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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 attention¹ because the derivatives bearing hydrogen, methyl, and substituted methyl as C-3 substituents are known to have potent antibacterial activity.^{14,2} 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 3methoxy-2-iso-oxacephalosporin in an optically active form.

The (3S)-amino lactone (1)^{1c} [prepared in 86% yield by NaBH₄ 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 (K₂CO₃, aq. acetone), esterification (CH₂N₂), O-protection (2,3-dihydropyran, p-TsOH, CH₂Cl₂), hydrolysis (NaOH, aq. MeOH), and hydrogenolysis (Pd-C, H₂, 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; $[\alpha]_D^{25} + 188.8^\circ$ (c 0.5, CHCl₃); 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 (2S,3S)-azido amino acid (9) (prepared in a stereoselective manner starting from L-aspartic acid ¹°) 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-O₂NC₆H₄CH₂NC, 30% aq. HCHO, MeOH, room temp., 12 h; ii, N₂O₄, AcONa, CHCl₃, 0 °C, 1 h, followed by ClCH₂CH₂Cl, reflux, 3 h; iii, HClO₄, aq. dioxane, 0 °C, 30 min; iv, 1,1'-carbonyldi-imidazole, CH₂Cl₂, room temp., 2 h; v, (TMS)₂NLi, THF, -78 °C, 5 min, then CH₂N₂, ether, room temp.; vi, Bu'Me₂SiCl, imidazole, DMF, room temp., 12 h; vii, H₂S, Et₃N, CH₂Cl₂, 0 °C, 1 h, then C₆H₅CH₂COCl, pyridine, CH₂Cl₂, 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 (3S)-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'-carbonyldiimidazole 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-oxacephalo433

sporin (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-4oxa-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 $(3 \times 5 \text{ ml})$. The combined extracts were washed with water, dried (MgSO₄), 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. $C_{23}H_{21}N_{3}O_{8}$ requires C, 59.11; H, 4.53; N, 8.99%); $[\alpha]_{D}^{25} + 133^{\circ}$ (c 0.1, CHCl₃); v_{max} (CH₂Cl₂) 1 770, 1 760, and 1 680 cm⁻¹; $\delta_{\rm H}(360 \text{ MHz; CDCl}_3) 3.56 (2 \text{ H, s, COCH}_2\text{Ph}), 3.86 (3 \text{ H, s}, 3.86)$ 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 $\delta_{\rm B}$ 5.38, J 13.7 Hz, COOCH₂), 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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