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Synthesis of (±) epipentenomycin I and III

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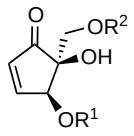
Abstract—A synthesis of (±) epipentenomycin I and III is reported from a regioselective epoxidation of racemic 3-hydroxy- and 3-acetoxy-2-methylene-4-cyclopentenone, respectively, with dimethyldioxirane followed by hydrolytic ring-opening of the resulting epoxide.

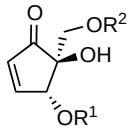
The pentenomycin group of natural products (compounds **1**–**4**) have antibacterial activities against both Gram-positive and Gram-negative bacteria. Pentenomycin I (**1**) and II (**2**) were first isolated from *Streptomyces eurythermus* in 1973[1] while pentenomycin III (**3**) was isolated three years later from *Streptoverticillium eurocidicum*.[2] Epipentenomycin I (**4**), however, was isolated in 1989[3] 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 analogues[8] (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.

Treatment of freshly prepared 3-hydroxy-2-methylene-4-cyclopentenone (**7**)[9] with freshly distilled dimethyldioxirane (DMDO) in acetone[10] 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]

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).



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)

Keywords: epipentenomycin I and III; epoxidation; dimethyldioxirane; epoxide hydrolysis.
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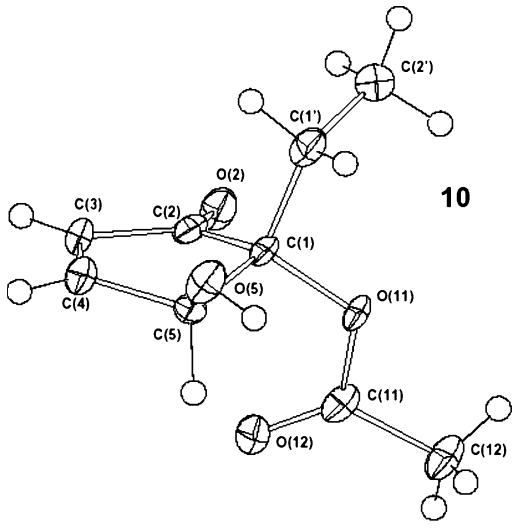
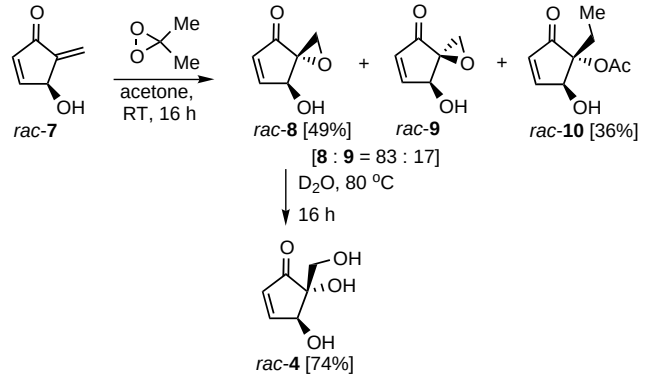
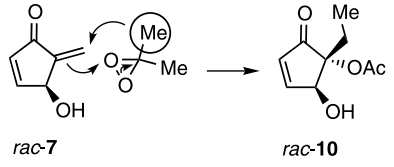


Figure 1. ORTEP plot of **10**.



Scheme 1.

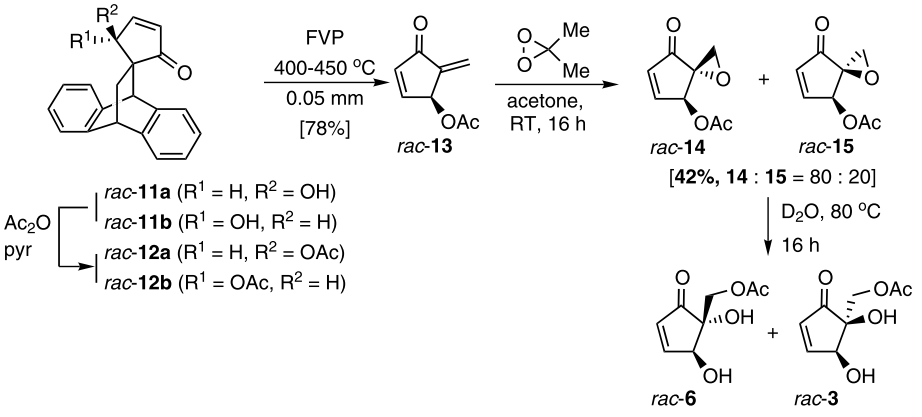


Scheme 2.

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.

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 (±) 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 (±) 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 (±) epipentenomycin II (**5**) we acetylated the known alcohols *rac*-**11a** and *rac*-**11b**, to give their respective allylic acetates, *rac*-**12a** and *rac*-**12b** (Scheme 3). 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 D_2O 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



Scheme 3.

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 ^{1}H NMR spectral data in $CDCl_3$ 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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References

1. Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot*. **1973**, *26*, 506.
2. Shomura, T.; Hoshida, J.; Kondo, Y.; Watanabe, H.; Omoto, S.; Inouye, S.; Niida, T. *Kenyu Nempo* **1976**, *16*, 1.
3. Bernillon, J.; Bonvin, J. F.; Pommier, M. T.; Arpin, N. *J. Antibiot*. **1989**, *13*, 1430.
4. Smith, A. B., III; Pilla, N. N. *Tetrahedron Lett*. **1980**, *21*, 4691.
5. Shono, T.; Matsumura, Y.; Yamane, S.; Suzuki, M. *Chem. Lett*. **1980**, 1619.
6. (a) Elliott, J. D.; Hetmanski, M.; Palfreyman, M. N.; Purcell, N.; Stoodley, R. J. *Tetrahedron Lett*. **1983**, *24*, 965; (b) Hetmanski, M.; Purcell, N.; Stoodley, R. J.; Palfreyman, M. N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2089; (c) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419; (d) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett*. **2000**, *41*, 4291; (e) Gallos, J. K.; Damianou, K. C.; Dellios, C. C. *Tetrahedron Lett*. **2001**, *42*, 5769.
7. (a) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem*. **1982**, *47*, 1855; (b) Pohmakotr, M.; Popuang, S. *Tetrahedron Lett*. **1991**, *32*, 275.
8. (a) Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett*. **1982**, *23*, 5463; (b) Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Tetrahedron Lett*. **1987**, *28*, 1329; (c) Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1989**, *45*, 7134.
9. Chantarasiri, N.; Dinprasert, P.; Thebtaranonth, C.; Thebtaranonth, Y.; Yenjai, C. *J. Chem. Soc., Chem. Commun*. **1990**, 286.
10. Murray, R. W.; Singh, M. *Org. Synth*. **1997**, *74*, 91.
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).
Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (br., 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.1 (CH_2), 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 $C_6H_7O_3$, 127.0395. Found, 127.0363 (M^+).
Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): 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).
Compound **10**: needles from DCM/petroleum spirit, mp = 98–100°C, ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.1 (CH_3), 21.6 (CH_3), 24.6 (CH_2), 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 $C_9H_{13}O_4$, 185.0814. Found, 185.0794 (M^+).
Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 (CH_3), 71.8 (CH), 120.7 (CH_2), 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 $C_8H_9O_3$, 153.0551. Found, 153.0552 (M^+).
12. Full *.cif* files have been deposited with the Cambridge Crystallographic Data Centre, CCDC 184070–184072. ^{1}H NMR (300 MHz, $CDCl_3$) **12a**: δ 1.77 (s, 3H); **12b**: δ 1.97 (s, 3H).
13. (a) Chow, K.; Danishefsky, S. *J. Org. Chem*. **1990**, *55*, 4211; (b) Murray, R. W.; Singh, M. *Tetrahedron Lett*. **1995**, *37*, 2441.
14. Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Aliyan, H.; Mirkhani, V. *Synth. Commun*. **2000**, *30*, 2365.
15. For the ring-opening of an epoxide with water, see: Lubineau, A.; Billault, I. *Carbohydr. Res*. **1999**, *320*, 49.