Enantioselective Synthesis of the Key Intermediate of a 1β-Methylcarbapenem Antibiotic by Way of Nitrone 1,3-Dipolar Cycloaddition

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Synthesis of the key intermediate of the 1β-methylcarbapenem antibiotic (**1**) was investigated by way of inter- and intra-molecular nitrone 1,3-dipolar cycloaddition. A highly enantioselective construction of (3*S*,4*R*)-(−)-3-[(1*R*)-1-(t-butyldimethylsiloxy)ethyl]-4-[(1*R*)-1-(hydroxymethyl)ethyl]-azetidin-2-one (**2**) was achieved *via* intramolecular cycloaddition of the nitrone (**6**).

Thienamycin and related naturally occurring carbapenems possess potent and broad-spectrum antibacterial properties[1,2] but they suffer serious disadvantages in that they are chemically unstable and readily metabolised by renal dehydropeptidase-1 (DHP-1). Recently, a Merck research group discovered that the introduction of a β-oriented methyl group at the C-1 position of the nucleus provided an equally potent antibiotic (**1**) with substantially increased chemical and metabolic stability.[3] Since then, considerable efforts have been devoted to the stereocontrolled synthesis of the optically active key precursors.[4] We envisaged a stereoselective assembly of one (**2**) of the key intermediates having four contiguous chiral centres by way of isoxazolidine derivatives (**3**) and (**5**), which would be constructed by inter- and intra-molecular 1,3-dipolar cycloaddition of nitrones (**4**) and (**6**), respectively (Scheme 1), and here describe our fruitful results.[5]

Intermolecular Cycloaddition Approach.—The chiral nitrone (**4**) was easily prepared from commercially available (*S*)-methyl 3-hydroxy-2-methylpropionate (**7**) or from methylmalonic acid. Namely, after protection of the hydroxy ester (**7**) with a t-butyldimethylsilyl group, the resulting ether (**8**) was reduced with di-isobutylaluminium hydride (DIBAL) in a mixture of dichloromethane and 1,2-dimethoxyethane at −78 °C to the aldehyde, which was treated with *N*-benzylhydroxylamine to afford the nitrone (**4**) as a single isomer. On the other hand, methylmalonic acid was condensed, according to our method,[6] with (+)-menthol to give the diastereoisomeric mixture of half-esters (**9**), which was chlorinated with oxalyl dichloride and then reduced with tetrabutylammonium borohydride[7] in dichloromethane at −78 °C to afford the separable alcohols. The major product (**10**) was converted into the nitrone (**4**) following to the same procedure as above.

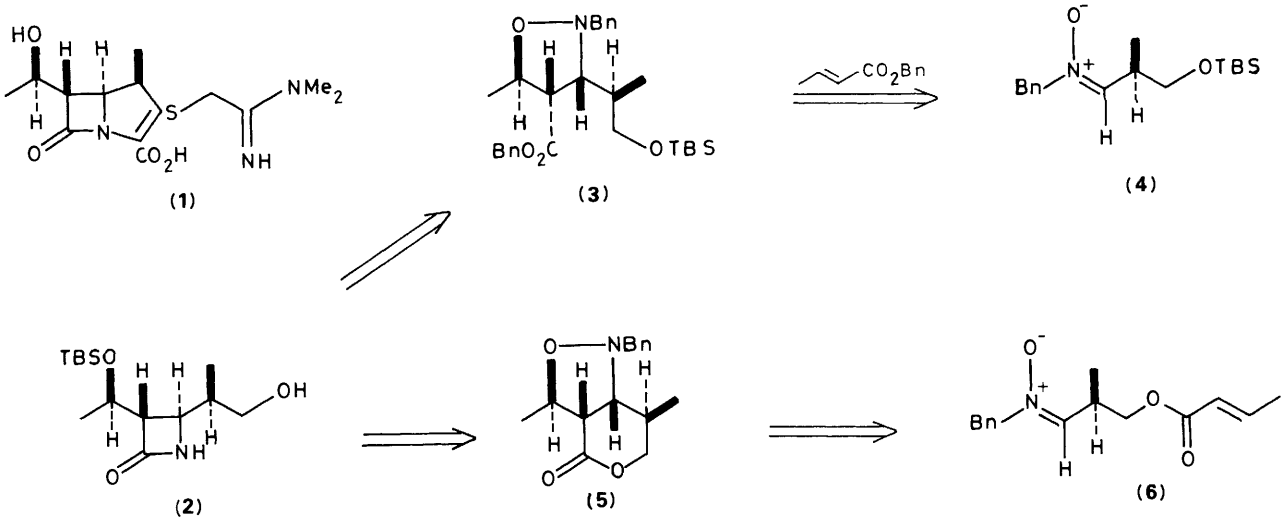
Without purification, the resulting nitrone (**4**) was heated for 10 h with benzyl crotonate in benzene to produce the adducts as a mixture of almost equal amounts of all the four possible diastereoisomers. A similar result was obtained by the independent work of Terashima and co-workers.[4n] One diastereoisomer (**3**), identical with the compound derived from the carboxylic acid (**23**) prepared through intramolecular cycloaddition (*vide infra*), was separated by careful h.p.l.c. The stereochemistry compound of (**3**), obtained in 21—23% yield, was determined by transformation into the known intermediate (**2**).

The t-butyldimethylsilyl group of compound (**3**) was first exchanged with an acetyl group by the action of acetic anhydride, triethylamine, 4-dimethylaminopyridine (DMAP), and tetrabutylammonium fluoride. The acetate (**12**), $[\alpha]_D^{26}$ + 31.35° (*c* 1.90 in $CHCl_3$), obtained in 77% yield (84% yield based on the consumed starting material), was converted into the β-lactam derivative (**14**) in two steps as follows. Hydrogenation of (**12**) in the presence of 10% palladium on activated carbon under hydrogen (5—6 atm) gave the corresponding amino acid (**13**), which was then, without purification, subjected to cyclisation carried out using dicyclohexylcarbodi-imide (DCC) in acetonitrile at 60 °C for 5 h. The hydroxy group of the β-lactam, $[\alpha]_D^{25}$ − 7.55° (*c* 0.27 in $CHCl_3$), obtained in 63% overall yield, was protected with t-butyldimethylsilyl chloride and imidazole in dimethylformamide (DMF) to form, quantitatively, the silyl ether (**15**), $[\alpha]_D^{24}$ − 22.37° (*c* 0.52 in $CHCl_3$). Reaction of compound (**15**) with sodium methoxide provided, in 77% yield, the primary alcohol (**2**), m.p. 89.5—90.5 °C; $[\alpha]_D^{24}$ − 21.1° (*c* 0.12 in $CHCl_3$) {lit.,[4g] 90—91 °C; $[\alpha]_D^{20}$ − 21.7° (*c* 0.46 in $CHCl_3$); lit.,[4n] 89—90 °C; $[\alpha]_D^{20}$ − 20.9° (*c* 0.37 in $CHCl_3$)}, whose spectral data were consistent with those of the authentic compound,[4g,n] correlated to the 1β-methylcarbapenem (**1**).[3,4g] Although the selectivity of the above 1,3-dipolar cycloaddition was poor, a new synthetic route to the optically pure (**2**) has been developed and stereochemistries of the above compounds (Scheme 2) were firmly determined.[5b]

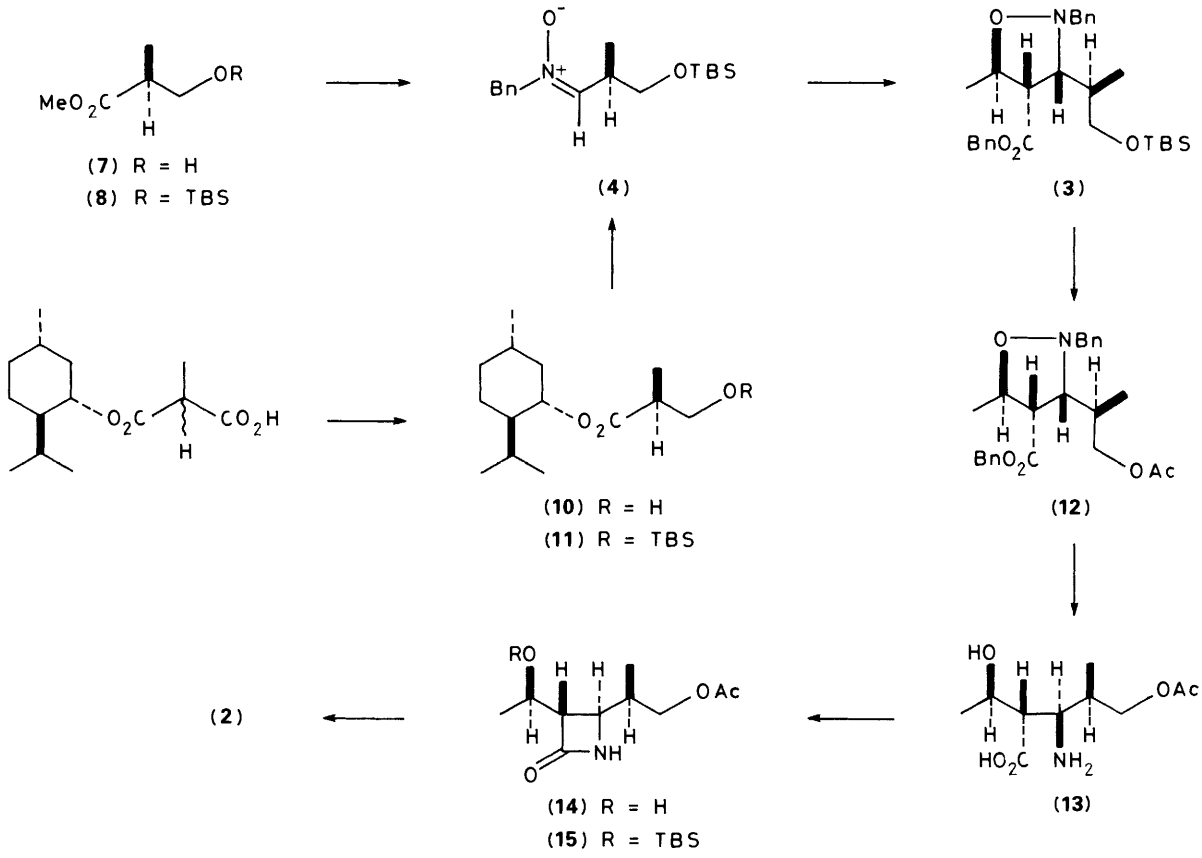
Intramolecular Cycloaddition Approach.—As described above, the intermolecular 1,3-dipolar cycloaddition proceeded with unsatisfactory stereoselectivity. However, high stereoselection was expected for the intramolecular cycloaddition from consideration of the transition states using Dreiding stereomodels, and this was realised as follows.[5a]

The optically active propane-1,3-diol drivative (**18**) was readily prepared from the commercially available (*R*)-ester (**16**) or the (−)-menthyl half-ester (**17**).[6] Condensation of compound (**18**) with crotonic acid yielded the ester (**19**), $[\alpha]_D^{24}$ − 4.83° (*c* 1.20 in $CHCl_3$), whose t-butyldimethylsilyl group was deblocked with dil. hydrochloric acid in tetrahydrofuran (THF). After oxidation of the resulting primary alcohol (**20**), $[\alpha]_D^{24}$ + 4.32° (*c* 6.2 in $CHCl_3$), with dipyridine chromium(VI) oxide,[8] the resulting aldehyde (**21**), obtained in 90% yield, was treated with *N*-benzylhydroxylamine in dichloromethane to afford the nitrone (**6**), whose n.m.r. spectrum indicated that a single isomer had been formed. Elimination of crotonic acid from the molecule readily occurred but the desired cycloaddition was achieved by refluxing of compound (**6**) in t-amyl alcohol. The isoxazolidine (**5**), m.p. 50—53 °C, $[\alpha]_D^{23}$ − 66.5° (*c* 1.90 in $CHCl_3$), having the correct stereochemistry, was

† Deceased 11th October 1988.



Scheme 1. TBS = t-butyldimethylsilyl; Bn = benzyl



Scheme 2.

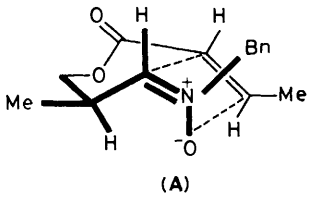
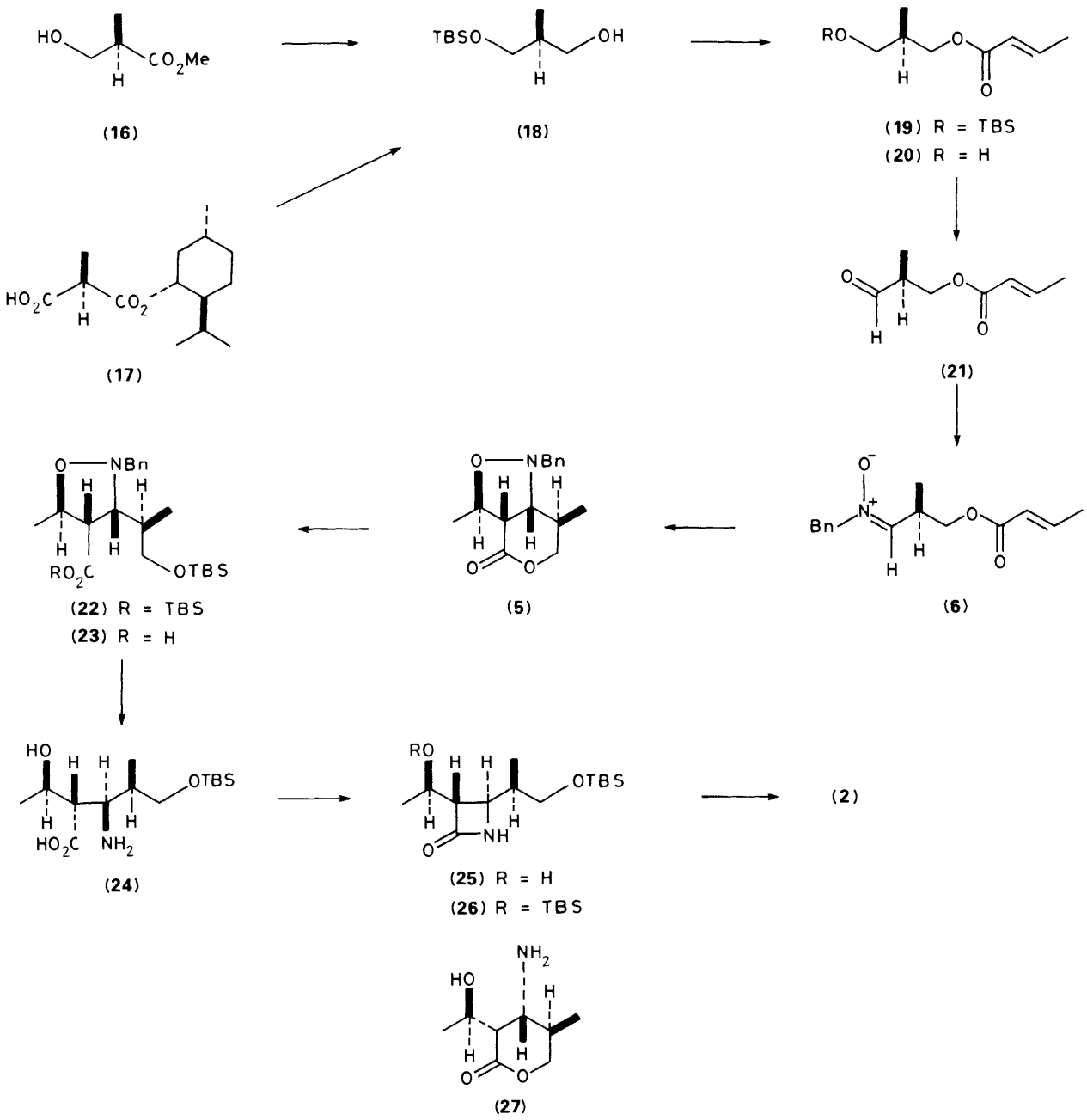


Figure.

obtained in 51% yield as a single stereoisomer. It was considered that the objective bicyclic product (**5**) was formed in a completely stereocontrolled manner through the most preferred conformation (**A**) of the (*Z*)-nitrone, which would be thermodynamically more stable than the (*E*)-isomer[9] (Figure).

Attempted hydrogenolysis of isoxazolidine (**5**), followed by β-lactam formation from the resulting amino alcohol (**27**) using a Grignard reagent,[10] resulted in failure. Therefore ring opening[11] of the lactone (**5**) was first carried out. Saponification of (**5**) with aqueous base, followed by silylation with t-butyldimethylsilyl chloride and imidazole in DMF and selective basic hydrolysis of the resulting silyl ester (**22**), gave a 99% yield of the carboxylic acid (**23**), which was convertible into the above benzyl ester (**3**), prepared by the intermolecular cycloaddition. The acid (**23**) was transformed into the β-lactam (**25**), $[\alpha]_D^{24}$ –



Scheme 3.

10.2° (*c* 1.17 in $CHCl_3$), in 78% yield *via* the amino acid (**24**) according to the same procedure as in the case of the acetate (**14**). Silylation of lactam (**25**) furnished quantitatively the bis-silyl ether (**26**), m.p. 87—89 °C; $[\alpha]_D^{25}$ − 8.53° (*c* 1.04 in $CHCl_3$), which was selectively desilylated using *N*-bromosuccinimide (NBS) in aqueous dimethyl sulphoxide (DMSO).[12] Spectral data of the primary alcohol (**2**), m.p. 89.5—90.5 °C; $[\alpha]_D^{24}$ − 21.9° (*c* 0.52 in $CHCl_3$), obtained in 78% yield, were identical with those of the authentic compound.[4g,n] Thus the chiral key intermediate (**2**) of the 1β-methylcarbapenem (**1**) was synthesized with complete diastereoselection by way of intramolecular 1,3-dipolar cycloaddition of the nitrone (**6**) (Scheme 3).

Experimental

General Methods.—M.p.s were determined on a Yanako micromelting-point apparatus and are uncorrected. I.r. spectra were taken on a Hitachi 260-10 spectrophotometer. ^1H N.m.r. spectra were recorded on JEOL JNM-PMS-60 (60 MHz), JEOL FX-90 (90 MHz), and JEOL GX-500 (500 MHz) spectrometers with tetramethylsilane as internal standard. Ordinary mass spectra were measured with a Hitachi M-52G instrument, while high-resolution mass spectroscopy was performed on a JEOL DX-300 spectrometer. Silica gel column chromatography was carried out with Merck Kieselgel 60 Art. 7734, and flash chromatography with Merck Kieselgel 60 Art. 9385. High-performance liquid chromatography (h.p.l.c.) was carried out with a Gilson h.p.l.c. system Model 302/303, monitored with u.v. and refractive-index detectors. Optical rotations were determined on a JASCO-DIP-340 polarimeter.

(S)-(+)-*Methyl* 3-(*t-Butyldimethylsiloxy*)-2-*methylpropionate* (**8**).—To a stirred solution of the (*S*)-ester (**7**) (5 g, 42.3 mmol), DMAP (100 mg, 0.81 mmol), and Et_3N (8.84 ml,

63.5 mmol) in a mixture of CH_2Cl_2 (50 ml) and DMF (5 ml) was added dropwise a solution of t-butyldimethylsilyl chloride (TBSCI) (6.99 g, 46.6 mmol) in CH_2Cl_2 (20 ml) at room temperature under N_2. After having been stirred for 3 h, the mixture was diluted with hexane, washed successively with 3% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and water, and dried (Na_2SO_4). Evaporation of the solvents gave a residue, which was subjected to silica gel column chromatography. Elution with AcOEt–hexane (5:95 v/v) gave the (S)-*ether* (**8**) (9.83 g, 100%) as an oil (Found: C, 56.8; H, 10.55. $C_{11}H_{24}O_3Si$ requires C, 56.85; H, 10.4%); $[\alpha]_D^{26}$ + 19.27° (*c* 6.68 in $CHCl_3$), whose spectral data were identical with those of the enantiomer.[6]

(1S,3S,4R)-3-*Menthyl Hydrogen Methylmalonate* (**9**).—To a stirred solution of methylmalonic acid (1.18 g, 10 mmol), (+)-menthol (1.56 g, 10 mmol), and DMAP (50 mg, 0.40 mmol) in a mixture of MeCN (30 ml) and CH_2Cl_2 (30 ml) at −40 to −30 °C was slowly added a solution of DCC (2.22 g, 10.7 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred for 6 h at the same temperature and then for 10 h at room temperature under Ar. After filtration, the filtrate was evaporated to give a residue, which was taken up into a mixture of a small excess of dil. aqueous $NaHCO_3$ and Et_2O. The aqueous layer was further washed with Et_2O and then acidified with conc. HCl. After extraction with Et_2O several times, the extract was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography with hexane–AcOEt (7:3 v/v) as eluant to afford the epimeric mixture of the *half-esters* (**9**) (1.45 g, 57%) as an oil (Found: C, 65.7; H, 9.65. $C_{14}H_{24}O_4$ requires C, 65.6; H, 9.45%); $[\alpha]_D^{24}$ + 58.46° (*c* 2.99 in $CHCl_3$), whose spectral data were identical with those of the compound derived from (−)-menthol and methylmalonic acid.[6]

(1S,3S,4R)-(+)-3-*Menthyl* (2S)-2-*t-Butyldimethylsiloxymethylpropanoate* (**11**).—A mixture of the above esters (**9**) (611 mg, 2.39 mmol) and $(COCl)_2$ (2.0 ml) in dry benzene (10 ml) was stirred for 20 h at room temperature and then evaporated under protection from moisture. A solution of the residue in dry CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of tetrabutylammonium borohydride[7] (600 mg) in dry CH_2Cl_2 (5 ml) at −78 °C and the mixture was stirred for 1 h at the same temperature. After dilution with CH_2Cl_2, the mixture was washed successively with 5% aqueous NaOH, 5% aqueous citric acid, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–Et_2O (4:1, v/v) afforded the epimeric alcohols (421 mg, 73%) in the ratio ~3:2. H.p.l.c. separation on Microsorb Si (4.6 × 250 mm; 5 μm) with hexane–Et_2O (4:1, v/v; 4 ml min^{-1}) as eluant gave the (*S*)-isomer (**10**) as a solid, m.p. 53—55 °C; $[\alpha]_D^{26}$ + 60.1° (*c* 1.55 in $CHCl_3$).

The above (*S*)-isomer (**10**) (82 mg, 0.339 mmol) was protected with a TBS group as in the case of compound (**7**) to give the *ether* (**11**) (115 mg, 95%) as an oil (Found: M^+ + 1, 357.2830. $C_{20}H_{41}O_3Si$ requires *m/z*, 357.2825); $[\alpha]_D^{26}$ + 49.7° (*c* 1.67 in $CHCl_3$), whose spectral data were identical with those of enantiomer.[6]

(3R,4S,5R)-(+)-*Benzyl* 2-*Benzyl*-3-[(R)-1-(*t-butyldimethylsiloxymethyl*)*ethyl*]-5-*methylisoxazolidine*-4-*carboxylate* (**3**).—(A) To a stirred solution of the ester (**8**) (80 mg, 0.34 mmol) in a mixture of CH_2Cl_2 (0.5 ml) and dry 1,2-dimethoxyethane (0.5 ml) was added 1M-DIBAL–hexane (0.34 ml; 0.34 mmol) during 5 min at −78 °C under Ar and the mixture was stirred for 30 min at −78 °C. After addition of water (0.34 ml), the mixture was stirred for 30 min at room temperature and then filtered through Celite. Filtrate and washings (Et_2O) were evaporated to give the aldehyde (70 mg, 100%) as an oil, δ_H (60 MHz; CCl_4) 0.00 (6 H, s, Me_2Si), 0.81 (9 H, s, Bu^t), 1.02 (3 H, d, *J* 7.0 Hz, 2-Me), 2.10—2.51 (1 H, m, 2-H), 3.75 (2 H, d, *J* 6.0 Hz, CH_2O), and 9.75 (1 H, br s, CHO), which was used for the next reaction without purification.

A solution of *N*-benzylhydroxylamine (42 mg, 0.34 mmol) in dry benzene (2 ml) was slowly added to the above aldehyde (70 mg, 0.34 mmol) and the mixture was stirred for 10 h under Ar. Addition of $MgSO_4$, followed by filtration and evaporation of the filtrate, gave the crude nitrone (**4**) (106 mg, 100%) as an oil, δ_H (60 MHz; $CDCl_3$) −0.01 and 0.00 (each 3 H, each s, Me_2Si), 0.83 (9 H, s, Bu^t), 1.08 (3 H, d, *J* 6.8 Hz, 2-Me), 3.65 (2 H, m, CH_2O), 4.83 (2 H, s, PhCH_2N), 6.53 (1 H, d, *J* 7.0 Hz, CH=N), and 7.30 (5 H, s, Ph), which was subjected to the next cycloaddition without purification.

A mixture of the above nitrone (**4**) (106 mg, 0.34 mmol) and benzyl crotonate (60 mg, 0.34 mmol) in dry benzene (2 ml) was refluxed for 10 h under Ar. After evaporation of the solvent, the residue was purified by silica gel column chromatography. Elution with hexane–AcOEt (9:1 v/v) gave a mixture of the isoxazolidines (141 mg, 85%) as an oil. H.p.l.c. separation of the mixture on Microsorb Si (4.6 × 250 mm; 5 μm) with hexane–AcOEt (95:5, v/v) afforded the *isoxazolidine* (**3**) (38 mg. 23%) as an oil (Found: M^+, 483.2795. $C_{23}H_{41}NO_4Si$ requires *M*, 483.2805); $[\alpha]_D^{26}$ + 13.23° (*c* 1.74 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 722 cm^{-1} (C=O); δ_H (90 MHz; $CDCl_3$) 0.00 (6 H, s, Me_2Si), 0.90 (9 H, s, Bu^t), 0.97 (3 H, d, *J* 8.0 Hz, CH_2CHMe), 1.40 (3 H, d, *J* 7.0 Hz, 5-Me), 1.65—1.90 (1 H, m, CH_2CHMe), 3.20—3.40 (3 H, m, CH_2OSi and 4-H), 3.83 (1 H, dd, *J* 4.0 and 9.0 Hz, 3-H), 3.94 and 4.12 (each 1 H, each d, *J* 12.0 Hz, PhCH_2N), 4.56 (1 H, dq, *J* 4.5 and 9.0 Hz, 5-H), 5.22 (2 H, s, PhCH_2O), and 7.27—7.46 (10 H, m, 2 × Ph).

(B) The above menthyl ester (**11**) (252 mg, 0.707 mmol) was similarly transformed into the isoxazolidine (**3**) (72 mg, 21%), $[\alpha]_D^{24}$ + 12.5° (*c* 0.08 in $CHCl_3$), whose properties were identical with those of the above compound, prepared by method (A).

(C) To an ice-cooled, stirred solution of the acid (**23**) (29 mg, 0.073 mmol), benzyl alcohol (30 mg, 0.27 mmol), and DMAP (5 mg, 0.04 mmol) in dry CH_2Cl_2 (1 ml) was slowly added a solution of DCC (30 mg, 0.145 mmol) in dry CH_2Cl_2 (1 ml) and the mixture was stirred for 20 h at room temperature. After dilution with benzene (20 ml), followed by filtration, the filtrate was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (95:5, v/v) afforded compound (**3**) (33 mg, 92%) as an oil, $[\alpha]_D^{25}$ + 13.2° (*c* 1.5 in $CHCl_3$), whose h.p.l.c. and spectral properties were identical with those of the sample prepared by the method (A).

(3R,4S,5R)-(+)-*Benzyl* 3-[(1R)-1(-*Acetoxymethyl*)*ethyl*]-2-*benzyl*-5-*methylisoxazolidine*-4-*carboxylate* (**12**).—To a stirred solution of the ether (**3**) (42 mg, 0.087 mmol) and DMAP (5 mg, 0.04 mmol) in dry THF (5 ml) were added 1M-tetrabutylammonium fluoride–hexane (0.5 ml; 0.5 mmol), Ac_2O (0.3 ml, 3.12 mmol), and Et_3N (0.3 ml, 2.15 mmol) at room temperature and the mixture was stirred for 24 h at the same temperature under Ar. After addition of further 1M-tetrabutylammonium fluoride–hexane (0.6 ml; 0.6 mmol), Ac_2O (0.3 ml, 3.12 mmol), and Et_3N (0.3 ml, 2.15 mmol), the mixture was stirred for a further 72 h at the same temperature and then diluted with benzene. The resulting mixture was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was subjected to silica gel column chromatography. Elution with AcOEt–isooctane(2,2,4-trimethylpentane) (1:9, v/v) gave the starting ether (**3**) (4.2 mg recovery) and further elution with AcOEt–isooctane (15:85, v/v) afforded the *title acetate* (**12**) (27 mg, 77%; 84% based on the consumed starting material) as an oil (Found: M^+, 411.2054. $C_{24}H_{29}NO_5$ requires *M*, 411.2046); $[\alpha]_D^{26}$ + 31.35° (*c* 1.90 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730 cm^{-1} (C=O); δ_H

(90 MHz; $CDCl_3$) 0.95 (3 H, d, *J* 8.0 Hz, CH_2CHMe), 1.42 (3 H, d, *J* 7.5 Hz, 5-Me), 1.78 (3 H, s, OAc), 1.70—1.90 (1 H, m, CH_2CHMe), 3.30—4.23 (6 H, m, 3- and 4-H, CH_2N, and CH_2OAc), 4.67 (1 H, dq, *J* 5.5 and 9.0 Hz, 5-H), 5.15 and 5.19 (each 1 H, each d, each *J* 14.0 Hz, $PhCH_2O$), and 7.20—7.40 (10 H, m, 2 × Ph).

(3S,4R)-(−)-4-[(1R)-1-(*Acetoxymethyl*)*ethyl*]-3-[(1R)-1-*hydroxyethylazetidin*-2-*one* (**14**).—A mixture of the acetate (**12**) (19 mg, 0.046 mmol) and 10% palladium on carbon (50 mg) in MeOH (5 ml) was shaken for 4 days under H_2 (5—6 atm) and then filtered through Celite. Evaporation of the filtrate yielded the crude amino acid (**13**), which was used for the next reaction without purification.

To a stirred solution of the above residue in MeCN (5 ml) was added a solution of DCC (30 ml, 0.145 mmol) in MeCN (5 ml) and the mixture was stirred for 5 h at 60 °C under Ar. After evaporation of the solvent, the residue was taken up into CH_2Cl_2 and filtered. Evaporation of the filtrate afforded a residue, which was purified by silica gel column chromatography. Elution with MeOH–benzene (3:97, v/v) gave the *azetidinone* (**14**) (6.2 mg, 63%) as an oil (Found: M^+, 229.1313. $C_{11}H_{19}NO_4$ requires *M*, 229.1314); $[\alpha]_D^{25}$ − 7.55° (*c* 0.27 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 425 (NH), 1 760 and 1 722 cm^{-1} (C=O); δ_H (500 MHz; $CDCl_3$) 1.03 (3 H, d, *J* 8.0 Hz, Me), 1.32 (3 H, d, *J* 8.0 Hz, Me), 1.97—2.10 (1 H, m, CH_2CHMe), 2.08 (3 H, s, OAc), 2.98 (1 H, ddd, *J* 0.3, 2.5, and 8.0 Hz, 3-H), 3.57 (1 H, dd, *J* 2.5 and 9.0 Hz, 4-H), 4.03 and 4.09 (each 1 H, each dd, each *J* 5.0 and 13.0 Hz, CH_2O), 4.13—4.19 (1 H, m, >CHO), and 5.97 (1 H, br s, NH).

(3S,4R)-(−)-4-[(1R)-1-(*Acetoxymethyl*)*ethyl*]-3-[(1R)-1-(*t-butyldimethylsiloxy*)*ethyl*]*azetidin*-2-*one* (**15**).—A mixture of the β-lactam (**14**) (6 mg, 0.028 mmol), TBSCl (10 mg, 0.066 mmol), and imidazole (5 mg, 0.073 mmol) in dry DMF (2 ml) was stirred for 2 days at room temperature under Ar. After dilution with benzene, the mixture was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography with AcOEt–hexane (3:7, v/v) as eluant to give the *ether* (**15**) (9.2 mg, 100%) as an oil (Found: $M^+ + 1$, 330.2090. $C_{16}H_{32}NO_4Si$ requires *m/z*, 330.2101); $[\alpha]_D^{24}$ − 22.37° (*c* 0.52 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 420 (NH) and 1 760—1 730 cm^{-1} (C=O); δ_H (500 MHz; $CDCl_3$) 0.09 (6 H, s, Me_2Si), 0.88 (9 H, s, Bu^t), 1.02 (3 H, d, *J* 8.0 Hz, Me), 1.23 (3 H, d, *J* 8.0 Hz, Me), 1.97—2.04 (1 H, m, CH_2CHMe), 2.07 (3 H, s, OAc), 2.92 (1 H, ddd, *J* 0.7, 2.5, and 7.5 Hz, 3-H), 3.62 (1 H, dd, *J* 2.5 and 8.5 Hz, 4-H), 3.92 and 4.11 (each 1 H, each dd, each *J* 7.0 and 13.0 Hz, CH_2O), 4.18 (1 H, quintet, *J* 7.5 Hz, >CHO), and 5.83 (1 H, br s, NH).

(S)-(−)-3-(*t-Butyldimethylsiloxy*)-2-*methylpropyl Crotonate* (**19**).—To a stirred, ice-cooled solution of the (*S*)-alcohol (**18**)[6] (4.49 g, 22 mmol), crotonic acid (1.89 g, 22 mmol), and DMAP (50 mg, 0.4 mmol) in dry CH_2Cl_2 (50 ml) was slowly added a solution of DCC (4.53 g, 22 mmol) in dry CH_2Cl_2 (50 ml) and the mixture was stirred for 20 h at room temperature. After filtration, the filtrate was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with AcOEt–hexane (7:93, v/v) afforded the *ester* (**19**) (4.55 g, 76%) as an oil (Found: $M^+ - Bu^t$, 215.1111. $C_{10}H_{19}O_3Si$ requires *m/z*, 215.1104); $[\alpha]_D^{24}$ − 4.83° (*c* 1.20 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) 0.00 (6 H, s, Me_2Si), 0.86 (9 H, s, Bu^t), 0.90 (3 H, d, *J* 7.0 Hz, 2-Me), 1.86 (3 H, dd, *J* 2.0 and 7.5 Hz, =CH*Me*), 1.80—2.15 (1 H, m, 2-H), 3.49 (2 H, d, *J* 7.0 Hz, 3-H_2), 3.80—4.10 (2 H, m, 1-H_2), 5.82 (1 H, dq, *J* 2.0 and 17.0 Hz, COCH=), and 6.95 (1 H, dq, *J* 7.5 and 17.0 Hz, =C*H*Me).

(R)-(+)-3-*Hydroxy*-2-*methylpropyl Crotonate* (**20**).—A mixture of the ester (**19**) (1.0 g, 3.67 mmol) and 3.5%HCl (15 ml) in THF (15 ml) was stirred for 30 min at room temperature before dilution with Et_2O. The resulting mixture was washed with brine and dried (Na_2SO_4). Evaporation of the solvent, followed by column chromatography on silica gel with AcOEt–hexane (3:7, v/v) as eluant, gave the *alcohol* (**20**) (580 mg, 100%) as an oil (Found: $M^+ - 1$, 157.0070. $C_8H_{13}O_3$ requires *m/z*, 157.0064); $[\alpha]_D^{24}$ + 4.32° (*c* 6.2 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) 0.98 (3 H, d, *J* 7.0 Hz, 2-Me), 1.90 (3 H, dd, *J* 2.0 and 7.5 Hz, =CH*Me*), 1.95—2.20 (2 H, m, 2-H and OH), 3.35—3.70 (2 H, m, 3-H_2), 3.98—4.35 (2 H, m, 1-H_2), 5.85 (1 H, dq, *J* 2.0 and 17.0 Hz, COC*H*=), and 7.00 (1 H, dq, *J* 7.5 and 17.0 Hz, =C*H*Me).

(3R,3aS,7R,7aR)-(−)-1-*Benzyl*-3,7-*dimethyl*-1,3,3a,6,7,7a-*hexahydropyrano*[4,3-c]*isoxazol*-4-*one* (**5**).—To a stirred solution of $CrO_3 \cdot 2C_5H_5N$[8] (979 mg, 3.79 mmol) in dry CH_2Cl_2 (20 ml) was added a solution of the alcohol (**20**) (100 mg, 0.63 mmol) in dry CH_2Cl_2 (1 ml) at room temperature and the mixture was stirred for 30 min at the same temperature. After addition of Et_2O (80 ml), the mixture was filtered through Celite and the filtrate was washed successively with 3% HCl, brine, saturated aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). Evaporation of the solvents gave a residue, which was subjected to short Florisil column chromatography with Et_2O as eluant to afford the aldehyde (**21**) (89 mg, 90%) as a volatile oil, δ_H (60 MHz; CCl_4) 1.13 (3 H, d, *J* 7.0 Hz, 2-Me), 1.87 (3 H, dd, *J* 2.0 and 7.0 Hz, =CH*Me*), 2.50—2.80 (1 H, m, 2-H), 4.26 (2 H, d, *J* 7.0 Hz, 1-H_2), 5.76 (1 H, dd, *J* 2.0 and 17.0 Hz, COCH=), 6.90 (1 H, dq, *J* 7.0 and 17.0 Hz, =C*H*Me), and 9.67 (1 H, br s, CHO).

To a stirred solution of the aldehyde (**21**) (25 mg, 0.16 mmol) in dry CH_2Cl_2 (1 ml) was added a solution of *N*-benzylhydroxylamine (19 mg, 0.16 mmol) in dry CH_2Cl_2 (1 ml) at room temperature and the mixture was stirred for 16 h at the same temperature under Ar. Addition of $MgSO_4$, followed by filtration and evaporation of the solvent, gave the nitrone (**6**) (42 mg) as an oil, δ_H (90 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 7.5 Hz, 2-Me), 1.87 (3 H, dd, *J* 2.0 and 7.5 Hz, =CH*Me*), 3.44 (1 H, m, 2-H), 4.00—4.30 (2 H, m, 1-H_2), 4.90 (2 H, s, $PhCH_2N$), 5.70 (1 H, dq, *J* 2.0 and 17.0 Hz, COCH=), 6.64 (1 H, d, *J* 7.0 Hz, O^-–N^+=CH), 6.92 (1 H, dq, *J* 7.5 and 17.0 Hz, =C*H*Me), and 7.25—7.40 (5 H, m, Ph), which was used for the next reaction without purification.

A stirred solution of the above nitrone (**6**) (42 mg) in dry t-amyl alcohol (5 ml) was heated at 110 °C for 16 h in a current of Ar. Evaporation of the solvent gave a residue, which was subjected to flash chromatography with AcOEt–hexane (15:85, v/v) as eluant to afford the *lactone* (**5**) (21 mg, 51%) as a solid, m.p. 50—53 °C (Found: M^+, 261.1375. $C_{15}H_{19}NO_3$ requires *M*, 261.1364): $[\alpha]_D^{23}$ − 66.5° (*c* 1.90 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 723 cm^{-1} (C=O); δ_H (500 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 7.8 Hz, 7-Me), 1.44 (3 H, d, *J* 7.2 Hz, 3-Me), 1.77 (1 H, m, 7-H), 2.95—3.00 (2 H, m, 3a-H and 7a-H), 4.00 (2 H, s, $PhCH_2N$), 3.99—4.04 (1 H, m, 6-H), 4.07—4.11 (1 H, m, 3-H), 4.67 (1 H, dd, *J* 2.5 and 10.0 Hz, 6-H), and 7.22—7.38 (5H, m, Ph).

(3R,4S,5R)-(+)-2-*Benzyl*-3-[(1R)-1-(*t-butyldimethylsiloxymethyl*)*ethyl*]-5-*methylisoxazolidine*-4-*carboxylic Acid* (**23**).—A mixture of the lactone (**5**) (87 mg, 0.33 mmol) and 1M-KOH–MeOH (8.7 ml; 8.7 mmol) in MeOH (4 ml) was stirred for 5 h at room temperature under Ar. Evaporation of the solvent gave a residue, to which were added a solution of imidazole (883 mg, 13.0 mmol) in dry DMF (2 ml) and then a solution of TBSCl (975 mg, 6.47 mmol) in dry DMF (2.7 ml) under ice cooling. The resulting mixture was stirred for 9 h at room temperature under Ar. After dilution with a mixture of Et_2O and benzene (1:1, v/v), the mixture was washed successively with 5% aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated. A mixture of the

crude ester (**22**) and 10 w/v% aqueous K_2CO_3 (7.6 ml) in MeOH (29 ml) was stirred for 1 h at room temperature. After evaporation, the residue was partitioned between Et_2O and 5% aqueous $KHSO_4$. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by silica gel column chromatography with CH_2Cl_2–MeOH (9:1, v/v) as eluant to give the *acid* (**23**) (130 mg, 99%) as needles, m.p. 77—79 °C (Found: M^+, 393.2323. $C_{21}H_{35}NO_4Si$ requires M, 393.2335); $[\alpha]_D^{23}$ + 2.27° (*c* 1.21 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 2 800—2 500 (OH) and 1 730 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 0.00 (6 H, s, Me_2Si), 0.86 (9 H, s, Bu^t), 1.01 (3 H, d, *J* 7.0 Hz, CH_2CHMe), 1.35 (3 H, d, *J* 7.0 Hz, 5-Me), 1.80—2.15 (1 H, m, CH_2CHMe), 2.95—3.50 (3 H, m, CH_2O and 4-H), 3.73 (1 H, dd, *J* 5.0 and 9.0 Hz, 3-H), 4.00 (2 H, s, CH_2N), 4.25—4.70 (1 H, m, 5-H), 6.55 (1 H, br s, COOH), and 7.28 (5 H, br, s, Ph).

(3S,4R)-(−)-4-[(1R)-1-(*t-Butyldimethylsiloxymethyl*)*ethyl*]-3-[(1R)-1-*hydroxyethyl*]*azetidin-2-one* (**25**).—A mixture of the carboxylic acid (**23**) (4.2 mg, 0.11 mmol) and 10% palladium on carbon (80 mg) in MeOH (10 ml) was shaken for 2 days under H_2 (5—6 atom) before filtration through Celite. Evaporation of the solvent gave the crude amino acid (**24**), which was subjected to cyclisation without purification.

The above product was dissolved in hot MeCN (15 ml) and the solution was then cooled to room temperature. After addition of DCC (42 mg, 0.20 mmol), the stirred mixture was heated at 60 °C for 5 h in a current of Ar. After evaporation of the solvent, the residue was taken up into CH_2Cl_2 and filtered. Evaporation of the solvent, followed by silica gel column chromatography with MeOH–$CHCl_3$ (1:99, v/v), afforded the *azetidinone* (**25**) (24 mg, 78%) as an oil (Found: $M^+ - 1$, 286.1837. $C_{14}H_{20}NO_3Si$ requires *m/z*, 286.1839); $[\alpha]_D^{24}$ − 10.2° (*c* 1.17 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 410 (NH) and 1 739 cm^{-1} (C=O); δ_H (500 MHz; $CDCl_3$) 0.10 (6 H, s, Me_2Si), 0.91 (9 H, s, Bu^t), 0.97 (3 H, d, *J* 6.9 Hz, Me), 1.34 (3 H, d, *J* 7.0 Hz, Me), 1.65—1.90 (2 H, m, CH_2CHMe and OH), 3.02 (1 H, dd, *J* 3.0 and 8.3 Hz, 3-H), 3.52 (1 H, dd, *J* 3.0 and 8.0 Hz, 4-H), 3.57 (1 H, dd, *J* 6.0 and 10.0 Hz, $CHHO$), 3.74 (1 H, dd, *J* 4.5 and 10.0 Hz, $CHHO$), 4.04—4.11 (1 H, m, >$CHOH$), and 6.05 (1 H, br s, NH).

(3S,4R)-(−)-3-[(1R)-1-(*t-Butyldimethylsiloxy*)*ethyl*]-4-[(1R)-1-(*t-butyldimethylsiloxymethyl*)*ethyl*]*azetidin-2-one* (**26**).—A mixture of the azetidinone (**25**) (22 mg, 0.076 mmol), TBSCl (30 mg, 0.2 mmol), and imidazole (20 mg, 0.29 mmol) in dry DMF (1 ml) was stirred for 2 days at room temperature under Ar. After dilution with benzene, the mixture was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography with AcOEt–hexane (15:85, v/v) as eluant to afford the *bis-ether* (**26**) (31 mg, 100%) as a powder, m.p. 87—89 °C (Found: M^+ − Me, 386.2563. $C_{19}H_{40}NO_3Si_2$ requires *m/z*, 386.2544); $[\alpha]_D^{23}$ − 8.53° (*c* 1.04 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420 (NH) and 1 746 cm^{-1} (C=O); δ_H (500 MHz; $CDCl_3$) 0.05 and 0.07 (each 6 H, each s, 2 × Me_2Si), 0.87 and 0.90 (each 9 H, each s, 2 × Bu^t), 0.97 (3 H, d, *J* 6.9 Hz, Me), 1.23 (3 H, d, *J* 7.0 Hz, Me), 1.76—1.84 (1 H, m, CH_2CHMe), 2.87—2.90 (1 H, m, 3-H), 3.52—3.62 (2 H, m, CH_2O), 3.72 (1 H, dd, *J* 3.2 and 7.5 Hz, 4-H), 4.16—4.20 (1 H, m, >CHO), and 5.72 (1 H, br s, NH).

(3S,4R)-(−)-3-[(1R)-1-(*t-Butyldimethylsiloxy*)*ethyl*]-4-[(1R)-1-(*hydroxymethyl*)*ethyl*]*azetidin-2-one* (**2**).—(A) A mixture of the acetate (**15**) (7 mg, 0.021 mmol) and 1M-NaOMe–MeOH (0.042 ml; 0.042 mmol) was stirred for 2.5 h at room temperature under Ar. After dilution with CH_2Cl_2, the mixture was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The crude product was purified by silica gel column chromatography with AcOEt–hexane (3:7, v/v) as eluant to afford the alcohol (**2**) (4.7 mg, 77%) as crystals, m.p. 89.5—90.5 °C (lit.,[4g] 90—91 °C; lit.,[4n] 89—90 °C); $[\alpha]_D^{24}$ − 21.1° (*c* 0.12 in $CHCl_3$) {lit., [4g], $[\alpha]_D$ −21.7 °(*c* 0.46 in $CHCl_3$); lit.,[4n] $[\alpha]_D^{20}$ − 20.9° (*c* 0.37 in $CHCl_3$)}, whose spectral data were consistent with those of the authentic compound.[4g,n]

(B) A mixture of the bis-ether (**26**) (9.3 mg, 0.023 mmol), NBS (4.9 mg, 0.027 mmol), DMSO (0.95 ml), and water (0.05 ml) in THF (0.7 ml) was stirred for 6 h at room temperature under Ar. After dilution with a mixture of Et_2O and benzene (1:1, v/v), the resulting mixture was washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by silica gel column chromatography as above gave the alcohol (**2**) (5.2 mg. 78%) as crystals, m.p. 89.5—90.5 °C; $[\alpha]_D^{24}$ − 21.9° (*c* 0.52 in $CHCl_3$), whose spectral data and chromatographical behaviour were identical with those of the above compound obtained by method (A).

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