Articles

Stereocontrolled Synthesis of 4-Acetoxy-2-azetidinone via Double Azetidinone Ring Formation : A Useful Precursor of Carbapenem and Penem Antibiotics

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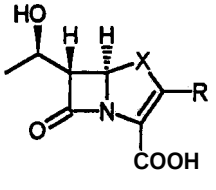
(3R,4R)-4-Acetoxy-3-[(1'R-tert-butyldimethylsilyloxy)ethyl]-2-azetidinone, one of the best synthons for carbapenems and penems was efficiently synthesized from readily available *L* -threonine *via* double azetidinone ring formation.

Introduction

Since the isolation of (+)-thienamycin by a Merck research group[1] in 1976, various analogs of carbapenem and penem antibiotics have been prepared and much efforts have been directed to the stereocontrolled total synthesis of these compounds.

Intensive effort has been placed on constructing a chiral azetidinone with suitable functional appendages to allow the facile formation of the 5-membered ring. The strategy toward their total synthesis has usually been focused on the elaboration the three requisite contiguous chiral centers.[2] It has been shown by several research groups that the (3R,4R)-4-acetoxy-3-[(1' *R-tert-* butyldimethylsilyloxy)ethyl]-2-azetidinone **(1),** constitutes one of the best precursors for the preparation of these antibiotics.[3] Although there are many methods for synthesizing this intermediate using optically active natural sources such as 6-APA,[4] *L* -aspartic acid,[5] *L-allo* -threonine,[6] *L* -threonine,[7] and (3R)-hydroxybutyrate,[8] simple and practical synthetic routes are still required.

Recently we have been working toward overcoming an industrial synthetic problems such as number of steps involved, overall yield, optimization of condition and so on. Here, we wish to report an stereoselective symthesis of **1** from naturally abundant *L*- threonine by a stereocontrolled method.

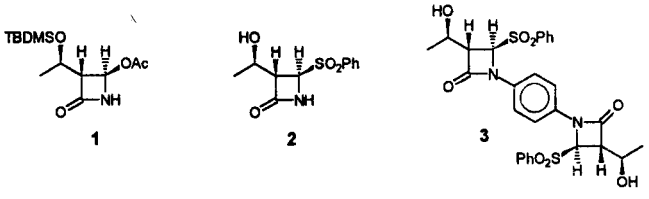


X = -CH_2- : Carbapenem

= -S- : Penem

Results and Discussion

Shiozaki has reported the synthesis of another precursor of carbapenems and penems, 2-phenylsulfonyl-3-(1-hydroxyethyl)-4-azetidinone **(2),**[9] which was generated from bisazetidinone **(3).** However, this approach has some disadvantages, in which the phenylsulfonyl group is less reactive than acetoxy group toward nucleophiles and deprotection of the protecting group on nitrogen was performed using 13 equivalents of expensive ceric ammonium nitrate (CAN).[10]

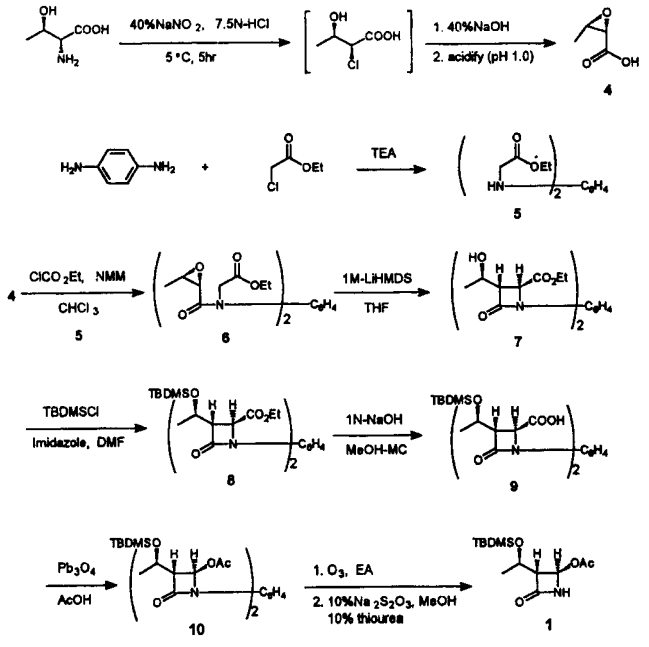


Our synthetic strategy is shown in Scheme 1. Two key features involve the introduction of ethoxycarbonylmethyl group which can be easily converted into acetoxy group as a counterpart of phenylsulfonyl group and the ozonolytic deprotection which would overcome the aforementioned problem,

The readily available *L*- threonine reacted with 40% aqueous sodium nitrite solution in 7.5 N-HCl leading to the corresponding chlorohydrin *via* diazotization, which upon treatment with 40% NaOH solution *in situ* and the subsequent acidic work up (pH 1.0) gave (2R,3R)-2,3-epoxybutyric acid **(4)** in good overall yield. The reaction proceeded with double inversion of the configuration of the carbon attached with amino group.

Originally the epoxy acid was synthesized from *L*- threonine by Hanessian with $NaNO_2$-KBr-H_2SO_4 system via bromohydrine in 70% overall yield,[7b] We substituted the intermediate chlorohydrin for bromohydrin using $NaNO_2$-HCl and obtained the desired epoxy acid in improved yield (70% $\rightarrow$ 90%) with the correct configuration. The 1,4-bis [(ethoxycarbonylmethyl)amino]benzene **(5)** was efficiently synthesized from ethyl chloroacetate and *p*- phenylenediamine in triethylamine under reflux. The crude epoxy acid **(4)** was condensed with amine **(5)** *via* active ester coupling to give the (2R,3R)-1,4-bis[(N-ethoxycarbonylmethyl-N-2,3-epoxybutyryl)amino]benzene **(6)** in 93% yield.

Next, cyclization of **(6)** was accomplished with 1 M-LiHMDS in THF at 0 °C leading to bis β -lactam **(7)** stereoselectively in 75% yield, in which *cis-cis* or *trans-cis* isomer could not be found. Protection of alcohol **(7)** with *tert-* butyldimethylsilyl chloride in DMF at 25 °C for 12h gave silylether **(8)** in 95% yield, which was hydrolyzed



Scheme 1.

with 1 N-NaOH in methanolic methylene chloride at room temperature to afford 4-carboxy-2-azetidinone derivative **(9).** Acetoxylation was accomplished with Pb_3O_4 in acetic acid.[11] Pb_3O_4 was added in portion at 40 °C and the reaction is exothermic, which was solidified on the addition of water. The crude solid **(10)** reacted with ozone[12] in ethyl acetate at – 20 °C followed by reductive work-up to give 4-acetoxy-2-azetidinone **(1)** in 48% overall yield over three steps. The reductive work-up consists of treatment of the reaction mixture with 10% aqueous sodium thiosulfate solution, warming at 40 °C for 30 min, evaporation of ethyl acetate, the addition of methanol and the subsequent reduction with 10% aqueous thiourea.[13] It is worthy of note that the addition of methanol is critical in the course of work-up.

Thus we have achieved a practical synthesis of an important precursor to carbapenem and penem antibiotics from *L*- threonine. The described synthesis has the attractive features of utilizing readily available inexpensive starting materials and involving simple ozonolytic deprotection which would be more economical for the large scale production.

Experimental

Melting points (mp) were determined on a Buchi 535 capillary melting apparatus. Optical rotations were obtained using JASCO DIP-1000 Polarimeter at room temperature using the sodium D line. ^{1}H NMR spectra were determined at 300 MHz with a ARX 300 using tetramethylsilane as an internal. Mass spectra were obtained on a ESI/MS (electrospray ionisation/mass spectrometer). Elemental analysis was performed by a FISONS EA 1108 analyzer.

(2R,3R)-2,3-Epoxybutyric acid (4). *L*- threonine (40.6 g, 341 mmol) was dissolved in 7.5 N-HCl (222 mL), 40% aqueous sodium nitrite solution (100 mL) was added over a period of 5 h at 5 °C. After addition was completed the reaction mixture was stirred vigorously at room temperature in order to eliminate nitrogen oxides. To the almost colorless reaction mixture cooled at 0 °C, 40% NaOH (204 mL) was added gradually. After stirring for 3.5 h at 40 °C, the reaction mixture was cooled down to 0 °C then acidified with c-HCl to pH 1.0 and extracted with ethyl acetate, dried over $MgSO_4$ and concentrated *in vacuo* to give 31.3 g of **4** (90%) as a slightly colored oil which was employed for the next reaction without purification: ^{1}H NMR ($CDCl_3$) δ 1.4 (3H, d, *J* =5.5 Hz), 3.4 (1H, m), 3.6 (1H, d, *J* =4.6 Hz), 9-10 (acid-H, brs): $[\alpha]_D = -11^\circ$ (c=1.1, MeOH) [lit. -10.58°, (c=3, MeOH)].

1,4-Bis[(ethoxycarbonylmethyl)amino]benzene (5). To a solution of *p*- phenylenediamine (20 g, 185 mmol) in triethylamine (100 mL) was added ethylchloroacetate (50 mL, 469 mmol) at 90 °C. After vigorous stirring for 10 min under reflux, the reaction mixture was cooled down to 60 °C then solidified with water to give 48 g of **3** (93%) as a yellow powder which was employed for the next reaction without purification. An analytical sample was recrystallized from MC-hexane: ^{1}H NMR ($CDCl_3$) δ 1.3 (6H, d, *J* =7.1 Hz), 3.79 (NH, brs), 3.84 (4H, s), 4.2 (4H, q, *J* =7.1 Hz), 6.6 (4H, s): ^{13}H NMR ($CDCl_3$) δ; 14.6 (CH_3), 61. 5 (CH_2), 47.5 (CH_2), 115.4 (CH, aromatic), 140.5 (C, aromatic), 185.0 (C=O) ; ESI/MS 281 $(M+H)^+$, 304 $(M+Na)^+$; mp 65.5 -66.3 °C; Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.08; H, 6.98; N, 10.08.

(2R,3R)-1,4-Bis[(N-ethoxycarbonylmethyl-N-2,3-epoxybutyryl)amino]benzene (6). To a stirred and cooled (– 20 °C) solution of the epoxy acid **(4,** 31.3 g, 307 mmol) in 350 mL of chloroform was added *N*- methylmorpholine (78.8 mL, 717 mmol) followed by ethyl chloroformate (57.6 mL, 602 mmol). After stirring 30 min at – 20 °C, the amine **(3,** 28.7 g, 102 mmol) was added as a solid and the solution was stirred for 1h warming slightly (40 °C). The reaction mixture was recooled at – 20 °C then *N*-methylmorpholine (10 mL) were added successively followed by stirring 1 h at 40 °C. The reaction mixture was quenched with 2 N-HCl (500 mL) at 0 °C then washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated *in vacuo* until the volume of the residue is *ca.* 100 mL. Then to this slurry was added hexane (500 mL) with vigorous stirring to precipitate 42.5 g of **6** (93%) which was employed for the next reaction without purification. An analytical sample was recrystallized from MC/ *n*- hexane.: ^{1}H NMR ($CDCl_3$) δ 1.3 (6H, d, *J* =7.1 Hz), 1.4 (6H, d, *J* =5.3 Hz) 3.1 (2H, m), 3.3 (2H, d, *J* =4.2 Hz) 4.2 (6H, m), 4.7 (2H, d, *J* =17.2 Hz), 7.4 (4H, s): ^{13}C NMR ($CDCl_3$) δ; 13.6 (CH_3), 14.5 (CH_3), 51.7 (CH), 54.4 (CH_2), 62 (CH), 129.6 (CH, aromatic), 142 (C, aromatic), 168.9 (C=O), 167 (C=O); ESI/MS 449 $(M+H)^+$; mp 139.8-140.6 °C; $[\alpha]_D = +326.9^\circ$ (c=0.3, MeOH) anal. Calcd for $C_{22}H_{28}N_2O_8$; C, 58.92; H, 6.29; N, 6.24. Found: C, 58.92; H, 6.43; N, 6.28.

(3S,4S)-1,4-Bis[3-(1' *R*- hydroxyethyl)-4-ethoxycarbonyl-2-azetidinone-1-yl]benzene (7). To a solution of **6** (42.5 g, 94.8 mmol) in THF was added 1 N-LiHMDS (227 mL) at ice cooling temperature. After stirring at room temperature for 30 min, the reaction mixture was diluted with ethylacetate, quenched with sat. NH_4Cl. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* followed by chromatography to give 31.9 g of **7** (75%) as a white solid. An analytical sample was recrystallized from Et_2O.: ^{1}H

NMR ($CDCl_3$) δ 1.3 (6H, d, *J* =7.1 Hz), 1.4 (6H, d, *J* =6.4 Hz), 3.3 (2H, m), 3.6 (2H, brs), 4.2 (4H, q, *J* =7.1 Hz) 4.4 (2H, m), 4.7 (2H, d, *J* =2.4 Hz), 7.1 (4H, s): ^{13}C NMR ($CDCl_3$) δ; 14.4 (CH_3), 21.5 (CH_3), 52.7 (CH), 62.3 (CH), 62.9 (CH_2), 63.7 (CH) 117.5 (CH, aromatic), 133.9 (C, aromatic), 164.4 (C=O), 170.7 (C=O); ESI/MS 449 $(M+H)^+$; mp 135.1-135.8 °C; $[\alpha]_D = -180.1°$ (c=0.3, MeOH) Anal. Calcd for $C_{22}H_{28}N_2O_8$; C, 58.92; H, 6.29; N, 6.24. Found: C, 59.16; H, 6.42; N, 6.28.

(3S,4S)-1,4-Bis[3-{(1' *R-tert*- butyldimethylsilyloxy)ethyl}-4-ethoxycarbonyl-2-azetidinone-1-yl] benzene (8). A mixture of **7** (31.9 g, 71.1 mmol), *tert*-butylmethylsilylchloride (27.8 g, 184 mmol), imidazole (19.4 g, 284.4 mmol) in DMF (350 mL) was allowed to stand at room temperature for 16 h. The reaction mixture was diluted with ethylacetate, washed with 1 N-HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash chromatography to give 45.8 g of **8** (95%) as a white solid.: ^{1}H NMR ($CDCl_3$) δ 0.0 (6H, s), 0.1 (6H, s), 0.7 (18H, s), 1.3 (12H, m), 3.3 (2H, m), 4.2 (2H, m), 4.3 (2H, m), 4.6 (2H, d, *J* =2.3 Hz), 7.3 (4H, s): ^{13}C NMR ($CDCl_3$) δ; – 4.8 ($SiCH_3$), -3.9 ($SiCH_3$), 14.5 (CH_3), 18.1 (C), 22.8 (CH_3), 25.9 (CH_3), 52.9 (CH), 62.1 (CH), 63.3 (CH_2), 64.8 (CH), 117.0 (CH, aromatic), 134.3 (C, aromatic), 164.5 (C=O), 170.7 (C=O); ESI/MS 678 $(M+H)^+$; mp 166.9-167.4 °C; $[\alpha]_D = -150.9°$ (c=0.5, $CHCl_3$) Anal. Calcd for $C_{34}H_{56}N_2O_8Si_2$; C, 60.32; H, 8.34; N, 4.14. Found: C, 60.71; H, 8.64; N, 4.15.

(3S,4S)-1,4-Bis[3-{(1' *R-tert*- butyldimethylsilyloxy)ethyl}-4-carboxy-2-azetidinone-1-yl]benzene (9). To a stirred solution of **8** (45.8 g, 67.6 mmol) in MeOH-MC (5 : 1, 600 mL) was added gradually 1 N-NaOH (149 mL, 1.1 eq) at room temperature. After stirring for 30 min, the reaction mixture was concentrated *in vacuo* and diluted with H_2O, washed with ethylacetate. The aqueous phase was acidified to pH 2 with 1 N-HCl, filtered and washed with *n*- hexane to give 42 g of **9** as a white solid which was employed for the next reaction without purification.: ^{1}H NMR (acetone-d^6) δ 0.0 (6H, s), 0.1 (6H, s), 0.7 (18H, s), 1.3 (6H, d, *J* =6.3 Hz), 3.4 (2H, m), 4.4 (2H, m), 4.6 (2H, d, *J* =2.5 Hz), 7.3 (4H, s): ^{13}C NMR (acetone-d^6) δ; 0.0 ($SiCH_3$), 0.8 ($SiCH_3$), 23.2 (C), 27.5 (CH_3), 31.0 (CH_3), 57.7 (CH), 68.7 (CH), 70.4 (CH_2), 122.6 (CH, aromatic), 139.9 (C, aromatic), 169.7 (C=O), 176.8 (C=O); ESI/MS 621 $(M+H)^+$; mp 209 °C (dec.); $[\alpha]_D = -166.2°$ (c= 0.25, MeOH) Anal. Calcd for $C_{30}H_{48}N_2O_8Si_2$; C, 58.03; H, 7.79; N, 4.51. Found: C, 57.07; H, 7.87; N, 4.40.

(3R,4R)-1,4-Bis[3-{(1' *R-tert*- butyldimethylsilyloxy)ethyl}-4-acetoxy-2-azetidinone-1-yl]benzene (10). The suspension of **9** (42 g, 67.6 mmol) in glacial acetic acid was heated at 60 °C followed by portionwise addition of Pb_3O_4 (111 g. 162 mmol). After stirring for 10 min, the reaction was quenched by addition of 2 mL of ethyleneglycol then concentrated. The residue was solidified with large exess of H_2O to give 41.6 g of **10** (95%) as a crystalline solid which was employed for the next reaction without purification. An analytical sample was prepared by flash chromatography followed by recrystallization from petroleum ether: ^{1}H NMR ($CDCl_3$) δ 0.0 (6H, s), 0.1 (6H, s), 0.7 (18H, s), 1.3 (6H, d, *J* =6.4 Hz), 2.1 (6H, s), 3.2 (2H, dd, *J* =2.6 Hz and *J* =0.6 Hz), 4.3 (3H, m), 6.6 (2H, s), 7.4 (4H, s): ^{13}C NMR ($CDCl_3$) δ; – 5.2 ($SiCH_3$), – 4.3 ($SiCH_3$), 17.7 (C), 21.0 (CH_3), 22.2 (CH_3), 25.5 (CH_3), 64.2 (CH), 65.6 (CH), 76.5 (CH), 117.8 (CH, aromatic), 132.9 (C, aromatic), 164.0 (C=O), 170.0 (C=O); ESI/MS 671 $(M+Na)^+$; mp 208.0-208.8 °C; $[\alpha]_D = -101.3°$ (c=0.5, $CHCl_3$) Anal. Calcd for $C_{32}H_{52}N_2O_8Si_2$; C, 59.23; H, 8.08; N, 4.32. Found: C, 59.46; H, 8.21; N, 4.28.

(3R,4R)-4-Acetoxy-3-[(1' *R-tert*- butyldimethylsilyloxy)ethyl]-2-azetidinone (1). A solution of **10** (1 g, 1.5 mmol) in ethyl acetate (50 mL) was treated with ozone at – 20 °C until the starting material was completely disappeared. Then 10% aqueous sodium thiosulfate solution (26 mL) was added and stirred for 30 min at 40 °C. After evaporation of ethyl acetate the reaction mixture was diluted with methanol (20 mL) and 10% aqueous thiourea (19 mL) was added dropwise. After stirring 3 h at 40 °C, the organic solvent was removed *in vacuo* then extracted with ethyl acetate, and organic layer was dried, concentrated and chromatographed with *n*- hexane/ethyl acetate (4/1) as the eluent to provide 447 mg of **1** as a white solid, identical in all respects with the material previously described by other author.

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Molecular Dynamics Simulation of Liquid Alkanes. II. Dynamic Properties of Normal Alkanes : *n*- Butane to *n*- Heptadecane

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In a recent paper[*Bull. Kor. Chem. Soc.* **17,** 735 (1996)] we reported results of molecular dynamic (MD) simulations for the thermodynamic and structural properties of liquid *n*- alkanes, from *n*- butane to *n*- heptadecane, using three different models. Two of the three classes of models are collapsed atomic models while the third class is an atomistically detailed model. In the present paper we present results of MD simulations for the dynamic properties of liquid *n*- alkanes using the same models. The agreement of two self-diffusion coefficients of liquid *n*- alkanes calculated from the mean square displacements (MSD) *via* the Einstein equation and the velocity auto-correlation (VAC) functions *via* the Green-Kubo relation is excellent. The viscosities of *n*- butane to *n*- nonane calculated from the stress auto-correlation (SAC) functions and the thermal conductivities of *n*- pentane to *n*- decane calculated from the heat-flux auto-correlation (HFAC) functions *via* the Green-Kubo relations are smaller than the experimental values by approximately a factor of 2 and 4, respectively.

Introduction

Green and Kubo[2] showed that the phenomenological coefficients describing many transport processes and time-dependent phenomena in general could be written as integrals over a certain type of function called a time-correlation function. These time-correlation functions play a somewhat similar role in nonequilibrium statistical mechanics that the partition function plays in equilibrium statistical mechanics. The analogy breaks down in one respect. Since the state of thermal equilibrium is unique, a single partition function gives all the thermodynamic properties, but since there are many different kinds of nonequilibrium states, a different time-correlation function for each type of transport process is needed. Determining the appropriate time correlation function to use for a particular transport process of interest is very important.

The Green-Kubo relations (Table 1) are the formal expressions for hydrodynamic field variables and some of the thermodynamic properties in terms of the microscopic variables of an N-particle system. The identification of microscopic expressions for macroscopic variables is made by a process of comparison of the conservation equations of hydrodynamics with the microscopic equations of change for conserved densities. The importance of these relations is three-fold: they provide an obvious method for calculating transport coefficients using computer simulation, a convenient starting point for constructing analytic theories for nonequilibrium processes, and an essential information for designing nonequilibrium molecular dynamics (NEMD) algorithm.

In previous works[3,4] we reported results of equilibrium molecular dynamics (EMD) and NEMD simulations for the thermal transport properties - the self-diffusion coefficients, shear viscosities, and thermal conductivities - of liquid argon[3] at 94.4 K and 1 atm and liquid water[4] at 298.15 K and 1 atm using TIP4P model[5] for the interaction between water molecules. For liquid argon, the overall agreement of the calculated thermal transport properties through EMD and NEMD with the experimental results was quite good.[3] However, in the case of liquid water, the Green-Kubo relations are applied with difficulty to the EMD results since the time-correlation functions are oscillating and not decaying rapidly enough but the NEMD results were found to agree within approximately ±30~40% error bars.[4]

In this paper, we present results of MD simulation studies to investigate the dynamic properties of liquid *n*- alkanes, *n*-butane to *n*- heptadecane, using the above referred models. Further studies also include the investigation of the thermodynamic, structural, and dynamic properties of branched-chain alkanes, and analyses of segmental motions of C-C backbone chains in long chain alkanes.

The paper is organized as follows. Section II contains a brief description of molecular models and MD simulation methods followed by Sec. III which presents the results of our simulations and Sec. IV where our conclusions are summarized.