

Highly Stereocontrolled Synthesis of the Key Intermediate of 1 β -Methylcarbapenem Antibiotic *via* Intramolecular Nitrone 1,3-Dipolar Cycloaddition

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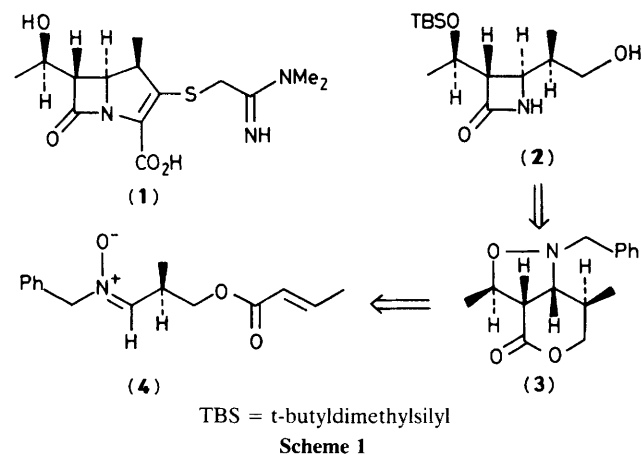
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The key synthetic intermediate of 1 β -methylcarbapenem antibiotic, (–)-(3*S*,4*R*)-3-[(1*R*)-1-*t*-butyldimethylsiloxyethyl]-4-[(2*R*)-2-(1-hydroxypropyl)]azetidin-2-one (**2**), was synthesised from (*R*)-methyl 3-hydroxy-2-methylpropionate with high stereoselectivity *via* intramolecular nitrone 1,3-dipolar cycloaddition.

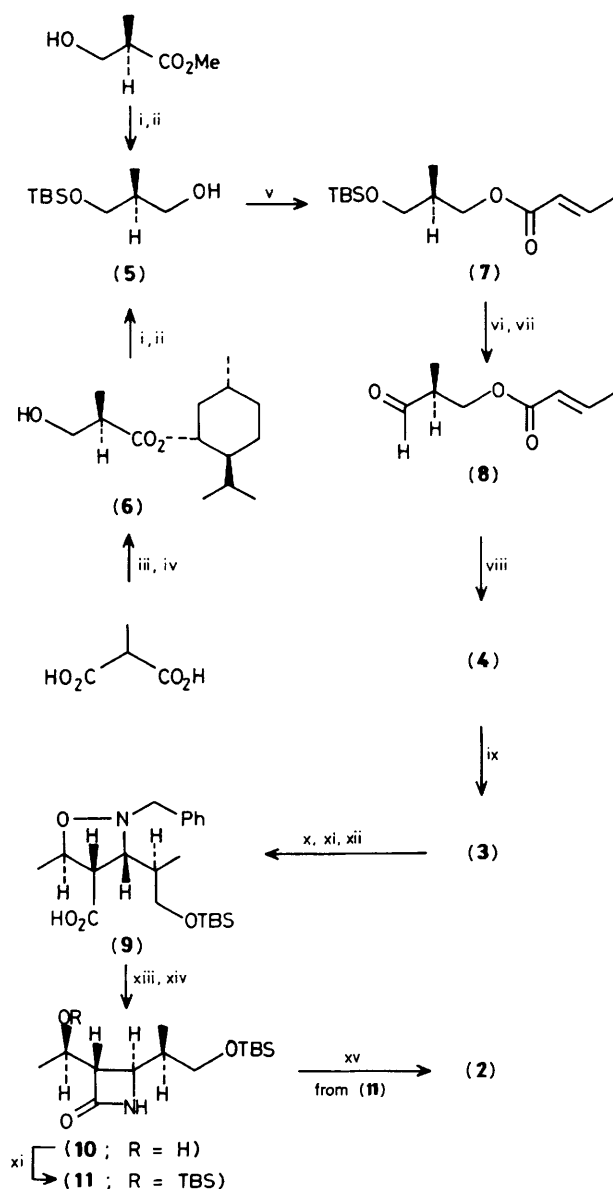
Since the synthetic carbapenem antibiotic, 1 β -methylcarbapenem (**1**),¹ possesses enhanced chemical and metabolic stability, key intermediates having four contiguous chiral centres have been the focus of current synthetic attention.^{2,3} We report here the successful synthesis of a key intermediate (**2**)³ from an isoxazolidine (**3**), stereoselectively constructed by intramolecular cycloaddition of a nitrone (**4**).

Commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate was converted by standard procedures into the alcohol (**5**), [α]_D²⁹ –13.22° (*c* = 0.61, CHCl₃), in 86% overall yield. The chiral propane-1,3-diol (**5**) was also prepared from methylmalonic acid by our method;⁴ condensation with 1-menthol followed by chlorination of the resulting half ester and reduction with Buⁿ₄NBH₄ gave a separable mixture of two epimeric alcohols [(**6**) and its epimer] in 62% overall yield, in a ratio of about 3:2. The major isomer (**6**) was transformed into the alcohol (**5**), [α]_D²⁵ –13.15° (*c* = 0.28, CHCl₃), by the same procedures as above. Condensation of (**5**) with crotonic acid afforded the ester (**7**) in 76% yield, [α]_D²⁴ –4.83° (*c* = 1.20, CHCl₃), which was deprotected utilizing 1 *M*-HCl in tetrahydrofuran (THF), then oxidized to the aldehyde (**8**) in 90% overall yield. Treatment of (**8**) with *N*-benzylhydroxylamine (1 mol equiv.) in CH₂Cl₂ yielded the nitrone (**4**),[†] whose n.m.r. spectrum indicated that a single

isomer formed. Cycloaddition was achieved by refluxing the nitrone (**4**) in *t*-amyl alcohol. The isoxazolidine (**3**),[†] m.p. 50–53 °C, [α]_D²³ –66.5° (*c* = 1.90, CHCl₃), was obtained in



[†] Spectral data for (**4**): n.m.r. (CDCl₃, 60 MHz), δ 1.66 (3H, d, *J* 7.0 Hz, Me), 1.83 (3H, dd, *J* 1.5 and 7.0 Hz, Me), 4.86 (2H, s, NCH₂Ph), and 6.60 (1H, d, *J* 6.5 Hz, O–N=CH); for (**3**) i.r. (CHCl₃) 1723 cm^{–1} (C=O); n.m.r. (CDCl₃, 500 MHz), δ 1.45 (3H, d, *J* 7.8 Hz, Me) and 1.44 (3H, d, *J* 7.2 Hz, Me); for (**10**) i.r. (CHCl₃) 3410 (NH) and 1739 cm^{–1} (C=O); n.m.r. (CDCl₃, 500 MHz), δ 0.10 (6H, s, SiMe₂), 0.91 (9H, s, Bu^t), 0.97 (3H, d, *J* 6.9 Hz, Me), 1.34 (3H, d, *J* 7.0 Hz, Me), 3.02 (1H, dd, *J* 3.0 and 8.3 Hz, C(3)–H), 3.52 (1H, dd, *J* 3.0 and 8.0 Hz, C(4)–H), and 4.04–4.11 (1H, m, >CHOH); for (**11**) i.r. (CHCl₃) 3420 (NH) and 1746 cm^{–1} (C=O); n.m.r. (CDCl₃, 500 MHz), δ 0.05 and 0.07 (each 6H, each s, 2 \times SiMe₂), 0.87 and 0.90 (each 9H, each s, 2 \times Bu^t), 0.97 (3H, d, *J* 6.9 Hz, Me), 1.23 (3H, d, *J* 7.0 Hz, Me), 2.87–2.90 (1H, m, C(3)–H), 3.72 (1H, dd, *J* 3.2 and 7.5 Hz, C(4)–H), and 4.16–4.20 (1H, m, >CH–OTBS).



Scheme 2. Reagents and conditions: i, Bu^tMe₂SiCl, Et₃N, 4-*N,N*-dimethylaminopyridine (DMAP); ii, di-isobutylaluminumhydride (DIBAL); iii, 1-menthol, DCC, DMAP; iv, (COCl)₂ then Buⁿ₄NBH₄; v, crotonic acid, DCC, DMAP; vi, 1 *M*-HCl; vii, CrO₃, pyridine; viii, PhCH₂NHOH, room temp.; ix, *t*-amyl alcohol, reflux; x, KOH; xi, Bu^tMe₂SiCl, imidazole, DMF; xii, K₂CO₃; xiii, H₂ (5–6 atm.), 10% Pd–C; xiv, DCC; xv, NBS, aq. DMSO.

51% yield as a single stereoisomer. The stereochemistry of (3) was determined by the following transformation into the known intermediate (2). The stereospecific formation of (3) could be accounted for by cycloaddition *via* the most stable transient of the (*Z*)- or (*E*)- nitron.

Saponification of (3) with aqueous base, followed by silylation with *t*-butyldimethylsilyl chloride and selective base hydrolysis⁵ gave the acid (9) in 86.5% overall yield. Hydrogenolysis of (9) was conducted by shaking the methanolic solution in the presence of 10% Pd-C under H₂ at medium pressure (5–6 atm.). The resulting amino acid was subsequently treated with dicyclohexylcarbodiimide (DCC) in MeCN at 60 °C for 4 h to give the β -lactam (10),[†] $[\alpha]_{\text{D}}^{24} -10.2^\circ$ ($c = 1.17$, CHCl₃), in 64.5% overall yield based on (9). Silylation of (10) formed quantitatively the bis-silyl ether (11),[†] m.p. 87–89 °C, $[\alpha]_{\text{D}}^{25} -8.5^\circ$ ($c = 1.04$, CHCl₃), which was selectively desilylated using *N*-bromosuccinimide (NBS) (1 mol equiv.) in aqueous dimethyl sulphoxide (DMSO)⁶ at room temperature. Spectral data of the primary alcohol (2), m.p. 89.5–90.5 °C [lit.,³ 90–91 °C], $[\alpha]_{\text{D}}^{24} -21.9^\circ$ ($c = 0.52$, CHCl₃) {lit.,³ $[\alpha]_{\text{D}}^{20} -21.7^\circ$ ($c = 0.46$, CHCl₃)}, obtained in 78% yield, was identical with those of the authentic compound,³ which had been correlated to 1 β -methylcarbapenem antibiotic (1).^{1,3} Thus a highly stereoselective synthesis of the key intermediate (2) of (1) was accomplished.

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