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

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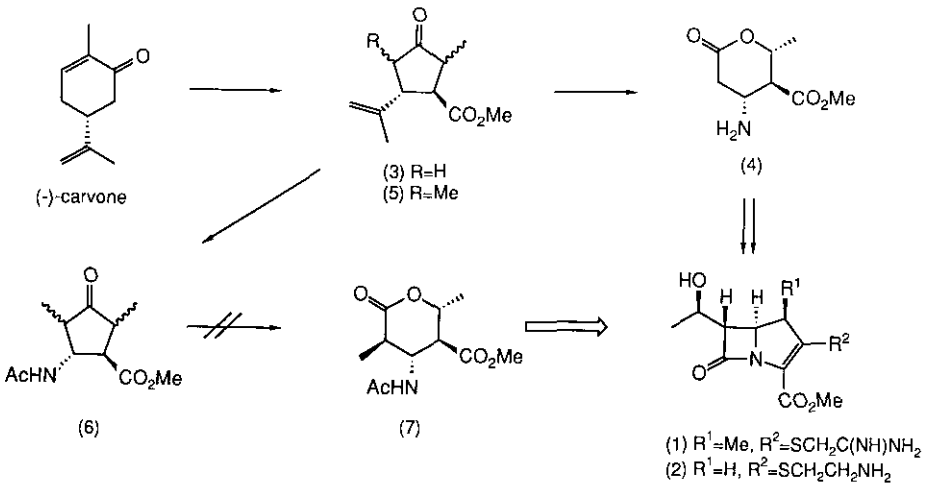
Abstract— An enantioselective synthesis of the key intermediate for the preparation of 1β-methylcarbapenem has been achieved by employing the cyclopentane derivative (8), as a chiral source, readily derived from (-)-carvone.

1β-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 1β-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 1β-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 1β-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

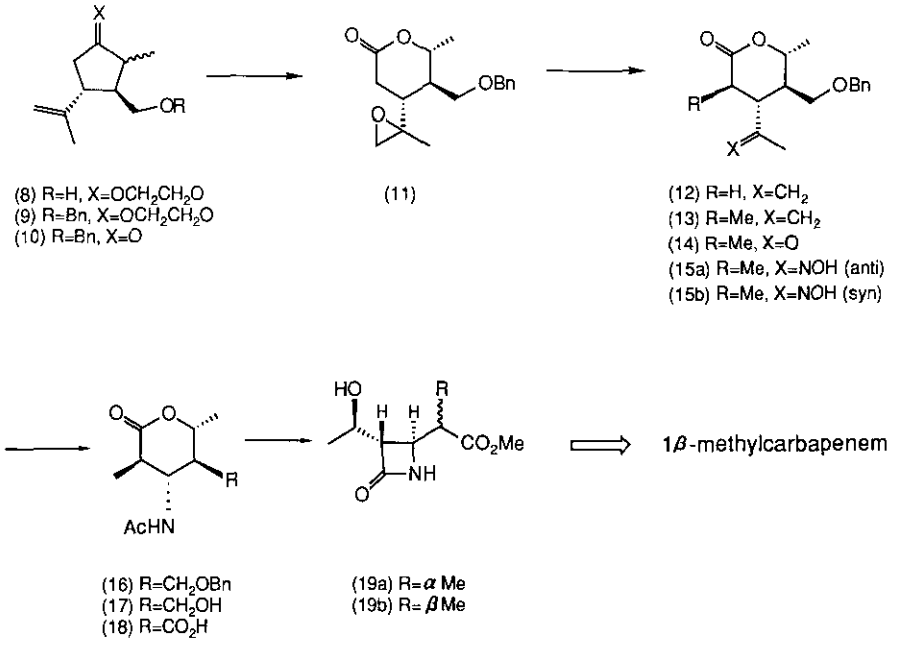
resulting ethylene ketal derivative with lithium aluminum hydride, was benzylated in a usual manner($PhCH_2Br$, NaH in DMF, at room temperature) to give the benzyl ether (**9**) in 89.6 % yield. Deketalization of **9** with p-toluenesulfonic acid in acetone and subsequent oxidation with m-chloroperbenzoic 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 **18**[8] into the β-lactam (**19**) was carried out according to Hatanaka's procedure[9][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]



(8) R=H, X=OCH_2CH_2O
(9) R=Bn, X=OCH_2CH_2O
(10) R=Bn, X=O

(11)

(12) R=H, X=CH_2
(13) R=Me, X=CH_2
(14) R=Me, X=O
(15a) R=Me, X=NOH (anti)
(15b) R=Me, X=NOH (syn)

(16) R=CH_2OBn
(17) R=CH_2OH
(18) R=CO_2H

(19a) R=α Me
(19b) R=β Me

Scheme 2

Thus, we could achieve the enantioselective synthesis of the key intermediate for the preparation of 1β-methylcarbapenems starting from the optically active cyclopentane derivative and the alternative way from **18** to **19b** without epimerization is under investigation.

REFERENCES AND NOTES

1) D.H.Shih, F.Baker, L.Cama, and B.G.Christensen, Heterocycles, 1984,21,29.

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° (c=2.90, $CHCl_3$); ir($CHCl_3$):3300, 1715,1670 cm^{-1}; ^1H nmr($CDCl_3$):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° (c=0.97, $CHCl_3$); ir($CHCl_3$): 3300,1705,1650 cm^{-1}; ^1H nmr($CDCl_3$):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 10.4Hz), 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° (c=1.99,$CHCl_3$); ir($CHCl_3$):3350, 3000,1700,1645 cm^{-1}; ^1H nmr($CDCl_3$):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.

9) M.Hatanaka, Tetrahedron Lett., 1987, **28**, 83.

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