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Enantioselective Synthesis and Absolute Configuration of Myoporone

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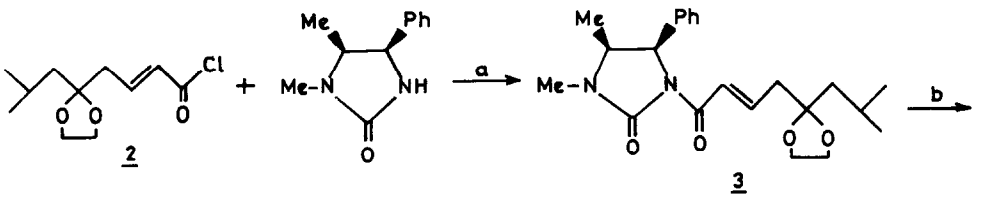
Abstract An enantioselective synthesis of myoporone has been accomplished in 91 7% e e to determine its absolute configuration.

Myoporone, a furanosesquiterpenoid, was first isolated from Myoporum bontioides A Gray and later its presence was detected in various other Myoporum species[2], Eremophila species[2], Eumophia sericea and E prostata[3] This compound has been assigned structure 1 on the basis of degradative studies, physical methods and a synthesis of its racemates[2] It has been recorded as a stress metabolite[4] of sweet potato and normal secondary metabolite of other plants. The absolute configuration of this natural product was investigated by Blackburne et al[2] who concluded that both R and S isomers exist together in nature with the latter being in larger proportion These workers reported $[\alpha]_D$ to be -7 3 for optically pure myoporone having the S configuration However, Burka and co-workers[4] have isolated the title compound with $[\alpha]_D$ = -8 5 without assigning any configuration In view of above reports, it was planned to carry out an enantioselective synthesis of the title compound to determine the optical rotation and configuration of the optically pure myoporone The key reaction involved in the synthesis is the diastereoselective conjugate addition of methyl cuprate to a chiral unsaturated imide bearing imidazolidinyl group as delineated below



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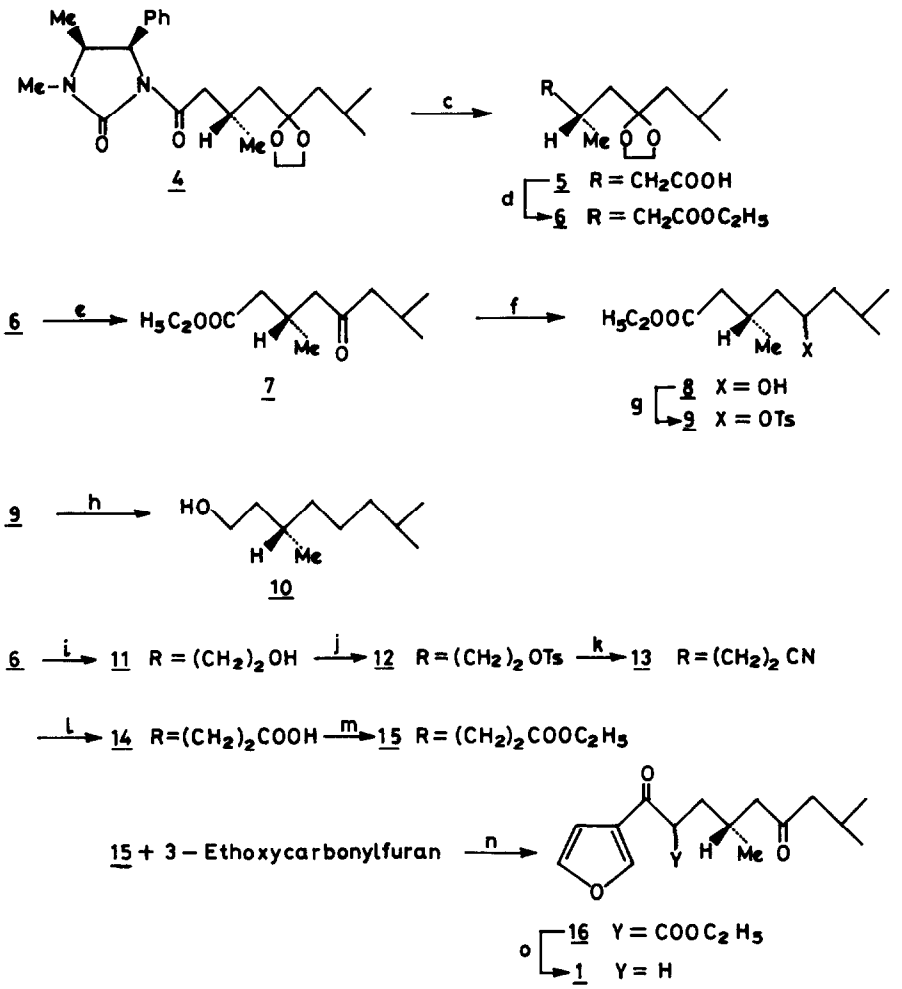

Reagents: (a) $C_6H_5N(CH_3)_2$-CH_2Cl_2, (b) CH_3MgBr-CuBr-$(CH_3)_2S$-THF, (c) LiOH-aqTHF, (d) C_2H_5Br-K_2CO_3-$(CH_3)_2CO$, (e) $(CH_3)_2CO$-HCl, (f) $NaBH_4$, (g) TosCl - Py, (h) LAH, (i) LAH, (j) TosCl-Py, (k) NaCN-DMSO, (l) Alc NaOH, (m) C_2H_5Br-K_2CO_3-$(CH_3)_2CO$, (n) NaH-C_6H_6, (o) $Ba(OH)_2$ - aqC_2H_5OH, H^+

(4R, 5S)-3-(5',5'-Ethylenedioxy-7'-methyl-2'-octenyl)-1,5-dimethyl-4-phenyl-2-imidazolidone 3, the suitably substituted intermediate was prepared by acylation of (4R, 5S)-1,5-dimethyl-4-phenyl-2-imidazolidone[5] with the ketal acid chloride 2[6] in $(CH_3)_2NC_6H_5$-CH_2Cl_2 The conjugated imide 3 was submitted to CH_3MgBr in the presence of CuBr - $(CH_3)_2S$ complex[7] in THF to provide the chiral imide 4. Hydrolysis of 4 with LiOH-aq THF afforded the acid 5. In order to determine the configuration and optical purity of acid 5, it was esterified with C_2H_5Br-K_2CO_3-$(CH_3)_2CO$ to ester 6 which was then deketalized in aq acetone-HCl to keto ester 7 Chemoselective reduction of 7 with $NaBH_4$-C_2H_5OH gave the hydroxy ester 8 which was transformed into 3,7-dimethyl-octanol 10 by reduction with excess of LAH of the corresponding its tosyl derivative 9 This alcohol 10 had $[\alpha]_D$=-4 8(c=1 5,CH_3OH) Lit [8] reports $[\alpha]_D$ = +5.23 for (3R)-3,7-dimethyl-octanol Therefore, the ketal ester 6 synthesized has S configuration and should be in 91 7% e e Homologation of the ketal ester 6 to ethyl (4R)-6,6-ethylenedioxy-4,8-dimethyl-nonanoate 15 was accomplished via reduction, tosylation, substitution by CN, hydrolysis and esterification as the reaction steps sequentially The ketal ester 15 was condensed with 3-ethoxycarbonylfuran in NaH-C_6H_6 system to secure the corresponding β-ketoester 16 which without isolation was decarbethoxylated with $Ba(OH)_2$-aq C_2H_5OH followed by acidic work up to have myoporone 1 The purified sample was identical in its IR, UV and NMR spectral data[2] and had $[\alpha]_D$ = +7 8 (c = 1 54, CH_3OH) In view of enantiopurity of chiral centre to be 91 7% (determined above), the naturally occurring optically pure (R)-(+)-myoporone should have $[\alpha]_D$ = +8 5 This supports the enantiopurity of the naturally occurring sample[4] of Burka et al but must have S configuration

EXPERIMENTAL[9]

(4R,5S)-3-(5',5'-Ethylenedioxy-7'-methyl-2'-octenoyl)-1,5-dimethyl-4-phenyl-2-imidazolidone(3)

A solution of (4R,5S)-1,5-dimethyl-4-phenyl-2-imidazolidone (19 0 g, 0 1 mol), acid chloride 2 (23 25 g, 0.1 mol) and $(CH_3)_2NC_6H_5$ (18 15 g, 0 15 mol) in CH_2Cl_2 (190 ml) was refluxed for 24 h The mixture was poured into $NaHCO_3$ solu tion and organic layer separated Aq layer was extracted with CH_2Cl_2 and combined organic layer were washed with water and dried The solvent was evaporated and the residue was chromatographed on silica gel (300 g) The desired product 3 (24 4 g) was obtained with n-hexane-ethyl acetate (85 15) as the eluent in 63 2% yield, mp 125-128°C, $\nu_{max.}$ 1720, 1670, 1630, 973 cm^{-1}, ^1H NMR δ0 85 (12H,m), 1 48 (2H,d, J=6Hz), 1 78 (1H,m), 2 68 (2H,dd, J = 2Hz, J = 8Hz), 2.82 (3H,s), 3 98 (5H,m), 5 33 (1H, d, J = 8Hz), 6 91 (1H,m), 7 25 (5H, m), 7 42 (1H, m), Calcd for $C_{22}H_{30}N_2O_4$ C,68 42, H, 7 77, N, 7 25, Found C, 68 38, H, 8 08,N,7 51

Ethyl(3S)-5,5-ethylenedioxy-3,7-dimethyl-octanoate(6)

A solution of CH_3MgBr, prepared from Mg (2 50 g, 0 0104 mol) and CH_3Br in ether (60 ml) was added to CuBr-$(CH_3)_2S$ complex (10 69 g, 0 052 mol) in THF (150 ml) at -25°C with stirring under N_2 After 0 5 h, conjugated imide 3 (10 g, 0 026 mol) in THF (15 ml) was added and the mixture was allowed to stir for 1 5 h at this temperature After stirring overnight at room temperature, the reaction

was quenched with a solution of NH_4Cl The organic layer was separated, the aq layer extracted with ether and the combined organic layer washed with brine After drying, the solvent was removed and the residue 4 was dissolved in THF (75 ml) This solution was stirred with a solution of LiOH (1 0g) in H_2O (100 ml) for 48 h at room temperature It was extracted with CH_2Cl_2 and the aq layer acidified at -5°C and extracted in ether The ether layer was washed with H_2O, dried and solvent removed to afford crude ketal acid 5 (4.8g) in 80 3% yield. This product was dissolved in $(CH_3)_2CO$ (50 ml) and stirred with K_2CO_3 (2 80 g) and C_2H_5Br (3 0g) at reflux After 10 h, the mixture was filtered, the solvent removed and the residue taken up in ether, washed with H_2O and dried. The solvent was evaporated and the residue chromatographed on silica gel followed by vacuum distillation at 156-159°C/6mm to obtain the ester 6 (3 14 g) in 58.4% yield; $[\alpha]_D^{26}$ = -28.3 (c=2, $CHCl_3$). ν_{max}. 1742 cm^{-1}; ^1H NMR· δ0 91 (9H,m), 1.23 (3H,t, J = 7Hz), 1.54 (4H, d, J = 6Hz),1 83(2H,m), 2 16 (2H,t, J = 7Hz), 4 02 (4H, s), 4.15 (2H, q, J = 7Hz), Calcd. for $C_{14}H_{26}O_4$ C, 65 15, H, 10.07; Found· C, 64.93, H, 10 37

(3S)-3,7-Dimethyloctanol (10)

A solution of ester 6 (1.80 g, 0 007 mol) in acetone (2 5 ml) and HCl (10%, 8 ml) was stirred for 2 h Acetone was removed, the aq layer extracted with ether, the ether layer washed with brine and dried Solvent was removed to give pure ketone 7 (1 40 g) in 93.3% yield; υ_{max} 1740, 1710 cm^{-1} To a stirred solution of 7 in ethanol (40 ml) was added $NaBH_4$ (0.20 g) in portions. After 2 h, the ethanol was removed, the residual oil was dissolved in ether, the ether layer was washed with H_2O, dried and the solvent removed to leave behind hydroxy ester 8 (1 37 g) in 97% yield, υ_{max} 3380, 1110, 1740 cm^{-1} This was dissolved in pyridine (12 ml) and tosyl chloride (2 0 g) added at 0-5°C with stirring The mixture was stirred for 4 h and poured in H_2O The aq layer was extracted in ether and the ether layer washed with H_2O, $CuSO_4$ solution (20%), H_2O and dried Solvent was evaporated to afford an oil 9 (1.78 g) in 78.8% yield, υ_{max} 1740, 820 cm^{-1} A solution of tosylate 9 (1 76 g) in THF (10 ml) was added to LAH (0 50 g) in THF (20 ml) The mixture was refluxed for 4h then cooled to 0°C, quenched with water (20 ml), and then worked up in the usual manner The residue on solvent removal was chromatographed on silica gel to alcohol 10 (0 44 g) in 58 6% yield, bp 130-135°C (bath)/10 mm; $[\alpha]_D^{26}$ = -4 8 (c = 1 5, CH_3OH), υ_{max} 3345, 1360, 1350, 1045 cm^{-1}, ^1H NMR δ0 92 (9H, d, J = 6 5 Hz), 1 41-1 68 (10H, m), 2.42 (1H, br, s, exchangeable with D_2O), 3 68 (2H, d, J = 7 Hz), Calcd for $C_{10}H_{22}O$ C, 75.97; H, 14.0; Found·C, 75 72, H, 14 03

Ethyl (4R)-6,6-ethylenedioxy-4,8-dimethylnonanoate (15)

A solution of the ester 6 (3 87 g, 0 015 mol) in ether (20 ml) was reduced with LAH (0 57 g, 0 015 mol) in ether (50 ml) The reaction was worked up in the usual way to furnish alcohol 11 (3 01 g) in 93% yield; bp 130-135°C/5-6 mm, υ_{max} 3310, 1055 cm^{-1}, ^1H NMR δ 0 88 (9H, m), 1 66 (6H, m), 1 83 (2H,m), 2 69(1H, br, exchangeable with D_2O), 3 70(2H, t, J=7 Hz), Calcd for $C_{12}H_{24}O_3$ C,66 69, H,11 0; Found C, 67 02, H, 11 50 The alcohol (2 90 g, 0134 mol) was transformed into the tosylate 12 using TosCl (4 38 g, 0 023 mol) in pyridine (20 ml) as described earlier to give 12 (4 58 g) in 92%

yield A solution of this crude tosylate (4 40g, 0 0119 mol) in DMSO (30 ml) was stirred with NaCN (1 50 g) at 60°C overnight The reaction was quenched with H_2O and extracted with ether which was washed with water and dried Solvent removal gave nitrile 13 (2.27 g) in 84.4% yield, ν_{max} 2250cm^{-1} This product (2.25 g) was refluxed with a solution of NaOH (0 72 g) in ethanol (22 ml) for 24 h The reaction was worked up as described earlier to afford acid 14 (1 932 g) in 79.2% yield; bp 164-166° C/5-6 mm, υ_{max} 3550-3100 cm^{-1} This acid (1 7 g, 0 007 mol) in acetone (20 ml) was stirred and refluxed with K_2CO_3(1 0 g) and C_2H_5Br (1 ml) for 12 h Usual work up gave ester 15 (1 67 g) in 88.1% yield after column chromatography on silica gel followed by vacuum distillation; bp 138-148°C/5 mm, $[\alpha]_D^{26}$ = +38 2(c = 2,CH_3OH); υ_{max} 1740 cm^{-1}, ^{1}H NMR· δ 0 92 (9H. d), 1.28 (3H,t,J = 7Hz), 1 63(6H, m), 1 78 (2H, m), 2.36 (2H,t,J = 7 Hz), 4 02 (4H,s), 4 23 (2H, q,J= 7Hz); Calcd. for $C_{15}H_{28}O_4$· C, 66 14; H, 10 36, Found C, 66 48, H, 10 32

(4R)-3-[4',8'-Dimethyl-6'-ketononanoyl]furan: [R-(+)Myoporone] (1)

To a stirred slurry of NaH (50 %, 0 576 g, 0 012 mol) (made freed of mineral oil by washing with n-hexane) in C_6H_6 (25 ml) was added 3-ethoxycarbonylfuran (1 68 g, 0 012 mol) and the mixture heated to 80°C after 0 5 h The ester 15 (1 58 g, 0 0058 mol) in C_6H_6 (6 ml) was then added to the above reaction mixture and stirring and refluxing continued for 6 h The reaction was quenched with H_2O, the benzene layer was separated and the aq layer acidified with HCl and extracted with ether The ether layer was washed with H_2O, dried and solvent removed The residue 16 was dissolved in C_2H_5OH (8 ml), H_2O (25 ml) and $Ba(OH)_2$ $8H_2O$ (3 50 g) added and the mixture refluxed under N_2 with stirring for 17 h The reaction was cooled, acidified to pH 2 and kept for 0 5 h Aq layer was saturated with NaCl, extracted with ether which was then washed with H_2O and dried Solvent was removed and the residue chromatographed on silica gel followed by vacuum distillation at 169-174°C (bath)/4 mm to (1) (1 352 g) in 41 6% yield, $[\alpha]_D^{26}$ = +7 8(c = 1 54, CH_3OH), υ_{max} 3120, 3055, 2955, 2920, 2866, 2704, 1714, 1687, 1561, 1508, 1458, 1402, 1380, 1360,1321, 1295, 1248, 1160, 1115, 1050, 1037, 1021, 1002, 928, 872, 822, 740, 642 cm^{-1}, λ_{max} (ε) 250 (~ 3350), 215 nm (~ 5800) ^{1}H NMR δ 0 92 (9H, d, J = 7 HZ), 1 40 (2H, m), 1 91 (2H, m), 2 25 (4H, m), 2 72 (2H, t, J = 7 5 Hz), 6.72 (1H,m), 7 45 (1H,m), 7 98 (1H,m), Calcd for $C_{15}H_{22}O_3$ C, 71 96, H, 8 85, Found C, 72 18, H, 9 12

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