Synthetic Studies of Carbapenem and Penem Antibiotics. III. A Synthesis of a Key Intermediate for 1 β -Methylcarbapenem

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We synthesized useful intermediates **5** and **6** for 1 β - and 1 α -methylcarbapenems from 4-carboxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone **4** as a starting material by using stereoselective hydrogenation and hydroboration, respectively. A practical synthetic route from **4** to the (3*S*,4*S*)-4-[(*R*)-1-carboxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone derivative **1**, a useful intermediate for the synthesis of 1 β -methylcarbapenem antibiotics, was established.

Keywords 1 α -methylcarbapenem; 1 β -methylcarbapenem; (3*S*,4*S*)-4-[(*R*)-1-carboxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone; stereoselective hydrogenation; stereoselective hydroboration

Since it was shown that introduction of a methyl group at the 1 β position on carbapenem antibiotics resulted in an enhancement of chemical and metabolic stability, while potent antibacterial activity was retained¹⁾ (Fig. 1), extensive efforts have been directed toward the stereoselective synthesis of the key intermediate **1** and many methods for synthesizing **1** have been reported so far²⁾ (Fig. 2). In our previous papers,³⁾ we reported a practical preparation of 4-carboxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone **4** and its effective transformation into 4-acetoxy-3-[(*R*)-1-hydroxyethyl]-2-azetidinone **3**, a key intermediate of penem and carbapenem antibiotics. Although the preparation of compound **1** from **3** has been reported,²⁾ we considered that a more direct synthetic route to **1** from **4**, in which the carboxyl carbon at C-4 in compound **4** should be utilized as the one-carbon unit of the 1-methylcarbapenem skeleton, was desirable. We selected 4-(1-

methylethenyl)-2-azetidinone **7** and 4-[1-(protected hydroxymethyl)-ethenyl]-2-azetidinone **8** as key intermediates, because these compounds could be easily obtained from **4**. Hydroboration of compound **7** and catalytic hydrogenation of compound **8** to obtain **5** and **6** were investigated. In the present paper, we report that the β -methyl isomer **5** is stereoselectively obtained by catalytic hydrogenation of **8**, while the α -methyl isomer **6** is predominantly formed by hydroboration of **7**.⁴⁾

Compounds **7** and **8** were prepared from compound **4** as follows. Esterification of **4** with methanol in the presence of sulfuric acid followed by Grignard reaction with methyl magnesium bromide at 0–5°C gave the carbinol **10** in 88% yield. After protection of the secondary hydroxy group in **10** with a benzyloxycarbonyl (*Z*) group, **11** was dehydrated with thionyl chloride at room temperature to give 4-(1-methylethenyl)-2-azetidinone **7a** in 89% yield. Removal of the di-*p*-anisylmethyl (DAM) group of **7a** was achieved by treatment with ceric ammonium nitrate (CAN) in aqueous acetonitrile to give **7b** in 72% yield.⁵⁾ Compound **7a** was converted to the allyl chloride **12a** by treatment with chlorine at 0–10°C. Compound **12a** was transformed to **8c** and **8d** as follows. Treatment of **12a** with cuprous oxide⁶⁾ in the presence of *p*-toluenesulfonic acid (*p*-TsOH) at 50–55°C provided the allyl alcohol **8a** in 75% yield from **7a**. Finally, treatment of **8a** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in dimethylformamide (DMF) gave compound **8c** in a quantitative yield. On the other hand, removal of the DAM group of **12a** was carried out in a similar manner

Fig. 1

Fig. 2

Chart 1

TABLE I. Hydroboration of Compound 7

Entry	7	R ²	Reagent	Yield (%) ^{a)}	Ratio (5/6) ^{b)}
1	7a	DAM	B ₂ H ₆	82	1/1
2	7b	H	B ₂ H ₆	40	1/1.5
3	7a	DAM	9-BBN	95	1/2.8
4	7b	H	9-BBN	85	1/3

a) Isolated yield based on the azetidinone 7. b) The 5/6 ratios were determined by ¹H-NMR analysis and HPLC analysis.

to that described for the preparation of 7b in 67% yield and the successive conversion to 8b was achieved in 83% yield as described for the preparation of 8a. Protection of the hydroxy group of 8b with a *tert*-butyldimethylsilyl (TBDMS) group provided 8d in 88% yield (Chart 1). First, we investigated the hydroboration of compound 7. The ratio of compounds 5 and 6 in the reaction mixture was determined by proton nuclear magnetic resonance (¹H-NMR) or high performance liquid chromatography

(HPLC) analysis (Table I). Concerning the hydroboration of 7 by diborane in tetrahydrofuran (THF), 7a having a DAM group as the *N*-substituent gave a mixture of the β-methyl isomer 5a and the α-methyl isomer 6a in 82% yield and the ratio of 5a and 6a was determined to be 1:1 from the ¹H-NMR spectrum (entry 1). A similar treatment of 7b, *N*-unsubstituted 2-azetidinone, afforded a mixture of 5b and 6b in 40% yield in a ratio of 1:1.5 (entry 2). With the aim of improving the stereoselectivity, we tried the hydroboration of 7 with the bulky hydroborane 9-borabicyclo[3.3.1]nonane (9-BBN). The reaction of 7a with 9-BBN gave a mixture of 5a and 6a in 95% yield in a ratio of 1:2.8 (entry 3), and the same treatment of 7b gave a mixture of 5b and 6b in 85% yield in a ratio of 1:3 (entry 4). Next, we investigated the catalytic hydrogenation of compound 8. The ratio of compounds 5 and 6 in the resultant mixture was determined by HPLC analysis. First of all, the effects of *N*- and *O*-substituents (R² and R³) were examined (Table II-i). The starting materials 8e–i were prepared from 8a and 8b by using various protective groups. Hydrogenation was carried out in acetonitrile under a hydrogen atmosphere in the presence of platinum oxide at 0–5 °C. The *Z* group in the 3-[(*R*)-1-hydroxyethyl] moiety was not deprotected under this condition. No stereoselectivity was observed in *N*-unsubstituted 8 (8d

TABLE II-i. Effect of N- and O-Protecting Groups in Catalytic Hydrogenation

Entry	8	R ²	R ³	Reaction time (h)	Yield (%)	Ratio (5/6) ^{a)}
1	8a	DAM	H	3	86	1.4/1
2	8c	DAM	TBDMS	4	>95	6.1/1
3	8d	H	TBDMS	4	95	1.0/1
4	8e	TBDMS	TBDMS	11	No reaction	
5	8f	DAM	SiPh ₂ Me	1.5	90	4.3/1
6	8g	DAM	THP	4	93	3.0/1
7	8h	H	THP	3	92	0.8/1
8	8i	THP	THP	3	95	2.4/1

a) The 5/6 ratios were determined by HPLC analysis.

TABLE II-ii. Catalytic Hydrogenation of 8c

Entry	Conditions				Product		
	Catalyst	Solvent-additives	Temp. (°C)	Time (h)	R ¹	Yield (%)	Ratio (5/6)
1	PtO ₂ (0.3) ^{a)}	MeCN	0—5	4	Z	>95	6.1/1
2	PtO ₂ (0.06)	MeCN	r.t.	18	Z	92	7.8/1
3	PtO ₂ (0.3)	EtOH	r.t.	0.5	H	>95	3.0/1
4	PtO ₂ (0.3)	EtOAc	r.t.	0.5	H	>95	2.4/1
5	PtO ₂ (0.15)	EtOAc-NEt ₃ (0.165)	0—5	2	Z	93	5.4/1
6	PtO ₂ (0.3)	EtOAc-NEt ₃ (0.6)	0—5	2	Z	>95	5.0/1
7	10% Pd-C (0.15)	MeCN	0—5	1	H	73	2.6/1
8	5% Pt-C	MeCN	10	4.5	Z	84	4.6/1
9	5% Pt-C	MeCN-H ₂ O (50:1)	10	14	Z	80	7.7/1
10	5% Pt-C	MeCN-H ₂ O (125:1)	20	7.5	Z	96	6.8/1
		-NEt ₃ (0.265)					
11	5% Pt-C	MeCN-H ₂ O (125:1)	20	5	Z	84.5	13.1/1
		-Py (0.331)					

a) Amount (eq).

and 8h). But the β -methyl isomer **5** was predominantly obtained in **8** with the *N*-DAM group (**8a**, **8c**, **8f** and **8g**) and the stereoselectivity was improved by introducing bulky *O*-substituents such as TBDMS, tetrahydropyranyl (THP) and diphenylmethylsilyl groups (**8c**, **8f** and **8g**). As for the *N*-substituents, the DAM group gave a higher selectivity than the THP group (compare **8g** and **8i**). When both protecting groups were TBDMS groups (**8e**), no reaction occurred, possibly because of excessive steric hindrance. The best selectivity was observed with the combination of *N*-DAM and *O*-TBDMS groups (**8c**). With the aim of improving the stereoselectivity, detailed examination of the catalyst, solvent and additives (Table II-ii) was conducted using **8c**. The 5% platinum-carbon catalyst (entries 8—11) showed similar selectivity to platinum oxide but 10% palladium-carbon caused re-

moval of the *Z* group and decreased the stereoselectivity (entry 7). As for the reaction solvent, acetonitrile gave the best result. Low stereoselectivity and removal of the *Z* group were observed in ethanol and ethyl acetate (entries 3 and 4). Therefore to prevent hydrogenolysis of the *Z* group, the effect of the additives was examined. It was found that the addition of triethylamine not only prevented the deprotection reaction but also enhanced the stereoselectivity (entries 5 and 6). The latter effect was also observed in acetonitrile, and the addition of water and amine (triethylamine or pyridine) was more effective to improve the stereoselectivity (entries 10 and 11). Considering this hydrogenation of **8c** from the viewpoints of the chemical yield and stereoselectivity, the best result was obtained by using 5% platinum-carbon in acetonitrile with the addition of triethylamine and water (entry 10).

Chart 2

7 : X=H
8 : X=OR³

Fig. 3

Almost pure **5c** (**5c**:**6c**=23:1) was obtained by crystallization from *n*-hexane and ethyl acetate.

Conversion of **5c** to **1a** was readily achieved by removal of the *N*- and *O*-protecting groups and successive oxidation of the 4-(1-methyl-2-hydroxyethyl) group. Removal of the TBDMS and DAM groups was simultaneously carried out with boron trifluoride etherate in the presence of 1,3-dimethoxybenzene to give the alcohol **5b**, which could be purified by crystallization from *n*-hexane and toluene in 85% yield. Jones oxidation of **5b** afforded the carboxylic acid **1a** in 84% yield. This synthetic route is practicable for large-scale production of **1a**, because most of the intermediates from **4** to **1a** (i.e., **9**, **10**, **7a**, **12a**, **8a**, **8c**, **5c**, **5b**) are crystalline compounds. The stereochemistry of **1a** was confirmed by conversion of **1a** to the known compound **1b** by changing the *Z* group to a TBDMS group (Chart 2).

Concerning the high stereoselectivity in the case of the hydrogenation of **8**, we considered that the vinyl group in **8** was fixed by the steric hindrance of the bulky *N*-substituent (*R*²) and CH₂X group (X=OR³), and the hydrogen would be constrained to attack on the side opposite to the *N*-substituent as shown in Fig. 3. It was strongly suggested that the stereoselectivity of the hydrogenation was dependent upon the bulkiness of the *N*-substituent (*R*²) and the *O*-substituent (*R*³) (Table II-i). In the case of hydroboration of **7**, the stereoselectivity could be explained by similar considerations. But there is a big structural difference between **7** and **8**, that is, X is not OR³ but hydrogen in **7** (Fig. 3). We considered that this resulted in the lower stereoselectivity in the hydroboration of **7** compared with that of the hydrogenation of **8** because of the decrease of the steric interaction, which related to the degree of the vinyl group fixing. The slight difference of stereoselectivity in the hydroboration of **7b** (N-H) and **7a** (N-DAM) could be explained by considering that diborane or 9-BBN is attached to the nitrogen atom of **7b** at first and acts as a bulky *N*-substituent.

In summary, we have developed synthetic procedures to obtain the 1 β -methyl isomer **5** and 1 α -methyl isomer **6** by using stereoselective hydrogenation and hydroboration, respectively, and we have succeeded in establishing a practical synthetic route to **1** from easily obtainable **4**.

Experimental

Melting points were measured using a Thomas-Hoover capillary melting points apparatus and were not corrected. Infrared (IR) spectral measurements were carried out with a Hitachi 260-10 IR spectrometer. ¹H-NMR spectra were measured with 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). Measurements of optical rotation were performed with JASCO DIP-181 and DIP-370 digital polarimeters. Silica gel 60 (70–230 mesh, E. Merck) was used as an adsorbent for column chromatography. Preparative thin layer chromatography (preparative TLC) was performed on Silica gel 60F₂₅₄ TLC plates (E. Merck).

1) Preparation of 7 and 8. (3*S*,4*S*)-1-(Di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-4-methoxycarbonyl-2-azetidinone (9**)** H₂SO₄ (98%; 2.9 g, 29.6 mmol) was added to a solution of **4** (34 g, 88.3 mmol) in MeOH (310 ml), and the resultant mixture was stirred at 65°C for 3 h, cooled to 40°C, neutralized with 8% aqueous NaOH (15 ml) and concentrated *in vacuo* until the reaction solution was about one-third of its original volume. The residue was diluted with 1,2-dichloroethane (105 ml) and washed with water. The aqueous layer was separated from the organic layer and extracted with 1,2-dichloroethane (105 ml). The extracts and the organic layer were combined, washed with water, dried over Na₂SO₄ and concentrated *in vacuo* to give **9** as a colorless solid (quantitative yield). This crude product was used for the next step without further purification. The analytical sample was prepared by preparative TLC. mp 102–104°C. [α]_D²⁵ = –19.3° (*c* = 1.00, CHCl₃). The IR and ¹H-NMR spectral data were identical with those of the racemic **9**.^{3a)}

(3*S*,4*S*)-1-(Di-*p*-anisylmethyl)-3-[(*R*)-1-hydroxyethyl]-4-(1-hydroxy-1-methylethyl)-2-azetidinone (10**)** A 1 M suspension of methyl magnesium bromide in THF (370 g) was added dropwise to a solution of **9** (32.5 g, 81.5 mmol) in THF (310 ml) at 0–5°C, and the mixture was stirred at the same temperature for 1 h. Then 20% HCl (350 ml) was poured into the suspension at 20–25°C, and the resultant mixture was stirred for 1 h, followed by extraction with AcOEt (110 ml × 2). The extracts were combined, washed successively with brine, aqueous NaHCO₃ and water, dried over Na₂SO₄ and concentrated *in vacuo* to give **10** as a colorless solid (28.6 g, 88%). mp 154–156°C. [α]_D²⁷ = –68.6° (*c* = 1.00, CHCl₃). IR (KBr): 3363, 1728 cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.20 (3H, s), 1.23 (3H, s), 1.27 (3H, d, *J* = 6.3 Hz), 2.86 (1H, dd, *J* = 2.3, 5.6 Hz), 3.71 (1H, d, *J* = 2.3 Hz), 3.78 (3H, s), 3.81 (3H, s), 4.10 (1H, m), 5.60 (1H, s), 6.84 (2H, d, *J* = 8.9 Hz), 6.89 (2H, d, *J* = 8.6 Hz), 7.21 (2H, d, *J* = 8.9 Hz), 7.35 (2H, d, *J* = 8.9 Hz). Anal. Calcd for C₂₃H₂₉NO₅: C, 69.15; H, 7.32; N, 3.51. Found: C, 68.87; H, 7.14; N, 3.58.

(3*S*,4*S*)-3-[(*R*)-1-Benzyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-(1-hydroxy-1-methylethyl)-2-azetidinone (11**)** **10** (26 g, 65.1 mmol) and 4-dimethylaminopyridine (16 g, 131 mmol) were dissolved in CH₂Cl₂ (200 ml). Benzyl chloroformate (20 g, 117 mmol) was added dropwise thereto over 1 h at 0–5°C and the resultant mixture was stirred for 2 h at the same temperature, then for 10 h at room temperature. A 5% HCl solution (100 ml) was poured into the reaction mixture at 0–5°C and the resultant mixture was stirred for 0.5 h and allowed to stand. The organic layer was washed successively with water, aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give **11** as a viscous oil (quantitative yield). This crude product was used for the next step without further purification. The analytical sample was prepared by preparative TLC. [α]_D²³ = –48.2° (*c* = 0.500, CHCl₃). IR (neat): 3450, 1738 cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.13 (3H, s), 1.16 (3H, s), 1.40 (3H, d, *J* = 6.3 Hz), 2.96 (1H, dd, *J* = 2.3, 7.6 Hz), 3.66 (1H, d, *J* = 2.3 Hz), 3.71 (3H, s), 3.79 (3H, s), 5.06 (1H, m), 5.16 (2H, s), 5.60 (1H, s), 6.79 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 7.18 (2H, d, *J* = 8.6 Hz), 7.33 (2H, d, *J* = 8.9 Hz), 7.37 (5H, s). Anal. Calcd for C₃₂H₃₅NO₇: C, 69.77; H, 6.61; N, 2.63. Found: C, 68.93; H, 6.55; N, 2.70.

(3*S*,4*S*)-3-[(*R*)-1-Benzyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-1-(1-methylethenyl)-2-azetidinone (7a**)** A solution of **11** (30 g, 56.3 mmol) in toluene (350 ml) was treated with thionyl chloride (9.0 g, 75.6 mmol)

at 20–30 °C for 5 h in the presence of pyridine (10 ml). Water (100 ml) was added to quench the reaction at 10–25 °C. The organic layer was separated, washed with water, dried over Na₂SO₄ and concentrated *in vacuo* to give an oily residue, which was crystallized from a mixture of cyclohexane and AcOEt to yield **7a** as a colorless solid (25.8 g, 89%). mp 117–118 °C. $[\alpha]_D^{25} + 38.4^\circ$ ($c=10.0$, CHCl₃). IR (KBr): 1757 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.39 (3H, d, $J=6.3$ Hz), 1.51 (3H, s), 3.07 (1H, dd, $J=2.3, 5.9$ Hz), 3.72 (6H, s), 4.16 (1H, d, $J=2.3$ Hz), 4.83 (1H, s), 4.89 (1H, s), 5.17 (2H, m), 5.18 (1H, m), 5.51 (1H, s), 6.76 (2H, d, $J=8.6$ Hz), 6.79 (2H, d, $J=8.9$ Hz), 7.17 (2H, d, $J=8.6$ Hz), 7.21 (2H, d, $J=8.9$ Hz), 7.39 (5H, m). Anal. Calcd for C₃₁H₃₃NO₆: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.33; H, 6.41; N, 2.82.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-methylethenyl)-2-azetidinone (7b) CAN (4.80 g, 8.75 mmol) was added in portions to a solution of **7a** (1.8 g, 3.5 mmol) in MeCN (81 ml) and water (9 ml) with ice-cooling. After being stirred for 0.5 h at room temperature, the reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **7b** as a viscous oil (0.72 g, 72%). $[\alpha]_D^{24} - 14.7^\circ$ ($c=1.00$, CHCl₃). IR (neat): 2981, 1749 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.45 (3H, d, $J=6.3$ Hz), 1.71 (3H, s), 3.03 (1H, m), 4.07 (1H, d, $J=2.0$ Hz), 4.85–5.10 (2H, m), 5.10–5.30 (1H, m), 5.16 (2H, s), 5.95 (1H, s), 7.37 (5H, s). Anal. Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.75; H, 7.15; N, 4.70.

(3S,4S)-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-chloromethylethenyl)-1-(di-*p*-anisylmethyl)-2-azetidinone (12a) **7a** (200 g, 0.39 mol) was dissolved in AcOEt (3 l), and a solution of 3.85% chlorine in CCl₄ (870 g, 0.47 mol) was added dropwise thereto at room temperature over 15 min, then the mixture was stirred for 1 h. Water (1 l) and then 10% aqueous sodium thiosulfate (50 ml) were poured into the reaction mixture, which was stirred for 0.5 h and allowed to stand. The organic layer was washed successively with aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give **12a** as a colorless solid (203 g, 95%). mp 84–85 °C. $[\alpha]_D^{26} + 17.3^\circ$ ($c=0.602$, CHCl₃). IR (KBr): 1759 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.42 (3H, d, $J=6.6$ Hz), 3.28 (1H, dd, $J=2.3, 5.9$ Hz), 3.73 (6H, s), 3.78 (2H, m), 4.30 (1H, d, $J=2.3$ Hz), 5.14 (1H, m), 5.18 (2H, m), 5.56 (1H, s), 6.78 (2H, d, $J=8.9$ Hz), 6.80 (2H, d, $J=8.9$ Hz), 7.16 (2H, d, $J=8.6$ Hz), 7.22 (2H, d, $J=8.6$ Hz), 7.39 (5H, m). Anal. Calcd for C₃₁H₃₂NO₆Cl: C, 67.69; H, 5.86; N, 2.55; Cl, 6.45. Found: C, 67.43; H, 5.67; N, 2.63; Cl, 6.6.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-chloromethylethenyl)-2-azetidinone (12b) Treatment of **12a** with CAN as described for the formation of **7b** gave **12b** as a viscous oil (67%). IR (neat): 1750 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.46 (3H, d, $J=6.0$ Hz), 3.12 (1H, dd, $J=2.5, 8.5$ Hz), 4.06 (2H, s), 4.31 (1H, d, $J=2.5$ Hz), 5.16 (2H, s), 5.30 (2H, brs), 6.37 (1H, brs), 7.36 (5H, s).

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-(1-hydroxymethylethenyl)-2-azetidinone (8a) Water (40 ml), cuprous oxide (6.76 g, 47.3 mmol) and *p*-TsOH monohydrate (7.6 g, 40.0 mmol) were successively added to a solution of **12a** (20 g, 36.4 mmol) in dimethylsulfoxide (DMSO) (16 ml), and the resultant mixture was warmed to 50–55 °C, stirred for 2 h at the same temperature, and allowed to cool to room temperature. Then 1% aqueous H₃PO₄ (90 ml) and AcOEt (200 ml) were poured into the reaction mixture, and the whole was stirred for 0.5 h. Insoluble material was removed by filtration over Celite and washed three times with AcOEt (20 ml). The filtrate and the washings were combined, and the aqueous layer was separated from the organic layer and extracted with AcOEt (200 ml). The organic layer and the extract were combined, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was crystallized from a mixture of toluene and *n*-hexane (1:1) to give **8a** as a colorless solid (15.27 g, 79%). mp 118–120 °C. $[\alpha]_D^{26} + 15.6^\circ$ ($c=1.00$, CHCl₃). IR (KBr): 3353 (br), 1740 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.41 (3H, d, $J=6.6$ Hz), 3.22 (1H, dd, $J=2.3, 6.3$ Hz), 3.73 (6H, s), 3.89 (2H, m), 4.23 (1H, d, $J=2.3$ Hz), 5.17 (3H, m), 5.55 (1H, s), 6.78 (2H, d, $J=8.6$ Hz), 6.80 (2H, d, $J=8.6$ Hz), 7.17 (2H, d, $J=8.3$ Hz), 7.22 (2H, d, $J=8.3$ Hz), 7.39 (5H, m). Anal. Calcd for C₃₁H₃₃NO₇: C, 70.04; H, 6.26; N, 2.64. Found: C, 69.79; H, 6.06; N, 2.71.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-hydroxymethylethenyl)-2-azetidinone (8b) Treatment of **12b** with cuprous oxide and *p*-TsOH in DMSO as described for the formation of **8a** gave **8b** as a viscous oil (83%). $[\alpha]_D^{26} - 27.4^\circ$ ($c=0.402$, CHCl₃). IR (neat): 3350 (br), 1738 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.43 (3H, d, $J=6.5$ Hz), 3.14 (1H, dd, $J=2, 8$ Hz), 4.09 (2H, brs), 4.18 (1H, brd, $J=2$ Hz), 5.12 (1H, m), 5.15

(2H, s), 6.57 (1H, brs), 7.36 (5H, s). Anal. Calcd for C₁₆H₁₉NO₅: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.18; H, 6.49; N, 4.44.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-*tert*-butyldimethylsilyloxymethylethenyl)-1-(di-*p*-anisylmethyl)-2-azetidinone (8c) A solution of **8a** (20 g, 37.7 mmol) and imidazole (5.6 g, 82.4 mmol) in DMF (45 ml) was treated with TBDMSCl (6.77 g, 48.2 mmol) at room temperature for 2 h. The reaction mixture was diluted with cold water (200 ml) and AcOEt (150 ml). The aqueous layer was extracted with AcOEt (150 ml). The combined extracts were washed successively with 5% aqueous HCl (80 ml $\times$ 2) and brine (80 ml), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was crystallized from isopropanol to give **8c** as a colorless solid (2.42 g, quantitative yield). mp 90–92 °C. $[\alpha]_D^{28} + 19.0^\circ$ ($c=1.00$, CHCl₃). IR (KBr): 1752 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.01 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 1.39 (3H, d, $J=6.6$ Hz), 3.27 (1H, dd, $J=2.3, 5.9$ Hz), 3.71 (3H, s), 3.73 (3H, s), 3.90 (2H, m), 4.15 (1H, d, $J=2.3$ Hz), 5.17 (3H, m), 5.49 (1H, s), 6.76 (2H, d, $J=8.6$ Hz), 6.79 (2H, d, $J=8.6$ Hz), 7.17 (2H, d, $J=8.9$ Hz), 7.21 (2H, d, $J=8.3$ Hz), 7.38 (5H, m). Anal. Calcd for C₃₇H₄₇NO₇Si: C, 68.80; H, 7.34; N, 2.17. Found: C, 68.12; H, 7.24; N, 2.30.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-*tert*-butyldimethylsilyloxymethylethenyl)-2-azetidinone (8d) Following the procedure described for the formation of **8c**, **8d** was obtained from **8b** (88%). IR (neat): 3264 (br), 1760 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.05 (6H, s), 0.89 (9H, s), 1.45 (3H, d, $J=6.3$ Hz), 3.17 (1H, dd, $J=2.3, 7.6$ Hz), 4.14 (3H, m), 5.0–5.3 (5H, m), 5.96 (1H, brs), 7.37 (5H, s).

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-*tert*-butyldimethylsilyl-4-(1-*tert*-butyldimethylsilyloxymethylethenyl)-2-azetidinone (8e) TBDMSCl (18.1 g, 120 mmol) was added to an ice-cold stirred solution of **8b** (12.1 g, 39.6 mmol) and triethylamine (22.26 ml) in DMF (120 ml). After being stirred for 3 h at room temperature, the reaction mixture was diluted with AcOEt (360 ml), washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel to yield **8e** as a viscous oil (14.2 g, 67%). IR (neat): 1750 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.05 (6H, s), 0.07 (3H, s), 0.28 (3H, s), 0.90 (9H, s), 0.95 (9H, s), 1.39 (3H, d, $J=6.4$ Hz), 3.19 (1H, dd, $J=2.6, 6.6$ Hz), 4.08 (1H, d, $J=2.6$ Hz), 4.14 (2H, s), 5.14 (2H, s), 7.35 (5H, s).

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-(1-diphenylmethylsilyloxymethylethenyl)-2-azetidinone (8f) Following the procedure described for the formation of **8c** but replacing TBDMSCl with diphenylmethylchlorosilane, **8f** was obtained from **8a** (67%). IR (neat): 1755 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.57 (3H $\times$ 0.6, s), 0.66 (3H $\times$ 0.4, s), 1.29 (3H, d, $J=6.4$ Hz), 3.16 (1H, dd, $J=2.4, 5.5$ Hz), 3.67 (3H, s), 3.70 (3H, s), 4.00 (2H, brs), 4.15 (1H, d, $J=2.2$ Hz), 5.0–5.3 (5H, m), 5.39 (1H, s), 6.6–6.9 (4H, m), 6.9–7.2 (4H, m), 7.35 (5H, s), 7.30–7.59 (10H).

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-[1-(2-tetrahydropyranloxy)methylethenyl]-2-azetidinone (8g) A solution of **8a** (106 mg, 0.199 mmol) and 3,4-dihydro-2H-pyran (25 mg, 0.297 mmol) in CH₂Cl₂ (1 ml) was treated with *p*-TsOH (1 mg, 0.005 mmol) at room temperature for 50 min. The reaction mixture was diluted with AcOEt, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give an oily residue, which was purified by preparative TLC to yield **8g** as a viscous oil (90 mg, 73%). IR (neat): 1756 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.39 (3H, d, $J=6.2$ Hz), 1.58 (6H, m), 3.72 (3H, s), 3.73 (3H, s), 5.18 (2H, s), 5.53 (1H, brs), 6.3–6.6 (4H, m), 6.7–7.0 (4H, m), 7.39 (5H, s).

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-[1-(2-tetrahydropyranloxy)methylethenyl]-2-azetidinone (8h) and **(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxymethylethenyl]-1-(2-tetrahydropyranyl)-4-[1-(2-tetrahydropyranloxy)methylethenyl]-2-azetidinone (8i)** Following the procedure described above but replacing the starting material with **8b**, **8h** (33%) and **8i** (49%) were obtained.

8h: IR (neat): 1753 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.44 (3H, d, $J=6.4$ Hz), 1.58 (6H, m), 3.0–4.0 (3H, m), 4.02 (1H, s), 4.1–4.4 (2H, m), 4.57 (1H, brs), 5.08 (1H, m), 5.15 (2H, s), 5.21 (2H, brs), 7.36 (5H, s).

8i: IR (neat): 1760 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.38–1.84 (15H, m), 3.22–4.34 (9H, m), 4.61 (1H, m), 4.97 (2H, m), 5.06 (1H, m), 5.15 (2H, s), 5.26 (1H, m), 7.36 (5H, s).

2) Stereoselective Hydroboration of 7. **(3S,4R)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-[(R)-1-hydroxymethylethenyl]-2-azetidinone (5a)** and **(3S,4R)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-[(S)-1-hydroxymethylethenyl]-2-azetidinone (6a)** Boron trifluoride etherate (1.81 g, 12.8 mmol) was added dropwise to a solution of NaBH₄ (0.32 g, 8.46 mmol) in THF (40 ml) at 10–20 °C, and

the resultant mixture was stirred for 1 h. 1,5-Cyclooctadiene (1.21 g, 11.2 mmol) was added and the whole was stirred for 1 h, then a solution of **7a** (2.63 g, 5.10 mmol) in THF (10 ml) was added dropwise thereto at 20–25 °C over 1 h. Stirring was continued for 3 h. Water (7 ml) was added dropwise to the reaction mixture and the resultant mixture was stirred for 1 h. After addition of 4% aqueous NaOH (5.3 ml) at 40–45 °C, the reaction mixture was treated with 35% H₂O₂ (5.3 ml) at 40–45 °C and cooled to room temperature. Na₂SO₃ (0.2 g, 1.59 mmol) and toluene were added, and the whole was stirred. The organic layer was separated and the aqueous layer was extracted with toluene. The combined extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel to yield **5a** (0.51 g, 19%) and **6a** (1.88 g, 69%).

5a: [α]_D²⁶ –31.7° (*c* = 0.610, CHCl₃). IR (neat): 3350 (br), 1740 cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.90 (3H, d, *J* = 6.9 Hz), 1.42 (3H, d, *J* = 6.3 Hz), 1.75 (1H, m), 3.17 (1H, dd, *J* = 2.3, 7.3 Hz), 3.47 (2H, m), 3.69 (1H, dd, *J* = 2.3, 5.0 Hz), 3.74 (3H, s), 3.76 (3H, s), 5.04 (1H, m), 5.11 (2H, m), 5.61 (1H, s), 6.81 (2H, d, *J* = 8.9 Hz), 6.83 (2H, d, *J* = 8.9 Hz), 7.19 (2H, d, *J* = 8.9 Hz), 7.24 (2H, d, *J* = 8.6 Hz), 7.38 (5H, m). Anal. Calcd for C₃₁H₃₅NO₇: C, 69.77; H, 6.61; N, 2.63. Found: C, 69.32; H, 6.50; N, 2.72.

6a: [α]_D²⁶ –35.8° (*c* = 0.200, CHCl₃). IR (neat): 3452 (br), 1746 cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.74 (3H, d, *J* = 6.9 Hz), 1.46 (3H, d, *J* = 6.3 Hz), 1.78 (1H, m), 3.05 (1H, dd, *J* = 2.3, 8.3 Hz), 3.25–3.55 (2H, m), 3.76 (6H, s), 3.90 (1H, dd, *J* = 2.3, 4.0 Hz), 5.06 (1H, m), 5.17 (2H, s), 5.60 (1H, s), 6.82 (2H, d, *J* = 8.9 Hz), 6.83 (2H, d, *J* = 8.9 Hz), 7.18–7.25 (4H, m), 7.38 (5H, m). Anal. Calcd for C₃₁H₃₅NO₇: C, 69.77; H, 6.61; N, 2.63. Found: C, 70.55; H, 6.65; N, 2.47.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-[(R)-1-hydroxymethylethyl]-2-azetidinone (5b) and (3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-[(S)-1-hydroxymethylethyl]-2-azetidinone (6b) Following the procedure described above but replacing the starting material with **7b**, **5b** (21%) and **6b** (64%) were obtained.

5b: mp 73.8–75.1 °C. [α]_D²⁴ –14.7° (*c* = 1.00, CHCl₃). IR (KBr): 3365 (br), 3212, 1751 (br) cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.95 (3H, d, *J* = 6.9 Hz), 1.47 (3H, d, *J* = 6.3 Hz), 1.77 (1H, m), 3.15 (1H, dd, *J* = 1.5, 9.1 Hz), 3.40–3.65 (3H, m), 5.08 (1H, m), 5.16 (2H, s), 5.97 (1H, s), 7.37 (5H, s). Anal. Calcd for C₁₆H₂₁NO₅: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.41; H, 6.79; N, 4.62.

6b: mp 74.0–77.0 °C. [α]_D²⁶ –17.8° (*c* = 0.610, CHCl₃). IR (KBr): 3377 (br), 2978, 1732 cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.83 (3H, d, *J* = 6.9 Hz), 1.46 (3H, d, *J* = 6.3 Hz), 1.79 (1H, m), 3.02 (1H, dd, *J* = 1.5, 8.4 Hz), 3.44 (2H, m), 3.70 (1H, m), 5.11 (1H, m), 5.15 (2H, s), 6.23 (1H, s), 7.37 (5H, s). Anal. Calcd for C₁₆H₂₁NO₅: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.61; H, 7.16; N, 4.74.

3) Stereoselective Hydrogenation of 8. (3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-(1-*tert*-butyldimethylsilyloxymethylethyl)-1-(di-*p*-anisylmethyl)-2-azetidinone (5c and 6c). Method A A solution of **8c** (1.0 g, 1.55 mmol) and triethylamine (0.06 ml) in AcOEt (50 ml) was stirred under a hydrogen atmosphere in the presence of platinum oxide (0.05 g, 0.22 mmol) at 0–5 °C for 2 h. After removal of the catalyst, the filtrate was washed successively with 2N HCl, brine, 5% aqueous NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo* to give a mixture of **5c** and **6c** (933 mg, 93%). IR (KBr): 1744 cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.01–0.05 (6H, m), 0.82 (3H × 0.15, d, *J* = 6.9 Hz), 0.91 (9H, s), 1.35 (3H × 0.15, d, *J* = 6.3 Hz), 1.44 (3H × 0.85, d, *J* = 6.3 Hz), 1.80 (1H, m), 3.08 (1H × 0.15, dd, *J* = 2.3, 6.6 Hz), 3.35 (1H × 0.85, dd, *J* = 2.3, 6.6 Hz), 3.41 (2H × 0.15, d, *J* = 5.9 Hz), 3.48 (2H × 0.85, d, *J* = 5.3 Hz), 3.77 (3H, s), 3.81 (3H, s), 5.12 (1H, m), 5.21 (2H, m), 5.62 (1H × 0.85, s), 5.66 (1H × 0.15, s), 6.75–6.95 (4H, m), 7.15–7.35 (4H, m), 7.43 (5H, m).

The ratio of the (*R*)-compound (**5c**) and the (*S*)-compound (**6c**) in the mixture was confirmed to be 5.4:1 by HPLC analysis.

Method B A solution of **8c** (20 g, 31 mmol) in MeCN (200 ml) was stirred under a hydrogen atmosphere in the presence of 5% platinum-carbon (4.0 g) and water (4 ml) at 10 °C for 14 h. After removal of the catalyst, the filtrate was washed with AcOEt and concentrated *in vacuo* to give a mixture of **5c** and **6c** (16.1 g, 80%).

The ratio of **5c** and **6c** in the mixture was confirmed to be 7.7:1 by HPLC analysis. Pure **5c** could be separated by crystallization with *n*-hexane and AcOEt (10:1).

5c: mp 78–81 °C. [α]_D²⁵ –23.0° (*c* = 1.00, CHCl₃). IR (KBr): 1743 cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.01 (3H, s), 0.02 (3H, s), 0.88 (9H, s), 1.41 (3H, d, *J* = 6.3 Hz), 1.80 (1H, m), 3.31 (1H, m), 3.44 (2H, d, *J* = 5.3 Hz), 3.74 (3H, s), 3.77 (3H, s), 5.08 (1H, m), 5.18 (2H, m), 5.58 (1H, s), 6.80 (2H, d, *J* = 8.6 Hz), 6.83 (2H, d, *J* = 8.3 Hz), 7.20 (2H, d, *J* = 8.6 Hz),

7.25 (2H, d, *J* = 8.3 Hz), 7.37 (5H, m). Anal. Calcd for C₃₇H₄₉NO₇Si: C, 68.59; H, 7.62; N, 2.16. Found: C, 68.14; H, 7.53; N, 2.21.

Compounds **5a–i** and **6a–i** were obtained by a similar procedure to that described above but changing the reaction conditions as shown in Table II-i and II-ii.

4) Determination of Stereochemistry. (3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-1-(di-*p*-anisylmethyl)-4-[(R)-1-hydroxymethylethyl]-2-azetidinone (5a) A solution of **5c** (0.40 g, 0.62 mmol) in MeOH (40 ml) was treated with 6N HCl (10 ml) with ice-cooling for 20 min. The reaction mixture was diluted with AcOEt (200 ml), washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give an oily residue, which was purified by preparative TLC to yield **5a** as a viscous oil (326 mg, 99%). This was identical with the minor product obtained in the hydroboration of **7a**.

The ratio of **5d–i** and **6d–i** obtained by hydrogenation was determined by HPLC or ¹H-NMR analysis. It was confirmed after conversion of the crude product to a mixture of **5a** and **6a** or **5b** and **6b** by removal of the *N*- or *O*-protecting group under acidic conditions as described for the preparation of **5a** from **5c**, when necessary.

(3S,4S)-4-(1-*tert*-Butyldimethylsilyloxymethylethyl)-1-(di-*p*-anisylmethyl)-3-[(R)-1-hydroxyethyl]-2-azetidinone (5j and 6j) A solution of **5c** and **6c** (**5c**:**6c** = 5.4:1) (50 mg, 0.08 mmol) in MeCN (5 ml) was stirred under a hydrogen atmosphere in the presence of 10% palladium-carbon (20 mg) at room temperature for 1.5 h. After removal of the catalyst, the filtrate was washed with MeCN and concentrated *in vacuo* to give a mixture of **5j** and **6j** (40 mg, quantitative yield). IR (neat): 3436 (br), 1732 cm^{–1}. ¹H-NMR (CDCl₃) δ : 0.03 (3H, s), 0.04 (3H, s), 0.72 (3H × 0.15, d, *J* = 6.9 Hz), 0.88 (9H, s), 1.27 (3H × 0.85, d, *J* = 6.6 Hz), 1.33 (3H × 0.15, d, *J* = 6.3 Hz), 1.80 (1H, m), 2.92 (1H × 0.15, dd, *J* = 2.3, 8.9 Hz), 3.07 (1H × 0.85, dd, *J* = 2.3, 6.9 Hz), 3.35–3.70 (3H, m), 3.79 (3H, s), 3.81 (3H, s), 4.02 (1H, m), 5.63 (1H × 0.85, s), 5.69 (1H × 0.15, s), 6.8–6.9 (4H, m), 7.1–7.3 (4H, m).

This mixture was used as the authentic sample in the determination of the diastereomeric ratio at entries 3, 4, and 7 in Table II-ii.

5) Synthesis of 1 from 5c. (3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-[(R)-1-hydroxymethylethyl]-2-azetidinone (5b) 1,3-Dimethoxybenzene (7.8 g, 56.5 mmol) and boron trifluoride etherate (23 g, 162 mmol) were added to a solution of **5c** (20 g, 30.9 mmol) in CH₂Cl₂ (200 ml) at 10–20 °C, and the resultant mixture was stirred at room temperature for 3 h and then heated under reflux for 3–5 h. The reaction mixture was cooled to 10–15 °C, washed successively with brine (200 ml × 2), 2.5% aqueous NaHCO₃ (200 ml) and brine (200 ml), dried over Na₂SO₄ and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel to yield **5b** (14.0 g, 85%). This was identical with the minor product obtained in the hydroboration of **7b**.

(3S,4S)-3-[(R)-1-Benzoyloxycarbonyloxyethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (1a) The Jones reagent, prepared from CrO₃ (2.78 g, 27.8 mmol), 98% H₂SO₄ (4.4 g, 44.9 mmol) and water (8.1 ml), was added to a solution of **5b** (6.1 g, 11.4 mmol) in acetone (60 ml) at 10–20 °C for 1 h. The reaction mixture was quenched with isopropanol (0.5 ml) at 10–20 °C for 15 min, diluted with AcOEt (122 ml) and washed with water (135 ml). The aqueous layer was separated from the organic layer and extracted with AcOEt (61 ml). The AcOEt extracts and the organic layer were combined and extracted with 5% aqueous NaHCO₃ (30 ml). The extract was washed with CH₂Cl₂ (60 ml) and acidified with 10% HCl (20 ml) with ice-cooling. The acidic solution was extracted twice with CH₂Cl₂ (60 ml). The extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give **1a** as a viscous oil (5.26 g, 84%). [α]_D²⁴ +5.2° (*c* = 0.496, CHCl₃). IR (neat): 3280 (br), 1748 (br) cm^{–1}. ¹H-NMR (CDCl₃) δ : 1.22 (3H, d, *J* = 7.3 Hz), 1.42 (3H, d, *J* = 6.3 Hz), 2.68 (1H, m), 3.20 (1H, dd, *J* = 1.8, 7.8 Hz), 3.85 (1H, dd, *J* = 2.3, 5.9 Hz), 5.0–5.3 (3H, m), 6.22 (1H, s), 7.36 (5H, s). Anal. Calcd for C₁₆H₁₉NO₆: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.89; H, 6.11; N, 4.42.

(3S,4S)-3-[(R)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (1b) A solution of **1a** (2.00 g, 6.23 mmol) in 99.5% EtOH (44 ml) containing 400 mg of 10% Pd-C was stirred at room temperature for 4 h under a hydrogen atmosphere, then filtered. The filtrate was concentrated *in vacuo*. The residual solid was dissolved in DMF (41 ml), then TBDMSCl (4.13 g, 27.4 mmol) and imidazole (2.54 g, 37.4 mmol) were added thereto and the resultant mixture was stirred for 15 h at room temperature. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed successively with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in MeOH (78 ml) and THF (26 ml), then a solution of K₂CO₃ (2.58 g, 18.7 mmol) in water (26 ml) was added thereto and the resultant

mixture was stirred for 0.5 h at room temperature. The reaction mixture was diluted with Et₂O (200 ml) and water (50 ml). The aqueous layer was separated and the organic layer was extracted twice with 0.3 N NaOH (20 ml). The alkaline extracts were combined with the aqueous layer, washed with Et₂O (100 ml) and acidified with 6 N HCl (12 ml) with ice-cooling. The acidic solution was extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give **1b** as a colorless solid (1.55 g, 82%). mp 137–139 °C (lit.¹⁾ mp 140–143 °C, lit.^{2e)} mp 146–147 °C, lit.²ⁱ⁾ mp 143.5–144 °C, lit.^{2x)} 138–141 °C). $[\alpha]_D^{24}$ –30.5° ($c=0.502$, MeOH) [lit.^{2e)} $[\alpha]_D^{20}$ –34.6° ($c=0.26$, MeOH), lit.²ⁱ⁾ $[\alpha]_D^{25}$ –36.9° ($c=0.469$, MeOH)]. IR (neat): 3267, 2950, 1716 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.07 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.20 (3H, d, $J=6.3$ Hz), 1.27 (3H, d, $J=6.9$ Hz), 2.75 (1H, m), 3.03 (1H, dd, $J=1.5, 4.5$ Hz), 3.94 (1H, dd, $J=2.3, 5.0$ Hz), 4.20 (1H, m), 6.27 (1H, s).

References and Notes

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