An Enantioselective Synthesis of 2-Isocephem and 2-Iso-oxacephem Nuclei

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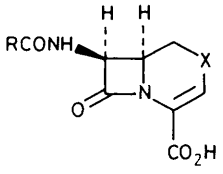
A stereocontrolled synthesis of optically active 2-isocephem and 2-iso-oxacephem nuclei is described starting from L-aspartic acid.

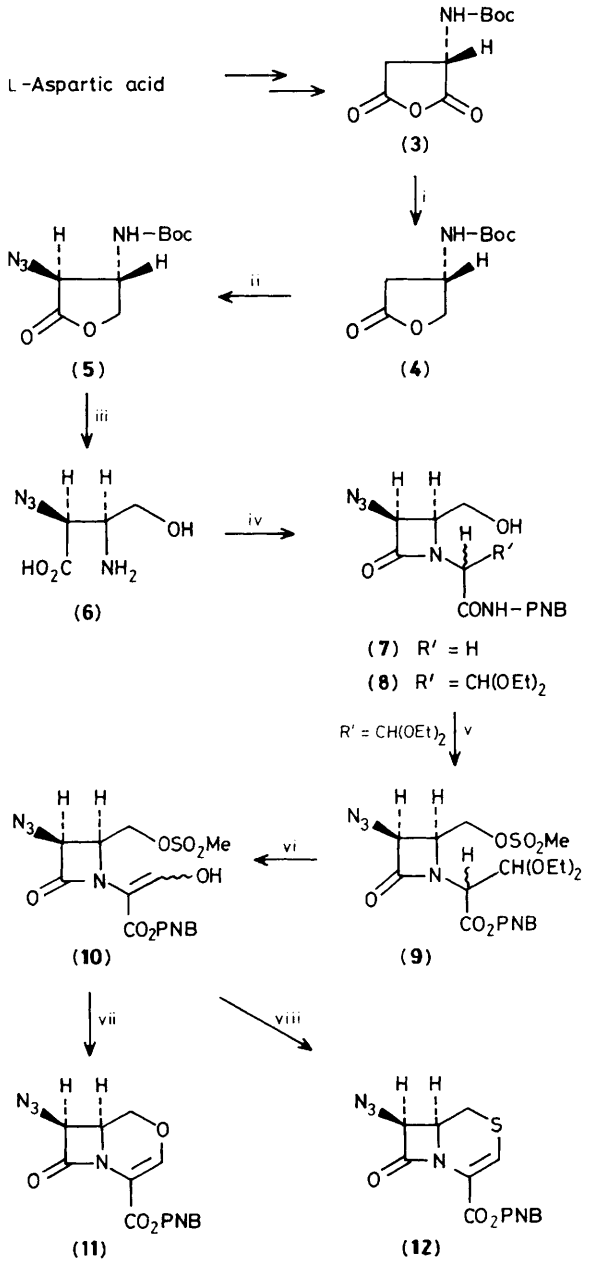
2-Isocephems and 2-iso-oxacephems have been reported to have potent antibacterial activity.[1,2] However, most previous syntheses have led to racemic compounds and could not give optically active derivatives without resolution.[2c,3] Herein we report a stereocontrolled synthesis of optically active 2-isocephalosporin (**1**) and its oxa analogue (**2**) starting from L-aspartic acid. The key step is the stereoselective introduction of the azide group into L-aspartic acid leading to the amino acid (**6**), which can be converted *via* a four-component condensation into chiral *cis*-3-azidoazetidinones.



(**1**) X = S
(**2**) X = O

The anhydride (**3**) was reduced with $NaBH_4$ in tetrahydrofuran (THF) at −20 to 0 °C to afford the lactone (**4**) {92% yield, m.p. 106—108 °C, $[\alpha]_D^{25}$ −61° (*c* 1.0, EtOH)}. The dianion of (**4**), [lithium di-isopropylamide (LDA; 2 equiv.), −67 °C] was treated with toluene-*p*-sulphonyl azide followed by an excess of chlorotrimethylsilane to give exclusively the expected *trans*-azide (**5**)[4]† in 58% yield. Attempted opening

† The spectral properties of all new compounds were in accord with the proposed structure. Selected physical data: (**5**): m.p. 110—111 °C; $[\alpha]_D^{25}$ −69° (*c* 1.0, EtOH); i.r. (KBr) 2100, 1780, and 1680 cm^{-1}. (**11**): m.p. 149—150 °C; $[\alpha]_D^{25}$ −34.2° (*c* 1.0, EtOH); $\lambda_{max.}$ (EtOH) 269 nm (log ε 4.22); ^1H n.m.r. ($CDCl_3$) δ 3.79 (1H, m), 3.94 (1H, dd, *J* 9.5, 11.3 Hz), 4.60 (1H, dd, *J* 3.7, 11.3 Hz), 5.27 (1H, d, *J* 5.2 Hz), 5.28 (1H, d, *J* 13.5 Hz), 5.43 (1H, d, *J* 13.5 Hz), 7.40 (1H, s), 7.60 (2H, *J* 8.9 Hz), and 8.23 (2H, d, *J* 8.9 Hz). (**12**): m.p. 147—148 °C; $[\alpha]_D^{25}$ −46.6° (*c* 0.5, dioxane); i.r. (KBr) 2100, 1760, and 1700 cm^{-1}; $\lambda_{max.}$ (EtOH) 302 nm (log ε 4.12); ^1H n.m.r. ($CDCl_3$) δ 3.03—3.16 (2H, m), 3.94 (1H, m), 5.22 (1H, d, *J* 5.1 Hz), 5.29 (1H, d, *J* 13.3 Hz), 5.41 (1H, d, *J* 13.3 Hz), 7.13 (1H, s), 7.60 (2H, d, *J* 8.8 Hz), and 8.24 (2H, d, *J* 8.8 Hz).



Scheme 1. PNB = *p*-nitrobenzyl, Boc = t-butoxycarbonyl. *Reagents:* i, $NaBH_4$ (1 equiv.), THF, −20 to 0 °C, 2 h, followed by benzene, reflux, 3 h; ii, LDA (2.1 equiv.), THF, −78 to −20 °C, 1 h, then *p*-$MeC_6H_4SO_2N_3$ (1.2 equiv.), THF, −78 °C, 1 h, followed by Me_3SiCl, −78 to 0 °C; iii, CF_3CO_2H, then Amberlite IRA-45, MeOH–H_2O, 0 °C; iv, (a) for preparation of (**7**): 30% aqueous HCHO, *p*-$O_2NC_6H_4NC$, MeOH, room temp., 10 h; (b) for preparation of (**8**): $(EtO)_2CHCHO$, *p*-$O_2NC_6H_4NC$, MeOH, room temp., 10 h; v, $MeSO_2Cl$, Et_3N, THF, room temp., 10 h, then N_2O_4, $CHCl_3$, AcONa, 0 °C, 1 h, followed by CCl_4, reflux, 3 h; vi, CF_3CO_2H; vii, Et_3N, CH_2Cl_2, reflux, 3 h; viii, $MeSO_2Cl$, Et_3N, THF, then H_2S, CH_2Cl_2, Et_3N, 0 °C.

of the lactone ring of (**5**) with aqueous alkali led to elimination of t-butoxyformamide. However, after removal of the t-butoxycarbonyl group with trifluoroacetic acid, neutralization of the resulting trifluoroacetate with Amberlite IRA-45 in aqueous methanol also effected opening of the lactone ring to give the crystalline amino acid (**6**) {m.p. 135—137 °C (decomp.), $[\alpha]_D^{25}$ −149° (*c* 1.0, H_2O)} in 76% yield.

The amino acid (**6**) was subjected to four-component condensation for constructing the azetidinone ring using *p*-nitrobenzyl isocyanide[5] as the isonitrile. An equimolar mixture of the amino acid (**6**), formaldehyde, and *p*-nitrobenzyl isocyanide was stirred in methanol at room temperature for 10 h to give the *cis*-azetidinone (**7**) in 95% yield. When 2,2-diethoxyacetaldehyde was used instead of formaldehyde, the *cis*-azetidinone (**8**) was obtained in 93% yield as a *ca.* 1 : 1 diastereoisomeric mixture. The resulting monocyclic azetidinones can serve as versatile intermediates for synthesis of a variety of bicyclic β-lactam compounds. For example, compound (**8**) could be readily transformed into 2-isocephalosporin and 2-iso-oxacephalosporin.

Methanesulphonylation of the hydroxy group of (**8**) followed by conversion of the *p*-nitrobenzylamide group into the *p*-nitrobenzyl ester *via* *N*-nitrosation gave compound (**9**) in 57% yield, which corresponded to the key intermediate in the synthesis of 2-iso-oxacephalosporins and 2-isocephalosporins reported by Doyle *et al.*[2a,b] Thus, according to the Doyle's procedure, compound (**9**) was converted into the 7-azido-2-iso-oxacephem (**11**) *via* (**10**) by treatment with trifluoroacetic acid followed by triethylamine. On the other hand, methanesulphonylation of (**10**) followed by treatment with hydrogen sulphide gave the 7-azido-2-isocephem (**12**). Compounds (**12**) and (**11**) can be converted into the 2-isocephalosporin and 2-iso-oxacephalosporin derivatives (**1**) and (**2**) having a variety of substituents R by standard sequences consisting of reduction of the azide group, acylation, and removal of the protective groups.

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