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TOTAL SYNTHESIS OF (±)-DIHYDROPROTOLICHESTERINIC ACID AND FORMAL SYNTHESIS OF (±)-ROCCELLARIC ACID BY RADICAL CYCLISATION OF AN EPOXIDE.USING A TRANSITION-METAL RADICAL SOURCE

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Abstract: A short and efficient total synthesis of (±)-Dihydroprotolichesterinic acid (**1**) and Formal synthesis of (±)-Roccellaric acid (**2**) has been acheived by radical cyclisation of epoxide using a transition metal radical source.

Keywords: *Dihydroprotolichesterinic acid, Roccellaric acid, radical cyclisation, epoxide, transition matal.*

The synthesis of γ-butyrolactone derivatives has attracted considerable attention over the years because of their wide occurrence in bioactive natural products.[1] These butyrolactone units are also important building blocks for many natural products such as alkaloids,macrocycilc antibiotics and pheromones.[2] Paraconic acids are substituted γ-lactones containing a carboxylic acid at the β-carbon of the lactone ring. Dihydroprotolichesterinic acid (**1**)[3] and Roccellaric acid (**2**)[4] are two important examples which are noted to be potent antibacterial agents.[5] Although several strategies for the synthesis of the title compounds are reported[6] the radical cyclisation route is still unexplored. We report here an efficient and short total synthesis of dihydroprotolichesterinic acid (**1**) and roccellaric acid (**2**) from the known[7] isomeric mixture of the epoxy alcohol **3** through intramolecular radical cyclisation of epoxides using a titanium(III) radical source.[8] Thus, compound **3** on treatment with NaH in THF-DMSO (10:1) in the presence of allyl bromide furnished the epoxides **4** as an inseparable mixture of two isomers in a ratio of 1:1 (Scheme-1). The crude epoxide **4**, on treatment with Cp_2TiCl (prepared *in situ* from Cp_2TiCl_2 and Zn dust) in THF afforded the cyclised product **5** as an inseparable mixture of two isomers in a ratio of 5:1. The ratio was determined from two distinguished doublets for the secondary -Me in the ^1H NMR spectrum which appeared at δ 1.00 (J = 7.2 Hz) for the major isomer and at δ 1.06 (J = 6.9 Hz) for the minor isomer. The crude alcohol **5** was subjected to oxidation in presence of $NaIO_4$ and a catalytic amount of $RuCl_3$ in a solvent mixture of H_2O-CCl_4-CH_3CN (2:1:1) to afford the mixture of acids **6** in a ratio of 5:1 as a light yellow solid. The major isomer (m.p. 107-108^{0}C) was separated by fractional crystallisation (ethyl acetate-petroleum ether) in 78% yield. This major acid was identical[3a,6a] in all respects with dihydroprotolichesterinic acid (**1**) (lit[6a] m.p. 106^{0}C). The minor acid could not be separated in pure form. In a separate experiment, the crude isomeric mixture of the acid **6** was treated with ethereal diazomethane and the methyl ester of dihydroprotolichesterinic acid **7**[6a,e] and the methyl ester of

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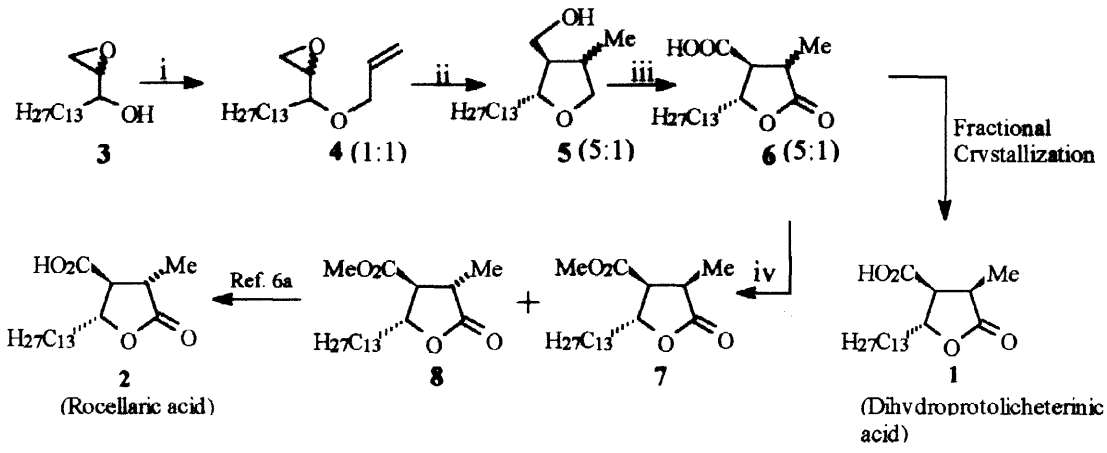

Scheme-1

Reagents and reaction conditions: I) NaH, THF-DMSO (10:1), allyl bromide, r.t., 6h, 81%; ii)Cp_2TiCl_2, Zn, THF, then 10% H_2SO_4, 76% iii) $RuCl_3$ (cat.), $NaIO_4$, H_2O-CCl_4-CH_3CN (2:1:1), 2h, 90% iv) Excess of CH_2N_2 in Et_2O.

roccellaric acid **8**[6a,e] were separated by preparative TLC in 80% and 16% yield respectively. Since, the conversion of **7** to dihydroprotolichesterinic acid (**1**) and that of **8** to roccellaric acid (**2**) is already reported,[6a] we claim the formal synthesis of roccellaric acid (**2**) via the radical cyclisation route. To justify our claim, the major component **7** was refluxed with NaOMe in MeOH for 10h to give an 1:1-equilibrium mixture[6a] of **7** and **8**. Compounds **7** and **8** were readily separated by preparative TLC and hence component **7** can be recycled to give **8**.

In conclusion, we successfully achieved the short and efficient total synthesis of (±)-dihydroprotolichesterinic acid and the formal synthesis of (±)-roccellaric acid by radical cyclisation of an epoxide using a titanium(III) radical source.

Experimental Section:

Melting points were determinded in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. NMR spectra were recorded on Bruker DPX-300 (300 MHz for ^1H and 75 MHz for ^{13}C) spectrometer with TMS as internal reference. Chemical shifts were expressed in ppm, coupling constants in Hz. Tetrahydrofuran and diethylether were distilled from sodium-benzophenon ketyl. Other solvents and reagents were purified by standard procedures as necessary. Column chromatography was performed on silica gel (60-120 mesh). Petroleum ether of boiling range from 60°C to 80°C was used for column chromatography.

Preparation of the epoxide 4. To a magnetically stirred suspension of NaH (50%) (120 mg, 2.53 mmol) [washed twice with petroleum ether] in dry THF-DMSO (16.5 mL, 10:1), a solution of the known[8] epoxy alcohol **3** (500 mg, 1.95 mmol) in dry THF (10 ml) was added dropwise at room temperature under nitrogen. After evolution of hydrogen ceased a solution of allyl bromide (290 mg, 2.34 mmol) in dry THF (10 ml) was added dropwise at 0°C and then stirred at room temperature for 6h. The reaction mixture was cooled and

decomposed carefully with ice-cold water. After removal of THF under reduced presure, the residue was extracted with ether (3x30 mL). The ether layer was washed with saturated brine and dried ($NaSO_4$). Removal of solvent afforded a light brown liquid which on column chromatography over silica gel (5% ethyl acetate in petroleum ether) furnished **4** (470 mg, 81%) as an inseparable isomeric mixture (1:1). IR (neat): ν_{max} 2930,2860,1470,1120,1080,920 cm^{-1}. ^1H NMR δ 0.87 (t, J=6 HZ, 3H), 1.24 (m, 24H), 2.48 (dd, J = 4.8 and 2.1 Hz, 0.5 H), 2.70-2.80 (m, 1.5 H), 2.86-2.90 (m, 0.5 H), 2.96-2.97 (m, 1H), 3.16 (q, J = 6Hz, 0.5H), 3.97-4.14 (m, 1.5H), 4.27 (dd, J = 12 and 6 Hz, 0.5 H), 5.15 (d, J = 12 Hz, 1H), 5.21- 5.32 (m, 1H), 5.85-5.97 (m, 1H). ^{13}C NMR: δ 14.0, 22.6, 25.1, 25.5, 29.29, 29.44, 29.48, 29.51, 29.53, 29.58, 29.61, 31.84, 32.3, 32.8, 43.2,45.58, 53.37, 54.9, 70.7, 71.15, 78.0, 80.48, 116.6, 116.7, 134.98, 135.0. Anal. Calcd. for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found C, 77.16; H, 12.20.

Preparation of the alcohol 5. To a stirred solution of titanocene dichloride (Cp_2TiCl_2) (1 g, 4.02 mmol) in THF (50mL) was added activated zinc dust (790mg, 12.08 mmol) and the mixture was vigorously stirred for 1 h under argon. Unreacted zinc was filtered off using a cannula transfer with a cotton plug at both ends.This green filtrate was added dropwise to a magnetically stirred solution of epoxide **4** (590 mg, 2 mmol) in dry THF (50mL) under argon at room temperature. The reaction mixture was stirred for 1 hr and then 10% H_2SO_4 (100 ml) was added to it. After stirring further for 30 minutes, THF was removed and the residue obtained was chromatographed over silica gel (20% ethyl acetate in petroleum ether) to afford the alcohol **5** (450 mg, 76%) as an inseparable mixture of two isomers (5:1) as a viscous oil. IR (neat): ν_{max} 3440 (br), 2960,2940, 2860, 1470, 1380,1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) : δ 0.87 (t, J = 6.3 Hz, 3H), 1.0 (d, J = 7.2 Hz, 5/6H) 1.06 (d, J= 6.9Hz, 1/6H), 1.25 (m 22H), 1.43-1.53 (m, 2H),1.66 (brs, -OH), 1.96-2.06 (m, 1H), 2.38-2.47 (m, 1H),3.25 (dd, J = 8.4 and 7.2 Hz, 1/6H), 3.41 (dd,J = 9 and 8.4 Hz, 5/6H), 3.59-3.77 (m, 3H), 3.94 (dd, J = 8.4 and 6.3 Hz, 5/6H), 4.07 (t, j = 8.1 Hz, 1/6H). ^{13}C NMR (75 MHz, $CDCl_3$): 12.5,14.0,17.6,18.4, 22.6, 26.2, 26.3, 29.28, 29.54, 29.57,29.58,29.59, 29.61, 29.70,30.24, 31.84, 35.15, 35.76, 35.88, 36.19, 37.22, 49.32, 51.12, 54.76, 61.61, 62.33, 63.72, 73.75, 74.21, 81.23, 82.63. Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45 ; H, 12.83. Found C, 76.20 ; H, 12.85.

Synthesis of (±)-Dihydroprotolichesterinic Acid (1). To a magnetically.stirred solution of $NaIO_4$ (142 mg, 0.67 mmol) and $RuCl_3$ (3 mg, 0.016 mmol) in water (2 ml), CCl_4 (1 mL) and CH_3CN (1 mL) was added a solution of the alcohol **4** (550 mg, 0.167 mmol) in CH_3CN (2 mL) at a time. The reaction mixture was stirred for 2 h. It was diluted with H_2O (10 mL) and extracted with diethyl ether (3 x 10 mL). The ether layer was washed with brine and dried (Na_2SO_4). Removal of solvent afforded a brownish crystalline solid as an isomeric mixture (5:1). Repeated recrystallisation from ethyl acetate-petroleum ether afforded pure dihydroprotolichesterinic acid **(1)** as colourless crystals (420mg , 78%). m.p. 107-108°C. IR (KBr): ν_{max} 2960, 2920, 2860, 1765 1730., 1700 ,1475, 1180 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$). δ 0.88 (t, J = 6.6 Hz, 3H), 1.27(m, 22H), 1.31 (d , J = 7.5 Hz, 3H), 1.70 (m , 2H), 3.04 (dq, J = 9.2 and 7.5Hz, 1H), 3.16 (dd, J = 9.2 and 6.2 Hz, 1H), 4.70 (q, J = 6.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 11.75, 14.06, 22.62, 25.28, 29.14, 29.29,

29.34, 29.43, 29.53, 29.57, 29.61(two peaks merged), 31.85, 34.61, 36.91, 49.65, 79.31, 174.41, 177.12. The other isomer could not be separated in pure form.

Synthesis of the methyl ester of roccellaric acid 8. A solution of the crude isomeric acid **6** (163 mg, 0.5 mmol) in Et_2O (5 ml) was treated with an excess of ethereal CH_2N_2. After removal of the solvent the residue was subjected to preparative TLC(10% ethyl acetate in petroleum ether) to afford the methyl ester **7**[6e] (135 mg, 80%):^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.4 Hz, 3H), 1.21(d, J = 7.2 Hz, 3H), 1.26(m, 20H), 1.51 (m , 2H), 1.60-1.66 (m, 2H), 2.97 (dq, J = 9.2 and 7.5Hz, 1H), 3.12 (dd, J = 9.2 and 6.1 Hz, 1H), 3.76 (s, 3H), 4.70(q, J = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.31, 14.52, 23.09, 25.73, 29.62, 29.75, 29.80, 29.89, 30.00 (two peaks merged), 30.04, 30.07, 32.32, 35.13, 37.56, 50.41, 52.58, 79.91, 171.01, 177.72 and the methyl ester **8**[6e] (27mg, 16%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J = 6.6 Hz, 3H), 1.24 (m, 20H), 1.31 (d, J = 7.2 Hz, 3H), 1.56 (m , 2H), 1.61-1.74 (m, 2H),), 2.62 (dd, J = 11.4 and 9.3 Hz, 1H), 2.95 (dq, J = 11.4 and 7.2 Hz, 1H), 3.77 (s, 3H), 4.35 (dt, J = 9.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.53, 14.87, 23.09, 25.67, 29.63, 29.75, 29.79, 29.90, 30.01, 30.04 (two peaks merged), 30.07, 32.32, 35.28, 40.32, 53.01, 54.61, 79.99, 171.62, 177.25.

Epimerisation of compound 7 to 8. A solution of the ester **7** (20 mg, 0.059 mmol) in MeOH (10 ml) was refluxed with NaOMe (27 mg, 0.5 mmol) for 10h. The reaction mixture was poured into water(20 ml) and extracted with diethyl ether(3 x 15 ml). The organic layer was washed with brine and dried(Na_2SO_4). After removal of solvent under reduced pressure the residue was subjected to preparative TLC (10 % ethyl acetate in petroleum ether) afforded the pure ester **7** (10 mg, 50%) and the pure ester **8** (10 mg, 50%).

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