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An Expeditious Stereoselective Total Synthesis of (±)-Podocarpa-2,8,11.13-Tetraene and 3-Oxygenated (±)-Podocarpa-8,11,13-Trienes by Acid-Catalyzed Cyclialkylation Route

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AN EXPEDITIOUS STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-PODOCARPA-2,8,11,13-TETRAENE AND 3-OXYGENATED (±)-PODOCARPA-8,11,13-TRIENES BY ACID-CATALYZED CYCLIALKYLATION ROUTE

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Abstract: An expeditious total synthesis of (±)-podocarpa-2,8,11,13-tetraene **(4)** and the epimeric (±)-3-hydroxypodocarpa-8,11,13-trienes **5** and **6** by a stereoselective cyclialkylation route is described.

An efficient and highly stereoselective aromatic cyclialkylation[1] of the methylenecyclohexane **1** to the trans-product **2**, prompted us to consider the extension of this route with the open chain esters **3a,b** for a potential synthesis of ring-A oxygenated diterpenoids[2]. We report here our first results of this study leading to a simple stereoselective synthesis of (±)-podocarpa-2,8,11,13-tetraene **(4)** and the (±)-3-hydroxypodocarpatrienes **5**[3] and **6**[3].

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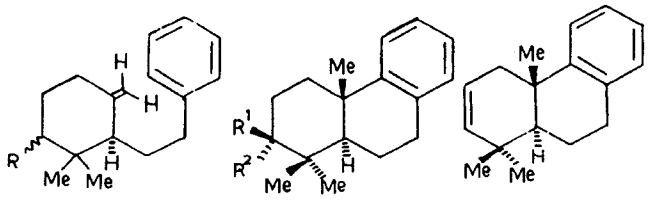


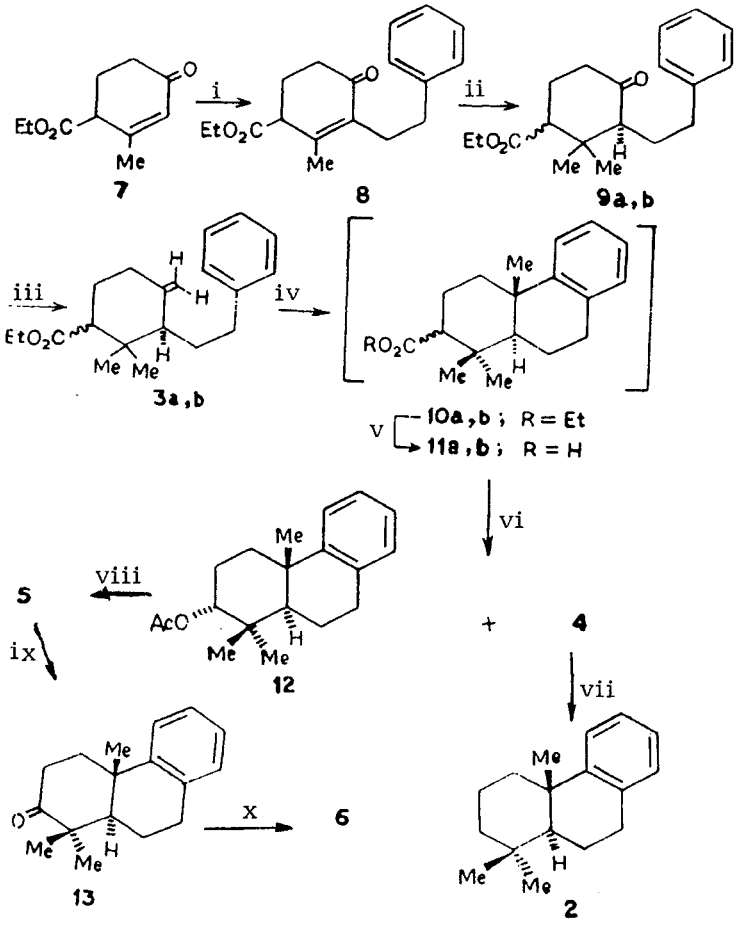
1, R= H
3a,b; R = CO_2Et

2, $R^1 = R^2 = H$
5, $R^1 = H$; $R^2 = OH$
6, $R^1 = OH$; $R^2 = H$

4

The readily accessible[4] unsaturated keto-ester **8**[5] from **7** on conjugate addition[6] with an excess of $LiMe_2Cu$ in Et_2O in the presence of $BF_3.Et_2O$ (Scheme-1) afforded epimeric keto-esters **9a,b** mixture in excellent yield. Wittig olefination of **9a,b** under forcing condition[7] gave the epimeric esters **3a,b** in good yield, which on cyclization with $MeSO_3H$-P_2O_5 under usual condition[1,6] afforded the cyclized epimeric inseparable esters **10a,b** in excellent yield. This mixture was directly saponified to the epimeric acids mixture **11a,b** and subjected to decarboxylation[8] with $Pb(OAc)_4$ in boiling benzene. The chromatography of the resulting products on neutral alumina gave the tetraene **4** and acetate **12** in 69% and 8% yields respectively. The stereochemistry of **4** was established by its smooth transformation to the known podocarpatriene **2**[9] by catalytic hydrogenation. The acetate **12** on saponification gave the known axial alcohol **5**[3]. This on oxidation with PCC in benzene followed by reduction of the resulting ketone **13**[10] with $Zn(BH_4)_2$[11] afforded the known equatorial alcohol **6** in excellent yield.

Scheme – 1



Reagents: i, $PhCH_2CH_2Br$, Bu^tOK-Bu^tOH, H^+; ii, $LiMe_2Cu$, $BF_3.Et_2O$, Et_2O; iii, Sodium t-pentoxide, $Ph_3P^+MeI^-$, toluene; iv, $MeSO_3H$: P_2O_5 (10:1); v, KOH, H_2O, ethylene glycol, H^+; vi, $Pb(OAc)_4$, pyridine, C_6H_6; vii, H_2, Pd-C (10%), EtOH; viii, KOH, H_2O, MeOH; ix, PCC, C_6H_6; x, $Zn(BH_4)_2$, DME.

In conclusion, the conjugate addition and cyclization method provides an expeditious total synthesis of ring-A functionalized (±)-podocarpatriene derivatives[9]. The stereochemical results of the cyclialkylation of **3a,b** leading only to the trans-cyclized products clearly supports our recently reported mechanistic analysis[1] on the open chain substrates such as **1** with unactivated aromatic ring and further revealed that an additional ester functionality in the cyclohexane ring has no influence on the stereochemical outcome of the ring juncture in the cyclialkylation products.

EXPERIMENTAL

The compounds described are all racemates. IR spectra were recorded on a Perkin-Elmer model PE-298 spectrometer. ^1H NMR spectra were recorded on a Varian EM-360L and a Varian XL-200 instrument. Chemical shifts are referred to TMS on the 'δ' scale. Analytical GC was performed on a Shimadzu GC-9A model with a flame ionization 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. Bhattacharya and S.K. Sarkar of this laboratory. Column chromatography was performed on neutral alumina (Brockman Grade-1). Petroleum ether and light petroleum refer to fractions of b.p. 60-80 and 40-60°C respectively.

bromide(1b) with chalcones(2a-d) in the presence of bases. We studied the effect of solvent, base and temperature on the reaction and selected the best reaction condition(see Table). The results show that base has a remarkable effect on the reaction. For example, in the presence of solid sodium hydroxide, 1b reacted with 2a under reflux for 8 hrs, to afford 1-phenyl-2-(p-chlorophenyl)-3-benzoylcyclopropane (7,yield: 90%). In the presence of solid sodium carbonate, however, the vinyl CH_3), 1.80-3.30 (m, 9H), 4.20 (q, J = 8 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 6.87-7.28 (m, 5H, ArH).

Ethyl 3-(β -phenethyl)-2,2-dimethyl-4-oxocyclohexancarboxylate (9a,b). To a stirred suspension of CuI (11.4 g, 60 mmol) in dry Et_2O (50 ml) under N_2 at -25°C was added MeLi in Et_2O (60 ml, 1.4 M, 52.4 mmol). The resulting yellow suspension was cooled to -50°C and $BF_3.Et_2O$ (5.24 ml, 42 mmol) was added. After 5 min the unsaturated keto-ester **8** (4 g, 14 mmol) in Et_2O (25 ml) was added dropwise and the mixture stirred at -30°C for 15 min. Additional $BF_3.Et_2O$ (5.24 ml, 42 mmol) was added and stirring continued at -30°C for 1 h. The mixture was allowed to warm to 0°C and then quenched with aqueous NH_4Cl. The resulting product was extracted with Et_2O, dried (Na_2SO_4) and the solvent was evaporated. The crude product on GC analyses showed the presence of two compounds in a ratio of

45:55 (91%, R_t's 3.33 min and 4.63 min at the column temperature 220°C) along with two other minor compounds (9%) with R_t's 2.82 and 5.96 min at the column temperature 220°C. The crude product was chromatographed over neutral alumina (120 g) using light petroleum as eluant to give epimeric keto-ester mixture **9a,b** (3.37 g, 80%). Anal. calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.16; H, 8.90%. IR (neat) 1725, 1710 and 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82, 0.92, 1.04, 1.07 (s, CH_3, for two epimers), 1.22-1.32 (m, $CO_2CH_2\underline{CH_3}$, for two epimers), 1.42-2.80 (m, methylenes and methines, for two epimers), 4.14-4.26 (m, $CO_2\underline{CH_2}CH_3$, for two epimers), 7.20-7.40 (m, ArH, for two epimers).

Ethyl 3-(β-phenethyl)-2,2-dimethyl-4-methylenecyclohexancarboxylate (3a,b). A suspension of methyl (triphenyl) phosphonium iodide (18.4 g, 45.63 mmol) in toluene (2 ml) and a toluene solution of freshly prepared sodium t-pentoxide (45.63 ml of 1M solution) was stirred at room temperature (~25°C) for 20 min. The ketone **9a,b** (4.5 g, 15 mmol) in toluene (5 ml) was added dropwise, the mixture refluxed for 2 h, the reaction quenched with saturated aqueous NH_4Cl, and the mixture extracted with Et_2O. The extract was washed with aqueous NH_4Cl and water and dried (Na_2SO_4). Evaporation yielded an oil which was immediately filtered through silica gel with Et_2O-petroleum ether (1:10). The eluent was evaporated to give an oil (2.73 g)

which was dissolved in petroleum ether (10 ml). Methyl iodide (3 ml) was added and the mixture set aside at room temperature for 1 h. The precipitated methyl(triphenyl)phosphonium iodide was filtered off and the filtrate concentrated in vacuo to give the crude alkene. The crude product on GC analyses showed the presence of two compounds in a ratio of 28:72 (95%, R_t's 4.56 min and 5.81 min at the column temperature 230°C) along with two other minor compounds (5%) with R_t's 1.54 and 4.06 min at the column temperature 230°C. The crude product was chromatographed over neutral alumina (80 g) using light petroleum as eluant to give mixture of products **3a,b** (2.68 g, 60%). Anal. calcd. for $C_{20}H_{28}O_2$: C, 79.92; H, 9.32. Found: C, 79.71; H, 9.08%; IR (neat) 1725, 1645 and 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95, 0.96 (s, CH_3, for two epimers), 1.28 (t, $CO_2CH_2\underline{CH}_3$, for two epimers), 1.60-2.66 (m, methylenes and methines), 4.08-4.20 (m, $CO_2\underline{CH}_2CH_3$, for two epimers), 4.70-4.90 (m, $=CH_2$, for two epimers), 7.20-7.38 (m, ArH, for two epimers).

(±)-Podocarpa-8,11,13-triene-3-carboxylic acids (11a,b). The cyclization[6] of the mixture of alkenes **3a,b** (500 mg, 1.66 mmol) in dry Et_2O (5 ml) with methane sulphonic acid (23 ml) and P_2O_5 (3.7 g) was performed for 5 min at 20°C. The reaction mixture was worked up with Et_2O, dried (Na_2SO_4) and solvent removed. The crude product on GC analyses showed the presence

of two major compounds in a ratio of 28:72 (95%, R_t's 4.56 min and 5.80 min at the column temperature 250°C) along with two other minor compounds (5%) with R_t's 1.54 and 4.08 min at the column temperature 250°C. The crude product was chromatographed over neutral alumina (15 g) using light petroleum as eluant to give epimeric mixture of the esters **10a,b** (450 mg, 90%).

This mixture of epimeric esters (400 mg) was hydrolysed by heating for 3 h in an oil bath at 200-210°C with a solution of KOH (0.26 g, 4.6 mmol) in water (0.5 ml) and distilled ethylene glycol (2.6 ml) under nitrogen. The homogeneous reaction mixture was poured into cold water and extracted with Et_2O. The Et_2O layer was washed with brine and dried (Na_2SO_4). Removal of the solvent afforded the unchanged ester (10 mg). The aqueous part was acidified with 6(N)HCl and extracted with Et_2O after saturated with sodium chloride. The Et_2O layer was washed with brine and dried (Na_2SO_4). On removal of the solvent a solid mass was obtained which on recrystallization once from ethylacetate gave epimeric acid mixture **11a,b** (340 mg, 94%) m.p. 180-210°C. Anal. calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found : C, 79.07; H, 8.98%; IR (KBr) 1705, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.01, 1.06, 1.10, 1.16, 1.26 (s, CH_3, for two epimers), 1.40-3.0 (m, methylenes and methines), 7.04-7.34 (m, ArH, for two epimers).

(±)-Podocarpa-2,8,11,13-tetraene (4) and (±)-3α-O-acetylpodocarpa-8,11,13-triene (12). The epimeric acid mixture **11a,b**

(500 mg, 1.6 mmol), in dry benzene (4 ml), dry pyridine (0.18 ml, 2.4 mmol), and lead tetra-acetate (1.37 g, 3.2 mmol) was stirred under N_2 at 20°C for 1 h and then heated under reflux for a further 3 h. The cooled mixture was filtered and filtrate concentrated to yield a light yellow liquid (450 mg). The GC analyses of this mixture indicated the presence of **4** and **12** in a ratio 89:11 (94%, R_t's 4.24 min and 5.58 min at the column temperature 250°C) along with other minor compound (6%) with R_t 2.9 min at the column temperature 250°C. The mixture was chromatographed on acid washed alumina (15 g). Elution with light petroleum gave a viscous alkene fraction **4** (261 mg, 69%); b.p. 125-130°C (0.2 mm). Anal. calcd. for $C_{17}H_{22}$: C, 90.16; H, 9.84. Found : C, 90.38; H, 9.58%; IR (neat) 1660 and 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.0 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.60-2.56 (m, 5H), 2.80-3.0 (m, 2H, Ar-CH_2), 5.52-5.68 (m, 2H, H-2 and H-3), 7.06-7.38 (m, 4H, Ar-H).

On further elution with light petroleum gave **12** (38 mg, 8%) as a viscous liquid, b.p. 155-160°C (0.2 mm). Anal. calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found : C, 79.40; H, 8.93%; IR (neat) 1730, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.53-3.0 (m, 10H), 1.96 (s, 3H, -$OCOCH_3$), 6.95-7.26 (m, 4H, Ar-H).

(±)-Podocarpa-8,11,13-triene (2). Alkene **4** (100 mg, 0.44 mmol) was subjected to hydrogenation in dry ethanol (6 ml) in the presence of Pd-C (10%) (50 mg). The uptake of hydrogen was very rapid and was completed within 1 h. The catalyst was filtered, ethanol was removed, the residue was taken into Et_2O and washed with water and dried (Na_2SO_4). On removal of the solvent **2** (91 mg, 90%) was obtained which was identical (GC, IR and ^1H NMR) with an authentic sample[9].

(±)-Podocarpa-8,11,13-triene-3α-ol (5). Acetate **12** (80 mg, 0.28 mmol) was heated under reflux with 2(N) methanolic NaOH (10 ml) for 2 h. Water was added and the excess methanol was removed by distillation and the remaining mixture was extracted with Et_2O. The solvent was dried (Na_2SO_4) and removed to afford **5** as a white solid which was recrystallized from chloroform - light petroleum (1:10) to yield fine needles of **5** (60 mg, 88%) m.p. 164°C (lit[3] m.p. 164-165°C); IR (KBr) 3360, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.46-2.22 (m, 8H), 2.90-3.0 (m, 2H, Ar-CH_2), 3.56 (br s, 1H, 3α-OH), 7.06-7.36 (m, 4H, Ar-H).

(±)-Podocarpa-8,11,13-trien-3-one (13). To a well-stirred ice-cold suspension of pyridinium chlorochromate (323 mg, 1.5 mmol) in benzene (5 ml) was added at a time a solution of **5** (250 mg, 1.02 mmol) in benzene (3 ml). After stirring for 2 h

at 0°C the reaction mixture was diluted with Et_2O (10 ml) and the black precipitate was repeatedly washed with Et_2O. The combined Et_2O layers were washed with 1% aqueous NaOH solution, followed by water until free from alkali and dried (Na_2SO_4). The solvent was removed to yield crude ketone which was recrystallized from Et_2O - petroleum ether (1:10) to give **13** (198 mg, 80%) m.p. 62°C [lit[10] b.p. 135-145°C (0.5 mm)]; IR (KBr) 1710, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.60-3.0 (m, 9H), 7.10-7.34 (m, 4H, Ar-H).

(±)-Podocarpa-8,11,13-triene-3β-ol (6). A solution of zinc borohydride (0.5 ml, 1.2 M, 0.61 mmol) in DME was added to the carbonyl compound **13** (150 mg, 0.61 mmol) in DME (2 ml) with stirring at 0°C for 30 min. The reaction mixture was quenched with careful dropwise addition of aqueous hydrochloric acid (0.5 N). The whole mixture was extracted with Et_2O and the Et_2O layer was washed with water, dried (Na_2SO_4) and solvent evaporated to give a crude product which on recrystallization from chloroform - light petroleum (1:10) to give **6** (136 mg, 90%) m.p. 112°C (lit[3] m.p. 111-112°C); IR (KBr) 3380 and 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.40-2.40 (m, 8H), 2.94-3.0 (m, 2H, Ar-CH_2), 3.30-3.38 (m, 1H, 3β-OH), 7.06-7.34 (m, 4H, Ar-H).

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