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A Total Synthesis of (±)-Herbertene

Asok Kumar Saha, Sarbani Das and Debabrata Mukherjee*

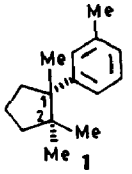
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India.

Frank R. Fronczek

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, U.S.A.

Abstract : A total synthesis of (±)-herbertene **(1)** has been accomplished using the benz[e]indenone 3 as a key intermediate.

(-)-Herbertene, a bicyclic sesquiterpene hydrocarbon, possesses a 1,2,2-trimethyl-1-*m*-tolylcyclopentane structure and was isolated[1] by Matsuo *et al* from the liverwort *Herberta adunca*. The racemic form of herbertene was isolated[2] by Fráter



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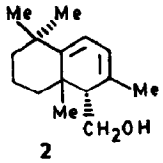

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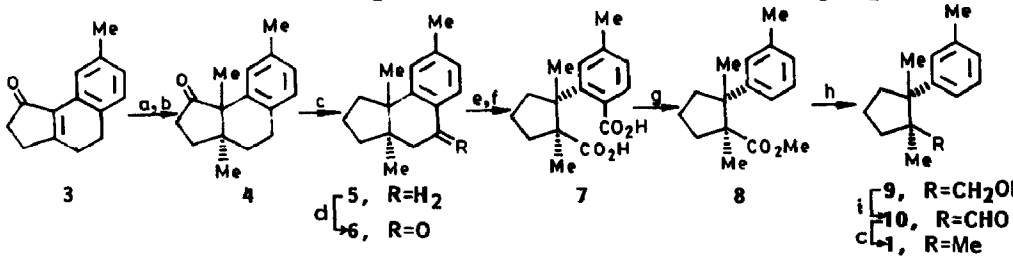
among other products from the carbonium ion rearrangement of the bicyclic alcohol 2. The synthesis of herbertene presents an interesting problem in view of steric congestion associated with two vicinal quaternary centres in a cyclopentane ring. A route to (±)-herbertene (1) was disclosed[3] by Leriverend and Vazeux and the first enantiocontrolled synthesis of (-)-herbertene has been reported[4] recently by Takano *et al*. In connection with our studies on conjugate additions to benz[e]indenones, we have developed an efficient route to (±)-herbertene from the benz[e]indenone 3 as outlined in Scheme 1.

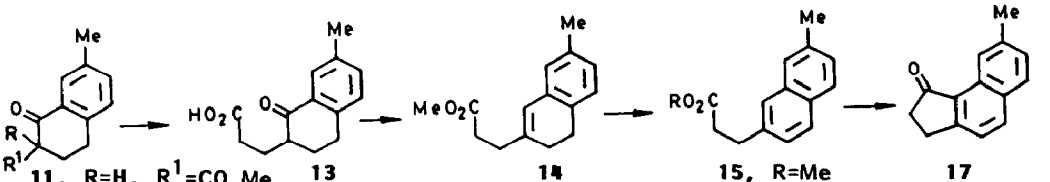
Conjugate addition of $LiMe_2Cu$ to 3 in the presence of $BF_3.Et_2O$ followed by



Scheme 1. Reagents and Conditions : a, CuI, MeLi, THF, $BF_3.Et_2O$, -40°C, 3h; b, $(Me)_2(Et)COK$, $(CH_2OMe)_2$, MeI, reflux, 4h; c, N_2H_4, $N_2H_4.2HCl$, $(HOCH_2CH_2)_2O$, 130°C, 2h then KOH, 210°C, 2h; d, CrO_3, AcOH, 24°C, 4h; e, HCO_2Et, NaH, C_6H_6, 0-25°C, 16h; f, aq. NaOH, H_2O_2 (30%), 25°C, 20h, H_3O^+; g, Cu, quinoline, 220°C, 2h; Et_2O, CH_2N_2; h, LAH, Et_2O, reflux, 4h; i, PCC, CH_2Cl_2, NaOAc, 25°C, 1.5h.

alkylation of the resulting product with MeI using potassium t-amyl oxide as the base afforded the ketone 4[5], m.p. 104-105°C in 67% overall yield. The trans-stereochemistry of the 6/5-ring fusion of 4 has been established by single crystal X-ray crystallography. Huang-Minlon reduction of 4 furnished the hydrocarbon 5 (85%) which on oxidation with CrO_3 delivered the ketone 6[5] in 82% yield. The ketone 6 was converted into the corresponding formyl derivative which on treatment with alkaline H_2O_2 furnished the diacid 7 (88%), m.p. 209-210°C. Selective decarboxylation of the aromatic carboxyl group of 7 followed by esterification with CH_2N_2 afforded the ester 8[5] (85%). Reduction of 8 with LAH and subsequent oxidation of the resulting alcohol 9[5] with pyridinium chlorochromate provided the aldehyde 10 in 82% overall yield. Huang-Minlon reduction of 10 furnished (±)-herbertene (1)[5] (80%). The spectral data of 1 agreed very well with those reported in the literature[1].

The enone 3 was conveniently prepared in the following manner. Conversion of 7-methyl-1-tetralone[6] into the β-ketoester 11 followed by Michael reaction with methyl acrylate afforded 12 in high yield. Treatment of 12 with 10% H_2SO_4 in refluxing AcOH furnished the keto-acid 13 (78%), m.p. 114-115°C. Reduction of 13 with $NaBH_4$ followed by treatment[7] of the crude product with MeOH in the presence of H_2SO_4 furnished the unsaturated ester 14 in 85% yield. Dehydrogenation of 14 with sulphur afforded 15



11, R=H, $R^1=CO_2Me$ 13 14 15, R=Me 17

12, $R=CH_2CH_2CO_2Me$, $R^1=CO_2Me$ 16, R=H

(88%), m.p. 95-96°C which on hydrolysis yielded the acid 16, m.p. 170-171°C. The acid chloride, prepared from 16, was cyclised with anhydrous $AlCl_3$ in nitrobenzene to afford 17 (82%), m.p. 105-106°C. Birch reduction of 17 with Na and EtOH in liquid ammonia provided the enone 3 (84%), m.p. 126-127°C.

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5. Selected spectral data for 4: IR (KBr): 1733, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 0.79 (s, 3H), 1.22 (s, 3H), 1.50-2.63 (m, 6H), 2.33 (s, 3H), 2.80-3.13 (m, 2H), 6.80-7.13 (m, 2H), 8.03 (bs, 1H). 6: IR (Film): 1689, 1606 cm^{-1}; ^1H NMR (CCl_4): δ 0.83 (s, 3H), 1.23 (s, 3H), 1.45-2.97 (m, 8H), 2.43 (s, 3H), 6.87-7.17 (m, 2H), 7.80 (d, 1H, J = 8 Hz). 8: IR (Film): 1727, 1608 cm^{-1}; ^1H NMR (CCl_4): δ 0.81 (s, 3H), 1.30 (s, 3H), 1.57-2.75 (m, 6H), 2.34 (s, 3H), 3.70 (s, 3H), 6.83-7.23 (m, 4H). 9: ^1H NMR ($CDCl_3$): δ 0.63 (s, 3H), 1.30 (s, 3H), 1.47-2.78 (m, 7H), 2.37 (s, 3H), 3.75 (s, 2H); 6.93-7.37 (m, 4H). 1: ^1H NMR ($CDCl_3$): δ 0.58 (s, 3H), 1.10 (s, 3H), 1.27 (s, 3H), 1.70 (br, m, 6H), 2.35 (s, 3H), 6.75-7.20 (m, 4H).
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