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AN APPROACH TO THE SYNTHESIS OF ISOLONGIFOLENE

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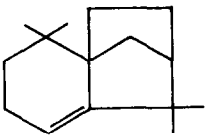
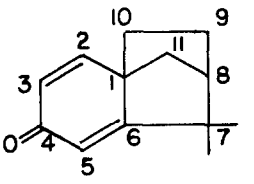
Abstract—An efficient synthesis of 7, 7-dimethyltricyclo [6.2.1.0^{1,6}] undeca-2, 5-dien-4-one **2**, an advanced intermediate for the synthesis of the tricyclic sesquiterpene isolongifolene **1**, has been carried out utilising Ar_1-5 participation reaction as the key step.

Isolongifolene **1**, a sesquiterpene artefact, is a rearrangement product of longifolene and incorporates[1] a novel tricyclo[6.2.1.0^{1,6}]undecane skeleton. In connection with our interest in the synthesis of bridged carbocyclic systems encountered in tricyclic sesquiterpenes, we have investigated intramolecular cyclisation of an appropriately substituted indane derivative as an expedient pathway to the tricyclic framework of isolongifolene. We now report a short and efficient synthesis of the dienone **2** involving Winstein's aryl participation (Ar_1-5) reaction[2] of the bromophenol **10** as the key step. The synthesis of the dienone **2** constitutes a formal synthesis of isolongifolene **1** since Piers and Zbozny converted[3] **2** into the sesquiterpene **1** through the incorporation of a gem-dimethyl group at C-2. The dienone **2** has also the potentiality of providing a convenient synthetic route to the sesquiterpenes of the zizaane family which are characterised by the tricyclo[6.2.1.0^{1,5}] undecane skeleton. A few members of the zizaane group have been synthesised through molecular rearrangements of compounds containing tricyclo[6.2.1.0^{1,6}] undecane ring systems.[4]

The starting material for the present synthesis, 3, 3-dimethyl-5-methoxy-1-indanone **3** was conveniently prepared[5] from 3-methoxyacetophenone in a few steps. Bromination of the indanone **3** was carried out in ether[6] to afford the 3-bromoindanone **4** in excellent yield. ^{1}H-NMR of **4** exhibited a sharp singlet at δ4.43 ppm due to the proton at C-2. Although gem-disubstituted at the 3-position, the bromo-ketone **4** readily underwent condensation with diethyl sodiomalonate in dimethoxyethane to give rise to the keto-diester **5** in good yield. The two vicinal protons [$>$CH–CH(CO$_2$Et)$_2$] in **5** appeared in the NMR as an AB quartet centred at δ3.22 and δ3.47 ppm. Partial hydrolysis of the diester **5** with NaOH (1 mole) in



1



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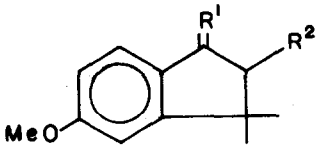

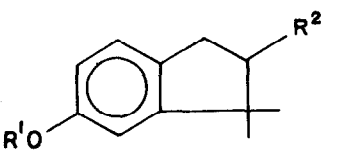

3 R^1=O, R^2=H

4 R^1=O, R^2=Br

5 R^1=O, R^2=CH(CO$_2$Et)$_2$

6 R^1=O, R^2=CH$_2$CO$_2$Et

7 R^1=  , R^2=CH$_2$CH$_2$OH

8 R^1=Me, R^2=CH$_2$CH$_2$OH

9 R^1=Me, R^2=CH$_2$CH$_2$Br

10 R^1=H, R^2=CH$_2$CH$_2$Br

aqueous EtOH and subsequent distillation of the product afforded the keto-ester **6**. Reduction of **6** with excess of $LiAlH_4$ furnished the diol **7**. In order to remove selectively the benzylic OH group, the crude diol was subjected to hydrogenolysis (H_2, 10% Pd–C) in acetic acid containing a few drops of perchloric acid. Uptake of calculated amount of H_2 was complete in about 2 hr. However, the primary OH group underwent partial esterification during the process as was evident from the appearance of weak NMR signals at δ2.0 and δ4.1 ppm in the crude product. A short treatment with 5% methanolic KOH afforded the hydroxy compound **8** which was converted into the bromide **9** with PBr_3. Demethylation of the bromo compound **9** was achieved with BBr_3 in CH_2Cl_2. The bromophenol **10** underwent intramolecular cyclisation on being heated with a 0.01 M soln of t-BuOK in t-BuOH. The dienone **2** was isolated as the only neutral product of the reaction. The m.p. and the spectral data of **2** agreed very well with those reported in the lit.[3]

EXPERIMENTAL

M.p.s were taken for samples in open capillaries in a H_2SO_4 bath. UV spectra were recorded for solutions in 95% EtOH with a Beckmann DU spectrophotometer, and IR spectra with a Perkin–Elmer 298 instrument. NMR spectra were determined with a Varian T-60 spectrophotometer (TMS as internal standard). For vpc, a Hewlett–Packard 5730 gas chromatograph with flame ionisation detector was used. Extracts were dried over Na_2SO_4. Light petroleum refers to the fraction of b.p. 60–80°.

3, 3-*Dimethyl-5-methoxy-1-indanone* **3**. A mixture of P_2O_5 (36 g) and H_3PO_4 (89%, 24 g) was heated at 100° for 1 hr. To this mixture, cooled to 60°, was added β-methyl-β-(3-methoxyphenyl) butyric acid[5] (5 g) and the contents were mixed thoroughly. The viscous mass was kept at 80° for 30 min, poured into ice water and extracted with ether. The extracts were washed with sat. $NaHCO_3$aq, water and dried. After the removal of the solvent, the residue was distilled at 130–132°/0.8 mm to afford a colourless oil (3.6 g). Gas chromatography (3% SE 52 column, temp. 170°) indicated the product to be a 9:1 mixture of two compounds. Chromatography of this material over neutral alumina (100 g) and elution with benzene-light petroleum (1:19–1:9) afforded **3** (3 g, 66%), m.p. 59–60° (from light petroleum); ν_{max}($CHCl_3$) 1690 and 1600 cm^{-1}; δ (CCl_4) 1.4 (s, 6H), 2.45 (s, 2H), 3.9 (s, 3H), 6.73–7.6 (m, 3H). (Found: C, 75.65; H, 7.56. $C_{12}H_{14}O_2$ requires: C, 75.76; H, 7.42%).

2-*Bromo*-3, 3-*dimethyl-5-methoxy-1-indanone* **4**. To a stirred soln of **3** (3 g) in anhyd ether (300 ml) at 10° was added Br_2 (2.6 g) during 20 min allowing each drop of Br_2 to decolourise before more was added. The mixture was stirred at 10° for another 2 hr and left at r.t. for 20 hr. It was then washed with sat $NaHCO_3$aq water and dried. Evaporation of the solvent left a residue which was distilled to furnish **4** (3.9 g, 92%), b.p. 158–160°/0.6 mm; δ (CCl_4) 1.38 (s, 3H), 1.5 (s, 3H), 3.92 (s, 3H), 4.43 (s, 1H), 6.75 – 7.02 (m, 2H), 7.66 (d, 1H, J = 9 Hz). (Found: C, 53.42; H, 5.14. $C_{12}H_{13}O_2Br$ requires: C, 53.55; H, 4.87%).

Diethyl 3, 3-*dimethyl-5-methoxy-1-oxo-2-indanylmalonate* **5**. A soln of **4** (3.6 g) in DME (4 ml) was added dropwise with shaking to diethyl sodiomalonate [prepared from NaH (500 mg) and diethyl malonate (5 g)] in DME (35 ml). The mixture was refluxed for 12 hr and then worked up to afford **5** (3.9 g, 84%), b.p. 200–202°/0.2 mm; ν_{max} (Film) 1752, 1735, 1705, 1600 cm^{-1}; δ (CCl_4) 1.17 (s, 3H), 1.28 (t, 3H, J = 7 Hz), 1.32 (t, 3H, J = 7 Hz), 1.50 (s, 3H), 3.22 (d, 1H, J = 10 Hz), 3.47 (d, 1H, J = 10 Hz), 3.88 (s, 3H), 4.18 (q, 2H, J = 7 Hz), 4.21 (q, 2H, J = 7 Hz), 6.73–6.97 (m, 2H), 7.56 (d, 1H, J = 9 Hz). (Found: C, 65.49; H, 7.12. $C_{19}H_{24}O_6$ requires: C, 65.50; H, 6.94%).

Ethyl 3, 3-*dimethyl-5-methoxy-1-oxo-2-indanylacetate* **6**. A mixture of **5** (3.5 g), NaOH (400 mg), EtOH (3 ml) and water (1 ml) was stirred at r.t. for 20 hr. The mixture was then refluxed for 30 min, cooled, diluted with water (3 ml) and extracted with ether. The aqueous phase was acidified with conc HCl, saturated with NaCl and extracted repeatedly with ether. The extracts were dried and the solvent evaporated off. The residue was distilled at 170°/0.5 mm to afford **6** (2.2 g, 79.5%), ν_{max} ($CHCl_3$) 1735, 1700, 1595 cm^{-1}; δ (CCl_4) 1.13 (s, 3H), 1.28 (t, 3H, J = 7 Hz), 1.48 (s, 3H), 2.0–3.07 (m, 3H), 3.87 (s, 3H), 4.14 (q, 2H, J = 7 Hz), 6.67–6.93 (m, 2H), 7.56 (d, 1H, J = 9 Hz). (Found: C, 69.36; H, 7.50. $C_{16}H_{20}O_4$ requires C, 69.54; H, 7.30%).

1, 1-*Dimethyl-2-(2-hydroxyethyl)-6-methoxyindane* **8**. To a stirred suspension of $LiAlH_4$ (500 mg) in anhyd ether (20 ml) was added dropwise a soln of **6** (2 g) in ether (10 ml). The mixture was stirred and refluxed for 3 hr and then worked up in the usual manner. A soln of the crude **7** (1.7 g) [ν_{max} 3360–3260 (b), 1600 cm^{-1}] in AcOH (10 ml) containing perchloric acid (a few drops) was hydrogenated over Pd–C (10%, 300 mg). Uptake of H_2 (180 ml) ceased after 2 hr. The mixture was filtered, diluted with water and extracted with ether. The extracts were washed with sat $NaHCO_3$aq and evaporated. The residue having NMR signals at δ 2.0 (OAc) and δ 4.1 ppm was refluxed for 30 min with 5% methanolic KOH (5 ml). Usual work-up afforded **8** (1.3 g, 82%), b.p. 130–132°/ 0.6 mm (Found: C, 76.10; H, 9.17. $C_{14}H_{20}O_2$ requires; C, 76.32; H, 9.15%).

1, 1-*Dimethyl-2-(2-bromoethyl)-6-methoxyindane* **9**. PBr_3 (700 mg) in benzene (1 ml) was added dropwise at 0° to a stirred soln of **8** (1 g) in benzene (4 ml). The mixture was stirred at 70° for 3 hr and then worked up to afford **9** (1 g, 78%), b.p. 128–130°/0.6 mm; δ (CCl_4) 0.97 (s, 3H), 1.3 (s, 3H), 1.83–3.55 (m, 7H), 3.73 (s, 3H), 6.4–6.98 (m, 3H). (Found: C, 59.39; H, 6.81. $C_{14}H_{19}OBr$ requires; C, 59. 37; H, 6.76%).

7, 7-*Dimethyltricyclo*[6.2.1.0^{1,6}]*undeca*-2, 5-*dien*-4-*one* **2**. To stirred soln of **9** (500 mg) in dry CH_2Cl_2 (4 ml) at 0° was added dropwise BBr_3 (500 mg) in CH_2Cl_2 (1 ml). The mixture was stirred at r.t. for 20 hr, poured into cold water and extracted with CH_2Cl_2. The organic extracts were washed with water, dried, and the solvent evaporated off. The NMR spectrum of the residue showed complete absence of the OMe group. A soln of the crude **10** (410 mg) in t-BuOH (2 ml) was added dropwise under N_2 to a stirred soln of t-BuOK [from K (60 mg)] in t-BuOH (150 ml). The mixture was stirred at 80° for 8 hr. Most of t-BuOH was removed under reduced pressure and the residue was diluted with water and extracted with ether. The extracts were washed with water, dried and evaporated. The residue was evaporatively distilled at 110°/0.4 mm to afford a colourless oil which crystallised from light petroleum to give **2** (200 mg; 60% from **9**). m.p. 72–73°; λ_{max} 246 nm (log ϵ 4.17); ν_{max} ($CHCl_3$) 1660, 1630 cm^{-1}; δ ($CDCl_3$) 1.07 (s, 3H), 1.13 (s, 3H), 1.25–2.22 (m, 7H), 6.0 (d, 1H, J = 1.5 Hz), 6.24 (d of d, 1H, J = 9.5, 1.5 Hz), 7.0 (d, 1H, J = 9.5 Hz). (Found: C, 82.70; H, 8.71. $C_{13}H_{16}O$ requires C, 82.93; H, 8.57%).

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