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Abstract

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Synthesis of (±) Epipentenomycin I and III

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Abstract: A synthesis of (±) epipentenomycin I and III is reported from a regioselective epoxidation of racemic 3-hydroxy- and 3-acetoxy-2-methylene-4-cyclopentenone, respectively, with dimethyldioxirane followed by hydrolytic ring-opening of the resulting epoxide.

Key words: epipentenomycin I and III, epoxidation, dimethyldioxirane, epoxide hydrolysis.

The pentenomycin group of natural products (compounds **1-4**) have antibacterial activities against both Gram-positive and Gram-negative bacteria. Pentenomycin I (**1**) and II (**2**) were first isolated from *Streptomyces eurythermus* in 1973¹ while pentenomycin III (**3**) was isolated three years later from *Streptoverticillium eurocidicum*.² Epipentenomycin I (**4**), however, was isolated in 1989³ from carpophores of *Perziza* sp., much later than its first synthesis in racemic form in 1980.^{4,5} Their biological activities and their highly oxygenated structures have attracted several synthetic studies on their total synthesis,⁶ the synthesis of their racemates^{4,5,7} and their analogues⁸ (e.g. epipentenomycin II (**5**) and III (**6**)). We report here a diastereoselective synthesis of (±) epipentenomycin I (**4**) and III (**6**) from the diastereoselective epoxidation of 3-hydroxy- and 3-acetoxy-2-methylene-4-cyclopentenone, respectively, with dimethyldioxirane followed by hydrolytic ring-opening of the resulting epoxide.

1; pentenomycin I ($R^1 = R^2 = H$)

2; pentenomycin II ($R^1 = Ac, R^2 = H$)

3; pentenomycin III ($R^1 = H, R^2 = Ac$)

4; epipentenomycin I ($R^1 = R^2 = H$)

5; epipentenomycin II ($R^1 = Ac, R^2 = H$)

6; epipentenomycin III ($R^1 = H, R^2 = Ac$)

Treatment of freshly prepared 3-hydroxy-2-methylene-4-cyclopentenone (**7**)⁹ with freshly distilled dimethyldioxirane (DMDO) in acetone¹⁰ at RT for 12 h produced an 83 : 17 mixture of the *anti*- and *syn*-epoxy-alcohols **8** and **9**, respectively and the unexpected product **10**. The crude mixture was separated by flash chromatography to give diastereomerically pure **8** and **10** in yields of 49% and 36%, respectively.¹¹ The *syn*-isomer **9** could not be isolated in pure form. The structure of **8** was clear from spectral analysis, although its relative stereochemistry could only be deduced from its transformation into (±) epipentenomycin I (**4**). The

NMR spectra of compound **10** indicated the presence of an ethyl and an acetate group and its structure was unequivocally determined by a single-crystal X-ray study (Fig. 1).¹²

Scheme 1

While the mechanism for the formation of **10** is not clear, this compound formally arises from the incorporation of one molecule of DMDO into **7** (Scheme 2). Interestingly, both products **8** and **10** arise from addition of DMDO *anti* to the allylic hydroxyl group in **7**. Our attempts to reverse the diastereoselectivity in favour of diastereomer **9**, which should yield pentenomycin I after hydrolytic epoxide ring-opening, were unsuccessful. The use of the less polar solvent CCl_4 in this reaction, conditions that should favour **9** by enhancing H-bonding between the allylic hydroxyl group in **7** and DMDO,¹³ led to poorer overall yields due to incomplete conversion of **7** and resulted in little changes in the diastereoselectivities.

Figure 1. ORTEP plot of **10**.

Scheme 2

Protic acid (H_2SO_4 or HClO_4) or Lewis acid (BiCl_3)¹⁴ catalysed hydrolysis reactions of the epoxide ring of *rac*-**8** to give ($\pm$) epipentenomycin I (**4**) were not clean and led to impure samples of the desired product. However, heating a solution of *rac*-**8** in D_2O ¹⁵ solution in an NMR tube at 80 °C, with monitoring by ^1H NMR spectroscopy, cleanly led to ring-opening of the epoxide group. After freeze-drying pure ($\pm$) epipentenomycin I (**4**) was obtained in 74% yield (Scheme 1). This sample had identical spectral characteristics to those reported in the literature for this compound.^{7a}

In an attempt to prepare ($\pm$) epipentenomycin II (**5**) we acetylated the known alcohols *rac*-**11a** and *rac*-**11b**, to give their respective allylic acetates, *rac*-**12a** and *rac*-**12b**. These compounds were highly crystalline and their relative stereochemistries were secured by single-crystal X-ray studies.¹² Treatment of the individual isomers *rac*-**12a** and *rac*-**12b** or a mixture of these isomers under flash vacuum pyrolysis (FVP) conditions gave the

novel allylic acetate *rac*-**13** in 78% yield.¹¹ Treatment of *rac*-**13** with freshly distilled DMDO in acetone at RT for 12 h produced an 80 : 20 mixture of the *anti*- and *syn*-epoxy-acetates, *rac*-**14** and *rac*-**15**, respectively. No product corresponding to the acetate derivative of **10** could be isolated. Purification by flash chromatography gave an inseparable 80 : 20 mixture of *rac*-**14** and *rac*-**15** in 42% yield. Hydrolytic ring-opening of this mixture in D₂O gave, as the major components from ¹H NMR analysis, about a 1 : 1 mixture of racemic epipentenomycins II and III formed from ring-opening of *rac*-**14** and then migration of the secondary acetate in *rac*-**5** to the more stable primary position. Smith^{7a} has demonstrated that in solution these isomeric acetates are in equilibrium and that chloroform solution favours the primary acetate isomer. Thus this mixture was freeze-dried and purified by PTLC using dichloromethane as eluant to give about an 80 : 20 mixture of epipentenomycin III and a second isomer, albeit in modest yield (22%). These compounds had ¹H NMR spectral data in CDCl₃ that matched closely and were similar, respectively, to that reported for epipentenomycin III and pentenomycin III, respectively.^{7a}

In conclusion we have developed a synthesis of epipentenomycin I *via* a diastereoselective epoxidation of **7** followed by mild hydrolysis of the resulting epoxide group. We have also found a novel oxidation product, the compound **10**, in this epoxidation reaction. We are currently working on the synthesis of enantiomerically pure **7** to allow the preparation of enantiomerically pure pentenomycins and their derivatives.

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11. *Synthesis of 8 and 9*: To a solution of **7** (50 mg, 0.45 mmol) in acetone (5 ml) was added a solution of DMDO (0.90 mmol, 0.07 M in acetone) at 0 °C, and the reaction was left to stir overnight at RT. The solvent was then evaporated and the mixture was purified by PLC (silica gel; 40% EtOAc/petroleum spirit) to obtain **8** (28 mg, 49%), as a viscous liquid and **10** (30 mg, 36 % yield). **8**: ¹H-NMR (300 MHz, CDCl₃) δ 2.31 (broad, OH), 3.14 (d, 1H, *J*=6 Hz), 3.28 (d, 1H, *J*=6 Hz), 4.96 (s, 1H), 6.53 (dd, 1H, *J*=6, 1 Hz), 7.69 (dd, 1H, *J*=6, 2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 50.1 (CH₂), 69.8 (CH), 137.7 (CH), 138.6 (C), 161.5 (CH), 186.0 (CO). CIMS (70 eV) *m/z* 127 (M⁺, 100). HRCIMS (70 eV) Calcd for C₆H₇O₃, 127.0395. Found, 127.0363 (M⁺). **9**: ¹H NMR (300 MHz, CDCl₃) δ 2.32 (br., OH), 3.34 (d, 1H, *J*=6 Hz), 3.41 (d, 1H, *J*=6 Hz), 5.12 (s, 1H), 6.63 (d, 1H, *J*=6 Hz), 7.82 (d, 1H, *J*=6 Hz). **10**: Needles from DCM/petroleum spirit, mp = 98-100 °C, ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, 3H, *J*=7.6 Hz), 1.71 (m, 1H, *J*=7.6 Hz), 2.08 (m, 1H), 2.15 (s, 3H), 3.27 (d, OH, *J*=4 Hz), 5.01 (br. t, 1H, *J*=2 Hz), 6.30 (dd, 1H, *J*=2, 5 Hz), 7.49 (dd, 1H, *J*=2, 5 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 8.1 (CH₃), 21.6 (CH₃), 24.6 (CH₂), 75.2 (CH), 89.2 (C), 132.7 (CH), 159.8 (CH), 171.9 (CO), 200.7 (CO). CIMS (70 eV) *m/z* 185 (M⁺, 100). HRCIMS (70 eV) Calcd for C₉H₁₃O₄, 185.0814. Found, 185.0794 (M⁺). **13**: ¹H-NMR (300 MHz, CDCl₃) δ 2.11 (s, 3H), 5.72 (s, 1H), 6.20 (s, 1H), 6.22 (s, 1H), 6.53 (d, 1H, *J*=3 Hz), 7.47 (dd, 1H, *J*=3, 4 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 21.3 (CH₃), 71.8 (CH), 120.7 (CH₂), 138.7 (CH), 141.2 (C), 154.6 (CH), 170.8 (CO), 193.3 (CO). CIMS (70 eV) *m/z* 153 (M⁺, 100). HRCIMS (70 eV) Calcd for C₈H₉O₃, 153.0551. Found, 153.0552 (M⁺).
12. Full .cif files have been deposited with the Cambridge Crystallographic Data Centre, CCDC 184070-184072. ¹H-NMR (300 MHz, CDCl₃) **12a**: δ 1.77 (s, 3H); **12b**: δ 1.97 (s, 3H).
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GRAPHICAL ABSTRACT

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