Synthesis of 3-Methoxy-2-iso-oxacephalosporin

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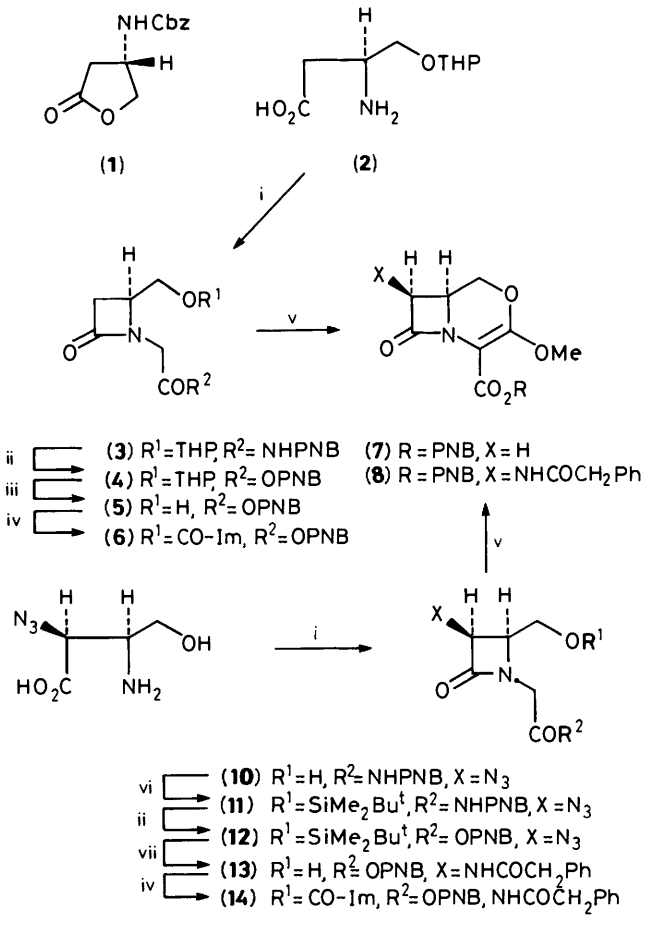
Optically active 3-methoxy-2-iso-oxacephalosporins are efficiently prepared *via* intramolecular acylation as a key step.

The synthesis of 2-iso-oxacephalosporin in an optically active form attracts considerable attention[1] because the derivatives bearing hydrogen, methyl, and substituted methyl as C-3 substituents are known to have potent antibacterial activity.[1d,2] However, there are a few reports concerning the synthesis of 3-heterosubstituted 2-iso-oxacephalosporins.[3] The previous reports have described that 3-hydroxycarbacephem and 2-oxocarbapenem ring systems could be prepared *via* an intramolecular acylation reaction as a key step.[4] Herein we report that this methodology is also applicable to the synthesis of 3-methoxy-2-iso-oxacephalosporin in an optically active form.

The (3*S*)-amino lactone (**1**)[1c] [prepared in 86% yield by $NaBH_4$ reduction of L-*N*-carbobenzyloxyaspartic anhydride] was converted into the *O*-protected amino acid (**2**), m.p. 158–160 °C, in 82% overall yield by the straightforward sequences consisting of hydrolysis (K_2CO_3, aq. acetone), esterification (CH_2N_2), *O*-protection (2,3-dihydropyran, *p*-TsOH, CH_2Cl_2), hydrolysis (NaOH, aq. MeOH), and hydrogenolysis (Pd–C, H_2, EtOH, 1 atm). The *O*-protected amino acid (**2**) was treated with equimolar amounts of formaldehyde and *p*-nitrobenzyl isocyanide in methanol to give the azetidinone (**3**) in 78% yield, which was then converted *via* *N*-nitrosation into the *p*-nitrobenzyl ester (**4**) in 64% yield. After removal of the tetrahydropyranyl entity compound (**5**) was treated with 1,1′-carbonyldi-imidazole to afford the carbamate (**6**) in 87% yield. Treatment of (**6**) with 2 equiv. of lithium bistrimethylsilylamide and followed by an excess of diazomethane gave the desired 3-methoxy-2-iso-oxacephem (**7**) in 64% yield, m.p. 146–147 °C; $[\alpha]_D^{25}$ +188.8° (*c* 0.5, $CHCl_3$); λ_{max}(MeOH) 278 nm (log ε 4.25). Attempted intramolecular acylation of the phenylthiocarbonate and chlorocarbonate of (**6**) in this way gave only poor (10% or less) yield of (**7**).

The (2*S*,3*S*)-azido amino acid (**9**) (prepared in a stereoselective manner starting from L-aspartic acid[1c]) was subjected to a four-component condensation with formaldehyde and *p*-nitrobenzyl isocyanide to give the *cis* azetidinone (**10**), m.p. 91–92 °C, in 95% yield. The hydroxy group of (**10**) was protected with t-butyldimethylsilyl chloride and converted *via* *N*-



Scheme. PNB = *p*-nitrobenzyl, Im = imidazol-1-yl. *Reagents and conditions:* i, p-$O_2NC_6H_4CH_2NC$, 30% aq. HCHO, MeOH, room temp., 12 h; ii, N_2O_4, AcONa, $CHCl_3$, 0 °C, 1 h, followed by $ClCH_2CH_2Cl$, reflux, 3 h; iii, $HClO_4$, aq. dioxane, 0 °C, 30 min; iv, 1,1′-carbonyldi-imidazole, CH_2Cl_2, room temp., 2 h; v, $(TMS)_2NLi$, THF, −78 °C, 5 min, then CH_2N_2, ether, room temp.; vi, Bu^tMe_2SiCl, imidazole, DMF, room temp., 12 h; vii, H_2S, Et_3N, CH_2Cl_2, 0 °C, 1 h, then $C_6H_5CH_2COCl$, pyridine, CH_2Cl_2, room temp., followed by 48% aq. HF, MeCN, room temp.

nitrosation into the *p*-nitrobenzyl ester (**12**) in 67% yield. Reduction of the azide group of (**12**) and subsequent acylation afforded the (3*S*)-phenylacetamidoazetidinone (**13**), m.p. 98–99 °C, in 75% yield, which was then converted by removal of the t-butyldimethylsilyl group and treatment with 1,1′-carbonyldi-imidazole into the carbamate (**14**), m.p. 153–154 °C, in 88% yield. Cyclization of the carbamate (**14**) in a similar manner to that described for (**7**) gave the 3-methoxy-2-iso-oxacephalosporin (**8**) in 53% yield. Biological evaluation of the free acids of (**7**) and (**8**) and their derivatives is being pursued.

Experimental

p-*Nitrobenzyl* (6S,7S)-3-*methoxy*-7-*phenylacetamido*-8-*oxo*-4-*oxa*-1-*azabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (**8**).—To a solution of the carbamate (**14**) (30 mg, 0.057 mmol) in THF (5 ml), was added at −78 °C, under argon, 1M lithium bis(trimethylsilyl)amide (0.18 ml) in THF. The mixture was stirred for 3 min at −78 °C, and treated with acetic acid (0.01 ml). The mixture was poured into 5% aqueous citric acid (2 ml), and extracted with ethyl acetate (3 × 5 ml). The combined extracts were washed with water, dried ($MgSO_4$), and treated with an excess of diazomethane in ether with ice-cooling. The mixture was then set aside at room temperature for 3 h, and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (benzene–ethyl acetate, 2:1, v/v) gave white crystals (14 mg, 53%), m.p. 142–143 °C (Found: C, 59.35; H, 4.3; N, 9.1. $C_{23}H_{21}N_3O_8$ requires C, 59.11; H, 4.53; N, 8.99%); $[\alpha]_D^{25}$ +133° (*c* 0.1, $CHCl_3$); $\nu_{max}(CH_2Cl_2)$ 1 770, 1 760, and 1 680 cm^{-1}; δ_H(360 MHz; $CDCl_3$) 3.56 (2 H, s, $COCH_2Ph$), 3.86 (3 H, s, OMe), 3.89 (1 H, m, 6-H), 4.00 (1 H, dd, *J* 9.8 and 10.8 Hz, 5-H), 4.58 (1 H, dd, *J* 3.9 and 10.8 Hz, 5-H), 5.28 (2 H, AB system δ_A 5.17 and δ_B 5.38, *J* 13.7 Hz, $COOCH_2$), 5.33 (1 H, dd *J* 4.9 and 5.3 Hz, 7-H), 6.67 (1 H, d, *J* 5.3 Hz, NH), 7.22–7.35 (5 H, m, ArH), 7.57 (2 H, d, *J* 8.7 Hz, ArH), and 8.17 (2 H, d, *J* 8.7 Hz, ArH).

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