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

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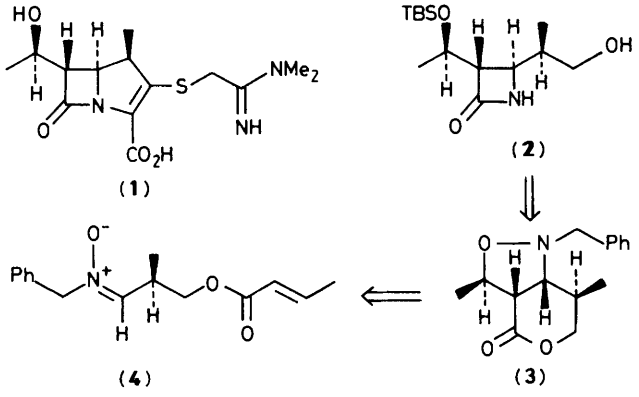
The key synthetic intermediate of 1β-methylcarbapenem antibiotic, (−)-(3*S*,4*R*)-3-[(1*R*)-1-t-butyldimethylsiloxyethyl]-4-[(2*R*)-2-(1-hydroxypropyl)]azetidin-2-one (**2**), was synthesised from (*R*)-methyl 3-hydroxy-2-methylpropionate with high stereoselectivity *via* intramolecular nitrone 1,3-dipolar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

Since the synthetic carbapenem antibiotic, 1β-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**).

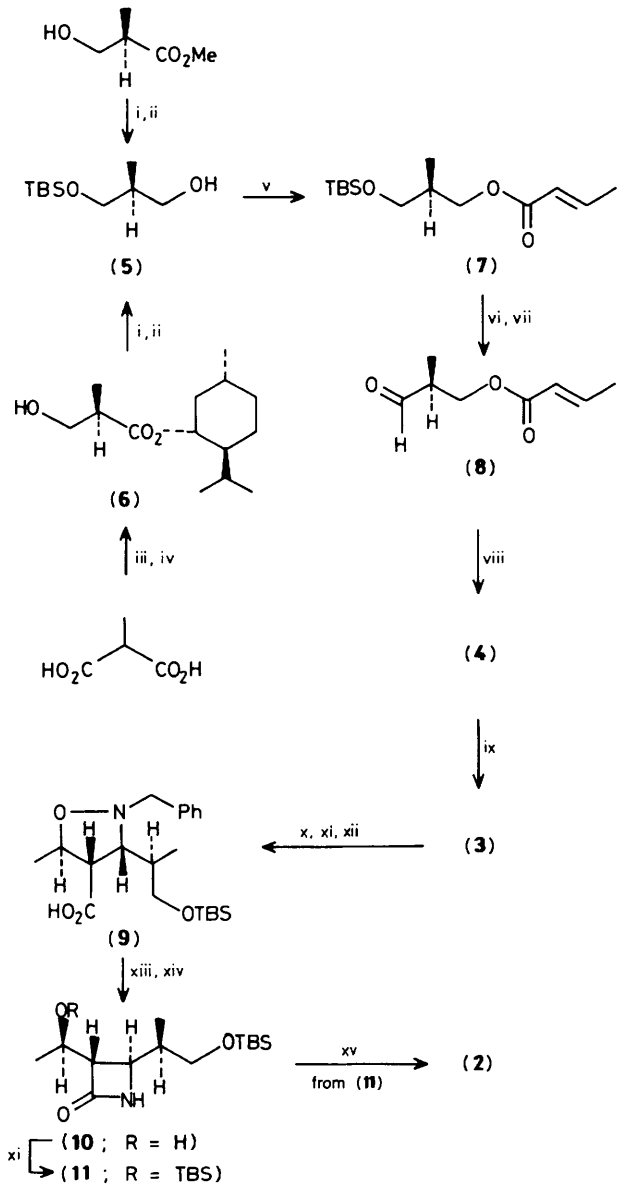
Commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate was converted by standard procedures into the alcohol (**5**), $[\alpha]_D^{29}$ −13.22° (*c* = 0.61, $CHCl_3$), in 86% overall yield. The chiral propane-1,3-diol (**5**) was also prepared from methylmalonic acid by our method:[4] condensation with 1-menthol followed by chlorination of the resulting half ester and reduction with $Bu^n_4NBH_4$ 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**), $[\alpha]_D^{25}$ −13.15° (*c* = 0.28, $CHCl_3$), by the same procedures as above. Condensation of (**5**) with crotonic acid afforded the ester (**7**) in 76% yield, $[\alpha]_D^{24}$ −4.83° (*c* = 1.20, $CHCl_3$), 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 CH_2Cl_2 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, $[\alpha]_D^{23}$ −66.5° (*c* = 1.90, $CHCl_3$), was obtained in



TBS = t-butyldimethylsilyl

Scheme 1

† *Spectral data* for (**4**): n.m.r. ($CDCl_3$, 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, NCH_2Ph), and 6.60 (1H, d, *J* 6.5 Hz, $\bar{O}$–$\overset{+}{N}$=CH); for (**3**) i.r. ($CHCl_3$) 1723 cm^{-1} (C=O); n.m.r. ($CDCl_3$ 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. ($CHCl_3$) 3410 (NH) and 1739 cm^{-1} (C=O); n.m.r. ($CDCl_3$, 500 MHz), δ 0.10 (6H, s, $SiMe_2$), 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, > *CH*OH); for (**11**) i.r. ($CHCl_3$) 3420 (NH) and 1746 cm^{-1} (C=O); n.m.r. ($CDCl_3$, 500 MHz), δ 0.05 and 0.07 (each 6H, each s, 2 × $SiMe_2$), 0.87 and 0.90 (each 9H, each s, 2 × 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^tMe_2SiCl, Et_3N, 4-*N*,*N*-dimethylaminopyridine (DMAP); ii, di-isobutyl(aluminium)hydride (DIBAL); iii, 1-menthol, DCC, DMAP; iv, $(COCl)_2$ then $Bu^n_4NBH_4$; v, crotonic acid, DCC, DMAP; vi, 1 M-HCl; vii, CrO_3, pyridine; viii, $PhCH_2NHOH$, room temp.; ix, t-amyl alcohol, reflux; x, KOH; xi, Bu^tMe_2SiCl, imidazole, DMF; xii, K_2CO_3; xiii, H_2 (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*)- nitrone.

Saponification of (**3**) with aqueous base, followed by silylation with t-butyldimethylsilyl chloride and selective base hydrolysis[5] 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 H_2 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**),† $[\alpha]_D^{24}$ −10.2° (c = 1.17, $CHCl_3$), in 64.5% overall yield based on (**9**). Silylation of (**10**) formed quantitatively the bis-silyl ether (**11**),† m.p. 87—89 °C, $[\alpha]_D^{25}$ −8.5° (c = 1.04, $CHCl_3$), 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], $[\alpha]_D^{24}$ −21.9° (c = 0.52, $CHCl_3$) {lit.,[3] $[\alpha]_D^{20}$ −21.7° (c = 0.46, $CHCl_3$)}, obtained in 78% yield, was identical with those of the authentic compound,[3] which had been correlated to 1β-methylcarbapenem antibiotic (**1**).[1,3] Thus a highly stereoselective sysnthesis of the key intermediate (**2**) of (**1**) was accomplished.

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