Improved synthesis of methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate, an A-ring intermediate for (±)strigol

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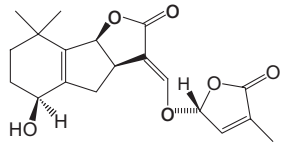
Methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate was synthesised over eight steps from the starting material of citral instead of α-ionone. $KMnO_4$, $HC(OEt)_3$ and O_2/TEMPO/CuCl were substituted for $NaIO_4$, CH_3I and pyridinium chlorochromate, respectively. Every step was simplified and gave a 48% overall yield. The procedure is suitable for large scale production.

Keywords: strigol, citral, α-cyclocitral, TEMPO, methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate

Strigol(**1**) is a highly potent seed germination stimulant for witchweed, a harmful parasitic plant that attacks numerous graminaceous crops. Several partial and total syntheses of (±) strigol had been reported[1-5].



Strigol(**1**)

Methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (**7**) is a key A-ring intermediate used in the synthesis of (**1**). Dee W. Brooks reported a simple and efficient synthesis of (**7**) from α-ionone in five steps (see Scheme 1). The synthesis utilises operationally simple procedures, involves no chromatography, and is suitable for large-scale preparation. However, expensive and hazardous reagents were used, such as $NaIO_4$, CH_3I and pyridinium chlorochromate.

The synthesis of (**7**) developed by Dee W. Brooks and co-workers formed the basis for our efforts to devise an improved practical synthesis (see Scheme 2).

According to ref. 6, α-cyclocitral (**2**) was obtained in overall 70% yield by three steps of aminisation, cyclisation and hydrolysis from the commercially available citral as the starting material. Oxidation of (**2**) with potassium permanganate afforded (**3**) in 90% yield. Epoxidation of (**3**) with *m*-chloroperoxybenzoic acid (MCPBA) gave a mixture of isomeric epoxides (**4a**) and (**4b**) in 98% yield. The mixture (**4a**) and (**4b**) was esterified with trimethyl orthoformate afford to (**5**) in 95% yield. Treatment of (**5**) with sodium methoxide in methanol resulted in opening of the epoxide to the allylic alcohol (**6**) in 96% yield. Oxidation of (**6**) with oxygen catalysed by TEMPO and CuCl gave the desired enone (**7**) in 90% yield.

The synthesis of (**7**) was accomplished in eight steps from the readily available and relatively inexpensive citral with a 48% overall yield. The synthesis utilises operationally simple procedures and is suitable for industrial use.

Experimental

General

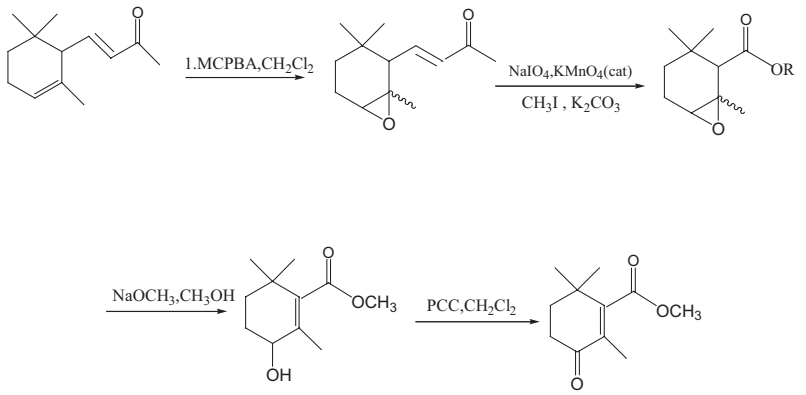
^1H NMR spectra were obtained in $CDCl_3$ at Bruker AC-400. Chemical shifts are given in ppm, with respect to internal TMS, *J* values are quoted in Hz. IR spectra were obtained neat with a Nicolet NEXUS-670 spectrophotometer, only the most significant absorptions in cm^{-1} are indicated. Mass spectra were obtained on a Trace DSQ GC-MS spectrometer.

α-Cyclocitral (**2**): Prepared according to the USP 4358614(1982).

Step 1: Methylamine 46.5 g (1.5 mol) was passed into citral 152 g (1.0 mol) (in the form of the commercial *cis–trans* isomer mixture) in the course of 45 min at 20–25°C, during which time an aqueous phase separated. After a further 10 mins, the aqueous phase was substantially separated (about 20 g of aqueous phase being obtained) and the organic residue was partially freed from excess methylamine at 20°C and 20 mbar.

Step 2: The crude citral N-methylaldimine prepared according to Step 1 was dripped into concentrated sulfuric acid 500 g in the course of 35 min under a nitrogen atmosphere at –10 to –15°C, with vigorous stirring. After the addition stirring was continued for 15 min at –15°C.

Step 3: Ice 600 g was first added to the reaction mixture, containing sulfuric acid, obtained from Step 2, and then sufficient 50% strength by weight sodium hydroxide solution was added at 40°C to give a pH of about 3.5. The pH rose to 6.8 in the course of 40 min, without the addition of further sodium hydroxide solution. The mixture was then brought to pH 7, after which, the aqueous phase and the sodium



Scheme 1

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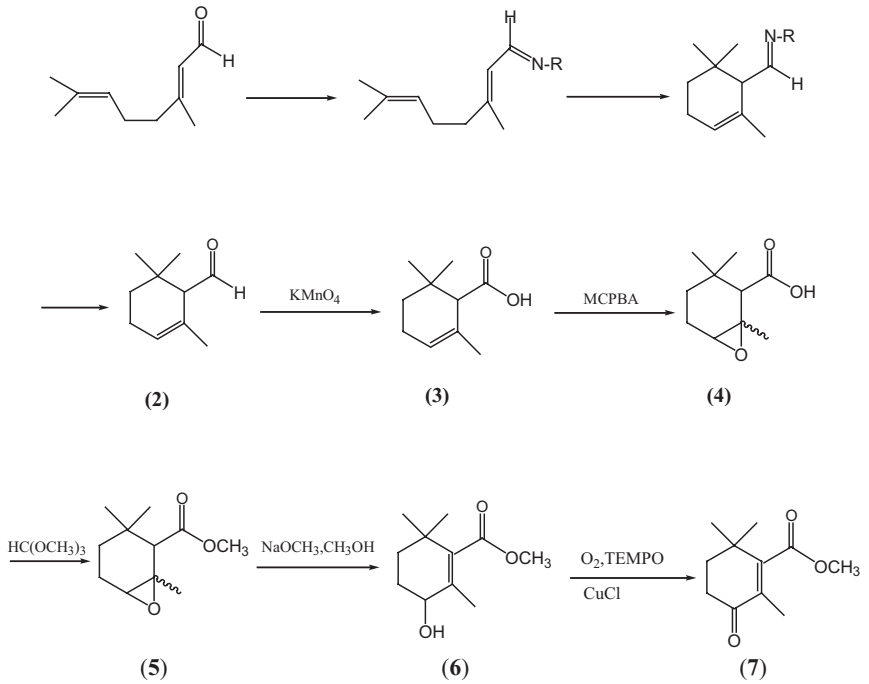

Scheme 1

sulfate which had crystallised out were separated off. The organic phase was then steam-distilled and the cyclocitral was extracted from the condensate (about 2.5l with diethyl ether (3 × 100 ml). The ether solution was dried and the ether removed, leaving the cyclocitral mixture 141.3 g. This corresponded to a yield of 90%, based on citral employed. The isomer mixture was separated by fractional distillation into pure 82 g α-cyclocitral (boiling point 39°C/0.4 mbar) and 51 g pure β-cyclocitral (boiling point 52°C/0.2 mbar).

α-Cyclocitral: ^{1}H NMR($CDCl_3$):δ1.1(3H, s), 1.32(3H, s), 1.7–2.1(4H, m), 1.81(3H, s), 2.62(1H, s), 5.28(1H, s), 9.51(1H, s). GC-MS(EI, 70Ev): *m/z*(%) = 153 (M^+ + H, 12), 152(M^+, 100), 123(76). Anal. Calcd for $C_{10}H_{16}O$: C, 78.95; H, 10.53. Found: C, 79.02; H, 10.55%.

2,6,6-Trimethylcyclohex-2-ene-1-carboxylic acid (**3**): To a solution of α-cyclocitral (**2**) 152 g (1.0 mol) in 2-propanol 2.5l, potassium carbonate 17 g (0.123 mol), and then potassium permanganate 17 g (1.08 mol) in water (2.5l) were added in succession. The reaction mixture was stirred for 5 h at room temperature. Then the solids were removed by suction filtration and washed with water (2 × 50 ml). The filtrate was concentrated on a rotary evaporator to approximately 2.5l and extracted with ether (2 × 300 ml). The aqueous layer was acidified to pH 2 with 1N HCl and extracted with ethyl acetate (4 × 500 ml). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give (3) as a yellow oil: 142.5 g (85%); crude oil 2 g was purified by column chromatography (AcOEt: Cyclohexane: AcOH = 10:10:1) for analysis; IR(KBr) 3450(br), 2960(s), 1725(s), 1608(s), 1510(s), 1360(m), 1250(br), 1040(m) cm^{-1}; ^{1}H NMR($CDCl_3$) δ1.0(3H, s), 1.50(3H, s), 1.7–2.1(4H, m), 1.82(3H, s), 2.55(1H, s), 5.15(1H, s), 9.40(1H,br s). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.47; H, 9.53%.

2,3-Epoxy-2,6,6-trimethylcyclohexane-1-carboxylic acid (**4a,b**): To a rapidly stirred solution of crude (**3**) 87 g (0.5 mol) from the previous reaction in dichloromethane (1.5l) was added *m*-chloroperoxybenzoic acid (MCPBA) 105 g (0.60 mol) at 0°C. The solution was kept between 0 and 5°C for 3 h. The solid was removed by suction filtration and washed with dichloromethane (2 × 50 ml). The filtrate was washed with aqueous saturated NaCl (1l), dried over $MgSO_4$, filtered, and evaporated to give 92 g (96%) of a mixture of isomers **4a** and **4b** as a pale yellow oil .The crude oil 2 g was purified by column chromatography (AcOEt:cyclohexane:AcOH = 10:10:1) for analysis: IR(KBr) 3450(br), 2960(s), 1725(s), 1370(m), 1250(br), 1040(m) cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.95(3H, s),1.0(3H, s), 1.50(3H, s), 1.7–2.1(4H, m), 2.55(1H, s), 3.15(1H, t, *J* = 2 Hz), 9.40(1H, br s). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.27; H, 8.77%.

Methyl 2,3-epoxy-2,6,6-trimethylcyclohexane-1-carboxylate (**5**): Crude (**4a,b**) 92 g, trimethyl orthoformate 64 g and *p*-toluenesulfonic acid 0.5 g was mixed. The mixture was stirred at room temperature over night. The lower boiling substances were removed on a rotary evaporator. The oil residue (**5**) 91 g was obtained. Crude oil 2 g was purified by column chromatography (AcOEt:cyclohaxane = 4:6) for analysis: IR(KBr) 2960(s), 1740(s), 1430(m), 1240(m), 1150(s) cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.90(3H, s), 0.95(3H, s), 1.39(3H, s), 1.7–2.0(4H, m), 2.45(1H, s), 3.0(1H, t, *J* = 2 Hz), 3.72(3H,s). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.70; H, 9.11%.

Methyl 3-hydroxy-2,6,6-trimethylcyclohex-ene-1-carboxylate (**6**): To a stirred solution of sodium metal 10.0 g (0.43 mol) dissolved in methanol (100 ml) was added dropwisely (**5**) 90.0 g in methanol 50 ml under a N_2 atmosphere. The solution was refluxed for 6 h, cooled to room temperature, and neutralised with $^1NH_2SO_4$, the excess methanol was removed on a rotary evaporator, and the aqueous residue was extracted with ethyl acetate (2 × 200 ml). The combined organic layers were washed with aqueous saturated NaCl solution (200 ml), dried over Na_2SO_4, filtered, and evaporated to give (**6**) 87 g (96%), Crude oil 3 g was purified by column chromatography AcOEt:cyclohaxane = 1:1) for analysis: IR(KBr) 3420(br), 2960(s), 1720(s), 1430(m), 1290(m) 1230(br), 1060(m), 1020(br), 900(m), 725(s) cm^{-1}; ^{1}H NMR($CDCl_3$) δ 1.05(3H, s), 1.10(3H, s), 1.2–2.1(4H, m), 1.78(3H, s), 2.2(1H, br s), 3.75(3H, s), 4.2(1H, m). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.72; H, 9.11%.

Methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (**7**): To a stirred mixture of TEMPO 3.5 g (0.02 mol) and CuCl 2.0 g (0.02 mol) in N,N-dimethyl formamide (150 ml) was added (**6**) 80 g. To the above mixture, oxygen was bubbled for. 15 h at room temperature, N,N-dimethyl formamide was then removed by distillation at reduced pressure. To the residue was added dichloromethane (200 ml), and the solid were removed by filtration, the filtrate was washed with aqueous saturated NaCl solution (100 ml), the organic layers dried with Na_2SO_4, filtered, and evaporated. The residue was then distilled at reduced pressure to give 75 g(90%) of pure (**7**): b.p. 75°C (0.02 mm Hg). ^{1}H NMR($CDCl_3$) δ 1.10(3H, s), 1.20(3H, s), 1.3–2.5(4H,m), 1.86(3H, s), 3.76(3H,s). GC-MS(EI, 70Ev): *m/z*(%) = 197 (M^+ + H, 10), 196(M^+, 100), 137(86). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.38; H, 8.02%.

Conclusions

We have designed an improved process for the synthesis of the target compound (**7**) from the starting material of citral without the need to remove three carbon atoms from α-ionone as described in Dee Brook's route. Every step was modified to be more simple and gave high yields. The present procedure is more effective and competitive, and is suitable for large scale production.

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References

1 (a) L.J. Dolby and G. Hanso, *J. Org. Chem.*, 1976, **41**, 563; (b) G.K. Cooper and L.J. Dolby, *J. Org. Chem.,* 1979, **44**, 3414; (c) A.B. Pepperman, 1981, *J. Org. Chem.,* **46**, 5039.
2 (a) J.B. Heather, R.S.D. Mittal and C.J. Sih, *J. Am. Chem. Soc*., 1974, **96**, 1976; (b) 1976, **98**, 3661.
3 (a) G.A. MacAlpine, R.A. Raphael, A. Shaw, A.W. Taylor and H.J. Wild, *J. Chem. Soc., Chem. Commun*., 1974, **20**, 834; (b) *J. Chem. Soc., Perkins Trans1: Organic and Bio-Organic Chemistry,* 1976, **4**, 410.
4 D.W. Brooks, E. Kennedy, H.S. Bevinakatti, A.B. Pepperman and J.M. Bradow, *ACS Symp. Series*, 1987, **355**, 433.
5 D.W. Brooks, H.S. Bevinakatti and D.R. Powell, *J. Org. Chem.*, 1985, **50**, 3779.
6 L. Janitschke and W. Hoffmann, US 4,358,614, 1982.