Synthesis of 6-Epithienamycin

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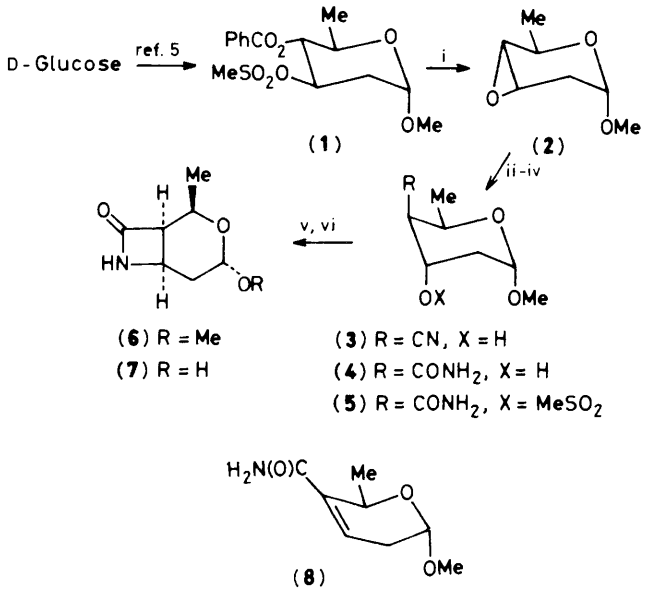
The title compound has been prepared from D-glucose.

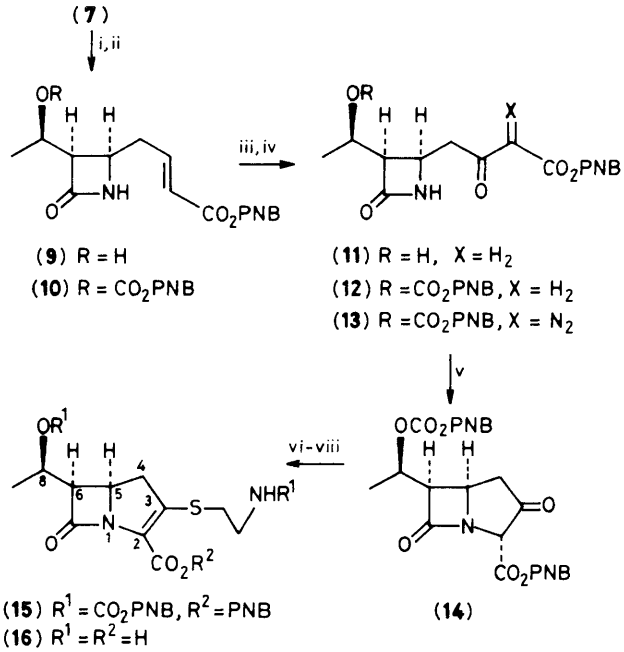
The biological activity of (5*R*) carbapenem antibiotics is markedly influenced by the configuration at C-6 and C-8.[1] Surprisingly, no carbapenem with 5*R*,6*R*,8*R*-configuration has ever been isolated, while representatives of all the other (5*R*) diastereoisomers occur in nature.[2] Availability of the all *R*-configured title compound (**16**) would allow full evaluation of the structure–activity relationships in the thienamycin series.



Scheme 1. i, NaOMe (2.0 equiv.), MeOH, 0 °C to room temp., 5 h, 90%; ii, Et_2AlCN (4.0 equiv.), Et_2O, −40 °C, 3 h, 65%; iii, H_2O_2 (3.0 equiv.), 1 M K_2CO_3 (2.0 equiv.), H_2O, room temp., 12 h, 90%; iv, $MeSO_2Cl$ (1.04 equiv.), pyridine, 0 °C to room temp., 12 h, 77%; v, Bu^{t}OK (1.6 equiv.), 18-crown-6 (1.6 equiv.), dimethylformamide, 0 °C, 3 h, 45%; vi, 70% aqueous HCO_2H, room temp., 2.5 h, 95%.

D-Glucose, so far only used in the preparation of 5,6-*trans*-carbapenem intermediates[3] was chosen as starting material. It was easily transformed into the D-ribo-epoxide[4] (**2**) {m.p. 31 °C, $[\alpha]_D^{25}$ +130.8° (*c* 2.62, $CHCl_3$)} *via* the known[5] benzoate (**1**) in an overall yield of 30%. Diethylaluminium cyanide transformed the epoxide (**2**) regioselectively[6] into the strongly hydrogen bonded 4-cyano compound (**3**) {m.p. 65 °C, $[\alpha]_D^{25}$ +167.5° (*c* 1.02, $CHCl_3$); ν_{max} 3505 and 2245 cm^{-1}; ^{1}H n.m.r. ($CHCl_3$) δ 2.82 (1H, X-part of an ABX system, $\Delta\nu_{\frac{1}{2}}$ = 7.5 Hz, 4-H)}. Direct cyclisation of the corresponding amide (**4**) [m.p. 131 °C; ν_{max} ($CHCl_3$) 3500, 3410, 3375, 1673, and 1582 cm^{-1}] under the conditions of the Mitsunobu reaction [Bu$^n_3$P, $(EtO_2C)_2N_2$, tetrahydrofuran (THF)] gave at best a 12% yield of the key intermediate (**6**). The amide (**4**) was however easily transformed into its methanesulphonate† (**5**). Treatment of (**5**) with base[7] gave a 45% yield of the desired azetidinone (**6**) {m.p. 134—135 °C, $[\alpha]_D^{25}$ +136.7° (*c* 0.42, $CHCl_3$; ν_{max} ($CHCl_3$) 3410 and 1755 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 3.18 [1H, ddd, *J*(3-H–4-H) 5.5, *J*(4-H–5-H) 2.5, and *J*(4-H–NH) 2 Hz, 4-H], 3.93 [1H, ddd, *J*(3-H–4-H) 5.5, *J*(3-H–2-H$_{ax}$) 3.5, and *J*(3-H–2-H$_{eq}$) 2.5 Hz, 3-H]} together with *ca.* 20% of unsaturated amide (**8**). Mild hydrolysis of (**6**) furnished the hemiacetal (**7**) {^{1}H n.m.r. (CD_3OD) δ 5.29 [1H, dd, *J*(1-H–2-H$_{ax}$) 8.5, *J*(1-H–2-H$_{eq}$) 6 Hz, 1-H]} (Scheme 1).

The carbon framework of (**16**) was completed by Wittig reaction of (**7**) to give the unsaturated ester (**9**) [oil; ν_{max} ($CHCl_3$) 3570, 3410, 1760, 1727, and 1655 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 6.01 (1H, d, *J* 15.7 Hz) and 6.99 (1H, dt, *J* 15.7 and 7.2 Hz, 2 × ethylenic H)]. Although (**9**) itself did not cyclise spontaneously, its hydroxy group had to be protected to avoid hemiacetal formation from the *cis*-hydroxyketoester (**11**). Oxidation of the protected ester (**10**) {m.p. 122 °C, $[\alpha]_D^{25}$ −0.6° (*c* 0.68, $CHCl_3$); ν_{max} ($CHCl_3$) 1768, 1750(sh), 1730(sh), and 1660 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 3.43 (1H, ddd, *J* 5.5, 4.5, and 1 Hz, 3-H) and 3.88 (1H, dt, *J* 9 and 5.5 Hz, 4-H)} by a modification of Tsuji's procedure[8] cleanly gave the β-ketoester (**12**) {m.p. 115 °C, ν_{max} ($CHCl_3$) 1768, 1746(sh), and 1720 cm^{-1}; ^{1}H n.m.r. ($CHCl_3$) δ 3.49 [2H, s, C(O)–C*H*$_2$–CO$_2$]}.



Scheme 2. PNB = 4-Nitrobenzyl. i, Ph_3P=CH–CO_2PNB (2 equiv.), MeCN, 80 °C, 3 h, 35%; ii, $ClCO_2$PNB (1.5 equiv.), 4-*N*,*N*′-dimethylaminopyridine (3 equiv.), CH_2Cl_2, −10 °C, 1 h, heat up to 0 °C, 4 h, 76%; iii, Bu^{t}OOH (10 equiv.), $PdCl_2$, Na_2PdCl_4, 50% aqueous HOAc, 60 °C, 70 min, 67%; iv, $MeC_6H_4SO_2N_3$ (1.5 equiv.), NEt_3 (4.5 equiv.), MeCN, 0 °C, 2 h, 85%; v, $Rh_2(OAc)_4$, C_6H_6, 80 °C, 2 h, 91%; vi, $(PhO)_2P(O)Cl$, Pr$^i_2$EtN (1.2 equiv. each), MeCN, 0 °C, 1 h; vii, (*in situ*) Pr$^i_2$EtN (4 equiv.), $HS[CH_2]_2NH$–CO_2PNB (1.4 equiv.), MeCN, 0 °C, 1 h, then −25 °C, 24 h, 82%; viii H_2, Pd/C, THF–sodium morpholinopropanesulphonate (0.05 M) 1 : 1, room temp., 1 h, 60%.

The synthesis was completed uneventfully by the Merck route[9] (Scheme 2): diazo transfer {(**13**) [ν_{max} ($CHCl_3$) 2140 cm^{-1}]} followed by carbene insertion provided the bicyclic lactam (**14**) {oil, $[\alpha]_D^{25}$ +83.5° (*c* 0.82, $CHCl_3$); ν_{max} ($CHCl_3$) 1775 and 1750 cm^{-1}} as a single diastereoisomer [^{1}H n.m.r. ($CHCl_3$) δ 4.75 (1H, s, 2-H)]. The exo-configuration at C-2 is inferred from computer modelling studies[9] on related bicyclic azetidinones. Introduction of the cysteamine side chain furnished the triply protected 6-epithienamycin (**15**) {oil, $[\alpha]_D^{25}$ −17° (*c* 0.6, $CHCl_3$), ν_{max} ($CHCl_3$) 3450, 1788, 1750(sh), and 1725 cm^{-1}; u.v. ($CHCl_3$) λ_{max} 266 and 312 nm; ^{1}H n.m.r. ($CDCl_3$) δ 1.44 (3H, d, *J* 6.5 Hz, 9-H), 2.98 (2H, m, 2 × 4-H), 3.18 (2H, m, S–CH_2), 3.41 (2H, q, *J* 7 Hz, C*H*$_2$–NH), 3.80 (1H, dd, *J* 7.5 and 6.5 Hz, 6-H), 4.33 (1H, dt, *J* 6.5 and 9.5 Hz, 5-H), 5.10—5.55 (8H, m, 3 × CH_2–Ar, 8-H, and NH), and 7.45—7.60 and 8.18—8.27 (12H, ArH); *m/z* (field desorption) 765 (M^+)}. The three racemic diastereoisomers of (**15**) have previously been synthesized by different routes.[10] Hydrogenolysis of (**15**) gave the title compound (**16**), completing the first synthesis of an enantiomerically pure 5,6-*cis*-carbapenem with three contiguous centres of chirality.‡§ Compound (**16**) is moderately stable: a 5 μM solution in

† Attempted preparation of the analogous triflate [$(CF_3SO_2)_2O$, pyridine, CH_2Cl_2] gave mainly the nitrile (**3**).

‡ The configuration of all the intermediates has been confirmed by 200 MHz ^{1}H n.m.r. spectroscopy.

§ To the best of our knowledge, (−)-carpetimycin is the only other enantiomerically pure *cis*-carbapenem that has been synthesized (ref. 11).

tris buffer at pH 8 lost approximately 30% of its activity within 60 min. It showed a similar spectrum and intensity of antibacterial activity against Gram positive and Gram negative bacteria as PS 5,[12] but had a much broader spectrum of β-lactamase inhibitory activity.

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