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STEREOCONTROLLED SYNTHESIS OF (+)-THIENAMYCIN FROM 3(*R*)-HYDROXYBUTYRIC ACID[1]

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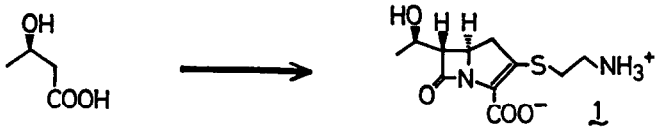
Summary: The vinyloxyborane(5), prepared from (+)-S-phenyl-3(R)-butanethioate, 9-BBN triflate and diisopropylethylamine, reacted with N-(3-benzyloxypropylidene)benzylamine to give the β-benzylamino thiol ester(6) in a moderate yield, which was efficiently converted to the optically pure thienamycin intermediate(10).

Thienamycin (**1**) has stimulated enormous activity in the area of β-lactam synthesis; this has resulted in the elegant synthesis of (+)-**1** from L-aspartic acid,[2] dimethyl β-aminoglutarate,[3] penicillin,[4] D-allothreonine,[5] L-threonine,[5] diethyl 1,3-acetonedicarboxylate[6] and (±)-4-acetoxyazetidin-2-one.[7] Nevertheless, retrosynthetic analysis of thienamycin (**1**) still suggests that if the efficient conversion of 3(*R*)-hydroxybutyric acid to (+)-thienamycin (**1**) is achieved, it could provide the most efficient synthetic route to (+)-thienamycin (**1**) and related β-lactam antibiotics. 3(*R*)-Hydroxybutyric acid is readily available and inexpensive material because it can be produced *via* microbial β-hydroxylation of *n*-butyric acid.[8] Success of this approach requires development of the methodology for the highly stereoselective aldol-type reaction of an ester enolate with an enolizable imine.



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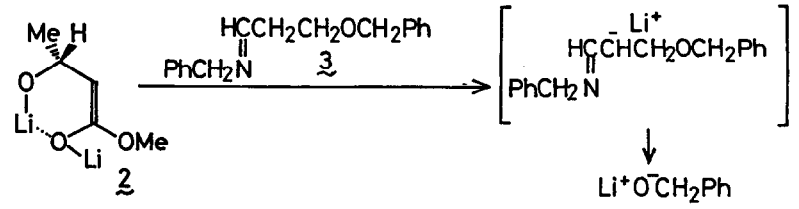
Recently Georg has reported a stereoselective synthesis of *trans* 3(*S**)-(1-hydroxyethyl)-1,4- diphenyl-2-azetidinone from 3-hydroxybutyric acid.[9] Also Hart and his coworkers have published a stereoselective but wrong synthesis of the thienamycin intermediate from 3-hydroxybutyric acid.[10] In both the syntheses the nonenolizable imines have been utilized. These reports prompt us to disclose our initial results on a stereocontrolled synthesis of (+)-thienamycin (**1**) from 3(*R*)-hydroxybutyric acid using the enolizable imine, which has been achieved for the first time.

In order to construct the thienamycin intermediate (**10**), the condensation of methyl 3(*R*)-hydroxybutyrate with the appropriately functionalized imine (**3**) was attempted under various reaction conditions. However, none of the desired product was formed in any case, probably because of the proton removal from the enolizable imine (**3**) bearing α-hydrogens adjacent to the imine functionality. In fact, benzyl alcohol was detected in the crude reaction mixture.



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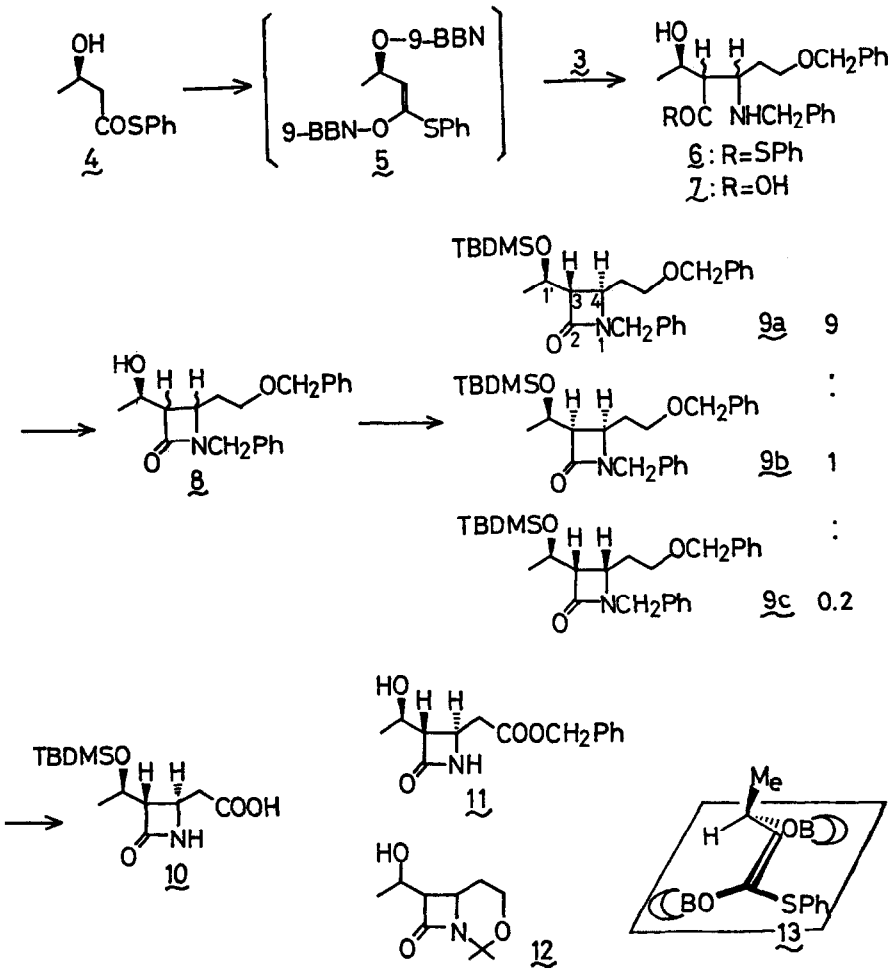
After several unsuccessful attempts, this difficulty in the aldol-type condensation was found to be overcome by the use of the vinyloxyborane instead of **2**. Methyl 3(*R*)-hydroxybutyrate was first converted to *S*-phenyl-3(*R*)-butanethioate (**4**),[11] $[\alpha]_D^{20}$ -42.25° (c 1.42, $CHCl_3$), in four steps (ca. 70% overall yield) [i. $^tBuMe_2SiCl$-imidazole in DMF, ii. KOH in aqueous MeOH, iii. thiophenol-DCC in CH_2Cl_2, iv. AcOH-H_2O-THF (3:1:1)].[12] The aldol-type condensation of the vinyloxyborane (**5**) with the enolizable imine (**3**) was carried out as described below. After treatment of *S*-phenyl-3(*R*)-butanethioate (**4**) (0.25 M dry CH_2Cl_2 solution) with 9-BBN triflate (1.05 equiv) and diisopropylethylamine (1.1 equiv) at -70 °C for 0.5 hr, the reaction mixture was gradually warmed up to -35 °C over 15 min, followed by being stirred at -20 °~ -35 °C for 1 hr. To a methylene chloride solution of the vinyloxyborane (**5**) thus generated was added the imine (**3**) (1.2 equiv; 0.25 M dry CH_2Cl_2 solution) at the same temperature. The reaction mixture was gradually warmed up to 5 °C over 1.5 hr, and then stirred at room temperature for an additional 1.5 hr. Finally, the reaction was quenched by the addition of pH 7 phosphate buffer (5 ml/mmol), methanol (5 ml/mmol) and aqueous 31% H_2O_2 (2.5 ml/mmol) at -25 °C, and the whole reaction mixture was stirred at 5 °C for 15 min and at room temperature for 15 min. Under the conditions described above, the desired β-benzylamino thiol ester (**6**)[11] was securely obtained in 36% yield [58% yield based on the recovered starting thiol ester (38% recovery)].[13] Stereochemistry of the newly formed chiral centers was not clear at this stage.

Hydrolysis of the β-benzylamino thiol ester (**6**) (KOH in aqueous THF) afforded the corresponding carboxylic acid (**7**), which was subsequently cyclized to the β-lactam (**8**)[11] using Ohno's method[14] (2,2'-dipyridyl disulfide-triphenylphosphine in CH_3CN, reflux for 3 hr) in 72% overall yield. Protection of hydroxy group as *t*-butyldimethylsilyl ether ($^tBuMe_2SiOSO_2CF_3$/2,6-lutidine in CH_2Cl_2[15]) gave the fully protected β-lactam (**9**)[11] in 89% yield. Here three stereoisomers formed were separated by silica gel column chromatography, showing that the desired β-lactam (**9a**), which is convertible to (+)-thienamycin (**1**), was obtained in a stereoselective manner (**9a** : **9b** : **9c** ≈ 9 : 1 : 0.2). Stereochemistry of these isomers were determined by converting to the known bicyclic β-lactam (**12**).[16]

At the beginning of this research, we considered the following stereochemical course. The stereochemistry of **5** should be assigned the (*E*)-vinyloxyborane on the basis of the report by Masamune.[17] The newly formed chiral center (C-3) adjacent to the original one should be controlled by Felkin type transition state (**13**) or chelation controlled transition state like **2**, and the stereochemistry of C-4 should be controlled by tightly coordinated six-membered transition state in the condensation of the enolate with the imine. Thus, β-benzylamino thiol ester leading to the stereoisomer (**9b**) should be obtained in a selective manner, requiring the epimerization at C-3 to obtain the thienamycin intermediate (**10**). We thought that this epimerization could be achieved at the β-lactam cyclization stage.[18] As was expected, the desired stereoisomer (**9a**) was obtained in a highly selective manner. Although much work should be done to clarify the detailed mechanism for this stereochemical outcome, it is noteworthy that the stereoselective synthesis of **9a** from 3(*R*)-hydroxybutyric acid has been achieved for the first time.



The fully protected β-lactam (**9a**), $[\alpha]_D^{20}$ -11.34° (c 1.64, $CHCl_3$), was transformed to **10**[11]; $[\alpha]_D^{20}$ +16.19° (c 1.00, $CHCl_3$), in two steps [i. Na in NH_3 (77%), ii. CrO_3 in pyridine (76%)], which should be a key intermediate for (+)-thienamycin (**1**) according to the report by Merck group.[2,6] In order to confirm the optical purity of **10** thus obtained, **10** was converted to **11**,[11] $[\alpha]_D^{20}$ +9.84° (c 2.10, $CHCl_3$), in two steps [i. $PhCH_2OH$-DCC-DMAP in CH_2Cl_2 (80%), ii. AcOH-H_2O-THF (3:1:1) (89%)], showing that the optical rotation of **11**[19] was identical with that of an authentic material,[20] $[\alpha]_D^{20}$ +9.9° (c 2.3, $CHCl_3$).

The synthetic route to (+)-thienamycin (**1**) described in this paper is not completely satisfactory at present regarding the overall yield. However, the first success of the stereoselective synthesis of thienamycin intermediate from 3(*R*)-hydroxybutyric acid will stimulate the synthetic work along this line. Further studies are currently under active investigation.[21]

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References and Notes

1) This paper is dedicated to Professor Shuin-ichi Yamada on the occasion of his 70th birthday.
2) T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen, and F.A. Bouffard, *J. Am. Chem. Soc.*, **102**, 6163 (1980); N. Ikota, H. Shibata, and K. Koga, *Heterocycles*, **14**, 1077 (1980).
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8) For example, Kanegafuchi Chemical Ind. Co., Ltd. is industrially producing 3(*R*)-hydroxybutyric acid.
9) G.I. Georg, *Tetrahedron Lett.*, **25**, 3779 (1984).
10) D.-C. Ha, D.J. Hart, and T.-K. Yang, *J. Am. Chem. Soc.*, **106**, 4819 (1984).
11) Satisfactory infrared, pmr and mass spectral data were obtained on all intermediates described herein using chromatographically homogeneous samples.
12) It is also possible to prepare *S*-phenyl-3(*R*)-butanethioate (**4**) directly from 3(*R*)-hydroxybutyric acid by treatment with PhSH and DCC in CH_2Cl_2.
13) Although the reason is not clear at present, *S*-phenyl-3(*R*)-*t*-butyldimetylsilyloxybutanethioate afforded none of the condensed product under the reaction conditions described in the text. Furthermore it was also found that the reaction of the vinyloxyborane prepared from *S*-t-butyl-3(*R*)-butanethioate and dicyclopentylboron triflate with the imine (**3**) didn't give the condensed product.
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15) E.J. Corey, H. Cho, C.Rücker, and D.H. Hua, *Tetrahedron Lett.*, **22**, 3455 (1981).
16) F.A. Bouffard, D.B.R. Johnston, and B.G. Christensen, *J. Org. Chem.*, **45**, 1130 (1980).
17) M. Hirama, D.S. Garvey, L.D.-L. Lu, amd S. Masamune, *Tetrahedron Lett.*, 3937 (1979).
18) Kametani and his coworkers already reported this kind of epimerization in their synthesis of (±)-thienamycin, see: T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, *J. Am. Chem. Soc.*, **102**, 2060 (1980).
19) The compound (**11**) has been already converted to thienamycin, see reference 6.
20) N. Ikota, O. Yoshino, and K. Koga, *Chem. Pharm. Bull.*, **30**, 1929 (1982).
21) After completion of this manuscript, Nakai has also reported a stereoselective but wrong synthesis of the thienamycin intermediate from 3(*R*)-hydroxybutyric acid using the non-enolizable imine, see: T. Chiba, M. Nagatsuma, and T. Nakai, *Chemistry Lett.*, 1927 (1984).

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