Tetrahedron Letters,Vol.28,No.1,pp 69-72,1987
Printed in Great Britain

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

A STEREOCONTROLLED SYNTHESIS OF THE KEY INTERMEDIATE OF (+)-THIENAMYCIN FROM (R)-(-)-3-HYDROXYBUTYRIC ACID ESTERS

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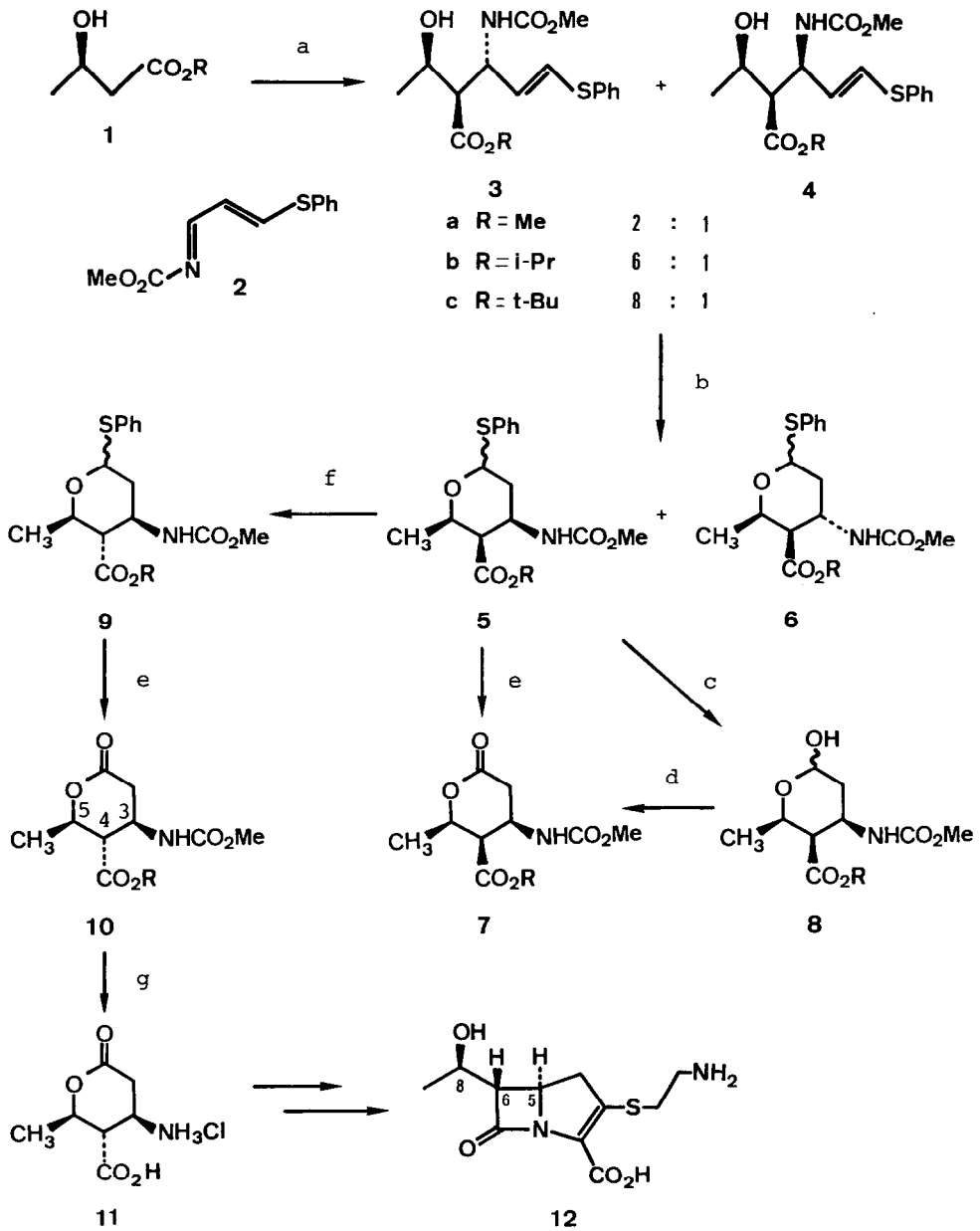
Summary: The chiral key intermediate of (+)-thienamycin is synthesized in a stereocontrolled manner from (R)-(-)-3-hydroxybutyric acid esters.

A potent β-lactam antibiotic, thienamycin (**12**), has attracted much attention of organic chemists.[1] Despite intensive efforts toward stereocontrolled synthesis of **12**, introduction of the three continuous chiral centers of the molecule remained a challenge. Recently, stepwise introduction of the (R)-1-hydroxyethyl group and/or the C-4 carbon unit into chiral azetidinone intermediates in stereocontrolled fashion has been developed successfully.[2] However, a route via chiral β-amino acid having the three chiral centers, such as Melillo's lactone (**11**)[3], is still one of most efficient approach. Herein we report a convenient synthesis of the six-carbon segments possessing the functionality and chirality of (+)-thienamycin starting from readily available (R)-(-)-3-hydroxybutyrate. Recent publications have described the reaction of the dianion of (R)-(-)-3-hydroxybutyrate with N-aryl or N-trimethylsilylaldimines, leading to direct formation of azetidinones possessing hydroxyethyl side-chain as found in thienamycin (**12**).[4] However, the resulting azetidinones could not be derived into thienamycin without some correction of the stereochemistry on the unstable azetidinone ring. To avoid this difficulty, we investigated the reaction of the dianion of 3-hydroxybutyrate with N-acylaldimine which found to provide high yield synthesis of the β-amino acid derivatives **3** in highly stereoselective fashion; **3** could be converted into Melillo's lactone (**11**) via inversion of the carboxyl group.[5]

Methyl (R)-(-)-3-hydroxybutyrate (**1a**, 98% ee) was converted by treatment with LDA in tetrahydrofuran at -78°C into the dianion, which was then treated with N-methoxycarbonyl (2-phenylthio)ethenylcarboxaldimine (**2**)[6] to give a 2:1 mixture of the (syn, anti)-product **3a** and the (syn, syn)-product **4a** in 96% yield.[7] The steroselectivity for the (syn, anti)-product formation was remarkably improved by the use of the bulkier ester of **1**. The isopropyl ester **1b** gave **3b** and **4b** in a ratio of 6:1 and the t-butyl ester **1c**[8] afforded **3c** and **4c** in a ratio of 8:1.

A 2:1 mixture of **3a** and **4a** was treated with one equivalent of dry hydrogen chloride in dichloromethane at room temperature for 12 hr, and chromatography of the crude product gave the cyclic hemithioacetal **5a** and **6a** in 51% and 12% yields, respectively, both in a form of isomeric mixtures relating to the



Reagents: a. (1) 2 equiv. LDA,THF, -78°C ~ -40°C. 1 h (2) **2**, THF, -78°C, 1 h; b. HCl, CH_2Cl_2, r.t., 12 h; c. $CuCl_2$, CuO, aqueous acetone, reflux; d. Jones reagent, acetone; e. 1,3-dibromo-5,5-dimethylhydantoin, aqueous CH_3CN, 40°C; f. K_2CO_3, MeOH, reflux; g. 12N HCl, reflux.

position 2. In an attempt to convert the major product **5a** into the lactone **7a**, the compound **5a** was treated with cupric chloride and cupric oxide in refluxing aqueous acetone to give the lactol **8a** quantitatively, which was oxidized with Jones reagent to afford **7a** only in poor yield. However, we found that the lactone **7a** (mp 126-128°C, $[\alpha]_D^{25}$ +144.5° (c 0.79, MeOH)) could be produced in 81% yield directly from **5a** by treatment with 1,3-dibromo-5,5-dimethylhydantoin in aqueous acetonitrile. This reaction might proceed via bromination at the position 2. The coupling constants ($J_{3,4}$=4.5 Hz, $J_{4,5}$=2.7 Hz) observed in the ^{1}H-NMR spectrum of **7a** are consistent with the (3R,4R,5R) configuration.[9]

In order to obtain the desired chiralities, inversion of the carboxyl group is needed. This was readily achieved by heating **5a** with potassium carbonate in refluxing methanol to give **9a** in 76% yield. Treatment of **9a** with 1,3-dibromo-5,5-dimethylhydantoin afforded the desired lactone **10a** (mp 94-95°C, $[\alpha]_D^{24}$ +11.3° (c 0.94, MeOH))in 84% yield. The stereochemistry of **10a** was confirmed by the coupling constants ($J_{3,4}$=9.8 Hz, $J_{4,5}$=10.4 Hz) observed in the ^{1}H-NMR spectrum. Thus, we achieved synthesis of the desired six-carbon segment possessing three chiral centers of thienamycin in a stereoselective manner. The stereoselctivity increases by using the isopropyl or t-butyl ester of (R)-3-hydroxybutyric acid as a starting material. In a typical run, the crude product containing **3b** and **4b** in a ratio of 6:1 obtained from **1b** was treated without purification with dry hydrogen chloride in dichloromethane. After evaporation of the solvent, the residue was refluxed with potassium carbonate in methanol and crystallization of the crude product gave pure **9b** in 54% total yield from **1b**. The compound **9b** was then converted into **10b** (mp 90-91°C, $[\alpha]_D^{22}$ +12.3° (c 0.47, MeOH) in 82 % yield.

Finally, hydrolysis of **10b** in refluxing 12N hydrochloric acid gave the crystalline Melillo's lactone **11** ($[\alpha]_D^{22}$ +17.7° (c 1.5, DMSO), lit.[3d], $[\alpha]_D$ +15.5° (DMSO)) quantitatively. Since the synthesis of thienamycin from **11** in racemic form has been reported, our results means formal total synthesis of (+)-thienamycin (**12**).

It is also noted that the (3R,4R,5R) lactone **7** can serve as versatile intermediate of analogous cis-carbapenem compounds, 6-epithienamycin and epi-thienamycin. The synthesis of these compounds and another approach to thienamycin from **10** using our method[10] is now in progress in our laboratory.

Acknowledgment. We thank Kanegafuchi Chemical Ind. Co., Ltd. for providing methyl (R)-3-hydroxybutyrate.

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(Received in Japan 19 August 1986)