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INFLUENCE OF METHOXY- AND METHYL-AROMATIC SUBSTITUENTS ON STEREOCHEMISTRY OF THE PRODUCTS IN THE ACID-CATALYZED CYCLIZATION OF 2-(2-ARYLETHYL)-1,3,3-TRIMETHYLCYCLOHEXANOLS: STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-NIMBIDIOL AND (±)-NIMBIOL.

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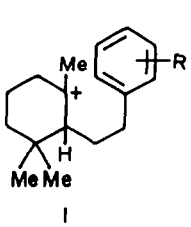
Abstract : The distributions of the trans-and the cis-podocarpatrienes (5c-g)and (6c-g) in the cyclialkylation reaction of the easily accessible cyclohexanols (4c-g) under a mild condition have been investigated. The cyclohexanol precursors having unactivated aromatic ring proceeds with high stereoselectivity leading to the respective trans-products, while the substrates with an electron donating methoxy or a methyl substituent with respect to the site of electrophilic attack result in the corresponding cis-and the trans-product mixtures. Consistent mechanisms for these stereochemical results have been advanced. Based on these results simple syntheses of the modified diterpenes (±)-nimbidiol (7) and (±)-nimbiolmethylether (18) have been realized.

The acid-catalyzed cyclialkylation reaction of 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl cation (1), generated either from the tertiary and the secondary alcohols, viz. 2 and 3 or the related cyclohexene intermediates has been widely used[1-8] for the synthesis of a group of naturally occuring tricarbocyclic ring-C-aromatic diterpenoids having a gem-dimethyl group, and various terpenoid intermediates. Despite the simplicity and converging nature of this method considerable confusion exists regarding the unpredictable stereochemical outcome of the cyclization products[5], which seems to depend upon the nature and position of the electron donating substituent(s) in the aromatic ring in the open chain substrates. From a detailed study Davis and his co-workers[9,10] have recently demonstrated that, under mild condition using a $MeSO_3H$-P_2O_5 mixture as the cyclization reagent, p-methoxyphenylethylcyclohexanols 2a (trans-OH) and 3a, and the corresponding o-methoxy



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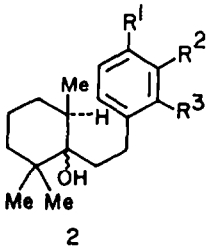
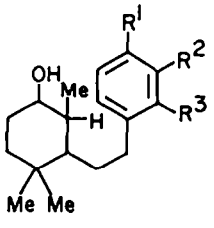


2

a, R^1 = OMe, R^2 = R^3 = H
b, R^1 = R^2 = H, R^3 = OMe
c, R^1 = R^3 = H, R^2 = OMe



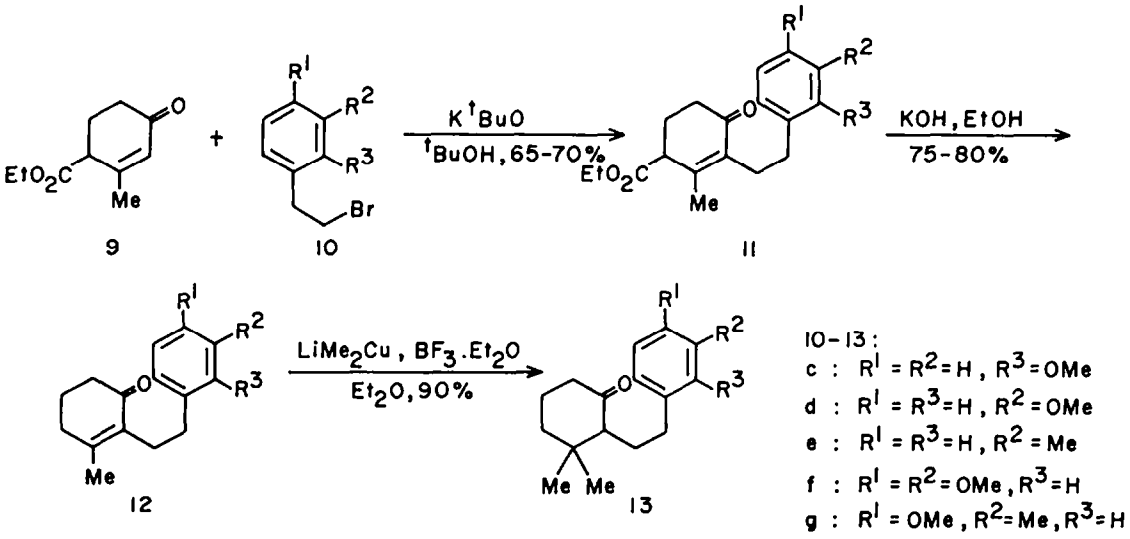
3

isomers (trans-OH) and 3b afford the respective trans-fused podocarpatriene derivatives 5b and 5c in good yields and stereochemical purity. In contrast, the m-methoxyphenylethyl substrates 2c (trans-OH) and 3c under similar condition, led to a mixture of trans-and cis-cyclized products 5d and 6d, where the trans-product predominates along with some other minor products. In our continued interests on the synthesis of tricarbocyclic diterpenoids,[11] we have recently developed[12] a convenient and high yield procedure for the synthesis of tertiary phenylethylcyclohexanols 4a and 4b which on cyclization by the method of Davis[9] gave the respective trans-podocarpanes 5a and 5b in over 95% purity and 93% yield, incorporating less than 1% of the corresponding cis-isomers 6a and 6b. The present investigations were undertaken in order to explore this simple convergent route for the synthesis of the recently reported keto-phenol, nimbidiol (7)[13] and the earlier characterized[14] biogenetically interesting diterpene, nimbiol (8) /isolated from the root bark and the stem bark, respectively, of Azadirachta indica A. Juss. (Indian neam)/ and also to define the influence of the methoxy and methyl substituents in the aromatic ring in phenylethylcyclohexanol precursors 4c-g on the stereoselectivity in the key cyclization step. We report herein our findings, particularly focusing on the utility of this simple cyclialkylation method for the highly stereocontrolled synthesis of natural diterpenoids[15] having trans-A/B ring junction.

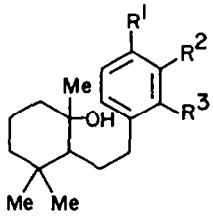
RESULTS AND DISCUSSION

The 2-arylethyl-3,3-dimethylcyclohexanones 13c-g, key intermediates for the cyclohexanols 4c-g, were prepared in over 90% yield by our recently developed procedure[12] involving conjugate addition[16] of a methyl group to the respective cyclohexenones 12c-g with an excess of $LiMe_2Cu$ in Et_2O at -30° to $-25^{\circ}C$ in the presence of $BF_3.Et_2O$. The cyclohexenones 12c-g were obtained in good yields by alkylation[17] of Hagemann's ester (9) with the appropriate phenylethylbromides 10c-g followed by alkaline hydrolytic decarboxylation of the corresponding C-3 alkylated products 11c-g, produced in over 95% purity (Scheme-1). The alcohols 4c-g, prepared by condensation of the ketones 13c-g with MeMgI were cyclized with $MeSO_3H$-P_2O_5

Scheme - 1



according to Axon et al.[9] A part of the crude cyclized product isolated from each of the reactions, was filtered through a short wide column of neutral alumina and subjected to analysis by GC and ^{1}H NMR (200 MHz). Quantitative evaluations of the trans-and the cis-cyclized products are outlined in Table, along with our earlier reported[12] results from the substrates 4a and 4b for comparison. In most case, the major trans-product from each of the cyclization reactions was identified



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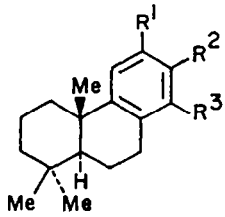

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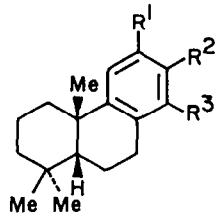


6

4-6: a : $R^1=R^2=R^3=H$
b : R^1=OMe, $R^2=R^3=H$
c : $R^1=R^2=H$, R^3=OMe
d : $R^1=R^3=H$, R^2=OMe
e : $R^1=R^3=H$; R^2=Me
f : $R^1=R^2$=OMe, $R^3=H$
g : R^1=OMe, R^2=Me, $R^3=H$

by GC and ^{1}H NMR comparisons with authentic samples and the minor cis-isomer was characterized specifically by the upfield signal[18] of the C-4α-methyl group (δH 0.3-0.4). The o-methoxyalcohol 4c gave virtually the pure trans-isomer 5c[19] (95% by GC) in which no up-field signal for the cis-isomer 6c was discernible in the ^{1}H NMR spectrum. However, the m-methoxyalcohol 4d produced a mixture of the trans- and the cis-cyclized ethers 5d[2,8,10] and 6d[3,8,20] (∿93%) as determined by

Table : Cyclization of Cyclohexanols (4a-g) with $MeSO_3H$-P_2O_5 : Ratio of trans-and cis-podocarpatrienes.

Entry	Cycloxanols	Products[a,b] trans + cis	Ratio[c] of trans / cis
1	4a	5a + 6a	99 : 1[d]
2	4b	5b + 6b	99 : 1[d]
3	4c	5c + 6c	100 : 0[e]
4	4d	5d + 6d	62 : 38[f]
5	4e	5e + 6e	70 : 30[g]
6	4f	5f + 6f	58 : 42
7	4g	5g + 6g	60 : 40

[a]Crude cyclized products (90-95% yield) after filtration through a short wide column of neutral alumina using petroleum as solvent.

[b]Products containing trans-and cis-isomers, at least 80-95%.

[c]Determined by GC comparisons with authentic trans-samples and integrated signal intensities of clearly separated peaks from ^{1}H NMR spectra in $CDCl_3$ (at 100 or 200 MHz).

[d]Estimated from the high field C-4α-methyl signal at δ 0.35-0.37.

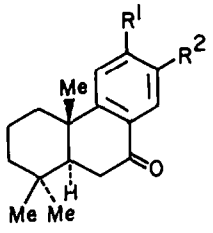
[e]Could not be detected by ^{1}H NMR.

[f]Determined by GC comparisons with authentic cis-and trans-samples.

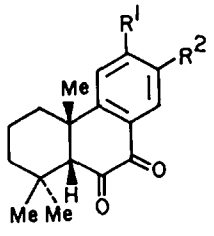
[g]Determined by ^{1}H NMR (200 MHz) only.

comparison with the authentic samples, along with three other very minor components (∿7%) arising[10] from o-cyclizations as well as from the uncyclized olefins as determined from ^{1}H NMR spectrum. Careful chromatography of this mixture on neutral alumina gave the trans-isomer 5d. However, the pure cis-isomer 6d could not be isolated. The m-methyl-alcohol 4e again gave a mixture of trans and cis isomers 5e and 6e accounting for 80% of the total cyclized products (87% yield) as determined

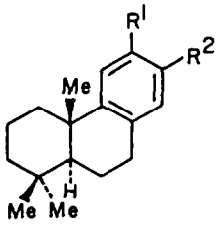
from the GC and ^{1}H NMR spectrum of the mixture (see Experimental); the remaining (20%) material containing eight other components could not be assigned. The benzylic oxidation[21] of this mixture with CrO_3-HOAc by usual method followed by chromatography of the resulting product on neutral alumina afforded the trans-monoketone 14 and the cis-diketone 15. Towards the synthesis of 7, we studied the cyclization of the dimethoxyaromatic substrate 4f. The product (90%) isolated from the reaction indicated the presence of mainly the trans-and the cis-isomers 5f[22] and 6f[22] in a ratio of 58:42, along with some minor products (13%). The oxidation of this mixture with CrO_3-HOAc and chromatographic separation of neutral alumina gave (±)-nimbidiolmethylether (16)[15] and the cis-diketone 17. Similarly, the direct cyclization of the methoxy-methylalcohol 4g gave a mixture of the respective trans-and the cis-cyclized products 5g and 6g which was oxidized with CrO_3-HOAc. Chromatography of the resulting product gave (±)-nimbiclmethylether (18)[23] and (±)-5-epi-6-oxonimbiolmethylether (19).[23f]



7, $R^1 = R^2 = OH$
8, $R^1 = OH, R^2 = Me$
14, $R^1 = H, R^2 = Me$
16, $R^1 = R^2 = OMe$
18, $R^1 = OMe, R^2 = Me$



15, $R^1 = H, R^2 = Me$
17, $R^1 = R^2 = OMe$
19, $R^1 = OMe, R^2 = Me$



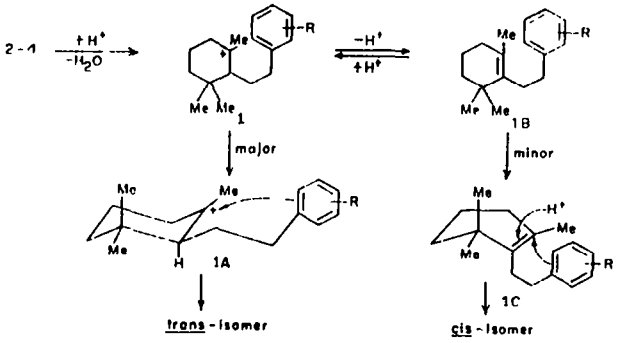
20, $R^1 = OMe, R^2 = COMe$
21, $R^1 = OMe, R^2 = OCOMe$
22, $R^1 = OH, R^2 = H$
23, $R^1 = OH, R^2 = CH_2NMe_2$
24, $R^1 = OH, R^2 = CH_2\overset{+}{N}Me_3I^-$
25, $R^1 = OH, R^2 = Me$

In view of the unfavourable stereochemical results in the direct route for the syntheses of 7 and 8, we developed an alternative highly efficient stereocontrolled route for these natural products based upon the readily available trans-ether 5b, by introduction of the required aromatic substituents. Thus, the acylether 20, prepared in excellent yield[12] from 5b, was subjected to Baeyer-Villiger oxidation with m-chloroperbenzoic acid in boiling 1,2-dichloroethane in the presence of p-toluenesulfonic acid to afford the desired acetate 21 in 90% yield. This was saponified and the crude phenol was methylated to give the dimethoxy compound 5f in excellent yield. Benzylic oxidation of 5f gave the mono-ketone 18 which on demethylation with BBr_3-CH_2Cl_2,[17] gave (±)-nimbidiol (7) in 80% yield. For synthesis of

(±)-nimbiolmethylether (18), the trans-ether 5b was demethylated with BBr_3-CH_2Cl_2 to give 22 in 93% yield. This was converted to the respective dimethylaminomethylphenol 23 in 80% yield by reaction with dimethylamine and formalin following the method of Wenkert et al.[23e] The quaternary methoiodide 24 obtained from 23 was directly subjected to reductive cleacage with Li-NH_3 (1) to afford 25 in 58% overall yield. Methylation of 25 gave the methylether 5g, which on oxidation gave (±)-nimbiolmethylether (18).

Our results (Table) on the stereochemistry of cyclialkylation of the cyclohexanol 4a-g, particularly under mild condition using $MeSO_3H$-P_2O_5 as the reagent, provide with some important generalizations. These results are also consistent and qualitatively comparable with the recent observations by Davis and coworkers[9,10] on the cyclizations of the related methoxyphenylethylcyclohexanols 2 and 3. The cyclohexanol substrates 4a-c with an unactivated aromatic nucleus lead cleanly to the respective trans-products 5a-c in excellent yield. In contrast, the cyclohexanols 4d-g that incorporate an electron donating methoxy or methyl substituent, para to the site of electrophilic attack on the aromatic ring, including disubstituted aromatic precursors (entries 6 and 7), generate[24] a more diverse array of products (including ortho-cyclization) containing substantial amounts of the respective cis-isomers 6d-g along with predominating trans-isomers 5d-g. It is important to note that it is the location of the activating methoxy or methyl group with respect the site of electrophilic attack that governs the reactivity of the aromatic ring. The stereochemical results of the present and the earlier works can be clearly explained by consideration that aromatic rings without the para activating group are not sufficiently nucleophilic to reaction through the concerted protonation cyclization pathway[11b] 1C (Scheme-2) of the olefin 1B, but require complete protonation to carbocation 1 which reacts with high stereoselectivity by pathway 1A due to minimum steric effects,[24,11b] to give trans-products. With an activating para substituent, the pathway 1C competes with pathway 1A to give a mixture of cis and trans-products. The exact ratio of products could vary significantly with small changes in reaction conditions or starting material.

Scheme - 2



In conclusion, we feel the operationally simple and efficient general convergent sequence developed during the present work certainly constitutes one of the shortest and highly stereocontrolled synthesis of the C-4-gem-dimethyl incorporating rinc-C-aromatic diterpenoids[25-27] as exemplified by the synthesis of (±)-nimbidiol (7) and (±)-nimbiol (8). In addition, the present investigation has provided substantial evidence of the importance on the positions of the methoxy or methyl aromatic sunstituent(s) on the nature and stereochemistry of the cyclization products from 2-(2-arylethyl-1,3,3-trimethylcyclohexanols with rational mechanistic analyses.

EXPERIMENTAL

The compounds described are all racemates. IR spectra were recorded on a Perkin-Elmer model PE 298 spectrometer. ^{1}H NMR spectra were taken on a Varian XL-200, Jeol FX-100 model or a Varian T-60 instruments. Chemical shifts are referred to TMS on the δ scale. Analytical GC was performed on a Shimadzu GC-9A model with a flame ionisation detector employing 1.5% OV-17 (6.5 ft x 0.25 in) column with N_2 as the carrier gas. Elemental analyses were performed by P.P. Bhattacharyya of this laboratory. Column chromatography was performed on neutral alumina (Brockman Grade 1) or silica gel [Glaxo Laboratories (India)]. Petroleum and petroleum ether refer to fractions of bp 60-80°C and 40-60°C respectively.

Preparation of keto-esters 11c and 11e-g. A typical procedure is given for the preparation of ethyl 3-(o-methoxyphenylethyl)-2-methyl-4-oxocyclohex-2-encarboxylate (11c). Hagemann's ester (9) (41.86 g, 0.23 mol) was alkylated with bromide 10c[28] (43.0 g, 0.2 mol) in the presence of potassium tert-butoxide in tert-butylalcohol, prepared from potassium metal (7.8 g, 0.2 mol) by following the procedure described previously.[17] The light yellow, viscous liquid alkylated product was fractionated twice (bp 200-210°C/0.2 mmHg) to afford 47.6 g (70%) in over 95% isomerically GC pure 8c; IR (neat) 1730, 1675, 1610 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 1.28 (3H, t, J = 7 Hz), 1.82 (3H, s), 2.06-3.30 (9H, m), 3.82 (3H, s), 4.22 (2H, q, J = 7 Hz), 6.80-7.32 (4H, m). Anal. calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found : C, 72.30; H, 7.71%.

Ethyl 3-(m-methylphenylethyl)-2-methyl-4-oxocyclohex-2-encarboxylate (11e) was prepared through alkylation of 9 with 10e[23f] in 71% (homogeneous in GC) bp 195-200°C/0.2 mmHg; IR (neat) 1730, 1670 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 1.21 (3H, t, J = 7 Hz), 1.75 (3H, s), 1.81-3.19 (total 12H, m), 2.52 (3H, s), 4.12 (2H, q, J = 7 Hz), 6.66-7.16 (4H, m). Anal. calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found : C, 75.72; H, 7.87%.

Ethyl 3-(3,4-dimethoxyphenylethyl)-2-methyl-4-oxocyclohex-2-encarboxylate (11f) was prepared through alkylation of 9 with 10f[29] in 70% (homogeneous in GC) bp 210-220°C/0.2 mmHg. IR (neat) 1730, 1670, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 1.21 (3H, t, J = 7 Hz), 1.72 (3H, s), 1.82-3.16 (total 9H, m), 3.74 (3H, s), 3.77 (3H, s), 4.1 (2H, q, J = 7 Hz), 6.66-6.72 (4H, m). Anal. calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found : C, 69.44; H, 7.82%.

Ethyl 3-(4-methoxy-3-methylphenylethyl)-2-methyl-4-oxocyclohex-2-encarboxylate (11g) was prepared through alkylation of 9 with 10g[23f] in 73% (homogeneous in GC) bp 205-215°C/0.2 mmHg; IR (neat) 1730, 1670, 1605 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 1.22 (3H, t, J = 7 Hz), 1.85 (3H, s), 2.02-3.25 (total 12H, m), 2.19 (3H, s), 3.79 (3H, s), 4.15 (2H, q, J = 7 Hz), 6.76-7.76 (3H, s). Anal. calcd. for $C_{20}H_{26}O_4$: C, 72.72; H, 7.88. Found : C, 72.61; H, 7.63%.

Preparation of unsaturated ketones 12c and 12e-g. A Typical procedure is given for the preparation of 2-(2-o-methoxyphenylethyl)-3-methylcyclohex-2-en-1-one (12c). The keto-ester 11c (54 g, 0.18 mol) was refluxed with a solution of KOH (56 g, 1 mol) in water (56 ml) and ethanol (400 ml) under N_2 for 12 h. The cooled reaction mixture was carefully acidified with an excess of HCl (6N). After usual work up, and on distillation, the enone 12c was obtained (30.78 g, 75%) bp 168-172°C/0.2 mmHg); IR (neat 1665, 1610 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 1.66 (3H, s), 1.72-2.66 (total 10H, m), 3.75 (3H, s), 6.59-7.23 (4H, m). Anal. calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found : C, 78.67; H, 8.54%.

2-(2-m-Methylphenylethyl)-3-methylcyclohex-2-en-1-one (12e) was prepared in 76%, bp 165-170°C/0.2 mmHg. IR (neat) 1670, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.69 (3H, s), 1.85-2.56 (total 13H, m), 2.24, (3H,s): 6.75-7.00 (4H, m). Anal. calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found : C, 84.21; H, 8.62%.

2-(3,4-Dimethoxyphenylethyl)-3-methylcyclohex-2-en-1-one (12f) was prepared in 75%, bp 175-180°C/0.2 mmHg; IR (neat) 1675, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 1.69 (3H, s), 1.78-2.72 (total 10H, m), 3.69 (3H, s), 3.72 (3H, s), 6.69-6.85 (3H, m). Anal. calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found : C, 74.53; H, 8.24%.

2-(4-Methoxy-3-methylphenylethyl)-3-methylcyclohex-2-en-1-one (12g) was prepared in 72%, bp 172-180°C/0.2 mmHg; IR (neat) 1675, 1600 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 1.78 (3H, s), 2.16 (3H, s), 2.51-2.66 (total 10H, m), 3.79 (3H, s), 6.66-7.75 (3H, m). Anal. calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found : C, 79.32; H, 8.61%.

Preparation of cyclohexanones 13c-g. A typical procedure is given for the preparation of 2-(o-methoxyphenylethyl)-3,3-dimethylcyclohexan-1-one (13c). To a stirred suspension of CuI (11.4 g, 60 mmol) in dry Et_2O (50 ml) under N_2 at -25°C (bath temperature) was added MeLi in Et_2O (70 ml. 1.4 M, 98 mmol). The resulting yellow suspension was cooled to -50°C and $BF_3.Et_2O$ (9.08 g, 64 mmol) was added. After 5 min the cyclohexenone 12c (4.56 g, 20 mmol) in Et_2O (25 ml) was added dropwise (15 min) and the mixture was stirred at -30°C for 15 min. An additional lot of $BF_3.Et_2O$ (9.08 g, 64 mmol) was added and stirring was continued at -30°C for 1 h. After work up, the crude product was purified by chromatography on neutral alumina (120 g) to afford 13c (4.49 g, 92%); IR (neat) 1705, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 0.76 (3H, s), 0.98 (3H, s), 1.06-2.68 (total 11H, m), 3.80 (3H, s), 6.84-7.30 (4H, m). Anal. calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found : C, 78.71; H, 9.36%.

2-(m-Methoxyphenylethyl)-3,3-dimethylcyclohexan-1-one (13d) was prepared from 12d[30] in 93%; IR (neat) 1705, 1610 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 0.76 (3H, s), 1.02 (3H, s), 1.04-2.80 (total 11H, m), 3.82 (3H, s), 6.78-7.30 (4H, m). Anal. calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found : C, 78.21: H, 9.18%.

2-(m-Methylphenylethyl)-3,3-dimethylcyclohexan-1-one (13e) was prepared in 90%, IR (neat) 1705, 1605 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 0.72 (3H, s), 0.98 (3H, s), 1.13-2.66 (total 14H, m), 2.33 (3H, s), 6.79-7.20 (4H, m). Anal. calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found : C, 83.46; H, 9.99%.

2-(3,4-Dimethoxyphenylethyl)-3,3-dimethylcyclohexan-1-one (13f) was prepared in 90%; IR (neat) 1705, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.69 (3H, s), 0.93 (3H, s), 1.12-3.0 (total 11H, m), 3.69 (3H, s), 3.72 (3H, s), 6.59-7.0 (3H, s). Anal. calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03%.

2-(4-Methoxy-3-methylphenylethyl)-3,3-dimethylcyclohexan-1-one (13g) was prepared in 91%; IR (neat) 1710, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.76 (3H, s), 1.0 (3H, s), 1.10-2.33 (total 14H, m), 2.19 (3H, s), 3.79 (3H, s), 6.67-6.94 (3H, m). Anal. calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found : C, 79.07; H, 9.65%.

Preparation of cyclohexanols 4c-g. A typical procedure is given for the preparation of 2-(2-o-methoxyphenylethyl)-1,3,3-trimethylcyclohexanol (4c). To a stirred ice-cold solution of the ketone (13c) (3.5 g, 13.4 mmol) in dry Et_2O (30 ml), an ethereal solution of MeMgI [prepared from Mg-turnings (1.1 g, 45 mg atom), MeI (6.39 g, 45 mmol) in dry Et_2O (20 ml)] was added dropwise for 1 h. The mixture was stirred for an additional 1 h at 0-5°C and finally refluxed for 2 h. After work up, the cyclohexanol 4c was obtained (3.3 g, 91%); IR (neat) 3380 (br), 1605 cm^{-1}; ^1H NMR (CCl_4) 0.90 (3H, s), 0.94 (3H, s), 1.19 (3H, s), 1.23-2.82 (total 12H, m), 3.71 (3H, s), 6.59-7.26 (4H, m).

2-(2-m-Methoxyphenylethyl)-1,3,3-trimethylcyclohexanol (4d) was prepared in 91%; IR (neat) 3410 (br), 1600 cm^{-1}; ^1H NMR (CCl_4) 0.87 (3H, s), 0.98 (3H, s), 1.16 (3H, s), 1.18-2.76 (total 12H, m), 3.69 (3H, s), 6.46-7.20 (4H, m).

2-(2-m-Methylphenylethyl)-1,3,3-trimethylcyclohexanol (4e) was prepared in 90%; IR (neat) 3380 (br), 1605 cm^{-1}; ^1H NMR (CCl_4) 0.85 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.19-2.60 (total 15H, m), 2.33 (3H, s), 6.72-7.19 (4H, m).

2-(3,4-Dimethoxyphenylethyl)-1,3,3-trimethylcyclohexanol (4f) was prepared in 90%; IR (neat) 3400 (br), 1605 cm^{-1}; ^1H NMR (CCl_4) 0.85 (3H, s), 0.96 (3H, s), 1.16 (3H, s), 1.19-2.82 (total 12H, m), 3.69 (3H, s), 3.72 (3H, s), 6.96-7.00 (3H, s).

2-(4-Methoxy-3-methylphenylethyl)-1,3,3-trimethylcyclohexanol (4g) was prepared in 95%; IR (neat) 3400 (br), 1600 cm^{-1}; ^1H NMR (CCl_4) 0.88 (3H, s), 0.94 (3H, s), 1.14 (3H, s), 1.16-2.69 (total 15H, m), 2.13 (3H, s), 3.70 (3H, s), 6.61-6.86 (3H, m).

Cyclization of the cyclohexanols 4c-e. A typical procedure is given for the cyclization of 4c to (+)-14-methoxypodocarpa-8,11,13-triene (5c). Cyclohexanol 4c (500 mg, 1.81 mmol) in dry Et_2O (5 ml) was added to the acid mixture [prepared from $MeSO_3H$ (34 g) and P_2O_5 (3.7 g) by stirring for 2 h at room temperature] at 20-25°C for 15 min. After usual work up[29], the residual oil was purified by filtration (in petroleum) through a short packed neutral alumina column (12 g) to afford 5c (444 mg, 95%), mp 116°C (lit[10], mp 113-116°C); ^1H NMR (200 MHz, $CDCl_3$) 0.92 (3H, s), 0.94 (3H, s), 1.19 (3H, s), 1.20-2.93 (total 11H, m), 3.79 (3H, s), 6.54-7.26) (3H, m).

Cyclization of 4d to 5d and 6d. Cyclization of 4d (1.81 mmol) gave an oil (93%). GC analyses of the product showed the presence of the cis-and the trans-isomers 6d and 5d in the ratio of 38:62 (93%, by co-injection with authentic samples) in addition to at least three other minor components in the ratio of 3:2:1 (7%). The ^1H NMR (200 MHz) also exhibited consistent spectrum[10]. Chromatography of this mixture (100 mg) on activated neutral alumina (10 g) and elution with petroleum gave pure 5d (20 mg, 20%), mp 85-86°C (lit[10], mp 82-86°C); ^1H NMR (200 MHz, $CDCl_3$) 0.92 (3H, s), 0.98 (3H, s), 1.16 (3H, s), 1.21-2.92 (total 11H, m), 3.76 (3H, s), 6.62 (1H, brs), 6.72 (1H, dd, J = 8 Hz), 7.22 (1H, d, J = 8 Hz).

Cyclization of 4e followed by CrO_3-HOAc oxidation of the cyclized product to (+)-13-methyl-7-oxopodocarpa-8,11,13-triene (14) and (+)-13-methyl-5-epi-6,7-dioxopodocarpa-8,11,13-triene (15). Cyclization of 4e gave an oil (87%); ^1H NMR (200 MHz, $CDCl_3$) 0.38 (s, C-4α-Me of 6e), 0.91 (s, C-4β-Me of 6e), 0.92 (s) and 0.94 (s) (C-4 Me x 2 of 5e), 1.16 (s, C-10-Me of 6e), 1.18 (s, C-10 Me of 5e), 2.26 (brs, Ar-Me); the intensity of the peaks for 5e and 6e are in a ratio of ~70:30. GC analyses of the product showed the presence of two major components in a ratio of ca 32:68 (80%) assignable to 6e and 5e in addition to at least eight other minor components (20%). A part of this hydrocarbon mixture (100 mg) in acetic acid (1 ml) was subjected to benzylic oxidation[21] with CrO_3 (150 mg) in acetic acid (1.5 ml) and water (0.5 ml). The mixture was stirred for 18 h at 25-30°C and finally heated to 60-65°C for 45 min. After work up, the residue was chromatographed on activated neutral alumina (5 g). Elution with petroleum gave a recovered hydrocarbon mixture (15%). Further elution with benzene-petroleum (1:4) gave 14 (30 mg, 29%) (homogeneous in GC); IR (neat) 1665, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.94 (3H, s), 0.99 (3H, s), 1.21 (3H, s), 1.26-2.71 (total 12H, m), 2.36 (3H, s), 7.30-7.94 (3H, m). Anal. calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found : C, 84.33; H, 9.35%. The later benzene-petroleum elutes (1:1) gave 15 (16 mg, 15%), mp 137°C; IR (KBr) 1715, 1670, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.39 (3H, s), 0.96 (3H, s), 1.19 (3H, s), 1.26-2.76 (total 10H, m), 2.42 (3H, s), 7.33-8.00 (3H, m). Anal. calcd. for $C_{18}H_{22}O_2$: C, 70.96; H, 8.20. Found : C, 79.60; H, 8.16%.

(+)-12-Methoxy-13-O-acetylpodocarpa-8,11,13-triene (21). A mixture of the acylether 20[12] (297 mg, 0.99 mmol), m-chloroperbenzoic acid (171 mg, 0.99 mmol, 100%) and p-TsOH (5 mg) in dichloroethane (8 ml) were refluxed for 5.5 h. Usual work up gave the acetate 21, (300 mg, 90%), mp 120°C; IR (KBr) 1765, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.92 (3H, s), 0.94 (3H, s), 1.18 (3H, s), 1.19-2.88 (total 14H, m), 2.29 (3H, s), 3.78 (3H, s), 6.66 (1H, s), 6.86 (1H, s). Anal. calcd. for $C_{20}H_{28}O_3$: C, 75.91: H, 8.92. Found : C, 75.80; H, 8.72%.

(+)-12,13-Dimethoxypodocarpa-8,11,13-triene (5f). The acetate 21 (200 mg, 0.66 mmol) was saponified with methanolic KOH solution (5%, 3 ml) by refluxing under N_2 for 2 h. The phenol, thus obtained, was directly methylated under usual condition[12] with K_2CO_3 and MeI in acetone to afford 5f (150 mg, 82%), mp 72°C (lit[22] described this as an oil); ^{1}H NMR (200 MHz, $CDCl_3$) 0.92 (3H, s), 0.95 (3H, s), 1.18 (3H, s), 1.26-2.84 (total 11H, m), 3.82 (3H, s), 3.84 (3H, s), 6.56 (1H, s), 6.80 (1H, s). Anal. calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found : C, 79.01; H, 9.60%.

(+)-Nimbidiolmethylether (16). Oxidation of 5f (100 mg) with CrO_3-HOAc as described above for oxidation of 5e and 6e gave 16 (60 mg, 57%) as a GC pure glassy solid; IR (KBr) 1660, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 0.94 (3H, s), 1.0 (3H, s), 1.25 (3H, s), 1.36-3.76 (total 9H, m), 3.92 (3H, s), 3.96 (3H, s), 6.83 (1H, s), 7.51 (1H, s). Anal. calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found : C, 75.47; H, 9.0%.

Cyclization of 4f and CrO_3-HOAc oxidation of the cyclized product to 16 and (+)-5-epi-6-oxonimbidiolmethylether (17). Cyclization of 4f (1.81 mmol) with $MeSO_3H$-P_2O_5 mixture as desceibed above for 4e gave an oil (90%). Analysis by GC with a sample of 5f described above, showed the presence of 5f (53%)[22] and 6f[22] (37%) along with some minor products (10%). The ^{1}H NMR (200 MHz) spectrum of this mixture is also consistent with the data. Oxidation of the cyclized product (100 mg) with CrO_3-HOAc as described for the cyclization product of 4e, after chromatography on neutral alumina (5 g) and elution with benzene-petroleum (1:4) gave 16 (31 mg, 30%), identical (IR, ^{1}H NMR and GC) with the sample described above. Further elution with benzene-petroleum (1:1) gave 17 (22 mg, 20%) mp 198°C; IR (KBr) 1715, 1660, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 0.46 (3H, s), 0.99 (3H, s), 1.24 (3H, s), 1.36-2.70 (total 7H, m), 3.96 (3H, s), 4.04 (3H, s), 6.85 (1H, s), 7.64 (1H, s). Anal. calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found : C, 72.0; H, 7.55%.

(+)-Nimbidiol (7). A solution of 16 (80 mg) and BBr_3 (0.1 ml) in CH_2Cl_2 (4 ml) was allowed to stand at 0-5°C for 2 h and was left overnight at room temperature. After work up, the solid product was crystallised to give (7) (57.6 mg, 80%), mp 223°C; IR (KBr) 3480, 3220, 1660, 1605 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 0.92 (3H, s), 0.98 (3H, s), 1.20 (3H, s), 2.08-2.75 (total 9H, m), 6.88 (1H, s), 7.71 (1H, s), identical (IR and ^{1}H NMR in $CDCl_3$) with the optically active sample[13]. Anal. calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found : 74.07; H, 7.79%.

(+)-12-Hydroxy-13-dimethylaminopodocarpa-8,11,13-triene (23). A formaldehyde solution (0.45 ml, 40%) was added dropwise under N_2 to a solution of the phenol 22 (480 mg, 1.63 mmol), prepared in 93% yield by demethylation of 5b with BBr_3 in CH_2Cl_2, in dimethylamine (0.8 ml, 40%) and ethanol (3 ml, 95%). The mixture was stirred at room temperature (ca 30°C) for 3.5 h; refluxed for an additional 5.5 h and worked up[23e] in the usual manner to afford 23 (400 mg, 81%); IR (neat) 3400 (br), 1605 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 0.91 (3H, s), 0.93 (3H, s), 1.17 (3H, s), 1.28-2.76 (total 12H, m), 2.29 (6H, s), 3.54 (2H, m), 6.60 (1H, s), 6.72 (1H, s). Anal. calcd. for $C_{20}H_{31}ON$: C, 79.67; H, 10.37. Found : C, 79.52; H, 10.30%.

(+)-Deoxynimbiol (25). A solution of the amine 23 (400 mg, 1.32 mmol) and MeI (3.6 g, 25.3 mmol) in dry Et_2O (20 ml) was converted to 24 (100 %), mp 216-217°C. This unstable compound 24 in THF (30 ml) was reductively cleaved[23e] with lithium metal (175 mg, 25.2 mg atom) in liq. NH_3 (60 ml) for 1 h. After usual work up, 25 (200 mg, 58%) was obtained as a glassy solid; IR (neat) 3410 (br), 1605 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 0.90 (3H, s), 0.92 (3H, s), 1.14 (3H, s), 1.34-2.86 (total 14H, m), 2.16 (3H, s), 4.78 (brs, 1H), 6.65 (1H, s), 6.78 (1H, s). Anal. calcd. for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found : C, 83.41; H, 10.01%.

(+)-Deoxynimbiolmethylether (5g). The crude phenol 25 (200 mg) was methylated with K_2CO_3 (2.0 g), CH_3I (2 ml) in acetone (6 ml) to afford GC pure 5g (150 mg, 71%); ^{1}H NMR (100 MHz, $CDCl_3$) 0.92 (6H, s), 1.24 (3H, s), 1.08-2.87 (total 17H, m) 2.12 (3H, s), 3.76 (3H, s), 6.76 (1H, s), 6.80 (1H, s). Anal. calcd. for $C_{19}H_{28}O$: C, 79.12; H,9.79. Found : C, 79.0; H, 9.60%.

(+)-Nimbiolmethylether (18). Oxidation[23b] of 5g (80 mg) with CrO_3-HOAc gave 18 (40 mg, 48%), mp 119-120°C (lit[23b], mp 117-118°C); IR (KBr) 1665, 1605 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 0.92 (3H, s), 0.96 (3H, s), 1.20 (3H, s), 1.30-2.68 (total 7H, m), 2.16 (3H, s), 3.84 (3H, s), 6.72 (1H, s), 7.80 (1H, s), identical (IR, ^{1}H NMR) with the optically active sample[14].

Cyclization of 4g and CrO_3-HOAc oxidation of the cyclized product to 18 and (+)-5-epi-6-oxo-nimbiolmethylether (19). Cyclization of 4g (1.81 mmol) with $MeSO_3H$-P_2O_5 mixture as described for 4e gave an oil (93%). Analysis by GC and ^{1}H NMR (at 200 MHz) with authentic compound 5g indicated the presence of 5g (49%) and 6g (38%) along with some unidentified minor products (13%). Oxidation of the cyclized material (100 mg) with CrO_3-HOAc as described above, followed by chromatography on neutral alumina (5 g) and elution with benzene-petroleum (1:4), gave 18 (30 mg, 29%), identical (mp, IR, ^{1}H NMR and GC) with the sample described above. Further elution with benzene-petroleum (1:1) gave 19 (17 mg, 15%), mp 200°C (lit[23f], mp 200°C); IR (KBr) 1715, 1670, 1605 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$), 0.44 (3H, s), 1.24 (3H, s), 1.44-2-65 (total 10H, m), 2.20 (3H, s), 3.96 (3H, s), 6.80 (1H, s), 7.94 (1H, s).

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