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Novel Synthesis of (+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone from Carbohydrate

A Formal Total Synthesis of (+)-Thienamycin†

Sir:

(+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone, that is (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-hydroxyethyl]-2-azetidinone (**1**), and its derivatives have been well-known as the highly versatile intermediates[1] for the synthesis of carbapenem antibiotics such as thienamycin (**2**)[2], imipenem, meropenem[3] and so on (Fig. 1).

The synthesis of **1** was initiated by Sankyo group[4], followed by Merck group[5], and culminated in the practical preparation by two Japanese companies[6,7] using Noyori-Murahashi's asymmetric procedures and chem-enzymatic procedures, respectively.

(+)-Thienamycin (**2**) was discovered in fermentation broths of *Streptomyces cattleya* to show exceptional antibacterial potency and spectrum[2]. The first stereocontrolled synthesis of **2** has been reported by Merck group[8], and the transformation of **1** to (+)-thienamycin (**2**) was also made more attractive by another Merck group[9]. Consequently, the synthesis of (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**1**) constitutes a formal total synthesis of (+)-thienamycin (**2**).

Herein, we report a novel enantiospecific synthesis of **1** from a carbohydrate through the skeletal rearrangement and stereoselective epimerization. Our starting material is commercially available methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside (**3**), which has been also isolated from natural sources[10].

Reaction of **3** with *o*-benzenedisulfonyl dichloride[11] gave the cyclic sulfonate **4** (Table 1), which was submitted to our developed skeletal rearrangement[11] including ring-contraction with potassium *tert*-butoxide (Scheme 1). The resulting 3-formyl-furanoside **5** was oxidized to the mixture of the carboxylic acids, which were readily separated on silica gel column chromatography ($CHCl_3$-MeOH 8:1). Both carboxylic acids were purified on Dowex 50×8 resin (Na-type) with H_2O to give the sodium salt **6** and its C-3 epimer **7** in 49% and 42% yields in 2 steps from **4**, respectively. Practically, both compounds could be used for the synthesis without separation, because they were found to be efficiently converted to a single lactone **11** by stereoselective epimerization later on. However, we now describe the synthesis from each of both compounds **6** and **7** as follows.

Removal of the *N*-sulfonyl group of **6** by Birch reduction produced the corresponding amino acid **8**. This was hydrolyzed and then esterified to give the furanose **9**. The oxidation of **9** to the lactone **10** was the key step of our strategy, although the lactone could not be obtained under usual oxidation conditions. Finally, we found that, on exposure to Ag_2CO_3/Celite[12] in benzene, the furanose **9** was smoothly oxidized to the γ-lactone **10** in spite of the presence of the amino group.

The next important operation in the synthesis was to epimerize stereoselectively the configurations at C-2 and C-3 positions of **10**. After a variety of conditions were examined, the best result was realized by using DBU in MeOH to afford predominantly the desired amino ester **11**.

Similarly, the epimer **7** was transformed to **11** through **12** and **13** in 57% overall yield.

The structure of **11** was reasonably confirmed by the NMR studies of **10**, **11** and **13**.

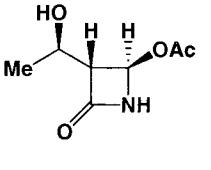
These results indicated that the C-4 configuration of **10** or **13** controlled the stereoselective construction of the C-2 and C-3 configurations of **11**.

Hydrolysis of **11** with 2 M NaOH according to the reported procedures[13] led to the hydroxy acid **14**, which was in turn submitted to the β-lactam formation (Scheme 2).

For our purpose, a Grignard-mediated cyclization of the silylated derivative seemed most promising[14]. Thus, **14** was silylated with trimethylsilyl chloride and hexamethyldisilazane (HMDS), and followed by treatment with *tert*-butylmagnesium chloride to give the bis-silylated β-lactam **15**[13].

Oxidative decarboxylation[9] of **15** by $Pb(OAc)_4$ gave

Fig. 1.



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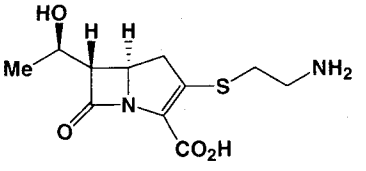

2: Thienamycin

† This paper is dedicated to the memory of Sir EDWARD ABRAHAM, a pioneer of β-lactam antibiotics science.

Table 1. Physico-chemical properties of compounds.

Compds.	Mp (°C)	$[\alpha]_D$	^{1}H-NMR (600 or 300MHz; δ ppm; *J* Hz)
1	108-110	+63° (*c* 0.74, $CHCl_3$)	($CDCl_3$) : δ 1.35(3H, d, *J*=6.2), 2.13(3H, s), 3.23(1H, dd, *J* =1.0&6.2), 4.22(1H, dq, *J*=6.2&6.2), 5.81(1H, d, *J*=1.0), 6.58(1H, br s)
4	190-196 (decomp.)	+142° (*c* 1.10, Me_2CO)	($CDCl_3$) : δ 1.36(3H, d, *J*=6.2), 2.73(1H, br s), 3.44(3H, s), 3.46(1H, dd, *J*=9.4&9.4), 3.78(1H, dq, *J*=6.2&9.4), 3.91(1H, ddd, *J*=3.6, 10.4&10.4), 4.82(1H, d, *J*=3.6), 5.03(1H, dd, *J*=9.4&10.4), 5.61(1H, br d, *J*=10.4), 7.70(1H, ddd, *J*=1.4, 8.0&8.0), 7.80(1H, ddd, *J*=1.4, 8.0&8.0), 8.24(1H, dd, *J*=1.4&8.0), 8.25(1H, dd, *J*=1.4&8.0)
6	Wax	-7.6° (*c* 0.71, MeOH)	(CD_3OD) : δ 1.15(3H, d, *J*=6.4), 2.87(1H, dd, *J*=8.4&8.4), 2.89(3H, s), 4.24(1H, d, *J*=4.8), 4.35(1H, dq, *J*=6.4&8.4), 4.36(1H, dd, *J*=4.8&8.4), 7.61(1H, ddd, *J*=1.4, 8.0&8.0), 7.68(1H, ddd, *J*=1.4, 8.0&8.0), 8.15(1H, dd, *J*=1.4&8.0), 8.24(1H, dd, *J*=1.4&8.0)
7	Wax	-2.5° (*c* 0.71, MeOH)	(CD_3OD) : δ 1.27(3H, d, *J*=6.2), 2.65(1H, dd, *J*=7.6&11.0), 2.68(3H, s), 4.18(1H, dd, *J*=5.0&11.0), 4.24(1H, dq, *J*=6.2&7.6), 4.25(1H, d, *J*=5.0), 7.61(1H, ddd, *J*=1.4, 8.0&8.0), 7.67(1H, ddd, *J*=1.4, 8.0&8.0), 8.11(1H, dd, *J*=1.4&8.0), 8.25(1H, dd, *J*=1.4&8.0)
8•HCl	210-215 (decomp.)	+182° (*c* 1.18, MeOH)	(CD_3OD-DCl/D_2O) : δ 1.24(3H, d, *J*=6.2), 3.32(1H, dd, *J*=7.6&8.4), 3.44(3H, s), 4.09(1H, dd, *J*=4.8&7.6), 4.63(1H, dq, *J*=6.2&8.4), 5.14(1H, d, *J*=4.8)
9•HCl	Oil		α-Anomer (DCl/D_2O) : δ 1.18(3H, d, *J*=6.4), 3.53(1H, dd, *J*=7.8&8.4), 3.81(3H, s), 4.25(1H, dd, *J*=5.0&7.8), 4.81(1H, dq, *J*=6.4&8.4), 5.69(1H, d, *J*=5.0)
10•HCl	152-157	+102° (*c* 1.06, MeOH)	(CD_3OD-DCl/D_2O) : δ 1.35(3H, d, *J*=6.8), 3.85(3H, s), 3.99(1H, dd, *J*=9.0&11.2), 4.81(1H, d, *J*=11.2), 5.15(1H, dq, *J*=6.8&9.0)
11	Oil	-26° (*c* 1.12, $CHCl_3$)	($CDCl_3$) : δ 1.53(3H, d, *J*= 6.0), 2.83(1H, dd, *J*=9.6&11.2), 3.81(3H, s), 4.09(1H, d, *J*=11.2), 4.53(1H, dq, *J*=6.0&9.6)
12•HCl	202-206 (decomp.)	+85° (*c* 0.32, MeOH)	(CD_3OD-DCl/D_2O) : δ 1.39(3H, d, *J*=6.2), 2.99(1H, dd, *J*=7.8&10.0), 3.44(3H, s), 4.03(1H, dd, *J*=5.2&10.0), 4.42(1H, dq, *J*=6.2&7.8), 5.15(1H, d, *J*=5.2)
13•HCl	150-154	-14° (*c* 1.32, MeOH)	(CD_3OD-DCl/D_2O) : δ 1.54(3H, d, *J*=6.6), 3.65(1H, dd, *J*=2.4&8.6), 3.84(3H, s), 4.80(1H, d, *J*=8.6), 5.03(1H, dq, *J*=2.4&6.6)
14	171-174 (decomp.)	+12° (*c* 0.14, MeOH)	(DMSO-d_6) : δ 1.13(3H, d, *J*=6.2), 2.91(1H, dd, *J*=3.8&6.2), 3.54(1H, d, *J*=3.8), 3.57(3H, s), 4.04(1H, dq, *J*=6.2&6.2)
15	Wax	-33° (*c* 0.17, $CHCl_3$)	($CDCl_3$) : δ 0.12(9H, s), 0.28(9H, s), 1.24(3H, d, *J*=12.0), 3.31(1H, dd, *J*=6.0&6.0), 4.21(1H, d, *J*=6.0), 4.28(1H, dq, *J*=6.0&12.0)

exclusively the desired (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**1**) with removal of silyl groups. This was identical in all respects with the authentic sample[9,13], which was prepared from commercially available *O-tert*-butyldimethylsilyl derivative.

Overall, the yield was approximately 32% in 12 steps from **3**. Key steps include our developed skeletal rearrangement with ring-contraction, oxidation of the 2-aminofuranose, and stereoselective epimerization to the desired configurations.

Acknowledgment

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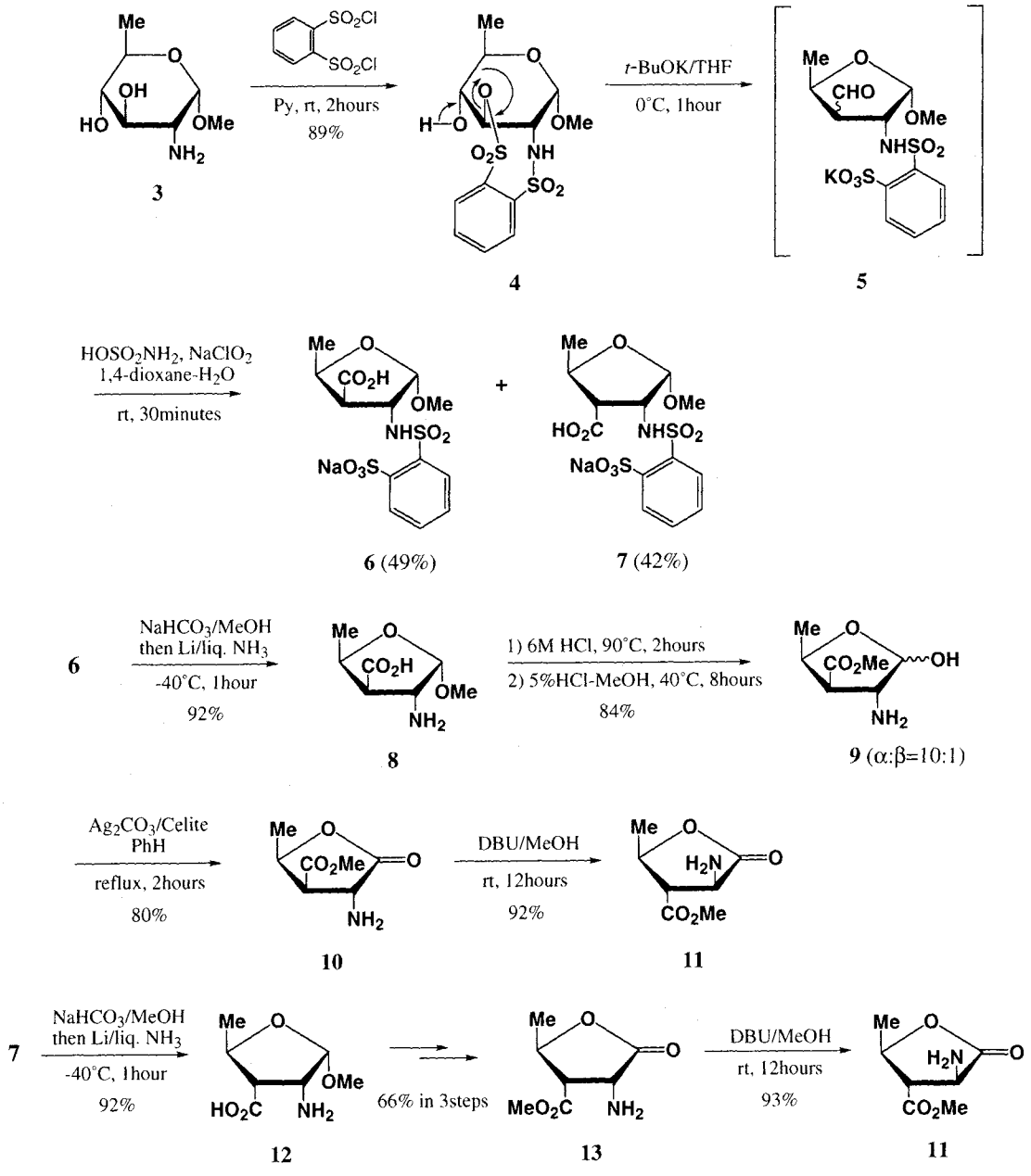
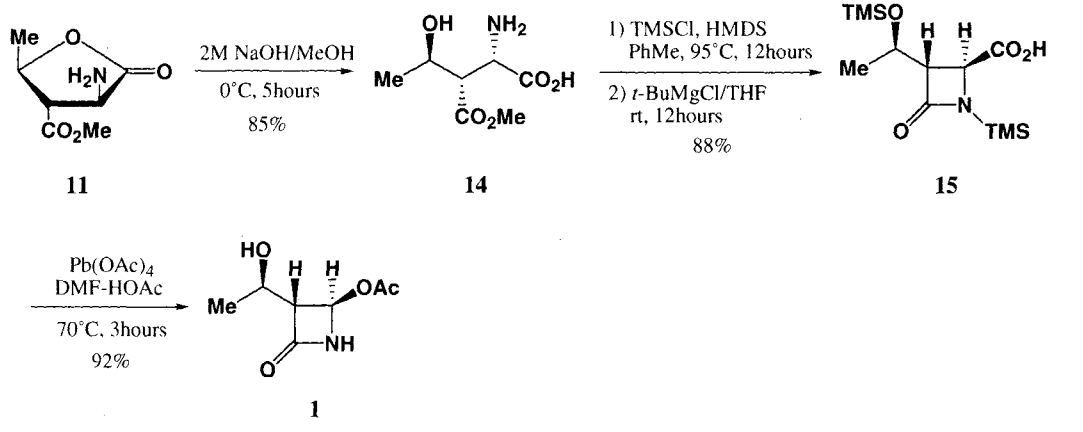
Scheme 1.



Scheme 2.



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