Stereocontrolled Total Synthesis of Pseudoclovene-B

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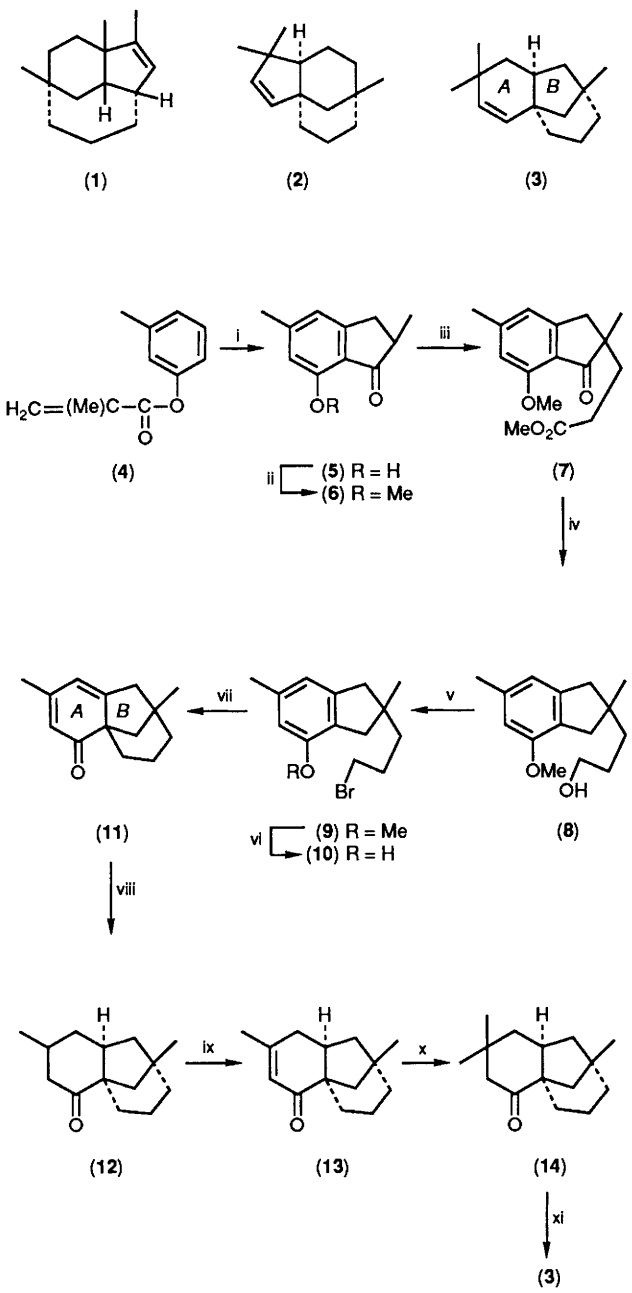
An efficient stereocontrolled synthesis of (±)-pseudoclovene-B (**3**) has been accomplished, involving aryl participated intramolecular cyclisation of the bromophenol (**10**) as the key step.

Sesquiterpene artefacts derived from acid treatment of caryophyllene and caryolan-l-ol possess novel skeletal features and have attracted considerable attention in recent years as challenging synthetic targets. Total syntheses of the tricyclic hydrocarbons isoclovene (**1**), a product of dehydration of caryolan-l-ol with polyphosphoric acid, and clovene (**2**), an acid-induced rearrangement product of caryophyllene, have recently been reported[1,2] by several groups. Pseudoclovene-B (**3**), another sesquiterpene hydrocarbon incorporating a tricyclo[6.3.1.$0^{1,6}$]dodecane skeleton, was isolated and



Scheme 1. *Reagents and conditions*: i, LiCl–$AlCl_3$ melt, 180 °C, 5 min, 60%; ii, MeI, K_2CO_3, Me_2CO, reflux, 6 h, 90%; iii, NaOMe, CH_2=$CHCO_2Me$, MeOH, reflux, 6 h, 76%; iv, $LiAlH_4$, Et_2O, reflux, 4 h then Li, liq. NH_3, NH_4Cl, 85%; v, PBr_3, benzene, 70 °C, 3 h, 75%; vi, BBr_3, CH_2Cl_2, 0—20 °C, 18 h, 88%; vii, Bu^tOK, Bu^tOH, 80 °C, 10 h, 78%; viii, H_2, Pd/C, EtOH, 100%; ix, Br_2, AcOH, 15 °C then LiBr, Li_2CO_3, DMF, 125 °C, 4 h, 75%; x, CuI, MeLi, BF_3·Et_2O, −50 °C, 2 h, 87%; xi, $NH_2NHSO_2C_6H_4Me$, MeOH, HCl (trace), reflux, 2 h, 100% crude then MeLi, Et_2O, 20 °C, 8 h, 72%.

characterised[3] along with (**1**) and several other sesquiterpenes when caryolan-1-ol was treated with polyphosphoric acid. The structure (**3**) of pseudoclovene-B was conclusively established through *X*-ray crystallographic analysis[4] of the corresponding dibromide. In connection with our studies on the synthesis of bridged carbocyclic systems encountered in tricyclic sesquiterpenes, we have accomplished a stereocontrolled synthesis of pseudoclovene-B (**3**) starting from *m*-cresol. The salient feature of our synthesis is an efficient aryl participated intramolecular cyclisation[5] of the bromophenol (**10**) to provide the dienone (**11**) in high yield and subsequent use of the functional groups in the ring *A* of (**11**) to generate stereoselectively the required *cis*-stereochemistry of the *A*/*B* ring juncture.

Reaction of *m*-cresol with 2-methylacryloyl chloride provided the phenolic ester (**4**) which on treatment with LiCl–$AlCl_3$ melt at 180 °C for a brief period furnished the hydroxyindanone (**5**),† by rearrangement and concomitant intramolecular cyclisation. The ketone (**5**) was easily purified by steam distillation and obtained in 60% yield from (**4**). The corresponding methyl ether (**6**) (b.p. 138—140 °C at 2 mmHg) was subjected to Michael reaction with methyl acrylate in the presence of NaOMe to afford the keto-ester (**7**) (b.p. 160 °C at 0.5 mmHg), in 76% yield. Reduction of (**7**) with $LiAlH_4$ and subsequent hydrogenolysis of the resulting diol with Li in liquid ammonia yielded the alcohol (**8**) (b.p. 130 °C at 0.5 mmHg) in 85% overall yield. Treatment of (**8**) with PBr_3 provided (**9**)† (75%) (b.p. 130 °C at 0.5 mmHg) which was converted into the bromophenol (**10**) (m.p. 50—51 °C) with BBr_3 in CH_2Cl_2, in 88% yield. In order to effect intramolecular cyclisation[5] of the bromophenol, a dilute (0.01 M) solution of (**10**) in dry Bu^tOH was heated with Bu^tOK (1 equiv.) at 80 °C for 10 h. The dienone (**11**)† (b.p. 115 °C at 0.5 mmHg) was isolated as the only neutral product of the reaction in 78% yield.

Catalytic hydrogenation of the dienone (**11**) proceeded stereoselectively with rapid uptake of two moles of hydrogen to furnish, in quantitative yield, the *A*/*B cis*-fused ketone (**12**)† which was found to be homogeneous by TLC and GC. Similar reduction of closely related systems had generated exclusively *cis*-stereochemistry at 6/5 ring junctures.[6,7] Bromination of the ketone (**12**) with Br_2 in glacial AcOH and subsequent dehydrobromination of the resulting α-bromoketone with LiBr and Li_2CO_3 in dimethylformamide (DMF) furnished the enone (**13**)† (b.p. 108—110 °C at 0.4 mmHg) in 75% overall yield. Conjugate addition of $LiMe_2Cu$ to the enone (**13**) in the presence of BF_3·Et_2O [8] provided the saturated ketone (**14**) (87%, m.p. 57—58 °C). The tosylhydrazone derivative of (**14**) was treated with MeLi (2.5 equiv.)[9] in Et_2O at 20 °C for 8 h. Chromatography of the crude product over neutral alumina and elution with hexane afforded the tricyclic hydrocarbon (**3**)† (b.p. 95 °C at 3 mmHg) in 72% yield from (**14**). The spectral data of (**3**) agreed very well with those reported[4] in the literature. The structure of (**3**) was further confirmed from ^{13}C NMR spectral studies and DEPT experiments.

† All compounds reported here gave spectral and analytical data consistent with assigned structures. *Selected spectral data* for (**5**): $\nu_{max.}$ (film) 3340, 1670, 1622, 1597 cm^{-1}; δ_H (CCl_4) 1.24 (d, 3H, *J* 7 Hz), 2.30 (s, 3H), 2.17—3.47 (m, 3H), 6.45 (s, 1H), 6.60 (s, 1H), 8.58 (br. s, 1H). (**9**): δ_H (CCl_4) 1.08 (s, 3H), 1.37—2.93 (m, 8H), 2.28 (s, 3H), 3.30 (t, 2H, *J* 6 Hz), 3.73 (s, 3H), 6.33 (s, 1H), 6.47 (s, 1H). (**11**): $\nu_{max.}$ (film) 1665, 1640 cm^{-1}; δ_H ($CDCl_3$) 1.10 (s, 3H), 2.03 (d, 3H, *J* 1 Hz), 1.38—2.80 (m, 10H), 5.62 (m due to allylic coupling, 1H), 5.82 (m, 1H). (**12**): $\nu_{max.}$ (film) 1700 cm^{-1}; δ_H ($CDCl_3$) 0.97 (d, 3H, *J* 6.5 Hz), 1.02 (s, 3H), 1.10—2.41 (m, 16 H). (**13**): $\nu_{max.}$ (film) 1660 cm^{-1}; δ_H (CCl_4) 1.03 (s, 3H), 1.90 (s, 3H), 1.13—2.60 (m, 13H), 5.68 (m, 1H). (**3**): δ_H ($CDCl_3$) 0.92 (s, 3H), 0.97 (s, 6H), 1.05—2.00 (m, 13H), 5.34 (s, 2H); δ_C ($CDCl_3$ δ 20.63, 27.70, 27.96, 31.12, 32.63, 38.00, 38.72, 38.93, 40.03, 44.81, 45.29, 45.58, 49.58, 132.71, 135.40.

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