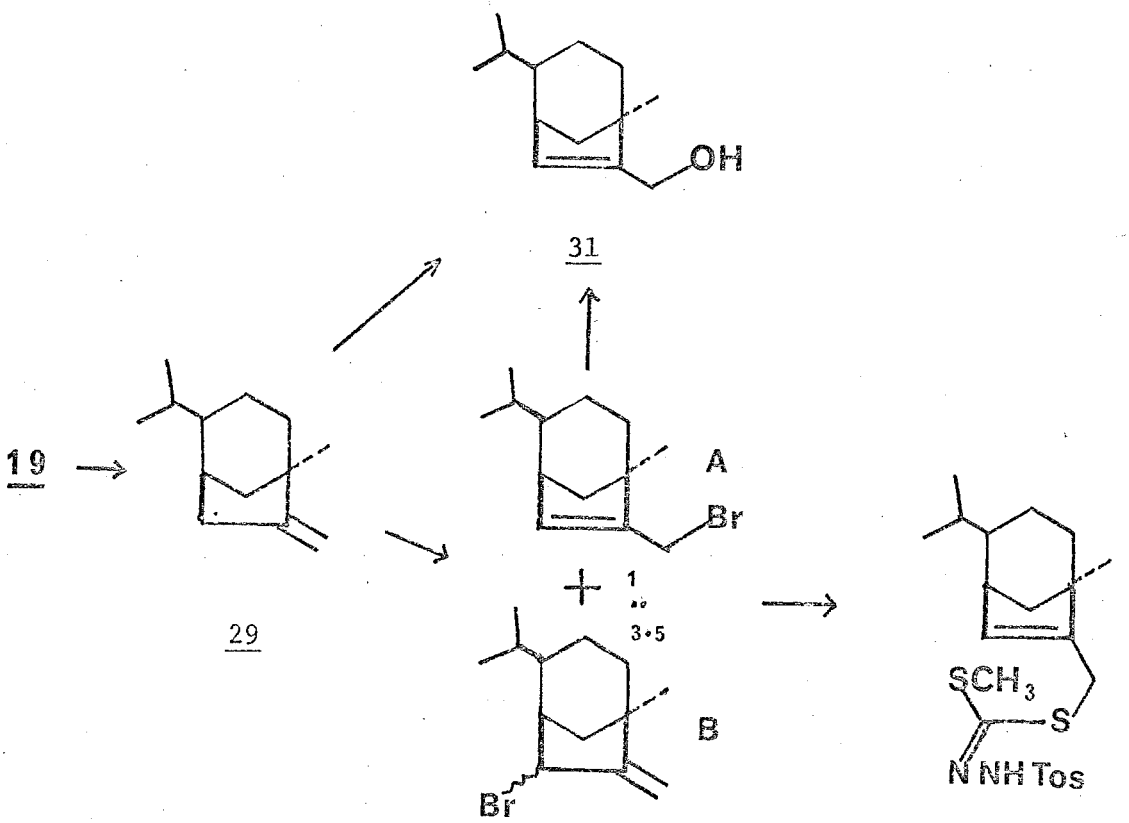
* We anticipated that, for steric reasons, both allylic bromides would alkylate at the primary position.[89,90]


19
OH
31
A
Br
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B
Br
29
30
SCH3
S
N NH Tos
32
5
6
CS2CH3
33
H3CSC
O
34
HOCH2
35

Scheme 7

Indeed, as indicated in Scheme 7, a methylene Wittig reaction[91] with the ketone 19 in ether at low temperature,* afforded, in high yield (97%), the olefin 29 which was converted to the desired bromides 30 (A and B, ratio 1:3.5 respectively) using N-bromosuccinimide (NBS) in boiling carbontetrachloride with benzoyl peroxide as an initiator.[93] The ratio of bromides most probably reflects the steric interference of the C1 methyl group (c/f pages 44 and 50).

The mixture of bromides was characterised spectroscopically and by conversion to the corresponding primary allylic alcohol 31 through treatment with damp, basic alumina. An authentic sample of alcohol 31, for G.C. and spectral comparison, was made from the olefin 29 by regiospecific, sensitised, photo-oxygenation, and hydride reduction of the resulting primary hydroperoxide.[94] Formation of the desired dithiocarbazone 32 proceeded readily from the bromides 30 and p-tosyl-S-methyldithiocarbazate[95] with potassium hydroxide in ethanol. After chromatography and recrystallisation, a colourless solid 32 was obtained which was fully characterised and therefore provided a convenient solid derivative of the allylic bromides 30.

---

* A reaction run at room temperature with excessive ylide returned some ketone, probably due to enolisation. Nucleophiles function more successfully as bases at higher temperatures.[92]

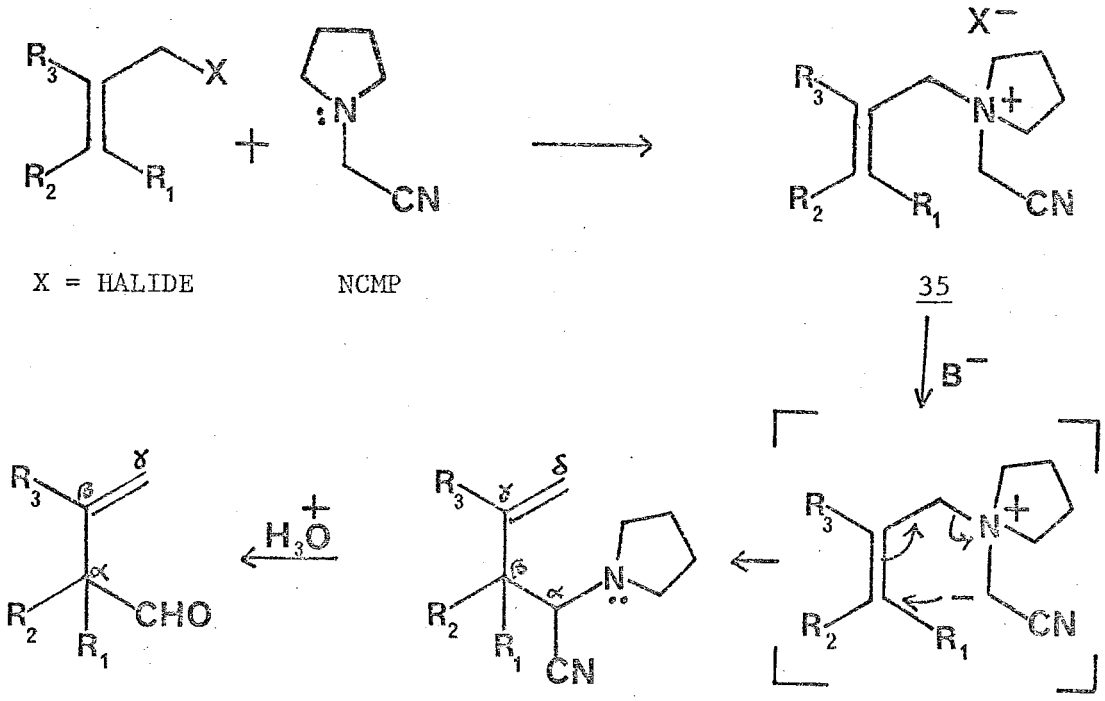
Bamford-Stevens type thermal decomposition of the sodium salt, from the dithiocarbazone 32 and sodium hydride, in pure, dry THF, gave only a gummy mixture which is at variance with the high yield of dithioester 27 in Baldwin and Walker's example.[86] When a solution of salt in cyclohexane, however, was heated under reflux, decomposition to a carbenoid ylide and concomitant rearrangement occurred normally to give the oily 6-exo-dithioester 33.*

Unexpectedly, all attempts to hydrolyse cleanly the dithioester to its corresponding acid 44 were unsuccessful, using both simple methods (alkali, water, alcohol) and those employing catalysis with cadmium,[73] mercuric,[96,97] and lead salts. Eventually, a combination of cupric chloride and cupric oxide in aqueous acetone[98] afforded the thiolmethylester 34 as a component (~60% by nmr) of a mixture obtained in 75% yield from the dithioester 33. Treatment of this mixture with lithium aluminium hydride (LAH) gave, in 61% yield, the carbinol 35 which was ultimately compared with a sample derived through the pyrrolidinium ylide sequence (see below). The overall yield (39%) of carbinol, from the allylic bromides, was clearly unsatisfactory and it was apparent that the problem of introducing an oxygenated C6 substituent onto the bicyclooctene skeleton 29 needed a novel solution.

---

* The 6-exo-configuration follows from the expected rearrangement on the less hindered exo-face of the molecule and from the HC6,HC5 coupling constant ($J \leq 2$Hz) in the nmr spectrum (see Experimental).

The concept of utilising a [2,3]-sigmatropic rearrangement was appealing for the reasons already outlined (page 20). In particular, we required an easily constructed ylide precursor, an efficient [2,3]-sigmatropic rearrangement, and the ready unmasking of a carbonyl group in the final product. We conceived that these conditions would be met by alkylating N-cyanomethylpyrrolidine (NCMP)[99] with allylic halides, followed by base induced [2,3]-rearrangement[100] of the resulting cyanomethylpyrrolidinium salts 35 as depicted in the general Scheme 8 below.



Scheme 8

It was anticipated that ylide rearrangement 36 would lead to γ,δ-unsaturated-α-pyrrolidinylnitriles 37, which could be readily hydrolysed with acid[101,102] to their corresponding β,γ-unsaturated aldehydes 38.

These proposals have been fully realised and provide a useful, new, one carbon homologation. This approach is discussed extensively in Chapter 7, page 70, in which the general applicability of the methodology has been demonstrated with a wide variety of substrates, designed to investigate steric and electronic influences, and a possible competing Stevens', [1,2]-sigmatropic rearrangement.[100] Therefore, both here and in Chapters 3 and 4, syntheses by this route of unsaturated aldehydes, related to helminthosporins, are described without detailed comment, except where specifically warranted.

Thus, as outlined in Scheme 9, NCMP in DMSO* was alkylated with the mixture of bicyclic bromides 30 to afford the primary allylic pyrrolidinium bromide 39 which was characterised by its nmr spectrum (DMSO-d6).

The DMSO-solution was diluted with dry THF, cooled, then treated with solid potassium tert-butoxide† Ylide formation and

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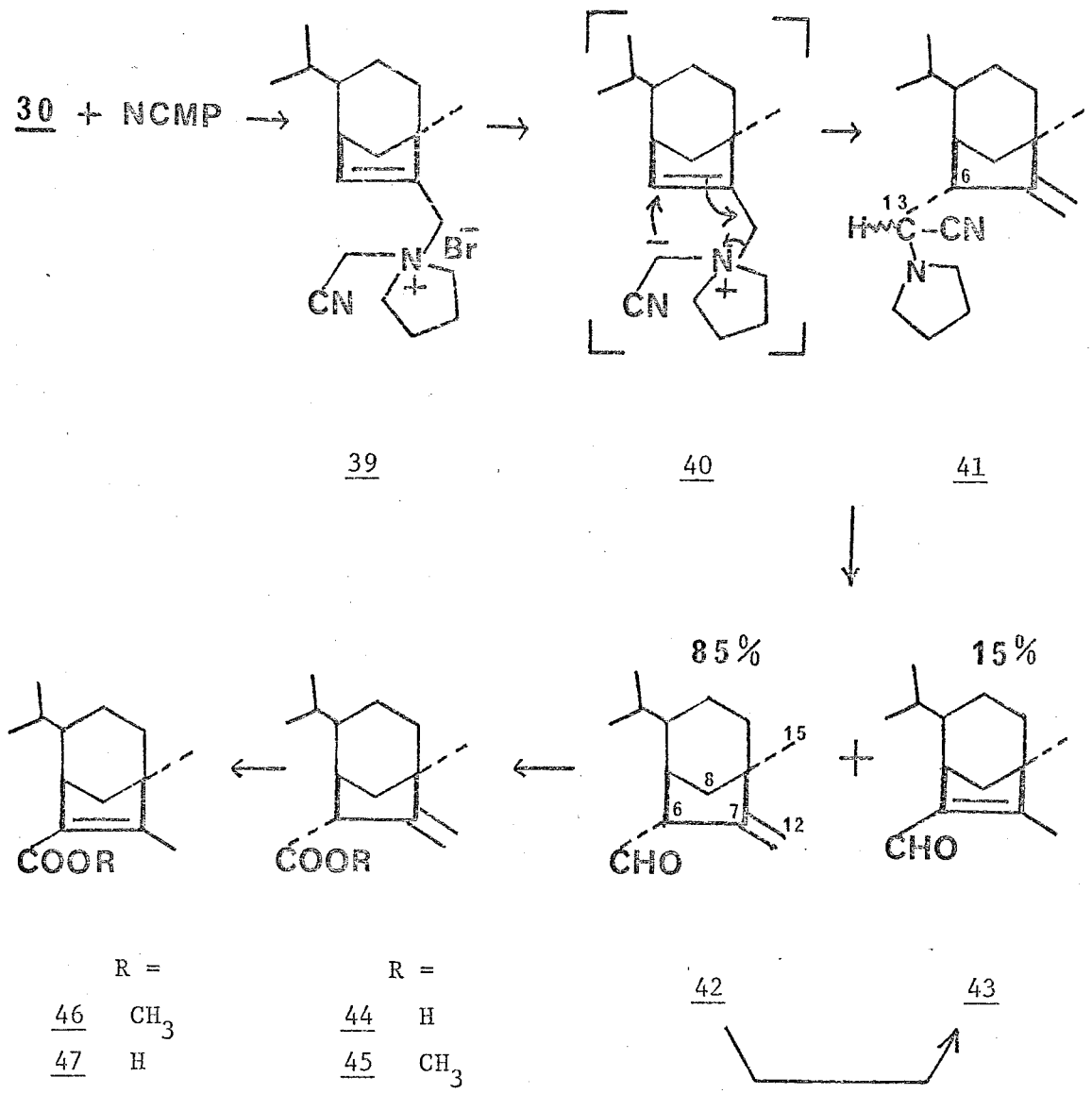
* An aprotic dipolar solvent, chosen to enhance the rate of salt formation.

† This was selected because potassium tert-butoxide is a strong base and a poor nucleophile.[103]



	R =		R =
46	CH_3	44	H
47	H	45	CH_3

Scheme 9

concomitant rearrangement 40 proceeded smoothly at -10^{o}, to afford the 6-exo-α-pyrrolidinylnitriles 41 which were diastereomeric at C13.* Recrystallisation of the mixture was achieved at low temperature and provided a sample for elemental analysis, but the nitriles 41 were invariably sufficiently pure, by the usual criteria, for immediate hydrolysis. Thus, under the mild conditions of boiling THF and aqueous oxalic acid, hydrolysis was complete within 15 min and gave in 90% yield from the bromides 30, the non-conjugated $\Delta^{7,12}$-14-norhelminthosporenoic aldehyde 42, and the conjugated $\Delta^{6,7}$-aldehyde 43, in a ratio of 17:3 respectively.

Synthesis of the $\Delta^{7,12}$-aldehyde 42 admirably fulfils the original desire for a versatile intermediate, late in the sequence, from which related helminthosporin analogues can be derived, as described below.

Chromatography allowed the isolation of pure $\Delta^{7,12}$-aldehyde 42 and a mixture of aldehydes 42 and 43 which afforded the $\Delta^{6,7}$-isomer 43 on treatment with base. Both aldehydes were liquids which were characterised spectroscopically; their solid semicarbazone (SCZ) derivatives were used for elemental analysis.

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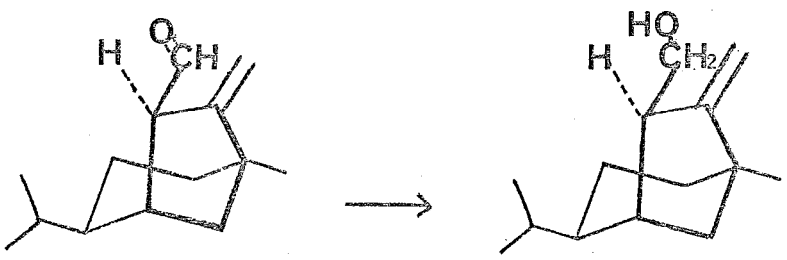
* The exo-configuration follows from the derived exo-aldehyde 42 and related compounds described later.

A sample of the $\Delta^{7,12}$-aldehyde 42 was reduced with LAH to the corresponding carbinol 35 which was identical in every respect with



42 35

that obtained through Baldwin and Walker's modified methodology described previously.[86]

The $\Delta^{7,12}$-aldehyde 42 was oxidised, without effecting conjugation, using Jones' reagent[31] at -10^{o} to afford 14-norhelminthospor-7(12)-enoic acid 44. A portion was methylated with diazomethane, to give the corresponding oily $\Delta^{7,12}$-methylester 45 which, with sodium methoxide in methanol, gave quantitatively (G.C. analysis) the conjugated $\Delta^{6,7}$-ester 46 as an oil.

On hydrolysis with sodium hydroxide in aqueous methanol, this oil yielded the corresponding $\Delta^{6,7}$-acid 47 (80%) together with some (20%) non-conjugated $\Delta^{7,12}$-acid 44. Presumably, the non-conjugated ester 45 is produced in low concentration under the basic hydrolytic conditions and hydrolyses faster than its conjugated isomer 46. Purification of the $\Delta^{6,7}$-acid 47 was readily achieved by recrystallisation.

Both aldehydes 42 and 43, the carbinol 35, the corresponding acids 44 and 47, and the ester 45, have been investigated for biological activity.

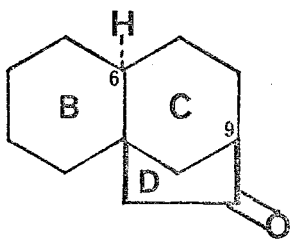
The conjugated aldehyde 43 and both carboxylic acids show a growth-stimulating propensity similar to that of helminthosporic acid 3 itself and the significance of this is discussed in Chapter 5.

With these encouraging results we turned our attention next to the synthesis of compounds designed to investigate the effect on activity of neglecting the C1 methyl group (C15) and introducing a non-polar B-ring appendage onto the basic bicyclo[3,2,1]-octane skeleton (e.g. 75); and these studies are described in the next chapter.

CHAPTER 3

SYNTHESIS OF TRICYCLIC HELMINTHOSPORIN-ANALOGUES 75 AND 78, MORE CLOSELY RELATED TO GIBBERELLINS

In the preceding chapter, a procedure was developed (Scheme 8) for elaborating the synthetic plant growth-regulators $\Delta^{7,12}$- and $\Delta^{6,7}$-14-norhelminthosporenoic acids 44 and 47, and we believed that the methodology would be generally applicable. The ketone 54 appeared, therefore, to be a readily accessible intermediate to serve in the preparation of the analogous tricyclic-acids 75 and 78* which, lacking a C9 methyl group† and possessing a B-ring, bear a somewhat closer relationship to the gibberellins.



54

The choice of a six-membered B-ring was made, not only to provide more versatile intermediates for projected syntheses (e.g. 53, B-ring contraction), but also because finding a significant growth effect with the acids 75 and 78 would indicate that related acids with a less sterically demanding five-membered B-ring should also exhibit similar biological activity.

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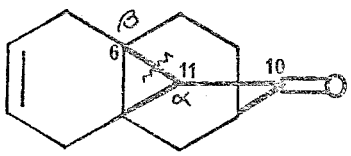
* These compounds have a carbon skeleton related to the B/C/D-rings of racemic phyllocladene (see Chapter 4).

† C9 is equivalent to C1 in the related helminthosporane skeleton.

We conceived that the tricyclic skeleton required would be accessible through a Birch reduction[45] of the cyclopropyl-ketone 51.



51

Molecular models reveal that the C6,C11 cyclopropyl bond has marginally better overlap with the π-system of the C10 carbonyl group, and therefore, from Dauben and Deviny's work,[57,58] cleavage of this bond is expected.* Stereochemical inversion was anticipated at the β-carbon atom leading to trans-fused B/C-rings,[104] although the sterochemical consequence of cyclopropyl bond-fission was unknown when this work was conducted. It was deemed necessary, therefore, to determine rigorously the configuration at C6 after bond-cleavage, and this investigation is described later. Recently, and subsequent to these studies, β-carbon-stereochemistry has been shown to undergo inversion by other workers,[105] nevertheless, the normal course of bond-fission may be upset by steric influences or ring strain.[57,106]

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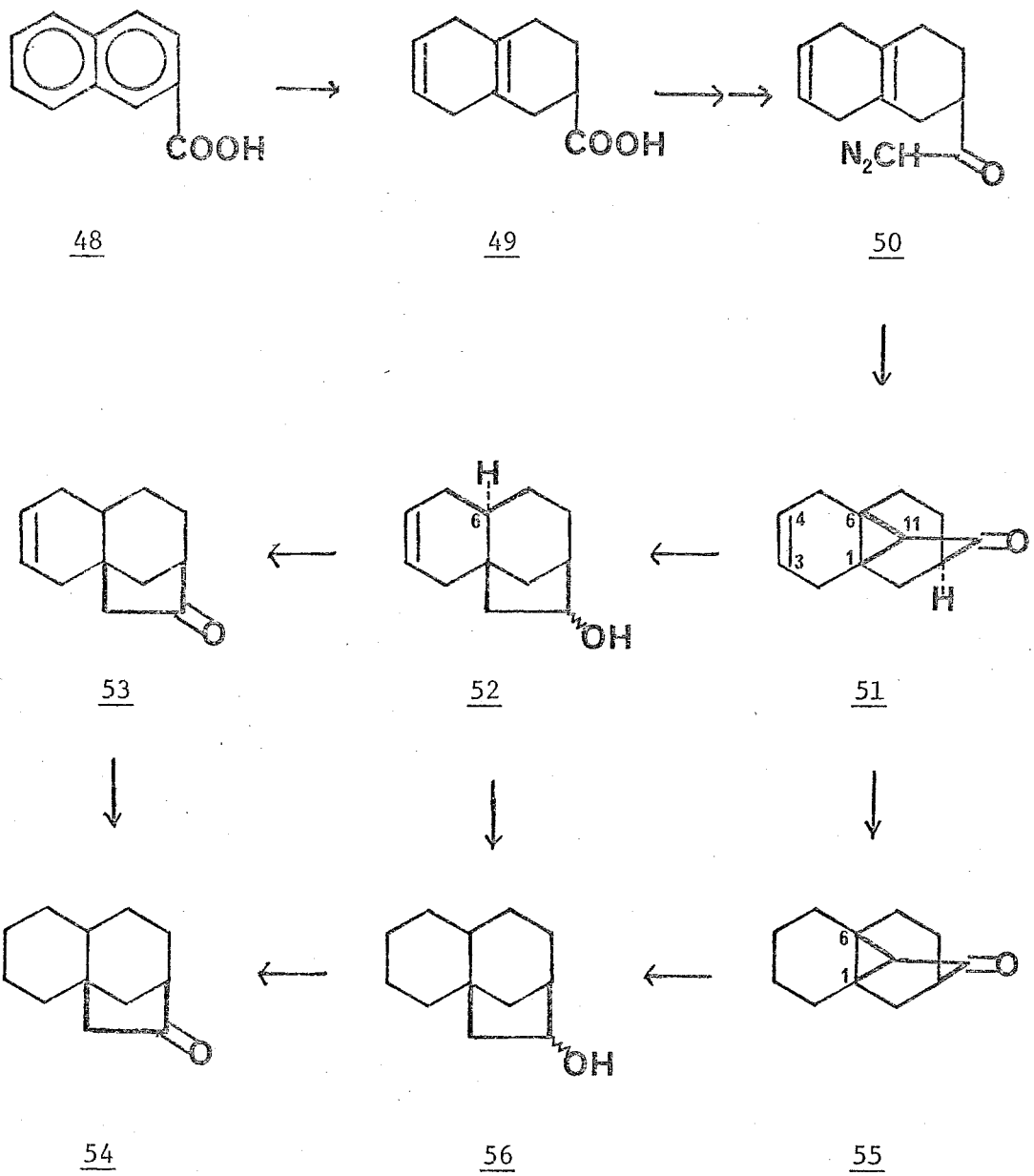
* See, however, the reduction of cyclopropyl-ketone 20, page 15.

Scheme 10 indicates the sequence of reactions leading to the cyclopropyl-ketone 51 and the steps following to the tricyclic-ketone 54.

Birch-Dryden[107] reduction of 2-naphthoic acid gave, as expected, the non-conjugated diene-acid 49, which was converted to its acid chloride using oxalyl chloride in the presence of pyridine to trap HCl which, otherwise, may have conjugated the 1,4-olefinic bonds. Routine formation of the diazo-ketone 50 (diazomethane)[46] and its subsequent copper catalysed decomposition[51-56] in boiling cyclohexane, furnished the crystalline cyclopropyl-ketone 51 in 91% yield.

Birch reduction[45] at low temperature of the olefinic-cyclopropyl-ketone 51, followed by oxidation[31] of the intermediate epimeric alcohols 52, afforded the tricyclic-ketone 53 in 90% yield with, initially, unknown stereochemistry at C6, but having a particularly diagnostic cyclopentanone-absorbance, in the infra-red spectrum, at 1738 cm^{-1}.

Catalytic hydrogenation gave, quantitatively, the saturated tricyclic-ketone 54. The high regioselectivity of the reductive cleavage is contrary to that found by House[108] with the cyclopropyl ketone 60 which gave, approximately, an equal mixture of bicyclo[3,2,1]octanone 60a and bicyclo[2,2,2]octanone 60b, after oxidation of intermediates.

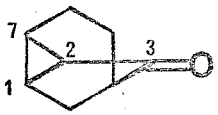


48 49 50

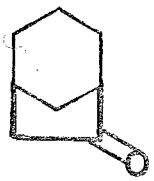
51 52 53

54 56 55

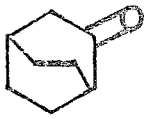
Scheme 10



60



60a



60b

In this example, predominant cleavage of the C2,C7 bond is expected by analogy with the cyclopropyl-ketone 51 and overlap considerations[57,58] discussed previously.

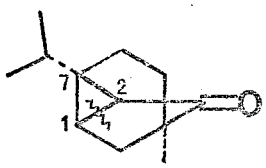
To preclude the possibility that the high regioselectivity, which we had observed, was due to some subtle influence of the C3,C4 olefinic bond, the cyclopropyl-ketone 51 was first hydrogenated using rhodium-on-alumina[109,110] catalyst*; then, the resulting saturated cyclopropyl-ketone 55 was reduced under Birch conditions and the alcohols 56, so obtained, oxidised with Jones' reagent. This afforded the same tricyclic-ketone 54 as had been obtained previously.

In a final investigation, we standardised our reduction conditions with those of House[108] by excluding an alcoholic proton-source from the reducing-medium. As expected, this also had no effect on regioselectivity; interestingly, some (21%) starting cyclopropyl-ketone 55 was recovered under these conditions.

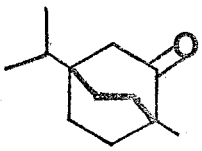
---

* Palladium or platinum catalysts promoted hydrogenolysis of the cyclopropyl ring.[111-113]

Nevertheless, it seems relevant to this apparent incongruity that regioselectivity is reversed on reduction of the cyclopropyl-ketone 20, where C1,C2 bond-fission predominates (86%) to afford mainly the bicyclo[2,2,2]octanone 23, after oxidation (page 15).



20



23

To account for all these observations, we propose that when the difference in overlap of two cyclopropyl bonds and the π-system of a carbonyl group is marginal, the stability of the possible incipient β-carbanions is important in the transition state leading to products.

Thus, in the exothermic cleavage of House's cyclopropyl-ketone 60 *via* developing secondary centres at C1 and C7, the transition state resembles starting material and ultimately both ketones 60a and 60b are obtained. In a presumably less exothermic, and therefore more selective, cleavage *via* potential tertiary centres at C1 and C6, in the cyclopropyl-ketones 51 and 55 the influence of overlap becomes significant and thus the transition state (Figure 4) is more like products 52 and 56.[114] As stated

previously (page 16), in the reduction of cyclopropyl-ketone 20 the controlling factor seems to be the incipient secondary carbanion at C1 overcoming the slightly better overlap of the C2,C7 bond, which on breaking leads to an incipient tertiary carbanion at C7.

These results appear to rule out the preponderance of developing β-carbon-radicals on cyclopropyl bond-rupture, which is consistent with the findings of other workers.[58]

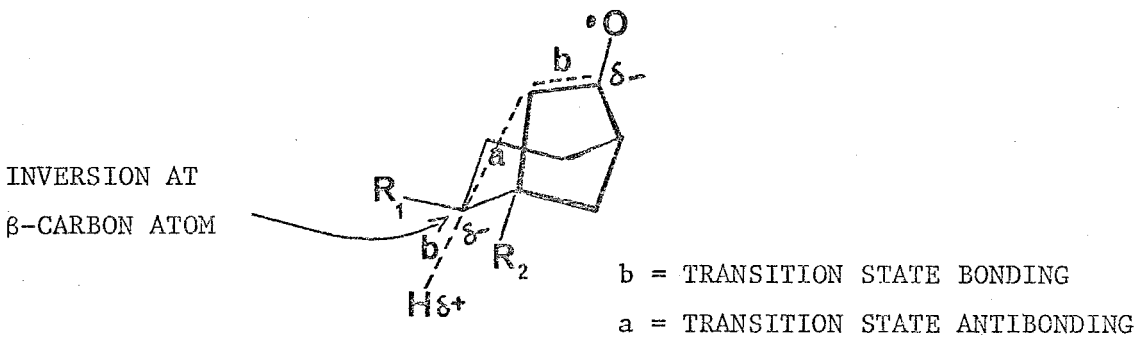
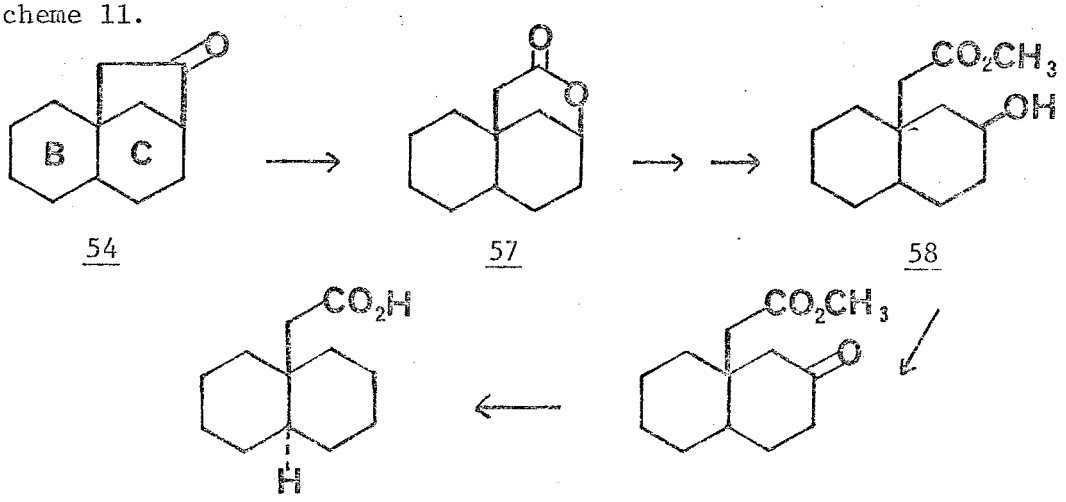


Figure 4

It is feasible that protonation by ammonia (pKa∿35)[115] or, more likely, alcohol (pKa∿19)[115] of the incipient β-carbanions (potential pKa>50)[116] could occur as the cyclopropyl bond is broken (Figure 4) with continuous orbital overlap, reminiscent of an Sn^2 displacement.[117-119]

Such a kinetically controlled process is likely to be highly stereoselective,[118-120] especially in cases where steric hindrance at the β-carbon unambiguously favours approach to one side of the molecule as in the cyclopropyl-ketones 20, 51 and 55. Indeed, the stereochemistry observed (inversion at the β-carbon) after reduction, fits the expectation based on these considerations. Proof of the assigned C6 configuration in ketone 54 is given below.

We decided to degrade the ketone 54 to a decalin-9-acetic acid,* and to make an authentic sample of trans-decalin-9-acetic acid 68, the anticipated degradation product, for direct comparison. An outline of the degradation sequence is given in Scheme 11.



54 57 58

68 = 68a 59

Scheme 11

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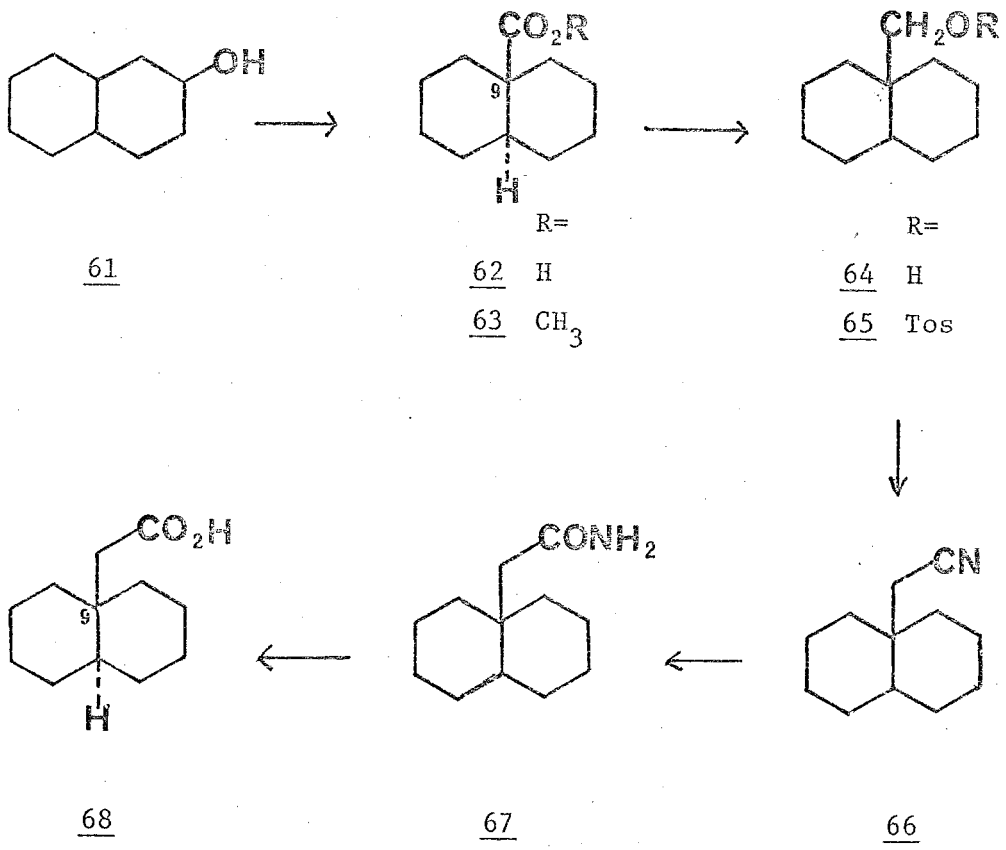
* Cis-decalin-9-acetic acid is a known compound.[121,122]

Baeyer-Villiger oxidation of the ketone 54 using peracetic acid with a trace of p-toluene sulphonic acid[123] gave the crystalline lactone 57 in high yield. The generally greater migratory aptitude of a secondary, over a primary, alkyl moiety in these oxidations is, of course, well established.[124-126] The lactone 57 was hydrolysed with base, then the acidified reaction mixture treated immediately with diazomethane to afford the hydroxy-methylester 58 which was not purified, but oxidised directly with Jones' reagent[31] to yield the corresponding keto-ester 59, in 90% purity. The minor (10%) component of the crude ester 59 had the longer G.C.-retention time, expected for the ketone having a cis-fused B/C-ring junction.

A Huang-Minlon modification of the Wolf-Kishner[127] reduction of the ketone 59 proceeded with concomitant hydrolysis of the ester group to furnish, as the major product (90%), a decalin-9-acetic acid 68a, together with a minor (10%) component having a longer retention time on G.C. analysis (methyl esters). The predominant acid had identical physical characteristics [mp, mmp, ir, G.C. (methyl esters)] with an authentic sample of trans-decalin-9-acetic acid 68, the preparation of which is detailed below, from which we can infer that the ketone 54 has the B/C-rings trans-fused.

Synthesis of authentic trans-decalin-9-acetic acid 68 as in Scheme 12 was not straightforward.



61

62 R= H

63 R= CH_3

64 R= H

65 R= Tos

66

67

68

Scheme 12

It is noteworthy that for a highly stereoselective preparation of trans-decalin-9-carboxylic acid 62,[128] it was preferable to dilute the reaction mixture with water (see Experimental), otherwise

cis- and trans-acids were formed as a mixture which co-crystallised.* Furthermore, conversion of the corresponding carbinol 64 with tosyl chloride into the known tosylate 65,[129,130] required using boiling benzene containing pyridine, which is contrary to the literature procedure.[130]

Homologation to the nitrile 66 needed forcing conditions, employing excessive sodium cyanide in hot DMSO for seven days;[132,133] nevertheless, tosylate-displacement occurred cleanly.

Doubtless, the reaction is retarded by the four 1,3-diaxial (butane-gauche) interactions characteristic[183] of C9 substituents in trans-fused decalins.[170,171]

The steric problem was further exemplified when basic hydrolysis of the nitrile 66 gave the amide 67, and only a small amount (9%) of trans-decalin-9-acetic acid 68. Nevertheless, with sodium nitrite and sulphuric acid,[134,135] the amide 67 hydrolysed readily, presumably via an acyl-diazonium intermediate and the authentic trans-decalin-9-acetic acid 68 thus obtained was compared directly with the decalin-9-acetic acid 68a derived from the ketone 54, as previously described.

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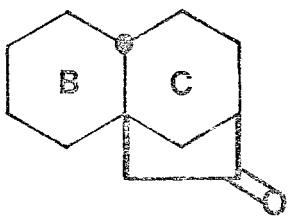
* A proposed Arndt-Eistert sequence[131] was untenable because the derived acid chloride (oxalyl chloride-pyridine) failed to react with ethereal diazomethane.



69

Our stereochemical assignment was reinforced when the known[68] ketone 69,* having a cis-fused B/C-ring junction, coincided on G.C. analysis with a small shoulder coming after the peak due to the tricyclic-ketone 54. Furthermore, the two ketones 54 and 69 had different derivative-melting points.

To summarise therefore: (1) Birch reduction of the olefinic-cyclopropyl-ketone 51 or its saturated analogue 55, proceeds in a highly regioselective manner, generating bicyclo[3,2,1]octane derivatives; (2) cyclopropyl bond-fission occurs with ≥90% stereochemical inversion at the β-carbon atom.

Having established an efficient route to the tricyclic ketone 54 and the configuration at C6, we were then in a position to elaborate the β,γ- and α,β-unsaturated tricyclic-acids 75 and 78,

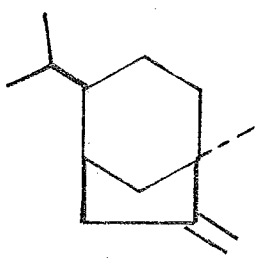
---

* Professor Rogers[68] generously provided a sample of a corresponding carbinol which was oxidised under Jones' conditions[31] to the ketone 69.

required for bio-assay, by applying the sequence of reactions developed in Chapter 2.

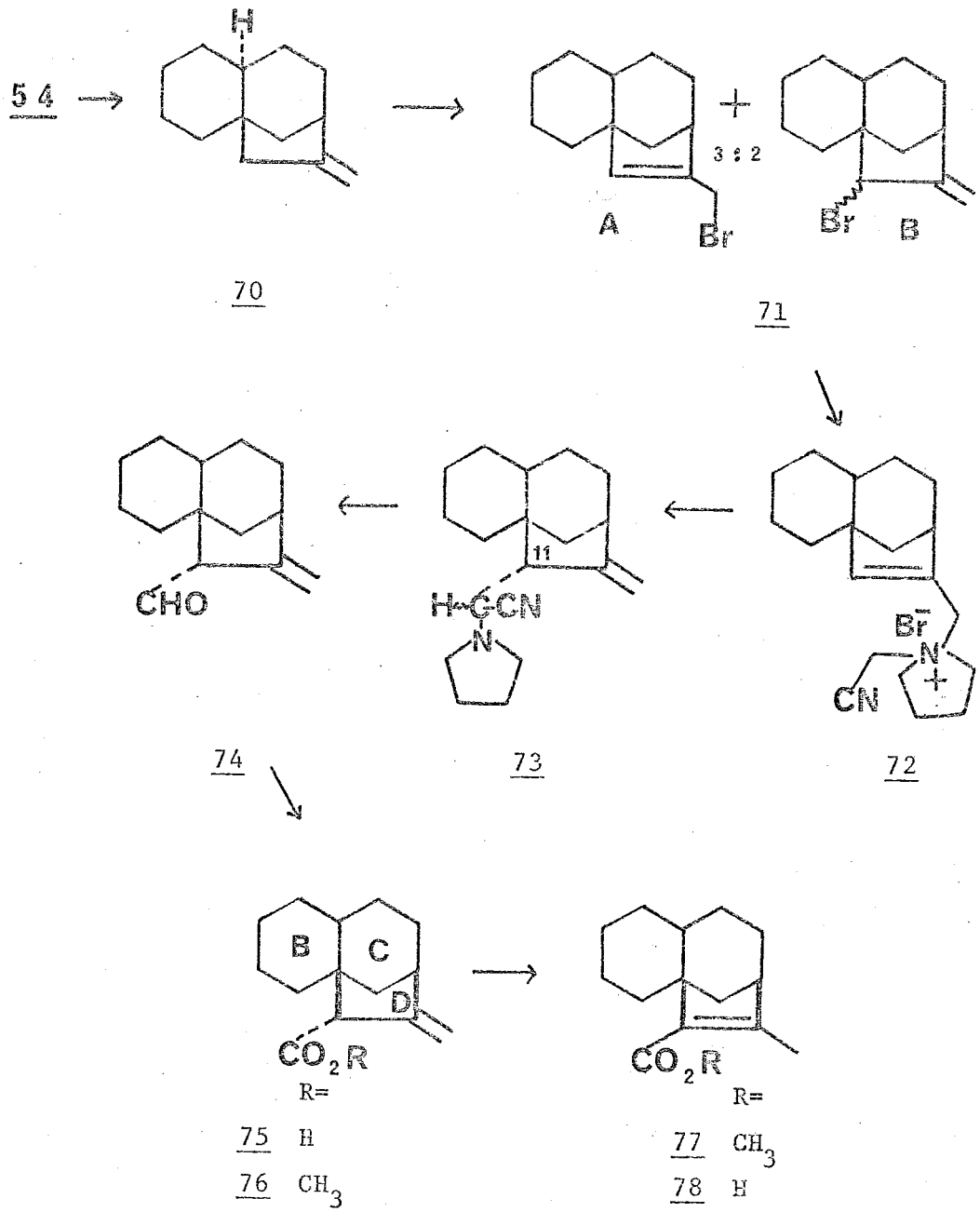
Thus, as outlined in Scheme 13, a methylene Wittig reaction[91] with the tricyclic-ketone 54 gave the corresponding olefin 70 in high yield (91%) which, with NBS[93] afforded a mixture of primary (A) and secondary (B) allylic bromides 71 in a 3:2 ratio respectively by nmr spectroscopy.

The ratio of bromides is indicative of the decreased steric hindrance at the primary carbon and the increased hindrance at the secondary position in the intermediate allylic radical, relative to that formed on bromination of the methylene bicyclo-[3,2,1]octane 29 which furnished primary (A) and secondary (B) bromides 30 in a 1:3.5 ratio.



29

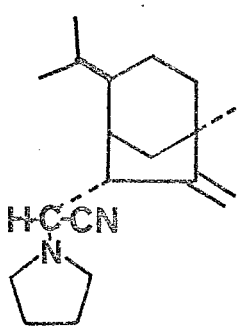
As expected, the mixture of tricyclic-bromides 71 alkylated NCMP to furnish the primary allylic salt 72 which underwent base-


54
H
A
Br
3 : 2
Br
B
70
71
72
73
74
CHO
H-C≡CN
N
11
Br⁻
N
CN
B
C
D
CO2R
R=
75 H
76 CH3
CO2R
R=
77 CH3
78 H

Scheme 13

induced rearrangement[100] with potassium tert-butoxide to the 11-exo-α-cyanomethylpyrrolidines 73.*

Interestingly, subsequent acidic hydrolysis afforded the β,γ-unsaturated aldehyde 74 contaminated (5%) by less corresponding conjugated aldehyde than was obtained (15%) from the analogous bicyclic-pyrrolidinylnitriles 41. This indicates that steric factors may influence the course of hydrolysis, an aspect covered fully in the next chapter.



41

The crude, oily, aldehyde 74 was analysed spectroscopically and by G.C., then characterised by Jones' oxidation[31] to the crystalline β,γ-unsaturated tricyclic-11-exo-carboxylic acid 75, required for biological testing.

The related conjugated acid 78 was elaborated through methylation of its unconjugated isomer 75 with diazomethane and subsequent

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* The exo-configuration is assigned by analogy with the exo-rearrangement of the bicyclic-pyrrolidinium ylide 40 described in the previous chapter.

basic isomerisation of the derived ester 76 by prolonged boiling* (six days) with methanolic sodium methoxide until G.C. analysis indicated >95% conversion to the conjugated ester 77. It was expected that, for steric reasons, attempted basic hydrolysis of the ester 77 under usual conditions (acyl-oxygen fission) would be fraught with complications (see page 30). We decided, therefore, to remove the methyl group by a process of alkyl-oxygen fission, which involved stirring the conjugated methyl ester 77 with lithium n-butylmercaptide in hexamethylphosphorictriamide (HMPTA)† and afforded the α,β-unsaturated tricyclic-11-carboxylic acid 78 without incident.

Both the unconjugated 75 and the conjugated 78 acids have been tested for biological activity and show a growth-stimulating effect which, however, is less pronounced that with the bicyclic analogues made in Chapter 2. The importance of this finding is discussed in Chapter 5.

We turned our attention next to the synthesis of an helminthosporin analogue with a non-polar A-ring, which we considered might completely inhibit activity, and this is described in the next chapter.

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* This reflects the relative inaccessibility of the 11-endo-hydrogen atom in the tricyclic-ester 76.

† This is a simple modification of the procedure developed by Bartlett and Johnson.[136]

CHAPTER 4

SYNTHESIS OF PHYLLOCLADENE-15-*EXO*-CARBOXALDEHYDE 83 AND PHYLLOCLADENE-15-*EXO*-CARBOXYLIC ACID 84

In the previous chapter, plant growth-regulators were synthesised which, in particular, possessed a B-ring approximating to that of gibberellins, and which lacked an angular C/D-ring methyl group common to helminthosporins.

Next we wanted to determine the effects on growth-promotion of an extended carbocyclic framework, containing a hydrophobic A-ring, as opposed to the relatively hydrophilic A-ring of gibberellins.

Since a sample of (+)-phyllocladene 79 was available*, we chose to prepare the acid 84, which seemed a suitable probe for this investigation. It is worth noting that despite obvious differences in stereochemistry between phyllocladene and gibberellins, models show that their overall shapes approximate well.†

The proposed sequence, utilising the now well-established cyanomethylpyrrolidinium-ylide rearrangement, is outlined in Scheme 14 and has been fully realised.

Thus, NBS-bromination of phyllocladene gave, as reported,[137] 17-bromoisophyllocladene 80 with no trace (nmr analysis) of a

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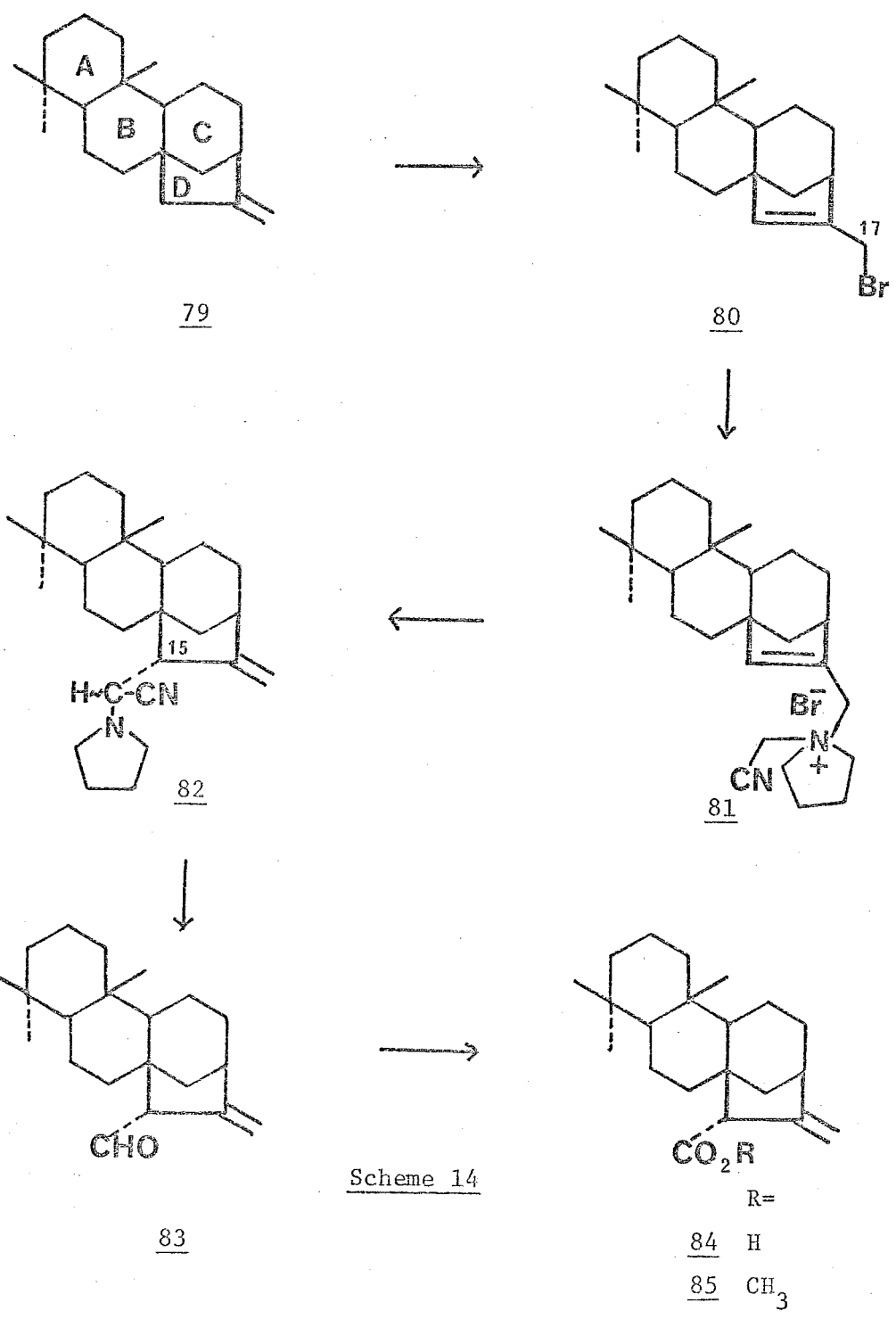
* We are grateful to Dr. B.R. Davis (University of Auckland, New Zealand) for this compound.

† It is highly unlikely that, in the synthetic growth-regulators, the antipode corresponding to the gibberellin configuration is responsible for activity (see page 7). Thus the choice of (+)-phyllocladene appears valid.



79 → 80 → 81 → 82 → 83 → 84 / 85

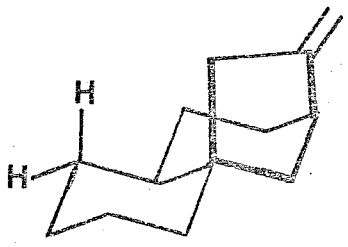
Scheme 14

R=

84 H

85 CH_3

corresponding secondary allylic bromide as was obtained from the analogous tricyclic-olefin 70 described earlier, in Chapter 3.



70

Presumably, the high regioselectivity is due to the fact that, in molecular models, attack of bromine at the secondary C15 carbon of the allylic radical (Figure 5), from the less hindered exo-face, places the C15 hydrogen atom in the endo-position, close to the methyl group at C10. A corresponding hydrogen-hydrogen interaction develops on secondary-bromination of the tricyclic-olefin 70, which lacks an analogous methyl substituent. The phyllocladene A-ring seems too remote from the site of reaction to influence regioselectivity.

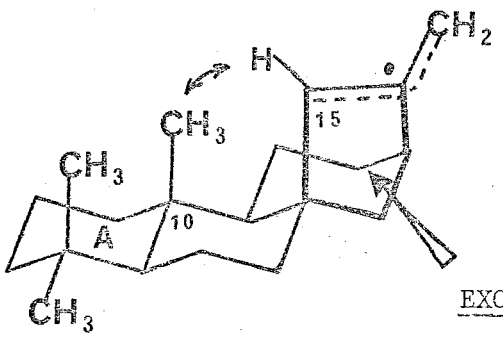
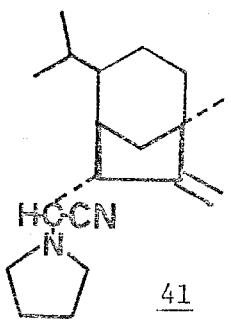


Figure 5

As anticipated, the bromide 80 readily alkylated NCMP to afford the allylic salt 81 which, with potassium tert-butoxide, underwent base-promoted ylide-rearrangement to the diastereomeric 15-exo-α-cyanomethylpyrrolidines 82.*

Mild acidic hydrolysis gave crystalline phyllocladene-15-exo-carboxaldehyde 83 with no evidence (nmr analysis) of a conjugated isomer as was obtained from hydrolysis of the bicyclic 41 (15%, page 29) and tricyclic 73 (5%, page 46) analogues described earlier.



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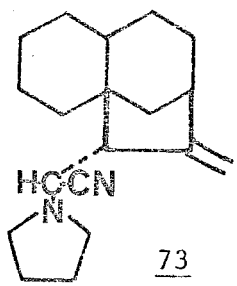


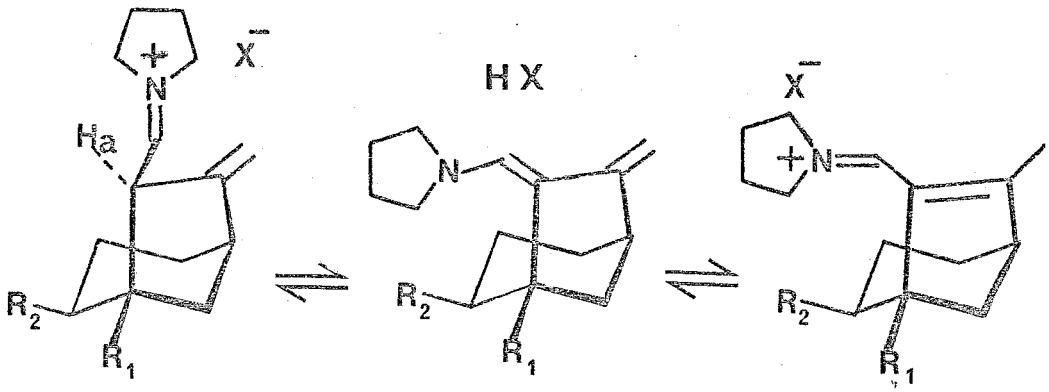
73

An inverse relationship is apparent between the non-bonded interactions in the cyanomethylpyrrolidinyl-region of the three bicyclo[3,2,1]octane derivatives 41, 73 and 82, and the amounts of related conjugated aldehyde obtained on hydrolysis. It will

---

* The exo-configuration is assigned by analogy with the rearrangements described in Chapters 2 and 3.

be shown in Chapter 7 that, in other cases, β,γ-unsaturated aldehydes themselves are stable to the hydrolytic conditions and thus conjugation presumably arises through equilibration of the intermediate imminium salts 85 and 87 via the dienamine 86.[138]



85 86 87

Clearly, those steric effects which render the hydrogen atom Ha less accessible, and which produce severe interactions in the dienamine 86 of the pyrrolidinyl-moiety with R_1 and R_2,* will disfavour dienamine formation, retard hydrolysis of the conjugated salt 87, and hence control the amount of conjugated aldehyde produced.

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* A cisoid-pyrrolidinyl group has bad interactions with the adjacent methylene function in molecular models.

Oxidation of phyllocladene-carboxaldehyde 83 with Jones' reagent[31] at -10° afforded crystalline phyllocladene-15-exo-carboxylic acid 84, which was homogeneous on G.C. analysis (methyl ester 85) and was characterised spectroscopically, including accurate mass, to conserve material for bio-assay.

Significantly, no biological activity of the acid 84 was detected, and this observation is discussed in the next chapter, together with the results of bio-assays on relevant compounds synthesised in the previous two chapters.

CHAPTER 5

RESULTS AND DISCUSSION OF BIO-ASSAYS WITH SYNTHETIC ANALOGUES OF HELMINTHOSPORINS AND GIBBERELLINS

The modified barley endosperm assay[16] was used to measure gibberellin-like activity in the synthetic compounds. This test is based upon the ability of gibberellins to trigger, in embryo-less barley endosperm, the production of α-amylase which catalyses a release of sugars into the medium,[7] thereby increasing its power to refract light.

The determination itself involved incubating ($30^{o}C$) specially prepared barley endosperm with known amounts ($0\text{-}1x10^{-4}$ g/cc, in triplicate, at least) of compound under test, in a buffered solution.

After a suitable time (usually 40 hr) the change in refract-ometer units* of the diluted incubation mixture was measured, the value of a reagent blank without endosperm subtracted, then the difference plotted against the respective concentration of test compound. Generally, consistent results were obtained for each compound in several such investigations; gibberellic acid was used as a standard to gauge the response for each run.

The graphs shown are from one experiment, but nevertheless are representative of the growth response induced by a particular compound.

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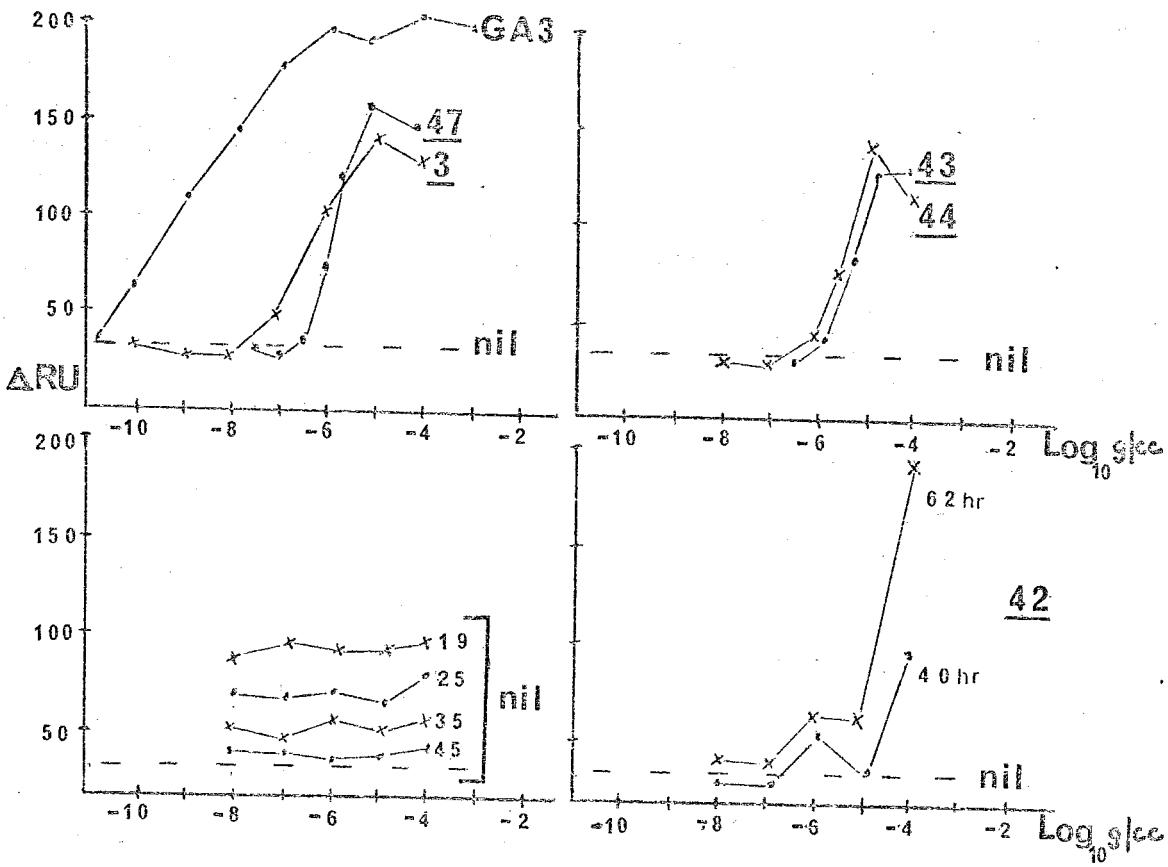
* Waters R4 differential refractometer (Stockport, England).

Results of the barley endosperm bio-assay

(1) Bicyclic analogues



The graphs above reveal that the bicyclic conjugated-acid 47 and helminthosporic acid 3 have a similar activity, which is slightly greater (∿3 times) than for the conjugated aldehyde 43 and non-conjugated acid 44. The related carbinol 35, the methyl ester 45, the ketone 19, and its hydroxymethylene derivative 25 (X=OH), are

all devoid of activity. The non-conjugated aldehyde 42 exhibits a pronounced growth effect only after 62 hr incubation; a particularly interesting discovery which will be discussed later.

The most striking feature of these results is that the C3 substituent (C14) is incidental to the gibberellin-like activity of helminthosporins. Moreover, it seems probable that for a growth effect, a suitably placed carboxyl group is implicated within the cell, and notably that conjugation with an olefinic bond is not vital since the α,β and β,γ-unsaturated acids are both active.

It is improbable that olefinic bond-isomerisation would occur under test conditions which enable differentiation between the corresponding α,β- and β,γ-unsaturated aldehydes.

The activity of the conjugated aldehyde could be ascribed to auto-[19] or biological oxidation to the corresponding acid; a process likely to be less favourable for the unconjugated aldehyde 42 where the formyl hydrogen atom is no longer allylic.

The significant finding that the unconjugated aldehyde 42 displays a pronounced growth effect only after prolonged incubation (62 hr), is consistent with slow, direct oxidation, and adds credence to the above assertions.*

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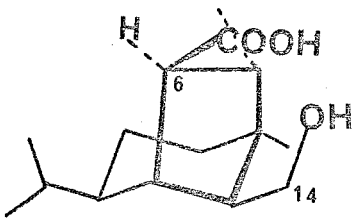
* Slow isomerisation to the conjugated aldehyde and subsequent oxidation cannot be ruled out.

The fact that the hydroxymethyl 35 and hydroxymethylene 25 (X=OH)* derivatives are inactive, indicates that the ionisation constant for the hydroxyl-containing moiety at C13 is important, and that the conjugate base (carboxylate anion) may be the crucial functionality for activity. Indeed, the reduced activity of the non-conjugated exo-acid 44 is plausibly due to the expected lower acidity and polarity than its conjugated isomer 47.[139]

It is possible, however, that the carboxyl group of the conjugated acid is more favourably oriented within the effector site owing to the constraints which conjugation imposes on rotational freedom about the C6,C13 bond.

An explanation is now clear for the surprising lack of a growth effect found by Tamura and Sakuri with the derived hydroxy-exo-acid 88, despite the fact that the epimeric endo-acid 89 was active.[24]



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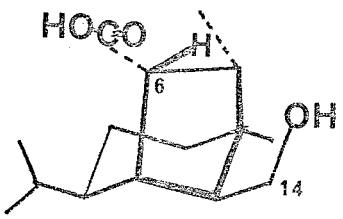

89

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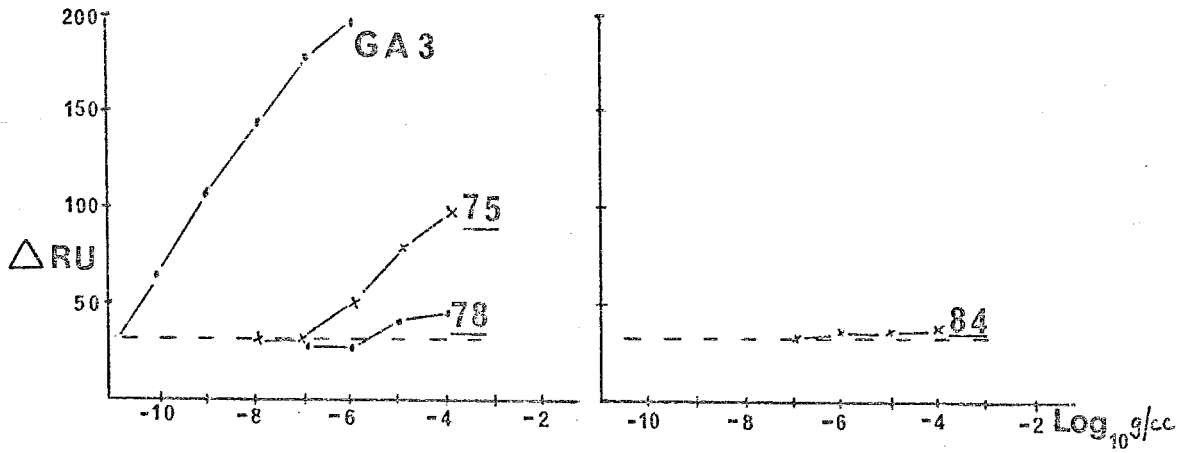
* A carbonyl group at C16 in GA3 does not greatly diminish activity,[14] but in this case the group is remote from the B-ring carboxyl function.

From molecular models, the C6 carboxyl (or carboxylate) function (C13) of the exo-acid 88 is able to hydrogen bond intramolecularly with the C14 hydroxyl group; this would tend to diminish any intermolecular association with a substrate.

Intramolecular bonding is not possible, of course, with the endo-acid 89 or helminthosporic acid 3 or, more significantly, with our synthetic exo-acid 44, which lacks a C8 substituent (C14).

(2) The tricyclic acids 75 and 78



The graphs indicate that the non-conjugated tricyclic-acid 75 has less influence on growth than the corresponding bicyclic analogue 44, and that the effect of the tricyclic conjugated acid 78 is extremely weak.

Lack of an angular C9 methyl group has not prevented activity and is unlikely to retard it. Reduced growth-promotion is probably due to steric hindrance about the carboxyl groups which is maximised for the conjugated isomer.

The steric effects about the B-ring carboxyl function in gibberellins could be outweighed by a greater binding capacity to the substrate, due to other (polar) features of the A-ring.*

(3) The tetracyclic acid 84

It can be seen from the graph above that the acid 84 had no

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* No competitive binding was detected between the synthetic analogues and GA3. The expected greater binding capacity of GA3 would probably overcome any concentration effect of a synthetic growth-regulator.

discernable effect on growth. The A-ring seems too far removed to sterically hinder the carboxyl group and therefore the lack of a growth response may be attributed to the inability of the receptor site to accommodate a non-polar moiety in the gibberellin A-ring region.

It is striking that the curves for the more active synthetic growth-regulators and helminthosporic acid are steeper than for GA3; thus the acid 47 at 10^{-6} g/cc has a potency of ∿1/5000 GA3 but this rises at 10^{-5} g/cc to ∿1/200 GA3. Also, the curves are bi-modal; at concentrations above 10^{-5} g/cc there is reduced growth promotion.*

These curve characteristics are difficult to explain and subtle effects such as product regulatory inhibition at binding and/or active sites must not be overlooked.[140]

Preliminary studies of activity using a Rumex leaf senescence bio-assay[16] show that both olefinic-bicyclic acids and the two tricyclic acids have some effect on growth, but as expected the bicyclic carbinol 35 is inactive.

The nature of this test is such that a subjective judgement is involved as to the moment of assay-termination, and further

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* A complete statistical analysis of these results has yet to be carried out.

experiments are under way.

The four acids also showed significant activity in the Murakami rice-assay,[141] but the growth effect was not large.

This could be attributed to a molecular-transport barrier since the test compound is applied outside the plant cuticle, in the angle between the first leaf sheath and the coleoptile.

In conclusion, it is worth noting that one gibberellin may evoke a different response for each bio-assay method used,[15] and that the gibberellin which produces the greatest response in a given plant may not be the major gibberellin for that plant.[7]

Clearly, the complexity of plant growth processes is such that many reasons can be advanced to rationalise perturbations, or lack thereof, due to a chemical compound, but extensive speculation serves only to confuse the issue.

The fact remains that the angular C1 methyl group (C15) and more especially the C8 substituent (C14) in helminthosporins are superfluous for inducing a gibberellin-like response in barley endosperm. This strongly supports the hypothesis in the Introduction that helminthosporins function in the gibberellin effector site. Substantiating this is the activity shown by the tricyclic acids 75 and 78, having a bulky appendage in the related region of the gibberellin B-ring, and the lack of activity shown by the analogous tetracyclic acid 84 with a non-polar A-ring.

This work has initiated an approach for examining the structure-function problem of gibberellin activity in a formerly unexplored, systematic manner. Without doubt, further vital information will come from determining the absolute minimal structural requirements for activity and from defining the growth response in relation to alternative ring-skeletons (e.g. a bicyclo[2,2,2]octane) and (polar) substituents.

The syntheses already established are amenable for introducing isotopic labels, particularly ^{13}C, at various sites (especially the carboxyl group) and this alone should be invaluable for examining possible interactions with substrates, utilising PFT ^{13}C nmr techniques.[142]

Already syntheses in this department are being conducted towards compounds with polar substituents, designed to probe the structure-function relationship with respect to the gibberellin A-ring and angular C/D-ring hydroxyl group. Indeed the next chapter deals with the synthesis of an hydroxy-gibberellenone as a possible intermediate for these latter investigations.

CHAPTER 6

SYNTHESIS OF A TETRACYCLIC GIBBERELLIN-ANALOGUE HAVING A C/D-RING ANGULAR HYDROXYL GROUP

Studies conducted so far into the structure-function problem of gibberellins and helminthosporins, have been concentrated on providing model compounds with a functional array similar to that found in helminthosporins, and on modifying the carbocyclic framework to which it is attached. This has provided a valuable insight into the flexibility of the effector site. Nevertheless, the complex oxygenation patterns found in gibberellins[7] suggest that several groups may be necessary for high activity.

A vital proposition, therefore, seems to be the systematic synthesis of hormone-analogues very similar to gibberellins, having in particular an angular C/D-ring hydroxyl group and relevant polar groups in an A-ring. Such a project would be even more worthwhile if it could serve to provide intermediates for gibberellin total synthesis, although this proposal introduces severe logistic and stereochemical problems attested to by the diverse and ingenious approaches taken by others engaged in this field.[27,39,143-156]

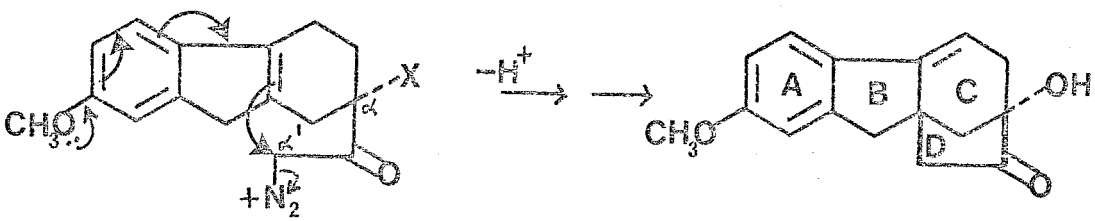
For our specialised requirements we needed a versatile tetracyclic molecule, based on the gibberellane framework, onto which could be added later helminthosporin-like bridge functionality, or alternatively a carboxyl group on the B-ring as found in gibberellins.

The gibberellenone 100, having a bridgehead hydroxyl group,

potentially fulfils this requirement since it is suitably functionalised in the D-ring and has an A-ring inert to most chemical transformations, but which nevertheless can be unmasked (e.g. Birch reduction), at an appropriate moment, as an aliphatic ring with a strategically placed oxygen function.

We conceived that the required gibberellane framework would be accessible from a polyhydrofluorene skeleton, by the introduction of a functionalised, two-carbon bridge embodying the D-ring.

The intramolecular displacement of nitrogen from an α'-keto-diazonium ion 90 by a suitably positioned olefinic bond, akin to the cyclisation discussed in Chapter 2, seemed an admirable solution to the bridging problem, providing the future bridgehead substituent (X) would not participate in the decomposition of the diazonium ion.*



90 100

A logical precursor to a suitable diazo-ketone was the α-hydroxy-acid 95, although the α-hydroxy-substituent would obviously have to be masked prior to the cyclisation step.

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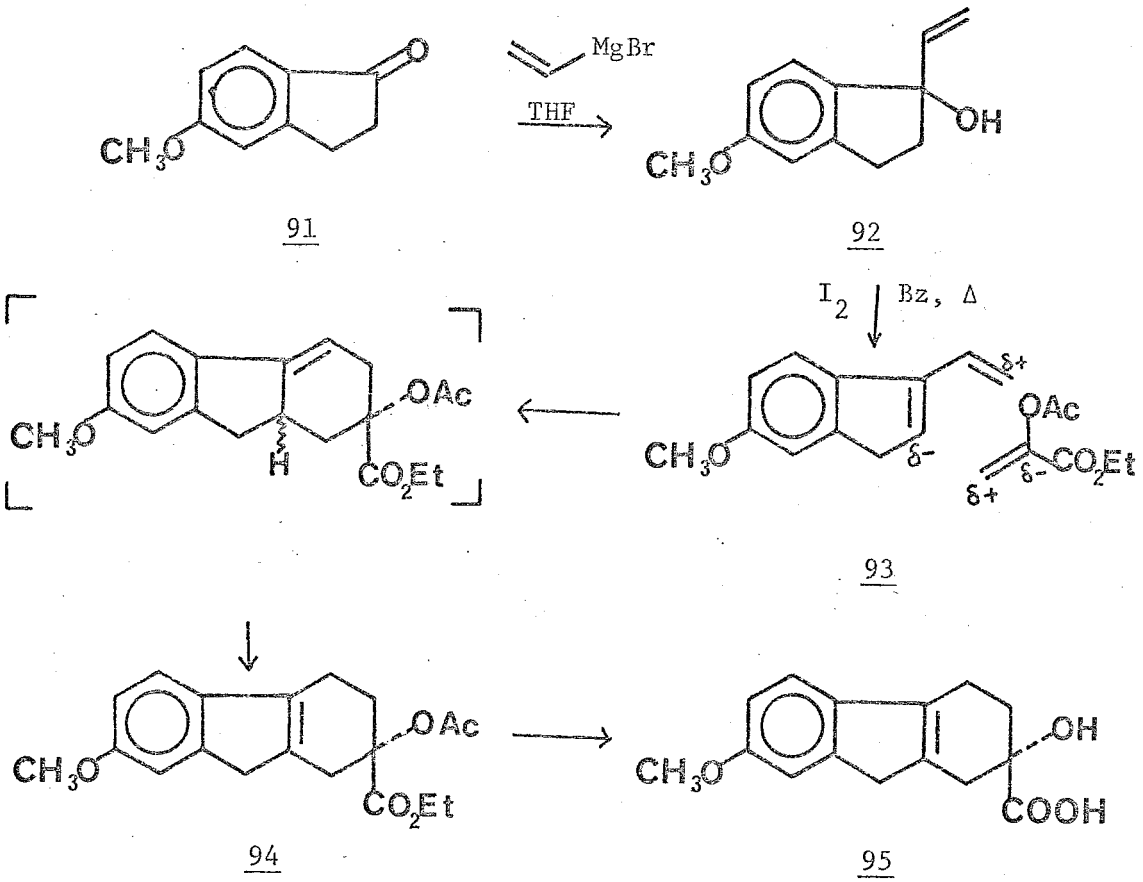
* Studies on related compounds in this department have demonstrated nucleophilic participation by α-hydroxy, α-bromo and α-acetoxy groups in the decomposition of α'-keto-diazonium ions.[27,65]

The acid 95 appeared accessible, as Scheme 15 indicates, via a Diels-Alder reaction between the known diene 93[156] and the enol-acetate of ethyl pyruvate (ethyl α-acetoxyacrylate).[157]



91 92 93 94 95

Scheme 15

Wharton and Aw[158] found that a cyclo-addition using methyl α-acetoxyacrylate yielded a diastereomeric mixture with very high (98%) orientational selectivity, comparable with acrylonitrile, which is known[156] to react with the diene 93 to afford the single

regio-adduct predicted from unlike dipole-dipole alignment of the diene and dienophile.[158-160] Thus, we expected our addition to occur with similarly high regioselectivity and to afford diastereomers.

The reaction of diene 93 and ethyl α-acetoxyacrylate in boiling benzene proceeded smoothly. Upon completion (tlc), it seemed expeditious to eliminate probable stereochemical ambiguity by immediately effecting migration of the olefinic bond to the tetrasubstituted position, in preparation for the cyclisation.

Accordingly, dry HCl gas[36] was passed through the Diels-Alder reaction mixture to afford the isomerised adduct 94 which was purified by chromatography, then hydrolysed with base to furnish the required α-hydroxy-acid 95 in 30% overall yield from the methoxyindanone 91 (five steps).

Before acid chloride formation, it was deemed necessary to protect the α-hydroxy function. A trifluoroacetoxy group was chosen, since this could serve another role - to render the tertiary oxygen substituent weakly nucleophilic, and therefore unlikely to compete with the olefinic bond for the electrophilic α'-keto-diazonium ion 90 (X=OTFA).

Thus, as depicted in Scheme 16, sequential treatment of the hydroxy-acid 95 with trifluoroacetic anhydride, water (96)*, then

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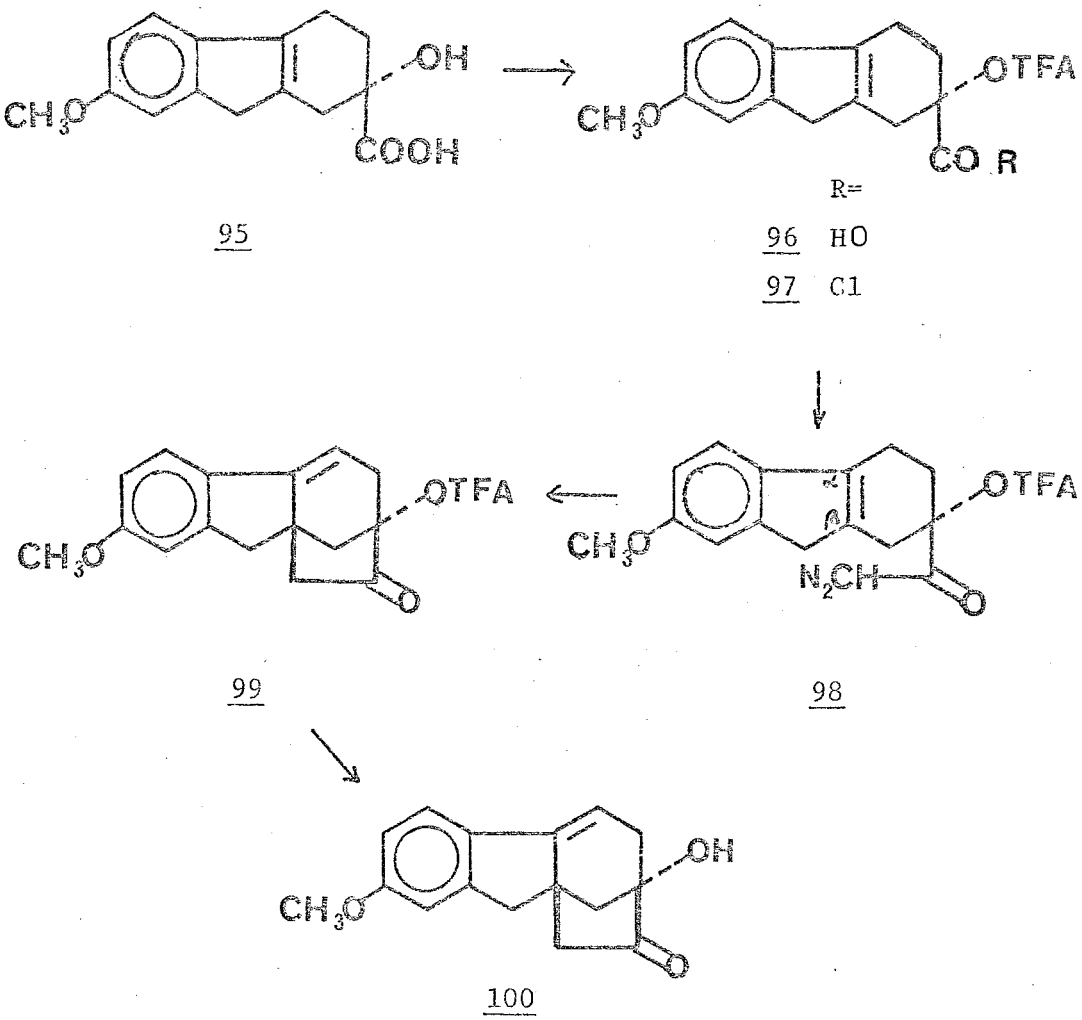
* Purification of compounds bearing a tertiary trifluoroacetoxy substituent was not attempted, but all had consistent spectral characteristics.



95 96 97 98 99 100

Scheme 16

oxalyl chloride-pyridine (97), and finally ethereal diazomethane, furnished the required trifluoroacetoxy-diazoketone 98. When added to rapidly stirred trifluoroacetic acid,* a copious evolution

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* c/f nitromethane BF_3-etherate, page 14.

of gas (nitrogen) ensued. The resulting tetracyclic-trifluoroacetate 99 was immediately hydrolysed with weak base to afford, after chromatography, the required hydroxygibberellenone 100 in 59% overall yield from the hydroxy-acid 95 (five steps).

The utility of the anisole synthon in this sequence is notable: (1) to direct the regioselectivity of the Diels-Alder addition; (2) to direct cyclisation to the β-terminus of the olefinic bond; (3) to serve as a malleable A-ring.

Sample limitations have restricted further work in this area. It is relevant, however, that in projected syntheses the function of the angular hydroxyl group is not trivial.

We believe that future stereochemistry at the B/C-ring junction can be modified with respect to asymmetry introduced elsewhere in the molecule by means of a pinacol-like rearrangement[150,162,163] involving the α-hydroxy-carbonyl moiety or derived functionality, as exemplified in Figure 6.

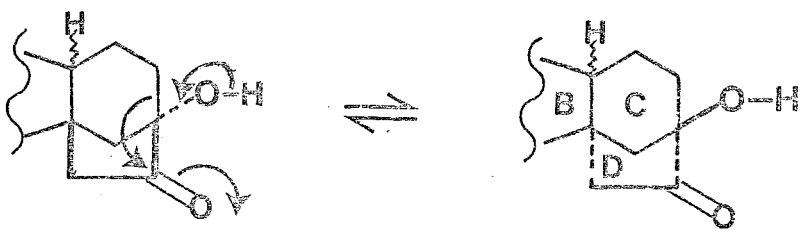


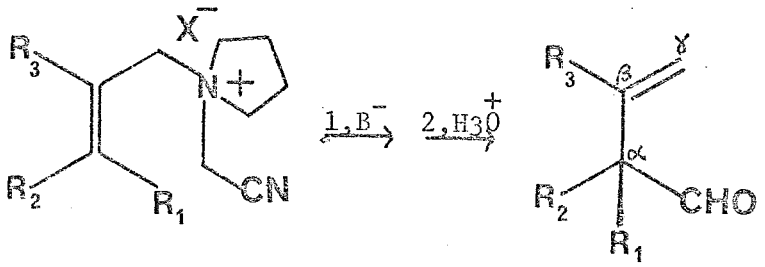
Figure 6

These proposals must await the optimisation of the overall yield in the sequence just described. Nevertheless, the feasibility of this approach to tetracyclic gibberellin analogues having a C/D-ring angular hydroxyl group, has been well demonstrated.

CHAPTER 7

STUDIES ON THE [2,3]-SIGMATROPIC REARRANGEMENT OF ALLYLIC PYRROLIDINIUM YLIDES FOR THE SYNTHESIS OF β,γ-UNSATURATED ALDEHYDES

In Chapter 2, a sequence (Scheme 8) involving the base induced [2,3]-sigmatropic rearrangement of allylic α-cyanomethyl-pyrrolidinium salts 35, was developed to overcome the difficulty of elaborating helminthosporin-like bridge functionality.



35 38

Since the approach seemed generally applicable for β,γ-unsaturated aldehyde 38 synthesis, we decided to investigate this potential with particular regard for the fundamental criteria, listed below, which define the usefulness of any synthetic methodology.

(1) substrate diversity;

(2) steric effects;

(3) stereoelectronic effects;

(4) side reactions: if a competing [1,2]-process can be induced;

(5) extension of the methodology.

Each point is discussed in turn later. It is pertinent at this juncture, however, to emphasise some of the features of this approach,

which in particular exemplifies the exceptional properties of a nitrile synthon.

Initially, the nitrile function controls the site of ylide-carbanion formation and hence directs rearrangement[100] towards the α-cyanomethyl moiety; subsequently it acts as a leaving group on hydrolysis of the rearranged α-pyrrolidinylnitrile to unmask a carbonyl group in the final product. The dual role of the nitrile group is probably difficult to duplicate.

Although the choice of a pyrrolidine derivative would seem optional, it was made so as to enhance the nucleophilicity of the amine and, further, to facilitate the eventual expulsion of cyanide (as HCN).[164]

The conditions for the [2,3]-rearrangement itself (low temperature, relatively low solvent-polarity) were chosen to reduce the possibility of a competing [1,2]-process,[100,165-167] while relatively mild hydrolytic conditions (THF-oxalic acid) were selected to minimise the chance of conjugating (where this is possible) the generated β,γ-unsaturated aldehydes.

Applications of the approach rationalised above have already been demonstrated in preceding chapters, now the scope and limitations are studied within the categories (1)-(5) below.

(1) Substrate diversity

The variety of substrates chosen to investigate stereochemical effects on the rearrangement illustrates the versatility of the method.

In particular, it is worth noting the alkylation of allylic amines with chloracetonitrile [see (3)]. This exemplifies a very useful preparation of ylide-precursors whose corresponding allylic halides are difficult to obtain.

(2) Steric effects

That steric effects influence the course of the rearrangement was obvious from the pioneering experiments conducted in Chapters 2, 3 and 4. We wanted to examine, however, a case where the alternative stereochemical pathways would be more equivocal and which, therefore, would allow us to study the effects of temperature on stereoselectivity.

The ylide 105, having a conformationally biassed cyclohexylidene ring-system,* seemed highly suited for our purpose since the aldehydes 107 and 108 were known compounds.[88] Furthermore, the rearrangement could function as a useful model for the elaboration of the α-vinyl-methyl function common to rosenonolactone[172,174] and a number of other diterpenoids.[173,175]

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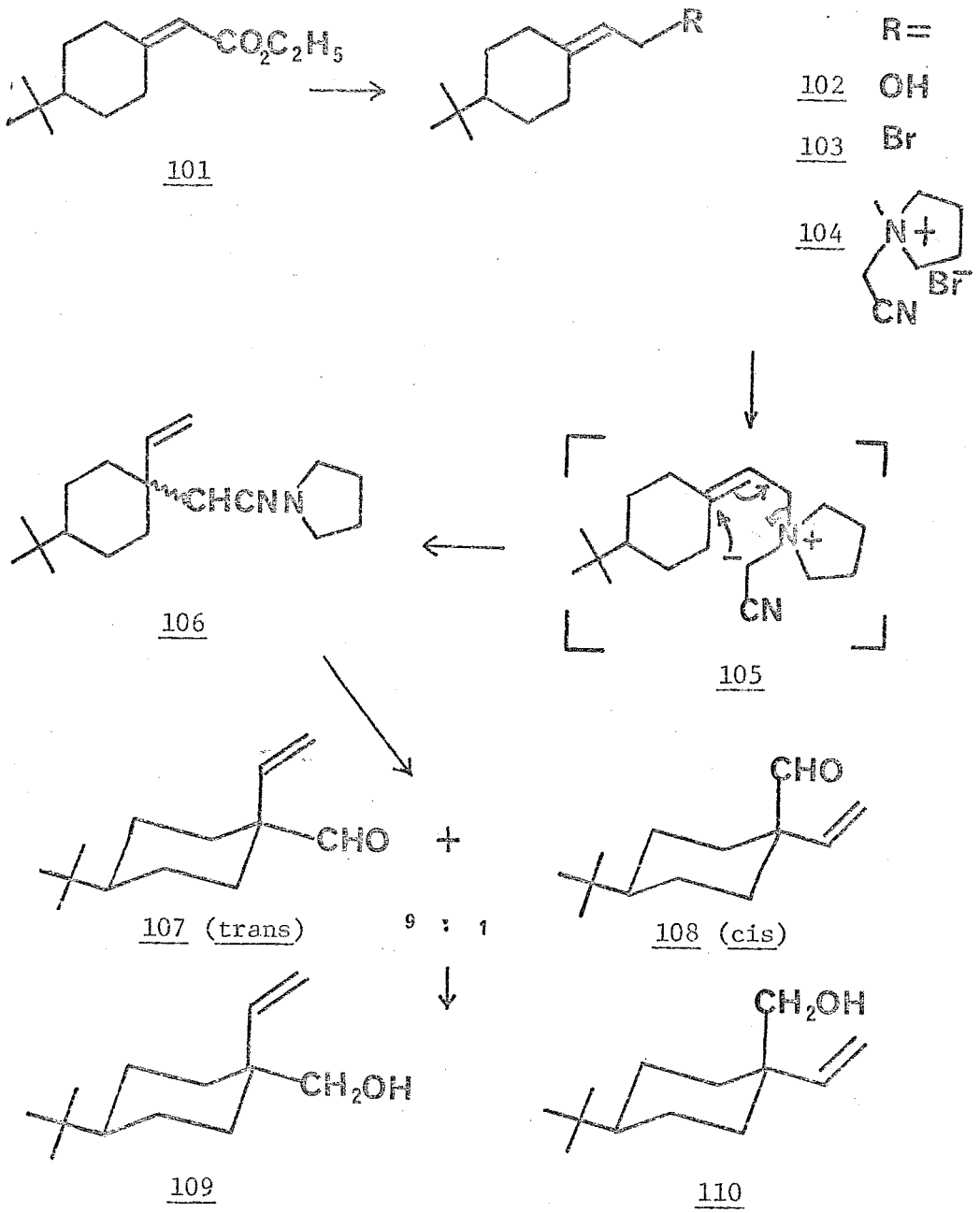
* The role of a tert-butyl group as an effective conformational lock is well established.[168]



101 106 105 107 (trans) 108 (cis) 109 110

Scheme 17

Construction of the ylide-precursor 104 is depicted in Scheme 17.

4-tert-butylcyclohexanone and ethyl diethylphosphonacetate with NaH[176] at low temperature afforded, in virtually quantitative yield, the ester 101, which was smoothly converted into the vinyl alcohol 102 with aluminium hydride, chosen to minimise the possibility of 1,4 reduction.[177-179]

Phosphorous tribromide with pyridine in ether[180] at low temperature cleanly gave the corresponding allylic bromide 103 as an oil which was fully characterised spectroscopically but could not be distilled without gross decomposition. Ylide-precursor 104 formation with NCMP was extremely rapid in DMSO and also occurred in an hydrocarbon solvent (X4), with ensuing precipitation which facilitated isolation of the salt.

Rearrangement, induced by the addition of potassium tert-butoxide in the usual manner (DMSO-THF, -10^{o}), led to a diastereomeric mixture of nitriles 106.

After hydrolysis, G.C. analysis of the resulting oil indicated two peaks in a ratio of 17:3. The major one, having the longer retention time, was tentatively attributed to the equatorial aldehyde. After careful chromatography, this was substantiated by nmr spectra of the major and minor components, which had stereo-

chemically diagnostic[88] formyl-proton resonances at δ9.30 and δ9.26 for the trans(equatorial) aldehyde 107 and the cis(axial) aldehyde 108 respectively.* Reduction (LAH) to the corresponding carbinols 109 and 110 and comparison with authentic spectra† established the stereochemical assignments unequivocally.

The aldehyde-ratio was increased to 9:1 when the solution was cooled to -78° before the addition of base. At this temperature, however, the reaction mixture became heterogeneous, which made stirring difficult. In an attempt to overcome this problem and also test the effects of an intermediate temperature, solutions of previously isolated salt 104 (see above) in liquid ammonia at -33° and -78° were treated with base. No significant changes in stereoselectivity were observed from those reactions in THF-DMSO at -10° and -78° respectively.

Clearly, in the limit, stereoselectivity is controlled in the transition state by the difference in the chair-like conformational free-energy values of the developing vinyl and cyanomethyl-pyrrolidinyl groups.ϕ

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* Trans and cis with respect to the tert-butyl and formyl groups is implied here and in the compounds which follow.

† Dr. D.H. Evans c/f ref.88 generously provided these spectra.

ϕ For a discussion of the Curtin-Hammett principle see ref.171, page 237.

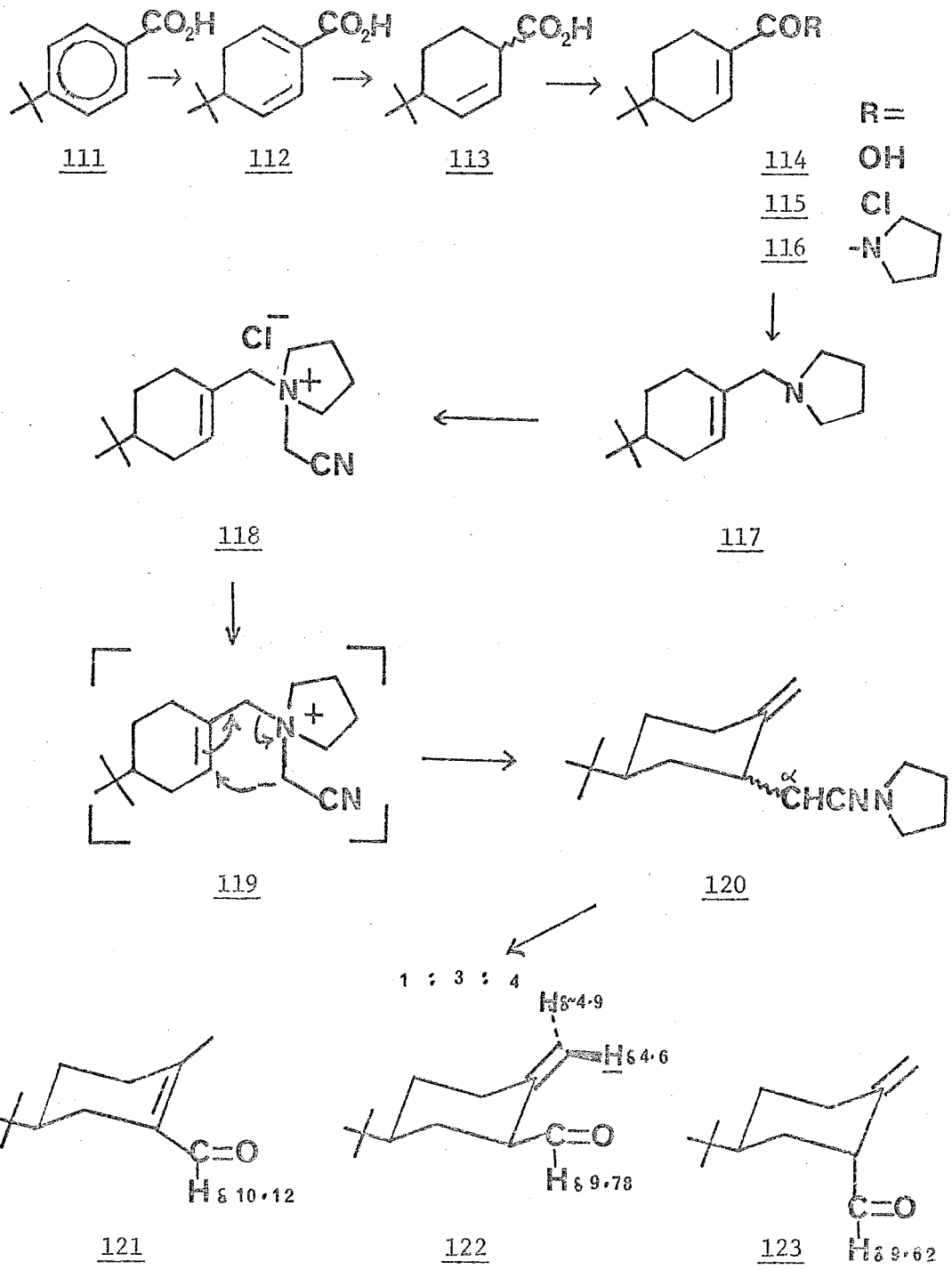
Undoubtedly, higher stereoselectivity could be obtained by using a bulkier amine or, more especially, by introducing substituents onto the cyanomethyl moiety, but these somewhat incidental modifications were not investigated.

(3) Stereoelectronic effect

We considered that a likely[181] stereoelectronic effect could most easily be determined by the rearrangement of an allylic ylide having an endocyclic olefinic bond in a conformationally weighted six-membered ring. In the absence of biassed steric influences, a stereoelectronic requirement would then be indicated by the predominance of an axial aldehyde in the final products.

Ylide 119 appeared to meet our requirements and was particularly appealing because the precursor salt 118 seemed accessible through alkylation of the allylic amine 117 with chloracetonitrile as Scheme 18 illustrates. This was borne out in practice and illustrates a useful alternative approach to ylide-precursor synthesis.

Preparation of the allylic amine 117 was relatively uncomplicated from 4-tert-butyl benzoic acid 111. Thus, two straightforward dissolving-metal reductions in liquid ammonia[33] (111→112→113) and final base induced conjugation of the β,γ-unsaturated acid 113 gave the α,β-unsaturated acid 114.[182] This was converted



111 112 113 114 OH 115 Cl 116 -N

118 117

119 120

121 122 123

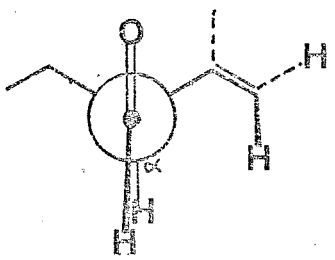
Scheme 18

into the amide 116, through treatment of the derived acid chloride 115 (oxalylchloride-pyridine) with pyrrolidine. The amine 117 was then obtained by reduction with aluminium hydride, chosen to diminish the possibility not only of 1,4-reduction,[117-119] but also of reductive fission of the acyl-pyrrolidine bond.[184,185]

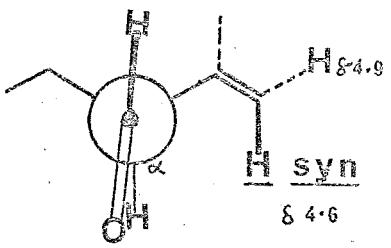
Alkylation with chloracetonitrile was surprisingly slow, and necessitated warming (45°) the amine 117 in DMSO for 18 hr. Under the usual conditions (DMSO-THF, -10°), base induced rearrangement of the derived salt 118, gave a diastereomeric mixture of pyrrolidinylnitriles 120 which, on hydrolysis with THF and oxalic acid for 5 min, gave the conjugated 121, cis(equatorial) 122, and trans(axial) 123 aldehydes in a ratio of 1:3:4 respectively. The same ratio of aldehydes was obtained after 15 min and 30 min under the hydrolytic conditions, which suggests that the conjugated isomer 121 is derived through a conjugated dienamine and hydrolysis of the pertinent imminium salt (see Chapter 4). The ratio of aldehydes follows from the integral values of their assigned formyl-proton resonances in the nmr spectrum of the mixture.

A minor downfield singlet (s) at δ10.12 was attributed to the conjugated formyl group (121); a doublet (d) at δ9.78, J=3Hz was ascribed to the equatorial formyl-proton (122) deshielded by the olefinic bond[186] relative to a singlet at δ9.62 which was assigned to the axial formyl-proton (123).

The formyl-proton multiplicities (d and s) ascribed to the equatorial 122 and axial 123 aldehydes are consistent with those which might be predicted from the respective dihedral angles (∿0 or 180° and ∿90°) between the HCα and formyl hydrogen atoms in maximally sterically-weighted conformers[187] as discerned from molecular models and illustrated in Diagram 2.

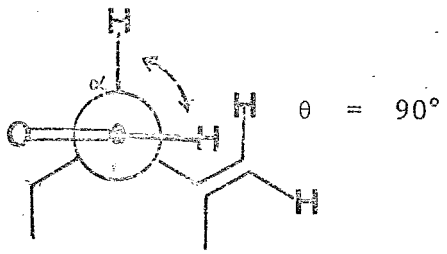


θ = 0°

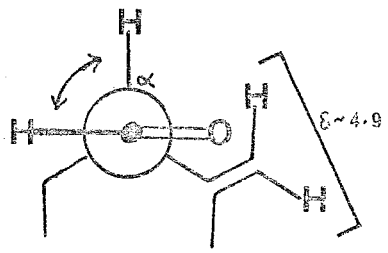


θ = 180°

Equatorial formyl group $J_{calc} \geq 3Hz$, $J_{obs} = 3Hz$



θ = 90°



Axial formyl group $J_{calc} = 0Hz$, $J_{obs} = 0Hz$

Diagram 2

This interpretation is reinforced by an olefinic resonance relatively upfield at δ4.6, which has the same integral value as the assigned equatorial formyl-proton resonance, and can by attributed to the syn-methylene proton, predominantly in the shielding region of the equatorial formyl group.[188] Unfortunately, G.C. analysis of the mixture was not helpful owing to partial isomerisation on the column.* Because of this instability, no further attempt was made to separate the aldehydes; they were characterised by basic isomerisation to the conjugated isomer 121 which was fully analysed.

In view of the known steric influence on the rearrangement, formation of a significant proportion of axial aldehyde suggested a stereoelectronic requirement; unfortunately, though, these results were not definitive.

It can be deduced from the aldehyde ratio above (1:3:4) that if the conjugated aldehyde 121 were derived only from the equatorial α-cyanomethylpyrrolidine derivative 120, the ylide 119 rearrangement had led indiscriminately to both α-cyanomethylpyrrolidines 120.†

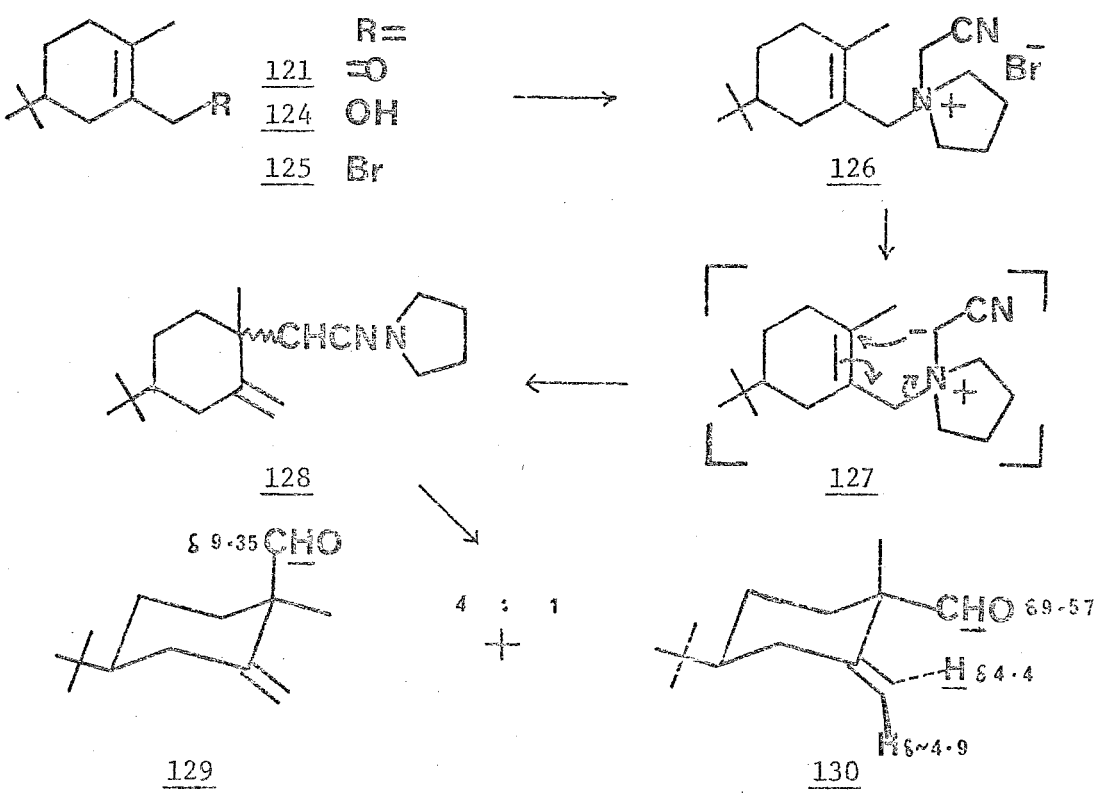
---

* This was evident from three characteristically broad "decomposition" peaks.

† Nmr analysis of the α-cyanopyrrolidine mixture 120 was confused by diastereoisomerism at the α-cyanomethyl carbon atoms.

It was difficult to decide which aldehyde precursor 120 (if either) would more easily give rise to the conjugated aldehyde 121. Relief of steric interactions favoured the axial isomer 120 on the one hand, while on the other kinetic loss of the allylic axial hydrogen atom favoured the equatorial isomer 120.

To resolve this dilemma, we decided to study another ylide rearrangement 127 as shown in Scheme 19, which was anticipated to afford, ultimately, the β,γ-unsaturated aldehydes 129 and 130 in which conjugation is blocked by tertiary methyl substituents.

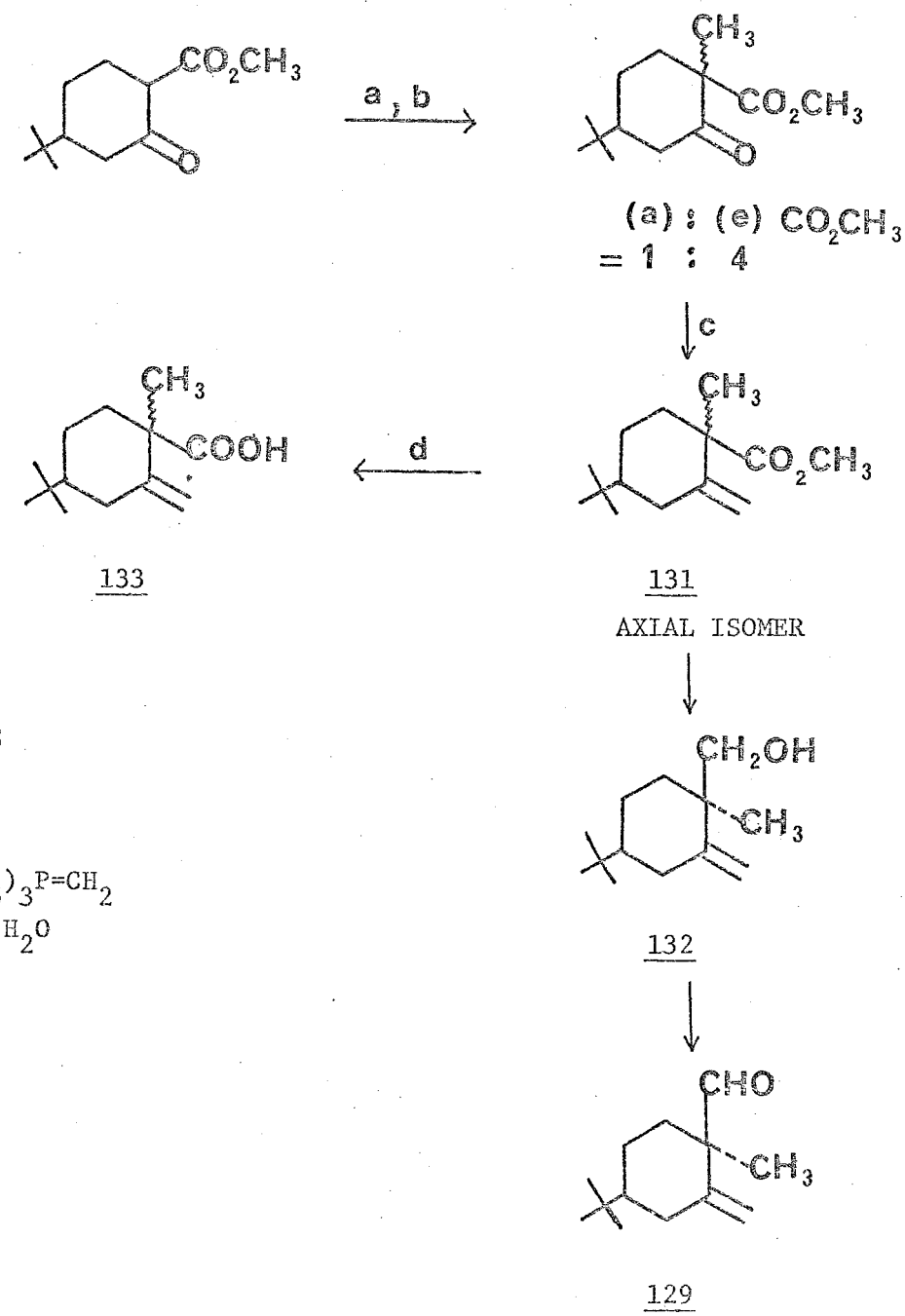


Scheme 19

This was a particularly attractive proposal because the corresponding epimeric acids 133 were known compounds, having been derived previously, as Scheme 20 indicates, for another investigation.[189]

As depicted in Scheme 19, reduction of the conjugated aldehyde 121 with LAH afforded the carbinol 124 which, with phosphorous tribromide and pyridine,[180] cleanly gave the corresponding bromide 125. Because of expected instability, this was characterised spectroscopically, then added directly to NCMP in DMSO to generate the salt 126.

Base induced rearrangement took place under the usual conditions, as anticipated, to furnish a diastereomeric mixture of pyrrolidinylnitriles 128. Mild acidic hydrolysis gave a mixture of cis(axial) 129 and trans(equatorial) 130 aldehydes in a ratio of 4:1 as established by G.C. analysis and direct comparison with authentic samples (see below). The ratio was confirmed by integration over the respective formyl-proton resonances in the nmr spectrum of the mixture. This showed a minor, relatively downfield, singlet at δ9.57 due to the proton of the equatorial formyl group, predominantly in the deshielding zone of the olefinic bond,[186] and a major singlet at δ9.35 caused by the axial formyl group. A relatively upfield olefinic resonance at δ4.4, having



REAGENTS

a, LiH

b, CH_3I

c, $(C_6H_5)_3P{=}CH_2$

d, KOH, H_2O

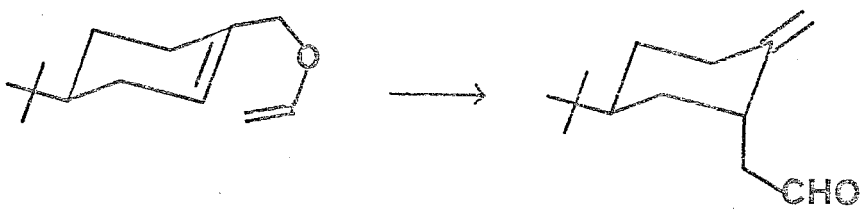
Scheme 20

the same integral value as the equatorial formyl proton, was diagnostic for the syn-methylene proton in the shielding region of the equatorial formyl group.[188]

Preparation of an authentic sample of the axial aldehyde 129 from the corresponding ester 131, was readily effected by consecutive LAH reduction to the alcohol 132 and modified Collins oxidation.[190] A trace of equatorial ester in the starting material served to distinguish the resulting equatorial aldehyde 130 from the axial aldehyde 129.

The above finding unequivocally established a stereoelectronic requirement for the rearrangement.

The greater stereoselectivity in the second example is undoubtedly due to the effects of the (ultimately) tertiary allylic-methyl groups. These will make the steric (equatorial) demands of the developing allylic substituents more equivalent in the transition state, and thus non-bonded interactions less influential in determining the final products.[191] Nevertheless, the stereoselectivity is less than in the Claisen rearrangement of the methyl vinyl ether 134, which on heating to 114° affords only the axial aldehyde 135.[192] Presumably, the transition state for the Claisen rearrangement with its higher activation energy (relatively low ground state energy compared with an ammonium ylide) is structured more like products.[114,193]



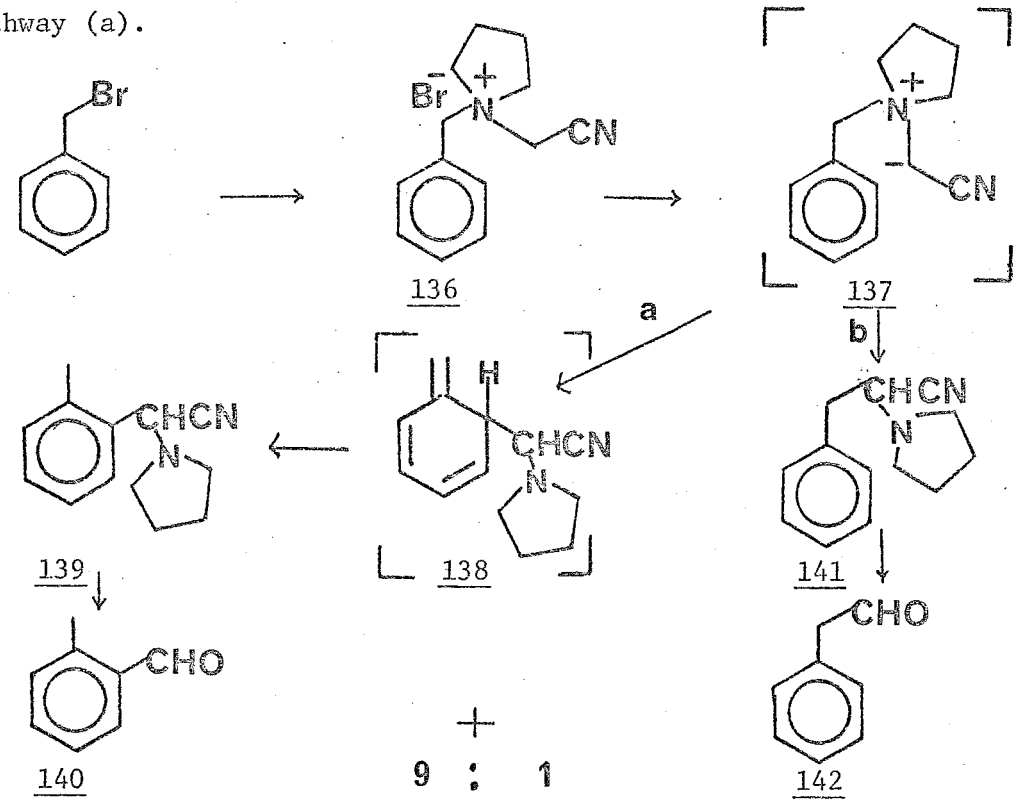
134 135

The stereoelectronic requirement of this pyrrolidinium ylide rearrangement offers a good synthetic potential. It can be seen from Scheme 20 that in a chair-like cyclohexane ring, mainly axial methylation of the β-keto-ester anion occurs under stereoelectronic control.[189,194] The pyrrolidinium ylide sequence just described is therefore complementary to that of direct methylation since the analogous predominant aldehyde 129 has the methyl group equatorially disposed. We plan to exploit this complementary stereoselectivity in future syntheses.

(4) A competing [1,2]-sigmatropic rearrangement

Although a competing [1,2]-pathway [(b) Scheme 21] had not been detected in any of the rearrangements studied with allylic systems, we anticipated that one would be observed with a benzylic analogue.[100] This was because the, presumably concerted, [2,3]-rearrangement must involve, formally at least, a non-aromatic

intermediate 138, thereby adding to the activation energy of this pathway (a).

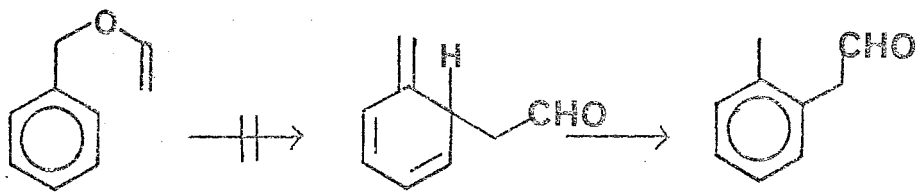


Scheme 21

The simplest case was studied because authentic samples of the expected final products, o-tolualdehyde 140 and phenylacetaldehyde 142 were available for direct comparison. Thus, as indicated in Scheme 21, alkylation of NCMP in DMSO with benzyl bromide rapidly gave the corresponding salt 136 which, on treatment with base, rearranged presumably via the ylide 137, to give a mixture of nitriles 139 and 141. Hydrolysis led to a mixture

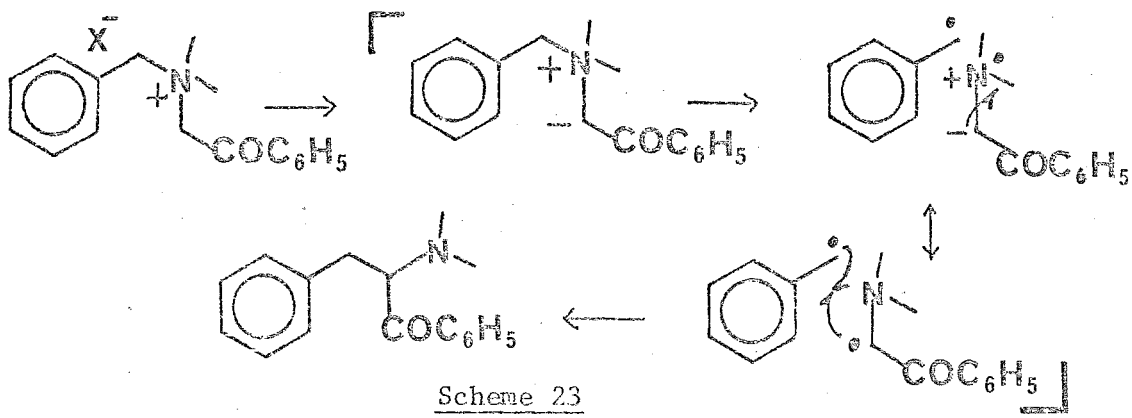
of o-tolualdehyde 140 and phenylacetaldehyde 142 in a ratio of 9:1 which was easily determined from the nmr spectrum. Unfortunately, the two aldehydes were not completely resolved by G.C., but spiking the mixture, and spectral comparisons left no doubt as to the authenticity of the products.

This result is particularly interesting on two accounts: (1) the homologous Claisen rearrangement[195] does not proceed* (Scheme 22); (2) similar ammonium-ylide rearrangements with



Scheme 22

phenacyl activating groups afford largely (∿90%) products from a [1,2]-process (Scheme 23).[100,202]



Scheme 23

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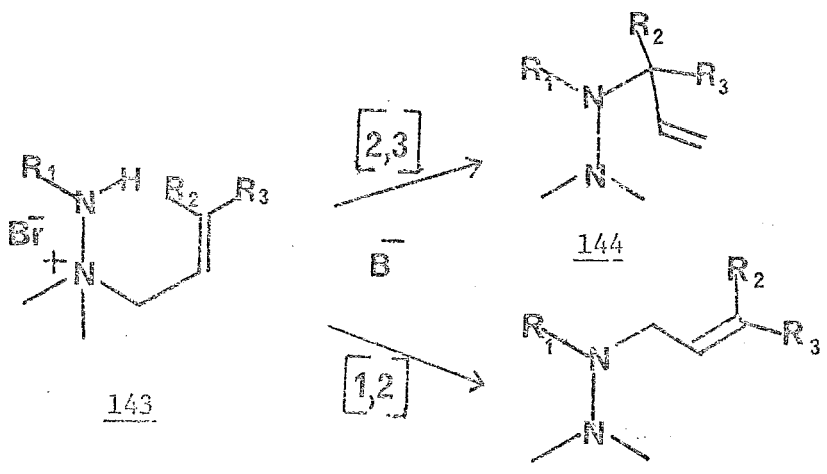
* Some related rearrangements, however, are known to occur.[196,197]

The failure of the Claisen rearrangement can be attributed to the relatively high activation energy required to produce a non-aromatic intermediate, whereas the higher ground-state energy of the analogous pyrrolidinium ylide enables this barrier to be surmounted.

The predominance of a [1,2]-process in the phenacyl case is probably due to the expected greater stability of the delocalised phenacyl ylide-anion, which would have a correspondingly lower nucleophilic capacity. This would increase the activation energy for the [2,3]-rearrangement and thus allow the non-concerted [1,2]-process to compete favourably.

Significantly, Baldwin, Brown and Cordell[198] have observed a similar duality of mechanism in the rearrangement of N-ammonio-amidates 143.



143 144 145

When R_1 was hydrogen, base promoted rearrangement afforded

products 144 from a [2,3]-process. In cases where R_1 was acyl (e.g. CH_3CO), then the rearrangement proceeded on heating, and yielded products 145 only from a [1,2]-process, through a radical dissociation-recombination mechanism.

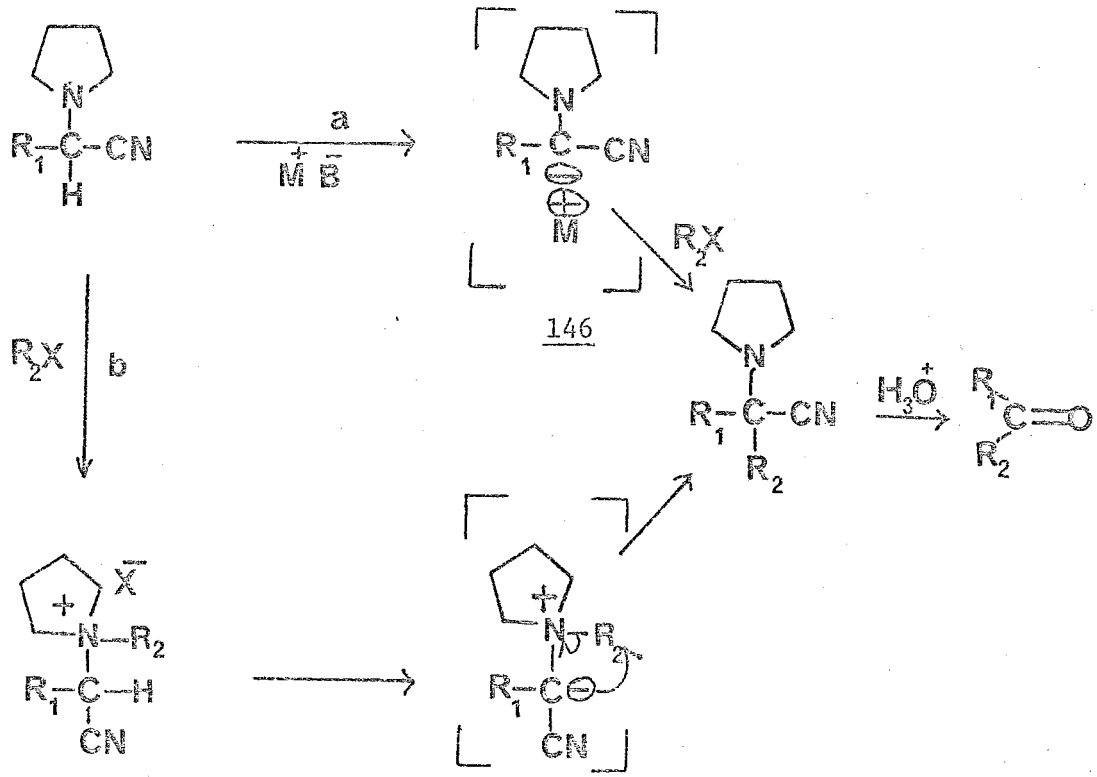
The analogy with the ammonium ylide rearrangement is plain - the extra stabilisation from charge delocalisation in the amidate anion lowers the ground-state energy of the ylide-anion and effectively increases the activation energy for the concerted [2,3]-rearrangement.

This study has demonstrated that base induced rearrangement of benzylic cyanomethylpyrrolidinium salts is a rapid and mild method for introducing a formyl group in high yield, ortho to an aliphatic substituent, something difficult to accomplish under the classical conditions of electrophilic substitution.

(5) Extension of the methodology

We realised that a particularly useful extension of this methodology would be utilisation of the metallated N-cyanoalkyl function 146 as an acyl carbanion equivalent (Scheme 24).[199,200] A preliminary experiment has indicated that a direct alkylation pathway (a) is a feasible proposition.

When base induced rearrangement of the benzylic salt 136 (Scheme 21) was conducted in DMSO-d6, a resonance in the nmr spec-



Scheme 24

trum at δ5.5, ascribable to the cyano-methine proton of the [2,3]-rearrangement product 139, rapidly disappeared. Hydrolysis in THF and acidic D_2O afforded toluic-D-aldehyde [ir(film) 2050, 1675 cm^{-1}, CD=O], which was devoid of resonances in the formyl-proton region of the nmr spectrum, and spiked with authentic o-tolualdehyde on G.C. analysis. Undeniably in this example, the adjacent aromatic ring confers added stability to the incipient carbanion* since, in a cursory investigation using an aliphatic analogue 106 (page 74), cyano-methine proton-exchange was extremely slow.

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* For a discussion of the benzoin condensation see ref.201.

Obviously a very strong base of low nucleophilicity[203] will be necessary to generate a relatively stable acyl carbanion equivalent suitable for direct alkylation.

An attractive alternative is to encourage initial nitrogen-alkylation of the N-cyanomethylpyrrolidinyl function and to effect alkyl group-transfer to the cyanomethyl-carbon by means of a suitable base induced sigmatropic rearrangement (pathway b).[204] Future work is intended on this type of process, which has, of course, the underlying principles of the original methodology.

In conclusion it is worth considering the nature of such ammonium ylide [2,3]-sigmatropic rearrangements in view of the predictability of many reaction pathways by considerations of orbital symmetry.[118-120,205]

It has been suggested that [2,3]-rearrangements of ammonium ylides* are ground-state pericyclic processes which proceed (suprafacially) through an aromatic-like transition state.[181] Clearly, the transition state for these rearrangements may be considered isoatomic and isoelectronic with the aromatic cyclopentadienyl anion 147 (5 atoms, 6 electrons), but it is probably not isoconjugate with it (see 148).[206]

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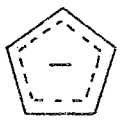
* A similar argument has been implied for a Wittig rearrangement.[167]



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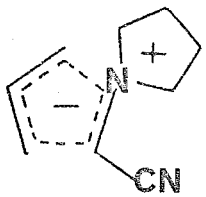

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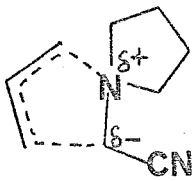

149

Isoconjugation would require using a pentavalent nitrogen atom, which is highly unlikely on energetic grounds.* This restriction is non-existent for analogous ylides with sulphur and phosphorous atoms, which can form the directional bonds necessary through "hybridisation" involving energetically accessible 3d atomic orbitals.[208,169]

Nevertheless, this does not detract from the likely concerted nature of the rearrangement in which the positive and negative charges of the ylide can be dissipated simultaneously through a delocalised allylic system 149.

Indeed, frontier-orbital symmetry analysis of the transition state 150 for an intermolecular $Sn^{2'}$ displacement leads to the prediction that the nucleophile Y- will enter on the same side of

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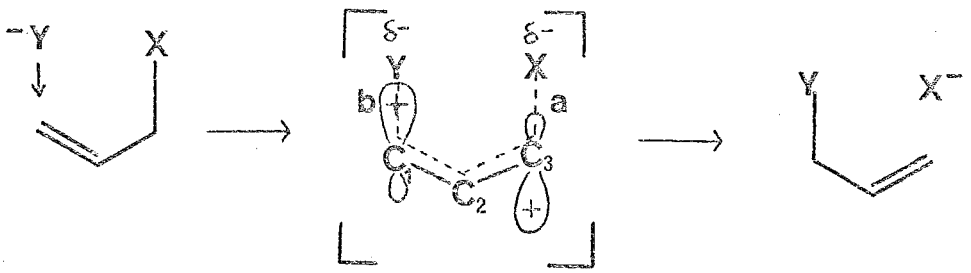
* 3pN atomic orbitals (AO) are estimated from atomic spectra to be at least 270 Kcals/mol higher in energy than a 2pAO.[207]

the allylic system as the leaving group X- with retention of stereochemistry at the allylic termini.[209]



b=bonding a=antibonding

150

A syn(suprafacial) mode of attack is known to occur in these reactions.[210]

The fact that the leaving group is next to the nucleophilic portion in an analogous intramolecular process 149 undoubtedly creates a very favourable entropy factor, but does not necessitate invoking a true pericyclic intermediate 148 to explain the observed stereoelectronic effects.

This latter discussion has been undertaken not to quibble over semantics, but in the belief that a more simple and general explanation can be used to describe this and related[166,167,181] [2,3]-sigmatropic rearrangements which involve anionic species and adjacent atoms with second shell valence electrons.

In summary, the problems encountered in the synthesis of helminthosporin analogues provided the stimulus for us to invent an alternative intramolecular approach for the synthesis of β,γ-unsaturated aldehydes, which has significant advantages over analogous procedures in terms of versatility, brevity, and high overall yield. In particular, the steric and stereoelectronic requirements of the [2,3]-rearrangement itself are attributes which should enable this methodology to be usefully employed in future stereochemically-controlled syntheses.

CHAPTER 8

EXPERIMENTAL

General Topics

(1) Melting points (mp) were determined by means of a Kofler hot-stage apparatus or with a heated Gallenkamp apparatus where sealed tube capillaries have been used. Melting points and boiling points (bp) are uncorrected.

(2) Infra-red spectra (ir) were recorded on either a Unicam SP 200 or a Perkin-Elmer 237 spectrophotometer.

(3) The ^{1}H nuclear magnetic resonance spectra (nmr) were determined with Varian DA-60IL or T-60 spectrometers operating at 60 MHz, using tetramethylsilane as an internal standard. Data are given in the following order: solvent; chemical shift (δ); multiplicity, s (singlet), d (doublet), t (triplet), q (quartet), d of d (doublet of doublets), m (multiplet), e (envelope), exch. means that the signal disappears on shaking the sample with D_2O; first-order coupling constant (J) is expressed in Hz, W1/2 means peak width at half-height; relative intensity as number of protons (H); assignment.

(4) Ultra-violet spectra (uv) were determined using a Unicam SP 800 spectrophotometer.

(5) Mass spectra were measured with an Hitachi Perkin-Elmer RMU-7D spectrometer. The data are recorded in the following order: operating voltage; m/e value; assignment with metastable peak (where observed); relative intensity to base peak (100).

(6) Gas Chromatographic Analyses (G.C.) were performed on Perkin-Elmer 880 and 881 models, using nitrogen carrier gas. The columns, constructed of stainless steel, were: (1) NPGS: Silicone GE XE-60 (NPX), 1:1, 3%, 3M x 1.6 mm, flow rate (FR) 30 cc/min; (2) FFAP, 3/4%, 6M x 1.6 mm, FR 25 cc/min (unless stated otherwise); (3) Apiezon M 5 %, 3M x 1.6 mm, FR 30 cc/min; (4) SE30 Silicone Golay, 46M x 0.25 mm, FR 2 cc/min. It has been assumed that compounds with similar structures evoke the same response from the recorder. The relative areas of peaks have been determined by triangulation. Data are recorded in the order: column; temperature; retention time (mins/sec); relative percentage of product in crude reaction mixture (where relevant). The conversion of carboxylic acids with ethereal diazomethane (see below) to methyl esters for G.C. analysis has been assumed to be quantitative.

(7) Chromatographic adsorbents used were Spence type H alumina, Sorbsil silica gel, and Florisil. Analytical and preparative thin layer chromatography (tlc) was effected using layers containing equal mixtures of Merk Kieselgel G and HF254.

(8) Solvents were usually purified by standard procedures.[211] In particular, tetrahydrofuran (THF), diethyl ether (ether), dimethoxyethane (DME) were dried by distillation from lithium

aluminium hydride (LAH). Dimethyl formamide (DMF), dimethylsulphoxide (DMSO), and hexamethylphosphorictriamide (HMPTA) were distilled under reduced pressure from calcium hydride. Nitromethane was distilled from P_2O_5 and stored over 4Å molecular sieves. X4 refers to light petroleum bp 45°-60°.

All organic solvent extracts were dried over anhydrous sodium sulphate unless specified otherwise.

Distilled ethereal diazomethane was prepared from N-nitroso-N-methylurea[212] or from p-tolylsulphonylmethylnitrosoamide[213] (Diazald) by normal procedures.

(9) Microanalyses were performed by the Australian Microanalytical Service, Melbourne. The convention of J.Org.Chem. has been adopted for recording these results.

(10) High Resolution Mass Spectrometry was carried out by Dr. J. Cable at the Research School of Chemistry, the Australian National University, Canberra, to whom we are grateful.

(11) Semicarbazone (SCZ) and 2,4-dinitrophenylhydrazone (2,4-DNP) derivatives of aldehydes and ketones and 3,5-dinitrobenzoate (3,5-DNB) derivatives of alcohols were prepared by standard methods[217] before analysis.

Execution of Scheme 2

Cuminic acid 12

(1) via p-bromocumene 10

Cumene (240 g, 280 cc, 2 mol) and iron filings (3.5 g) were treated with bromine (335 g, 116 cc, 4.2 mol) at such a rate as to maintain the temperature at 10°. Light was excluded from the reaction mixture by means of aluminium foil. After a total of 2.5 hr at 10°, stirring was continued for a further 3 hr at 20°, then the reaction mixture diluted with water (750 cc). Solid $NaHSO_3$ was added (caution) until the bromine-colour disappeared. The lower layer was washed with sodium hydroxide (10%) to pH9, then boiled under nitrogen with a solution of KOH (15 g) in ethanol (130 cc) for 16 hr. The cooled mixture was poured onto water (500 cc) and the lower layer washed with water to neutrality, dried, and distilled under nitrogen. The fraction (105 g, 38%) boiling between 96° and 98° at 15 mm (lit.[30] 104°, 17 mm) was a mixture of o- and p-bromocumenes: G.C. NPX (110°) 07/53 (78%), 06/80 (22%); features of the major component dominated the spectra:
ir (film) 1080 and 1020 (2ν C-Br), 830 (st. p-subst Ar), 760 cm^{-1} (m, o-subst Ar).
nmr (CCl_4) δ1.2 (d, 6H, isopropyl CH_3), 2.9 (m, 1H, isopropyl CH), 7.1 (d, J=8Hz, 2H, Ar HC2, HC6), 7.4 (d, J=8Hz, 2H, Ar HC3, HC5).

The mixture of bromocumenes (40 g, 0.2 mol) was metallated with lithium (3.8 g, 0.56 g-at) in dry ether (200 cc) according to the literature procedure for p-bromotoluene.[214] The reaction mixture was then poured onto crushed, solid carbon dioxide (250 g) in dry ether (400 cc). After 16 hr water (300 cc) was added, and the mixture extracted with ether (2 x 500 cc), then acidified (cHCl) and extracted with more ether (3 x 300 cc). The combined latter extract was washed with water (1 x 500 cc), dried and concentrated to a pale solid (23.5 g, 71%). Recrystallisation from X4 gave p-cuminic acid 12 (13 g, 39%):

mp 117-118° (lit.[215] 117-118°);

ir (nujol) 3300-2700 (OH), 1690 (C=O), 1610 (Ar), 1290 (C-O), 950 (COOH), 860 cm^{-1} (Ar);

G.C. FFAP (methyl ester) (175°)06/22 (>99%).

(2) from cuminic aldehyde

A solution of cuminic aldehyde (71 g, 0.5 mol) in acetone (200 cc) was treated dropwise with Jones' reagent (over 4 hr) at such a rate as to maintain the temperature of the reaction mixture at 30°. When tlc indicated the absence of starting material, sufficient isopropyl alcohol was added to turn the solution-colour green, then enough water was added to generate a heavy green

precipitate. The organic layer was decanted and extracted with methylene chloride (3 x 250 cc). The pooled extract was washed with sodium carbonate (20%, 3 x 200 cc), then the combined aqueous material cooled to 0° and cautiously acidified (cHCl). The precipitate was collected (78 g, 99%) and recrystallised from X4 to yield (63 g, 80%) pure cuminic acid 12:
mp 117-118°; spectroscopically indistinguishable from the acid 12 obtained above;
G.C. FFAP (methyl ester)(175°) 06/21 (spiked).

cis- and trans-1,4-Dihydro-4-isopropyl-1-methylbenzoic acid 14

Dry ammonia (500 cc) was distilled onto cuminic acid 12 (24 g, 147 mmol) suspended in dry ether (168 cc) at -40° under nitrogen. The resulting solution was stirred, and pieces (∿100 mg) of lithium (3.15 g, 450 mg-at) added over 20 min until the solution remained blue for 25 min. The solution was cooled to -70° and dry methyl iodide (208.5 g, 91.8 cc, 1.47 mol), previously cooled to -50°, added dropwise initially, until the blue faded (this avoids a violent reaction with an induction period of ∿3 min), then, with care, rapidly. After 15 min the colourless solution was treated cautiously with solid ammonium chloride (42 g) and the solvent allowed to evaporate overnight to leave a pale solid. This was dissolved in water (300 cc) and successively extracted with methylene chloride (2 x 150 cc), acidified to pH3 (cHCl), and extracted

with more methylene chloride (6 x 150 cc). The total final extract was washed with water (2 x 150 cc), dried, and evaporated to a pale viscous liquid (24.07 g, 92%), which had two major components (G.C. methyl esters) and was characterised spectrally.
ir (film) 3300-2650 (broad, OH), 3020 (=CH), 1700 (C=O), 1640 (C=C), 1295, 1260, 1115, 940 (broad), 840, 760 and 720 cm^{-1} (=CH);
nmr ($CDCl_3$) δ0.9 (broad d, J=7Hz, 6H, isopropyl CH_3), 1.3 (s, 3H, H_3CCCO_2H), 1.9 (m, 1H, isopropyl CH), 2.6 (e, 1H, =CHCH), 5.8 (broad d of d as t, J=10Hz, 4H, HC=HC), 12.0 (broad s, 1H, CO_2H);
The methyl esters showed:
ir (film) 3020 (=CH), 1730 (C=O), 1635 (C=C), 1395 and 1375 (isopropyl), 1245 and 1120 (C-O), 840, 795, 720 cm^{-1} (=CH);
Mass spectrum (70eV) m/e 194 (M^+, $C_{12}H_{18}O_2$ requires M^+ 194)(3), 135 ($M^+-CO_2CH_3$)(27), 93(100), 91(50);
G.C. FFAP (methyl ester) (120°) 09/30 (45.5%) and 11/42 (51.5%).

1,2-Dihydro-4-isopropyl-1-methylbenzoic acid 15

KOH (240 gm, 4.2 mol) was added, with stirring, to ethylene glycol (1.5 l.), followed by the 2,5-diene acid 14 (24 g, 134 mmol). The resulting solution was heated under reflux for 20 hr in an atmosphere of nitrogen, cooled, and poured slowly onto water (1.5 l.). The solution was cooled to 0°, acidified to pH3 (cHCl), then

extracted with methylene chloride (6 x 300 cc). The pooled extract was washed with water (2 x 300 cc), dried, and evaporated under vacuum to leave a pale mobile oil (24 g, quant.). A sample was distilled before analysis:

bp 88° (block), 0.1 mm;

ir(film) 3300-2650 (broad, OH), 1700 (C=O), 1650 (shoulder) and 1600 (wk) (C=C), 1420, 1395 and 1375 (isopropyl CH_3), 1300 (OH), 1135 (C-O), 950 (broad), 800 and 765 cm^{-1} (=CH);

nmr ($CDCl_3$) δ1.1 (d, J=7Hz, 6H, isopropyl CH_3), 1.3 (s, 3H, CH_3), 2.0-3.0 (m, 3H, $\underline{H}_2CHC=C$ and isopropyl CH), 5.4 (e, 1H, $H_2C\underline{H}C=C$), 5.9 (broad d of d as t, J=9Hz, 2H, HC=CH), 12.1 (broad s, 1H, CO_2H);

G.C. FFAP (methyl ester) (120°) 09/34 (92.5%),(115°) 11/18;

Anal. calcd for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95. Found: C, 73.6; H, 9.05.

1,2,3,6-Tetrahydro-4-isopropyl-1-methybenzoic acid 16

Onto the 3,5-diene acid 15 (24 g, 133 mmol), dissolved in dry ether (165 cc) and t-butyl alcohol (40 g, 51.5 cc, 540 mmol), was distilled ammonia (500 cc) under nitrogen. Pieces (∿100 mg) of lithium (2.87 g, 410 mg-at) were added over ∿20 min and the blue colour allowed to persist for 15 min. Ethanol (50 cc) was

added and the colourless solution allowed to evaporate overnight. The residue was dissolved in water (200 cc) and the resulting solution extracted with methylene chloride (2 x 200 cc), cooled to 0°, acidified (cHCl) to pH3, and finally extracted with more methylene chloride (3 x 200 cc). The total latter extract was washed with water (2 x 150 cc), dried, and concentrated to a pale mobile oil (23 g, 95%). This crystallised from methanol:water (2:1) at -50° as colourless plates (14.5 g, 60%, mp 44-46°). The analytical sample, obtained after a further recrystallisation from the same solvent pair had:

mp 44-46°;

ir (nujol) 3200-2650 (OH), 1700 (C=O), 1240, 1130 (C-O), 950 (broad) 820 cm^{-1} (=CH);

nmr ($CDCl_3$) δ1.0 (d, J=7Hz, 6H, isopropyl CH_3), 1.2 (s, 3H, CH_3), 1.4-2.8 (broad m, 7H), 5.4 (e, 1H, C=CH), 12.0 (e, 1H, exch., CO_2H);

G.C. FFAP (methyl ester) (115°) 10/15 (87%);

Anal. calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 10.0. Found: C, 72.1; H, 10.1.

Diazomethyl-[4-isopropyl-1-methylcyclohex-3-en-1-yl] ketone 17 via the acid chloride

The acid 16 (10 g, 55 mmol) was dissolved in dry benzene (250 cc), containing pyridine (5.04 g, 65 mmol), and added over 30 min to a stirred solution of oxalyl chloride (46.5 cc, 69 g, 550 mmol) and benzene (65 cc) under nitrogen. The reaction mixture was stirred for a further 45 min (evolution of CO_2 and CO had ceased), then the filtered (celite) solution evaporated under reduced pressure, and a slow stream of nitrogen. The residue was dissolved in dry benzene (50 cc) and the solvent removed as before. The latter step was repeated twice to furnish the acid chloride as a pale oil (11 g, quant.) which was used directly:
ir (film) 1785 (C=O), 1670 (wk, C=C), 1395 and 1375 (isopropyl), 925, 900, 820, 800, 770 cm^{-1}.

The crude acid chloride (11 g, 55 mmol), dissolved in dry ether (75 cc), was dropped over 30 min onto a stirred, ice-cold solution of diazomethane (∿310 mmol from 108 g Diazald) in dry ether (700 cc). The reaction mixture was allowed to warm to room temperature during 18 hr then heated to 40° to remove the excess of diazomethane. Concentration of the solution under reduced pressure revealed a pale yellow oil (11.2 g, 99%) which was used without purification. A small sample was distilled before analysis:

bp 56° (block), 0.005 mm;

ir (film) 3100 (HCN_2), 2140 and 1635 ($COCHN_2$), 1360 (broad), 1160, 1050, 820 cm^{-1} (C=CH); crude material showed also 1740-1730 cm^{-1} (v. wk, $COCH_2Cl$);

nmr ($CDCl_3$) 1.0 (d, J=7Hz, 6H, isopropyl CH_3); 1.2 (s, 3H, CH_3), 1.6-2.8 (m, 7H), 5.4 (e, 1H, C=CH), 5.5 (s, 1H, $COCHN_2$);

Anal. calcd for $C_{12}H_{18}N_2O$: C, 69.9; H, 8.8; N, 13.6. Found: C, 69.85; H, 8.9; N, 13.8.

The endocyclic (A) and exocyclic (B) olefinic-ketones 18

A stirred solution of diazo-ketone 17 (10 g, 49.6 mmol) in dry nitromethane (200 cc) was cooled to between -10° and 0° and treated dropwise with BF_3-etherate (2 g, 14 mmol). After 10 min sodium carbonate (sat., 2cc) was added, and after a further 10 min the solution was poured onto brine (sat., 200 cc) and diluted with methylene chloride (200 cc). The lower layer was washed with brine (200 cc), water (200 cc), dried, and concentrated under vacuum to a pale oil. The remaining traces of nitromethane were removed as an azeotropic mixture, first with ethanol, and then benzene. The olefinic-ketones 18 were obtained as a pale, mobile oil (8.6 g, quant.):

ir (film) 3050 (=CH), 1738 (C=O), 1645 (C=C), 1410, 1380, 1055, 825, 795 cm^{-1};

nmr ($CDCl_3$) δ1.0 (1 major s in m, 4.2H, CH_3-$\overset{|}{C}$-, A and B; isopropyl CH_3, A), 1.7 (broad 2s, 4.8H, $(CH_3)_2$ C=C), 2.1 (m, 2H, H_2CCO), 3.4 (e, 0.8H, W1/2=16Hz reduces to W1/2=10Hz on double irradiation at 2.1; HCC=C,B), 5.1 (e, 0.20H, HC=C,A);

G.C. FFAP (140°) 08/03 (20%, A), 10/43 (80%, B);

Mass Spectrum (70eV): m/e 178 (M^+, $C_{12}H_{18}O$ requires M^+ 178)(47), 93 (100), 91 (34).

Equilibration study of olefinic-ketones 18 (A and B)

BF_3-etherate (26.5 mg, 0.188 mmol) was added to a solution of diazo-ketone 17 (120 mg, 0.593 mmol) in dry nitromethane (1.2 cc) at 18°. Aliquots (100 μ l. each) were removed at the times indicated, and immediately quenched by addition to separate tubes, containing a mixture of sodium carbonate (sat., 84.5 mg) and ether (37.5 mg). The ethereal layer of each sample was analysed by G.C. using standard injections (0.4 μ l.) The absolute concentration of the isomers combined was virtually constant (>98%); their relative proportions are tabulated.

FFAP (140°)	Reaction time (hr)						
	1(min)	20(min)	1	2	3	9	24 and 48
08/03 (%A)	20	22	25	27	31	37.5	45
10/43 (%B)	80	78	75	73	69	62.5	55

The combined products after 2-48 hr reaction were isolated in the normal manner and showed:

nmr ($CDCl_3$) δ1.0 (4s, 5H, isopropyl CH_3, A, and CH_3-C-A and B), 1.7 (broad 2s, 4H, $(CH_3)_2C=$,B) 5.1 (e, 0.33H, HC=C, A), ratio H(A):H(B) = 1:2.

12,13,14-Trinorhelminthosporan-7-one 19

The mixture of olefinic-ketones 18 (8.6 g, 48 mmol) was dissolved in methanol (150 cc) and shaken with palladium-on-carbon (5%, 860 mg), under hydrogen (4 at.) at room temperature, until the reaction was complete (G.C. analysis, ∿12 hr). The filtered (celite) solution was concentrated under reduced pressure to an oil which was chromatographed on a column of Sorbsil (250 g) in X4. Elution with benzene:ether (5:1) gave the ketone 19 as a colourless oil (8.6 g, 99%). A small sample was distilled before analysis:

bp 60° (block), 0.01 mm.

ir (film) 1738 (C=O), 1415, 1395 and 1375 (isopropyl CH_3), 1145, 1055; 880, 850, 790 cm^{-1} (wk bands).

nmr ($CDCl_3$) δ0.9-1.0 (m, isopropyl CH_3), 1.0 (broad s, CH_3C-) (9H under 0.9-1.0), 2.0 (m, 2H, H_2CCO);

Mass spectrum (70eV) m/e 180 (M^+, $C_{12}H_{20}O$ requires M^+ 180) (25), 93 (99), 81 (100);

G.C. FFAP (140°) 09/09 (91%);

Anal. calcd for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 80.1; H, 11.0.

Execution of Schemes 3 and 4

7-Isopropyl-4-methyltricyclo[3,2,1,$0^{2,7}$]octan-3-one 20

The diazo-ketone 17 (1.5 g, 7.3 mmol) in cyclohexane (50 cc, spectroscopic grade) was added over 1.5 hr to a suspension of copper powder ("Merk", 4 g, previously dried at 80° for 15 min) in boiling cyclohexane (150 cc) under nitrogen. After a further 2 hr, the cooled mixture was filtered (celite) and concentrated under reduced pressure to afford a pale oil which crystallised on standing at 0° (1.3 g, quant.); a sample (1.03 g) was chromatographed on Sorbsil (30 g in X4). Elution with X4:ether (17:3 than 4:1) gave very pale crystals of cyclopropyl-ketone (1 g, 97%). The remainder (270 mg) was distilled before analysis and formed colourless prisms on cooling;

mp 40-42°;

bp 74° (block), 0.005 mm;

ir (nujol) 3010 (cyclopropyl H), 1720 (C=O), 1275, 1205, 1165, 1130, 1100, 915 and 880 cm^{-1} (cyclopropyl H);

nmr ($CDCl_3$) δ0.9-1.0 (m, 9H, CH_3 and isopropyl CH_3), 1.7-2.3 (m, 9H, remainder);

G.C. FFAP (145°) 10/57 (98%), (130°) 11/50;

Anal. calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.2. Found; C, 80.5, H, 10.1.

The 12,13,14-trinorhelminthosporan-7-one 19 and the 4-isopropyl-1-methylbicyclo[2,2,2]octan-2-one 23 via their corresponding alcohols 21 and 22

The cyclopropyl-ketone 20 (700 mg, 3.9 mmol), dissolved in dry THF (5 cc) containing t-butyl alcohol (1.98 g, 2.52 cc, 26.8 mmol), was added to dry ammonia (100 cc). The solution was cooled to -70° and pieces of lithium added (109 mg, 15.6 mg-at) under a stream of nitrogen, until the blue colour had persisted for 25 min. Ethanol (5 cc) was added cautiously and the ammonia allowed to evaporate. The residue was treated with water (20 cc), the pH adjusted to ∿6 (cHCl), then the solution extracted with methylene chloride (3 x 20 cc). The pooled extract was washed with water (2 x 100 cc), dried, and reduced under vacuum to afford the alcohols 21 and 22 as a pale viscous oil (700 mg, 98%);

ir (film) 3450 (OH), 1395 and 1375 (isopropyl), 1050 (C-O), 955, 920, 865, 820 cm^{-1};

nmr ($CDCl_3$) δ0.9 (m, 9H, CH_3 and isopropyl CH_3), 3.6 (e, 1H, HCOH);

G.C. FFAP (145°) 11/20 (12%), 11/44 (86%) - partial resolution.

The mixture of alcohols (670 mg, 3.68 mmol) was dissolved in acetone (60 cc) and treated with Jones' reagent in excess. After 5 min, the red solution was turned to green by the addition of isopropyl alcohol. Water was added and a mixture of ketones 19 and 23 (665 mg quant.) isolated from a methylene chloride-extract in the normal manner. This showed:

ir (film) 1738 (shoulder) and 1718 cm^{-1} (s) (C=O);

G.C. FFAP (145°) 08/07 (12%, spiked with authentic bicyclo[3,2,1]-ketone 19), 09/47 (86%).

Chromatography on Sorbsil (30 g in X4) gave, on elution with X4:ether (100:3 then 20:1), sequentially: a mixture of ketones 19 and 23 (40 mg); mainly [2,2,2] ketone 23 (400 mg, 60%); [2,2,2] ketone 23 (80 mg, 12%). Re-chromatographing the major fraction, as above, afforded a mixture of ketones (50 mg), then [2,2,2] ketone 23 (350 mg, 53%) as a colourless oil. A sample was distilled before analysis; the SCZ derivative was deposited from aqu. ethanol as colourless crystals:

bp 45° (block), 0.005 mm;

mp SCZ, 192-194°;

ir (film) 1718 (6-membered ring C=O), 1410 (-$\overset{|}{\underset{|}{C}}CH_3$), 1395 and 1375

(isopropyl), 1210, 1100 cm^{-1};

nmr ($CDCl_3$) δ0.9-1.0 (3s, 9H, CH_3 and isopropyl CH_3), 1.6 (e, 9H, CH_2CH_2 and isopropyl CH), 2.1 (s, 2H, $H_2CC{=}O$);

G.C. FFAP (145°) 09/47;

Anal. calcd for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 79.6; H, 11.05;

Calcd for SCZ $C_{13}H_{23}N_3O$: C, 65.8; H, 9.8; N, 17.7. Found: C, 66.0; H, 9.9; N, 18.0.

1-Isopropyl-5-methylbicyclo[3,2,1]oct-2-en-4-one 24

Cyclopropyl-ketone 20 (170 mg, 0.96 mmol) was dissolved in trifluoroacetic acid:BF_3-etherate (2:1, 4 cc) under nitrogen, and heated at 94° in a sealed tube for 4.5 hr. The reaction mixture was cooled, poured onto water (5 cc), the solution neutralised (Na_2CO_3, sat.), then extracted with methylene chloride (3 x 10 cc). The combined extract was washed with water (10 cc), dried, and evaporated to reveal a pale, homogeneous (G.C.; tlc, benzene), oil (170 mg, quant.). Before analysis, a sample was filtered through a short column of Sorbsil (in X4, elution with X4:ether, 20:1), then distilled:

bp 45° (block) 0.01 mm;

ir (film) 3010 (HC=), 1680 (C=O), 1610 (C=C), 1380 and 1390 (isopropyl), 1180, 1130, 1040, 850 and 820 cm^{-1} (HC=);

nmr ($CDCl_3$) δ1.0 (2d's, J=4Hz, 6H, isopropyl CH_3), 1.3 (s, 3H, CH_3), 1.5 (m, W1/2=5Hz, collapses W1/2=3Hz on double irradiation at 7.2; methylene proton long range coupled to olefinic proton), 1.8 (m, 6H), 6.0 (d, J=10Hz, 1H, HC=CHCO), 7.2 (d of d, J=10Hz and J'=2Hz long range coupled to proton at 1.5, J'=0Hz on double irradiation at 1.5, 1H, HC=CHCO);

uv λ_{max}^{EtOH} 223 nm, calc. 227 nm;

Mass spectrum (70eV) m/e 178 (M^+, $C_{12}H_{18}O$ requires M^+ 178)(27), 135 ($M^+-C_3H_7$, M* 102.5)(64), 107 ($135-C_2H_4$, M* 85)(100);

G.C. FFAP (130°) 13/40 (≥99%);

Anal. calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.2. Found: C, 80.5; H, 10.2.

Examples of unsuccessful intermolecular approaches to elaborate the helminthosporin-like bridge functionality as in Scheme 5

12,14-dinor-7-oxohelminthospor-6(13)-en-13-ol 25 (X=OH) and the isopropyl- and n-butanethio-enolether derivatives

In a typical experiment, ethyl formate (2.08 g, 28 mmol) was added dropwise to NaH (0.336 g, 14 mmol) and the ketone 19 (500 mg, 2.8 mmol) in THF (50 cc) under nitrogen. The reaction mixture was stirred for 18 hr at 40°, poured onto ice and water

(50 cc), then extracted with benzene:ether (20 cc, 1:1). The aqueous material was acidified at -10° (cHCl) and immediately extracted with benzene:ether (3 x 30 cc, 1:1). These latter extracts were combined and washed once with water (30 cc), dried, and evaporated to a pink solid (570 mg, 98%) which was homogeneous on tlc (benzene:ether, 9:1). Recrystallisation from ether:X4 gave small colourless prisms (mp 96-100°), which rapidly darkened in the air and gave an unsatisfactory elemental analysis. The spectroscopic data were diagnostic for the hydroxymethylene-ketone 25 (X=OH):

ir (mujol) 3500-2750 (OH), 1695 and 1635 (broad, O=C.C=CHOH), 1150 (broad C-O), 950, 830, 810, 780 cm^{-1};

nmr ($CDCl_3$) δ1.0 (m, 9H, CH_3 and isopropyl CH_3), 2.9 (e, 1H, HCC=CHOH), 6.9 (s, 0.9H, C=CHOH), 9.5 (s, ≤0.1H, HC=O tautomer), 10.5 (e, 0.9H, C=CHOH);

Mass spectrum (70eV) m/e 208 (M^+, $C_{13}H_{20}O_2$ requires M^+ 208)(17), 180 (M^+-CO)(11), 126 (100).

The isopropyl-enolether derivative was prepared in the normal manner[70,71] from the hydroxymethylene-ketone (140 mg, 0.67 mmol) and isopropyl alcohol (720 mg, 12 mmol) in benzene (30 cc) containing p-toluene sulphonic acid (10 mg). The oily enol ether darkened in air and was used without purification:

ir (film) 1715 (C=O), 1645 and 1215 and 1050 (enolether), 960 cm^{-1};

nmr (CCl_4) 1.0 (m, 9H, CH_3 and isopropyl CH_3) 1.4 (d, J=6Hz, 6H, O-isopropyl CH_3), 3.2 (e, 1H, HCC=CHO), 4.2 (septet, J=6Hz, 1H, O-isopropyl CH), 7.2 (s, 1H, C=CHO isopropyl);

Mass spectrum (70eV) m/e 250 (M^+, $C_{16}H_{26}O_2$ requires M^+ 250)(12), 126 (100).

The n-butanethio-enolether derivative was made in the normal way[72,73] from the hydroxymethylene-ketone 25 (X=OH) (500 mg, 2.4 mmol), n-butanethiol (490 mg, 5.4 mmol) and p-toluenesulphonic acid (15 mg) in benzene (50 cc). The reaction was monitored by tlc (benzene) and the presumably isomeric oily thio-enolethers were used without purification:

ir (film) 1705 (C=O), 1600 (C=CHSnBu), 1070, 850, 800, 760 cm^{-1};

nmr ($CDCl_3$) δ1.0 (m, CH_3 and isopropyl CH_3 amongst other resonances), 2.9 (e, 2H, SCH_2CH_2), 3.2 (e, 1H, HCC=CHSnBu), 7.4 (m, collapses to 2s, 2Hz apart on double irradiation at 3.2, 1H, HCC=CHSnBu);

Mass spectrum (70eV) m/e 280 (M^+, $C_{17}H_{28}O_3$ requires M^+ 280)(100), 223 (M^+-nBu)(25).

Attempts at 1,2-addition to the enolethers

In a typical reaction which returned starting material: the

isopropyl-enolether 25 (130 mg, 0.52 mmol) in THF (2 cc) was added dropwise to methyl magnesium iodide (5.2 mmol) in THF (20 cc). The reaction mixture was heated under reflux for 47 hr under nitrogen, cooled, then NH_4Cl (0.5 g) added, followed by water (10 cc). The mixture was extracted with methylene chloride (3 x 20 cc), then the pooled extract washed with water (50 cc), dried, and concentrated to a dark oil (120 mg). Analysis by ir (film) and tlc showed this was unchanged enolether.

The thio-enolether 25 (250 mg, 1.2 mmol) in THF (10 cc) was added to methyl magnesium iodide (9.6 mmol) in THF (15 cc) and the solution heated under reflux for 24 hr. After this time, no starting material was detected by tlc. NH_4Cl (0.75 g) was added and the mixture worked up as above to reveal a red oil (230 mg). This was a multi-component mixture by tlc (benzene).
ir (film) 3450 (wk, OH), 1738 (st C=O), 1600 cm^{-1} (wk, C=CHS*n*Bu); nmr ($CDCl_3$) δ1.0-2.0 (broad e, undiagnostic methylene), 2.9 (broad e, SCH_2), 5.6 and 6.2 (2s, ∿1.5%, total H, possibly C=C*H* ∿S*n*Bu); this material was not investigated further.

Intramolecular methods for elaborating the helminthosporin-like bridge functionality

(1) Scheme 7 - the carbenoid sulphur-ylide approach

13,14-Dinorhelminthospor-7(12)-ene 29

A mixture of methylphosphonium iodide (34.4 g, 85 mmol) and potassium t-butoxide (10.1 g, 84 mmol) in dry ether (200 cc) was stirred under reflux for 1.5 hr, then cooled to -70°. The ketone 19 (5 g, 27.8 mmol), in ether (20 cc), was added over 0.25 hr to the stirred yellow mixture, which was allowed to warm to room temperature during 6 hr, then stirred for a further 12 hr. The mixture was heated under reflux for 0.5 hr, cooled to 0°, and treated cautiously with methanol (80%, 40 cc).* Ether was removed by distillation under reduced pressure, more methanol added (80%, 10 cc), and the mixture extracted with X4 (3 x 120 cc). The combined extract was washed with methanol (80%, 200 cc), water (200 cc), dried, and evaporated to a pale oil (5.5 g). Distillation under reduced pressure furnished the olefin 29 as a colourless liquid (4.8 g, 97%):

bp 100° (block), 13 mm; 112-115°, 23 mm;

ir (film) 3050 ($=CH_2$), 1655 (C=C), 1395 and 1380 (isopropyl), 890 and 880 cm^{-1} ($=CH_2$);

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* Methanol (80%) means methanol:water = 4:1.

nmr (CCl_4) δ0.9 (m, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3), 2.2 (broad s, 2H, $\underline{H}_2CC{=}CH_2$), 4.7 (m, 2H, $C{=}CH_2$);

G.C. FFAP (130°) 4/54; (100°) 6/57;

Anal. calcd for $C_{13}H_{22}$: C, 87.6; H, 12.4. Found: C, 87.9; H, 12.5.

The bicyclic primary (A) and secondary (B) allylic-bromides 30

To the olefin 29 (1 g, 5.6 mmol) dissolved in carbontetrachloride (60 cc) was added pure N-bromosuccinimide (NBS) (1.04 g, 5.84 mmol) and 5 crystals of benzoyl peroxide. The mixture was heated under reflux for 30 min, during which the heavy precipitate of NBS gave way to a light precipitate of succinimide. The cooled solution was filtered (celite) and evaporated under reduced pressure. The residue was chromatographed on a short column of Sorbsil (10 g) in X4. Elution with X4 gave the bromides 30 as a colourless oil (1.29 g, 89%), which was analysed spectrally. The bromides afforded a single p-tosyl-S-methyldithiocarbazone derivative 32 (see below):

ir (film) 1650 and 1630 (C=C), 1395 and 1375 (isopropyl), 905 ($=CH_2$), 770 cm^{-1} (C-Br);

nmr (CCl_4) δ0.9 (t, J=6Hz, 6H, isopropyl CH_3), 1.1 (broad 2s, 3H, CH_3), 4.0 (s, 0.444H, CH_2Br, A), 5.9 (m, 0.222H, C=CH, A), 4.7

(m, 0.778H, CHBr, B), 5.0 (d, J=1.8Hz) and 5.3 (d, J=1.6Hz)(1.556H, $C=CH_2$, B), i.e. ratio H(A):H(B)=1:3.5;

Mass spectrum (70eV) m/e 256, 258 (M^+, $C_{13}H_{21}Br$ requires M^+ 256, 258)(14), 255, 257 (M^+-H)(46); 177 (M^+-Br)(100). See below for elemental analysis of derivative 32 of bromides 30.

13,14-Dinor-12-hydroxyhelminthospor-6-ene 31

(1) By photo-oxygenation of the olefin 29

To the olefin 29 (1.0 g, 5.6 mmol) in methanol (130 cc), containing t-butylalcohol (10 cc) as a co-solvent, and pyridine (1 cc) as an acid-inhibitor, was added haematoporphyrin (15 mg). A stream of oxygen (51 cc/min) was passed through the water-cooled solution, which was irradiated for 6 days using a Phillips "Arga-photo" lamp (250 V, 500 W) placed 60 cm from the apparatus. The volume was reduced to 10 cc under reduced pressure, then the solution treated with methanol (10% aqu., 10 cc) containing $NaBH_4$ (2 g, 52.5 mmol); after 15 min, water (3 cc) was added. When no more hydrogen was evolved, the solution was filtered (celite), diluted with water (17 cc), and extracted with methylene chloride (3 x 40 cc). The total extracted was washed with water (60 cc), dried, and evaporated to a pale oil. Chromatography on neutral alumina (8 g, in X4) gave on elution with X4, olefin 29 (500 mg, 50%) then, with X4:ether (4:1), allylic-alcohol 31 (400 mg, 37%) as a colourless viscous oil. The 3,5-DNB derivative

crystallised as faint yellow prisms from X4:ether (X2):

mp 3,5 DNB, 74-76°;

ir (film) 3350 (OH), 1635 (C=C), 1395 and 1375 (isopropyl), 1080, 1025, 995, 830 cm^{-1} (HC=);

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.0 (s, 3H, CH_3), 1.6 (e, partly exchangeable with D_2O, OH amongst other resonances), 2.6 (e, 1H, HCCH=C), 4.1 (broad s, 2H, H_2COH), 5.6 (e, 1H, HC=C);

G.C. FFAP (170°) 09/19;

The 3,5-DNB showed:

ir (nujol) 3100 (H-Ar), 1730 (C=O), 1650 (NO_2), 1360 (C-NO_2) 1280, 1170, 1080, 860 and 840, (Ar), 780 cm^{-1} (C=CH);

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.2 (s, 3H, CH_3Cl), 2.7 (e, 1H, HC5), 5.0 (broad s, 2H, $H_2COCOAr$), 6.0 (e, 1H, HC=C), 9.2 (m, 3H, Ar);

Anal. calcd for $C_{20}H_{24}N_2O_6$: C, 61.8; H, 6.2; N, 7.2. Found: C, 61.8; H, 6.3; N, 7.4.

(2) The allylic-alcohol 31 from the allylic-bromides 30(A and B)

The mixture of bromides 30 (70 mg, 0.27 mmol) was left on a column of alumina (Spence, 14 g, in X4) for 18 hr; elution with X4 gave bromides 30 (14 mg, 20%), then with ether, the primary allylic-alcohol 31 (42 mg, 80%) contaminated (∿14%, G.C., nmr) by,

presumably less polar, secondary allylic-alcohol;

tlc, low Rf major, high Rf minor spots (benzene:ether, 20:1);

G.C. FFAP (170°) 07/00 (14%), 09/16 (86%, spiked with authentic primary allylic-alcohol 31);

ir (film) indistinguishable from the authentic primary alcohol above;

nmr ($CDCl_3$) 0.9 (m, 6H, isopropyl CH_3), 1.0 (s, 3H, CH_3), 2.6 (e, 1H, HC5), 4.1 (broad s, 1.72H, $C=CCH_2OH$), 4.75, 4.9, 5.1 (3m, 0.42H, $HOCHC=CH_2$), 5.6 (e, 0.86H, HC=C).

p-Toluenesulphonyl-[S-methyl-S'-(13,14-dinorhelminthospor-6-en-12-yl)]dithiocarbazone 32

To p-tosyl-S-methyldithiocarbazate* (1.37 g, 4.96 mmol), suspended in absolute ethanol (36 cc) at ambient temperature under nitrogen, was added a solution of KOH (328 mg, purity 86%, 4.96 mmol) in ethanol (12 cc) over 3 min; during the addition, the solid dissolved. The bromides 30 (1.21 g, 4.7 mmol) in ethanol (12 cc) were added over 3 min, and the stirred solution kept at 40° for 20 hr. Water (60 cc) was added, followed by two drops of HCl (50%), and the solution extracted with methylene chloride (3 x 60 cc). The total extract was washed with water

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* This compound was prepared according to the literature.[95]

(60 cc), dried, and evaporated to a pale oil (2.07 g), which crystallised on standing. Chromatography on Sorbsil (30 g) in X4 gave, on elution with X4, unreacted bromides (150 mg, 12%); on elution with benzene:X4:ether (25:24:1), the dithiocarbazone 32 (1.73 g, 81%, 92% based on consumed bromides) as a colourless solid. A small amount was recrystallised from X4:ether before analysis:

mp 93-95°;

ir (nujol) 3150 (NH), 1625 (C=C), 1600 (Ar), 1390 and 1350 and 1170 (SO_2), 865, 820, 705 cm^{-1};

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3C1), 2.3 (s, 3H, CH_3Ar), 2.4 (s, 3H, CH_2S), 2.5 (m, 1H, HC5), 3.6 (s, 2H, $SCH_2C=$), 5.7 (m, 1H, C=CH), 7.3 (broad d, J=8Hz, each peak m, 2H, o-Ar), 7.8 (broad d, J=8Hz, each band m, 2H, m-Ar), 7.9 (s, superimposed on low field band of d, 7.8; 1H, NH);

Anal. calcd for $C_{22}H_{32}O_2S_3N_2$: C, 58.4, H, 7.1; N, 6.2; S, 21.2. Found: C, 58.3; H, 7.2; N, 6.3; S, 20.9.

14-Norhelminthospor-7(12)-en-13-dithioic acid, methylester 33

The dithiocarbazone 32 (250 mg, 0.59 mmol) in cyclohexane (20 cc, spectroscopic grade) was added under nitrogen to a stirred suspension of NaH (56.6 mg, 2.36 mmol) in cyclohexane (4 cc) at 7°. After 4 hr the supernatant was removed with a syringe, and transferred to a flask containing nitrogen, then heated under reflux for

2 hr. The yellow mixture was cooled, filtered (celite), and concentrated under reduced pressure and a stream of nitrogen, to reveal the dithioester 33 as an orange oil (136 mg, 92%), which showed:

nmr (film) δ0.9 (2d, J=3.5Hz, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3C1), 2.6 (s, 3H, CH_3S), 4.1 (m, W1/2=6Hz, collapses to broad s, W1/2=4Hz on double irradiation of 2d, 5.0; 1H, HC6), 5.0 (2d, both J=2Hz, collapses to 2s, 3Hz apart on double irradiation of m, 4.1; 2H, $=CH_2$), thus $J_{H5,H6}\leq 2Hz$. Calcd for epimer $J_{H5,H6}$=d, J=6-7Hz, see data for ester 45.

G.C. FFAP (160°, prog. to 200° 14/00) 25/00.

The bicyclic-thiolmethylester 34

To the dithioester 33 (48 mg, 0.179 mmol) under nitrogen was added $CuCl_2.2H_2O$ (122 mg, 0.714 mmol) and CuO (128 mg, 1.431 mmol) in acetone (8 cc, 3% water). The solution was heated under reflux for 10 hr, then cooled, diluted with water (10 cc), and extracted with benzene (15 cc x 2). The total extract was washed with water (10 cc), dried, and concentrated to a yellow oil (34 mg, 75%), which contained ∿60% thiolmethylester 34 (nmr analysis):

ir (film) 3050 ($=CH_2$), 1695 (broad, C=O), 1395 and 1375 (isopropyl), 1035 (broad), 900 ($=CH_2$), 835 cm^{-1};

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.1 (broad s, 3H, CH_3Cl), 2.3 (s, 9/5H, CH_3S), 5.1 (m, 6/5H, $C{=}CH_2$).

13-Hydroxy-14-norhelminthospor-7(12)-ene 35

The crude thiolmethylester 34 (34 mg, 0.135 mmol) was dissolved in dry ether (2 cc) and added to LAH (38 mg, 1 mmol) in ether (4 cc). The mixture was stirred under reflux overnight in an atmosphere of nitrogen, then cooled to -10° and, in the hood (smell), treated cautiously with water until the grey precipitate became white. Ether was decanted and the precipitate washed with benzene (6 cc). The pooled ether and benzene was washed to neutrality with water, dried, and evaporated to a colourless oil (17 mg, 61%). This had spectral and G.C. (spiked) characteristics indistinguishable from the alcohol 35 derived through the pyrrolidinium ylide sequence (detailed on page 131).

(2) Scheme 9 - the cyanomethylpyrrolidinium ylide approach

N-cyanomethyl-N-(13,14-dinorhelminthospor-6-en-12-yl)pyrrolidinium bromide 39

The allylic-bromides 30 (1.29 g, 5 mmol) were added dropwise to a stirred solution of NCMP[99] (0.59 g, 5.3 mmol) in dry DMSO (5 cc) under nitrogen, and the reaction mixture was stirred at 45° for 18 hr. The progress of salt 39 formation, in a parallel experiment (0.1 scale) using DMSO-d6, was monitored by nmr spectroscopy:

δ0.9 (t, J=5Hz, isopropyl CH_3, amongst other resonances), 1.1 (s, CH_3, amongst other resonances), 2.2 (m, 4H, $\overset{+}{N}(CH_2\underline{CH_2})_2$), 3.8 (m, 4H, $\overset{+}{N}(\underline{CH_2}CH_2)_2$), 4.3 (s, 2H, $\overset{+}{N}CH_2CN$), 5.1 (s, 2H, $\overset{+}{N}\underline{CH_2}C{=}CH$), 6.3 (m, 1H, $\overset{+}{N}CH_2C{=}\underline{CH}$),

N-(13-cyano-14-norhelminthospor-7(12)-en-13-yl)pyrrolidines 41, (C13 epimers)

The solution of the salt 39 (5 mmol) in DMSO (5 cc) was diluted with dry THF (25 cc), cooled to -10°, and treated with solid potassium t-butoxide (0.74 g, 6.6 mmol). The reaction mixture was stirred for 3 hr, diluted with benzene:ether (9:1, 50 cc), washed with brine (3 x 20 cc), water (2 x 20 cc), dried and finally concentrated to a pale oil (1.44 g, quant.), which

crystallised on standing. A small sample was chromatographed on a short column of neutral alumina (in X4, eluting with X4:Bz, 4:1), and recrystallised from X4 at -70° before elemental analysis:

mp (epimeric mixture) 55-86°;

ir (nujol) 2250 (wk, C≡N), 1645 (C=C), 1140, 1120, 1100, 925 and 900 cm^{-1} (=CH_2);

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3), 1.8 (m, 4H, $N(CH_2\underline{CH}_2)_2$), 2.7 (m, 4H, $N(\underline{CH}_2CH_2)_2$), 3.5 (m, 1H, epimeric $\underline{CH}CNN(CH_2CH_2)_2$), 5.2 (m, 2H, $C=CH_2$);

Anal. calcd for $C_{19}H_{30}N_2$: C, 79.7; H, 10.6. Found: C, 79.9; H, 10.65.

14-Norhelminthospor-7(12)-en-13-oic aldehyde 42 and its conjugated isomer 14-norhelminthospor-6-en-13-oic aldehyde 43

The pyrrolidinylnitriles 41 (1.32 g, 4.62 mmol) were dissolved in THF (36 cc) and treated with a warm solution of oxalic acid (36 cc, 30% W/V). The two-phase mixture was heated under reflux for 15 min, cooled, then extracted with X4 (2 x 50 cc). The combined fractions were washed with brine (2 x 30 cc), then water to neutrality, dried, and evaporated to a pale oil (1.05 g, quant.); in particular, the ir (film) showed bands 1720 (st, unconj. HC=O), 1660 cm^{-1} (wk, conj. HC=O) and, the nmr ($CDCl_3$) had resonances δ9.6 (d, J=2Hz, coupled with HC6, 0.85H, HC$\underline{CH}$O), 10.1 (s, 0.15H, C=CCHO). Chromatography on Sorbsil (75 g in X4) gave

sequentially, eluting with X4: unreacted secondary allylic bromide 30 (55 mg, 5%); the oily unconjugated aldehyde 42 (705 mg, 67%); an oily mixture of aldehydes 42 and 43 (240 mg, 23%) which was treated with base (see below). The unconjugated aldehyde 42, which afforded an SCZ derivative as colourless small needles from aqu. ethanol, had the following properties:

mp SCZ 177-179°;

ir (film) 3050 ($=CH_2$), 2700 (CHO), 1720 (HC=O), 1650 (C=C), 1395 and 1380 (isopropyl CH_3), 900 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3), 2.7 (broad d, J=7Hz, 1H, HC5), 3.1 (m, W1/2=6Hz, coupled with $C=CH_2$ and CHO, 1H, HCCHO), 5.0 (d, J=2Hz, coupled with HC6, 2H, $C=CH_2$), 9.6 (d, J=2Hz, coupled with HC6, 1H, CHO), thus $J_{5H,6H} \leq 2Hz$;

Mass spectrum (70eV) m/e 206 (M^+, $C_{14}H_{22}O$ requires M^+ 206)(43), 177 (M^+-HCO)(54), 93 (100), 91 (94);

G.C. FFAP (150°) 07/48;*

Anal. calcd for SCZ $C_{15}H_{25}N_3O$: C, 68.4; H, 9.6; N, 16.0.

Found: C, 68.7; H, 9.7; N, 16.35.

The mixture of aldehydes (240 mg, 1.16 mmol) was dissolved, under

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* Some isomerisation to conjugated aldehyde 43.

nitrogen, in methanol (25 cc) containing sodium methoxide (5.4 mg, 0.1 mmol). The solution was stirred for 20 hr at room temperature, poured onto water (25 cc), then extracted with X4 (2 x 40 cc). The combined X4 extract was washed with brine (40 cc), water (40 cc), dried, and concentrated to furnish the conjugated aldehyde 43 as a colourless viscous oil (240 mg, quant.); this gave an SCZ derivative as colourless prisms from aqu. ethanol, and showed:

mp SCZ 204-207°;

ir (film) 2700 (CHO), 1660 (HC=O), 1615 (C=C), 1380, 1370 (isopropyl), 1170, 1040, 785, 670 cm^{-1};

nmr ($CDCl_3$) δ0.9 (m, isopropyl CH_3, amongst other resonances), 1.1 (s, CH_3Cl, amongst other resonances), 2.0 (s, 3H, $CH_3C=C$), 3.2 (broad d, J=6Hz, 1H, HC5), 10.1 (s, 1H, CHO);

G.C. FFAP (150°) 11/28;

Anal. calcd for SCZ $C_{15}H_{25}N_3O$: C, 68.4; H, 9.6; N, 16.0.

Found: C, 68.5; H, 9.5; N, 15.7.

14-Norhelminthospor-7(12)-en-13-oic acid 44 and the corresponding methyl ester 45

The unconjugated aldehyde 42 (250 mg, 1.22 mmol) was dissolved in acetone (20 cc) and the solution cooled to -10°. Jones' reagent was cooled to -10° and added dropwise up to an orange

end-point. After 15 min, sufficient isopropyl alcohol was added to turn the colour to green, then the mixture diluted with benzene (30 cc) and water (20 cc). The aqueous layer was extracted with benzene (30 cc) and the total benzene fractions washed with brine (2 x 40 cc), water until colourless, then dried, and evaporated to afford the acid 44 as a colourless solid (270 mg, quant., mp 90-100°). Two recrystallisation from X4 gave regular colourless prisms (105 mg, 39%, mp 106-107°); the combined mother liquors contained ∿2% starting material, ∿98% acid 44 (nmr anal.):
ir (nujol) 3200-2700 (broad, OH), 3050 ($=CH_2$), 1700 (C=O), 1650 (C=C), 1375 (isopropyl), 1300, 1240 (C-O), 955, 900 cm^{-1} ($=CH_2$);
nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3), 2.5 (broad d, J=5Hz, 1H, HC5), 3.2 (m, W1/2=8Hz, collapses to broad s, W1/2=6Hz, upon double irradiation at 4.8 or 5.1, 1H, $\underline{H}CCO_2H$), 4.8 and 5.1 (2m, 2H, $C=CH_2$), 7.8 (broad s, 1H, exch., OH), thus $J_{5H,6H} \leqslant 4Hz$;
Anal. calcd for $C_{14}H_{22}O_2$: C, 75.6; H, 10.0. Found: C, 75.4; H, 9.9.

The methyl-ester 45 was prepared by treating the acid 44 (222 mg, 1.0 mmol) with excessive ethereal diazomethane in the normal way. Evaporation of solvent gave the ester 45 (236 mg, quant.) as a colourless oil which showed:

ir (film) 3050 ($=CH_2$), 1730 (C=O), 1650 (C=C), 1390 and 1375 (isopropyl), 1155 (broad, C-O), 900 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (2d, 6H, isopropyl CH_3), 1.1 (s, 3H, CH_3), 2.6 (broad d, J=5Hz, 1H, HC5), 3.3 (m, W1/2=6Hz, collapses to m, W1/2=4Hz on double irradiation at 4.9 or 5.1, 1H, $\underline{H}CCO_2CH_3$), 3.7 (s, 3H, OCH_3), 4.9 and 5.1 (2d, both J=2Hz, allylic coupling to HC6, 2H, $C=CH_2$), thus $J_{5H,6H} \leqslant 2Hz$;

G.C. FFAP (150°) 09/30; (160°) 07/57;

The nmr data above, together with that from the aldehyde 42 and acid 44, are consistent only with a C6 exo-isomer.[24]

14-Norhelminthospor-6-en-13-oic acid 47 via the corresponding conjugated methyl ester 46

Unconjugated ester 45 (236 mg, 1.0 mmol) was boiled in methanol (40 cc), containing sodium methoxide (40 mg, 0.74 mmol), for 48 hr in an atmosphere of nitrogen. The solution was concentrated to 1 cc, then poured onto X4:ether (4:1) and washed with water to neutrality. The solution was dried, then evaporated under vacuum to reveal the conjugated ester 46 as a homogeneous (G.C. anal.), colourless oil (233 mg, 99%) which had the following properties:

ir (film) 1705 (C=O), 1630 (C=C), 1200 (C-O), 1070, 1050, 795 cm^{-1};

nmr ($CDCl_3$) δ(ppm) 0.8-1.0 (m, isopropyl CH_3) 1.0 (broad s, CH_3Cl) (9H under 0.8-1.0 e), 2.0 (s, 3H, $CH_3C{=}C$), 3.1 (broad d, J=6Hz, C=CCH), 3.7 (s, 3H, OCH_3), no resonances in olefinic region;

Mass spectrum (70eV) m/e 236 (M^+, $C_{15}H_{24}O_2$ requires M^+ 236)(12), 177 ($M^+-CO_2CH_3$)(16), 93(58), 91(53), 55(100);

G.C. FFAP (160°) 11/52.

Hydrolysis of the conjugated ester 46

The ester 46 (230 mg, 0.97 mmol) was dissolved in methanol (20 cc) containing water (2 cc) and NaOH (100 gm, 2.5 mmol). The solution was heated under reflux in a nitrogen-atmosphere for 20 hr, cooled, diluted with water (30 cc), acidified to pH3 (cHCl), and finally extracted with X4:ether (4:1, 3 x 40 cc). The entire extract was washed with water (50 cc), dried, and evaporated under vacuum to a colourless solid, (200 mg, 92%): nmr ($CDCl_3$) 2.0 (s, 2.4H, $CH_3C{=}C$), 3.1 (m, 1H, HC5), 4.8 and 5.0 (2m, 0.4H, $C{=}CH_2$), i.e. 80% conjugated acid 47. Recrystallisation from X4 gave crystals mp 126-128°; one more recrystallisation from X4 afforded colourless prisms:

mp 127-129°;

ir (nujol) 3200-2600 (broad, OH), 1665 (C=O), 1615 (C=C), 1305, 1295, 1275, 1165, 1140, 945 cm^{-1} (broad, C-O);

nmr ($CDCl_3$) δ0.9 (d, isopropyl CH_3, amongst other resonances),

1.1 (broad s, CH_3Cl, and isopropyl CH_3, amongst other resonances), 2.0 (s, 3H, $CH_3C{=}C$), 3.1 (broad d, J=5Hz, 1H, C=CCH), 11.1 (e, 1H, CO_2H);

Anal. calcd for $C_{14}H_{22}O_2$: C, 75.6; H, 10.0. Found: C, 75.8; H, 10.1.

Reduction of the aldehyde 42 to 13-Hydroxy-14-norhelminthospor-7(12)-ene 35

A solution of aldehyde 42 (60 mg, 0.29 mmol) in dry ether (1 cc) was dropped onto LAH (11 mg, 0.29 mmol) in ether (4 cc) at 0°, under nitrogen. The mixture was stirred for 18 hr at room temperature, cooled to 0°, and treated cautiously with drops of water until the grey precipitate turned white. Ether was decanted and the precipitate washed with benzene (3 x 5 cc). The total benzene-ether solution was washed with water to neutrality, dried, and concentrated to a colourless viscous oil (60 mg, 99%), homogeneous by G.C. A 3,5-DNB derivative was prepared in the normal manner; this crystallised from X4:ether (X2) as faint yellow plates;

mp 3,5DNB, 99-102°;

ir (film) 3350 (OH), 3050 ($=CH_2$), 1650 (C=C), 1395 and 1380 (isopropyl), 1030 (C-O), 895 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (m, 6H, isopropyl), 1.1 (s, 3H, CH_3), 2.5 (broad t, J=7Hz, $HOCH_2\underline{CH}$), 3.5 (d, J=7Hz, collapses to broad s on double

irradiation at 2.5; 2H, $HOC\underline{H}_2CH$), 5.9 (2d, both J=2Hz, collapses to 2s, 5Hz apart on double irradiation at 2.5; 2H, $=CH_2$);

Mass spectrum (70eV) m/e 208 (M^+, $C_{14}H_{24}O$ requires 208)(19), 177 (M^+-CH_2OH, M* 150.6)(41), 93 (99), 91 (100);

G.C. FFAP (185°) 07/29 (spiked with alcohol derived from thiolester 34);

Anal. calcd for $C_{21}H_{26}N_2O_6$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.7; H, 6.6; N, 7.0.

Routes to the tricyclic-ketone 54

Execution of Scheme 10

1,2,3,4,5,8-Hexahydronaphthalene-2-carboxylic acid 48

Ammonia (600 cc) was distilled onto a solution of 2-naphthoic acid 48 (20 g, 116 mmol) in dry THF (100 cc) and dry t-butyl alcohol (160 cc, 1.7 mol) under nitrogen. Lithium (12 g, 1.7 g-at) pieces (ca. 100 mg) were added to the stirred solution under reflux over 1.5 hr, then, after a further 0.25 hr, ethanol (50 cc) was added to destroy the blue colour, and the solution allowed to evaporate during 18 hr. The white cake was treated with iced water (800 g), the slurry carefully acidified (3NHCl) to pH3, and immediately extracted with chloroform (3 x 300 cc). The combined extract was washed with water (2 x 200 cc), dried, and evaporated to afford a colourless solid (20.6 g, quant.). This was recrystallised from aqueous methanol to give colourless needles (17 g, 86%, mp 79-82°). The mother liquor furnished more crystals (2.8 g, 14%, mp 75-79°) and the analytical sample was obtained after one further recrystallisation:

mp 79-82°;

ir (nujol) 3200-2700 (OH), 3000 (shoulder =CH), 1700 (C=O), 1320, 1300 (C-O), 965, 680 cm^{-1} (=CH);

nmr ($CDCl_3$) δ2.0 (m, 6H, CH_2), 2.6 (broad s, 4H, =CHC$\underline{H}_2$ CH=), 5.6 (broad s, 2H, HC=CH), 11.5 (e, 1H, CO_2H);

uv λ_{max}^{EtOH} no absorbance above 210 nm;

Mass spectrum (70eV) m/e 178 (M^+, $C_{11}H_{14}O_2$ requires M^+ 178)(42), 91(100);

Anal. calcd for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.4; H, 7.9.

2-Diazoacetyl-1,2,3,4,5,8-hexahydronaphthalene 50 via 1,2,3,4,5,8-Hexahydronaphthalene-2-carboxylic acid chloride.

The diene-acid 49 (20.7 g, 116 mmol) in dry benzene (500 cc) containing pyridine (9.0 cc, 116 mmol) was added over 1 hr under nitrogen to a stirred solution of oxalylchloride (37 g, 25 cc, 290 mmol) in dry benzene (150 cc) at room temperature. After a further 1 hr the filtered (celite) solution was evaporated under reduced pressure and a slow stream of nitrogen. The residue was taken up in dry benzene (60 cc) and the solvent removed as before. The latter step was repeated twice to afford a viscous, sweet-smelling liquid, a portion of which was used directly in the next reaction:

ir (film) 3000 (=CH), 1790 (C=O), 750 (C-Cl), 665 cm^{-1} (=CH);

nmr (CCl_4) δ2.1 (m, 6H, CH_2), 2.6 (broad s, 4H, =CHC$\underline{H}_2$CH=), 5.6 (broad s, 2H, HC=CH).

The acid-chloride (14.3 g, 73 mmol) in dry ether (100 cc) was dropped over 30 min onto a stirred, ice-cold solution of diazomethane (~370 mmol from 129 g Diazald) in dry ether (1000 cc). The reaction mixture was allowed to warm to room temperature during 18 hr, then heated to 40° to drive off excessive diazomethane. Concentration of the solution under vacuum furnished a yellow oil which solidified on standing, and after recrystallisation from X4-ether gave the diazo-ketone 50 as yellow needles (10.5 g, 71%, mp 39-43°). An analytical sample was prepared by one further recrystallisation; the combined mother liquors yielded material on evaporation (3.4 g, 28%, mp 35-42°):

mp 42-43°;

ir (nujol) 3050 (HCN_2), 3000 (HC=), 2125 and 1635 ($COCHN_2$), 1380, 1345, 665 cm^{-1} (HC=);

nmr (CCl_4) δ1.9 (e, 6H, CH_2), 2.6 (e, 5H, $=CHCH_2CH=$ and HCCO), 5.1 (s, 1H, $COCHN_2$), 5.6 (broad s, HC=CH);

Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.3; H, 7.0; N, 13.85. Found: C, 71.5; H, 6.9; N, 14.1.

Tetracyclo[7,2,1,$0^{1,6}0^{6,11}$]dodec-3-en-10-one 51

The diazo-ketone 50 (10 g, 495 mmol) in cyclohexane (350 cc, spectroscopic grade) was dropped over 3 hr onto a stirred suspension of copper powder (Merk, 28 g, previously dried at 80° for 20

min) in cyclohexane (1000cc) under reflux in a nitrogen atmosphere. After a further 0.5 hr, the reaction mixture was cooled, filtered (celite), and concentrated under vacuum to reveal a pale solid. Distillation (100°, 0.01 mm, cold finger) gave analytically pure cyclopropyl-ketone 51 as colourless needles (7.85 g, 91%);

m p 71-73°;

ir (nujol) 3000 (HC=), 1720 (C=O), 1100, 1055, 1010, 955, 890 (cyclopropyl H), 690 cm^{-1} (HC=);

nmr (CCl_4) δ1.6 (s, 1H, cyclopropyl H), 2.0 (broad s amongst other resonances, =CHC$\underline{H}_2$), 5.5 (broad s, 2H, HC=CH);

Mass spectrum (70eV) m/e 174 (M^+, $C_{12}H_{14}O$ requires M^+ 174)(100), 105 (95), 91 (99);

G.C. SE30 (170°) 07/22; NPX (230°) 03/32; FFAP (180°) 13/27;

Anal. calcd for $C_{12}H_{14}O$: C, 82.7; H, 8.1. Found: C, 82.5; H, 8.0.

6-exo-H-Tricyclo[7,2,1,$0^{1,6}$]dodec-3-en-10-one 53 via the tricyclic-carbinol 52

A stirred, dry, solution of unsaturated cyclopropyl-ketone 51 (4.2 g, 24.1 mmol) in ammonia (300 cc) containing THF (60 cc) and t-butyl alcohol (40 cc) was cooled to -70° under nitrogen and

treated with pieces of lithium (840 mg, 120 mg-at). After the blue colour had persisted for 25 min, ethanol (40 cc) was added and the solution allowed to evaporate overnight. Water (150 cc) was added to the residue and the mixture extracted with X4:ether (1:1, 2 x 200 cc). The pooled extract was washed with brine (300 cc) then water (200 cc), dried and evaporated under reduced pressure to yield a pale oil (4 g, 95%), which crystallised on standing. A sample was chromatographed on Sorbsil (in X4, eluting with benzene:ether, 9:1) to give an alcohol which was recrystallised three times from X4:ether before analysis and shown (G.C.) to be the major component of the crude product:

mp (major isomer) 164-167°;

ir (nujol) 3400 (OH), 3000(HC=), 1650 (C=C), 1050, 1000, 840, 770, 655 cm^{-1} (HC=);

nmr ($CDCl_3$) δ1.0-2.3 (e, 15H), 4.5 (m, 1H, HCOH), 5.6 (e, 2H, HC=CH);

G.C. SE30 (150°) 05/55; FFAP (160°) 13/20 (1%, spiked with ketone 53), 15/25 (1.5%), 19/00 (97.5%);

Anal. calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.2. Found: C, 80.85; H, 10.2.

The crude alcohol 52 (1.25 g, 7 mmol) was stirred in acetone (80 cc) and treated dropwise with Jones' reagent until the solution became

red. After 5 min, sufficient isopropyl alcohol was added to turn the colour from red to green. After a further 5 min water was added to engender a green precipitate and the organic layer was decanted. The precipitate was decomposed with sodium hydroxide (5 cc, 10%), extracted with X4:ether (4:1, 3 x 20 cc) and the pooled acetone and ether extracts washed with water (3 x 15 cc), dried and evaporated to afford the ketone 53 as a pale oil (1.19 g, 95%). The SCZ derivative crystallised as colourless plates from aqu. ethanol:

mp SCZ 219-221° (dec);

ir (film) 3000 (HC=), 1738 (C=O), 1655 (C=C), 1460, 1440, 1410, 1160, 1070, 1000, 665 cm^{-1} (HC=);

nmr ($CDCl_3$) δ1.2-2.6 (broad e), 5.6 (m, HC=CH);

Mass spectrum (70eV) m/e 176 (M^+, $C_{12}H_{16}O$ requires M^+ 176)(61), 133 (78), 91 (100);

G.C. SE30 (180°) 05/40; FFAP (160°) 13/20;

Anal. calcd for SCZ, $C_{13}H_{19}N_3O$: C, 66.9; H, 8.2; N, 18.0.
Found: C, 66.8; H, 8.2; N, 18.0.

Tetracyclo[7,2,1,$0^{1,6}$$0^{6,11}$]dodecan-10-one 55

The unsaturated cyclopropyl-ketone 51 (700 mg, 4 mmol) in methanol (25 cc) was stirred with rhodium-on-alumina (5%, 70 mg)

under hydrogen at ambient temperature and pressure. When the hydrogen uptake was 90 cc (4.02 mmol), the filtered (celite) solution was concentrated to a colourless oil (700 mg, quant.), which was chromatographed on Sorbsil (70 g in X4) and the fractions monitored by G.C. Elution with X4 (10 x 250 cc fractions) gradating to X4:ether (9:1, over 18 x 250 cc fractions) gave sequentially; unidentified products (193 mg total) then, the saturated cyclopropyl-ketone 55 (507 mg, 72%) as colourless prisms. A sample was distilled before analysis and the SCZ derivative (colourless plates from aqu. ethanol) prepared in the usual manner:

mp 20-21°; bp 70° (block), 0.01 mm;

mp SCZ 213-215°;

ir (film) 3050 (cyclopropyl H), 1720 (C=O), 1260, 1190, 1155, 1130, 1090, 1055, 1000, 925, 880 cm^{-1} (cyclopropyl-H);

nmr ($CDCl_3$) δ1.3 (e), 1.5 (s, amongst other resonances, cyclopropyl H), 1.9 (broad s, amongst other resonances, cyclopropyl-CH_2), no resonances in olefinic region;

G.C. SE30 (170°) 07/22; FFAP (180°) 11/38, (190°) 10/08;

Anal. calcd for $C_{12}H_{16}O$: C, 81.8; H, 9.15. Found: C, 81.8; H, 9.45;

Calcd for SCZ $C_{13}H_{19}N_3O$: C, 66.9; H, 8.2; N, 18.0. Found: C, 66.8; H, 8.2; N, 17.8.

6-exo-H-Tricyclo[7,2,1,$0^{1,6}$]dodecan-3-ol 56

(1) From the olefinic-alcohol 52

The alcohol 52 (2.35 g, 13.2 mmol) was stirred with rhodium-on-alumina (200 mg) in methanol at room temperature and pressure under hydrogen until the uptake was complete (ca. 3 hr, 300 cc, 13.4 mmol). The filtered (celite) solution was evaporated under reduced pressure to reveal a colourless solid (2.38 g, quant.) physically indistinguishable from the major product obtained below.

(2) From the saturated cyclopropyl-ketone 55 by Birch reduction

Lithium pieces (40 mg, 5.7 mg-at) were added under nitrogen to a stirred dry solution of cyclopropyl-ketone 55 (200 mg, 1.14 mmol) in ammonia (50 cc), THF (4 cc) and t-butyl alcohol (4 cc) at -70°. After 25 min the blue colour was destroyed with ethanol (4 cc) and the ammonia allowed to evaporate overnight. Water (10 cc) was added and the mixture extracted with X4:ether (4:1, 75 cc), then the extract washed to neutrality with water, dried, and evaporated under reduced pressure to afford a colourless glass, which crystallised on standing (195 mg, 96%). The major product (G.C. analysis) was obtained for analysis as colourless needles after two recrystallisations from X4:

mp 101-102°;

ir (nujol) 3400 (OH), 1200, 1325, 1070, 1050, 1040, 1010, 990, 850 cm^{-1}; the crude product showed also 1738 (wk, C=O);

nmr ($CDCl_3$) δ1.0-2.4 (e), 4.4 (m, HCOH), no resonances in olefinic region;

G.C. FFAP (168°) 10/54 (12%, spiked with tricyclic ketone 54), 12/55 (1%), 15/13 (87%);

Anal. calcd for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 79.4; H, 10.9.

6-exo-H-Tricyclo[7,2,1,$0^{1,6}$]dodecan-10-one 54

(1) From the olefinic-ketone 53

The unsaturated ketone 53 (300 mg, 1.7 mmol) in methanol (20 cc) was shaken with palladium-on-carbon (5%, 30 mg) under hydrogen at ambient temperature and pressure until (~30 min) the uptake was 39 cc (1.75 mmol). The filtered (celite) solution was evaporated under reduced pressure to leave an oil with a camphor-like smell (300 mg, quant.), physically indistinguishable from that obtained below.

(2) From the saturated alcohol 56

The alcohol 56 (200 mg, 1.11 mmol) in acetone (20 cc) was stirred with a slight excess of Jones' reagent until the oxidation

was complete. Sufficient isopropyl alcohol was added to change the red solution to green, then water added to generate a green precipitate. The ketone 54 was obtained as a colourless oil by extraction with X4:ether (4:1) and isolation in the usual way (190 mg, 95%). The SCZ derivative formed as colourless plates from aqu. ethanol and the 2,4-DNP as red needles from ethanol:
mp SCZ 225°; 2,4-DNP 200-204°;
ir (film) 1738 (C=O), 1460, 1410, 1280, 1260, 1235, 1165, 1080, 1060, 1000, 980, 965, 920, 905, 885, 845, 835 cm^{-1};
nmr ($CDCl_3$) δ1.0-2.2 (broad e), 2.4 (m, H_2CCO and HCCO), no resonances in olefinic region;
Mass spectrum (70eV) m/e 178 (M^+, $C_{12}H_{18}O$ requires M^+ 178)(46), 135 (100);
G.C. SE30 (180°) 05/42; NPX (160°) 09/31; FFAP (160°) 10/53;
Anal. calcd for SCZ, $C_{13}H_{21}N_3O$: C, 66.35; H, 9.0; N, 17.9. Found: C, 66.2; H, 9.0; N, 18.2;
Calcd for 2,4-DNP $C_{18}H_{22}N_4O_4$: C, 60.3; H, 6.2; N, 15.6. Found: C, 59.8; H, 6.0; N, 15.4.

Metal-ammonia reduction of the cyclopropyl-ketone 55

Lithium (23.2 mg, 3.32 mg-at) was added under nitrogen to a stirred dry solution of cyclopropyl-ketone 55 (113 mg, 0.74 mmol)

in ammonia (20 cc) containing THF (10 cc). After 30 min the blue solution was changed to colourless by the careful addition of solid ammonium chloride (2 g) and the ammonia allowed to evaporate. Water (50 cc) was added and the mixture extracted with X4:ether (1:1, 50 cc) and the extract washed with brine (25 cc), then with water to neutrality, dried, and concentrated to a colourless oil (133 mg) which crystallised on standing and was subjected to G.C. analysis: FFAP (180°) 07/55 (3.5%, spiked with tricyclic-ketone 54) 08/44 (5.5%), 09/45 (70%, spiked with tricyclic-alcohol 56), 11/00 (20.9%, spiked with cyclopropyl-ketone 55). The mixture showed: ir (film) 3400 (broad, OH), 1738 (shoulder, C=O), 1720 (cyclopropyl-C=O), 925, 880 (wk, cyclopropyl H) cm^{-1}.

A portion (20 mg) of the mixture was oxidised in acetone (2 cc) using an excess of Jones' reagent and the reaction mixture worked up in the normal way. The product (19 mg), isolated as a pale oil, was analysed by G.C.; FFAP (180°) 08/00 (74%, spiked with tricyclic-ketone 54), 08/45 (5%), 11/02 (21%, spiked with cyclopropyl-ketone 55).

Determination of C6 stereochemistry in ketone 54

The execution of Scheme 11

trans-Decalinaceto-9,2-lactone 57

To the ketone 54 (210 mg, 1.17 mmol) and p-tosic acid (10 mg) in acetic acid (3 cc, glacial) was added peracetic acid (1.15 g, ∿30%, ∿4.5 mmol). The solution was stirred in the dark at 20° for 20 hr, then poured onto water (25 cc) and extracted with methylene chloride (3 x 20 cc). The combined extract was washed with water to neutrality, dried, and evaporated under reduced pressure to reveal a colourless oil (220 mg, 97%) which crystallised on standing. The analytical sample was prepared as colourless prisms by recrystallisation from X4:ether:

mp 70-74°;

ir (nujol) 1730 (C=O), 1215, 1120, 1025 (C-O), 960 cm^{-1};

nmr ($CDCl_3$) δ1.4 (e), 2.1 (d, J_g=19Hz, 1H, HCCO), 2.9 (d of d, J_g=19Hz and J'=2Hz long range coupling, 1H, HCCO), 4.8 (e, 1H, HCO);

Mass spectrum (70eV) m/e 194 (M^+, $C_{12}H_{18}O_2$ requires M^+ 194) (4), 150 (M^+-CO_2)(23), 41 (100);

Anal. calcd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 73.95; H, 9.5.

2-Oxo-trans-decalin-9-acetic acid, methyl ester 59 via the corresponding 2-hydroxydecalinacetic acid, methyl ester 58

The unpurified lactone 57 (210 mg, 1.08 mmol) was dissolved in ethanol (5 cc) and aqu. NaOH (5 cc, 25%) under nitrogen and the solution boiled for 18 hr. The cooled reaction mixture was poured onto water (25 cc), extracted with methylene chloride (3 x 10 cc), then carefully acidified to pH3 (HCl, 10%) and immediately extracted with ether (2 x 20 cc). The combined ethereal extract was washed once with water (20 cc) then treated with ethereal diazomethane until the pale yellow persisted. The excess of diazomethane was allowed to evaporate, then the solution dried, and concentrated to the pale oily alcohol 58 (170 mg, 70%) which was characterised spectrally:

ir (film) 3500 (OH), 1735 (C=O), 1200 (OH), 1130, 1110, 1025 (C-O), 980, 970 cm^{-1};

nmr ($CDCl_3$) δ1.0-2.0 (e), 2.6 (d, J=12Hz, 1H, restricted rotation $\underline{H}CCO_2CH_3$), 3.1 (d, J=12Hz, 1H, $\underline{H}CCO_2CH_3$), 3.7 (s, 3H, CO_2CH_3), 4.1 (e, 1H, $\underline{H}COH$).

The crude hydroxy ester 58 (170 mg, 0.75 mmol) was dissolved in acetone (15 cc) and Jones' reagent added to impart a red colouration for 5 min. Isopropyl alcohol was added to turn the red solution green, then the mixture made alkaline (10%, NaOH) and worked up in the normal way. A colourless oil (160 mg, 95%),

composed of a major and minor component (G.C. anal.) was isolated from benzene:ether (4:1) and distilled before analysis:

bp 65-67° (block), 0.01 mm;

ir (film) 1740-1710 (broad, C=O), 1185 (broad, C-O), 1095, 1015, 980, 960, 895, 850 cm^{-1};

nmr ($CDCl_3$) δ1.0-1.8 (methylene e), 2.2 (m), 2.4 (broad m), 2.6 (broad s), 2.8 (broad s) (6H, $\underline{H_2}CCO_2CH_3$ and $(H_2C)_2CO$), 3.6 (s, 3H, CO_2CH_3);

Mass spectrum (70eV) m/e 224 (M^+, $C_{13}H_{20}O_3$ requires M^+ 224)(2), 193 (M^+-OCH_3)(4), 151 (193-H_2CCO, M* 118)(100);

G.C. Apiezon M (200°) 07/43 (90%), 10/03 (10%);

Anal. calcd for $C_{13}H_{20}O_3$: C, 69.6; H, 9.0. Found: C, 69.5; H, 8.8.

trans-Decalin-9-acetic acid 68a from the keto-ester 59

The keto-ester 59 (60 mg, 0.27 mmol), KOH (56 mg, 1.0 mmol) and hydrazine hydrate (120 mg, 85%, 2.8 mmol) were heated in ethylene glycol (10 cc) at 90° until the KOH dissolved, then under reflux for 3.5 hr. The cooled solution was poured onto HCl (50%, 10 cc) and extracted with methylene chloride (3 x 15 cc), then this pooled, and extracted with sodium bicarbonate (10%, 2 x 10 cc).

The combined bicarbonate solution was acidified (HCl, 20%), extracted with methylene chloride (3 x 15 cc) and this washed with water (10 cc), dried, and evaporated under reduced pressure to leave a pale solid (45 mg, 85%, mp 128-132°) which had two components (G.C. methyl ester). Recrystallisation from aqueous acetone gave colourless plates:

mp (sealed tube) 139-141°, mmp authentic sample 68 139-141° (c/f lit.[121,122] mp corresponding cis-acid 114-115°);

ir (nujol) as for the authentic trans-acid 68;

G.C. (methyl ester) Apiezon M (170°) 09/00 (90%, spiked with authentic trans-ester), 09/59 (10%); FFAP (180°) 07/21 (90%, spiked with authentic trans-ester), 07/57 (10%).

Elaboration of Scheme 12

trans-Decalin-9-carboxylic acid 62 and the methyl ester 63

Formic acid (90%, 9 g, 0.176 mol) was added to sulphuric acid (95-98%, 390 cc) containing water (22.5 g) and stirred well at 0°. When the solution foamed (evolution of carbon monoxide), 2-hydroxydecalin 61 (60 g, 0.39 mol) and formic acid (90%, 120 g, 2.35 mol) were added slowly and separately over 4 hr while maintaining the temperature at ∿5°. After a further 0.75 hr, the

mixture was poured onto crushed ice (∿2 kg) and the solid collected by suction filtration, dissolved in ether (250 cc), and the solution extracted with sodium carbonate (30%, 250 cc x 3). The extract was carefully acidified (cHCl) and the acid 62 isolated by suction filtration. One recrystallisation from acetone gave colourless plates (15 g, 21%, mp 134-135°, lit.[128] 135°); the mother liquors yielded more material (8 g, 9%, mp 129-133°):
ir (mujol) 3200-2700 (broad, OH), 1690 (broad, C=O), 1320, 1250, 1220 (C-O), 1150, 1120, 1020, 970, 950, 930 (COOH), 800, 740 cm^{-1}.

The methyl ester 63 was prepared by adding slowly, an ethereal solution of diazomethane, to a stirred solution of acid 62 (5 g, 27.5 mmol) in ether (50 cc) at 0°, until the pale yellow persisted. Evaporation of the ether and diazomethane afforded a colourless oil (5.35 g, quant.), which had the following spectral features:
ir (film) 1735 (C=O), 1325, 1195, 1140, 1115 (C-O), 995, 940, 810 cm^{-1};
nmr (CCl_4) δ1.0-2.0 (methylene e, 17H), 3.6 (s, 3H, OCH_3).

trans-9-Hydroxymethyldecalin 64

Unpurified methyl ester 63 (from acid 62 5 g, 27.5 mmol,

see above) in dry THF (50 cc) was dropped onto LAH (1.06 g, 27.5 mmol) stirred in THF (150 cc) at -50° under nitrogen. The mixture was allowed to warm to room temperature then stirred under reflux for 20 hr, cooled to -50° and cautiously treated successively with wet ether (50 cc), sodium sulphate (1 g, anhydrous), and water dropwise until the grey precipitate became white. The supernatant was decanted, the precipitate extracted with ether: benzene (4:1, 3 x 50 cc). The combined organic material was washed with water to neutrality, dried, and concentrated to reveal colourless crystals (4.6 g, quant.). Recrystallisation from aqu. ethanol furnished colourless needles of alcohol 64 (4.5 g, 98%, mp 83-84°, lit.[129,130] 77-78°, 82-85°) and the mother liquor afforded more needles (0.1 g, 2%, mp 80-83°):

ir (nujol) 3300 (OH), 1150, 1030 (C-O), 960, 950, 920, 860, 830 cm^{-1};

nmr ($CDCl_3$) δ1.0-2.0 (methylene e), 2.3 (broad s, 1H, exch., OH), 3.8 (s, 2H, $\underline{H}_2COH$).

trans-Decalin-9-methyl-p-toluenesulphonate 65

The alcohol 64 (2.5 g, 14.0 mmol) was dissolved with p-tosyl chloride (15.2 g, 80.0 mmol) in dry benzene (100 cc), containing

pyridine (25 cc), and the stirred solution heated under reflux for 44 hr, in an atmosphere of nitrogen. Water (1 cc) was added dropwise to the cooled (20°) reaction mixture, which became warm during the addition, and was stirred for 10 min before dilution with water (50 cc) and benzene (100 cc). The benzene layer was washed with HCl (10%, 4 x 30 cc), water (2 x 30 cc), dried, and evaporated to a pale solid which was recrystallised from acetone to yield the tosylate 65 as colourless prisms (3.5 g, 73%, mp 143-144°, lit.[129,130] 138-142°, 141-142°) and the mother liquor gave more crystals (0.25 g, 5%, mp 142-143°):

ir (nujol) 1600 (Ar), 1340 and 1160 (both broad, S=O), 1090 (broad), 840, 810, 720, 660 cm^{-1} (Ar);

nmr ($CDCl_3$) δ1.0-2.0 (methylene e), 2.4 (s, 3H, $ArCH_3$), 4.2 (s, 2H, H_2COTos), 7.3 (broad d, J=8Hz, 2H, H2,H6 Ar), 7.8 (broad d, J=8Hz, 2H, H3,H5 Ar).

trans-9-Cyanomethyldecalin 66

The red solution of tosylate 65 (3 g, 9.3 mmol) and sodium cyanide (24 g, 490 mmol) in dry DMSO (200 cc) was warmed at 95° for 7 days under nitrogen. The reaction was monitored periodically by the disappearance of the high Rf spot (tosylate) on tlc (benzene: ether, 9:1), and the solution colour-change from red to yellow.

The cooled solution was poured slowly onto chilled (ice-bath) water (150 cc) and extracted with benzene (3 x 150 cc). The extracts were combined, washed with water to neutrality, dried, and concentrated under vacuum to a colourless oily nitrile 66 (1.65 g, quant.). A sample, distilled for analysis, formed colourless crystals:

mp 47-50°; bp 65-68° (block) 0.005 mm;

ir (film) 2200 (m, C≡N), 1260, 970, 920, 850, 830 cm^{-1};

nmr (CCl_4) δ1.0-2.0 (methylene e), 2.3 (s, 2H, H_2CCN);

Mass spectrum (70eV) m/e 177 (M^+ $C_{12}H_{19}N$ requires M^+ 177)(9) 137 (M^+-H_2CCN)(45), 95 (68), 81 (100), 67 (68), 41 (75);

Anal. calcd for $C_{12}H_{19}N$: C, 81.3; H, 10.8. Found: C, 81.5; H, 11.0.

trans-Decalin-9-acetamide 67

A solution of nitrile 66 (1 g, 5.65 mmol) in ethanol (15 cc) and KOH (50%, 15 cc) under nitrogen was boiled for 3 days. Ethanol was removed under reduced pressure and suction filtration (the filtrate was saved, see below) used to collect the solid. This was washed with water, then recrystallised twice from aqueous acetone to give the amide 67 as colourless needles (800 mg, 73%, mp 123-128°). A sample was recrystallised again before analysis:

mp 129-130°;

ir (nujol) 3470, 3350 (broad) and 3200 (NH_2), 1650 (broad, amide 1 and 2), 1220, 1115, 970 cm^{-1};

nmr ($CDCl_3$) δ1.0-2.0 (methylene e), 2.4 (s, 2H, $\underline{H_2}CCONH_2$), 5.5 (e, 2H, NH_2);

Anal. calcd for $C_{12}H_{21}NO$: C, 73.8; H, 10.8; N, 7.2. Found: C, 73.4; H, 10.6; N, 7.4.

trans-Decalin-9-acetic acid 68

(1) The amide filtrate (see above) was acidified (cHCl) and extracted with ether (3 x 20 cc). The total extract was washed with water to neutrality, dried, and concentrated to a colourless solid. Two recrystallisations from aqueous acetone afforded the acid 68 as colourless plates (100 mg, 9%, mp 140-141°).

(2) From the amide 67

Nitrogen was blown over a stirred suspension of amide 67 (240 mg, 1.23 mmol) in sulphuric acid (70%, 20 cc) at 20°. A solution of sodium nitrite (10%) was added dropwise until the frothing stopped and after 15 min, ether (50 cc) was added. The ethereal layer was washed with brine (3 x 30 cc), then water

(30 cc), dried, and evaporated to a pale solid which was recrystallised twice from aqueous acetone to give colourless plates (180 mg, 75%):

mp (sealed tube) 140-141°;

ir (nujol) 3200-2600 (broad OH), 1700 (C=O), 1310, 1260, 1215 (C-O), 1120, 1030, 960 (broad, CO_2H), 915, 835, 830, 725 cm^{-1};

nmr ($CDCl_3$) δ1.0-2.0 (methylene e), 2.5 (s, 2H, $\underline{H}_2CCO_2H$), 10.0 (e, 1H, CO_2H);

G.C. (methyl ester) Apiezon M (170°) 09/00; FFAP (180°) 07/21;

Anal. calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.5; H, 10.0.

6-endo-H-Tricyclo[7,2,1,$0^{1,6}$]dodecan-10-one 69

The ketone 69 (lit.[68] mp 2,4-DNP, 144-147°) was obtained from an authentic sample (∿4 mg) of a corresponding carbinol by oxidation with Jones' reagent in acetone in the normal manner and showed:

ir (film) 1745 (C=O), 1165, 1150, 1055, 875 cm^{-1};

G.C. NPX (160°) 10/17; FFAP (160°) 11/43.

The elaboration of the tricyclic-acids 75 and 78

Execution of Scheme 13

6-exo-H-10-Methylenetricyclo[7,2,1,$0^{1,6}$]dodecane 70

A mixture of methylphosphonium iodide (15.05 g, 37.2 mmol) and potassium t-butoxide (4.1 g, 36.6 mmol) in dry ether (100 cc) was stirred and heated under reflux for 2 hr in an atmosphere of nitrogen. The resulting yellow mixture was cooled to -70°, a solution of the ketone 54 (2.2 g, 12.4 mmol) in ether (10 cc) added over 0.25 hr, then the mixture allowed to warm to room temperature during 6 hr. After a further 12 hr at this temperature the mixture was heated under reflux for 0.5 hr, cooled to 0°, methanol (80%, 20 cc) added cautiously, and the ether removed under reduced pressure to leave a dark mixture which was diluted with methanol (80%, 60 cc) and extracted with X4 (3 x 60 cc). The total extract was washed with methanol (80%, 2 x 60 cc), water (2 x 60 cc), dried, and concentrated to a pale liquid which was distilled under reduced pressure to afford a colourless oil (1.98 g, 91%):

bp 115° (block), 11 mm;

ir (film) 3050 (=CH), 1750 (wk, 2ν $=CH_2$), 1655 (C=C), 990, 880 cm^{-1} ($=CH_2$);

nmr (CCl_4) δ1.0-2.0 (methylene e), 2.5 (e, 3H, $H_2CC=C$ and $HCC=C$),

4.7 (broad s, 2H, C=CH_2);

Mass spectrum (70eV) m/e 176 (M^+, $C_{13}H_{20}$ requires M^+ 176) (55), 133 ($M^+-C_3H_7$, M*100.5) (100);

G.C. FFAP (140°) 05/40, (100) 09/45;

Anal. calcd for $C_{13}H_{20}$: C, 88.6; H, 11.4. Found: C, 88.8; H, 11.35.

The tricyclic primary (A) and secondary (B) allylic-bromides 71

To a solution of the olefin 70 (880 mg, 5 mmol) in carbon tetrachloride (50 cc) was added pure NBS (930 mg, 5.25 mmol), and 5 crystals of benzoylperoxide. The mixture was heated under reflux for 30 min, during which the heavy precipitate of NBS disappeared and a light precipitate of succinimide formed. The cooled solution was filtered (celite), concentrated under vacuum and the residue chromatographed on a short column of Sorbsil (15 g in X4). Elution with X4 gave the bromides as a colourless oil (1.03 g, 82%) which was analysed spectrally:

ir (film) 3050 (=CH), 1650 and 1620 (C=C), 1210, 1195, 980, 900 (=CH_2), 840 cm^{-1} (=CH);

nmr (CCl_4) δ1.0-2.0 (methylene e), 2.6 (e, 1H, HC9), 4.0 (s, 1.2H, CH_2Br, A), 4.8 (e, 0.4H, CHBr, B), 5.1 and 5.3 (2 broad s, 1.2H, C=CH_2,B), 5.8 (s, 0.6H, C=CH, A), ratio H(A):H(B)=3:2;

Mass spectrum (70eV) m/e 254, 256 (M^+, $C_{13}H_{19}Br$ requires M^+ 254,

256) (5), 175 (M^+-Br, M* 121.5) (100).

N-Cyanomethyl-N-(6-exo-H-tricyclo[7,2,1,$0^{1,6}$]dodec-10-en-10-yl)-methylpyrrolidinium bromide 72

The allylic-bromides 71 (1 g, 3.92 mmol) were added dropwise to a stirred solution of NCMP (462 mg, 4.2 mmol) in dry DMSO (11 cc) under nitrogen, and the reaction mixture stirred at 45° for 18 hr. A concomitant experiment (0.04 scale) was set up, using DMSO-d6, and the reaction monitored by nmr spectroscopy;
δ1.0-2.0 (methylene e), 2.2 (m, 4H, $\overset{+}{N}CH_2\underline{CH_2}$), 3.8 (m, 4H, $\overset{+}{N}\underline{CH_2}CH_2$), 4.3 (broad s, 2H, $=C\underline{CH_2}\overset{+}{N}$), 4.9 (s, 2H, $\overset{+}{N}\underline{CH_2}CN$), 6.4 (s, 1H, HC=C).

N-[Cyano-(6-exo-H-10-methylenetricyclo[7,2,1,$0^{1,6}$]dodecan-11-exo-yl)methyl]pyrrolidines 73

The solution of salt 72 (3.92 mmol) in DMSO (11 cc) was diluted with dry THF (55 cc), cooled to -10°, and treated with solid potassium t-butoxide (590 mg, 5.3 mmol). After 2.25 hr, the reaction mixture was diluted with X4:ether (4:1, 70 cc), washed with brine (3 x 50 cc), water (2 x 50 cc), dried, and evaporated to a viscous pale oil (1.04 g, quant.) which was hydrolysed directly:
ir (film) 3050 ($=CH_2$), 2250 (wk, $C\equiv N$), 1680 (wk, in crude product), 1650 (C=C), 1155, 1140, 1120, 900 cm^{-1} ($=CH_2$);

nmr (CCl_4) δ1.0-2.0 (methylene e), 2.6 (m, 4H, NCH_2CH_2), 3.9 (broad m, 1H, epimeric HCCN), 5.0 and 5.5 (2 broad s, 2H, $=CH_2$).

6-exo-H-10-Methylenetricyclo[7.2.1.$0^{1,6}$]dodecane-11-exo-carboxaldehyde 74

The mixture of nitriles 73 (see above) (1.04 g, 3.92 mmol) was dissolved in THF (32 cc), a warm solution of oxalic acid added (32 cc, 30% W/V), and the two-phase mixture heated under reflux for 15 min. The cooled mixture was extracted with X4 (2 x 50 cc) and the whole extract washed with brine (2 x 30 cc), water to neutrality, dried, then evaporated to afford the aldehyde 74 as a pale oil (800 mg, quant.), contaminated (∿5%, nmr anal.) with its conjugated isomer. The crude aldehyde was oxidised to the corresponding crystalline acid 75 (see below) for elemental analysis:

ir (film) 3050 ($=CH_2$), 2700 (HCO), 1710 (HC=O), 1675 (wk, conj. HC=O), 1655 ($=CH_2$), 1150, 1100, 1070, 900 cm^{-1} ($=CH_2$);

nmr (CCl_4) δ1.0-2.0 (methylene e), 2.7 (e, 1H, HC9), 3.2 (broad d, J=5Hz, collapses to broad s on double irradiation at 9.4, 0.95H, HCCHO), 4.7 and 5.1 (2d, J=2Hz, collapses to 2s on double irradiation at 3.2, 1.90 H, $=CH_2$), 9.4 (d, J=5Hz, collapses to s on double irradiation at 3.2, 0.95H, HCCHO), 10.2 (s, 0.05H, =CCHO);

Mass spectrum (70eV) m/e 204 (M^+, $C_{14}H_{20}O$ requires M^+ 204)(15), 41 (100);

G.C. FFAP (150°) 15/01*

6-exo-H-10-Methylenetricyclo[7,2,1,$0^{1,6}$]dodecane-11-exo-carboxylic acid 75 and the corresponding methyl ester 76

A solution of aldehyde 74 (800 mg, 3.92 mmol) in acetone (50 cc) was cooled to -10° and treated, dropwise, with Jones' reagent up to an orange end-point. After 15 min, sufficient isopropyl alcohol was added to turn the colour to green, then water (30 cc) was added and the solution extracted with X4:ether (4:1, 2 x 50 cc). The combined extract was washed with brine (2 x 40 cc), water until colourless, dried, and concentrated to a pale solid (800 mg, 93%). Chromatography on Sorbsil (20 g, in X4, eluting with X4:ether, 9:1), then recrystallisation from X4:ether (X2) gave analytically pure acid 75 (230 mg, 36%).†

mp 141-142°;

ir (nujol) 3200-2700 (broad, OH), 3050 (shoulder, $=CH_2$), 1690 (C=O), 1655 (C=C), 1210 (C-O), 1100, 969 (broad, CO_2H), 900 cm^{-1} ($=CH_2$);

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* Some isomerisation occurs on the column to the conjugated isomer, retention time 19/00. A small sample of aldehyde 74 was conjugated with methanolic sodium methoxide for spiking purposes.

† The mother liquors contained mainly acid 75 (ir anal.), but this was not isolated.

nmr ($CDCl_3$) δ1.0-2.0 (methylene e), 2.7 (e, 1H, HC9), 3.4 (broad s, W1/2=6Hz, reduces to W1/2=4Hz on double irradiation at 5.0, 1H, $\underline{H}CCO_2H$), 5.0 (broad s, 2H, $=CH_2$), 10.0 (e, 1H, CO_2H);
Mass spectrum (70eV) (direct) m/e 220 (M^+, $C_{14}H_{20}O_2$ requires M^+ 220) (32), 202 (M^+-H_2O, M* 185.5) (7), 192 (M^+-CO) (13), 41 (100);
Anal. calcd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.15. Found: C, 76.3; H, 9.1.

The methyl ester 76 was prepared by treating the acid 75 (30 mg, 0.136 mmol) with an excess of diazomethane in the normal fashion. Evaporation of solvent gave the ester 76 (32 mg, quant.) as a colourless oil which exhibited:
ir (film) 3050 ($=CH_2$), 1730 (C=O), 1650 (C=C), 1150 (C-O), 1030, 980, 895 cm^{-1} ($=CH_2$);
nmr ($CDCl_3$) δ2.6 (e, 1H, HC9), 3.4 (m, W1/2=6Hz, collapses to broad s, W1/2=3Hz on double irradiation at 4.9, 1H, $\underline{H}CCO_2CH_3$), 3.7 (s, 3H, OCH_3), 4.9 (m, W1/2=8Hz, reduces to 2s, 5Hz apart on double irradiation at 3.4, 2H, $C=CH_2$);
G.C. FFAP (150°) 16/00, (175°) 09/05.

6-exo-H-10-Methyltricyclo[7,2,1,$0^{1,6}$]dodec-10-ene-11-carboxylic acid 78 via the corresponding conjugated methyl ester 77

Unconjugated ester 76 (30 mg, 0.136 mmol) was heated under

reflux in methanol (10 cc), containing sodium methoxide (sodium 20 mg, 0.87 mg-at) under nitrogen for 6 days. The solution was cooled, poured onto water (20 cc), then extracted with X4:ether (5:1, 30 cc x 2). The extract was washed with water to neutrality, dried, and evaporated to reveal a pale, oily, conjugated methyl ester 77 (20 mg, 67%), which was used immediately (see below):
ir (film) 1715 (conj. C=O), 1640 (C=C), 1250 (C-O), 1190, 1140, 1070, 975 cm^{-1};
nmr ($CDCl_3$) δ1.0-1.6 (methylene e), 1.8 (s, 3H, $=CCH_3$), 2.3 (e, 1H, HCC=), 3.7 (s, 3H, OCH_3), no resonances in olefinic region;
G.C. FFAP (175°) 08/22.

Crude ester 77 (20 mg, 0.09 mmol) was treated with lithium n-butylmercaptide in HMPTA (0.2 cc, 0.5 M, i.e. 0.1 mmol) under nitrogen. The solution stirred for 1.5 hr at room temperature, diluted with X4:ether (9:1, 15 cc), and poured onto HCl (1M, 10 cc). The upper layer was washed with HCl (1M, 10 cc), water to neutrality, dried, and evaporated to a colourless solid (21 mg) with a mercaptan-like odour. This material was chromatographed on a short column of Sorbsil (in X4, eluting with X4:ether, 4:1) and the solid (18 mg, 96%) recrystallised from X4:ether to yield the acid 78 as colourless, regular, plates (10 mg, 53%):*

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* To conserve material for bio-assay, accurate mass was determined.

mp 166-167°;

ir (nujol) 3100-2600 (OH), 1660 (C=O), 1600 (C=C), 1325, 1295, 1280, 930 cm^{-1} (broad, CO_2H);

nmr ($CDCl_3$) δ1.0-1.8 (methylene e), 1.9 (s, 3H, $=CCH_3$), 2.3 (e, 1H, HCC=);

Accurate mass calcd mol. wt for $C_{14}H_{20}O_2$: 220.1463. Found: 220.1460.

The elaboration of phyllocladene-15-exo-carboxylic aldehyde 83 and acid 84

Execution of Scheme 14

17-Bromophyllocl-15-ene 80

To phyllocladene (mp 93-95°, 102 mg, 0.375 mmol), dissolved in carbon tetrachloride (3.5 cc), was added pure NBS (70 mg, 0.394 mmol) and 3 crystals of benzoylperoxide. The mixture was heated under reflux for 30 min, then cooled and filtered through a short column of Sorbsil (2 g in X4). Elution with benzene:X4 (1:4) and evaporation of solvent, afforded a colourless, viscid, 17-bromaisophyllocladene 80, which crystallised on standing (127.5 mg, 97%). This was used without purification:

mp 61-64° (lit.[1 37] 68-69°;

ir (film) 1625 (C=CH), 1390 and 1370 (gem-CH_3), 1200 (broad, 2ν,

C-Br), 1115, 995, 975, 855 cm^{-1}; identical with an authentic spectrum;*

nmr (CCl_4) δ0.8 (s, 3H, CH_3), 0.9 (2s, 6H, gem-CH_3), 2.5 (m, 1H, HCC=C), 4.0 (s, 2H, H_2CBr), 5.8 (broad s, 1H, C=CH).

N-[Cyano-(phyllocladen-15-exo-yl)methyl]pyrrolidines 82 via the corresponding cyanomethylpyrrolidinium bromide 81

17-Bromoisophyllocladene 80 (127 mg, 0.362 mmol) was added to a stirred solution of DMSO (1.1 cc) and NCMP (42.7 mg, 0.378 mmol) under nitrogen. After 10 min at 45° (a colourless precipitate had formed), the mixture was diluted with dry THF (1 cc) and the stirring continued at 45° for 3 hr, after which formation of salt 81 was complete:

nmr (DMSO/THF) δ0.8-0.9 (3s, gem-CH_3 and CH_3), 5.1 (broad s, $^{+}NCH_2CN$, amongst other resonances), 6.4 (broad s, C=CH).

The mixture was cooled to 0°, treated with potassium t-butoxide (53 mg, 0.472 mmol), and stirred for 4 hr. X4 (40 cc) was added, then the mixture washed with brine (2 x 20 cc), water (2 x 20 cc), dried, and concentrated under reduced pressure to afford the rearranged nitriles 82 (137.5 mg, quant.) as a viscous oil which was hydrolysed directly:

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* Kindly provided by Dr. L.N. Mander, University of Adelaide.

ir (film) 3050 ($=CH_2$), 2225 (wk, $C\equiv N$), 1670 (wk) and 1645 (C=C), 1390, 1375, 1355 (CH_3), 1140, 1125, 1115, 900 cm^{-1} ($=CH_2$);
nmr ($CDCl_3$) δ0.9 (3s, 9H, $3CH_3$), 2.7 (e, $N(CH_2CH_2)_2$, amongst other resonances), 3.6 and 4.1 (2d, J=6Hz and 4Hz, 1H, HCCN), 5.1 and 5.5 (2m, 2H, $C=CH_2$).

Phyllocladene-15-exo-carboxylic aldehyde 83

The nitrile-mixture 82 (137.5 mg, 0.362 mmol) was dissolved in THF (4 cc), a warm solution of oxalic acid (3 cc, 30% W/V) added, and the mixture boiled for 15 min. After cooling, X4 (40 cc) was added, then the mixture washed with brine (2 x 20 cc), water (2 x 10 cc), dried and solvent evaporated to reveal a colourless solid (109 mg, quant.). A sample was recrystallised from X4 (X2) to afford the aldehyde 83 as colourless needles for accurate mass determination:*
mp 86-88°;
ir (semi-cryst. film) 3050 ($=CH_2$), 2700 (CHO), 1710 (HC=O), 1650 (C=C), 1395 and 1375 (gem-CH_3), 1070, 995, 900 cm^{-1} ($=CH_2$);
nmr ($CDCl_3$) δ0.8 (2s, 6H, gem-CH_3), 1.0 (s, 3H, CH_3), 2.7 (e, 1H, HC13), 3.5 (m, W1/2=11.5Hz, collapses to m W1/2=6Hz on double irradiation at 9.3: 1H, HCCHO), 4.7 and 5.1 (2m, W1/2=4.5Hz,

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* To conserve material.

collapses to 2 broad s, both W1/2=4Hz on double irradiation at 3.5; 2H, C=CH_2), 9.4 (d, J=5.5Hz, collapses to s on double irradiation at 3.5, 1H, CHO);

Mass spectrum (70eV) (direct) m/e 300 (M^+) (80), 285 (M^+-CH_3) (30), 271 (M^+-CHO) (52), 257 ($M^+-C_3H_7$) 25, 91 (100);

Accurate mass calcd mol. wt for $C_{21}H_{32}O$: 300.2453. Found: 300.2450.

Phyllocladene-15-exo-carboxylic acid 84

The aldehyde 83 (91 mg, 0.304 mmol) was stirred in acetone (6 cc), the solution cooled to -10°, then treated dropwise with Jones' reagent until the orange colour had persisted for 15 min. Enough isopropyl alcohol was added to turn the colour green, then, after 5 min, benzene (20 cc) and water (2 cc) were added. The benzene layer was washed with brine (3 x 15 cc), water (2 x 15 cc), dried, and concentrated to a colourless solid (95 mg, 99%). Fine colourless needles of acid 84 were obtained, for accurate mass determination,* after recrystallisation from X4 (X2). Homogeneity of the product was confirmed by G.C. analysis of the corresponding methyl ester 85 (see below):

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* To conserve material for bio-assay.

mp 159-162°;

ir (nujol) 3050 ($=CH_2$), 2700 (broad OH), 1700 (C=O), 1655 (C=C), 1200 (C-O), 900 ($=CH_2$) cm^{-1};

nmr ($CDCl_3$) δ0.8 (broad s, 6H, gem-CH_3), 1.0 (s, 3H, CH_3), 2.6 (e, 1H, HC13), 3.6 (broad s, 1H, $HCCO_2H$), 4.8 and 5.0 (2m, W1/2=4.5 Hz, collapses to 2 broad s, both W1/2=3.5Hz on double irradiation at 3.6; 2H, $C=CH_2$), 9.5 (e, 1H, CO_2H);

Mass spectrum (70eV) (direct) m/e 316 (M^+) (100), 301 (M^+-CH_3, M* 287) (35), 273 ($M^+-C_3H_7$, M* 236) (50);

Accurate mass calcd mol. wt for $C_{21}H_{32}O_2$: 316.2402. Found: 316.2408.

The methyl ester 85 was obtained as a white solid from three crystals of acid and diazomethane-ether:

mp 78-82°;

G.C. FFAP (190°) 41/10; FFAP 1%, 2.0 M, N_2 30 cc/min, (210°) (5/24);

Mass spectrum (70eV) (direct) m/e 330 (M^+) (43), 315 (M^+-CH_3), 287 ($M^+-C_3H_7$, M* 250), 271 ($M^+-CO_2CH_3$) (13), 69 (100);

Accurate mass calcd mol. wt for $C_{22}H_{34}O_2$: 330.2559. Found: 330.2556.

The route to the hydroxy-gibberellenone 100

Execution of Scheme 15

5-Methoxy-1-vinylindan-1-ol 92

Vinyl magnesium bromide was prepared from vinyl bromide (23 g, 15.3 cc, 234 mmol) and magnesium (2.8 g, 116 mg-at) in dry tetrahydrofuran (180 cc) in the normal way.[216] The stirred Grignard reagent was cooled to -30°, then treated dropwise with a solution of 5-methoxyindanone 91 (7.5 g, 46.3 mmol) in THF (200 cc) over 2 hr. The mixture was allowed to warm to room temperature during 17 hr, then poured over ammonium chloride solution (40 g, 300 cc water) and ice (100 g). The slurry was extracted with benzene:ether (5:1, 3 x 350 cc) and the pooled extracts were washed with water (3 x 500 cc), dried, and concentrated to yield a pale yellow partly-crystalline solid (8.75 g, 99%), which was dehydrated immediately:

ir (film) 3400 (OH), 1685 (wk, s.m. C=O), 1610 (st, vinyl), 1270 (C-O), 1100, 1040, 940 and 850 cm^{-1} (vinyl);

nmr ($CDCl_3$) δ2.1 (m, 2H, $ArCH_2\underline{CH_2}$), 2.9 (m, 2H, $Ar\underline{CH_2}CH_2^{\alpha}$), 3.8 (s, 3H, $O\underline{CH_3}$), 5.1 (m, 2H, $HC=\underline{CH_2}$), 6.1 (d of d, 1H, J_{cis}=10Hz, J_{trans}=16Hz, $\underline{HC}=CH_2$), 7.0 (m, 3H, Ar);

Mass spectrum (70eV) m/e 172 (M^+-H_2O) (70), 78 (100).

5-Methoxy-1-vinylindene 93

The vinyl carbinol 92 (8.5 g, 447 mmol) was heated to reflux (5 min) in deoxygenated benzene (450 cc) under nitrogen in a 500 cc flask fitted with a Dean-Stark water separator. Quinoline (5.8 cc) was added, followed immediately by a solution of iodine in benzene (10 cc, 0.5% W/V), with further additions every 6 min for a total 96 min. The reaction was monitored by the collection of water and tlc (benzene:X4, 1:10, Rf vinylindene 0.8). After cooling, the reaction mixture was washed with aqueous sodium thiosulphate (5%, 100 cc), water (3 x 200 cc), dried, and concentrated to a mobile oil (7.7 g, quant.), which was used promptly. The oil became gummy and eventually solid if allowed to stand:

ir (film) 1685 (wk, res. C=O), 1600 (vinyl), 1485, 1260 (C-O), 1140, 1040, 920, 820 and 790 cm^{-1} (vinyl).

nmr (CCl_4) δ3.1 (broad s, 2H, methylene), 3.6 (s, 3H, OCH_3), 5.1, 5.3, 5.6, 5.9, 6.2 (m, 4H,olefinic, 7.2 (m, Ar plus some quinoline).

Ethyl α-acetoxyacrylate

The title compound was prepared, just prior to use, from ethylpyruvate (20 g, 172 mmol) acetic anhydride (40 g, 382 mmol)

and p-toluene sulphonic acid (1 g) by analogy with the reported preparation of methyl α-acetoxyacrylate.[157] Distillation gave 15 g (55%) pure ethyl acetoxyacrylate as a colourless liquid;

bp 90-92°, 13 mm;

ir (film) 1760 ($OCOCH_3$), 1730 ($CO_2C_2H_5$), 1645 (C=C), 1380, 1300, 1215 and 1150 (C-O), 1020 cm^{-1} ($C=CH_2$);

nmr (CCl_4) δ1.3 (t, J=6Hz, 3H, $OCH_2\underline{CH_3}$), 4.2 (q, J=6Hz, 2H, $O\underline{CH_2}CH_3$), 5.4 and 6.0 (2d, both J=2Hz, 1H, $C=CH_2$);

Mass spectrum (70eV) m/e 158 (M^+, $C_7H_6O_4$ requires M^+ 158) (1), 116 (M^+-H_2CCO, M*, 85) (12), 43 ($\overset{+}{C}OCH_3$) (100).

2-Hydroxy-7-methoxy-1,2,3,4-tetrahydrofluorene-2-carboxylic acid 95 via the 2-Acetoxy-7-methoxy-1,2,3,4-tetrahydrofluorene-2-carboxylic acid ethyl ester 94

The crude diene 93 (3.9 g, 22.8 mmol) and ethyl α-acetoxyacrylate (8.0 g, 50 mmol) were boiled in benzene under nitrogen. The reaction was monitored by tlc (benzene:ether, 7:1). After 5 hr, dry HCl gas was passed for 15 min through the cooled solution which was subsequently washed with sodium bicarbonate (10%, 2 x 50 cc), water to neutrality, dried, and concentrated. Chromatography of the residue on Sorbsil (120 g, in benzene:X4, 1:1) and elution with benzene:X4:ether (14:5:1) gave the acetoxyester 94

as a pale yellow oil (2.2 g, 32%), which was hydrolysed immediately.
ir (film) 1760-1720 ($OCOCH_3$ and $CO_2C_2H_5$), 1620 (C=C), 1590 (Ar), 1300-1220, 1160, 1110, 1080,1020 (series of C-O), 840 cm^{-1} (Ar);
nmr ($CDCl_3$) δ1.3 (t, J=6Hz, 3Hz, $OCH_2\underline{CH}_3$), 2.0 (s, 3H, $OCOCH_3$), 2.5 (e, 4H, CH_2), 3.0 (e, 2H, $=CC\underline{H}_2C$), 3.3 (e, 2H, $ArC\underline{H}_2C=$), 3.8 (s, 3H, OCH_3), 4.3 (q, 2H, $OC\underline{H}_2CH_3$), 6.8 (d of d, J=8Hz, J'=2.5Hz, 1H, HC6), 7.0 (d, J'=2.5Hz, masked, 1H, HC8), 7.1 (d, J=8Hz, 1H, HC5).

The crude acetoxyester 94 (2.2 g, 7.3 mmol) was boiled in ethanol (20 cc) and sodium hydroxide (10%, 7 cc) under nitrogen for 18 hr. The cooled solution was extracted with benzene:ether (20 cc, 5:1), acidified to pH4 (20% HCl). The precipitate was extracted into chloroform:ethylacetate (5:1, 5 x 50 cc); the latter extract washed with water (200 cc), dried, and concentrated to reveal the hydroxy-acid 95 as a colourless solid (1.8 g, 95%, mp 212-216°).

The analytical sample was obtained after recrystallisation from ethylacetate.
mp 215-218°;
ir (nujol) 3450 (OH), 3300-2600 (COOH), 1705 (C=O), 1615 (C=C), 1590 (Ar), 1300, 1210 (broad), 820 cm^{-1} (Ar);

nmr ($CDCl_3$-DMSO-d6) δ2.0 (m, 2H, $\underline{H}_2C3$), 2.4 (e, 3H masked by DMSO), 2.8 (e, 1H, HC1 cis to CO_2H), 3.2 (e, 2H, $ArC\underline{H}_2$), 3.7 (s, 3H, OCH_3), 6.8 (d of d, J=8Hz, J'=2.5Hz, 1H, HC6), 7.0 (d, J'=2.5Hz, masked, 1H, HC8), 7.1 (d, J=8Hz, 1H, HC5), 8.0 (e, 2H exch., OH);

Mass spectrum (70eV) m/e 260 (M^+, $C_{15}H_{16}O_4$ requires M^+ 206) (23), 242 (M^+-H_2O, M* 225) (19), 172 (M^+-"$H_2C{=}COHCO_2H$", retrograde Diels-Alder);

Anal. calcd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.5; H, 6.3.

Execution of Scheme 16

7-Methoxy-2-trifluoroacetoxy-1,2,3,4-tetrahydrofluorene-2-carboxylic acid 96

Hydroxy-acid 95 (350 mg, 1.35 mmol) was stirred at room temperature for 4 hr in trifluoroacetic anhydride (25 cc). The excessive anhydride was removed under reduced pressure and the residue taken up in methylene chloride (25 cc). The solution was washed with water to neutrality, dried, and concentrated to a pale yellow solid 96 (462 mg, 95%), which was used immediately:

ir (nujol) 3200-2550 (COOH), 1785 ($COCF_3$), 1720 (CO_2H), 1620 (C=C), 1590 (Ar), 1300, 1220, 1170 (broad CF_3), 880, 820, 780 cm^{-1} (Ar);

nmr ($CDCl_3$) δ2.6 (e, 4H, H_2C3 and H_2C4), 3.2 (e, 4H, H_2C1 and H_2C9), 3.9 (s, 3H, OCH_3), 7.0 (m, 3H, Ar), 8.0 (e, 1H, CO_2H).

2-Diazoacetyl-7-methoxy-2-trifluoroacetoxy-1,2,3,4-tetrahydrofluorene 98 via the acid chloride 97

To the trifluoroacetoxy-acid 96 (462 mg, 1.26 mmol) in oxalyl chloride (3.8 g, 30 mmol) and benzene (25 cc) under nitrogen was added pyridine (110 mg, 1.37 mmol). The mixture was warmed at 60° until no more gas was evolved (∿2 hr). The filtered solution was concentrated and the last traces of solvent removed using an oil vacuum-pump to leave a dark yellow, oily, acid chloride 97 (480 mg, quant.) ir (film) 1785 cm^{-1} (broad, COCl and $COCF_3$).

The crude acid chloride 97 (480 mg, 1.26 mmol) in ether (5 cc) was added slowly to diazomethane (12 mmol) in ether (50 cc) at 0°. The solution was left in the hood overnight, then concentrated to reveal the diazo-ketone 98 as an orange gum (490 mg, quant.) which was cyclised immediately:

ir (film) 2150 (HCN_2), 1780 ($COCF_3$), 1630 ($COCHN_2$), 1590 and 830 cm^{-1} (Ar);

nmr ($CDCl_3$) δ2.4-3.0 (e, 6H, CH_2), 3.1 (e, 2H, $ArCH_2$), 3.7 (s, 3H, OCH_3), 5.7 (s, 1H, $COCHN_2$), 6.9 (m, 3H, Ar).

2-Hydroxy-7-methoxy-2,9a-ethano-1,2,3,10a-hexahydrofluoren-11-one 100 via the tetracyclic trifluoroacetoxy-ketone 99

The diazo-ketone 98 (490 mg, 1.26 mmol) in methylene chloride (10 cc) was added slowly to stirred trifluoroacetic acid (20 cc) and the resulting solution concentrated to reveal the tetracyclic trifluoroacetoxy-ketone 99 as an orange gum; this was hydrolysed immediately:

ir (film) 1780 ($COCF_3$), 1750 (C=O), 1700 (broad, wk, unknown), 1610 (C=C), 1590 and 820 cm^{-1} (Ar). The crude ketone 99 was stirred in methanol (25 cc) and sodium hydroxide (10%, 5 cc) under nitrogen for 7 hr at 17°. The reaction mixture was extracted with benzene:ethylacetate (1:1, 5 x 30 cc), then the pooled extract washed once with water (50 cc), dried, and evaporated to a dark solid. Chromatography on Sorbsil (7 g in benzene) and elution with benzene:ethylacetate (5:1) gave the hydroxy-ketone 100 (200 mg, 62%, mp 175-179°) as pale crystals. Recrystallisation from ethylacetate:ether afforded colourless crystals for analysis: mp 179-181°;

ir (nujol) 3400 (OH), 1745 (C=O), 1610 (C=C), 1585 (Ar), 1290, 1260, 1110, 1020, 840 and 800 cm^{-1} (Ar and =CH);

nmr ($CDCl_3$)δ2.0-3.0 (broad e, 9H, OH and CH_2), 3.8 (s, 3H, OCH_3), 5.7 (t, J=4Hz, 1H, C=CH), 6.8 (m, 2H, HC6 and HC8), 7.3 (d of d, J=8Hz, J'=1.5Hz, HC5);

Mass spectrum (70eV) m/e 256 (M^+, $C_{16}H_{16}O_3$ requires M^+ 256) (77), 185 (M^+-"CH_2=COH-CO", M*, 133.6, retrograde Diels-Alder followed by α-cleavage to C=O) (100);

Anal. calcd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3. Found: C, 74.85; H, 6.3.

Studies on the base induced [2,3]-sigmatropic rearrangement of allylic cyanomethylpyrrolidinium salts

Execution of Scheme 17

Ethyl-(4-t-butylcyclohexylidene)acetate 101

The literature[176] method was modified as follows: a stirred syspension of NaH (3.2 g, 134 mmol) in DME, at -40° under nitrogen, was treated over 2 hr with ethyl diethylphosphonacetate (30 g, 134 mmol) and the reaction mixture stirred for a further 2 hr. 4-t-butylcyclohexanone (15.4 g, 100 mmol) in dry DME (100 cc) was added over 1 hr, and the stirred mixture allowed to warm to ambient temperature during 3 hr, then left for 18 hr. The mixture was poured onto water (250 cc), extracted with X4 (3 x 350 cc), the pooled extract washed with water to neutrality, dried, and concentrated to a colourless, homogeneous (G.C.), mobile oil (22.4 g, quant.); this was distilled under nitrogen to give the olefinic-ester 101 (21 g, 92%):

bp 114°, 0.7 mm (lit.[176] bp 77-84°, 0.1 mm);

ir (film) 1715 (C=O), 1655 (C=C), 1190, 1170, 1150 (C-O), 1050, 870 cm^{-1} (=CH);

nmr (CCl_4) δ0.9 (s, 9H, t-butyl), 1.2 (t, J=7Hz, 3H, $OCH_2\underline{CH_3}$), 3.8 (e, $\underline{H}CC=CHCO_2C_2H_5$, CH(e) syn to ester), 4.0 (q, J=7Hz, 2H, OCH_2CH_3), 5.4 (s, 1H, C=CH);

G.C. FFAP (200°) 06/00.

2-(4'-t-Butylcyclohexylidene)ethan-1-ol 102

$AlCl_3$ (2.7 g, 25 mmol) in dry ether (10 cc) was added slowly to LAH (28.5 g, 75 mmol) in ether (50 cc) at -10°, and the suspension stirred for 1.5 hr. Ester 101 (5 g, 22.3 mmol) in ether (20 cc) was added slowly and the mixture stirred for 1.5 hr at 0°, then for 18 hr at ambient temperature. The cooled mixture (ice-salt bath) was treated carefully with sufficient water to turn the precipitate from grey to white, ether was decanted, then the precipitate washed with ether:X4 (1:1, 50 cc x 2). The total ether:X4 fractions were washed with water (100 cc), dried, and condensed to afford the alcohol 102 as a colourless, homogeneous (G.C. anal.), oil (4 g, 98%). A sample was distilled before analysis:

bp 100° (block), 0.6 mm;

ir (film) 3300 (OH), 1665 (C=C), 1395 and 1370 (t-butyl), 1000 (broad, CO), 850 cm^{-1} (=CH);

nmr (CCl_4) δ0.9 (s, 9H, t-butyl), 2.6 (broad s, 1H, exch, OH), 4.0 (d, J=7Hz, 2H, C=CHC$\underline{H}_2$OH), 5.2 (t, J=7Hz, 1H, C=C$\underline{H}$CH_2OH);

G.C. FFAP (110°, inj. 130°) 33/45, some decomp, at higher col. and inj. temp.

Anal. calcd for $C_{12}H_{22}O$: C, 79.1; H, 12.2. Found: C, 79.45; H, 12.3.

2-(4'-t-Butylcyclohexylidene)ethyl-1-bromide 103

A solution of PBr_3 (1.35 g, 5 mmol), in dry ether (10 cc), was added over 20 min to a stirred, dry, solution of alcohol 102 (1.82 g, 1 mmol) and pyridine (0.59 g, 5 mmol) in ether (10 cc), cooled to -10° under nitrogen. After a further 30 min, enough sodium bicarbonate solution (sat.) was added cautiously, to destroy the excess of PBr_3, then the ethereal layer separated. The aqueous layer was extracted with X4 (10 cc x 2); ether and X4 fractions were combined, washed with water to neutrality, dried, and evaporated under vacuum to a pale, mobile, oil (2.16 g, 88%). This decomposed (G.C., nmr anal.) on distillation for elemental analysis; thus purity of the bromide 103 was established using G.C. and spectroscopy:

bp 115° (block), 0.4 mm, decomposes;

ir (film) 1650 (C=C), 1395 and 1370 (t-butyl), 1200 (ν½2, C-Br), 850 cm^{-1} (=CH);

nmr (CCl_4) δ0.9 (s, 9H, t-butyl), 3.9 (d, J=8Hz, 2H, C-CHC$\underline{H}_2$Br), 5.4 (t, J=8Hz, 1H, C=C$\underline{H}$CH_2Br);

Mass spectrum (70eV) M^+ absent, 164 (M^+-HBr) (8), 91 (80), 79 (100);

G.C. FFAP (110°, inj. 140°) 08/06 (≥98%).

N-[2-(4'-t-Butylcyclohexylidene)ethyl]-N-cyanomethylpyrrolidinium bromide 104

Allylic-bromide 103 (490 mg, 2.0 mmol) was dropped onto a stirred solution of NCMP (240 mg, 2.14 mmol) in dry DMSO (6 cc) at 18°, and the reaction mixture stirred, conveniently, for 17 hr. A concomitant reaction (0.1 scale) in d6-DMSO, was followed by nmr; this showed salt 104 formation almost complete after 2 min and entire after 30 min.

nmr (DMSO-d6) δ0.9 (s, 9H, t-butyl), 2.2 (m, $\overset{+}{N}(CH_2C\underline{H}_2)_2$ amongst other resonances), 3.7 (m, 4H, $\overset{+}{N}(C\underline{H}_2CH_2)_2$), 4.2 (d, J=8Hz, 2H, C=CHC$\underline{H}_2\overset{+}{N}$), 5.0 (s, 2H, $\overset{+}{N}CH_2CN$), 5.4 (t, J=8Hz, 1H, C=C$\underline{H}$C$H_2\overset{+}{N}$).

N-Cyano-(cis and trans-4-t-butyl-1-vinylcyclohexan-1-yl)methyl-pyrrolidines 106

The salt 104 (2.0 mmol), stirred in DMSO (6 cc), was diluted with dry THF (30 cc), cooled to -10°, and treated with potassium t-butoxide (308 mg, 2.56 mmol). After 3 hr, X4 (50 cc) was added, the mixture washed with brine (2 x 20 cc), water (2 x 20 cc), dried, and reduced under vacuum to a light viscous oil (671 mg, 94%). A small quantity was distilled before analysis to afford a diastereomeric mixture of nitriles 106 as a colourless liquid:

bp 110° (block) 0.1 mm;

ir (film) 3050 (vinyl CH), 2225 (wk, C≡N), 1635 (C=C), 1395 and 1370 (t-butyl), 925 cm^{-1} (vinyl CH);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.8 (m, $N(CH_2\underline{CH_2})_2$, amongst other resonances), 2.7 (m, 4H, $N(\underline{CH_2}CH_2)_2$), 3.5 (s, 0.85H, trans-HCCN), 4.1 (s, 0.15H, cis-HCCN), 5.4 (ABC m, 3H, $HC=CH_2$);

Mass spectrum (70eV) m/e 274 (M^+, $C_{18}H_{30}N_2$ requires M^+ 274) (1), 109 ($\overset{+}{C}HCNN(CH_2CH_2)_2$) (100);

Anal. calcd for $C_{18}H_{30}N_2$: C, 78.8; H, 11.0. Found: C, 79.15; H, 11.15.

cis-4-t-Butyl-1-vinylcyclohexane-1-carboxylic aldehyde 108 and trans-4-t-Butyl-1-vinylcyclohexane-1-carboxylic aldehyde 107

The mixture of pyrrolidinylnitriles (see above) (179 mg, 0.5 mmol) was dissolved in THF (4 cc), a warm solution of oxalic acid added (4 cc, 30% W/V), and the mixture boiled for 15 min. The cooled mixture was extracted with X4 (2 x 20 cc), then the entire extract washed with brine (2 x 30 cc), water to neutrality, dried, and concentrated to a pale mobile oil (97 mg, quant.), which had two components:

G.C. FFAP (140°) 07/14 (15%), 08/00 (85%).

Careful chromatography on Sorbsil (15 g, in X4, eluting with X4), monitored by G.C., gave cis-aldehyde 108 (14 mg, 15%), then trans-aldehyde 107 (83 mg, 85%). The cis-aldehyde showed:

ir (film) 3050 (vinyl CH), 2675 (CHO), 1720 (HC=O), 1630 (C=C), 1395 and 1370 (t-butyl), 1000, 990, 925 cm^{-1} (vinyl CH);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.0-2.1 (methylene e), 5.4 (ABC m, 3H, $HC=CH_2$), 9.26 (s, 1H, cis-CHO)(lit.[88] cis-CHO, 9.26);

G.C. FFAP (140°) 07/14;

The trans-aldehyde exhibited:

ir (film) 3050 (vinyl CH), 2675 (CHO), 1720 (HC=O), 1630 (C=C), 1395 and 1370 (t-butyl), 1000, 980, 925 cm^{-1} (vinyl CH);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.0-2.1 (methylene e), 5.4 (ABC m, 3H, $HC=CH_2$), 9.30 (s, 1H, trans-CHO) (lit.[88] trans-CHO), 9.30);

G.C. FFAP (140°) 08/00.

Reduction of the aldehydes 107 and 108 to their corresponding carbinols 109 and 110

A mixture of pyrrolidinylnitriles 106 (400 mg, 1.46 mmol) was hydrolysed, as described above (X3 scale), to afford a mixture of aldehydes 107 and 108 (275 mg, 97%);

ir (film) 2675 and 1720 (HC=O), 1630 and 930 cm^{-1} (vinyl);

G.C. FFAP (140°) 07/18 (15%, cis-CHO 108) 08/06 (85%, trans-CHO 107).

The aldehyde mixture (270 mg, 1.39 mmol) was dissolved in dry ether (15 cc), cooled to -10°, and treated with LAH (54 mg, 1.42 mmol). The mixture was stirred for 18 hr at room temperature, cooled (ice-salt bath), and water added cautiously until the grey precipitate became white. Ether was decanted, combined with X4:ether-extracts (4:1, 20 cc x 2) of the precipitate , washed with water (2 x 20 cc), dried, and evaporated to a colourless viscous oil (268 mg, 98%).

In particular, the following spectral features were evident:

ir (film) 3350 (broad, OH), 3050 and 1635 (vinyl), 1040 (broad C-O), 920 cm^{-1} (vinyl);

nmr (CCl_4) δ0.9 (2s, 9H, t-butyl), 1.0-2.1 (methylene e), 3.1 (s, 0.85H, trans-CH_2OH), 3.4 (s, 0.15H, cis-CH_2OH), 5.4 (ABC m, 3H, $HC=CH_2$); resonances of the major component dominated the olefinic region, which was practically indistinguishable from that of an authentic spectrum (CCl_4) of trans-alcohol 109. In addition, authentic spectra (CCl_4) indicate δ3.1, trans-CH_2OH and 3.4, cis-CH_2OH.

Ylide 105 rearrangements at temperatures below -10°

(1) DMSO-THF solvent system

The ylide precursor 104 was prepared from the allylic-bromide 103 (245 mg, 1 mmol) and NCMP (120 mg, 1.07 mmol) in DMSO (3 cc) as described previously (0.5 scale). Dry THF (15 cc) was added and the stirred reaction mixture, cooled to -78° (a precipitate formed), treated with potassium t-butoxide (154 mg, 1.28 mmol), and allowed to warm to -10° over 4.5 hr. Work-up as before (p.177) (0.5 scale) gave the rearranged nitriles 106 as a colourless oil (359 mg, quant.):

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.8 (m, $N(CH_2CH_2)_2$, amongst other resonances), 2.7 (m, 4H, $N(CH_2CH_2)_2$), 3.5 (s, 0.90, trans-HCCN), 4.1 (s, 0.10H, cis-HCCN), 5.4 (characteristic ABC m, 3H, $HC=CH_2$).

A portion of the nitrile mixture (227 mg, 0.632 mmol) was hydrolysed

in THF (5 cc) and oxalic acid (5 cc, 30% W/V) for 15 min and a corresponding mixture of aldehydes 107 and 108 obtained from an X4-extract (25 cc x 2) in the normal way (123 mg, quant.); this was analysed by G.C. FFAP (140°) 07/35 (10%, cis-CHO 108), 08/25 (90%, trans-CHO 107).

(2) Ylide 105 rearrangements in liquid ammonia

(a) At -33°

NCMP (120 mg, 1.07 mmol) was added dropwise to the allylic-bromide 103 (245 mg, 1.0 mmol) stirred in X4 (2 cc), and the solution warmed (water bath) at 40° for 15 min. X4 was removed from the precipitated, white, pyrrolidinium bromide 104 using a bulb pipette, the salt washed with X4 (5 cc, removed as before), then dried under reduced pressure and a slow stream of nitrogen (314 mg, 88%). Ammonia (50 cc) was distilled onto the powdered salt, under nitrogen, then finely-crushed potassium t-butoxide (154 mg, 1.28 mmol) added with stirring. After 4 hr, excessive NH_4Cl (solid, 1 g) was added and the ammonia allowed to evaporate. The residue was diluted with water (30 cc) and extracted with X4 (2 x 30 cc); the entire extract was washed with brine (30 cc), water (2 x 30 cc), dried, and reduced under vacuum to afford the nitriles 106 as a colourless, viscous oil (240 mg, quant.) which revealed:

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.8 (m, $N(CH_2\underline{CH_2})_2$, amongst other resonances), 2.7 (m, 4H, $N(\underline{CH_2}CH_2)_2$), 3.5 (s, 0.85H, trans-HCCN), 4.1 (s, 0.15H, cis-HCCN), 5.4 (characteristic ABC m, 3H, $HC=CH_2$).

(b) At -78°

The experiment above was repeated, only the reaction mixture was cooled to -78° before the addition, over 15 min, of potassium t-butoxide; NH_4Cl (1 g) was added after 4.5 hr. Isolation of the rearranged nitriles 106 (18 mg, 7.5%), from X4, was complicated by the detergent effect of unreacted pyrrolidinium salt 104. The nitrile mixture displayed:

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.8 (m, $N(CH_2\underline{CH_2})_2$, amongst other resonances), 2.7 (m, 4H, $N(\underline{CH_2}CH_2)_2$, 3.5 (s, 0.90H, trans-HCCN), 4.1 (s, 0.10H, cis-HCCN), 5.4 (characteristic ABC m, 3H, $HC=CH_2$).

Execution of Scheme 18

4-t-Butyl-3-dihydrobenzoic acid 112

To 4-t-butylbenzoic acid 111 (20 g, 112 mmol), stirred in dry ether (120 cc) and ammonia (350 cc) cooled to -70°, was added pieces (∿100 mg) of lithium (2.35 g, 336 mg-at) until the blue

colour persisted for 15 min. Ethanol (23 g, 500 mmol) was cooled to -70° and added over 6 min, then the solvent allowed to evaporate. The white cake was dissolved in water (100 cc), extracted with X4 (2 x 100 cc), acidified carefully (cHCl), and extracted with methylene chloride (2 x 100 cc). The total latter extract was washed with water (150 cc), dried, and reduced under vacuum to a white solid (20 g, 99%). A single recrystallisation of a small sample, from X4, afforded analytically pure acid 112 as colourless prisms:

mp 138°;

ir (nujol) 3200-2600 (broad, OH), 1680 (C=O), 1635 and 1590 (C=C), 1280 (OH), 1090, 945, 730, 700 cm^{-1} (=CH);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 2.3 (m, 3H, =CH-CHCH$_2$-HC=), 5.9 (d, J=10Hz, each band d J'=3Hz, 1H, HC=CH-CCO_2H), 6.4 (d, J=10Hz, each band m, 1H, HC=CH-CCO_2H), 7.1 (m, 1H, HC=CCO_2H), 11.5 (e, 1H, CO_2H);

G.C. (methyl ester) FFAP (185°) 05/57;

Anal. calcd for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95. Found: C, 73.3; H, 8.7.

4-t-Butylcyclohex-1-enecarboxylic acid 114 via the cis- and trans-4-t-Butylcyclohex-2-enecarboxylic acid 113

A solution of diene-acid 12 (18.9 g, 105 mmol) in dry ammonia (325 cc) and ether (110 cc) was cooled to -70° and treated with pieces (100 mg) of lithium (2.2 g, 315 mg-at). After the blue colour had remained for 15 min, ethanol (25 g, 550 mmol) was added cautiously and ammonia allowed to evaporate. Isolation of the cis- and trans-carboxylic acids 113, as in the analogous experiment above, revealed a partly-crystalline mass (18.9 g, 99%):

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.9 (e, 5H, CH_2CH_2CH), 3.1 (e, 1H, $HCCO_2H$), 5.9 (m, 2H, HC=CH), 11.1 (e, 1H, CO_2H);

G.C. (methyl esters) FFAP (185°) 04/57 (25%), 05/13 (75%).

A portion of acid mixture 113 (15 g, 82.5 mmol) was dissolved in a warm solution of NaOH (33 g, 825 mmol) in water (132 cc) and ethylene glycol (50 cc), and boiled under nitrogen for 45 hr (a white solid formed). The reaction mixture was cooled (ice-salt bath), carefully acidified (cHCl), then extracted with methylene chloride (2 x 200 cc). The pooled extract was washed with water (200 cc), dried, and concentrated to afford the conjugated olefinic-acid 114 as a pale solid (15 g, quant.). One recrystallisation

from chloroform gave colourless crystals (10 g, 67%):

mp 182-183° (lit.[182] 182-183°);

ir (nujol) 3200-2600 (OH), 1675 (C=O), 1640 (C=C), 940 cm^{-1} (broad, CO_2H);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.2 (e, 2H, $HCCH_2CH_2$), 2.0 (broad e, 6H, 4 allylic and 2 methine), 7.1 (e, 1H, HC=C), 10.6 (e, 1H, CO_2H);

G.C. (methyl ester) FFAP (185°) 05/55.

4-t-Butylcyclohex-1-enecarboxylic acid pyrrolidinamide 116 via the carboxylic acid chloride 115

The olefinic-acid 114 (5 g, 27.5 mmol) was dissolved in dry benzene (100 cc) containing pyridine (2.3 g, 29 mmol) and dripped, during 1 hr, onto a stirred solution of oxalyl chloride (34.5 g, 23.2 cc, 275 mmol) and benzene (63 cc), at room temperature, under nitrogen. After a further 1 hr, the filtered (celite) solution was concentrated under reduced pressure, and a stream of nitrogen, to furnish a pale oil. The oil was dissolved in benzene (20 cc) and the solvent removed as before; repeating this step twice, gave the sweet-smelling acid-chloride 115 as a pale liquid which was used directly (5.5 g, quant.):

ir (film) 3020 (=CH), 1745 (C=O), 1640 (C=C), 1400 and 1370 (t-butyl), 1143, 825 cm^{-1} (C-Cl).

The crude acid-chloride 115 (5.5 g, 27.5 mmol), in dry benzene (100 cc), was added slowly under nitrogen to a stirred solution of pyrrolidine (5.15 g, 72.5 mmol) and benzene (50 cc). The reaction mixture, which became warm during the addition, was stirred for 18 hr, then washed with HCl (10%, 3 x 50 cc), water (2 x 50 cc), dried, and evaporated under reduced pressure to expose a pale, viscous, oily amide 116 (6.4 g, 99%):

bp 130° (block), 0.01 mm;

ir (film) 1655 (shoulder, C=C), 1615 (C=O), 1420 (broad), 1370 (t-butyl), 920, 840 cm^{-1};

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.9 (m, $N(CH_2\underline{CH_2})_2$, amongst other resonances), 3.4 (m, 4H, $N(\underline{CH_2}CH_2)_2$), 5.9 (m, 1H, C=CH);

Anal. calcd for $C_{15}H_{25}ON$: C, 76.5; H, 10.7; N, 5.95. Found: C, 76.2; H, 10.6; N, 6.05.

N-(4-t-butylcyclohex-1-enyl)methylpyrrolidine 117

$AlCl_3$ (1.41 g, 10.6 mmol) in dry ether (5 cc) was added carefully to LAH (1.21 g, 31.8 mmol) stirred in ether (25 cc) at -10° under nitrogen. After 1.5 hr, amide 116 (2.5 g, 10.6 mmol),

dissolved in ether (10 cc), was added slowly and the mixture stirred for 1.5 hr at 0°, then 18 hr at ambient temperature. The cooled mixture (ice-salt bath) was treated cautiously with water until the grey precipitate became white. Ether was decanted, the precipitate washed with ether:X4 (1:2, 25 cc x 2), and the entire ether:X4 solution washed with water (70 cc), dried, and evaporated to give the amine 117 as a pale oil (2.2 g, 94%). A hydrochloride derivative was made in the normal manner (dry HCl and methylene chloride) and this crystallised from methylene chloride:X4 (X2) as small regular colourless plates which were hygroscopic. A sample was dried under oil pump vacuum before analysis:

mp (HCl salt) 208-210°, sublimes;

ir (nujol, HCl salt) 2560 and 2500 ($\overset{+}{N}H\overset{-}{Cl}$), 1660 (C=C), 1380 and 1370 (t-butyl), 920, 845 cm^{-1} (=CH);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.8 (m, $N(CH_2\underline{CH_2})_2$, amongst other resonances), 2.4 (m, 4H, $N(\underline{CH_2}CH_2)_2$), 2.9 (s, 2H, $NCH_2C=$), 5.6 (m, 1H, C=CH);

nmr ($CDCl_3$, HCl salt) δ0.9 (s, 9H, t-butyl), 2.2 (m, $\overset{+}{N}(CH_2\underline{CH_2})_2$, amongst other resonances), 3.2 (m, 4H, $\overset{+}{N}(\underline{CH_2}CH_2)_2$), 3.5 (s, 2H, $\overset{+}{N}\underline{CH_2}C=$), 5.9 (m, 1H, C=CH);

Anal. calcd for $C_{15}H_{28}NCl$: C, 69.9; H, 10.95; N, 5.4. Found: C, 69.5; H, 11.0; N, 4.9.

N-(4-t-Butylcyclohexen-1-yl)methyl-N-cyanomethylpyrrolidinium chloride 118

Chloracetonitrile (473 mg, 6.3 mmol) was added to the allylic-amine 117 (1.38 g, 6.25 mmol) in DMSO (18 cc), under nitrogen, and the reaction mixture stirred well for 18 hr at 45°. Examination of the solution by nmr showed:
δ0.9 (s, 9H, t-butyl), 4.2 (s, 2H, $C{=}CCH_2\overset{+}{N}$), 5.1 (s, 2H, $\overset{+}{N}CH_2CN$), 6.2 (m, 1H, C=CH).

Preliminary experiments revealed that lower temperature, and using THF as a co-solvent, retarded the rate of salt formation.

N-cyano-(2-methylene-5-t-butylcyclohexan-1-yl)methylpyrrolidines 120

The solution of salt 118 (6.25 mmol) was diluted with dry THF (90 cc), cooled to -10°, and solid potassium t-butoxide (885 mg, 7.9 mmol) added over 3 min, with stirring, under nitrogen. After 2 hr, the reaction mixture was poured onto X4 (50 cc), washed with brine (50 x 2 cc), water (50 x 2 cc), dried, and evaporated to expose a mixture of rearranged nitriles 120 (1.58 g, 92%) as a dark oil which was hydrolysed immediately:
ir (film) 3050 (=CH), 2200 and 2160 (wk, $C{\equiv}N$), 1645 (C=C), 1395 and 1370 (t-butyl), 900 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (2s, 9H, t-butyl), 1.9 (m, $N(CH_2\underline{CH_2})_2$, amongst other resonances), 2.6 (m, $N(\underline{CH_2}CH_2)_2$, amongst other resonances), 3.9 (m, 1H, HCCN, diastereomeric), 4.8 (m, 2H, $C=CH_2$);

4-t-Butylmethylenecyclohexane-2-carboxylic aldehyde, cis 122 and trans 123, and 4-t-Butyl-1-methylcyclohex-1-ene-2-carboxylic aldehyde 121

A solution of pyrrolidinylnitriles (see above) (1.58 g, 5.77 mmol) in THF (24 cc) was treated with a warm solution of oxalic acid (24 cc, 30% W/V). The mixture was boiled for 5 min, cooled, extracted with X4 (2 x 40 cc), then the whole extract washed with brine (2 x 60 cc), water to neutrality, dried, and concentrated to give an oily mixture of aldehydes (1.03 g, 99%, 91% from allylic amine 117):

ir (film) 3050 ($=CH_2$), 2700 (CHO), 1720 (st, HC=O), 1665 (m, conj. HC=O), 1640 (C=C), 1400 and 1370 (t-butyl), 900 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (2s, 9H, t-butyl), 3.2 (m, 0.875H, C=CC<u>H</u>CHO), 4.6 (m, 0.375H, C=CH, syn to cis-CHO), 4.9 (m, 1.375H, $C=CH_2$ of trans-CHO and, C=CH anti to cis-CHO), 9.62 (s, 0.50H, trans-CHO), 9.78 (d, J=3Hz, 0.375H, cis-CHO), 10.12 (s, 0.125H, conj-CHO);

i.e. ratio aldehydes 121:122:123 = 1:3:4; the same ratio was obtained after 15 min and 30 min hydrolyses;

G.C. FFAP (140°) 06/07, 12/05, and 13/23 (broad peaks).

The mixture of aldehydes (above) was stirred in methanol (80 cc) containing KOH (200 mg, 3.50 mmol) for 4 hr under nitrogen at room temperature. The solution was diluted with water (80 cc) then extracted with X4:ether (4:1, 3 x 50 cc). The conjugated aldehyde 121 was isolated from the total extract, as an oil, in the normal way (1.02 g, 99%) and showed:

mp SCZ, 204-207°, decomposes:

ir (film) 2710 (CHO), 1720 (v.wk, unconj. HC=O), 1665 (conj. HC=O), 1640 (C=C), 1400 and 1370 (t-butyl), 1220, 760 cm^{-1};

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 2.2 (s, 3H, CH_3C=CCHO), 10.2 (s, 1H, CHO);

Mass spectrum (70eV) m/e 180 (M^+, $C_{12}H_{20}O$ requires M^+ 180) (100);

G.C. FFAP (140°) 13/22.

Anal. calcd for $C_{13}H_{23}N_3O$: C, 65.8; H, 9.8; N, 17.7. Found: C, 66.1; H, 10.1; N, 17.4.

Execution of Scheme 19

4-t-Butyl-2-hydroxymethyl-1-methylcyclohex-1-ene 124

The aldehyde 121 (700 mg, 3.9 mmol) in ether (10 cc) was added dropwise to ether (40 cc), containing LAH (148 mg, 3.9 mmol) and stirred under nitrogen at -10°. After 45 min water was added cautiously to turn the grey precipitate white. Ether was decanted, the precipitate triturated with X4 (2 x 20 cc), and the combined X4:ether washed with water to neutrality, dried, and evaporated to a pale viscous oil (680 mg, 96%). Chromatography on neutral alumina (20 g in X4) and sequential elution with X4:ether (9:1), (4:1), (7:3) gave a colourless viscous alcohol 124 (670 mg, 95%). A sample was distilled before analysis:

bp 80°, 0.05 mm;

ir (film) 3300 (OH), 1395 and 1370 (t-butyl), 1240 (OH), 1000 cm^{-1} (C-O);

nmr (CCl_4) δ0.9 (s, 9H, t-butyl), 1.3 (e, 3H, HC4 and H_2C5), 1.6 (s, 3H, $C{=}CCH_3$), 2.0 (e, 4H, allylic H_2C3 and H_2C6), 2.6 (e, 1H, exch., OH), 4.0 (t, J_g=12Hz AA' system, 2H, CH_2OH);

Mass spectrum (70eV) m/e 182 (M^+, $C_{12}H_{22}O$ requires M^+ 182) (13), 57 (100);

G.C. FFAP (160°) 10/34;

Anal. calcd for $C_{12}H_{22}O$: C, 79.1; H, 12.2. Found: C, 79.0; H, 12.0.

2-Bromomethyl-4-t-butyl-1-methylcyclohex-1-ene 125

A solution of PBr_3 (135 mg, 0.5 mmol) in dry ether (1.5 cc) was added over 20 min to a stirred solution of allylic alcohol 124 (182 mg, 1.0 mmol) in dry ether (2.5 cc), containing pyridine (59 mg, 0.5 mmol), at -10° under nitrogen. After a further 45 min, sufficient sodium bicarbonate solution (sat.) was added to destroy the excessive PBr_3. X4 (10 cc) was then added and the mixture extracted with water to neutrality, dried, and concentrated to reveal the bromide 125 as a pale oil (202 mg, 82%). This material was sufficiently pure (nmr anal.) for immediate use:
ir (film) 1660 (C=C), 1395 and 1370 (t-butyl), 1200 cm^{-1} (2ν, C-Br);
nmr (CCl_4) δ0.9 (s, 9H, t-butyl), 1.3 (e, 3H, HC4 and H_2C5), 1.7 (s, 3H, $C=CCH_3$), 2.0 (e, 4H, allylic H_2C3 and H_2C6), 3.9 (2d, J_g=9Hz, AB system 22Hz between outer peaks, 2H, CH_2Br);
Mass spectrum (70eV) m/e 224, 226 (M^+, $C_{12}H_{21}Br$ requires M^+ 224, 226) (2), 164 (M^+-HBr), 193 (100).

N-(5-t-Butyl-2-methylcyclohexen-1-yl)methyl-N-cyanomethylpyrrolidinium bromide 126

NCMP (90 mg, 0.88 mmol) in DMSO (2 cc) was added to the allylic-bromide 125 (200 mg, 0.82 mmol) stirred at 19°. Analysis

of the solution by nmr after 15 min indicated virtually complete salt 126 formation. For convenience, the reaction mixture was stirred for 18 hr:

nmr (DMSO) δ0.9 (s, 9H, t-butyl), 1.9 (s, 3H, $C{=}CCH_3$), 4.4 (2d, J_g=14Hz, AB system, 40Hz between outer peaks, 2H, $C{=}CCH_2\overset{+}{N}$), 5.1 (s, 2H, $\overset{+}{N}CH_2CN$).

N-Cyano-(cis and trans-4-t-butyl-2-methylene-1-methylcyclohexan-1-yl)methylpyrrolidines 128

The salt 126 (0.82 mmol) stirred in DMSO (2 cc) was diluted with dry THF (10 cc), cooled to -10° (ice-salt), then treated with potassium t-butoxide (126 mg, 1.05 mmol). After 3.5 hr, X4 (40 cc) was added, and the mixture washed with brine (3 x 30 cc), water (4 x 20 cc), dried, and evaporated to furnish the mixture of pyrrolidines 128 as a pale oil (212 mg, 94%) which was hydrolysed immediately:

ir 3050 ($=CH_2$), 2220 (wk, $C{\equiv}N$), 1640 (C=C), 1400 and 1370 (t-butyl), 900 and 890 cm^{-1} ($=CH_2$);

nmr (CCl_4) δ0.9 (s, 9H, t-butyl), 1.2 (2s, 3H, CH_3), 1.8 (e, $N(CH_2\underline{CH_2})_2$ amongst other resonances), 2.7 (e, 4H, $N(\underline{CH_2}CH_2)_2$), 4.0 (m, 1H, HCCN, diastereomeric), 4.8 (m, 2H, $C{=}CH_2$);

Mass spectrum (70eV) m/e 274 (M^+, $C_{18}H_{30}N_2$ requires M^+ 274) (1), 109 ($HCCNN^+(CH_2CH_2)_2$) (100).

cis-4-t-Butyl-1-methyl-2-methylenecyclohexane-1-carboxylic aldehyde 129 and trans-4-t-butyl-1-methyl-2-methylenecyclohexane-1-carboxylic aldehyde 130

The mixture of pyrrolidinylnitriles 128 (210 mg, 0.77 mmol) was dissolved in THF (8 cc), a warm solution of oxalic acid added (8 cc, 30% W/V), and the mixture heated under reflux. After 15 min, the cooled reaction mixture was diluted with X4 (30 cc) then washed with brine (2 x 20 cc), water (2 x 20 cc), dried, and concentrated to yield a pale oily mixture of aldehydes 129 and 130 (146 mg, 98%) whose proportions were determined by spectral and G.C. analysis:

ir (film) 3050 ($=CH_2$), 2675 (HCO), 1720 (C=O), 1640 (C=C), 1395 and 1370 (t-butyl), 900 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.13 (s, 2.4H, cis-$CHOCCH_3$) 1.17 (s, 0.6H, trans-$CHOCCH_3$), 4.4 (broad s, 0.2H, C=CH, syn to trans-CHO), 4.9 and 5.1 (2m, 1.8H, $C=CH_2$ of cis-CHO and C=CH, anti to trans-CHO), 9.35 (s, 0.8H, cis-CHO), 9.57 (s, 0.2H, trans-CHO); authentic aldehydes (see below) show in particular δ1.13, cis-$CHOCCH_3$; 1.17, trans-$CHOCCH_3$ and 9.35, cis-CHO; 9.57, trans-CHO; thus, aldehyde ratio 129:130=4:1;

G.C. FFAP (130°) 07/03 (80%, spiked with authentic cis-aldehyde 129), 07/53 (20%, spiked with authentic trans-aldehyde 130).

Preparation of authentic cis-aldehyde 129 via the corresponding allylic-alcohol 132

cis-4-t-Butyl-1-methyl-2-methylenecyclohexane-1-carboxylic acid methyl ester 131 containing ∿12% (nmr, G.C. anal.) trans-ester for reference purposes (100 mg, 0.45 mmol),[189] in ether (5 cc), was added to LAH (21.6 mg, 0.45 mmol) in ether (1 cc) at 0°. The mixture was stirred at 0° for 2 hr, then water added cautiously to turn the grey precipitate white. Ether was decanted and the precipitate washed with X4 (2 x 15 cc). The ether:X4 fractions were combined, washed with water (2 x 20 cc), dried, and concentrated to reveal the cis-carbinol 132 (predominantly) as a viscous liquid (87 mg, quant.) which was oxidised immediately:
ir (film) 3350 (OH), 3050 (=CH_2), 1635 (C=C), 1395 and 1370 (t-butyl), 1050 and 1030 (C-O), 900 and 880 cm^{-1} (=CH_2);
nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.1 (s, 3H, CH_3), 3.3 and 3.7 (2d, both J_g=10Hz, AB system, 2H, CH_2OH), 4.8 and 5.0 (2m, 2H, $C=CH_2$);
Mass spectrum (70eV) m/e 196 (M^+, $C_{13}H_{24}O$ requires M^+ 196)(3), 166 (M^+-H_2CO, M* 141 retrograde Prins reaction) (18), 69 (100).

The alcohol 132 (87 mg, 0.45 mmol) was stirred with modified Collins' reagent[190] (9 mmol) for 18 hr. Ether (30 cc) was added and the mixture filtered (celite). The filtrate was diluted with X4 (10 cc), washed with water until colourless, dried, and concentrated to reveal an oil (84 mg, 99%). Chromatography on Sorbsil (5 g, in X4), eluting with X4:ether (49:1), gave the cis-aldehyde 129, together with the marker (~12%, nmr, G.C. anal.) trans-aldehyde 130 (72 mg, 85%). This material, which was used to authenticate the aldehydes 129 and 130 derived through the rearrangement sequence above, showed:

ir (film) 3050 ($=CH_2$), 2675 (HCO), 1720 (C=O), 1640 (C=C), 1395 and 1370 (t-butyl), 900 cm^{-1} ($=CH_2$);

nmr ($CDCl_3$) δ0.9 (s, 9H, t-butyl), 1.13 (s, cis-$CHOCCH_3$) and 1.17 (shoulder, trans-$CHOCCH_3$) (3H over 1.13 and 1.17), 4.4 (broad s, 0.12H, C=CH, syn to trans-CHO), 4.9 and 5.1 (2m, 1.88H, $C=CH_2$ of cis-CHO and C=CH, anti to trans-CHO), 9.35 (s, 0.88H, cis-CHO), 9.57 (s, 0.12H, trans-CHO);

G.C. FFAP (130°) 07/04 (88%, cis-CHO), 07/54 (12%, trans-CHO).

Ylide rearrangement with an aromatic substrate

Execution of Scheme 21

N-Benzyl-N-cyanomethylpyrrolidinium bromide 136

Benzylbromide (684 mg, 4 mmol) was added dropwise to NCMP

(440 mg, 4 mmol), stirred, under nitrogen, in cooled (water bath) DMSO (6 cc) and the stirring continued, conveniently, for 17 hr at room temperature. An accompanying reaction (0.05 scale) with DMSO-d6 (0.6 cc) was followed by nmr spectroscopy; appropriate integration showed ∿70% salt 136 after 5 min and ∿90% after 20 min: δ2.2 (m, 4H, $\overset{+}{N}(CH_2\underline{CH}_2)_2$), 3.8 (m, 4H, $\overset{+}{N}(\underline{CH}_2CH_2)_2$), 4.9 (s, 2H) and 5.1 (s, 2H) ($\overset{+}{N}CH_2CN$ and $ArCH_2\overset{+}{N}$), 7.6 (m, 5H, Ar).

Rearrangement and subsequent hydrolysis

o-Tolualdehyde 140 and phenylacetaldehyde 142

The salt 136 (4 mmol), stirred in DMSO (6 cc), was diluted with dry THF (30 cc), the solution cooled to 0°, then solid potassium t-butoxide (616 mg, 5.12 mmol) added. After 3 hr stirring at room temperature, X4 (50 cc) was added and the mixture washed with brine (2 x 20 cc), water (2 x 20 cc), dried, and evaporated to a pale oil (732 mg, 92%); a portion was hydrolysed immediately. Initially, an analogous reaction run between -10° and -5° for 1 hr gave, after the standard work-up, rearranged nitriles 139 and 141 in reduced yield (100 mg, 12.5%): nmr ($CDCl_3$) δ1.8 (m, 4H, $N(CH_2\underline{CH}_2)_2$), 2.4 (s, 2.7H, $ArCH_3$), 2.6 (m, 4H, $N(\underline{CH}_2CH_2)_2$), 3.4 (t, 0.1H, $CH_2\underline{CH}CN$), 5.1 (s, 0.9H, $Ar\underline{CH}CN$), 7.3 (m, Ar).

The mixture of pyrrolidinylnitriles 139 and 141 (see above) (300 mg, 1.5 mmol) was dissolved in THF (6 cc), treated with a

warm solution of oxalic acid (6 cc, 30% W/V), and the mixture heated under reflux for 15 min. The cooled mixture was poured onto X4 (50 cc) and washed with brine (2 x 30 cc), water (2 x 30 cc), dried, and reduced under vacuum to a colourless oil (180 mg, quant.):

ir (film) 2700 (HCO), 1720 (wk, $CH_2HC=O$), 1690 (st, ArHC=O), 1600, 1210, 1195, 870, 840, 750 cm^{-1} (Ar);

nmr ($CDCl_3$) δ2.6 (s, 2.7H, $ArCH_3$), 3.6 (d, J=2.5Hz, 0.2H, $C\underline{H}_2CHO$), 7.3 (m, Ar), 9.8 (t, J=2.5Hz, 0.1H, $CH_2C\underline{H}O$), 10.3 (s, 0.9H, $ArC\underline{H}O$);

G.C. FFAP (105°) 09/30 (∿90%, spiked with o-tolualdehyde), 10/07 (∿10%, spiked with phenylacetaldehyde), peaks not completely resolved.

o-Toluic-D-aldehyde

A solution of N-benzyl-N-cyanomethylpyrrolidinium bromide 136 (0.2 mmol) in DMSO-d6 (0.6 cc) (see above) was frozen (ice-salt) then solid potassium t-butoxide added (30.8 mg, 0.256 mmol). The DMSO was thawed quickly (water bath) and the mixture stirred vigorously, then analysed by nmr spectroscopy:

After 5 min, δ1.7 (m, 4H, $N(CH_2C\underline{H}_2)_2$), 2.4 (s, ∿3H, $ArC\underline{H}_3$), 2.5 (m, $N(C\underline{H}_2CH_2)$, masked by DMSO), 5.5 (s, 0.1H, $ArC\underline{H}CN$, exchanging), 7.3 (m, ∿4H, Ar); After 30 min, δ1.7 (m, 4H), 2.4 (s, ∿3H, no resonances at 5.5, 7.3 (m, ∿4H).

The reaction mixture was poured onto D_2O (10 cc), extracted with X4 (2 x 10 cc), then the total extract washed with D_2O (2 x 10 cc), dried, and evaporated to a pale oil (39 mg, 97%), which was hydrolysed immediately.

nmr ($CDCl_3$) δ1.8 (m, 4H, $N(CH_2\underline{CH_2})_2$), 2.4 (s, ∿3H, $Ar\underline{CH_3}$), 2.6 (m, 4H, $N(\underline{CH_2}CH_2)_2$, 7.3 (m, ∿4H, Ar).

The α-D-nitrile (39 mg, 0.195 mmol) was heated under reflux in a mixture of THF (1 cc) and oxalic acid (1 cc, 30% W/V, D_2O) for 15 min. The cooled reaction mixture was diluted with X4 (4 cc), washed with water to neutrality, then dried, and concentrated to afford mainly o-toluic-D-aldehyde 140 (23 mg, 98%):

ir (film) 2050 (DCO), 1675 cm^{-1} (ArDC=O);

nmr ($CDCl_3$) devoid of resonances at δ3.6 (enolisation on work-up) and 10.3, c/f non-deuterated products above;

G.C. FFAP (105°) 09/29 (spiked with o-tolualdehyde), 10/04 (part of tail, spiked with phenylacetaldehyde).

APPENDIX

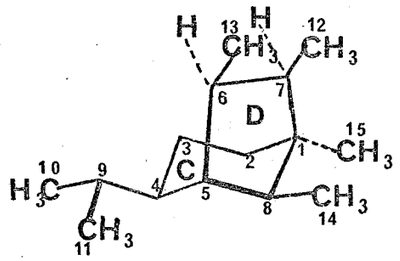
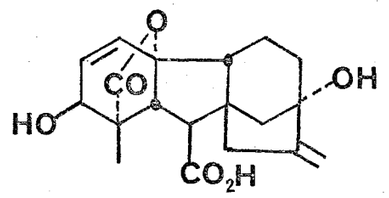


DIAGRAM 1



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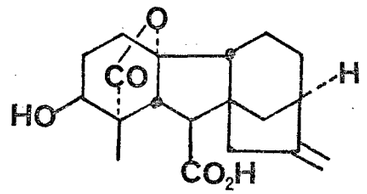

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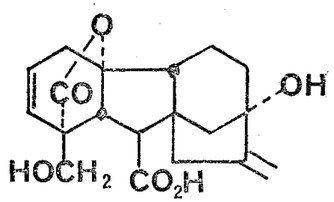

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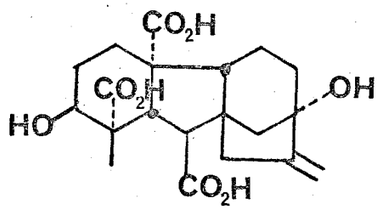

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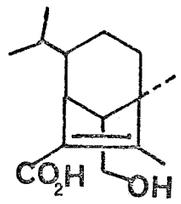

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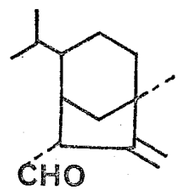

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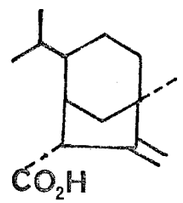

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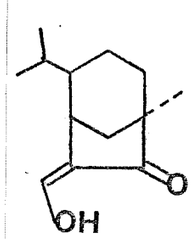

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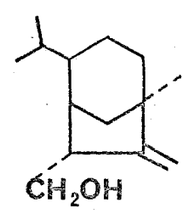

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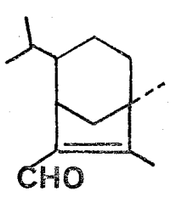

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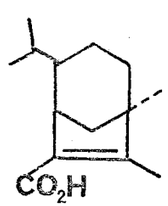

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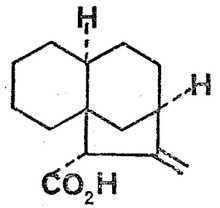

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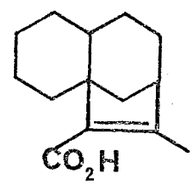

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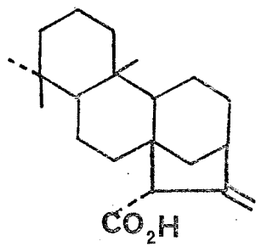

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