

A very short and convenient synthesis of 2-methyl-6-(2'-oxo-4'-methyl-cyclohex-3'-en-1'-yl)-2-heptene and (\pm)-12-hydroxy-2-oxobisabol-3-ene

JASVINDER SINGH, AJAY K ARORA, ANUPAM KHURANA AND
G L KAD*

Department of Chemistry, Panjab University, Chandigarh 160 014, India

MS received on 1 May 1995

Abstract. 2-methyl-6-(2'-oxo-4'-methyl-cyclohex-3'-en-1'-yl)-2-heptene (II) and (\pm)-12-hydroxy-2-oxobisabol-3-ene (III), two naturally occurring terpenic ketones isolated from the *Stevia species* and aerial parts of *Polychyrys fuscus* respectively have been synthesized utilising tandem-phenylation reduction as a key reaction.

Keywords. Terpenic ketones; tandem-phenylation reduction; SeO₂ hydroxylation.

1. Introduction

2-Methyl-6-(2'-oxo-4'-methyl-cyclohex-3'-en-1'-yl)-2-heptene (II) and (\pm)-12-hydroxy-2-oxobisabol-3-ene (III), two naturally occurring terpenes have been isolated by Bohlman *et al* (1976) and Pritschow *et al* (1991) from the *Stevia species* and aerial parts of *Polychyrys fuscus* respectively. Literature records multistep synthesis (Vig *et al* 1978; Sharma *et al* 1994) of compounds II and III albeit in low yields. We report herein a short and facile syntheses of the title compounds utilising tandem-phenylation reduction (Hallstan and McEnroe 1975) and SeO₂ hydroxylation (Rabjohn 1976).

2. Reaction strategy

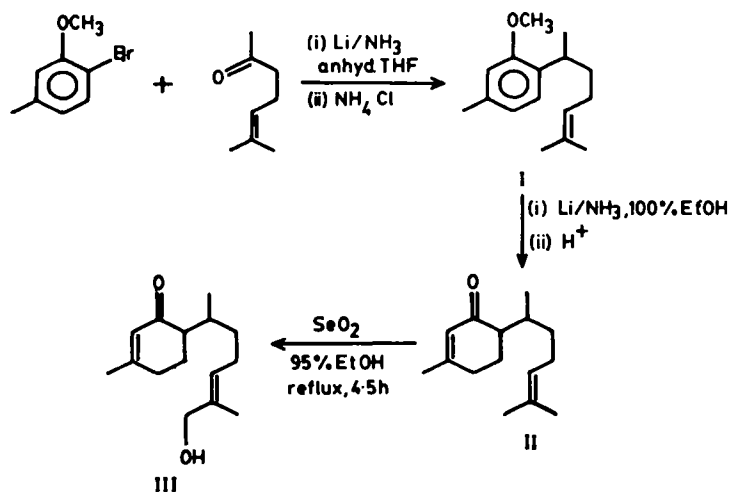
The sequence of reactions followed have been outlined in scheme 1.

Tandem-phenylation reduction of 6-methyl-hept-5-ene-2-one with 2-bromo-5-methylanisole in lithium–ammonia afforded compound I, which was subjected to Birch reduction to obtain compound II. Allylic hydroxylation of II with SeO₂ afforded the required compound III in good yields after chromatographic purification.

3. Experimental

¹H NMR spectra were recorded in CDCl₃ or CCl₄ on a Varian EM-390 (90 MHz) spectrometer utilising tetra-methylsilane as internal standard; chemical shifts in ppm (δ -scale), coupling constants (*J*) in Hz. IR spectra of thin films were recorded on a Perkin–Elmer infrared 337 spectrophotometer (ν_{\max} in cm⁻¹). Unless otherwise stated, all organic extracts were dried over anhydrous sodium sulphate. Silica gel (ASC, Bombay) impregnated with calcium sulphate was used for TLC.

*For correspondence



Scheme 1.

3.1 2-Methyl-6-(2'-methoxy-4'-methylphenyl)-2-heptene (I)

To a metal ammonia reaction vessel containing a stirred mixture of lithium (2.8 g, 400 mmole) in anhydrous tetrahydrofuran (100 ml) was slowly added a solution of 2-bromo-5-methylanisole (10.05 g, 50 mmole) in anhydrous tetrahydrofuran (70 ml). After 1 h the solution of 6-methyl-hept-5-ene-2-one (3.15 g, 25 mmole) in anhydrous tetrahydrofuran (80 ml) was added slowly and stirred further for 1 hour. Liquid ammonia (250 ml) was slowly added to prevent excessive splattering. Once the dark blue colour of the mixture was established, NH_4Cl (29.4 g 550 mmole) was added carefully to discharge the blue colour and ammonia was allowed to evaporate. Then the residue was partitioned between aqueous sodium chloride solution and ether. The aqueous layer was extracted with ether and the combined organic layer was dried, concentrated and chromatographed over alumina using pet. ether as solvent to afford pure I; yield 4.93 g (85.0%) IR: 2965, 2930, 2840, 1610, 1255, 1185, 1035, 865 and 740 cm^{-1} NMR (CCl_4): δ 1.15 (*d*, 3H, $J = 7$, $-\text{CH}_3$); 1.40 (*m*, 2H, $-\text{CH}_2-$); 1.55, 1.64 (2*s*, 3 H each, chain $=(\text{CH}_2)_2$); 1.85 (*m*, 2 H, chain $=\text{CH}-\text{CH}_2-$); 2.3 (*s*, 3 H, Ar- CH_3) 3.05 (*m*, 1 H, Ar- CH); 3.80 (*s*, 3 H, $-\text{OCH}_3$); 5.3 (*t*, 1 H, $J = 7$, chain $>\text{C}=\text{CH}$); 6.8–7.1 (*m*, 3 H, Ar-H). Analysis – Found: C, 82.5–, H, 10.5%; $\text{C}_{16}\text{H}_{24}\text{O}$ requires C, 82.7, H, 10.4%.

3.2 2-Methyl-6-(2'-oxo-4'-methylcyclohex-3'-en-1-yl)-2-heptene (II)

A solution of I (3.20 g, 13.8 mmole) in dry ether (15 ml) was added to anhydrous liquid ammonia (50 ml) with stirring and to this homogeneous solution was added lithium (0.48 g, 6.8 mmole) in small pieces for 10 minutes. After stirring for 30 minutes absolute alcohol (3.8 ml) was added dropwise for 30 minutes. When the bluish brown colour disappeared completely, ammonia was allowed to evaporate; solid residue was decomposed with cold water and extracted with ether ($3 \times 50\text{ ml}$). The combined ether extract was washed with saturated brine, evaporation of ether gave an oil which was hydrolysed with 10% HCl for 30 minutes, extracted with ether ($2 \times 50\text{ ml}$). The ethereal layer was washed with 5% NaHCO_3 solution and dried. Evaporation of the solvent followed by

column chromatography over alumina using ether-light pet. ether (2:3) as eluant gave pure II, yield 1.45 g (48%). IR 2980, 2870, 1675, 1625, 860 and 720 cm^{-1} . NMR (CCl_4): 0.90 (*d*, 3 H, $J = 7$ $-\text{CH}_3$); 1.2–1.5 (*m*, 4 H, $2 \times -\text{CH}_2-$); 1.62, 1.7 (2*s*, 3 H each, chain $=\text{C}(\text{CH}_3)_2$); 1.9 (*t*, 2 H, $J = 7$ ring $=\text{C}(\text{CH}_3)-\text{CH}_2-$); 2.0 (*s*, 3 H, ring $-\text{CH}_3$); 2.05 (*m*, 2 H, chain $=\text{C}(\text{H})\text{CH}_2-$); 2.15 (*d*, 1 H, $J = 7$ $>\text{C}(-\text{CO})-\text{H}$); 2.35 (*m*, 1 H, chain $-\text{C}(-\text{CH}_3)-\text{H}$); 5.30 (*t*, 1 H, $J = 7$ chain $>\text{C}=\text{CH}$); 5.90 (*s*, 1 H, ring $\text{H}_3\text{C}-\text{C}=\text{C}-\text{H}$); Analysis – Found: C, 81.6, H, 11.0%; $\text{C}_{15}\text{H}_{24}\text{O}$ requires C, 81.8, H, 10.9%.

3.3 (\pm)-12-Hydroxy-2-oxobisabol-3-ene (III)

Compound II (0.220 g, 1 mmole) and freshly sublimed SeO_2 (0.033 g, 0.30 mmole) in 95% ethanol (20 ml) were refluxed for 4.5 hours. Removal of ethanol was followed by extraction of the residue with ether. The ethereal layer was washed with aqueous NaHCO_3 solution. Evaporation of the solvent under reduced pressure followed by column chromatography over alumina eluting with ether-light pet. ether (4:1) afforded pure III yield 0.125 g (51.0%). IR 3400, 2880, 1685, 1630, 1380, 1250, 980 and 880 cm^{-1} . NMR (CCl_4): 0.90 (*d*, 3 H, $J = 7$, $-\text{CH}_3$); 1.2–1.5 (*m*, 4 H, $2 \times \text{CH}_2-$); 1.7 (*s*, 3 H, chain $=\text{C}(-\text{CH}_3)(-\text{CH}_2\text{OH})$); 1.9 (*t*, 2 H, $J = 7$, ring $=\text{C}(\text{CH}_3)-\text{CH}_2-$); 2.0 (*s*, 3 H, ring $-\text{CH}_3$); 2.05 (*m*, 2 H, chain $=\text{C}(\text{H})-\text{CH}_2-$); 2.15 (*d*, 1 H, $>\text{C}(-\text{H})-\text{C}=\text{O}$); 2.35 (*m*, 1 H, chain $>\text{C}(-\text{CH}_3)-\text{H}$); 3.1 (*bs*, 1 H, $-\text{OH}$, D_2O exchangeable); 3.6 (*s*, 2 H, $-\text{CH}_2\text{OH}$); 5.25 (*t*, 1 H, $J = 7$, chain $>\text{C}=\text{C}-\text{H}$); 5.8 (*s*, 1 H, ring $\text{H}_3\text{C}-\text{C}=\text{C}-\text{H}$). Analysis – Found C, 73.6, H, 9.5%; $\text{C}_{15}\text{H}_{24}\text{O}_2$ requires C, 73.5, H, 9.4%.

References

- Bohlmann F, Zdero C and Schoneweiss S 1976 *Chem. Ber.* **109** 3366
 Hallstan S and McEnroe J F 1975 *J. Org. Chem.* **40** 271
 Pritschow P, Jakupovic J, Bittner M, Nremeyer H M and Bohlmann F 1991 *Phytochemistry* **30** 893
 Rabjohn N 1976 *Org. React.* **24** 261
 Sharma M, Arora R and Chand T 1994 *Indian J. Chem.* **B33** 874
 Vig O P, Sharma S D and Handa V K 1978 *Indian J. Chem.* **B16** 112