Stereocontrolled Total Synthesis of (±)-Isocomene and (±)-β-Isocomene *via* Ring Enlargement

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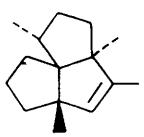
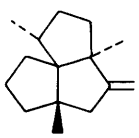
A total synthesis of (±)-isocomene (**1**) and (±)-β-isocomene (**2**) employing a chelation-controlled regioselective epoxide–carbonyl rearrangement as the key step has been realized.

Recently, triquinane sesquiterpenes have received growing interest because of their unique carbon skeletons.[1] Isocomene (**1**)[2] and β-isocomene (**2**)[3] are representative members of angular triquinane sesquiterpenes having a tricyclo-[6.3.0.$0^{1,5}$]undecane framework and several syntheses of (±)-(**1**)[4] and (±)-(**2**)[4a,g] have been reported. We report herein a stereocontrolled total synthesis of (±)-(**1**) and (±)-(**2**) employing chelation-controlled regioselective ring enlargement by means of an epoxide–carbonyl rearrangement as the key step, a method which has been successfully applied to the total synthesis of (±)-modhephene, a propellane type triquinane.[5] In the present case, the migratory regioselectivity in this rearrangement is controlled by chelation of the lithium cation with the hydroxy group.

Irradiation (300 nm) of the enone (**3**)[6] with an excess of allene in dichloromethane at −78 °C gave the head-to-head adduct (**4**)† as the sole product in 77% yield. Reduction of (**4**) with lithium triethylborohydride in diethyl ether at −78 °C gave the *endo*-alcohol (**5**) predominantly (selectivity, 91 : 9) which was isolated in 87% yield. The alcohol (**5**) was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) (Na_2HPO_4, CH_2Cl_2, 0 °C) to afford exclusively the *syn*-epoxide (**6**) in 70% yield. The epoxide–carbonyl rearrangement of (**6**) [LiBr, hexamethylphosphoramide (HMPA), benzene, 80 °C] proceeded regioselectively to furnish the hydroxy ketone (**7**), m.p. 61—64 °C, as the sole product in 81% yield. It should be emphasised that the epoxide–carbonyl rearrangement of (**6**) as well as the *m*-CPBA oxidation of (**5**) proceeded with complete regio- and stereo-selectivity because of the strong chelating or hydrogen-bonding ability of the hydroxy group.‡



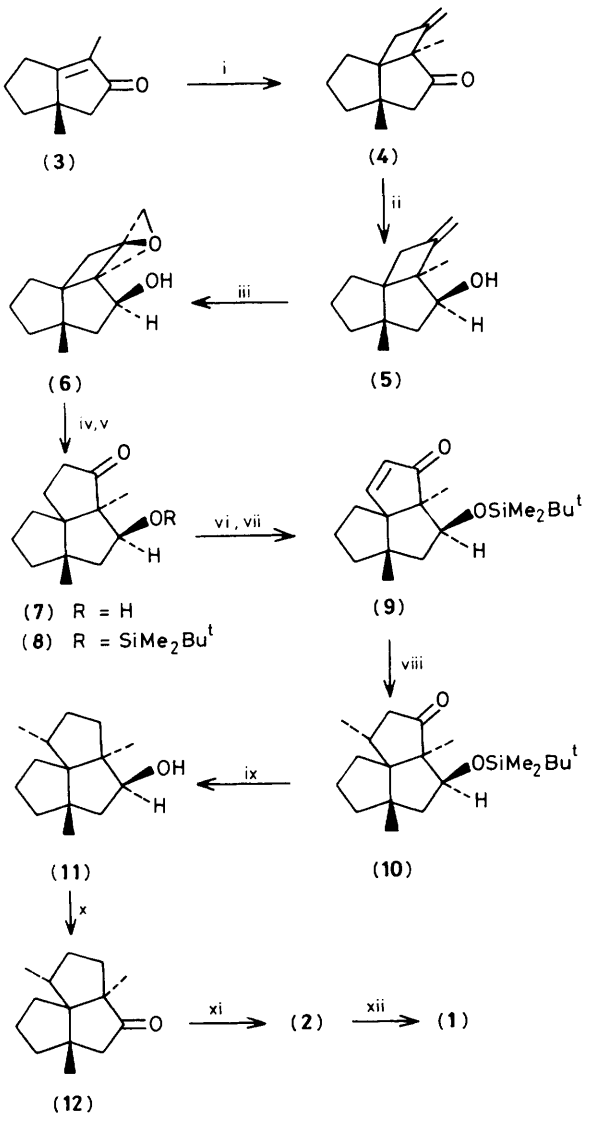
(**1**)



(**2**)

† Satisfactory spectral and analytical data were obtained for all new compounds.

‡ In the case of the ethylene acetal of (**4**), both epoxidation (*syn* : *anti* 1.1 : 1.0) and the subsequent rearrangement of the *syn*-epoxide (9 : 1 selectivity) proceeded with lower selectivity. See also ref. 5.



Scheme 1. i, *hv*, allene, CH_2Cl_2, −78 °C; ii, $LiEt_3BH$, Et_2O, −78 °C; iii, *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C; iv, LiBr, HMPA, C_6H_6, 80 °C; v, Bu^tMe_2SiCl, imidazole, DMF, 35 °C; vi, LDA, PhSeCl, THF, −78 °C; vii, H_2O_2, pyridine, CH_2Cl_2; viii, $LiMe_2Cu$, Et_2O, 0 °C; ix, $N_2H_4 \cdot H_2O$, K_2CO_3, triethylene glycol, 200 °C; x, PCC, CH_2Cl_2; xi, Ph_3MePBr, $EtC(Me)_2ONa$, toluene, 110 °C; xii, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2.

With the synthesis of the key intermediate (**7**) realized, we next focused on the stereoselective introduction of the *exo* C(2) methyl group. After protection of the hydroxy group [Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF), 35 °C, 84%], the siloxy ketone (**8**) was subjected to phenylselenenylation [lithium di-isopropylamide (LDA), PhSeCl, tetrahydrofuran (THF), −78 °C, 82%] followed by oxidative selenoxide elimination (H_2O_2, pyridine, CH_2Cl_2) to give the siloxy enone (**9**), m.p. 26—27 °C, in 82% yield. Conjugate addition of lithium dimethylcuprate (Et_2O, 0 °C) to (**9**) occurred exclusively on the convex face of the tricyclic ring system to afford only the ketone (**10**), m.p. 84—85 °C, with an *exo* C(2) methyl group, in 76% yield. Wolff–Kishner reduction of (**10**) (N_2H_4, K_2CO_3, triethylene glycol) with concomitant deprotection gave the alcohol (**11**), m.p. 82—85 °C (68% yield), which was oxidized with pyridinium chlorochromate (PCC) (CH_2Cl_2) to give the ketone (**12**), m.p. 81—83 °C, in 86% yield. Wittig olefination of (**12**) ($Ph_3MeP^+Br^-$, sodium 1,1-dimethylpropoxide, toluene, 110 °C) furnished (±)-β-isocomene (**2**) in 98% yield. Acid-catalysed isomerization of (**2**) (toluene-*p*-sulphonic acid, CH_2Cl_2) gave (±)-isocomene (**1**) in 99% yield. The spectral data of (**1**) and (**2**) (i.r., ^1H and ^{13}C n.m.r.) were identical with those of authentic samples.

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