Tetrahedron Letters,Vol.27,No.19,pp 2149-2152,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

SIMPLE, STEREOCONTROLLED SYNTHESIS OF 1β-METHYLCARBAPENEM ANTIBIOTICS FROM 3(R)-HYDROXYBUTYRIC ACID

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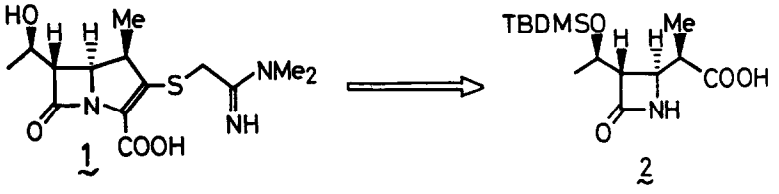
Summary: A simple, stereocontrolled synthesis of 1β-methylcarbapenem antibiotics has been accomplished. The synthesis involves stereoselective aldol-type condensation of vinyloxyborane derived from S-phenyl 3(R)-hydroxybutanethioate with N-3-trimethylsilyl-2-propynylidenebenzylamine, regiocontrolled hydroesterification of terminal acetylene and stereoselective 1,4-reduction of the α,β-unsaturated ester as key steps.

One of the current topics awaiting solution in the β-lactam field is how to achieve the simple and stereoselective synthesis of the 1β-methyl carbapenem antibiotics (**1** and its analogues), which was first synthesized by Shih et al..[1a] Although thienamycin and the related antibiotics have potent and broad spectrum antibacterial activities, these antibiotics are susceptible to renal dipeptidase-I. On the other hand, the 1β-methyl-substituted carbapenem antibiotics (**1** and its analogues) are fairly insensitive to the enzyme while retaining excellent antibacterial activities.[1a] Already a few papers describing the synthesis of the 1β-methylcarbapenem antibiotics have been reported.[1,2,7d] However, unfortunately, stereoselective introduction of the 1β-methyl group has never been achieved. In this communication we wish to report a simple, stereoselective synthesis of the key intermediate **2**, required for the synthesis of the 1β-methylcarbapenem antibiotics, starting from readily available 3(R)-hydroxybutyric acid (**3**).[3] The synthesis features stereoselective construction of four contiguous chiral centers involved in **2** from one chiral center in **3**.



1 2

Very recently, in the synthesis of (+)-thienamycin,[4] we have developed the stereocontrolled aldol type condensation of an ester enolate with an imine, resulting in the stereoselective construction of three contiguous chiral centers [C-8, C-6 and C-7 (carbapenem numbering)] from 3(R)-hydroxybutyric acid.[5] Accordingly we planned to employ this methodology at the first stage in the synthesis of 1β-methylcarbapenem antibiotics. First of all we examined the reaction of the boron enolate **4**[6] with the optically active imine **5a** on the direct analogy of our previous work. However, none of the desired product **6a** was formed. We speculated that the methyl substituent might disturb the condensation because

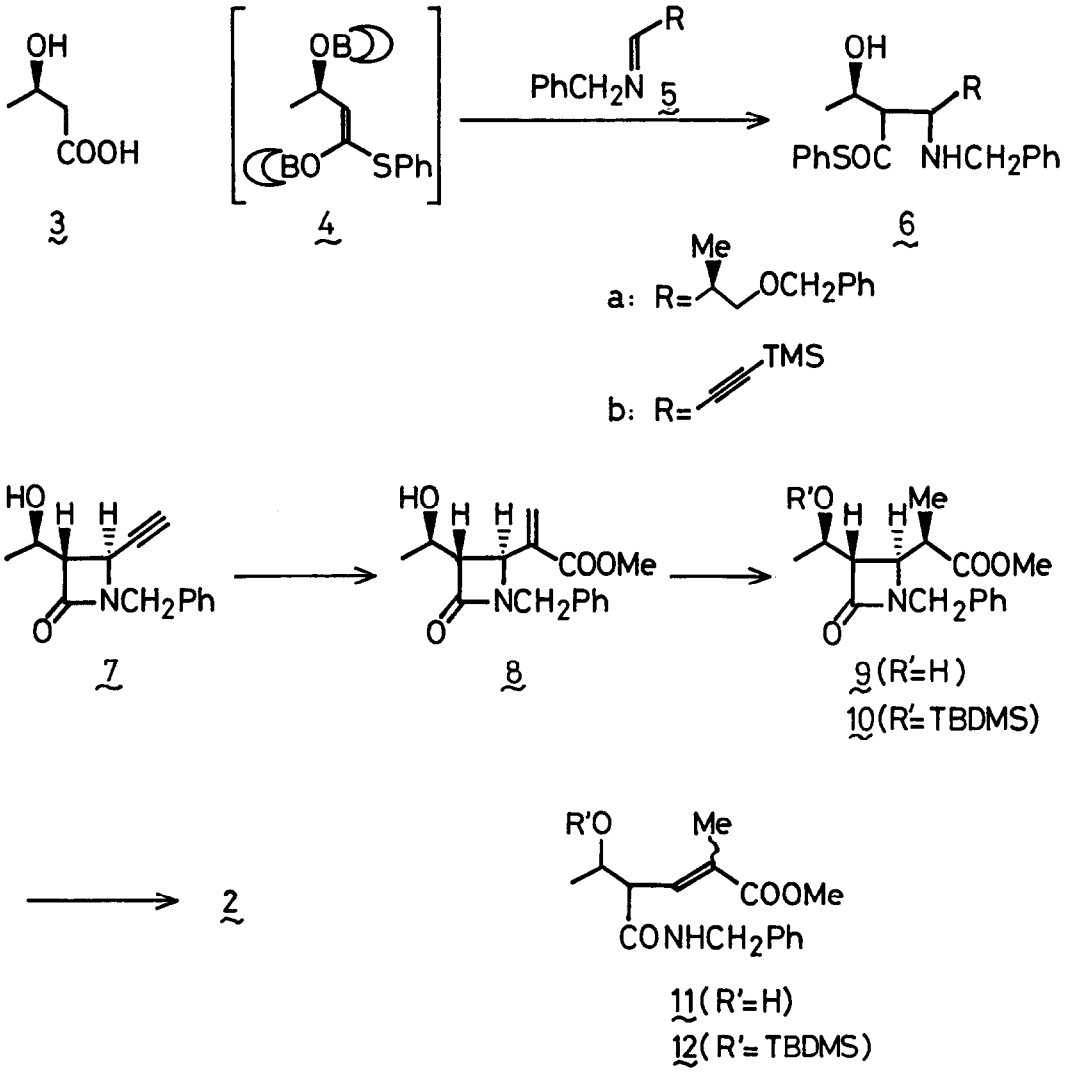
of its steric hindrance, and came to a conclusion that the 1β-methyl unit should be introduced after the β-lactam cyclization. Along this consideration we searched another imine which was devisable for the later introduction of the 1-methyl functionality. Acetylene group was expected to be a good candidate for the construction of a methyl unit. Accordingly the aldol type reaction of the vinyloxyborane **4** with the acetylene imine **5b** was investigated.[7] Under the previously reported conditions,[4] the β-amino thiol ester **4b** was nicely obtained in 55% yield. Hydrolysis of **6b** and following cyclization [1) KOH in aq. THF. 2) $(PyS)_2$-Ph_3P in CH_3CN[8]] afforded the corresponding β-lactam **7**[9] with its stereoisomers stereoselectively[5] (ca. 90% selectivity) in 76% overall yield. The stereochemically desired β-lactam **7**, [mp. 132~133°C; $[\alpha]_D^{20}$= 20.05° (c 1.00, $CHCl_3$)], was easily purified by recrystallization from CH_2Cl_2-hexane.

Next elaborative step for introducing one carbon unit to the acetylene group of **7** was achieved by the use of Pd catalyzed methoxycarbonylation.[10] Namely, treatment of the β-lactam **7** with Pd-black (10 mol%) and HI (50 mol%) in methanol at 20 kg/cm_2 of carbon monoxide at 65°C for 16hr afforded the α,β-unsaturated ester **8** in 70% yield. Application of this novel reaction made the synthetic route to **2** much shorter than the use of conventional method combination.

With a framework of the key intermediate **2** in hand, the most crucial step in the present synthesis was studied. Stereoselective double bond reduction of **8** was not easily achievable by usual reducing agents. Namely, Pd/C or $RhCl(PPh_3)_3$ catalyzed hydrogenation of **8** resulted in the formation of stereoisomers (α:β = 2:3)[11] in a nearly nonstereoselective manner. Furthermore, in the cases of cationic rhodium complexes, $[Rh(COD)(PPh_3)_2]BF_4$ and $[Rh(NOD)(dppb)]BF_4$[12], the reaction was considerably slow and the formation of the undesired stereoisomer was slightly predominant (α:β = 3:2)[11]. However, 1,4-reduction of the α,β-unsaturated ester **8** with a hydride reagent gave a better result; that is, although the by-product **11** was mainly produced, high β-selectivity was observed in the reduction of **8** with L-Selectride in THF.[13] After many unsuccessful attempts, we finally found that the formation of this by-product could be reduced nearly completely just by using sec-BuOH as a co-solvent. Treatment of **8** with L-Selectride in sec-BuOH-THF (1:2) at -78°C and following protection of the hydroxy group by TBDMSCl and imidazole in DMF afforded the fully protected β-lactam **10** (α:β = ca. 1:8)[11] in 77% yield with a small amount of the by-product **12**. Deprotection of **10** [1) KOH in aq. MeOH 2) Na in NH_3] and chromatographic separation afforded the known key intermediate **2** for the synthesis of 1β-methylcarbapenem antibiotics in 56% yield (2 steps), whose spectral data were identical with those of an authentic sample.[1] Here we have achieved an efficient construction of the 1β-methylcarbapenem intermediate stereoselectively.

In summary, a stereoselective and short step synthesis of the key intermediate **2** for the 1β-methylcarbapenem antibiotics was accomplished by the sequence of novel reactions, (1) stereoselective aldol type condensation of boron enolate with imine, (2) palladium catalyzed methoxycarbonylation of acetylene and (3) stereoselective reduction of α,β-unsaturated ester with L-Selectride in sec-BuOH-THF.

Acknowledgement. We are grateful to Dr. H. Urata, Sagami Chemical Research Center, for valuable discussion.



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2) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. ibid. **1985**, 26, 4739.

3) 3(R)-Hydroxybutyric acid is a readily available material with high optical purity (97% e.e.). For example, Kanegafuchi Chemical Ind. Co., Ltd. in Japan is industrially producing it via microbial β-hydroxylation of n-butyric acid.

4) Iimori, T.; Shibasaki, M. Tetrahedron Lett. **1985**, 26, 1523.

5) The mechanistic studies of this stereochemical outcome are discussed in the following paper in this issue.

6) Hirama, M.; Garvey, D.S.; Lu, L.D.-L.; Masamune, S. Tetrahedron Lett. **1979**, 3937. The reaction of a vinyloxyborane with an aromatic imine was first reported by Ohno et al: Ohtsuka, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. Tetrahedron Lett. **1981**, 22, 2109.

7) For the utilization of acetylene imine **i** like **5b** in the carbapenem synthesis: (a) Ha, D.-C.; Hart, D.J.; Yang, T.-K. J. Am. Chem. Soc. **1984**, 106, 4819. (b) Chiba, T.; Nagatsuma, M.; Nakai, T. Chem. Lett. **1984**, 1927. (c) Chiba, T.; Nakai, T. Chem. Lett. **1985**, 651. (d) Chiba, T.; Nagatsuma, M.; Nakai, T. Chem. Lett. **1985**, 1343. (e) Chiba, T.; Nakai, T. Tetrahedron Lett. **1985**, 26, 4647. Application of **i** to the present reaction failed of success. For other carbapenem syntheses from 3-hydroxybutyric acid: (a) Georg, G.I. Tetrahedron Lett. **1984**, 25, 3779. (b) Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, D. ibid. **1985**, 26, 937.

8) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. J. Am. Chem. Soc. **1981**, 103, 2406.

9) The stereochemistry of **7** was determined by converting to **ii**. The reaction sequence is as follows: 1) TBDMSCl, imidazole in DMF, 2) Lindlar cat. H_2 in pet. ether, 3) 9-BBN in THF then H_2O_2, 4)NaH, $PhCH_2Br$ in THF-DMF. The β-lactam **ii** was previously converted to the known bicyclic β-lactam, see reference 4.

10) Mori, K.; Mizoroki, T.; Ozaki, A. Chem. Lett. **1975**, 39 and earlier references cited therein. They reported that carbonylation of methylacetylene produced methyl methaacrylate and methyl crotonate (ca. 9:1). Although carbonylation at the terminal position of acetylene was not observed in our case, double carbonylation product **iii** was obtained in 13% yield as a major by-product. For palladium catalyzed carbonylation of acetylenic alcohols, which affords methylene lactones, see; (a) Murray, T.F.; Norton, J.R. J. Am. Chem. Soc. **1979**, 101, 4107. (b) Murray, T.F.; Samsel, E.G.; Varma, V.; Norton, J.R. ibid. **1981**, 103, 7520. Application to our system produced only **iii** even at the early stage of the reaction. Nickel carbonyl is also known to be an useful reagent for carbonylation of acetylenes: (a) Jones, E.R.H.; Shen, T.Y.; Whiting, M.C. J. Chem. Soc. **1950**, 230. (b) Jones, E.R.H.; Shen, T.Y.; Whiting, M.C. ibid. **1951**, 48.

11) The stereoselectivity of these reactions was analyzed by ^1H NMR. The stereochemistry of **9** and its isomer was determined unambiguously by converting to the known methyl ester of **2** and its isomer[1a].

12) (a) Brown, J.M.; Chaloner, P.A.; Kent, A.G.; Murrer, B.A; Nicholson, P.N.; Paker, D.; Sidebottom, P.J. J. Organomet. Chem. **1981**, 216, 263 (b) Evans, D.A.; Morrissey, M.M. J. Am. Chem. Soc. **1984**, 106, 3866. (c) Brown, J.M.; Naik, R. J. Chem. Soc., Chem. Commun. **1982**, 348. (d) Brown, J.M.; Cutting, I. ibid. **1985**, 578. COD = 1,5-cyclooctadiene, NOD = norbornadiene, dppb = 1,4-bis(diphenylphosphino)butane.

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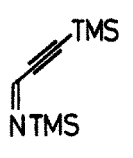

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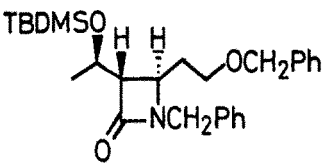

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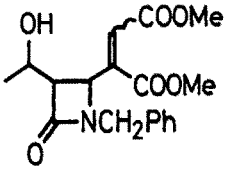

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(Received in Japan 13 March 1986)