Chem. Pharm. Bull. **39**(8) 1931—1938 (1991)

Synthetic Studies of Carbapenem and Penem Antibiotics. I. Facile Synthesis of a Key Intermediate: 4-Acetoxy-3-(1-hydroxyethyl)-2-azetidinone

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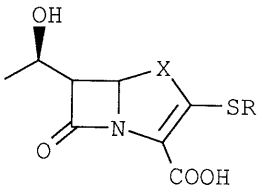
A highly efficient synthesis of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone, which is a key intermediate for the synthesis of carbapenem and penem antibiotics, was accomplished. It was found that oxymercuration-reduction of easily obtainable 4-alkyloxycarbonyl-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone could be employed as a key stereoselective reaction. The chiral starting material was obtained by optical resolution or asymmetric (2+2) cycloaddition. The desired product was afforded in four steps, that is, oxymercuration-reduction, oxidative decarboxylation, protection of the hydroxy group and removal of the N-protecting group.

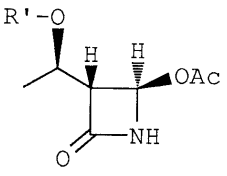
Keywords penem; carbapenem; (*R*)-1-hydroxyethyl group; (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone; (2+2) cycloaddition; oxymercuration-reduction; oxidative decarboxylation

Carbapenem and penem antibiotics **1** possess potent antibacterial activities as well as broad spectra of action. Therefore, much attention has been focused on synthetic studies of these compounds. In those studies, the (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone derivative **2** has been widely utilized as a versatile intermediate. Many methods for synthesizing **2** have been reported[1] (Fig. 1). For the purpose of total synthesis of **1**, we initiated studies on the synthesis of **2** by new methodology. We describe here a facile synthesis of **2**.

Synthetic Design We designed the synthetic strategy shown in Chart 1. We selected the 3-ethenyl-2-azetidinone **3** as the starting material, because **3** can be easily obtained by (2+2) cycloaddition reaction of crotonyl chloride and Schiff base.[2] The key point of this synthetic route was how to obtain a high stereoselectivity in the conversion of the ethenyl group to a 1-hydroxyethyl group. We presumed that this might be achieved by using the oxymercuration-reduction method, which is well known to proceed according to the Markownikoff rule. We considered that the side of the olefin attacked by mercuric acetate would be controlled simply by the steric hindrance of the substituent on C-4 and the desired *threo* isomer could be obtained as the major product.



1
X=CH_2, CH–Me, S

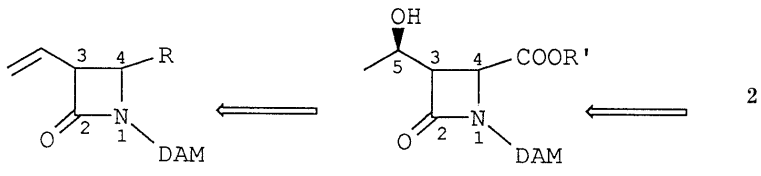


2
R′: protecting group

Fig. 1

Concerning the acetoxy group on C-4, we expected that conversion of the ester group on C-4 to an acetoxy group could be achieved by alkaline hydrolysis followed by oxidative decarboxylation with lead tetraacetate.

Preparation of 3 To study the stereoselectivity of the oxymercuration reaction, the 3-ethenyl-2-azetidinone **3** in racemic form was prepared as follows. The (2+2) cycloaddition reaction of crotonyl chloride and the Schiff base **6a**, prepared from di-*p*-anisylmethylamine (DAM-NH_2) **4** and *n*-butyl glyoxylate **5a**, was carried out in the presence of triethylamine in toluene to afford the *n*-butyl ester **3a** in 94% yield. The stereochemistry of **3a** was assigned as 3,4-*cis* on the basis of the coupling constant between H-3 and H-4 in the proton magnetic resonance (^{1}H-NMR) spectrum ($J_{3,4}$=5.8 Hz). The alkaline hydrolysis of the *cis*-isomer **3a** in aqueous tetrahydrofuran (THF) and methanol (MeOH) afforded the thermodynamically more stable *trans*-carboxylic acid **3b** ($J_{3,4}$=1.3 Hz) in 85% yield. To identify the epimerization site, alkaline hydrolysis was performed in CD_3OD and D_2O (5:1). It was found that the epimerization took place at C-3, because the signal of H-3 disappeared while the H-4 signal remained in the ^{1}H-NMR spectrum.[3] Compounds **3c**—**e** were obtained as follows. Compound **3b** was treated with *p*-methoxybenzyl chloride and triethylamine in dimethylformamide (DMF) to give the *p*-methoxybenzyl ester **3c** in 95% yield. Reduction of **3a** with lithium borohydride in THF gave the alcohol



3

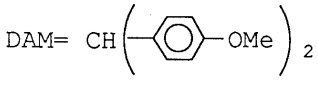


Chart 1

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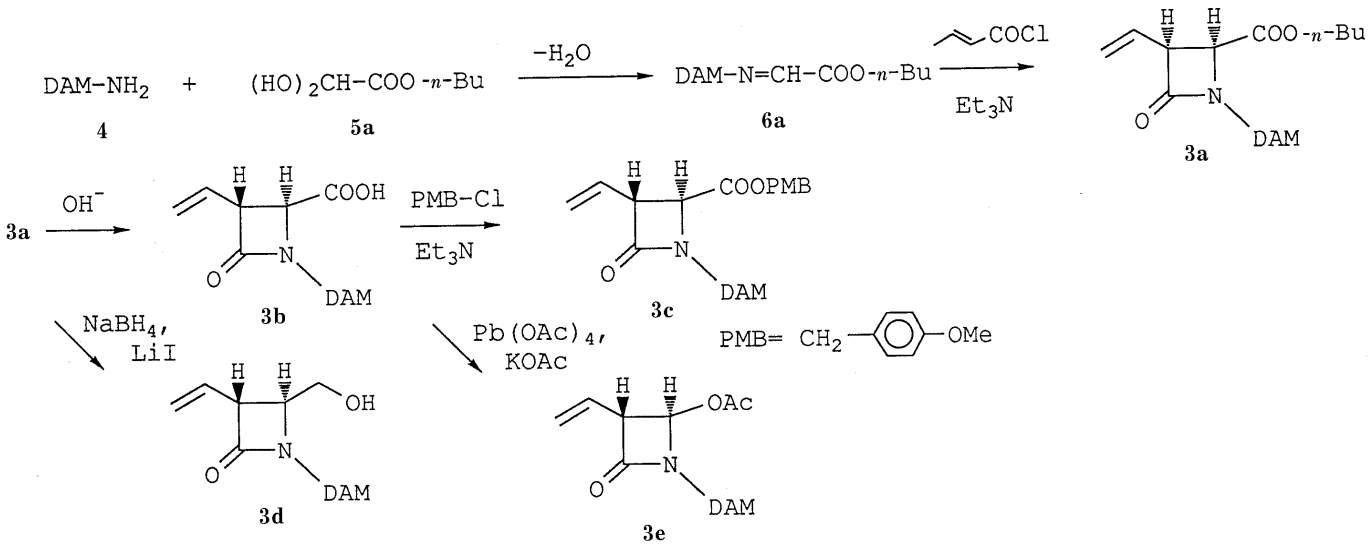
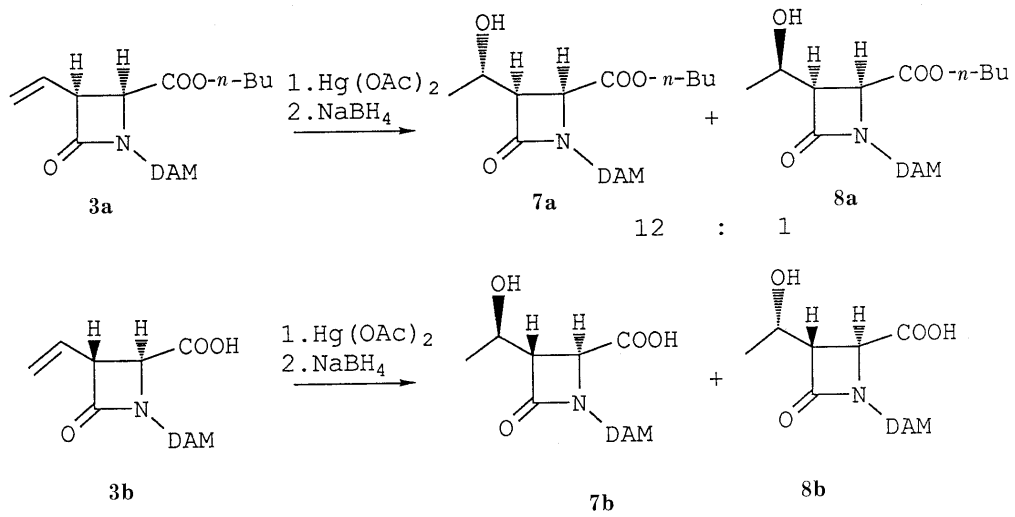


Chart 2



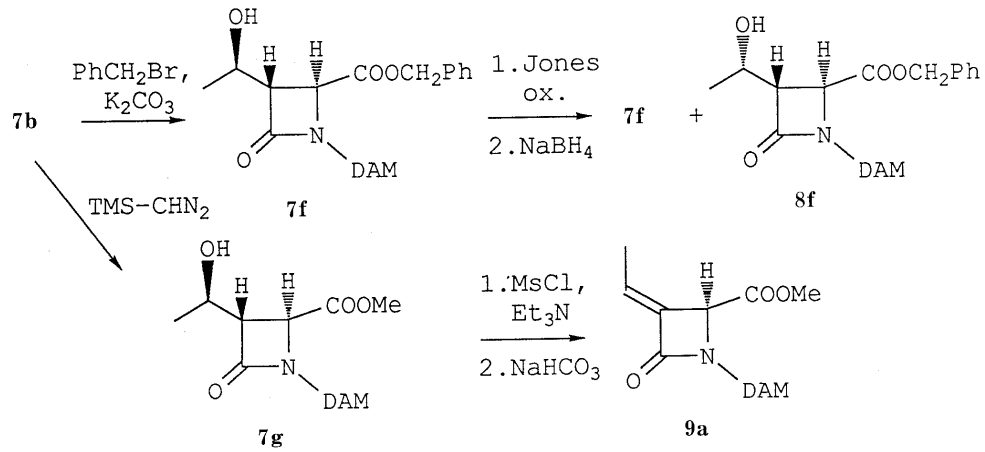


Chart 3

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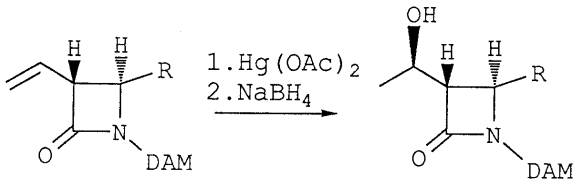
3d in 88% yield. The conversion of the carboxy group in **3b** to an acetoxy group was carried out with lead tetraacetate in the presence of potassium acetate in DMF to afford the acetate **3e** in a good yield[1b,4] (Chart 2).

Oxymercuration-Reduction Reaction of 3 The oxymercuration-reduction of the ethenyl group was investigated using β-lactams (**3a**—**e**) as shown in Charts 3 and 4. The treatment of **3a** with mercuric acetate in aqueous THF followed by reaction with sodium borohydride in the presence of alkali afforded 3-(1-hydroxyethyl)-2-azetidinone as a mixture of two isomers, **7a** and **8a**, in 85% yield. The ratio of **7a** and **8a** was determined to be 12 : 1 based on the integration of the H-3 signal in the ^{1}H-NMR. The major product **7a** was determined to be the 3,5-*threo* isomer based on the coupling constant between H-3 and H-5 in the ^{1}H-NMR ($J_{3,5}$=9.6 Hz in $CDCl_3$).[1e] Oxymercuration-reduction of the 3,4-*trans*-β-lactam **3b**, giving the diastereomeric products **7b** and **8b**, was performed in a similar manner to that of **3a**. The yield was 86% and the ratio of **7b** and **8b** determined by high performance liquid chromatography (HPLC) analysis was 80 : 1. In order to confirm that **8b** was the epimer of **7b** at C-5, the following transformation was examined. Esterification of **7b** with benzyl bromide and potassium carbonate in acetone gave **7f**, which was oxidized with Jones reagent and then reduced with sodium borohydride to give a 1 : 1 mixture of **7f** and **8f**. Compound **8f** could be separated from the mixture by preparative thin layer chromatography (preparative TLC) and converted into the corresponding carboxylic acid **8b** by hydrogenolysis. The minor product of the oxymercuration-reduction procedure was identified as **8b** derived from **7b** by HPLC analysis. Finally, the configurations of the 1-hydroxyethyl side chain in **7b** and **8b** were determined on the basis of the results of dehydration to the 3,5-ene derivatives.[5] After esterification of **7b** with trimethylsilyldiazomethane (TMS-CHN_2), the resultant methyl ester **7g** was mesylated and then treated with sodium bicarbonate in MeOH to afford **9a** exclusively in 67% yield. On the other hand, the same treatment of the methyl ester **8g** derived from **8b** gave a mixture of **9b** (47%) and **9a** (9%). Assignments by ^{1}H-NMR for the pair of ene lactams **9a** and **9b** were based on the anisotropic deshielding effect of the β-lactam carbonyl on the vinyl methyl group and the vinyl proton. The vinyl methyl group of **9a** appeared at δ 1.74, at higher field than that of **9b**, which appeared at δ 2.03. The vinyl proton of **9a** appeared at δ 6.26, at lower field than that of **9b**, which appeared at δ 5.74. Presuming *trans* coplanar elimination of methanesulfonic acid, it is concluded that the configuration of the 1-hydroxyethyl side chain of **7b** is 3,5-*threo* and that of **8b** is 3,5-*erythro* (Chart 3).

The oxymercuration-reduction of **3c**, **3d** and **3e** showed similar stereoselectivity to that of **3b** and afforded **7c** (90%), **7d** (85%) and **7e** (88%), respectively. The stereochemistry of **7c** and **7e** was determined by comparison with authentic samples derived from **7b** (Chart 4).

As described above, it was found that the conversion of the ethenyl group to a 1-hydroxyethyl group can be achieved highly stereoselectively, and the stereoselectivity was better in the case of *trans*-**3** (**3b**—**e**) than *cis*-**3** (**3a**). These results could not be completely explained by our presumption; that is, we considered that the conformation of the vinyl group



3c—**e** **7c**—**e**

c: R=COOPMB, **d**: R=CH_2OH, **e**: R=OAc

Chart 4

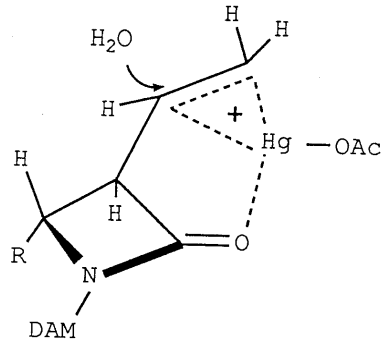


Fig. 2

was arranged so as to avoid the steric hindrance of the substituent on C-4. Mercuric acetate attacked from the less hindered side of the olefin, then a water molecule attacked from the opposite side and the subsequent reduction gave the *threo* isomer. If only the steric hindrance of the substituent at C-4 fixes the conformation of the vinyl group, the stereoselectivity would be higher in the case of *cis*-**3** (**3a**) than *trans*-**3** (**3b**—**e**). To explain the difference, other factors influencing the stereoselectivity should be considered. The extremely high stereoselectivity in the case of *trans*-**3** (**3b**—**e**) could probably be explained by postulating that in addition to the steric hindrance of the substituent (hydrogen atom) on C-4, mercuric acetate plays a role by coordinating with the carbonyl group of the β-lactam as well as the vinyl group[2c] (Fig. 2). The decrease of the stereoselectivity in the case of *cis*-**3** (**3a**) could be explained by the additional participation of the interaction between mercuric acetate and the carbonyl group of the ester group on C-4.

Preparation of Optically Active 3b With the aim of synthesizing optically pure **2**, the preparation of optically active **3b** was attempted by two methods, optical resolution and asymmetric (2+2) cycloaddition reaction. The optical resolution of **3b** was examined as follows. Compound **3b** was treated with oxalyl chloride and then with *l*-menthol in the presence of *N*,*N*-dimethylaminopyridine and triethylamine to afford a diastereomeric mixture of *l*-menthyl esters **10a** and **10b** (1 : 1, determined by HPLC: Lichrosorb SI-60, 1.5% iso-propanol in *n*-hexane). The recrystallization of the mixture from MeOH gave crystalline (3*R*,4*S*)-*l*-menthyl ester **10a** in an optically pure form (mp 114—115 °C, $[\alpha]_D^{22}$ +20.2° (*c*=0.26, $CHCl_3$)). The alkaline hydrolysis of **10a** with sodium hydroxide gave the corresponding acid (+)-**3b** ($[\alpha]_D^{22}$ +63.3° (*c*=0.12, $CHCl_3$)), which was converted into the methyl ester **11** using TMS-CHN_2.

Asymmetric (2+2) cycloaddition reactions using chiral Schiff bases were investigated as shown in Chart 6. This approach was found to be effective for the preparation of

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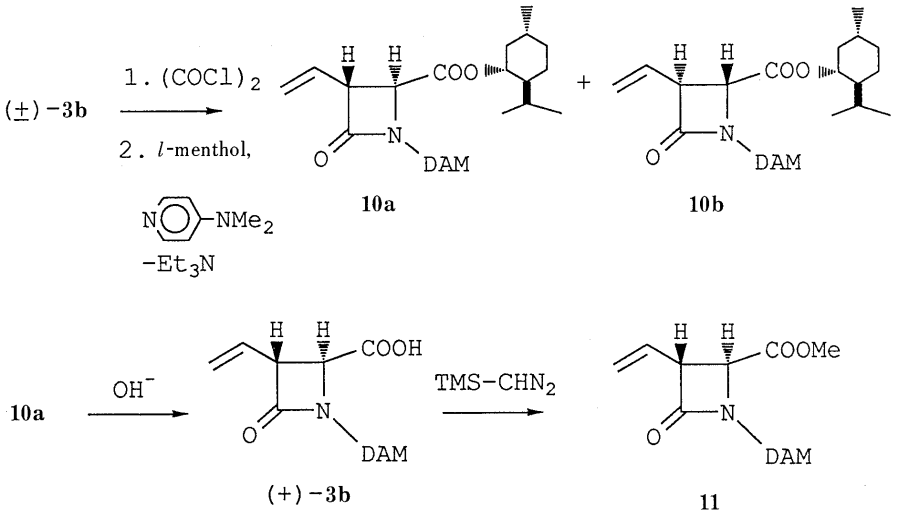
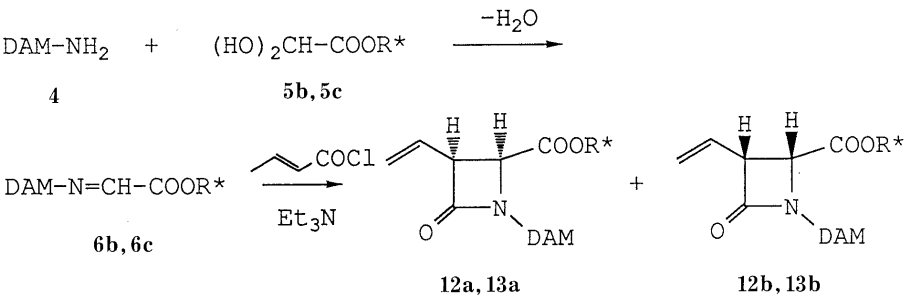


Chart 5



5b, 6b, 12a, 12b : R* = *l*-menthyl, **12a** : **12b** = 1 : 2

5c, 6c, 13a, 13b : R* = *d*-menthyl, **13a** : **13b** = 2 : 1

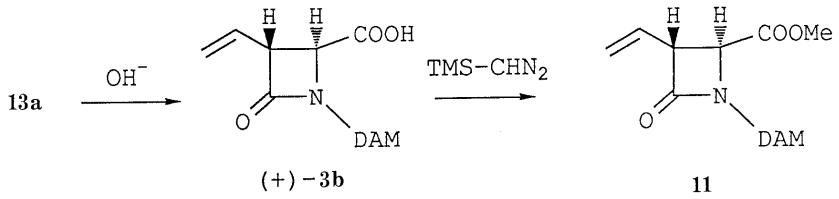


Chart 6

optically active **3b**.

First, a preliminary study was carried out using *l*-menthyl glyoxylate **5b**[6] and it was found that the undesired (3*R*,4*R*) isomer was the major product. That is, the Schiff base **6b**, prepared from DAM-NH_2 **4** and **5b**, was treated with crotonyl chloride to afford a mixture of **12a** and **12b** in the ratio of 1 : 2 (by HPLC analysis: Lichrosorb SI-60, 1.0% iso-propanol in *n*-hexane) in 92% yield. The structures of **12a** and **12b** were confirmed by derivatizing the mixture of **12a** and **12b** (2 : 5) to a mixture of **10a** and **10b** (**10a** : **10b** = 2 : 5.2, by HPLC analysis) by alkaline hydrolysis and esterification with *l*-menthol. Therefore, the *d*-menthyl moiety was selected as the chiral auxiliary in the asymmetric synthesis. A mixture of *d*-menthyl esters **13a** and **13b** was obtained in 82% yield using *d*-methyl glyoxylate **5c** in a similar manner to that described above. The ratio of **13a** and **13b** was 2 : 1 by HPLC analysis. Pure **13a** was obtained by recrystallization from MeOH. Then alkaline hydrolysis of **13a** gave the desired (+)-**3b**. The treatment of (+)-**3b** with TMS-CHN_2 gave the methyl ester **11**, which was identical with that obtained from **10a**.

Preparation of 2 Optically active (+)-**3b** was converted into the (*R*)-1-hydroxyethyl derivative (+)-**7b** (86%) by the treatment of (+)-**3b** with mercuric acetate and then with sodium borohydride. Transformation of (+)-**7b** into 4-acetoxy-3-(1-hydroxyethyl)-2-azetidinones **2** could be achieved through three reactions, that is, 1) oxidative decarboxylation to give an acetoxy group,[1b,4] 2) protection of the hydroxy group and 3) deprotection of the N-protecting group, di-*p*-anisylmethyl (DAM).[7] These reactions could be carried out in any sequence. Among the practical routes, the route from (+)-**7b** *via* (+)-**7e** seemed

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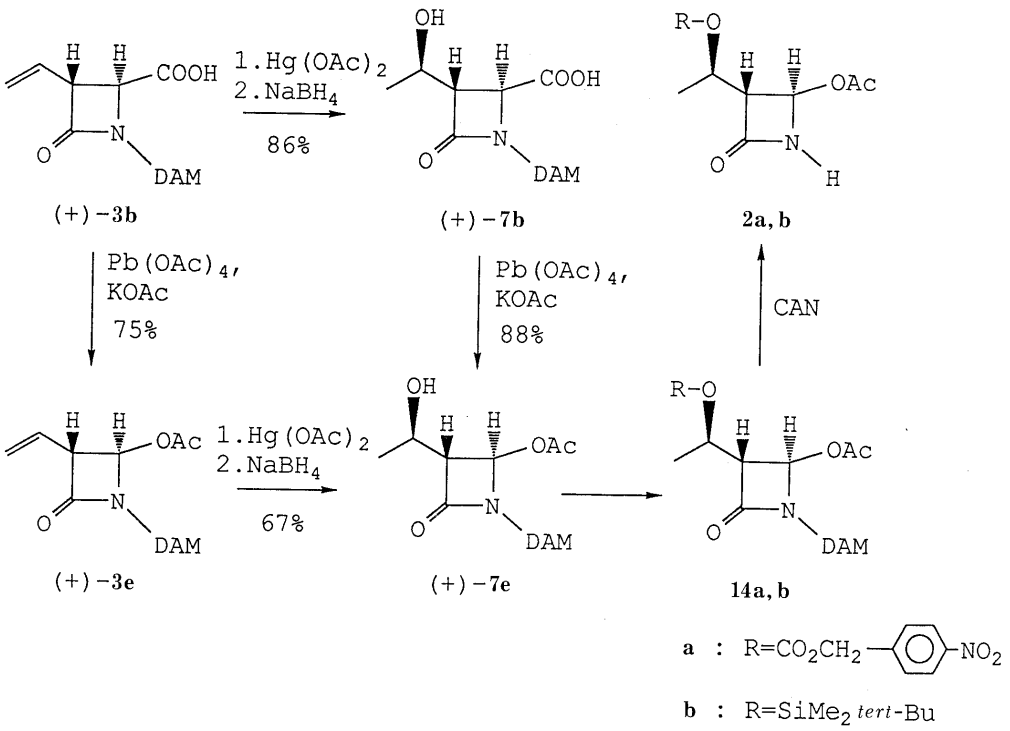

Chart 7

to be preferable because it gave the best overall yield. Thus, oxidative decarboxylation of (+)-**7b** to the acetate (+)-**7e** was accomplished by treatment with lead tetraacetate in a mixture of DMF and toluene in the presence of potassium acetate in 88% yield. The protection of the hydroxy group of (+)-**7e** with *p*-nitrobenzyl chloroformate in the presence of *N*,*N*-dimethylaminopyridine afforded **14a** in 90% yield and with *tert*-butyldimethylsilyl chloride in the presence of imidazole afforded **14b** in 86% yield. Subsequently the DAM group of **14a** and **14b** was oxidatively removed with cerium(IV) ammonium nitrate (CAN) in acetonitrile (MeCN) and water (9 : 1) to furnish the key intermediate **2a** ($[\alpha]_D^{22}$ +36.6° (c=0.09, $CHCl_3$)) in 94% yield and **2b** (mp 100—102 °C, $[\alpha]_D^{26}$ +48.2° (c=1.01, $CHCl_3$))[1a,c,d] in 68% yield, respectively.

The synthetic route from (+)-**3b** by way of (+)-**3e** and (+)-**7e** was also examined but the overall yield was less than that of the above route.

Conclusion

In summary, we have succeeded in establishing an effective method to synthesize **2**, which serves as a useful intermediate for the preparation of penem and carbapenem antibiotics. Taking into account the high stereoselectivity in the oxymercuration-reduction procedure and the use of easily obtainable 3-ethenyl-2-azetidinone as a starting material, the overall process is one of the most practical routes so far developed for preparing **2**.

Experimental

Melting points were measured using a Thomas-Hoover capillary melting point apparatus and were not corrected. Infrared (IR) spectral measurements were carried out with a Hitachi 260-10 infrared spectrometer. ^{1}H-NMR spectra were measured with a JEOL FX-90Q (90 MHz) and GX-270 (270 MHz) spectrometers. Chemical shift values are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ-values). Mass spectra (MS) were taken with a Hitachi M-80B mass spectrometer. Measurements of optical rotation were performed with a JASCO DIP-181 digital polarimeter. Silica gel 60 (70—230 mesh, E. Merck) was used as an adsorbent for column chromatography. Preparative TLC was performed on Silica gel 60 F_{254} TLC plates (E. Merck).

Preparation of 3-Ethenyl-2-azetidinone (3) (3*RS*,4*RS*)-4-*n*-Butoxycarbonyl-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone (**3a**): A mixture of di-*p*-anisylmethylamine (10.0 g, 41.2 mmol) and *n*-butylglyoxylate monohydrate (7.3 g, 49.3 mmol) in toluene (600 ml) was dehydrated azeotropically under reflux to give a solution of the Schiff base **6a**. After addition of triethylamine (Et_3N) (6.2 g, 61.3 mmol), a solution of crotonyl chloride (5.1 g, 49.5 mmol) in toluene (25 ml) was added dropwise at 70 °C over 1 h, followed by stirring for 2 h at the same temperature. The reaction mixture was cooled to 10 °C and washed successively with 2 N HCl, 5% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **3a** as a viscous oil (16.5 g, 94%). IR (neat): 1762, 1735 (sh), 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 1.27 (2H, m), 1.46 (2H, m), 3.78 (3H, s), 3.80 (3H, s), 3.97 (1H, d, J=5.8 Hz), 4.00 (2H, m), 4.14 (1H, d, J=5.8 Hz), 5.27—5.43 (2H, m), 5.69—5.82 (1H, m), 5.80 (1H, s), 6.81—6.90 (4H, m), 7.15 (2H, d, J=8.8 Hz), 7.29 (2H, d, J=8.8 Hz). MS (EI) m/z: 423 (M^+).

(3*RS*,4*SR*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone (**3b**): A 1 N NaOH solution (42 ml) was added to a solution of **3a** (16.9 g, 40 mmol) in THF (600 ml) and MeOH (500 ml) at room temperature, and the mixture was stirred for 2 h. After neutralization with 2 N HCl (22 ml), the reaction mixture was reduced to a quarter of the original volume *in vacuo*. The residue was diluted with 1 N NaOH (42 ml) and brine (450 ml), and washed with toluene (200 ml × 2). The alkaline aqueous layer was acidified with 2 N HCl (47 ml) and extracted with toluene (400 ml × 2). The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give **3b** as a viscous oil (12.5 g, 85%). IR ($CHCl_3$): 1753, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 3.84 (3H, s), 3.85 (1H, d, J=1.3 Hz), 5.30—5.43 (2H, m), 5.80—5.99 (1H, m), 5.84 (1H, s), 6.82—6.86 (4H, m), 7.15 (2H, d, J=8.6 Hz), 7.23 (2H, d, J=8.2 Hz). *Anal.* Calcd for $C_{21}H_{21}NO_5 \cdot H_2O$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.30; H, 5.57; N, 3.60.

(3*RS*,4*SR*)-1-(Di-*p*-anisylmethyl)-3-ethenyl-4-*p*-methoxybenzyloxycarbonyl-2-azetidinone (**3c**): Et_3N (3.30 g, 33.0 mmol) and *p*-methoxybenzyl chloride (5.12 g, 33.0 mmol) were added to a solution of **3b** (10.0 g, 27.0 mmol) in DMF (50 ml). The reaction mixture was stirred for 20 h at 70 °C, diluted with AcOEt, and washed successively with water, 2 N HCl, and aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography

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on silica gel to give **3c** as a viscous oil (12.5 g, 95%). IR (neat): 1762, 1740 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (3H, s), 3.78 (3H, s), 3.81 (3H, s), 3.7—3.9 (2H, m), 4.88 (2H, m), 5.2—5.45 (2H, m), 5.75—6.00 (1H, m), 5.85 (1H, s), 6.80 (2H, d, J=8.9 Hz), 6.83 (2H, d, J=8.9 Hz), 6.86 (2H, d, J=8.9 Hz), 7.08 (2H, d, J=8.9 Hz), 7.16 (2H, d, J=8.9 Hz), 7.20 (2H, d, J=8.9 Hz). MS (FD) m/z: 487 (M^+).

(3*RS*,4*RS*)-1-(Di-*p*-anisylmethyl)-3-ethenyl-4-hydroxymethyl-2-azetidinone (**3d**): LiI (317 mg, 2.36 mmol) and $NaBH_4$ (90 mg, 2.36 mmol) were added in portions to a solution of **3a** (500 mg, 1.18 mmol) in THF (8 ml). The mixture was refluxed for 4 h, concentrated *in vacuo*, and diluted with AcOEt and brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **3d** as a viscous oil (367 mg, 88.0%). IR (neat): 3420 (br), 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (2H, m), 3.63 (1H, m), 3.71 (1H, m), 3.81 (3H, s), 3.82 (3H, s), 5.1—6.0 (3H, m), 6.02 (1H, s), 6.88 (2H, d, J=8.9 Hz), 6.90 (2H, d, J=8.9 Hz), 7.22 (4H, d, J=8.6 Hz). MS (FD) m/z: 353 (M^+).

(3*RS*,4*RS*)-4-Acetoxy-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone (**3e**): Lead tetraacetate (2.17 g, 4.90 mmol) was added in portions to a solution of **3b** (1.50 g, 4.10 mmol) and AcOK (0.80 g, 8.2 mmol) in DMF (7.5 ml) with stirring at room temperature. After being stirred for 1 h, the reaction mixture was diluted with water and AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **3e** as a viscous oil (1.17 g, 75%). IR ($CHCl_3$): 1760, 1735 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, s), 3.79 (6H, s), 5.0—5.7 (3H, m), 5.74 (1H, d, J=1.4 Hz), 5.91 (1H, s), 6.7—7.4 (8H, m). MS (FD) m/z: 381 (M^+).

Oxymercuration-Reduction of 3 (Preparation of 7) (3*SR*,4*SR*)-4-*n*-Butoxycarbonyl-1-(di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-2-azetidinone (**7a** and **8a**): A mixture of **3a** (4.2 g, 10 mmol) and mercuric acetate (3.2 g, 10 mmol) in THF (10 ml) and water (4 ml) was stirred at 25 °C for 1 h. After addition of 1 N NaOH (9 ml) at 0 °C, a solution of $NaBH_4$ (0.4 g) in 1 N NaOH (2 ml) was added dropwise at the same temperature and the whole was stirred for 20 min. The reaction mixture was neutralized with 1 N HCl, diluted with Et_2O and filtered over Celite to remove insoluble materials. The organic layer was washed successively with 10% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give a mixture of **7a** and **8a** (12 : 1) as a viscous oil (3.75 g, 85%). IR (neat): 3470 (br), 1740 (br), 1720 (sh), 1607 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 1.2—1.4 (2H, m), 1.38 (3H, d, J=5.9 Hz), 1.4—1.6 (2H, m), 2.02 (1H, d, J=4.3 Hz), 3.20 (1H × 1/13, m), 3.39 (1H × 12/13, dd, J=5.6, 9.6 Hz), 3.78 (3H, s), 3.80 (3H, s), 4.01 (2H, m), 4.12 (1H × 12/13, d, J=5.6 Hz), 5.77 (1H × 12/13, s), 5.86 (1H × 1/13, s), 6.84 (2H, d, J=8.6 Hz), 6.87 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.26 (2H, d, J=8.6 Hz). MS (EI) m/z: 441 (M^+).

Compounds **7b—e** were obtained a similar manner to that described for **7a**.

(3*SR*,4*SR*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-2-azetidinone (**7b**): Amorphous powder (86% yield). It contained a small amount of the 3,5-*erythro* isomer **8b** (**7b** : **8b** > 80 : 1 by HPLC). IR (Nujol): 3250, 1750, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=6.6 Hz), 3.23 (1H, m), 3.76 (3H, s), 3.77 (3H, s), 4.16 (1H, d, J=2.6 Hz), 5.83 (1H, s), 6.83 (2H, d, J=8.9 Hz), 6.84 (2H, d, J=8.9 Hz), 7.18—7.26 (4H, m).

(3*SR*,4*SR*)-1-(Di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-4-*p*-methoxybenzyloxycarbonyl-2-azetidinone (**7c**): Viscous oil (90% yield). IR ($CHCl_3$): 3400, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6.0 Hz), 3.13 (1H, dd, J=2.2, 3.4 Hz), 3.73 (3H, s), 3.76 (3H, s), 3.84 (3H, s), 4.12 (1H, d, J=2.2 Hz), 4.88 (2H, s), 5.82 (1H, s), 6.66—7.50 (12H, m). MS (FD) m/z: 505 (M^+).

(3*SR*,4*SR*)-1-(Di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-4-hydroxymethyl-2-azetidinone (**7d**): Viscous oil (85% yield). IR ($CHCl_3$): 3425, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6.0 Hz), 3.33 (4H, m), 3.75 (6H, s), 5.87 (1H, s), 6.60—7.40 (8H, m). MS (FD) m/z: 371 (M^+).

(3*RS*,4*RS*)-4-Acetoxy-1-(di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-2-azetidinone (**7e**): Viscous oil (67% yield). IR ($CHCl_3$): 1752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.27 Hz), 3.11 (1H, dd, J=0.7 Hz, 6.6 Hz), 3.79 (3H, s), 3.80 (3H, s), 4.10 (1H, m), 5.80 (1H, d, J=0.7 Hz), 5.93 (1H, s), 6.86 (2H, d, J=8.9 Hz), 6.87 (2H, d, J=8.9 Hz), 7.15 (2H, d, J=8.6 Hz), 7.23 (2H, d, J=8.6 Hz). MS (FD) m/z: 399 (M^+).

Determination of Stereochemistry in 7b and 8b (3*SR*,4*SR*)-4-Benzyloxycarbonyl-1-(di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-2-azetidinone (**7f**): K_2CO_3 (5.52 g, 40 mmol) was added to a solution of **7b** (7.7 g, 20 mmol) and benzyl bromide (4.1 g, 24 mmol) in acetone (100 ml). After being refluxed for 2.5 h, the reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in AcOEt. This solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallized from hexane to give **7f** (9.47 g, quantitative yield). IR (KBr): 3424, 1741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6.3 Hz), 3.21 (1H, dd, J=2.3, 3.3 Hz), 3.76 (3H, m), 3.77 (3H, m), 4.14 (1H, d, J=2.3 Hz), 4.28 (1H, m), 4.96 (2H, s), 5.84 (1H, s), 6.79 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.9 Hz), 7.1—7.4 (9H, m). *Anal.* Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.47; H, 6.13; N, 2.95.

(3*SR*,4*SR*)-4-Benzyloxycarbonyl-1-(di-*p*-anisylmethyl)-3-[(*SR*)-1-hydroxyethyl]-2-azetidinone (**8f**): a) Jones reagent (1.5 g) was added to a solution of **7f** (950 mg, 2.0 mmol) in acetone (15 ml) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, diluted with AcOEt and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the corresponding ketone (950 mg, quantitative yield). This was used for the next treatment without purification. IR (Nujol): 1762, 1739, 1719 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.73 (6H, s), 4.19 (1H, d, J=2 Hz), 4.45 (1H, d, J=2 Hz), 4.87 (2H, s), 5.80 (1H, s), 6.50—7.4 (13H, m).

b) A solution of $NaBH_4$ (76 mg, 2.0 mmol) in water (2 ml) was added to a solution of the crude ketone in iso-propanol (30 ml) at 0 °C. The mixture was warmed to room temperature, diluted with $CHCl_3$ and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a mixture of **7f** and **8f** (1.01 g). The crude mixture (45 mg) was purified by preparative TLC (benzene–Et_2O (1 : 1)) to give **8f** as a viscous oil (15.6 mg). IR (neat): 3470, 1742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, J=6.3 Hz), 3.20 (1H, dd, J=2.3, 5.3 Hz), 3.76 (3H, s), 3.78 (3H, s), 3.94 (1H, d, J=2.3 Hz), 4.09 (1H, m), 4.96 (2H, m), 5.84 (1H, s), 6.7—6.9 (4H, m), 7.1—7.4 (9H, m). MS (FD) m/z: 475 (M^+).

(3*SR*,4*SR*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-[(*SR*)-1-hydroxyethyl]-2-azetidinone (**8b**): A solution of **8f** (15 mg, 0.32 mmol) in AcOEt (5 ml) containing 10 mg of 10% Pd–C was stirred at room temperature for 3.5 h under a hydrogen atmosphere. After filtration, the filtrate was concentrated *in vacuo* to give **8b** as a viscous oil (12 mg, quantitative yield). IR (neat): 3360, 1738, 1718 (sh), 1700 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.6 Hz), 3.24 (1H, dd, J=2.3, 5.6 Hz), 3.77 (3H, s), 3.78 (3H, s), 3.90 (1H, d, J=2.3 Hz), 4.12 (1H, m), 5.79 (1H, s), 6.77 (2H, d, J=8.9 Hz), 6.79 (2H, d, J=8.9 Hz), 7.19 (2H, d, J=8.6 Hz), 7.24 (2H, d, J=8.6 Hz). MS (FD) m/z: 385 (M^+).

(3*SR*,4*SR*)-1-(Di-*p*-anisylmethyl)-3-[(*RS*)-1-hydroxyethyl]-4-methoxycarbonyl-2-azetidinone (**7g**): A 10% solution of trimethylsilyldiazomethane (TMS-CHN_2) in hexane (0.6 mmol) was added to a solution of **7b** (77 mg, 0.2 mmol) in MeOH (1 ml). The mixture was stirred for 1 h and concentrated *in vacuo*. The residue was purified by preparative TLC (toluene–AcOEt (1 : 1)) to give **7g** (80 mg, quantitative yield). IR (neat): 3430 (br), 1750 (sh), 1738, 1602, 1504 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=6.6 Hz), 3.21 (1H, dd, J=2.3, 4.0 Hz), 3.52 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 4.14 (1H, d, J=2.3 Hz), 4.28 (1H, m), 5.87 (1H, s), 6.75—6.95 (4H, m), 7.05—7.35 (4H, m). *Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.24; H, 6.39; N, 3.51.

(3*SR*,4*SR*)-1-(Di-*p*-anisylmethyl)-3-[(*SR*)-1-hydroxyethyl]-4-methoxycarbonyl-2-azetidinone (**8g**): Treatment of **8b** (15 mg, 0.039 mmol), prepared from **7b**, as described above gave **8g** (12.5 mg, 80%). IR (neat): 3450 (br), 1750 (sh), 1738 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, J=6.6 Hz), 3.21 (1H, dd, J=2.3, 5.3 Hz), 3.54 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 3.94 (1H, d, J=2.3 Hz), 4.11 (1H, m), 5.86 (1H, s), 6.75—6.95 (4H, m), 7.10—7.40 (4H, m). MS (FD) m/z: 399 (M^+).

1-(Di-*p*-anisylmethyl)-(*E*)-3-ethylidene-4*SR*-methoxycarbonyl-2-azetidinone (**9a**): A solution of MsCl (17 mg, 0.15 mmol) in CH_2Cl_2 (0.5 ml) was added to a solution of **7g** (40 mg, 0.1 mmol) and Et_3N (20 mg, 0.2 mmol) in CH_2Cl_2 (1.5 ml) at 0 °C. The mixture was stirred for 30 min, quenched with dilute HCl and extracted with CH_2Cl_2. The organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the corresponding mesylate. A solution of the mesylate in MeOH (0.8 ml) was treated with $NaHCO_3$ (8 mg, 0.1 mmol) and the mixture was refluxed for 30 min, then concentrated *in vacuo*. The residue was purified by preparative TLC (toluene–AcOEt (2 : 1)) to give **9a** as a viscous oil (12.2 mg, 67%). IR (neat): 1756, 1608, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, dd, J=0.7, 7.3 Hz), 3.55 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 4.48 (1H, dd, J=0.7, 1.7 Hz), 5.95 (1H, s), 6.26 (1H, dq, J=1.7, 7.3 Hz), 6.85 (2H, d, J=8.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz). MS (EI) m/z: 381 (M^+).

1-(Di-*p*-anisylmethyl)-(*Z*)-3-ethylidene-4*SR*-methoxycarbonyl-2-azetidinone (**9b**): Treatment of **8f** (7.8 mg, 0.02 mmol), prepared from **8b**, as described above gave **9b** (3.6 mg, 47%) and **9a** (0.7 mg, 9%) as viscous

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oils. **9b**: IR (neat): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, dd, J=1.0, 7.3 Hz), 3.59 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 4.34 (1H, m), 5.74 (1H, dq, J=1.3 Hz, 7.3 Hz), 5.90 (1H, s), 6.85 (2H, d, J=8.7 Hz), 6.87 (2H, d, J=8.7 Hz), 7.16 (2H, d, J=8.7 Hz), 7.26 (2H, d, J=8.7 Hz). MS (EI) m/z: 381 (M^+).

Preparation of Optically Active 3b. Method A: Optical Resolution (3*R*,4*S*)-1-(Di-*p*-anisylmethyl)-3-ethenyl-4-(*l*-menthyloxycarbonyl)-2-azetidinone (**10a**): A solution of oxalyl chloride (4.82 g, 38 mmol) in CH_2Cl_2 (10 ml) was added dropwise over 20 min to a solution of (±)-**3b** (11.66 g, 31.8 mmol) in CH_2Cl_2 (80 ml) containing DMF (1.2 g) at room temperature, followed by stirring for 1.5 h. The resulting acid chloride solution was added dropwise to a mixture of *l*-menthol (6.96 g, 44.6 mmol), Et_3N (8.58 g, 85 mmol) and *N*,*N*-dimethylaminopyridine (0.516 g, 4.2 mmol) in CH_2Cl_2 (10 ml) at 0 °C and the whole was stirred at the same temperature for 2 h. The reaction mixture was diluted with toluene (200 ml) and washed with brine. The organic layer was washed successively with 2 N HCl, 10% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from MeOH to give a mixture of two diastereomers of *l*-menthyl ester (**10a** and **10b**, **10a**:**10b**=*ca.* 1:1) as a crystalline material (11.7 g, 73%). mp 96—97 °C. IR ($CHCl_3$): 1760, 1740 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H×1/2, d, J=6.9 Hz), 0.71 (3H×1/2, d, J=6.9 Hz), 0.83 (3H×1/2, d, J=6.9 Hz), 0.85 (3H×1/2, d, J=6.9 Hz), 0.88 (3H, d, J=6.6 Hz), 0.89 (3H, d, J=6.6 Hz), 0.6—1.9 (9H, m), 3.78 (3H, s), 3.79 (3H, s), 4.62 (1H, m), 5.2—5.5 (2H, m), 5.83 (1H×1/2, s), 5.84 (1H×1/2, s), 5.8—6.0 (1H, m), 6.84 (2H, d, J=8.6 Hz), 6.87 (2H, d, J=8.6 Hz), 7.13 (2H×1/2, d, J=8.6 Hz), 7.14 (2H×1/2, d, J=8.6 Hz), 7.28 (2H, d, J=8.6 Hz).

Seed crystals of **10a** could be obtained by fractional recrystallization of the mixture from MeOH. The mixture (11.7 g) was dissolved in MeOH (480 ml) under heating at 60 °C, and the MeOH solution was gradually cooled to 20 °C. After seeding of (+)-*l*-menthyl ester (4 mg), the mixture was further cooled to 0 °C over 2 h and stirred at 0 °C overnight. The resulting precipitate was collected by filtration to give the *l*-menthyl ester (**10a** and **10b**, **10a**:**10b**=4.5:1), which was purified by recrystallization from MeOH to give optically pure **10a** (2.15 g, 18%). **10a**: mp 114—115 °C. $[\alpha]_D^{22}$ +20.2° (c=0.26, $CHCl_3$). IR (Nujol): 1765, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, d, J=6.9 Hz), 0.85 (3H, d, J=7.3 Hz), 0.88 (3H, d, J=6.6 Hz), 0.7—1.8 (9H, m), 3.79 (3H, s), 3.79 (3H, s), 4.62 (1H, m), 5.2—5.4 (2H, m), 5.83 (1H, s), 5.8—6.0 (1H, m), 6.84 (2H, d, J=8.9 Hz), 6.86 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz). *Anal.* Calcd for $C_{31}H_{39}NO_5$: C, 73.63; H, 7.77; N, 2.77. Found: C, 73.37; H, 7.76; N, 2.73.

(3*R*,4*S*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone ((+)-**3b**): Treatment of **10a** with 1 N NaOH as described for the formation of racemic **3b** gave the acid (+)-**3b** (74%). $[\alpha]_D^{22}$ +63.3° (c=0.12, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with those of racemic **3b**.

(3*R*,4*S*)-4-Methoxycarbonyl-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone (**11**): A solution of (+)-**3b** (73 mg, 0.2 mmol), prepared from **10a**, in MeOH (3 ml) was treated with 10% TMS-CHN_2 in hexane (0.4 mmol). The mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was purified by preparative TLC (5:1) to give **11** (55 mg, 72%). mp 102—103 °C. $[\alpha]_D^{24}$ +39° (c=0.37, $CHCl_3$). IR (neat): 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (3H, s), 3.80 (3H, s), 3.80 (3H, s), 3.86 (1H, d, J=2.3 Hz), 5.25—5.45 (2H, m), 5.80—6.00 (1H, m), 5.89 (1H, s), 6.80—6.90 (4H, m), 7.14 (2H, d, J=8.6 Hz), 7.21 (2H, d, J=8.6 Hz). *Anal.* Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.00; H, 6.08; N, 3.69.

Method B: Asymmetric Synthesis (3*S*,4*S*)-1-(Di-*p*-anisylmethyl)-3-ethenyl-4-(*d*-menthyloxycarbonyl)-2-azetidinone (**13a**): A mixture of di-*p*-anisylmethylamine (243 mg, 1.00 mmol) and *d*-menthylglyoxylate monohydrate (230 mg, 1.00 mmol) in toluene (24 ml) was dehydrated azeotropically under reflux to give a toluene solution of the Schiff base. After addition of Et_3N (151 mg, 1.5 mmol), a solution of crotonyl chloride (126 mg, 1.2 mmol) in toluene (2 ml) was added dropwise at 70 °C over 20 min, followed by stirring for 3 h at the same temperature. The reaction mixture was diluted with toluene and washed successively with brine, 1 N HCl, brine, 5% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give a mixture of **13a** and **13b** (414 mg, 82%). The ratio of **13a** and **13b** was as determined 2:1 by HPLC analysis and from the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H×2/3, d, J=6.6 Hz), 0.66 (3H×1/3, d, J=6.9 Hz), 0.79 (3H×2/3, d, J=7.3 Hz), 0.83 (3H×1/3, d, J=7.3 Hz), 0.89 (3H, d, J=6.6 Hz), 3.78 (3H, s), 3.79 (3H×2/3, s), 3.80 (3H×1/3, s), 4.02 (1H, m), 4.08 (1H×1/3, d, J=5.9 Hz), 4.09 (1H×2/3, d, J=5.9 Hz), 4.59 (1H, m), 5.2—5.5 (2H, m), 5.7—5.8 (1H, m), 5.82 (1H, s), 6.80—6.95 (4H, m), 7.1—7.4 (4H, m). Recrystallization of the mixture from MeOH gave optically pure **13a**, mp 162—163 °C, $[\alpha]_D^{25}$ +5.8° (c=0.21, $CHCl_3$). IR (KBr): 1774, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, d, J=6.9 Hz), 0.79 (3H, d, J=6.9 Hz), 0.89 (3H, d, J=6.6 Hz), 3.78 (3H, s), 3.79 (3H, s), 4.02 (1H, m), 4.09 (1H, d, J=5.9 Hz), 4.57 (1H, m), 5.25—5.45 (2H, m), 5.70—5.81 (1H, m), 5.82 (1H, s), 6.80—6.95 (4H, m), 7.13 (2H, d, J=8.6 Hz), 7.33 (2H, d, J=8.3 Hz). *Anal.* Calcd for $C_{31}H_{39}NO_5 \cdot 1/4H_2O$: C, 72.98; H, 7.80; N, 2.75. Found: C, 73.13; H, 7.73; N, 2.72.

(3*R*,4*S*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone ((+)-**3b**): Treatment of **13a** with 1 N NaOH as described for the formation of racemic **3b** gave the acid (+)-**3b** (88%), $[\alpha]_D^{21}$ +58.0° (c=1.28, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with those of racemic **3b**.

(3*R*,4*S*)-1-(Di-*p*-anisylmethyl)-3-ethenyl-4-methoxycarbonyl-2-azetidinone (**11**): Treatment of (+)-**3b** prepared from **13a** (64 mg, 0.18 mmol) as described above gave **11** (49 mg, 74%), $[\alpha]_D^{22}$ +39° (c=0.99, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with those of **11** derived from **10a**.

Preparation of 2 (3*S*,4*S*)-4-Carboxy-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-2-azetidinone ((+)-**7b**): Treatment of (+)-**3b** with mercuric acetate and then $NaBH_4$ as described for the formation of racemic **7b** gave (+)-**7b** (86%), which was recrystallized from CH_2Cl_2 to give pure (+)-**7b**, mp 86—88 °C, $[\alpha]_D^{27}$ +11.0° (c=0.21, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.27; H, 6.04; N, 3.61. The IR and ^{1}H-NMR spectral data were identical with those of racemic **7b**.

(3*R*,4*R*)-4-Acetoxy-1-(di-*p*-anisylmethyl)-3-ethenyl-2-azetidinone ((+)-**3e**): Treatment of (+)-**3b** with lead tetraacetate as described for the formation of racemic **3e** gave (+)-**3e** (75%), $[\alpha]_D^{25}$ +79.0° (c=0.158, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with those of racemic **3e**.

(3*R*,4*R*)-4-Acetoxy-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-2-azetidinone ((+)-**7e**): Method A: Lead tetraacetate (2.7 g, 6.0 mmol) was added portionwise to a mixture of (+)-**7b** (2.0 g, 5.2 mmol) and AcOK (0.5 g, 5.1 mmol) in DMF (20 ml) and toluene (20 ml). The slurry was immersed in an oil-bath at 40 °C and stirred for 1 h. After decomposition of the residual lead tetraacetate with ethylene glycol, the reaction mixture was diluted with toluene and filtered over Celite. The organic layer was washed successively with brine, 10% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give (+)-**7e** (1.83 g, 88%).

Method B: Treatment of (+)-**3e** with mercuric acetate and then $NaBH_4$ as described for the formation of racemic **7e** gave (+)-**7e** (67%), $[\alpha]_D^{22}$ +26.0° (c=0.04, $CHCl_3$). The IR and ^{1}H-NMR spectral data were identical with those of racemic **7e**.

(3*R*,4*R*)-4-Acetoxy-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-*p*-nitrobenzyloxycarbonyloxyethyl]-2-azetidinone (**14a**): A solution of *p*-nitrobenzyl chloroformate (2.94 g, 13.6 mmol) in CH_2Cl_2 (6.4 ml) was added dropwise to a mixture of (+)-**7e** (3.02 g, 7.6 mmol) and *N*,*N*-dimethylaminopyridine (1.86 g, 15.2 mmol) in CH_2Cl_2 (46 ml) at 0 °C, followed by stirring for 2 h. The mixture was quenched with dilute HCl and diluted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **14a** (3.90 g, 90%), $[\alpha]_D^{22}$ +40.5° (c=0.38, $CHCl_3$). IR (neat): 1770 (sh), 1740, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, d, J=6.3 Hz), 1.87 (3H, s), 3.27 (1H, dd, J=1.0, 5.6 Hz), 3.75 (3H, s), 3.77 (3H, s), 5.15 (1H, m), 5.25 (2H, s), 5.89 (1H, s), 6.11 (1H, d, J=1.0 Hz), 6.79 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.20 (2H, d, J=8.3 Hz), 7.55 (2H, d, J=8.9 Hz), 8.25 (2H, d, J=8.9 Hz). *Anal.* Calcd for $C_{30}H_{30}N_2O_{10}$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.19; H, 5.39; N, 4.70.

(3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-*p*-nitrobenzyloxycarbonyloxyethyl]-2-azetidinone (**2a**): A solution of ceric (IV) ammonium nitrate (CAN) (12.8 g, 23.4 mmol) in water (8 ml) was added in portions to a solution of **14a** (5.76 g, 9.95 mmol) in MeCH (72 ml) at room temperature over 1 h. After being stirred for 0.5 h, the mixture was diluted with toluene and washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **2a** as a viscous oil (2.26 g, 94%), $[\alpha]_D^{22}$ +36.6° (c=0.09, $CHCl_3$). IR (neat): 3300, 1774, 1745, 1602 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, d, J=6.3 Hz), 2.11 (3H, s), 3.38 (1H, dd, J=1.3, 6.3 Hz), 5.16 (1H, m), 5.26 (2H, s), 5.86 (1H, d, J=1.3 Hz), 6.53 (1H, s), 7.55 (2H, d, J=8.9 Hz), 8.24 (2H, d, J=8.9 Hz). MS (FD) m/z: 353 ($M+1$)$^+$. *Anal.* Calcd for $C_{15}H_{16}N_2O_8$: C, 51.14; H, 4.58; N, 7.95. Found: C, 51.54; H, 4.86; N, 8.04.

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(3*R*,4*R*)-4-Acetoxy-1-(di-*p*-anisylmethyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**14b**): Imidazole (143 mg, 2.10 mmol) and *tert*-butyldimethylsilyl chloride (316 mg, 2.10 mmol) were added to a solution of (+)-**7e** (399 mg, 1.00 mmol) in DMF (1.9 ml). After being stirred for 2 h, the reaction mixture was diluted with water and benzene. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **14b** as a viscous oil (440 mg, 86%), $[\alpha]_D^{27}$ +23.8° (c=0.505, $CHCl_3$). IR (neat): 1765, 1750 (sh), 1607 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.82 (9H, s), 1.22 (3H, d, J=6.3 Hz), 1.84 (3H, s), 3.11 (1H, dd, J=1.0, 3.6 Hz), 3.79 (3H, s), 3.79 (3H, s), 4.17 (1H, m), 5.89 (1H, s), 6.17 (1H, d, J=1.0 Hz), 6.84 (2H, d, J=8.9 Hz), 6.85 (2H, d, J=8.9 Hz), 7.18 (2H, d, J=8.9 Hz), 7.23 (2H, d, J=8.9 Hz). MS (FD) m/z: 513 (M^+).

(3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**2b**): Treatment of **14b** (514 mg, 1.00 mmol) with CAN as described for the preparation of **2a** gave **2b** (196 mg, 68%), mp 100—102 °C (lit.[1a] mp 104 °C, lit.[1c] mp 101—103 °C, lit.[1d] mp 107—108 °C), $[\alpha]_D^{26}$ +48.2° (c=1.01, $CHCl_3$) (lit.[1c] $[\alpha]_D^{25}$ +47.9° (c=1.00, $CHCl_3$), lit.[1d] $[\alpha]_D$ +50.0° (c=0.41, $CHCl_3$)). IR (Nujol): 1776, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 1.25 (3H, d, J=6.3 Hz), 2.11 (3H, s), 3.19 (1H, dd, J=1.3, 3.3 Hz), 4.23 (1H, m), 5.84 (1H, d, J=1.3 Hz), 6.49 (1H, s).

References and Notes

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3) A solution of **3a** (12 mg, 0.028 mmol) in CD_3OD (0.5 ml) and D_2O (0.1 ml) was treated with NaOH (1.1 mg, 0.028 mmol) at room temperature, and the mixture was allowed to stand for 3 h, then the ^{1}H-NMR spectrum was measured. ^{1}H-NMR ($CD_3OD:D_2O$=5:1) δ: 3.72 (1H, s, H-4), 3.78 (3H, s), 3.80 (3H, s), 5.2—5.45 (2H, m), 5.76 (1H, s), 5.8—6.1 (1H, m), 6.87 (2H, d, J=8.6 Hz), 6.91 (2H, d, J=8.6 Hz), 7.24 (2H, d, J=8.9 Hz), 7.30 (2H, d, J=8.9 Hz). Compound **3b** (8.3 mg, 0.023 mmol) was also treated in the same manner as described above and the ^{1}H-NMR spectrum of the sodium salt of **3b** was measured. ^{1}H-NMR ($CD_3OD:D_2O$=5:1) δ: 3.65 (1H, m, H-3), 3.73 (1H, d, J=2.3 Hz, H-4), 3.79 (3H, s), 3.80 (3H, s), 5.2—5.45 (2H, m), 5.76 (1H, s), 5.9—6.1 (1H, m), 6.87 (2H, d, J=8.9 Hz), 6.91 (2H, d, J=8.9 Hz), 7.24 (2H, d, J=8.6 Hz), 7.30 (2H, d, J=8.6 Hz).

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