

AN ENANTIOSELECTIVE SYNTHESIS OF THE KEY INTERMEDIATE FOR THE PREPARATION OF 1 β -METHYLCARBAPENEM ANTIBIOTICS

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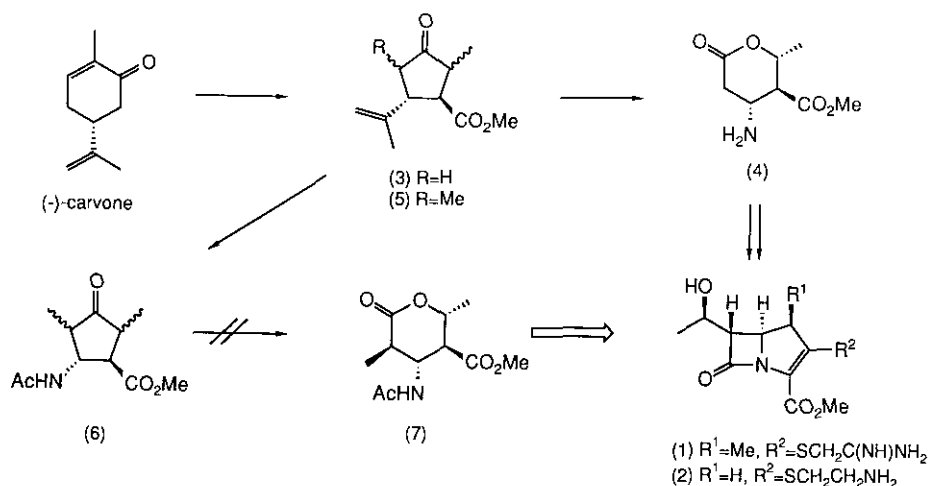
Abstract— An enantioselective synthesis of the key intermediate for the preparation of 1 β -methylcarbapenem has been achieved by employing the cyclopentane derivative (8), as a chiral source, readily derived from (-)-carvone.

1 β -Methylcarbapenem (1),¹ a synthetic analogue of thienamycin (2), has recently received considerable attentions owing to its broad spectrum and potent antibacterial activity in addition to remarkable metabolic stability against renal dehydropeptidase-1, therefore a number of synthetic methods and strategies for 1 β -methylcarbapenem or its key intermediate, (3S,4S)-3-[(R)-1-hydroxyethyl]-4-[(R)-1-(methoxycarbonyl)ethyl]-2-azetidinone (19b), have been developed to date.² Among them, much difficulties were usually encountered in the construction of contiguous four chiral centers presented in this class of antibiotics. We here report a novel chiral synthesis of the key intermediate (19b) for the preparation of 1 β -methylcarbapenems.

Recently we have succeeded in the chiral synthesis of Melillo's lactone (4), a key intermediate for thienamycin, employing the cyclopentane derivative (3), as a starting material, easily prepared from (-)-carvone as shown in Scheme 1.³

Although the same strategy using the compound (5), derived by methylation of 3, was first attempted to synthesize the key intermediate for 1 β -methylcarbapenem, none of the desired product (7) could be isolated, because the compound (6) stubbornly resisted the Baeyer-Villiger oxidation.

Thus, the modified procedure was investigated as follows. The alcohol (8),⁴ prepared from 3 by ketalization with ethylene glycol followed by reduction of the



Scheme 1

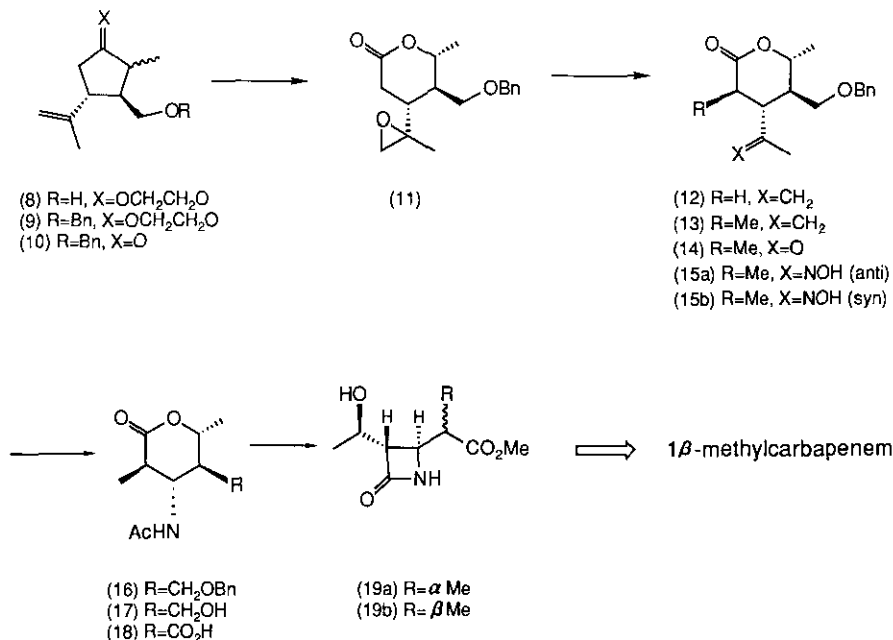
resulting ethylene ketal derivative with lithium aluminum hydride, was benzylated in a usual manner (PhCH₂Br, NaH in DMF, at room temperature) to give the benzyl ether (9) in 89.6 % yield. Deketalization of 9 with *p*-toluenesulfonic acid in acetone and subsequent oxidation with *m*-chloroperbenzoic acid (5 eq.) in dichloromethane afforded the epoxy-lactone (11) in 92.7 % yield from 9. Reduction of the epoxy group of 11 using the combination of zinc dust, sodium iodide, and sodium acetate in acetic acid regenerated the isopropenyl group to provide 12 in 60.2 % yield. Methylation of 12 with lithium isopropylcyclohexylamide and methyl iodide proceeded stereoselectively to afford the mono-methylated compound (13) as a sole product in 31.5 % yield together with the recovery of starting material in 64.9 % yield (89.7 % yield based on the consumed starting material). The recovered starting material could be subjected to this methylation to give the desired product in more than 65 % total yield.

Conversion of isopropenyl group into acetamido group was achieved by adopting the previously developed procedure.³ Reaction of the compound (13) with a catalytic amount of osmium tetroxide and an excess of sodium metaperiodate furnished the ketone (14), in 64.9 % yield, which on treatment with hydroxylamine hydrochloride in the presence of pyridine gave the corresponding anti- (15a) and syn-oximes (15b) in 59.2 % and 26.6 % yields, respectively. These oximes were easily separated by silica gel column chromatography and undesired syn-oxime could

be equilibrated into a mixture of syn- and anti-oximes in a ratio of 2:7 in 97.3 % yield by treatment with *p*-toluenesulfonic acid in ether. The Beckmann rearrangement of 15a was accomplished on treatment with phosphoryl chloride in pyridine to give the amide (16)⁵ in 82.1 % yield.

Since the introduction of an amino function at the desired position was accomplished, we turned our attention to the conversion of 16 into the known β -lactam (19). Debenzylation of the amide (16) by hydrogenation over palladium on carbon afforded the alcohol (17)⁶ quantitatively, which on oxidation with pyridinium dichromate in dimethylformamide gave the acid (18),⁷ having the desired four chiral centers, in 73.5 % yield. The conversion of 18⁸ into the β -lactam (19) was carried out according to Hatanaka's procedure⁹[1) 10 N HCl, reflux; 2) MeOH; 3) DCC, propene oxide, MeOH] to yield the desired β -lactam (19b) and the epimer (19a) in a ratio of 1:1 in 40.4 % yield.

The structures of these compounds were confirmed by their conversion into the corresponding *tert*-butyldimethylsilyl ethers, and the physicochemical properties including the optical rotation of 19b were identical with those reported.⁹



Scheme 2

Thus, we could achieve the enantioselective synthesis of the key intermediate for the preparation of 16-methylcarbapenems starting from the optically active cyclopentane derivative and the alternative way from 18 to 19b without epimerization is under investigation.

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- 2) Y.Ito and S.Terashima, Yuki Gosei Kagaku Kyokai Shi, 1989, **47**, 606, and references cited therein.
- 3) T.Kametani, T.Honda, H.Ishizone, K.Kanada, K.Naito, and Y.Suzuki, J. Chem. Soc., Chem. Commun., 1989, 646.
- 4) T.Kametani, Y.Suzuki, C.Ban, and T.Honda, Heterocycles, 1987, 26, 1491.
- 5) Physical data for **16**: mp 122 °C; $[\alpha]_D -2.8^\circ$ (c=2.90, CHCl₃); ir(CHCl₃): 3300, 1715, 1670 cm⁻¹; ¹H nmr(CDCl₃): δ 1.34(3H, d, J=7.3 Hz), 1.40(3H, d, J=6.1 Hz), 1.92(3H, s), 2.66(1H, dq, J=9.8 and 7.3 Hz), 3.48(2H, d, J=3.1 Hz), 3.95(1H, ddd, J=9.8, 9.8 and 10.4 Hz), 4.45(2H, s), 4.46(1H, dq, J=10.4 and 6.1 Hz), 5.96(1H, br d), 7.27-7.39(5H, m).
- 6) Physical data for **17**: mp 179-180 °C; $[\alpha]_D +57.3^\circ$ (c=0.97, CHCl₃); ir(CHCl₃): 3300, 1705, 1650 cm⁻¹; ¹H nmr(CDCl₃): δ 1.41(3H, d, J=7.3 Hz), 1.48(3H, d, J=6.1 Hz), 2.13(3H, s), 2.40(1H, dq, J=7.3 and 11.0 Hz), 3.81(1H, dd, J=6.7 and 8.6 Hz), 4.10(1H, ddd, J=9.2, 11.0 and 10.4 Hz), 4.63(1H, dq, J=10.4 and 6.1 Hz), 5.49(1H, br d, J=9.2 Hz).
- 7) Physical data for **18**: mp 193 °C; $[\alpha]_D +27.9^\circ$ (c=1.99, CHCl₃); ir(CHCl₃): 3350, 3000, 1700, 1645 cm⁻¹; ¹H nmr(CDCl₃): δ 1.34(3H, d, J=6.7 Hz), 1.42(3H, d, J=6.1 Hz), 1.96(3H, s), 2.52(1H, dq, J=11.0 and 11.0 Hz), 4.58(1H, dq, J=10.4 and 6.1 Hz).
- 8) The synthesis of the methyl ester of racemic **18** and its conversion into the racemic **19b** has been published; R.Bayles, A.P.Flynn, R.H.B.Galt, S.Kirby, and R.W.Turner, Tetrahedron Lett., 1988, 29, 6345.
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