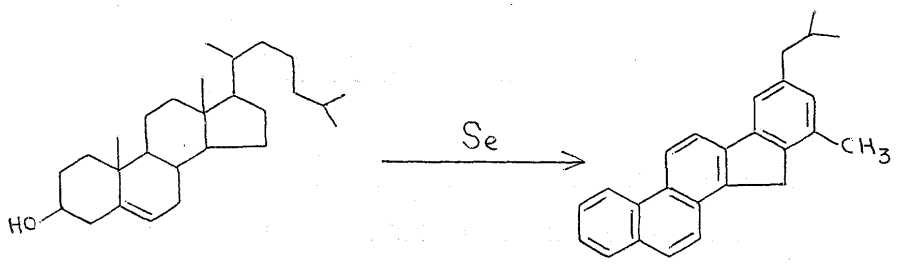
S Y N O P S I S

Part I: Synthesis of 8-Isobutyl-10-methyl-11H-indeno [2,1-a] phenanthrene, (Second Diels Hydrocarbon) a Minor Dehydrogenation Product of Cholesterol.

Dehydrogenation of cholesterol I afforded along with 3'-methyl-1,2-cyclopentenophenanthrene (commonly known as Diels hydrocarbon), a higher hydrocarbon, $C_{26}H_{24}$ as a minor product.[1] Several structures were suggested for this second Diels hydrocarbon but none proved to be correct. In 1977, the structure II was proposed from our laboratory[2]



I II

based mainly on ^1H n.m.r. spectral data and also from mechanistic ground. Recently, Rao et al[3] reported the synthesis of 11-oxo-derivative of an isomeric hydrocarbon

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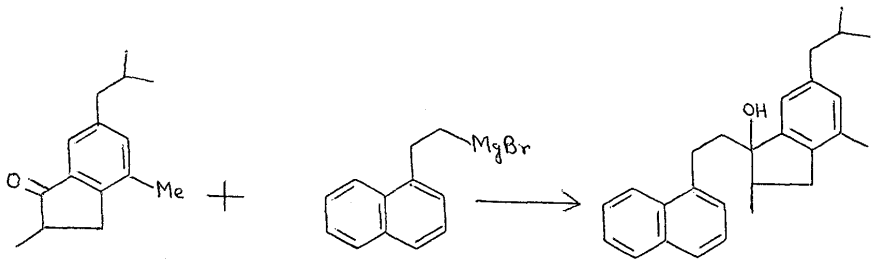
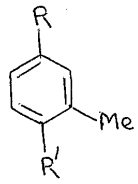
1. L. F. Fieser and M. Fieser, 'Natural Products Related to Phenanthrene', 3rd Edn., Reinhold Publishing Corporation, New York, 1949, p. 154.
2. D. Nasipuri, P. K. Bhattacharya, and D. N. Roy, J.C.S. Perkin I, 1977, 1814.
3. A. Rao, K. Chakravorty, and R. R. Rao, Indian J. Chem., 1978, 16B, 381.

(7-isobutyl-9-methyl-11H-indenophenanthrene) which was supposedly identical with that derived from the second Diels hydrocarbon in contradiction to one of our previous observation.[4] The present synthesis of the compound II now unequivocally proves the correctness of our structural assignment. The synthetic steps are as follows:

The key intermediate in the synthesis was 2,4-dimethyl-6-isobutylindan-1-one III which on condensation



III IV



V

a : R = NH_2, R' = Br

b : R = CN, R' = Br

c : R = $COCHMe_2$, R' = Br

d : R = CH_2CHMe_2, R' = Br

e : R = $COCHMe_2$, R' = OH

f : R = CH_2CHMe_2, R' = CHO

g : R = CH_2CHMe_2, R' = CH_2Br

h : R = CH_2CHMe_2, R' = $CH_2CHMeCO_2H$

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4. D. Nasipuri, J. Chem. Soc., 1961, 4230.

with 2-(1-naphthyl)ethylmagnesium bromide afforded the alcohol IV. The latter on cyclisation with polyphosphoric acid and the product on dehydrogenation with selenium gave 8-isobutyl-10-methyl-11H-indeno[2,1-a]phenanthrene II identical in all respect (i.r., n.m.r. and u.v.) with the second Diels hydrocarbon from cholesterol.

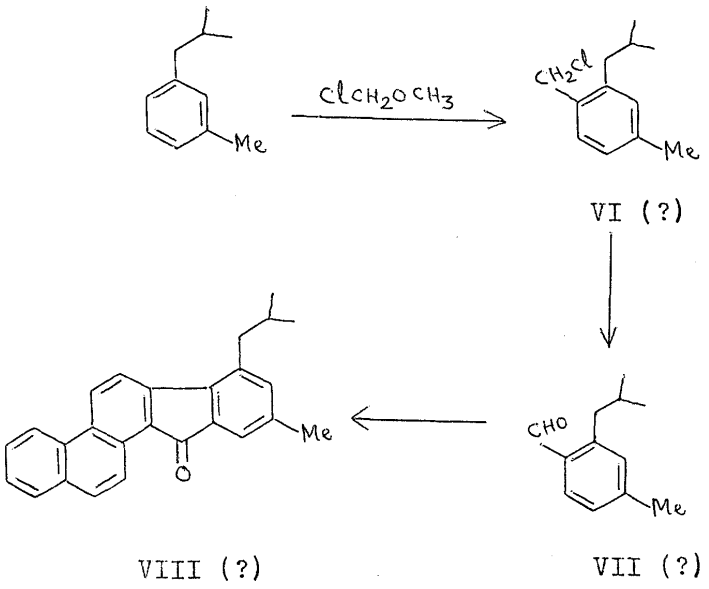
To achieve an unambiguous synthesis of the indanone III, m-acetotoluidide was brominated and hydrolysed to 4-bromo-3-methylaniline Va which on Sandmeyer reaction with cuprous cyanide afforded 4-bromo-3-methylbenzonitrile Vb contaminated with a little of 2,4-dibromo-5-methylbenzonitrile. The latter was readily removed by distillation and crystallisation. The bromonitrile Vb on treatment with isopropylmagnesium bromide furnished 4-bromo-3-methyl-1-phenyl isopropyl ketone Vc easily convertible into 4-isobutyl-2-methyl-1-bromobenzene Vd by Clemmensen reduction. Since this was a key compound in the synthesis, its structure was confirmed by an alternative synthesis wherein o-cresol was acylated with isobutyryl chloride, the resultant ketone Ve reduced (Clemmensen), and the phenolic OH replaced by Br using triphenylphosphine and bromine. The yield in the last reaction was very poor (15%); nevertheless, its identity with the bromide Vd described above (superimposable i.r. and n.m.r. spectra) dispelled any doubt regarding the orientation of the bromine atom in compound Vd. Moreover, 4-bromo-3-methylbenzonitrile Vb and 2,4-dibromo-5-methylbenzonitrile were hydrolysed into the known

4-bromo-3-methylbenzoic acid and 2,4-dibromo-5-methylbenzoic acid respectively, prepared by entirely different methods.

The structure of the bromocompound Vd being thus assured, it was converted into 4-isobutyl-2-methylbenzaldehyde Vf through Grignard reaction with ethyl orthoformate and thence into the corresponding benzyl alcohol and benzyl bromide Vg. Condensation of the latter with diethyl malonate, followed by methylation, hydrolysis, and decarboxylation afforded 3-(4-isobutyl-2-methyl-1-phenyl)-2-methylpropionic acid Vh. Cyclisation of this with polyphosphoric acid, or of the derived acid chloride with stannic chloride furnished 2,4-dimethyl-6-isobutylindan-1-one III. The structure of the ketone was further confirmed by its ^{1}H n.m.r. spectrum which showed the two aromatic protons as two singlets at δ 7.33 and 7.13 (7-H and 5-H respectively). The synthesis of the second Diels hydrocarbon was thus effected unambiguously. The corresponding 11-oxo-derivative and trinitrofluorenone complex of the hydrocarbon were also prepared and compared with those derived from natural hydrocarbon.

4-Isobutyl-2-methylbenzaldehyde Vf was found to resemble a compound described by Rao *et al*[3] as 2-isobutyl-4-methylbenzaldehyde VII (identical semicarbazone and dinitrophenylhydrazone), and used for the synthesis of an 11-oxoindenophenanthrene VIII[4] supposedly identical with the ketone derived from natural Diels hydrocarbon. The

structure Vf for this aldehyde seems more likely from its method of preparation, which consists of a Friedel-Crafts reaction of 3-isobutyltoluene with chloromethyl ether and Sommelet reaction of the resultant benzyl chloride VI. The chloromethyl group is expected to take up the position next to methyl rather than next to isobutyl in the benzene ring, which means that these two groups are interchanged in all subsequent products described by these workers who, incidentally, have withdrawn their claim for



the synthesis of Diels hydrocarbon derivative.[5]

The chapter on this particular aspect of steroid chemistry is thus satisfactorily closed.

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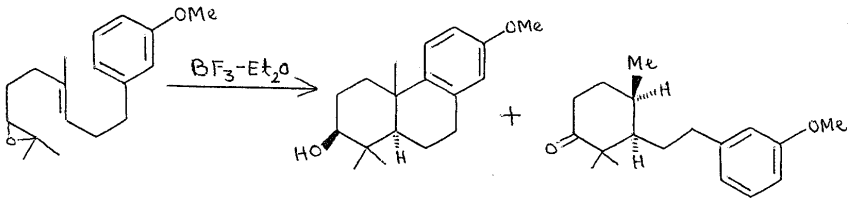
5. A. Rao, K. Chakravorty, and R. R. Rao, Indian J. Chem., 1978, 16B, 946.

Part II : Biogenetic-type Cyclisations of Epoxyolefins and Related Compounds.

Appropriate polyolefins with a terminal epoxide group often undergo concerted biogenetic-type cyclisation under acid catalysis to polycyclic compounds of predictable stereochemistry.[6] As a part of a programme of biomimetic synthesis of tricyclic diterpenes[7] and also



IX X XI

some furanosesquiterpenes[8], (6E)-2,3-epoxy-9-m-methoxyphenyl-2,6-dimethylnon-6-ene IX has previously been cyclised in our laboratory[9] to synthetically useful (±)-13-methoxy-

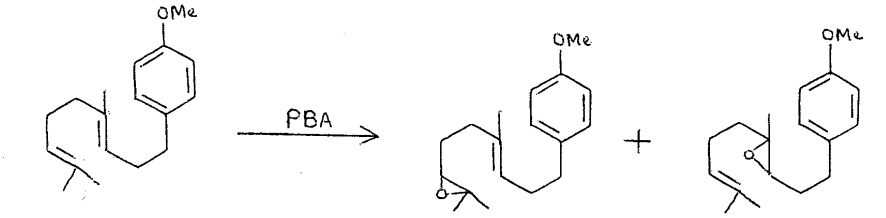
6. J. W. ApSimon, 'Elucidation of Organic Structures by Physical and Chemical Methods', Part III, Wiley-Interscience, New York, 1972, 351; E. E. van Tamelen, Acc. Chem. Res. 1968, 1, 111.

7. D. Nasipuri, Chem. and Ind., 1957, 425.

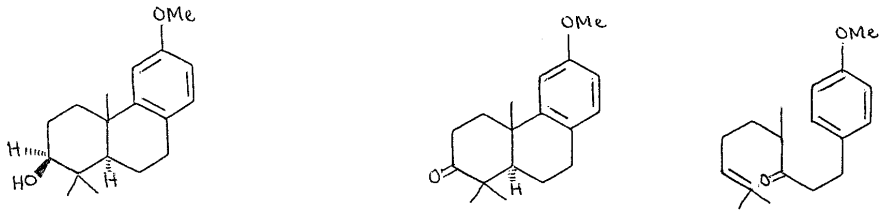
8. D. Nasipuri and G. Das, J. C. S. Perkin I, 1979, 2776.

9. D. Nasipuri and S. R. Raychaudhuri, J. C. S. Perkin I, 1975, 262.

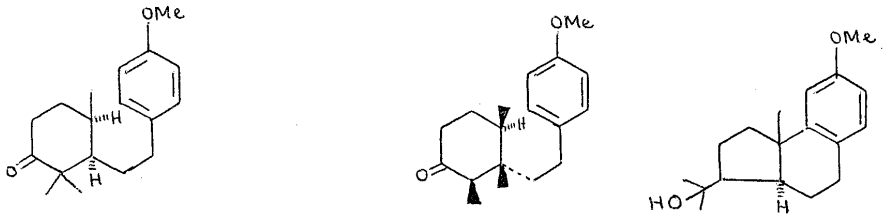
podocarpa-8,11,13-triene-3β-ol X with the cyclohexanone derivative XI as a rearranged minor product. In the present work, a detailed study of the cyclisation reaction using (6E)-2,3-epoxy-9-p-methoxyphenyl-2,6-dimethylnon-6-ene XIII has been made, a new biomimetic synthesis of (±)-hinokiol methyl ether XXIII has been achieved, and a di-epoxide has been cyclised to a novel oxygen heterocycle.



XII XIII XIV



XV XVI XVII



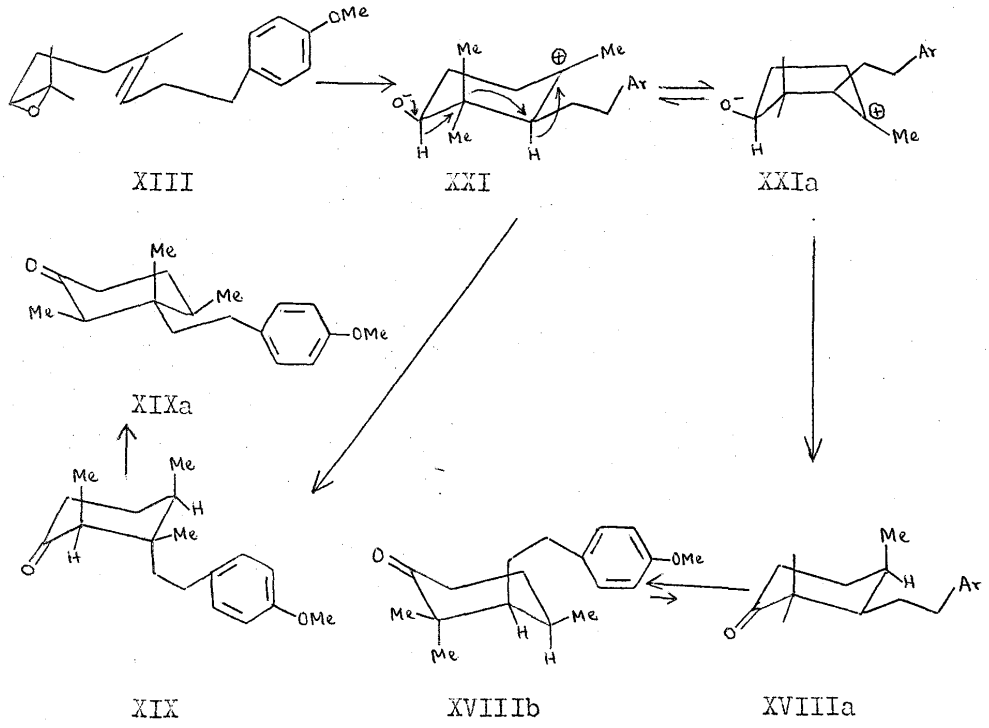
XVIII XIX XX

(6E)-9-p-methoxyphenyl-2,6-dimethylnona-2,6-diene XII easily accessible by coupling p-methoxybenzylmagnesium

chloride with geranyl chloride on monoepoxidation with perbenzoic acid afforded mainly the 2,3-epoxy-derivative XIII contaminated with 10-15% of the isomeric 6,7-epoxide XIV which could not be separated. The mixture was cyclised with boron trifluoride etherate to give a product from which three ketones and two alcohols were isolated by column chromatography. The first ketone turned out to be 7-oxo-9-p-methoxyphenyl-2,6-dimethylnon-2-ene XVII (i.r., n.m.r. and mass spectra), presumably formed by a facile intramolecular hydride transfer in the 6,7-epoxide XIV. The second one was isolated in 20% yield and identified as 2,2,4-trimethyl-3-p-methoxyphenethylcyclohexanone XVIII from spectral data (i.r., n.m.r. and mass) which was conceivably formed by an intramolecular 1,4-hydride shift[9] in the intermediate cation XXI *via* its boat conformation XXIa leading originally to 2,4-syn-axial dimethylcyclohexanone XVIIIa which flips to the more stable 2,4-diequatorial conformer XVIIIb. The *cis* configuration follows from the mechanism; no experimental proof could be provided.

The third ketone, a crystalline solid was proved to be *cis* 2,3,4-trimethyl-3-p-methoxyphenethylcyclohexanone XIX presumably formed by three consecutive 1,2-H,Me shifts in the reactive intermediate XXI, the cationic centre at one end and the negative oxygen (complexed with BF_3) at the other supplying the necessary driving force. The structure of the ketone XIX was established unequivocally by i.r. (1707 cm^{-1}, saturated ketone) and ^1H n.m.r. in which

2-Me appeared as a doublet at δ 1.002(J = 6.3 Hz), 4-Me also as a doublet at 0.975 (J = 6.3 Hz), and 3-Me as a sharp singlet at 0.593. The preferred conformation of the ketone is not as shown in XIX but the inverted one XIXa in which 2,4-dimethyl groups are diequatorial. It may



be observed that the signal due to the axial 3-Me in XIXa appeared at an unusually high field (δ 0.593). This is attributed to '<u>cis</u>-effect' which has previously been observed by Segre and Musher[10] for an axial hydrogen flanked by two equatorial methyls shifting the proton signal upfield to the extent of 0.73 ppm with respect to an axial proton in simple cyclohexane. The axial 3-Me

protons in XIXa similarly flanked by two adjacent equatorial methyls might have undergone analogous but understandably reduced shielding. The stereochemical aspect of the ketone has been discussed.

The first of the two alcoholic components was a liquid and was tentatively given the structure XX because of absence of methine proton (C<u>H</u>OH). The second alcohol, the last to be eluted was the desired (±)-12-methoxypodocarpa-8,11,13-trien-3β-ol XV obtained in 10% yield as a crystalline solid, m.p. 110°. The structure was confirmed by the usual spectral data (i.r., n.m.r. and mass) and also by its quantitative conversion by Jones' oxidation into the ketone XVI, m.p. 70°. The latter was first prepared by Rao and Raman[11] as a gum through a different route. For the first time, the alcohol XV and the ketone XVI were obtained stereochemically homogeneous form.

A typical cyclisation product of the mono-epoxy-olefins afforded, on column chromatography, 25% of deoxygenated (except for OMe) compounds, 15% of the ketone XVII, 20% and 5% respectively of the rearranged ketones XVIII and XIX, 5% of the tertiary alcohol XX, and 10% of 3-oxygenated podocarpatriene derivative XV.

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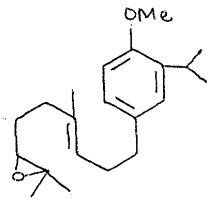
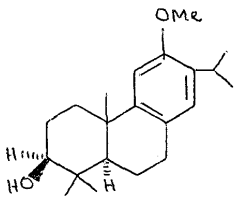
10. A. Segre and J. I. Musher, <u>J. Amer. Chem. Soc.</u>, 1967, <u>89</u>, 706.
11. P. N. Rao and K. Raman, <u>Tetrahedron</u>, 1958, <u>4</u>, 294.

The diene XII was also cyclised with benzoyl peroxide according to the procedure of Julia et al[12] and the product on column chromatography afforded (±)-12-methoxypodocarpa-8,11,13-trien-3β-ol XV in 20-25% yield. The method thus appears to be superior to and simpler than the cyclisation of the expoxyolefins, although it may not work for substrates containing groups susceptible to free radical oxidation.

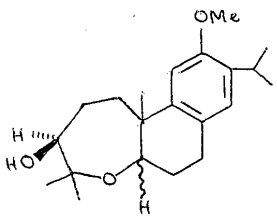
In another sequence of reactions, 4-methoxy-3-isopropylbenzyl chloride was coupled with geranyl chloride and the resultant diene converted into the epoxide XXII



XXII



XXIII



XXIV

and the latter cyclised with boron trifluoride etherate without much purification. Only the alcoholic part was separated by column chromatography from the product which on rechromatography afforded an oil and a solid in 7% and

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12. J. Y. Lallemand, M. Julia, and D. Mansuy, Tetrahedron Letters, 1973, 4461.

5% yields respectively. The oil appeared to be identical with (±)-hinokiol methyl ether XXIII in all respects (i.r., n.m.r. and mass spectra). This is the first biomimetic synthesis of the methylated diterpene; however, in absence of direct comparison with natural specimen[13], the synthesis remains unauthentic.

The second alcohol, m.p. 118° was characterised by the formation of an acetate. The alcohol and the acetate analysed for $C_{21}H_{32}O_3$ and $C_{23}H_{34}O_4$ respectively and had one oxygen atom more than hinokiol methyl ether and its acetate. It was evident that the alcohol was formed by cyclisation of the di-epoxide (see later), present as an impurity in the starting epoxyolefin XXII. Of the various possibilities, the structure XXIV with a seven-membered A-oxa-ring was assigned to it by careful analysis of the fragmentation patterns in the mass spectra of both the alcohol and the acetate.

Cyclisation of acid-catalysed di-epoxide is yet an unknown reaction and may provide interesting polycyclic systems containing oxygen as one of the ring hetero-atom. In order to study the reaction further, (6E)-9-m-methoxyphenyl-2,6-dimethylnona-2,6-diene was converted into the

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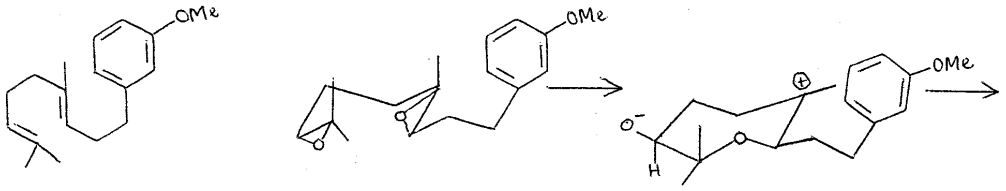
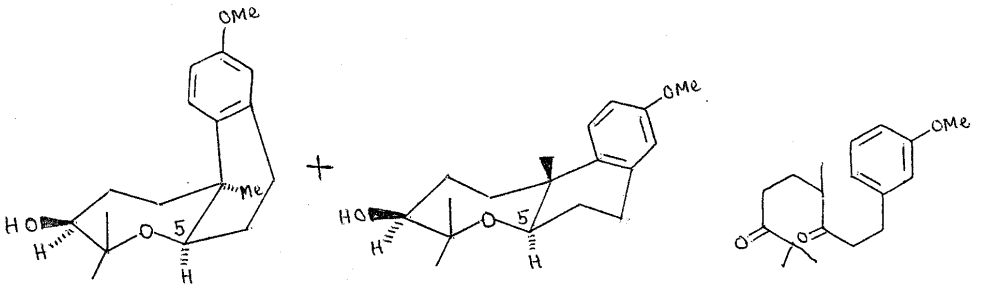
13. Y-L. Chow and H. Erdtman, Acta Chem. Scand., 1962, 16, 1301.

di-epoxide XXVI by treatment with an excess of perbenzoic acid. The n.m.r. spectrum showed complete absence of olefinic proton and the presence of two epoxy-ring protons at δ 2.80 (m). The di-epoxide was cyclised with boron trifluoride etherate as before and the gummy product was submitted to extensive chromatography on silica-gel. Two pure components, a ketone and an alcoholic fraction were isolated in 7 and 50% yields respectively. The ketone was proved to be 9-m-methoxyphenyl-2,6-dimethyl-3,7-dioxononane XXX on the basis of spectral data (i.r., n.m.r. and mass), formed presumably from the di-epoxide by intramolecular hydride transfer.



XXV XXVI XXVII



XXVIII XXIX XXX

The alcoholic fraction was found to be a stereoisomeric

mixture of A-homo-4a-oxa-13-methoxypodocarpa-8,11,13-trien-3β-ol XXVIII and XXIX which could not be separated even on repeated chromatography and remained as a gum. The structure, however, was fully supported by spectral data (i.r., n.m.r. and particularly mass). The mixture of the alcohols was converted into acetates, the ^{1}H n.m.r. spectra of which were more diagnostic showing a full proton peak at δ 4.93 (m) for CHOAc eliminating the possibility of other modes of ring-closure. The 5-H appeared fractionally at δ 4.20 (0.4H, t) and at 3.80 (0.6H, m) and corresponded respectively to trans XXIX and cis XXVIII isomers. Dreiding models of the compounds showed that 5-H in the cis isomer will be less deshielded by aromatic ring current than that in the trans. The cyclisation of the di-epoxide is by no means concerted but takes place in two steps : the central epoxide oxygen first makes a nucleophilic attack on the terminal epoxide (complexed with BF_3) forming a seven-membered oxa-ring and generating a carbocation XXVII which then undergoes cyclisation with the aromatic ring in a non-stereospecific way. It is interesting to note the difference in the cis and trans ratio (60:40) in the present cyclisation and in a similar cyclisation of the diene (as XXV) leading to cis and trans podocarpa-8,11,13-triene in a 30:70 ratio reported earlier from the present laboratory.[14] This may conceivably be due to the absence of any severe steric interaction between axial 4-Me and the phenyl ring in the transition state leading to A-homo-cis isomer XXVIII. This

interaction, on the other hand is very much prominent in the transition state leading to cis podocarpa-8,11,13-trienes. A conformational analysis of the cis and trans podocarpa-8,11,13-trienes has been done by Nasipuri and De Dalal[14] showing greater thermodynamical stability of the cis isomer but the rationale of the analysis may not be strictly valid[15] (see ref. 16).

Part III: Asymmetric Reduction of a Few N,N-Dialkylamino-methyl Phenyl Ketones.

Asymmetric synthesis is one of the most active field of research in which considerable work has been done recently with good deal of success.[17] For some time past, our laboratory is engaged in asymmetric reduction of a

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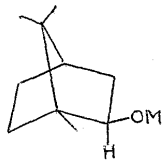
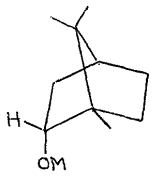
14. D. Nasipuri and I. De Dalal, J. C. S. Perkin I, 1976, 19.
15. R. C. Cambie, B. R. Davis, R. C. Hayward and P. D. Woodgate, Aust. J. Chem., 1975, 28, 631.
16. D. Nasipuri, A. K. Samaddar, and G. Das, Indian J. Chem., 1980, 19B, 727.
17. For a comprehensive review, see J. D. Morrison and H. S. Mosher, 'Asymmetric organic reactions', Prentice-Hall, New Jersey, 1971; for a recent review, see J. W. ApSimon and R. P. Seguin Tetrahedron, 1979, 35, 2797.

variety of ketones with halometal derivatives of naturally occurring chiral alcohols, e.g., (-)-bornan-2-exo-ol (as XXXI), (-)-bornan-2-endo-ol (as XXXII), and (-)-p-menthan-3-ol (as XXXIII). Some of the significant data are shown in Table 1.[18] It may be noted that the extent of asymmetric induction is quite high and the absolute configuration of



XXXI



XXXII

XXXIII

a : M = $AlCl_2$

b : M = MgBr

the preponderant enantiomer is in agreement with the preferred six-membered cyclic transition state.[19]

In view of the fact that many chiral amino-alcohols possess interesting physiological properties and may be

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18. D. Nasipuri and P. K. Bhattacharya, J. C. S. Perkin I, 1977, 576, and earlier papers mentioned therein.

19. D. Nasipuri and P. R. Mukherjee, J. Indian Chem. Soc., 1974, 51, 171.

useful in pharmaceutical industry, we undertook to reduce a few aminoketones with the reagent XXXIa (the most reactive of the group). In an earlier collaborative work with S. K. Konar*, the present author reduced three β-dialkylaminopropiophenones (Mannich bases of acetophenone)

Table 1[a]

Substrate	Reagent	e.e.(%)[b]	Abs.confn.
$PhCOPr^i$	XXXIa	84.0	(R)
$PhCOBu^i$	XXXIa	66.0	(R)
$PhCOCO_2H$	XXXIIa	57.4	(R)
PhCHO	∝-d-XXXIb	64.0	(S)
PhCDO	XXXIIb	64.5	(R)
$PhCOCF_3$	XXXIIa	68.0	(S)
$PhCOCF_3$	XXXIIIa	77.0	(S)

[a] Taken from D. Nasipuri, Golden Jubilee Brochure, Institute of Chemists, 1978, p.45. [b] Enantiomeric excess.

along with three acetylpyridines with the reagent XXXIa. The extent of asymmetric induction (Table 2) ranged from 50-86%. One advantage of the method was that the product

* S. K. Konar, Ph.D. thesis, I.I.T., Kharagpur, 1980.

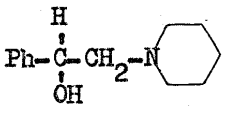
could be easily purified from the mixture by extraction with aqueous mineral acid. In the present work, three more amino-ketones, namely, N,N-dimethylaminomethyl phenyl ketone XXXIV, N-piperidinomethyl phenyl ketone XXXV, and N-morpholinomethyl phenyl ketone XXXVI have been asymmetrically

Table 2

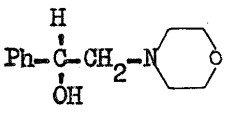
Entry	Amino-ketones	$[\alpha]_D^{25}$ of amino-alcohols	e.e. (%)	Abs. confn.
1	$PhCOCH_2CH_2NMe_2$	$+17.0^\circ$	62	(R)
2	$PhCOCH_2CH_2N$⟨⟩	$+14.66^\circ$	50	(R)
3	$PhCOCH_2CH_2N$⟨O⟩	$+9.80^\circ$	86	(R)
4	$PhCOCH_2NMe_2$ (XXXIV)	$+24.65^\circ$	59	(S)
5	$PhCOCH_2N$⟨⟩ (XXXV)	$+25.5^\circ$	56	-
6	$PhCOCH_2N$⟨O⟩ (XXXVI)	$+30.1^\circ$	65	-

reduced with (-)-bornan-2-exo-yloxyaluminium dichloride XXXIa. The results are given in Table 2 along with those obtained from the homologous ketones (entries 1-3). The reduction was carried out with an excess of the reagent (4-6 moles) at $0^\circ C$. The absolute rotation of the amino-alcohol derived from dimethylaminomethyl phenyl ketone XXXIV is known in the literature. But those of the other

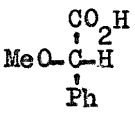
two (from ketones XXXV and XXXVI) are unknown. The enantiomeric purity of the two asymmetrically reduced alcohols, XXXVII and XXXVIII was determined by converting them into a mixture of diastereomeric esters with O-methyl-L-(+)-mandelic acid XXXIX and measuring the relative intensity of



XXXVII



XXXVIII



XXXIX

the two methoxy signals in n.m.r.[20] The amino-alcohol XXXVIII was also studied by ^{1}H n.m.r. using chiral shift reagent*. None of the two alcohols XXXVII and XXXVIII could be completely resolved at our hand using (-)-dibenzoyltartaric acid. Their absolute configurations could not be determined although from analogy, they should have (S)-configuration.

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* By kind courtesy of Professor E. L. Eliel.

20. R. Andrisano, A. S. Angeloni, and S. Mazocchi, Tetrahedron, 1973, 29, 913.