Pergamon

Tetrahedron Letters 42 (2001) 5769–5771

TETRAHEDRON LETTERS

A new total synthesis of pentenomycin

John K. Gallos,* Katerina C. Damianou and Constantinos C. Dellios

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 540 06, Greece

Received 2 May 2001; revised 12 June 2001; accepted 20 June 2001

Abstract—A new total synthesis of enantiomerically pure pentenomycin has been achieved by the intramolecular nitrone cycloaddition of the proper γ-unsaturated aldehyde, easily accessible from L-arabinose, followed by reductive N–O bond cleavage and further oxidative deamination of the resulting aminocyclopentitol. © 2001 Elsevier Science Ltd. All rights reserved.

Pentenomycin antibiotics constitute a family of natural hydroxylated cyclopentanoids, which are produced by *Streptomyces* species and show moderate activity against Gram-positive and Gram-negative bacteria.[1,2] Among them, pentenomycin I **1**, usually referred to simply as pentenomycin, has attracted considerable attention and a number of syntheses of racemic and enantiopure material have been reported.[2] We now wish to report an efficient synthesis of enantiomerically pure pentenomycin, starting from the naturally abundant L-arabinose. The crucial step of formation of the five-membered ring involves an intramolecular nitrone cycloaddition, a reaction we had applied some time ago[3] to the synthesis of aminocyclopentitols **4** from the unsaturated aldehyde **2**, via the adduct **3** (Fig. 1).

In order to construct the two chiral centres of pentenomycin with the correct absolute configuration, we started from L-arabinose, which was readily converted to the protected L-erythrose **5** (Scheme 1).[4] The hydroxymethyl group was introduced by treatment of **5** with CH_2O in the presence of K_2CO_3 according to the literature[5] and subsequently was tritylated by standard procedures.[6] Wittig olefination of **6** with $Ph_3P{=}CH_2$ yielded the alcohol **7**, which was then subjected to Swern oxidation, condensation with MeNHOH and reflux of the resulting nitrone in chlorobenzene[3] to give in good overall yield the bicyclic oxazine **8**, together with its diastereomeric adduct in a ratio of ca. 8:1 (the major isomer shown hereafter in Scheme 1). Since both diastereoisomers give the same final product, they were used further as a mixture, although they are easily separable chromatographically.[7,8]

The best conditions found for the N–O bond cleavage were hydrogenolysis with H_2 over $Pd(OH)_2$ in MeOH; the aminocyclitol **9** formed was methylated with an excess of MeI to afford the ammonium salt **10a**, expected to give the desired protected pentenomycin **11b** upon oxidation of the unprotected hydroxyl group and spontaneous elimination of the ammonium group.[9] Swern oxidation, however, gave the detritylated **11b** in low yield, whereas oxidation with PDC afforded the iodinated compound **11a** in quantitative yield (98%). Evidently, the PDC oxidises iodide to molecular iodine, which in the presence of pyridine (from PDC) iodinates the enone already formed.[10] Repeated washing of **10a** with aqueous NaCl caused partial replacement of iodide by chloride and further PDC oxidation gave the desired **11b** (42%) together with **11a** (32%). Much more

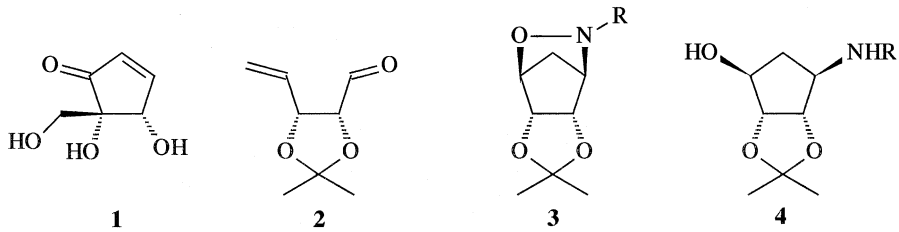
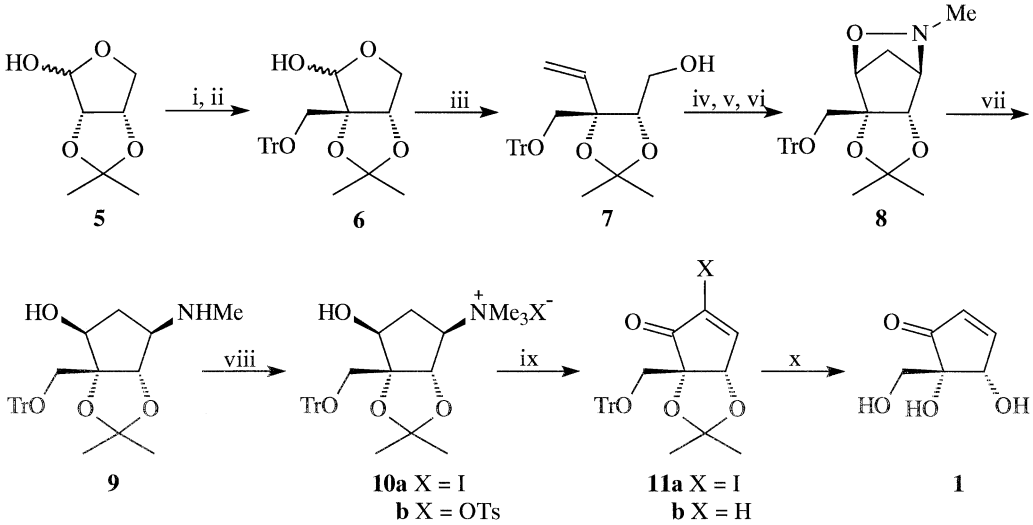


Figure 1.

* Corresponding author. Fax: ++31-997679; e-mail: igallos@chem.auth.gr

PII: S0040-4039(01)01099-1



Scheme 1. *Reagents and conditions*: (i) CH_2O, K_2CO_3, MeOH, reflux, 3 days, 82%; (ii) Ph_3C-Cl, pyridine (dry), 60°C, 2 days, 59%; (iii) $Ph_3P^+CH_3Br^-$, 12-crown-4, *n*-BuLi, THF, −70→0°C, 98%; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −50 to 20°C, 30 min; (v) MeNHOH·HCl, Na_2CO_3, EtOH, 20°C, 15 min; (vi) PhCl, reflux, 15 min, 53% from **7**; (vii) $Pd(OH)_2/C$, H_2, MeOH, 20°C, 15 h, 52%; (viii) MeI, K_2CO_3, THF, 20°C or MeOTs, K_2CO_3, THF, reflux; (ix) PDC, CH_2Cl_2, 20°C, 2 h, 66% of **11b** from **9** via **10b**; (x) aqueous HCl 1N, THF, 20°C, 12 h, 90%.

satisfactory results were obtained when the quaternisation of amine **9** was attempted with methyl *p*-toluenesulfonate. The resulting trimethylammonium *p*-toluenesulfonate **10b** was smoothly oxidised with PDC to give **11b** in 66% yield from **9**. Deprotection of **11b** with 1N aqueous HCl in THF gave pentenomycin **1** in 90% yield, with spectroscopic and physical data identical to those reported in the literature.[2]

In short, we have developed a new synthesis of enantiopure pentenomycin, utilising cheap and easily available materials, applying simple and convenient methods. The methodology used could be developed as a new general synthesis of chiral cyclopentenones, the scope and limitation of which is under consideration. In addition, the aminocyclopentitols intermediates such as **9** are also of considerable importance as glycosidase inhibitors and carbocyclic nucleoside precursors.[11]

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7. All new compounds gave spectral and analytical data consistent with the proposed structures. Selected NMR and physical data are listed. Compound **7**: oil, $[\alpha]_D$ −11.9 (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.49 (s, 3H), 3.18 (d, 1H, J=9.0 Hz), 3.27 (d, 1H, J=9.0 Hz), 3.65 (two dd as m, 2H), 4.12 (dd, 1H, J=7.0, 4.7 Hz), 5.24 (dd, 1H, J=10.6, 2.2 Hz), 5.45 (dd, 1H, J=17.2, 2.2 Hz), 5.93 (dd, 1H, J=17.2, 10.6 Hz), 7.25 (m, 9H), 7.35 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.9, 62.4, 68.1, 81.5, 83.3, 87.3, 109.0, 116.2, 127.1, 127.9, 128.7, 135.9, 143.4; HRMS (MALDI-FTMS) calcd ($C_{28}H_{30}O_4Na$) 453.2036 (M+Na), found 453.2037, σ 0.2 ppm. Compound **8**: oil, $[\alpha]_D$ −7.5 (*c* 1.29, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.07 (s, 3H), 1.44 (s, 3H), 1.98 (d, 1H, J=11.1 Hz), 2.17 (d, 1H, J=11.1 Hz), 2.56 (s, 3H), 3.30 (s, 1H), 3.34 (d, 1H, J=9.7 Hz), 3.41 (d, 1H, J=9.7 Hz), 3.75 (s, 1H), 4.72 (s, 1H), 7.27 (m, 9H), 7.52 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.4, 27.0, 28.7, 45.2, 64.3, 65.9, 77.4, 81.2, 86.5, 89.4, 111.6, 126.8, 127.6, 128.9, 144.1; HRMS (MALDI-FTMS) calcd ($C_{29}H_{31}NO_4Na$) 480.2145 (M+Na), found 480.2159, σ 2.9 ppm. Compound **9**: oil, $[\alpha]_D$ −30.8 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.40 (s, 3H), 1.79 (d, 1H, J=14.2 Hz), 2.20 (dt, 1H, J=14.2, 4.4 Hz), 2.30 (br s, 2H, OH, NH), 2.36 (s, 3H), 3.05 (d, 1H,

$J=4.4$ Hz), 3.40 (d, 1H, $J=9.8$ Hz), 3.69 (d, 1H, $J=9.8$ Hz), 4.13 (s, 1H), 4.20 (d, 1H, $J=4.4$ Hz), 7.28 (m, 9H), 7.54 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.7, 27.9, 34.2, 35.1, 65.4, 66.7, 79.4, 85.8, 87.2, 94.2, 110.9, 127.0, 127.8, 128.8, 143.8; HRMS (MALDI-FTMS) calcd ($C_{29}H_{33}NO_4Na$) 482.2302 (M+Na), found 482.2301, σ 0.2 ppm. Compound **11b**: oil, $[\alpha]_D$ +15.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.34 (s, 3H), 3.29 (d, 1H, *J* 8.8 Hz), 3.48 (d, 1H, $J=8.8$ Hz), 5.05 (d, 1H, $J=2.0$ Hz), 6.28 (d, 1H, $J=5.9$ Hz), 7.25 (m, 15H), 7.66 (dd, 1H, $J=5.9$, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 28.4, 28.6, 62.6, 82.1, 83.8, 87.1, 115.3, 127.2, 127.9, 128.7, 134.9, 143.3, 160.1, 204.3; HRMS (MALDI-FTMS) calcd ($C_{28}H_{26}O_4Na$) 449.1723 (M+Na), found 449.1729, σ 1.3 ppm.

8. The absolute configuration of the newly formed stereocentres in the major isomer of cycloadduct **8** (and therefore for **9** and **10**) was deduced from NOE experiments. The significant signal enhancement of the *endo*-Me of the acetonide group (δ 1.44) when irradiating the *endo*-H of the bridged methylene group (δ 2.17) is mostly characteristic and leaves little doubt on the structure of **8**.
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