Tetrahedron Letters,Vol.28,No.1,pp 83-86,1987
Printed in Great Britain

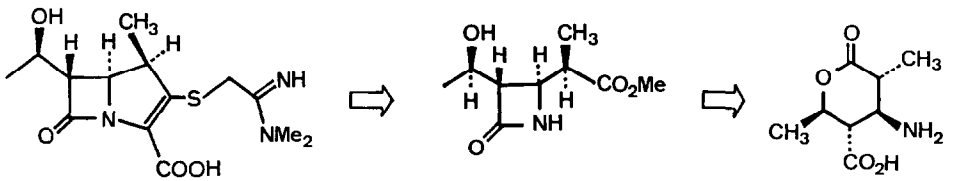
0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

A STEREOSELECTIVE APPROACH TO 1β-METHYLCARBAPENEM ANTIBIOTIC STARTING FROM (R)-(-)-3-HYDROXYBUTYRIC ACID ESTER

Minoru Hatanaka
The Institute of Scientific and Industrial Research,
Osaka University, Mihogaoka, Ibaraki, Osaka 567, Japan

Summary; The chiral key intermediate of 1β-methylcarbapenem antibiotic is synthesized via (2R,3R,4S,5R)-3-amino-2,5-dimethyl-5-pentanolide-4-carboxylic acid, which is prepared in a stereoselective manner from (R)-(-)-3-hydroxybutyrate.

Synthetic carbapenem antibiotic, 1β-methylcarbapenem (**1**), has attracted much attention.[1] Thienamycin and related naturally occurring carbapenem compounds, in spite of their potent, broad-spectrum antibacterial activity, suffer serious disadvantages that they are chemically unstable and metabolized by renal dehydropeptidase-I (DHP-I). In intensive efforts to improve the properties by the chemical modification of these antibiotics, Shih et al. have first synthesized 1β-methylcarbapenem compound **1**,[1a] which showed enhanced chemical stability and resistance to DHP-I. The major problem in the synthesis of this compound is a stereocontrolled construction of the four continuous chiral centers in the molecule. Although several recent publications have dealt with the synthesis of **1**,[1,2] most of the methods was not satisfactory in terms of stereoselectivity and/or practical sense. Herein we report a stereocontrolled synthesis of the key intermediate **2** of 1β-methylcarbapenem compound via the lactone **3** containing the chirality and functionality of **1**.

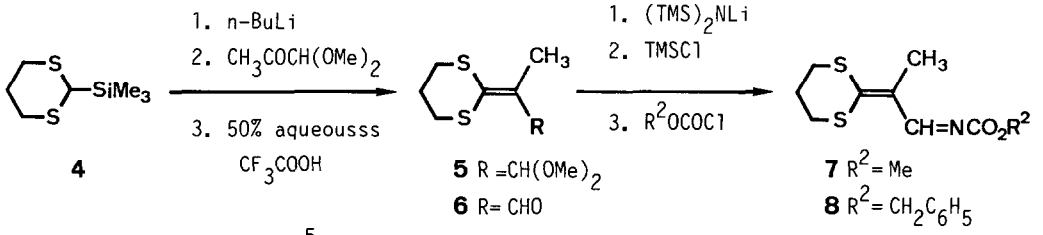


1 **2** **3**

In the preceding paper, we described the reaction of the dianion of (R)-(-)-3-hydroxybutyrate with N-acylaldimine leading to the (+)-thienamycin precursor having the three continuous chiral centers.[3] The methodology was applied successfully to synthesis of **3**, in which the chirality of the starting material, (R)-(-)-3-hydroxybutyric acid, controlled construction of the four continuous chiral centers in a highly stereoselective manner.[4]

The starting material, 2-(1,3-dithian-2-ylidene)-propanal (**6**, mp 80-82

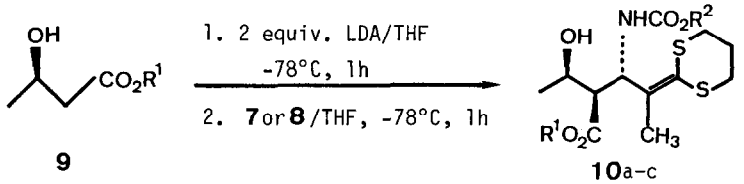
°C), was prepared in 71% yield by condensation of 2-trimethylsilyl-1,3-dithiane (**4**) with pyruvaldehyde dimethylacetal followed by acid hydrolysis. The aldehyde **6** was then converted quantitatively in one-pot into the N-alkoxycarbonylimine **7** (mp 85-88 °C) and **8** (mp 89-91 °C) by treating in turn with lithium bis(trimethylsilyl)amide (-78°C, 1h), chlorotrimethylsilane (-78°C ~ r.t., 1.5h) and then benzyl chloroformate and methyl chloroformate,



4 **5** R = $CH(OMe)_2$ **6** R = CHO **7** R^2 = Me **8** R^2 = $CH_2C_6H_5$

respectively (r.t., 10h).[5]

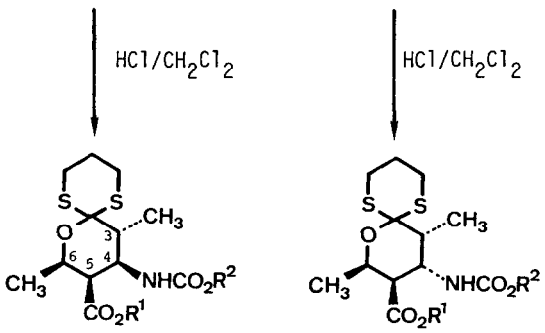
The N-alkoxycarbonylimines thus obtained were subjected to reaction with the dianions of R-(-)-3-hydroxybutyric acid esters in a similar manner to that reported[3] (Table 1). The methyl ester of **9** reacted with **7** and **8** to give 2:1 mixtures of the (syn, anti)-products **10** and the (syn, syn)-products **11**. Although the t-butyl ester of **9** gave a 4:1 mixture of **10c** and **11c** with better stereoselection,[6] the methyl esters **10a** and **10b** were used in subsequent transformation because the t-butyl ester of **9** was obtained only in poor yield via titanate-mediated transesterification of the methyl ester[7]. When the compounds



9 **10**a-c + **11**a-c

Table 1. Yield and ratios of **10** and **11**

	R^1	R^2	Yield (%)	Ratio (**10**/**11**)
a	Me	$CH_2C_6H_5$	91	2/1
b	Me	Me	95	2/1
c	t-Bu	Me	87	4/1

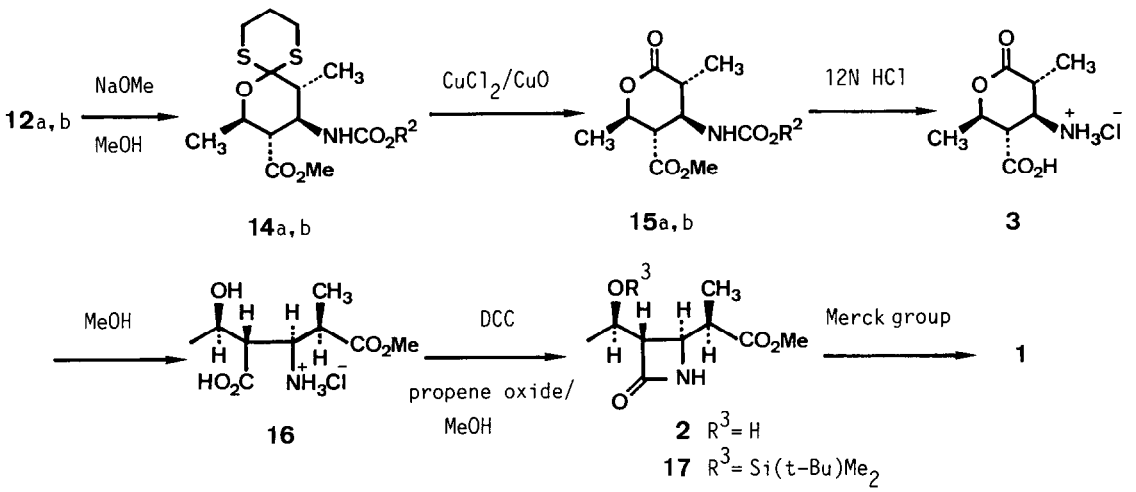


12a-c **13**a-c

10a and **10b** were treated with catalitic amounts (below 0.1 molar equivalent) of hydrogen chloride in dichloromethane at 0°C, cyclization proceeded smoothly and stereoselectively to give almost exclusively the desired 3α-methyl cyclic dithioorthoesters **12a** (oil, $[\alpha]_D^{29}$ +133.6° (c 0.75, MeOH)) and **12b** (mp 72-74°C,

$[\alpha]_D^{29}$ +166° (c 1.0,MeOH)) in 87% and 86% yields, respectively. The stereochemistry of **12** was estimated on the basis of the coupling constants (for example **12b:** $J_{3,4}$=11.5 Hz, $J_{4,5}$=4.8 Hz, $J_{5,6}$=3.8 Hz) observed in their ^{1}H-NMR spectra. Cyclization of **11a** and **11b** under the same conditions also afforded the 3α-methyl compounds **13a** and **13b** in 71% and 68% yields, respectively. It is noted that highly preferred formation of the 3α-methyl products from both of **10** and **11** implies that this cyclization process may provide a general method for 1,4-chiral transfer.[8]

The remaining problem of the stereochemistry was resolved by heating **12a** with sodium methoxide in refuxing methanol in the presence of methyl acetate, which effected inversion of the methoxycarbonyl group at C-5 to give **14a** (mp 145-146°C, $[\alpha]_D^{29}$ +81.7° (c 0.85, MeOH), ^{1}H-NMR: $J_{3,4}$=11.1 Hz, $J_{4,5}$=10.8 Hz,



$J_{5,6}$=10.6 Hz) in 74% yield. The compound **14a** was then converted in 91% yield by treatment with cupric chloride and cupric oxide in aqueous acetone into the desired lactone **15a**[9] having the same chirality with 1α-methylcarbapenem **1.** Treatment of **15a** with 12N hydrochloric acid at room temperature gave the amino acid **3** as the hydrochloride quantitatively. On the other hand, an attempt to remove the methoxycarbonyl group of **15b,** prepared through the same reaction sequences from **12b,** in refluxing 12N hydrochloric acid was accompanied by epimerization of the C-2 methyl group. Finally, methanolysis of **3** followed by cyclization of **16** with dicyclohexylcarbodiimide (DCC) furnished the β-lactam **2**[10] in 75% yield. The stereochemistry of **2** was confirmed by converting into the known O-protected β-lactam **17,** the key intermediate of Merck's synthesis of **1,**[1] the physical properties of which were identical with those reported by Shih et al..[1a]

Thus, we achieved highly stereoselective and short-step synthesis of the key intermediate of **1** via continuous construction of the four chiral centers from (R)-(-)-3-hydroxybutyrate[11].

References and Notes

1. a) D. H. Shih, F. Baker, L. Cama and B. G. Christensen, Heterocycles, **21**, 29 (1984); b) D. H. Shih, J. A. Fayter, L. Cama, B. G. Christensen and J. Hirshfield, Tetrahedron Lett., **26**, 583 (1985); c) D. H. Shih, L. Cama and B. G. Christensen, ibid., **26**, 587 (1985).
2. a) T. Chiba, M. Nagatsuma and T. Nakai, Chem. Lett., 1343 (1985); b) T. Shibata, K. Iino, T. Tanaka, T. Hashimoto, Y. Kameyama and Y. Sugimura, Tetrahedron Lett., **26**, 4739 (1985).
3. M. Hatanaka and H. Nitta, Tetrahedron Lett., The preceding paper.
4. After this work finished, an alternative approach to the β-lactam **17** starting from (R)-(-)-3-hydroxybutyric acid has been published: T. Iimori and M. Shibasaki, Tetrahedron Lett., **27**, 2149 (1986).
5. The literature method was modified: R. Kupger, S. Meier and E-U. Wurthmein, Synthesis, 688 (1984).
6. In comparison with the reaction of **9** with N-methoxycarbonyl (2-phenylthio)ethenylcarboxaldimine (see ref. 3), the effect of the ester moiety of **9** on stereoselection was lowered in the present case, presumably due to increasing steric bulkiness of N-methoxycarbonylaldimine **7**.
7. D. Seebach, E. Hungerbuhler, R. Naef, P. Schnurrenberger, B. Wiedmann, and M. Zuger, Synthesis, **1982**, 138.
8. After this paper was completed, Suzuki et al., have reported quite similar type of cyclization of ketene dithioacetal-alcohol, which proceeded via thermodynamically controlled process: K. Suzuki, T. Masuda, Y. Fukazawa, and G. Tsuchihashi, Tetrahedron Lett., **27**, 3661 (1986).
9. The compound **15a**: mp 143-145°C, $[\alpha]_D^{29}$ +22.4° (c 1.35, $CHCl_3$), IR (CH_2Cl_2) 3440, 1740, 1515 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1.37 (3H, d, J=6.1 Hz), 1.39 (3H, d, J=6.9 Hz), 2.66 (1H, m), 2.83 (1H, t, J=10.9 Hz), 3.63 (3H, s), 3.92 (1H, ddd, J=11.0, 10.9, 9.0 Hz), 4.53 (1H, m), 4.89 (1H, d, J=9.0 Hz), 5.10 (2H, s), 7.35 (5H, m).
10. The compound **2**: mp 102-104°C; $[\alpha]_D^{29}$ -44.7° (c 0.45, $CHCl_3$); IR (CH_2Cl_2) 3410, 1768, 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.27 (3H, d, J=7.1 Hz), 1.31 (3H, d, J=6.3 Hz), 2.67 (1H, m), 2.98 (1H, dd, J=2.1, 7.0 Hz), 3.72 (3H, s), 3.77 (1H, dd, J=2.1, 7.7 Hz), 4.16 (1H, m), 6.09 (1H, broad s).
11. After this paper was completed, stereoselective syntheses of **17** have been reported both of which included, as a key step, condensation of 4-acetoxyazetidinone with chiral enolates: Y. Nagao, T. Kumagai, S. Tamai, T. Abe, Y. Kuramoto, T. Taga, S. Aoyagi, Y. Nagase, M. Ochiai, Y. Inoue and E. Fujita, J. Am. Chem. Soc., **108**, 4673 (1986); L. M. Fuentes, I. Shinkai and T. N. Salzmann, ibid., **108**, 4675 (1986).

(Received in Japan 26 August 1986)