

A CHIRAL SYNTHESIS OF THE KEY INTERMEDIATE OF 1 β -METHYLCARBAPENEM ANTIBIOTIC[#]

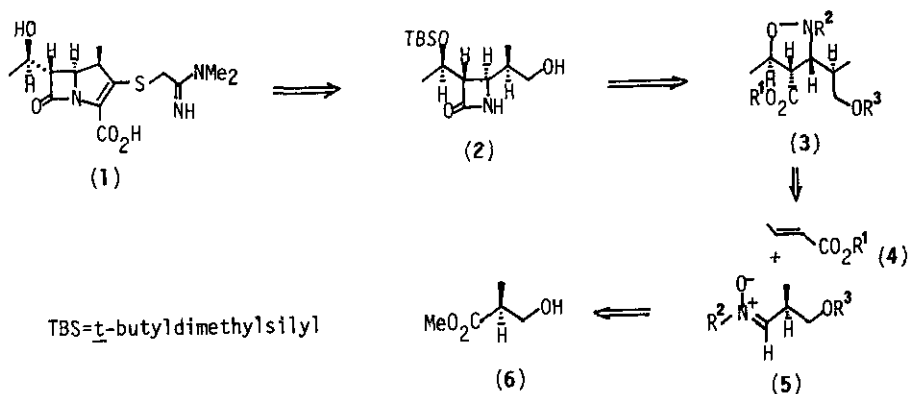
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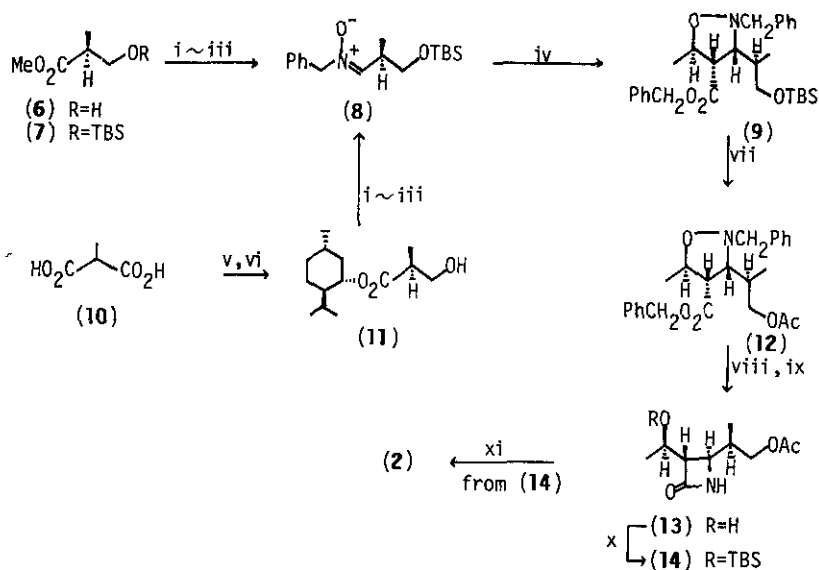
Abstract — The synthetic intermediate, (-)-(3S,4R)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1R)-1-hydroxymethylethyl]azetidin-2-one (2), of 1 β -methylcarbapenem antibiotic was synthesized from (S)-methyl 3-hydroxy-2-methylpropionate through the intermolecular nitron 1,3-dipolar cycloaddition.

Thienamycin and related naturally occurring carbapenems possess potent broad-spectrum antibacterial property¹ but they suffer serious disadvantages that they are chemically unstable and readily metabolized by renal dehydropeptidase-I (DHP-I). Recently Merck researchers found that introduction of the β -methyl substituent at the C-1 position of nucleus resulted in an extraordinary increase of stability; 1 β -methylcarbapenem such as (1) showed excellent antibiotic activity.² Therefore the key intermediate having four contiguous chiral centers is the focus of current synthetic attention.³ We planned the synthesis of the chiral intermediate (2)³ⁱ from the isoxazolidine derivative (3), which could be prepared by the 1,3-dipolar cycloaddition between crotonate (4) and the nitrone (5) derived from (S)-methyl 3-hydroxy-2-methylpropionate (6) and wish to communicate the result.⁴



Scheme 1

After protection of the commercially available ester (6) with *t*-butyldimethylsilyl group (98 % yield), the ester (7) was reduced with diisobutylaluminum hydride in a mixture of dichloromethane and 1,2-dimethoxyethane at -78°C. The resulting aldehyde was condensed with *N*-benzylhydroxylamine to give the nitron (8), which was subsequently heated in the presence of benzyl crotonate for 10 h in refluxing benzene producing the stereoisomeric mixture of isoxazolidines. One major isomer, (9)[†], [α]_D²⁶+13.23° (c=1.74, CHCl₃), was purified by careful hplc separation and the stereochemistry of (9), obtained in 23 % overall yield from (7), was determined by the transformation into the known intermediate (2). The same isoxazolidine (9) was also prepared from methylmalonic acid (10) as follows.⁵ Condensation of (10) with *d*-menthol followed by chlorination of the resulting half ester and reduction with tetra-*n*-butylammonium borohydride in dichloromethane at -78°C afforded the separable mixture of two epimeric alcohols (11 and its epimer) in 60 % overall yield in the ratio of about 3:2. The major product (11) was converted into the isoxazolidine (9), [α]_D²⁴+12.5° (c=0.08, CHCl₃), according to the same procedures as above.



Reagents and conditions: i, *t*BuMe₂SiCl, Et₃N, DMAP; ii, DIBAL, CH₂Cl₂, DME, -78°C; iii, PhCH₂NHOH, 20°C; iv, MeCH=CHCO₂CH₂Ph, benzene, reflux; v, *d*-menthol, DCC, DMAP; vi, (COCl)₂ then ⁿBu₄NBH₄, CH₂Cl₂, -78°C; vii, Ac₂O, Et₃N, DMAP, ⁿBu₄NF, THF; viii, H₂ (5~6atm), 10% Pd-C; ix, DCC, MeCN, 60°C; x, *t*BuMe₂SiCl, imidazole, DMF; xi, MeONa, MeOH.

Scheme 2

Exchange of the *t*-butyldimethylsilyl group of (9) with acetoxyl group was carried out by the action of acetic anhydride, triethylamine, 4-dimethylaminopyridine and tetrabutylammonium fluoride in tetrahydrofuran at room temperature. The acetate (12)[†], $[\alpha]_D^{26} + 31.35^\circ$ ($c=1.90$, CHCl_3), obtained in 77 % yield (84 % yield based on the consumed starting material), was hydrogenated in the presence of 10 % palladium on activated carbon under hydrogen (5 ~ 6 atm) and the resulting amino acid was sequentially treated with dicyclohexylcarbodiimide in acetonitrile at 60°C for 5 h to provide the β -lactam (13)[†], $[\alpha]_D^{25} - 7.55^\circ$ ($c=0.27$, CHCl_3), in 63% overall yield. Protection of (13) using *t*-butyldimethylsilyl chloride and imidazole in dimethylformamide gave quantitatively the ether (14)[†], $[\alpha]_D^{24} - 22.37^\circ$ ($c=0.52$, CHCl_3). Reaction of the acetate (14) with sodium methoxide provided in 77 % yield the primary carbinol (2), mp 89.5-90.5°C, $[\alpha]_D^{24} - 21.1^\circ$ ($c=0.12$, CHCl_3) [lit.³ⁱ mp 90-91°C, $[\alpha]_D^{20} - 21.7^\circ$ ($c=0.46$, CHCl_3)], whose spectral data were consistent with those of the authentic compound,³ⁱ correlated to 1 β -methylcarbapenem (1).^{1,3i}

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- † Ir(CHCl₃) and nmr(CDCl₃) data: (9) ir, 1722 cm⁻¹ (C=O); nmr(90 MHz), δ 0.90(9H, s, ^tBu), 0.97(3H, d, J 8.0 Hz, Me), 1.40(3H, d, J 7.0 Hz, Me), and 5.22(2H, s, CH₂Ph); (12) ir, 1730 cm⁻¹ (C=O); nmr(500 MHz), δ 0.95(3H, d, J 8.0 Hz, Me), 1.42(3H, d, J 7.5 Hz, Me), 1.78(3H, s, OAc) and 5.15 and 5.19 (each 1H, each d, each J 14 Hz, CH₂Ph); (13) ir, 3425(NH) and 1760 ~ 1722 cm⁻¹ (C=O); nmr (500 MHz), δ 1.03(3H, d, J 8.0 Hz, Me), 1.32(3H, d, J 8.0 Hz, Me), 2.08(3H, s, OAc), 2.98(1H, ddd, J 0.3, 2.5 and 8.0 Hz, C₃-H), 3.57(1H, dd, J 2.5 and 9.0 Hz, C₄-H), and 5.97(1H, br s, NH); (14) ir, 3420(NH) and 1760 ~ 1730 cm⁻¹ (C=O); nmr(500 MHz), δ 0.09(6H, s, SiMe₂), 0.88(9H, s, ^tBu), 1.02(3H, d, J 8.0 Hz, Me), 1.23(3H, d, J 8.0 Hz, Me), 2.07(3H, s, OAc), 2.92(1H, ddd, J 0.7, 2.5 and 7.5 Hz, C₃-H), 3.62(1H, dd, J 2.5 and 8.5 Hz, C₄-H), 4.18(1H, quintet, J 7.5 Hz, >CHOTBS), and 5.83(1H, br s, NH).

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