Synthetic Studies of Carbapenem and Penem Antibiotics. IV. Stereoselective Reduction of 3-Acetyl-2-azetidinone with Aminoalkoxyborane

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The transformation of 3-acetyl-2-azetidinone into 3-[(*R*)-1-hydroxyethyl]-2-azetidinone was achieved by highly stereoselective reduction with *N*-benzylaminoethoxyborane in the presence of trifluoroborane etherate. The combination of this reduction method and optical resolution using *l*-norephedrine provides a practical synthetic method for (3*S*,4*S*)-4-carboxy-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-2-azetidinone, which is a key intermediate in the synthesis of carbapenem and penem antibiotics.

Keywords 3-acetyl-2-azetidinone; 3-[(*R*)-1-hydroxyethyl]-2-azetidinone; stereoselective reduction; amine–borane complex; *N*-benzylaminoethoxyborane; optical resolution; *l*-norephedrine

(3*S*,4*S*)-4-Carboxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone derivative **1** is a versatile intermediate for the synthesis of carbapenem and penem antibiotics. This compound has been prepared by several efficient methods.[1] We previously reported on the utility of the [2+2] cycloaddition of diketene and the Schiff base **2** derived from *l*-menthyl glyoxylate and di-*p*-anisylmethylamine to provide optically active 3,4-*trans*-3-acetyl-2-azetidinone **3a**, which can be readily converted into **1a**.[2]

For the reduction of the acetyl group adjacent to the β-lactam carbonyl into an (*R*)-1-hydroxyethyl group, some highly stereoselective methods have been reported using potassium selectride–potassium iodide[3] and diisopropylaminoborane–magnesium trifluoroacetate.[1a,4] However, the application of these methods to large-scale production presents difficulties from the viewpoints of commercial availability and handling of the reaction agents on a large scale. The present work was undertaken in order to establish practical and effective means of preparing (3*S*,4*S*)-3-[(*R*)-1-hydroxyethyl]-2-azetidinone **4a** from **3a** by using reagents which are readily available and easy to handle. Here we describe the stereoselective reduction of **3a** by aminoalkoxyborane in the presence of trifluoroborane etherate (BF_3–Et_2O).

First, to search for an amine–borane complex which can produce **4a** having the desired stereochemistry, various types of amine–borane complex were prepared from commercially available amines and reduction of **3a** was examined in a mixture of toluene and tetrahydrofuran (THF) in the presence of BF_3–Et_2O at −5——10 °C. Some representative results are shown in Table I. The ratio of **4a** and **4b** in the resultant mixture was determined by high performance liquid chromatography (HPLC) analysis. Favorable results could be obtained with amine–borane complexes prepared using *N*-benzylethanolamine, *N*-methylethanolamine and *N*,*N*-dimethylethanolamine.

In order to improve the stereoselectivity, reaction conditions were examined by employing *N*-benzylaminoethoxyborane, which afforded the desired reduction product in good yield. As shown in Table II, the stereoselectivity was influenced by the amounts of BF_3–Et_2O and solvent. The use of 1.4 molar eq of BF_3–Et_2O and a 20-fold amount

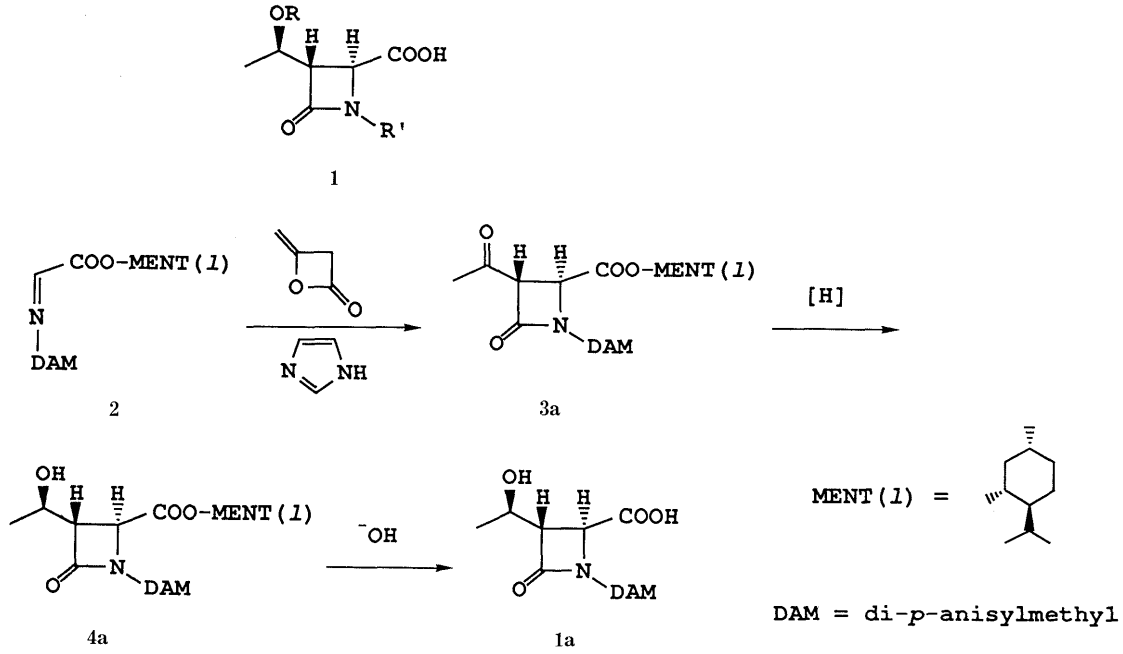

Chart 1

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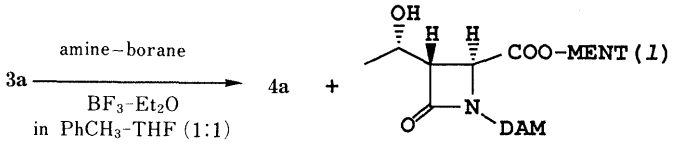
of a (1 : 1) mixture of toluene and THF to **3a** gave the best result. The stereoselectivity also depended on the molar ratio of *N*-benzylaminoethoxyborane. The optimum amount of this amine–borane complex was found to be 2.5 molar eq. The results with respect to reaction temperature indicated that the stereoselectivity was poor at lower temperature.

Furthermore, when BF_3–Et_2O was not used in the reaction, no stereoselectivity of the reduction was observed at all. Therefore, it seems that BF_3–Et_2O works by chelating with the 1,3-disposed carbonyl groups of the ketone and lactam and the reduction reaction proceeds stereoselectively owing to this chelation.

Based on these studies, a stereoselective reduction procedure for the acetyl group of **3a** could be established. That is, reduction of **3a** was carried out with *N*-benzylaminoethoxyborane (2.5 eq) in a (1 : 1) mixture of toluene and THF at −5——10 °C in the presence of BF_3–Et_2O (1.4 eq) to afford a diastereomeric mixture of **4a** and **4b** with the ratio of 86 : 14 in a quantitative yield. The desired isomer, (3*S*,4*S*)-3-[(*R*)-1-hydroxyethyl]-2-azetidinone **4a** could be readily obtained by crystallization of the mixture from *n*-hexane and diethyl ether. The *l*-menthyl



4b

Chart 2

TABLE I. Reduction[a] of **3a** with Amine–Borane Complex

3a → 4a + 4b

Entry	Amine	Yield (%)	Ratio (**4a**/**4b**)[b]
1	Et_3N	92	48/52
2	iso-Pr_2NH	92	45/55
3	$H_2NCH_2CH_2NH_2$	90	57/43
4	$H_2NCH_2CH_2CH_2OH$	85	38/62
5	$MeNHCH_2CH_2OH$	96	67/33
6	$PhCH_2NHCH_2CH_2OH$	Quant.	66/34
7	$Me_2NCH_2CH_2OH$	Quant.	65/35
8	$Et_2NCH_2CH_2OH$	94	62/38
9	*n*-$Pr_2NCH_2CH_2OH$	89	50/50
10	$H_2NCH_2CH_2NHCH_2CH_2OH$	Quant.	53/47

a) All reactions were performed at −5——10 °C in toluene–THF (1 : 1, 6 w/w of **3a**) using amine–borane (2.5 molar eq) and BF_3–Et_2O (5.6 molar eq) for 2 h. *b*) Determined by HPLC analysis.

TABLE II. Reduction[a] of **3a** with *N*-Benzylaminoethoxyborane

3a → 4a + 4b

Entry	BF_3–Et_2O (molar eq)	Solvent/**3a** (w/w)	Borane (molar eq)	Ratio (**4a**/**4b**)[b]
1	0.7	6	2.5	67/33
2	1.4	6	2.5	69/31
3	3.0	6	2.5	65/35
4	5.6	6	2.5	66/34
5	1.4	12	2.5	69/31
6	1.4	20	2.5	86/14
7	1.4	30	2.5	77/23
8	1.4	40	2.5	76/24
9	1.4	20	1.25	76/24
10	1.4	20	3.0	80/20
11	1.4	20	2.5	75/25 (at −45 °C)

a) All reactions were performed at −5——10 °C in toluene–THF (1 : 1) for 2 h except entry 11 and the mixture of **4a** and **4b** was obtained in 95%—quantitative yield. *b*) Determined by HPLC analysis.

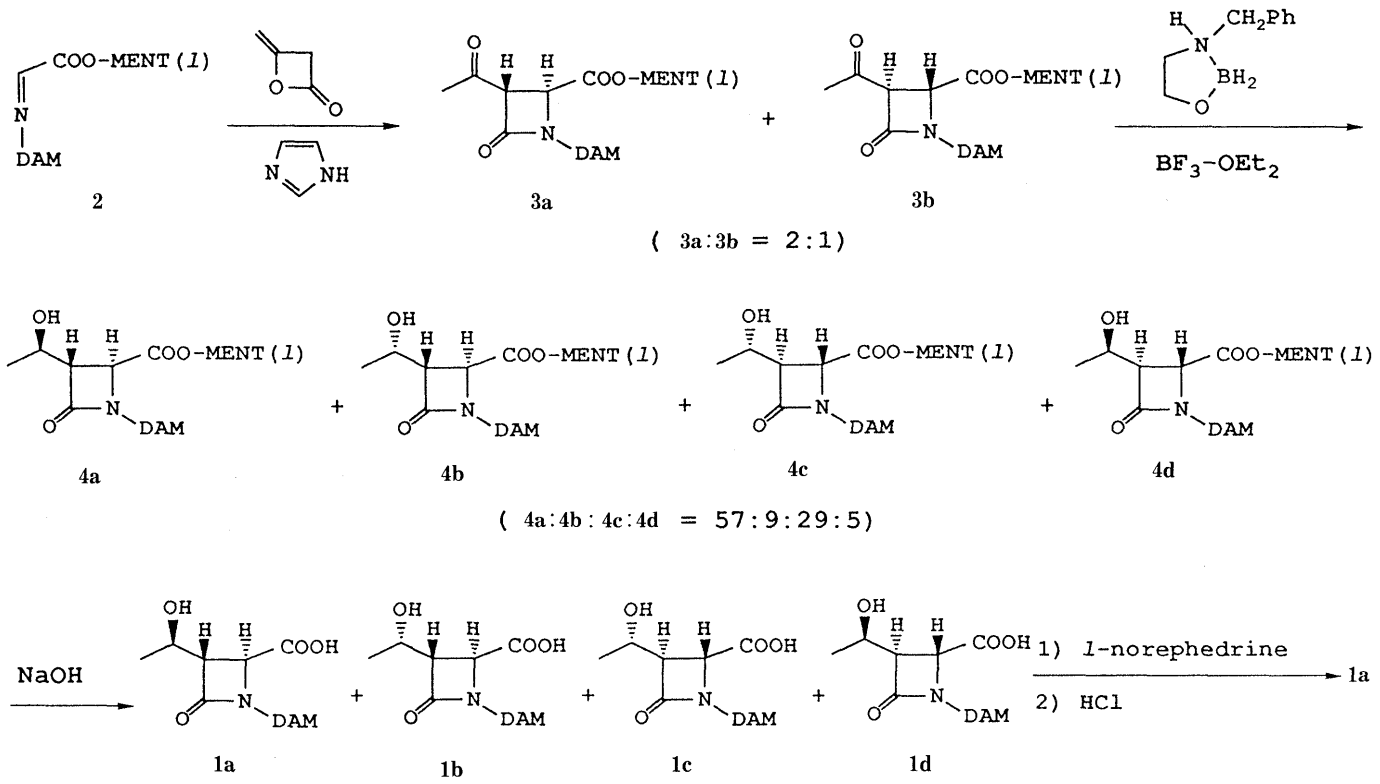


Chart 3

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ester of **4a** was easily hydrolyzed with 1 N NaOH in THF and MeOH to provide the optically active carboxylic acid **1a** in a quantitative yield.

Preparation of optically active **1a** from the mixture of **3a** and **3b** (2 : 1), the products of [2+2] cycloaddition of diketene and the Schiff base **2**, was studied to establish a practical method applicable to large-scale production. The mixture of **3a** and **3b** (2 : 1) was subjected to reduction with *N*-benzylaminoethoxyborane under the reaction condition described above to afford four stereoisomers of 3-(1-hydroxyethyl)-2-azetidinone (**4a**, **4b**, **4c**, **4d**), the ratio of which was determined to be 57 : 9 : 29 : 5 by HPLC analysis. The major product was the desired isomer **4a**, but it could not be isolated from the mixture of four isomers by crystallization. Therefore, after alkaline hydrolysis of **4**, we tried to isolate **1a** by optical resolution of the salts of the carboxylic acid **1** with various kinds of optically active amines. It was found that *l*-norephedrine afforded the most favorable result among the examined optically active amines, and the isolation of the *l*-norephedrine salt of **1a** could be achieved by crystallization from the mixture of salts in ethanol. Then, the salt was treated with 1 N HCl to give the optically active carboxylic acid **1a** as colorless crystals, mp 88—90 °C, $[\alpha]_D^{28}$ +10.7° (c=0.20, $CHCl_3$). Compound **1a** was obtained in 48% yield from the mixture of [2+2] cycloaddition products (**3a** and **3b** (2 : 1)) by reduction with *N*-benzylaminoethoxyborane following the optical resolution of the *l*-norephedrine salt. The overall yield of **1a** from the Schiff base **2** was 43%.

As mentioned above, we have succeeded in establishing a stereoselective reduction procedure for the 3-acetyl-2-azetidinone **3** using *N*-benzylaminoethoxyborane. A practical and effective synthetic route to **1a** starting from [2+2] cycloaddition of diketene and Schiff base **2** was developed by the combination of the above procedure with the stereoselective reduction and the optical resolution of the *l*-norephedrine salts. The present process is applicable to the large-scale production of **1a**.

Experimental

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were not corrected. Infrared (IR) spectra were measured on a Hitachi 260-10 IR spectrometer. ^{1}H-NMR spectra were recorded on a JEOL GX-270 (270 MHz) spectrometer. Chemical shift values are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ values). Measurements of optical rotation were performed with a JASCO DIP-181 digital polarimeter.

(3*S*,4*S*)-1-(Di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-4-(−)-menthyloxycarbonyl-2-azetidinone (4a) *N*-Benzylethanolamine (17.2 g, 0.114 mol) was added to a THF solution of diborane, which was prepared with sodium borohydride (3.6 g, 94.7 mmol) and BF_3–Et_2O (20.4 g, 0.144 mol) in THF (210 ml), at 0—10 °C and stirred for 4 h at the same temperature to give a THF solution of *N*-benzylaminoethoxyborane. (3*S*,4*S*)-3-Acetyl-1-(di-*p*-anisylmethyl)-4-(−)-methyloxycarbonyl-2-azetidinone **3a**[2] (20 g, 38.4 mmol) was dissolved in toluene (210 ml) and cooled to −5—−10 °C. To this toluene solution, BF_3–Et_2O (7.7 g, 54.2 mmol) was added at the same temperature and the mixture was stirred for 0.5 h. Subsequently, a THF solution of *N*-benzylaminoethoxyborane was added dropwise at −5—−10 °C over 2 h. The reaction mixture was stirred for 1 h at the same temperature, and acidified with 10% HCl (80 ml). The organic layer was separated, washed with saturated aqueous NaCl, then dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave a solid residue, which was a mixture of **4a** and **4b** (20 g). The ratio of **4a** and **4b** was found to be 86 : 14 by HPLC analysis. The mixture was purified by recrystallization from *n*-hexane and Et_2O to give pure **4a** as colorless crystals (11 g, 55%). mp 105—107 °C. $[\alpha]_D^{27}$ −17.2° (c=1.50, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with the reported data.[2]

(3*S*,4*S*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-2-azetidinone (1a) A 1 N NaOH solution (20.6 ml) was added to a solution of **4a** (7.19 g, 13.7 mmol) in THF (65 ml) and MeOH (55 ml) at room temperature and the mixture was stirred for 3 h at 35 °C. The reaction mixture was neutralized with 1 N HCl (20.6 ml), concentrated *in vacuo*, and diluted with toluene (35 ml) and 20% NaCl (100 ml). The mixture was alkalified with 1 N NaOH (31 ml). The aqueous layer was washed with toluene (30 ml), acidified with 1 N HCl (62 ml) and extracted with CH_2Cl_2 (35 ml). After re-extraction of the aqueous layer with CH_2Cl_2 (25 ml), the combined extracts were washed with 20% NaCl (25 ml), then dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave **1a** (5.25 g, quantitative yield). An analytical sample was prepared by crystallization with CH_2Cl_2–CCl_4. mp 86—88 °C. $[\alpha]_D^{28}$ +12.0° (c=0.21, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with the reported data.[5]

Resolution of the Mixture of (1′*R*,3*S*,4*S*)-, (1′*S*,3*S*,4*S*)-, (1′*S*,3*R*,4*R*)- and (1′*R*,3*R*,4*R*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-(1-hydroxyethyl)-2-azetidinone (1a—d) *l*-Norephedrine (48 g, 0.317 mol) was added to a suspension of a mixture of **1a**, **1b**, **1c** and **1d** (57 : 9 : 29 : 5) (102 g, 0.265 mol) in EtOH (1000 ml) with warming at 60 °C. After the mixture was completely dissolved, the solution was gradually cooled from 60 °C to 30 °C over 2 h and then kept at 0—5 °C for 4 h. The resulting white crystals were collected by filtration and recrystallized from EtOH to give the **1a**-*l*-norephedrine salt (39 g) as white crystals. mp 196—197 °C, $[\alpha]_D^{25}$ +7.96° (c=0.20, MeOH). *Anal.* Calcd for $C_{30}H_{36}N_2O_7$: C, 67.15; H, 6.76; N, 5.22. Found: C, 67.15; H, 6.86; N, 5.20. A suspension of the **1a**-*l*-norephedrine salt in CH_2Cl_2 (200 ml) was mixed with 1 N HCl (150 ml) and vigorously stirred for 1 h. After re-extraction of the aqueous layer with CH_2Cl_2 (150 ml), the combined extracts were washed with 20% NaCl (200 ml), dried over Na_2SO_4 and seeded with 10 mg of **1a** at room temperature. The resulting suspension was stirred for 2 h at the same temperature, then for 1 h with ice-water cooling. A precipitated solid was collected by filtration, and dried *in vacuo* at 30—40 °C to afford **1a** (28.1 g, 48% yield). mp 88—90 °C. $[\alpha]_D^{28}$ +10.7° (c=0.20, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with the reported data.[5]

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