Total synthesis of (±)-methylenolactocin by radical cyclisation of an epoxide using a transition-metal radical

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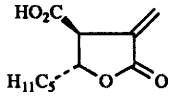
1 PERKIN COMMUNICATION

A stereoselective total synthesis of (±)-methylenotocin 1 is achieved *via* the radical cyclisation of an epoxide as a key step, using a titanium radical source.

α-Methylene-γ-butyrolactone derivatives have attracted much attention over the years since the α-methylene-γ-butyrolactone unit is an important basic structure in a wide range of biologically active natural products.[1] Methylenolactocin, a small but densely functionalised and isomerisation-prone antibiotic, has attracted interest because of its selective antibacterial activity against Gram-positive bacteria and its antitumour activity[2] and was first isolated[2] from the culture filtrate of *Penicillium sp.* in 1988. Following the first total synthesis of methylenolactocin by de Azevedo *et al.*,[3] only one other total synthesis[4] and a couple of formal syntheses[5,6] have been reported. We report here a total synthesis of racemic methylenolactocin **1** using a radical cyclisation as the key step. The carbon-centred radical was selectively generated from an epoxide using a titanium radical.[7]



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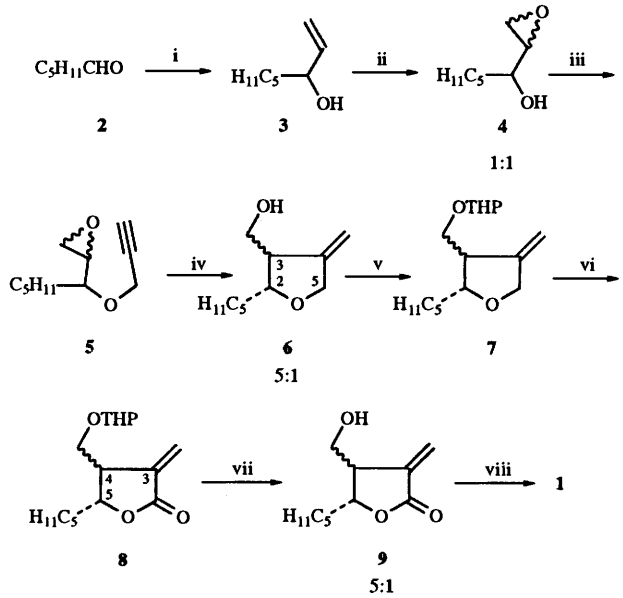
Treatment of the allylic alcohol **3** (prepared from **2** by a vinyl Grignard reaction) with *m*-chloroperbenzoic acid (MCPBA) in $CHCl_3$[8] afforded an inseparable isomeric mixture of epoxides **4** (Scheme 1) in a ratio of 1:1. The ratio was determined from the signals of the proton adjacent to the hydroxy group in the ^1H NMR spectrum, which appeared as multiplets centred at δ_H 3.26 for one isomer and at δ_H 3.50 for the other. The crude alcohol **4** was allowed to react with prop-2-ynyl bromide in the presence of NaH in THF–DMSO (10:1) to furnish **5** as an inseparable isomeric mixture (1:1). The mixture of epoxides **5** was treated with Cp_2TiCl (prepared *in situ* from Cp_2TiCl_2 and Zn dust)[7d] in THF to yield an inseparable isomeric mixture of alcohols **6** in a ratio of 5:1. The ratio was determined from the signals in the ^1H NMR spectrum for 3-H, which appeared as multiplets centred at δ_H 2.45 for the major isomer and at δ_H 2.65 for the minor one. The radical cyclisation occurs without retention of the stereochemistry of the epoxide and the major isomer obtained is the most stable product from the radical intermediates. Attempted double oxidations of crude **6** in one step to methylenolactocin **1** by various methods were unsuccessful, giving only intractable solids. To avoid this problem, the free alcohol was first protected with 3,4-dihydro-2*H*-pyran in presence of a catalytic amount of pyridinium toluene-*p*-sulfonate (PPTS) to afford the tetrahydropyranyl ether **7** as an inseparable isomeric mixture. The crude **7** was oxidised with pyridinium dichromate (PDC) in DMF[9] to give the lactone **8** which was treated with toluene-*p*-sulfonic acid (PTSA) in MeOH to yield the lactone **9** as an inseparable mixture of two isomers in a ratio of 5:1. The presence of the γ-lactone was confirmed by a strong absorption at 1770 cm^{-1} in the IR spectrum. The ratio of the isomers of crude **9** was



Scheme 1 *Reagents and conditions:* i, Vinylmagnesium bromide, THF, 0 °C to RT, 85%; ii, MCPBA, $CHCl_3$, RT, 80%; iii, NaH, prop-2-ynyl bromide, THF–DMSO (10:1), RT, 75%; iv, Cp_2TiCl (generated *in situ* from Cp_2TiCl_2 and activated Zn dust), THF, then 10% H_2SO_4, 72%; v, PPTS, 3,4-dihydro-2*H*-pyran, CH_2Cl_2, RT, 98%; vi, PDC, DMF, 0 °C to RT, 63%; vii, PTSA, MeOH, 93%; viii, Jones' reagent, actone, 0 °C, 80%

determined by ^1H NMR, from the identifiable signals for 4-H and 5-H which appeared as multiplets centred at δ_H 2.87 and 4.38 for the major isomer and at δ_H 3.22 and 4.57 for the minor isomer, respectively. All attempts to separate the isomers at any stage by usual chromatographic methods were unsuccessful and NOE experiments could not elucidate the stereochemistry of the two isomers of crude **9** either. Although the decoupling of the methylene protons of the side chain adjacent to C-4 provided two clear doublets for 4-H, at δ_H 4.40 (J 4.2 Hz) and δ_H 4.58 (J 7 Hz) for the major and minor isomers, respectively, there was insufficient information to solve the problem. Interestingly, however, on Jones' oxidation the crude lactone **9** afforded **1** as the only isolable product. No other isomer could be detected even in the crude product. Probably, isomerisation of the enolisable C-3 centre under the strongly acidic Jones' conditions gives only the thermodynamically more stable isomer[10] methylenolactocin **1**, which was spectroscopically and chromatographically identical with previously reported samples.[2]

Experimental

[1-(Prop-2-ynyloxy)hexyl]oxirane 5

Spectroscopic data: ν_{max}(neat)/cm^{-1} 3300, 2960, 1470 and 1460; δ_H($CDCl_3$) 0.89 (3 H, t, J 6.3,† Me), 1.29–1.64 (8 H, m),

† J Values in Hz.

2.39–2.41 ($\frac{1}{2}$ H, m, C≡CH for one isomer), 2.49 ($\frac{1}{2}$ H, dd, *J* 2.9 and 4.9, C≡CH for other isomer), 2.73–2.79 (2 H, m), 2.89–2.99 (1 H, m), 3.08–3.17 ($\frac{1}{2}$ H, m), 3.34–3.43 ($\frac{1}{2}$ H, m), 4.21–4.25 (1 H, m) and 4.34 (1 H, dd, *J* 2.3 and 6.7).

3-Hydroxymethyl-4-methylidene-2-pentyltetrahydrofuran 6

Spectroscopic data: ν_{max}(neat)/cm^{-1} 3420, 2960, 1470 and 1460; δ_H($CDCl_3$) 0.79–0.85 (3 H, m, Me), 1.23–1.56 (8 H, m), 1.80 (1 H, br s, OH), 2.38–2.43 ($\frac{5}{6}$ H, m, 3-H for the major isomer), 2.62–2.71 ($\frac{1}{6}$ H, m, 3-H for the minor isomer), 3.55–3.71 (2 H, m, CH_2OH), 3.75–3.85 (1 H, m, 2-H), 4.14–4.34 (2 H, m, 5-H) and 4.92–5.06 (2 H, m, C=CH_2); δ_C($CDCl_3$) 149.3, 105.0, 82.2, 70.2, 63.1, 51.4, 34.4, 31.8, 25.5, 22.5, 13.9 (for the major isomer) and 149.7, 105.7, 81.9, 70.0, 61.1, 48.8, 34.4, 29.5, 26.2 (distinguishable signals for the minor isomer).

4-Hydroxymethyl-3-methylidene-5-pentyltetrahydrofuran-2-one 9

Spectroscopic data: ν_{max}(neat)/cm^{-1} 3450, 2980, 1770, 1670, 1470 and 1380; δ_H($CDCl_3$) 0.89 (3 H, t, *J* 6.6, Me), 1.27–1.77 (8 H, m), 2.82–2.92 ($\frac{5}{6}$ H, m, 4-H for the major isomer), 3.18–3.30 ($\frac{1}{6}$ H, m, 4-H for the minor isomer), 3.75 (2 H, d, *J* 6.2, CH_2OH), 4.35–4.41 ($\frac{5}{6}$ H, m, 5-H for the major isomer), 4.55–4.64 ($\frac{1}{6}$ H, m, 5-H for the minor isomer), 5.69 ($\frac{1}{6}$ H, d, *J* 2.2, C=CH for the minor isomer), 5.71 ($\frac{5}{6}$ H, d, *J* 2.3, C=CH for the major isomer), 6.30 ($\frac{1}{6}$ H, d, *J* 2.4, C=CH for the minor isomer) and 6.34 ($\frac{5}{6}$ H, d, *J* 2.4, C=CH).

(±)-Methylenolactocin 1

Spectroscopic data: ν_{max}(neat)/cm^{-1} 3460, 3100, 2960, 1750, 1720, 1660, 1470 and 1400; δ_H($CDCl_3$) 0.80 (3 H, t, *J* 6.6, Me), 1.15–1.55 (6 H, m), 1.62–1.74 (2 H, m, CH_2), 3.54–3.59 (1 H, m, 4-H), 4.75 (1 H, q, *J* 6, 5-H), 5.96 (1 H, d, *J* 2.6, C≡CH) and 6.39 (1 H, d, *J* 3, C=CH); δ_C($CDCl_3$) 173.9, 168.4, 132.5, 125.8, 79.0, 49.5, 35.6, 31.3, 24.4, 22.3 and 13.8.

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