Tetrahedron Letters Vol. 21, pp 4691 - 4694 0040-4039/80/1201-4691$02.00/0

A STEREOSPECIFIC TOTAL SYNTHESIS OF (±)-EPIPENTENOMYCIN I, (±)-EPIPENTENOMYCIN II AND (±)-EPIPENTENOMYCIN III

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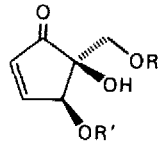
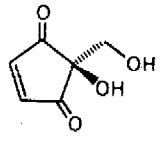
Summary: *A highly efficient, stereospecific synthesis of the epimeric pentenomycins is reported utilizing the stereospecific addition of OsO_4 to substituted cyclopentenes.*

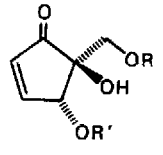
Recently we reported the stereospecific syntheses of the cyclopentenoid antibiotics, (±)-pentenomycin I (1), (±)-pentenomycin II (2) and dehydropentenomycin I (3).[2,3,4] Our continuing interest in this area prompted us to investigate the synthesis of the epimeric series, termed the epipentenomycins I, II and III[4] (5-7 respectively), both to develop new methodology for generating such systems, as well as by the potential pharmacological importance of the cyclopentenone structural unit suggested to be the reactive functionality in a variety of structurally complex antitumor agents.[5] Indeed these structures had been postulated for antibiotics C-2554-B, A-II and A-I, isolated from *Streptomyces lavenduligriseus* C-2554.[6] More recently, however these antibiotics were shown to be identical with the pentenomycins.[7]



(1): R = R' = H
(2): R = H, R' = Ac
(4): R = Ac, R' = H

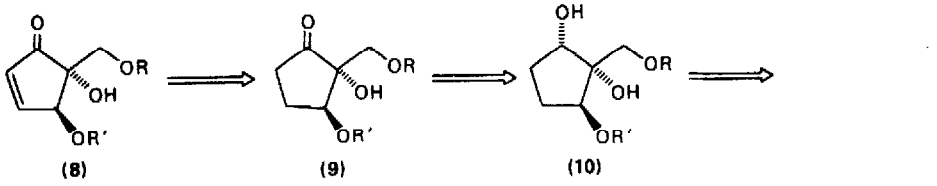


(3)

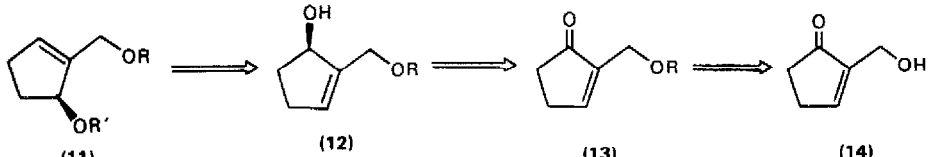


(5): R = R' = H
(6): R = H, R' = Ac
(7): R = Ac, R' = H

From a retrosynthetic perspective, diol 10 appeared to be an ideal intermediate, from which the three epimeric pentenomycins could be elaborated by appropriate choice of oxygen substituents. Careful oxidation of 10 would then lead to saturated α-hydroxy ketone 9, which in turn could be elaborated to 5-7 through introduction of unsaturation followed by deprotection. Central to generation of 10 is introduction of the vicinal cis-hydroxyl groups trans to the -OR' substituent. Here addition of OsO_4 to olefin 11 from the side of the molecule opposite the -OR' group was anticipated. Olefin 11 in turn, could be generated in three steps from α-hydroxymethylcyclopentenone 14, readily available in our laboratory.[8]



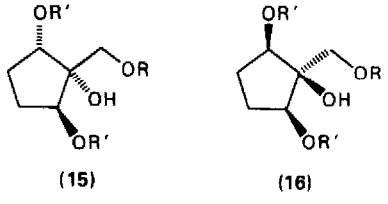
(8) (9) (10)



(11) (12) (13) (14)

(a): R = R' = $SiMe_2t$-Bu
(b): R = $SiMe_2t$-Bu, R' = Ac
(c): R = Ac, R' = $SiMe_2t$-Bu

With epipentenomycin I (5) as our initial target, 14 was converted to 10 via initial protection as the tert-butyldimethylsilyl (TBDMS) ether 13a[9] (TBDMSCl/imidazole/DMF, 77%[10]).[11] Subsequent reduction with $NaBH_4$ in the presence of $CeCl_3 \cdot H_2O$[12] afforded 12a in 93%[10] yield. The allylic alcohol was then protected as the bis-TBDMS ether (11a,[9] 89%). Cis-hydroxylation of 11a with 1.0 equiv. OsO_4 in pyridine[13] followed by reductive cleavage (aq. $NaHSO_3$) of the derived osmate ester provided a *single* compound in 90% yield.[14] Although it is reasonable to assume that this compound had the stereochemistry shown for 10a, the structure was rigorously assigned via the tris-TBDMS ether 15a[9] (76% from 13a). If cis-hydroxylation had occurred cis to the -OR' group in 11a, one would obtain, after silylation, a compound containing a plane of symmetry (i.e. 16a). On the other hand the product arising from trans addition would afford the unsymmetrical isomer, 15a. Carbon-13 NMR analysis could then be used to define stereochemistry. That is, the number of non-equivalent carbon atoms in 15a is eighteen, while the number for 16a is 10. In the event, the spectrum of the tri-silyl ether displayed 14 lines. The number 14 is the result of overlapping methyl and t-butyl carbon resonances. More significant is the fact that the two carbons bearing the secondary O-silyl groups display as two distinct doublets in the off-resonance decoupled spectrum, while the two methylene carbons appear as slightly separated triplets. Such a spectrum is consistent only with unsymmetrical structure 15a.



(15) (16)

(a): R = R' = $SiMe_2t$-Bu
(b): R = $SiMe_2t$-Bu, R' = Ac
(c): R = Ac, R' = $SiMe_2t$-Bu

With diol 10a in hand and the stereochemistry secure, we turned to complete the synthesis of epipentenomycin I (5). Oxidation of 10a following the Swern procedure (TFAA/DMSO/TEA)[15] afforded an 80% yield of 9a.[9] Dehydrogenation employing SeO_2[16] yielded 8a,[9] albeit in modest yield (ca. 25%). Final hydrolysis of the silyl groups (aq. HOAc, THF) afforded (±)-epipentenomycin I (5)[9] as a colorless oil (84%). That this compound was indeed (±) epipentenomycin I was apparent from its spectroscopic properties (IR, 100 MHz ^1H NMR) as well as by comparison with pentenomycin I (1).[17]

Synthesis of (±)-epipentenomycin II (6) proceeded in a similar manner without **event via 8b**. Alcohol 12a, generated as described, was acetylated to afford 11b[9] (93%). Cis-hydroxylation (OsO_4) again yielded a *single* compound as a white crystalline solid (mp 64-66° C) in 85% yield.[14] That this compound had the stereochemistry shown for 10b was verified as before through ^{13}C NMR and 360 MHz ^1H NMR analysis of the derived diacetate, 15b[9] (53%). With 11b in hand, Swern oxidation[15] (61%) followed by SeO_2 dehydrogenation[16] afforded 8b[9] (58%). All attempts to effect hydrolysis of 8b afforded at best a mixture of epipentenomycin II (6) and epipentenomycin III (7) as evidenced by the ^1H NMR spectrum in D_2O. Furthermore, upon dissolution in $CDCl_3$, this mixture was converted cleanly to epipentenomycin III. Presumably the cis relationship of the secondary acetate and the hydroxymethyl group in (6) renders this transfer quite facile. The closely related pentenomycin II (2) on the other hand shows no propensity for rearrangement.

Turning to the synthesis of epipentenomycin III (7) the same protocol was executed on 11c,[9] obtained via acetylation, reduction and protection (TBDMS ether) of 14 (62% overall from 14). Cis-hydroxylation of 11c again afforded a *single* compound 10c (78%[10])[14] The bis-TBDMS ether was then prepared (66%) and as before the ^1H NMR (360 MHz) and ^{13}C NMR data confirmed the assigned structure (i.e. 15c). Swern oxidation (61%), followed by SeO_2 dehydrogenation and deprotection afforded epipentenomycin III (7)[9] as a colorless oil, identical with the rearrangement product from epipentenomycin II. Final confirmation of structure 7 was via its spectroscopic properties as well as by comparison with pentenomycin III (4).[18]

Acknowledgements. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant No. CA-19033. In addition we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and the Middle Atlantic Regional NMR Facility (NIH RR #542) at the University of Pennsylvania where the 220 and 360 ^1H NMR spectra were recorded.

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9. Analytical samples of this compound, obtained either by preparative vapor phase chromatography (VPC), recrystallization or chromatography (TLC or LC) gave satisfactory IR ($CHCl_3$) and 360-MHz NMR ($CDCl_3$) spectra as well as elemental analysis ($\pm$ 0.4%).

10. All yields recorded here were based on isolated material after purification via distillation, recrystallization or chromatography (TLC or LC on silica gel).

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14. Careful examination of the crude reaction mixture by high field (250 MHz) ^1H NMR did not reveal the presence (i.e. $<$ 5%) of a second isomer. Work is continuing in our laboratory on the stereoselective oxidation of related cyclopentene derivatives with OsO_4.

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17. Epipentenomycin I: ^1H NMR (60 MHz, D_2O) δ 3.88 (2H, d, J = 2Hz), 5.00 [1H, app.t (d of d), J = 2 Hz], 6.58 (1H, dd, J = 2, 6.5 Hz), 7.90 (1H, dd, J = 2.0, 6.5 Hz). Pentenomycin I: ^1H NMR (60 MHz, D_2O) δ 3.55 (2H, s), 4.68 (1H, dd, J = 3, 1.5 Hz), 6.30 (1H, dd, J = 6.0, 1.5 Hz), 7.70 (1H, dd, J = 6.0, 3.0 Hz).

18. Epipentenomycin III: ^1H NMR (360 Hz, $CDCl_3$) δ 2.07 (3H, s), 3.03 (1H, bs), 3.44 (1H, bs), 4.32 (2H, ABq, J = 12 Hz), 4.90 (1H, bs), 6.32 (1H, dd, J = 2.5, 6.0 Hz), 7.50 (1H, dd, J = 1.7, 6.0 Hz). Pentenomycin III: ^1H NMR (60 Mz, $CDCl_3$) δ 2.02 (3H, s), 3.85 (2H, b), 4.25 (2H, d, J = 2Hz), 4.75 (1H, bs), 6.35 (1H, dd, J = 1.0, 6.0 Hz), 7.67 (1H, dd, J = 2.2, 6.0 Hz); (360 Mz, $CDCl_3$) δ 2.08 (3H, s), 2.78-3.64 (2H, m), 4.26 (2H, ABq, J = 13 Hz), 4.72 (1H, bs), 6.33 (1H, d, J = 6 Hz), 7.64 (1H, dd, J = 2.0, 6.0 Hz).

(Received in USA 28 July 1980)