Tetrahedron Letters, Vol.32, No.2, pp 275-278, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

INTRAMOLECULAR ACYLATION OF α-SULFINYL CARBANION: A FACILE SYNTHESIS OF (±)-PENTENOMYCIN I AND (±)-EPIPENTENOMYCIN I.

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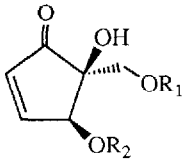
Summary: (±)-Pentenomycin I and (±)-epipentenomycin I were synthesized, starting from methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate. The key reaction involved the intramolecular acylation of α-sulfinyl carbanion and pyrolysis of the resulting product.

Highly oxygenated cyclopentenoids [1a,b,c] are of increasing interest, because a number of natural products contain of such basic skeleton, and some of them exhibit biological activities, e.g. pentenomycin antibiotics.[1d] Among these antibiotics, pentenomycin I (**1**) was isolated by *Umino and co-workers* in 1973 from culture broths of *Streptomyces eurythermus*,[2] while epipentenomycin I (**2**) was first reported to be isolated from carpophores of *Perziza sp.* by *Bernillon and co-workers* in 1989.[3] Syntheses of both antibiotics and their analogues were reported.[4] In connection with our recent reports for the synthesis of 4-oxygenated spirocyclopentenones [5] and 5-alkylidene 4-hydroxy-2-cyclopentenones [6] based on the intramolecular acylation of α-sulfinyl carbanions, we wish to describe here a new facile route to (±)-pentenomycin I (**1**) and (±)-epipentenomycin I (**2**). As shown in Scheme I, the spirocyclopentenone of type **7** appears to be a precursor for **1** and **2**. This type of compound should be readily obtained from compounds **5** and **6** *via* intramolecular acylation of α-sulfinyl carbanion followed by sulfoxide elimination.

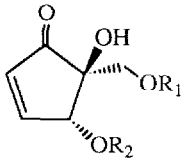


Pentenomycins

1, I $R_1 = R_2 = H$

II $R_1 = Ac, R_2 = H$

III $R_1 = H, R_2 = Ac$

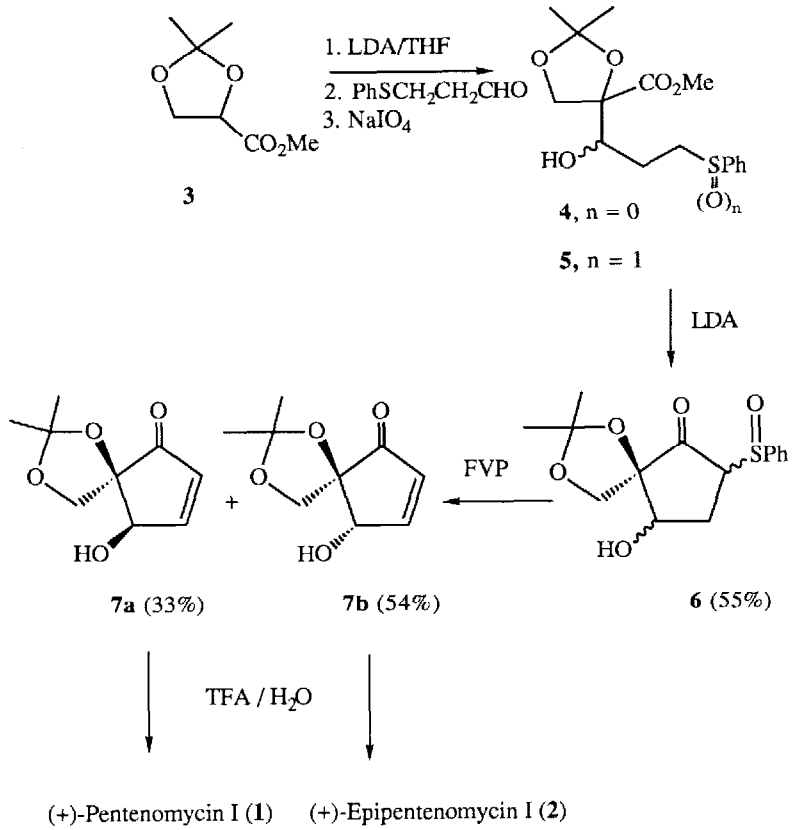


Epipentenomycins

2, I $R_1 = R_2 = H$

II $R_1 = Ac, R_2 = H$

III $R_1 = H, R_2 = Ac$



Scheme I

Lithiation of methyl 2,2-dimethyl-1,3-dioxolane-1-carboxylate (**3**)[7,8] was accomplished by using lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78° for 1.5 hr. The resulting lithium enolate anion (1 equiv.) reacted smoothly at -78° for 2 hr with freshly prepared 3-phenylthiopropanal (1.1 equiv.) to provide hydroxysulfide **4** in 63% yield after preparative thin layer chromatography (SiO_2) as an inseparable mixture of two stereoisomers.[9] Oxidation of the hydroxysulfide **4** with sodium metaperiodate in aqueous methanol at 0 ° to room temperature (10 hr) furnished a diastereomeric mixture of the hydroxysulfoxide **5**[10] in quantitative yield, which was used without purification in the next step. Treatment of the crude hydroxysulfoxide **5** (1 equiv.) with LDA (3.1 equiv.) in THF at -78° for 2 hr and at 0° for 2 hr resulted in the formation of the expected spiro-ketosulfoxide **6** in 55% yield (overall from **4**) as solid product after flash column chromatography (SiO_2). Compound **6**[10] was obtained as a mixture of diastereomers. Flash vacuum thermolysis of the purified spiro-

ketosulfoxide **6** (340° C, 0.10 Torr) afforded a separable mixture of the desired pentenomycin I acetonide **7a** (33%, less polar) and epipentenomycin I acetonide **7b**[11] (54%, more polar) after preparative thin layer chromatography (silica gel, EtOAc/hexane). Lower yields of **7a** and **7b** (41-46%) were obtained, when FVP was carried out by using the crude spiro-ketosulfoxide **6**. It should be noted here that pyrolysis of **6** under the conventional methods, either neat under reduced pressure or in refluxing toluene, led to a very low yield of the expected products **7a** and **7b**. This may be due to the decomposition of **7a** and **7b** under the pyrolytic conditions. Having (±)-pentenomycin I acetonide **7a** and (±)-epipentenomycin I acetonide **7b** in hand, they were subjected to hydrolysis in order to remove the acetonide group by employing 90% trifluoroacetic acid.[12] As expected, (±)-pentenomycin I (**1**) as an amorphous powder and epipentenomycin I (**2**) as a syrup could be achieved in quantitative yields after removal of solvents by freeze-drying overnight. The ^{1}H-NMR spectra (60 MHz) of **1** and **2** are consistent with the assigned structures and identical with those of reported values.[13]

The results described herein provided an efficient synthesis of both (±)-pentenomycin I (**1**) and (±)-epipentenomycin I (**2**). Since the requisite esters of type **3** could be easily obtained, thus our synthetic strategy appears to give a general procedure for the preparation of alkyl substituted pentenomycin analogues,[14] which might show interesting biological activities.

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7. (±)-Methyl 2,2-dimethyl-1,3-dioxolane-1-carboxylate (3) was prepared in 27% (overall yield) from commercially available (±)-α,β-isopropylidene glycerol according to the known procedure (ClCOCOCl/DMSO/Et_3N in CH_2Cl_2 followed by MeOH / Br_2 / H_2O / $NaHCO_3$): D.R.Williams, F.D.Klinger, E.E.Allen and F.W.Lichtenthaler, *Tetrahedron Lett., **29**,5087 (1988).*
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9. The ^{1}H-NMR (CCl_4) spectrum of **4** showed two signals of the methoxyl group at 3.63 and 3.66 ppm.
10. Compounds **5** (after PLC on silica gel) and **6** were fully characterised by IR, ^{1}H-NMR, MS and microanalyses.
11. **7a**: viscous liquid. IR (neat): 3475, 1725 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.55 (s, 6H, Me_2C), 3.1 (br. OH), 4.0 and 4.21 (each d, J = 8 Hz, AB-system of -CH_2O), 4.53 (m, 1H, -CHO), 6.33 (dd, J = 6, 2 Hz, 1H, olefinic proton), 7.61 (dd, J = 6, 2.5 Hz, 1H, olefinic proton). MS: 184 (M^+).
7b: viscous liquid. IR (neat): 3450, 1725 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.53 and 1.56 (each s, 6H, Me_2C), 3.8 and 4.45 (each d, J = 8 Hz, AB-system of -CH_2O), 6.3 (dd, J = 6, 2 Hz, 1H, olefinic proton), 7.5 (dd, J = 6, 2.5 Hz, 1H, olefinic proton). MS: 184 (M^+). The ^{1}H-NMR spectrum of **7b** is identical to that of reported in the literature.[3]
12. cf. Ref. 4e.
13. **1**: ^{1}H-NMR (60 MHz, D_2O): 3.66 (br. s, 2H, -CH_2O), 4.76 (m under the br. s of HOD, 1H, -CHO), 6.36 (dd, J = 6, 2Hz, 1H, olefinic proton), 7.76 (dd, J = 6, 2.5Hz, 1H, olefinic proton).
2: ^{1}H-NMR (60 MHz, D_2O): 3.66 and 3.9 (each d, J = 12Hz, AB-system of - CH_2O), 4.86 (t, J = 2Hz, 1H, -CHO), 6.43 (dd, J = 6, 2Hz, 1H, olefinic proton), 7.76 (dd, J = 6, 2.5Hz, 1H, olefinic proton). The spectra of **1** and **2** are identical with those of reported in the liturratures.[2,3]
14. The synthesis of alkyl substituted pentenomycin analogues will be reported elsewhere.

(Received in UK 13 November 1990)