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TOTAL SYNTHESIS OF (±)-ATRACTYLON AND (±)-LINDESTRENE

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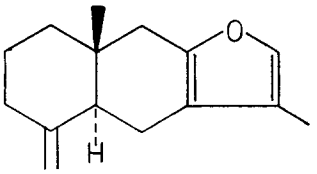
Summary: The total synthesis of the eudesmane furanosesquiterpenes (±)-atractylon (1) and (±)-lindestrene (2) is described. Both 1 and 2 were synthesized via the methyl xanthate intermediate (10).

Atractylon (1) and lindestrene (2) are representative furanoeudesmane sesquiterpenes. Atractylon (1) has been isolated from Atractylis ovata[1] and Atractylodes japonica[2]. Lindestrene (2) has been isolated from the root of Lindera strychnifolia[3] and from Neolitsea sericea[4]. Both (±)-1 and (±)-2 have been individually synthesized by Minato and Nagasaki[5,6]. Mander and co-workers[7] have reported that the reductive alkylation of α-tetralone derivatives leads to suitably functionalized decalins which can be used for the synthesis of germacrane sesquiterpenes[8]. We now report the use of this process applied to the total synthesis of two eudesmane sesquiterpenes, (±)-atractylon (1) and (±)-lindestrene (2).



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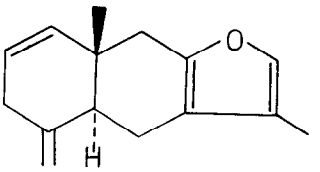

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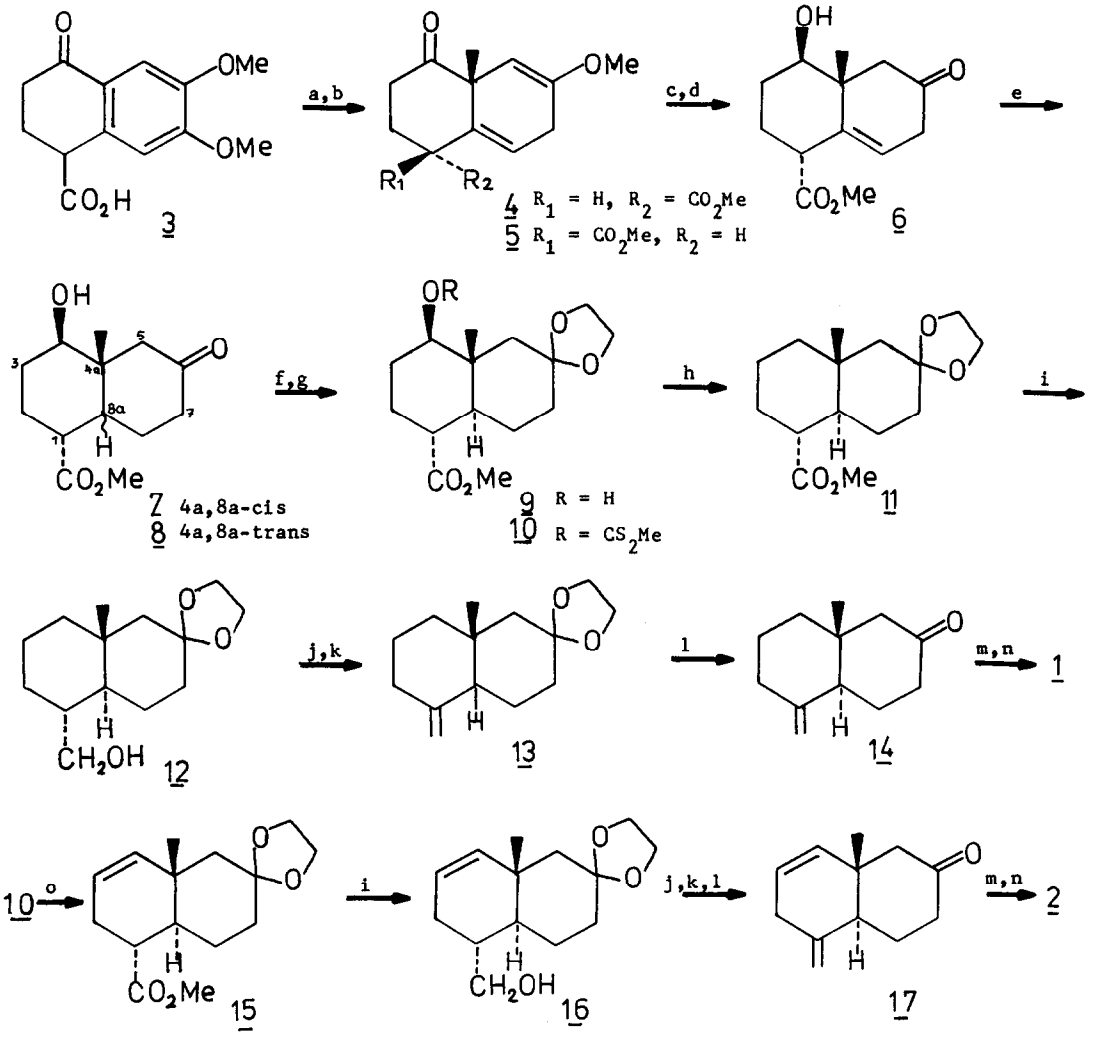
Our synthesis began with the α-tetralone (3)[7] which we have previously employed in the stereoselective synthesis of the furanogermacrane sesquiterpene sericenine[8]. Reductive C-methylation of 3, followed by esterification with diazomethane, gave the two diastereomeric esters (4), mp 123-125 °C, (51%) and (5), mp 89-90 °C, (14%)[7,8]. Reduction of 4 with sodium borohydride, followed by hydrolysis of the methyl enol ether with oxalic acid, gave exclusively the β-alcohol (6), mp 108 °C, (90% overall). Hydrogenation of 6 with palladium-on-carbon yielded both the cis-decalin (7), mp 91-94 °C, (29%) and the



(a) KO^{t}Bu, ^{t}BuOH, K, NH_3, LiBr, THF, -78°C; (ii) MeI, THF-H_2O(1:1), -78°C; (b) CH_2N_2, Et_2O, -10°C, 0.5h; (c) $NaBH_4$, EtOH, 0°C, 0.5h; (d) 0.5M $(CO_2H)_2$, rt, 0.5h; (e) H_2, Pd-C, EtOH, rt; (f) $(CH_2OH)_2$, cat. p-TsOH, PhH, reflux; (g) (i) NaH, THF, rt, 3h; (ii) CS_2, MeI, rt, 40h; (h) Bu_3SnH, cat. AIBN, toluene, reflux; (i) $LiAlH_4$, THF, rt; (j) o-$C_6H_4(NO_2)SeCN$, $^{n}Bu_3P$, THF, rt, 0.5h; (k) 30% H_2O_2, THF, rt, 16h; (l) 1N-HCl-THF(1:2), rt, 16h; (m) LDA, $ZnCl_2$, $MeCOCH_2OTHP$, -78°C⟶ -20°C; (n) cat. p-TsOH, THF-H_2O(2:1), 60°C, 0.5h; (o) $(C_6H_5)_2$, 210°C, 16h.

trans-decalin (8), mp 80-81 °C, (57%). The trans ring junction of 8 was established by X-ray crystallographic analysis on the crystalline tosylate of 8. The ketone group of 8 was protected as the ethylene ketal (9), (81%). Treatment of the generated sodium alkoxide of 9 with carbon disulphide and methyl iodide yielded after 40 hr at room temperature the methyl xanthate (10), mp 134-136 °C, (80%).

The methyl xanthate (10) was chosen as our common intermediate in the synthesis of (±)-1 and (±)-2, since it allowed for either the deoxygenation[9] at C_4 or the formation of a double bond at C_3-C_4[10].

Reduction of 10 with tributyltin hydride in refluxing toluene in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) gave the desired decalin derivative (11), (92%)[9]. Reduction of 11 with lithium aluminium hydride in THF gave the alcohol (12), (90%). Treatment of 12 with o-nitrophenylselenyl cyanide in the presence of tri-n-butylphosphine[11], followed by oxidation with 30% H_2O_2, yielded the exocyclic alkene (13), (69% overall). Hydrolysis of the ketal group of 13 afforded the ketone (14), (80%). Aldol condensation of the generated zinc enolate of 14 with 1-tetrahydropyranyloxy-2-propanone, followed by treatment of the crude aldol adduct with a catalytic amount of p-toluenesulphonic acid in hot aqueous THF[12], furnished (±)-atractylon (1) in 53% yield.

In a similar fashion, (±)-lindestrene (2) was synthesized from the methyl xanthate (10). Pyrolysis of 10 in biphenyl (210 °C, 16 hr) yielded the desired alkene (15), (80%)[10]. Reduction of 15 with lithium aluminium hydride in THF gave the alcohol (16), (79%). Formation of the exocyclic double bond[11], followed by mild acid hydrolysis of the ketal group, afforded the ketone (17) in 39% overall yield. Methyl furan annulation[12] of 17 gave (±)-lindestrene (2) in 58% yield.

Both synthetic (±)-lindestrene (2) and (±)-atractylon (1) were completely identical in their spectral data (IR and ^{1}H-NMR) with the corresponding natural products.

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References and Notes

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13. All compounds have been characterized by elemental analysis and/or high resolution mass spectra. Selected spectral data are reported below:
6: IR (CH_2Cl_2) 3460, 2960, 1745, 1730, 1620 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 1.03 (3H, s, CH_3), 1.54-1.94 (4H, m), 2.31 (1H, bs, OH), 2.49 (1H, d, $J_{5,5'}$ = 13.3 Hz, H-5), 2.63 (1H, dd, $J_{5',5}$ = 13.3 Hz, $J_{5',7'}$ = 1.5 Hz, H-5'), 2.71-3.02 (2H, m, H-7,7'), 3.13-3.19 (1H, m, H-1), 3.56 (1H, dd, $J_{4,3}$ = 11.2 Hz, $J_{4,3'}$ = 4.2 Hz, H-4), 3.71 (3H, s, OCH_3), 5.20 (1H, dt, $J_{8,1}$ = 2.0 Hz, $J_{8,7}$ = $J_{8,7'}$ = 3.7 Hz, H-8) ; mass spectrum, m/e, M^+, 238.1211. $C_{13}H_{18}O_4$ requires, M^+, 238.1205.
14: IR (CH_2Cl_2) 2950, 1700, 1640, 910 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 0.69 (3H, d, J = 0.6 Hz), 1.22-2.46 (13H, m), 4.50 (1H, d, J = 1.5 Hz), 4.81 (1H, d, J = 1.5 Hz) ; mass spectrum, m/e, M^+, 178.1354. $C_{12}H_{18}O$ requires, M^+, 178.1538 ; microanalysis, calcd. for $C_{12}H_{18}O$: C 80.85, H 10.18. Found: C 80.66, H 10.38.
17: IR (CH_2Cl_2) 2940, 1710, 1650, 1610, 910 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 0.74 (3H, d, J = 0.8 Hz), 1.60-2.61 (7H, m), 2.73-3.01 (2H, m), 4.67 (1H, bs), 4.93 (1H, bs), 5.42 (1H, dt, J = 9.7, 2.1 Hz), 5.57 (1H, dt, J = 9.7, 3.7 Hz) ; mass spectrum, m/e, M^+, 176.1196. $C_{12}H_{16}O$ requires, M^+, 176.1201.

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