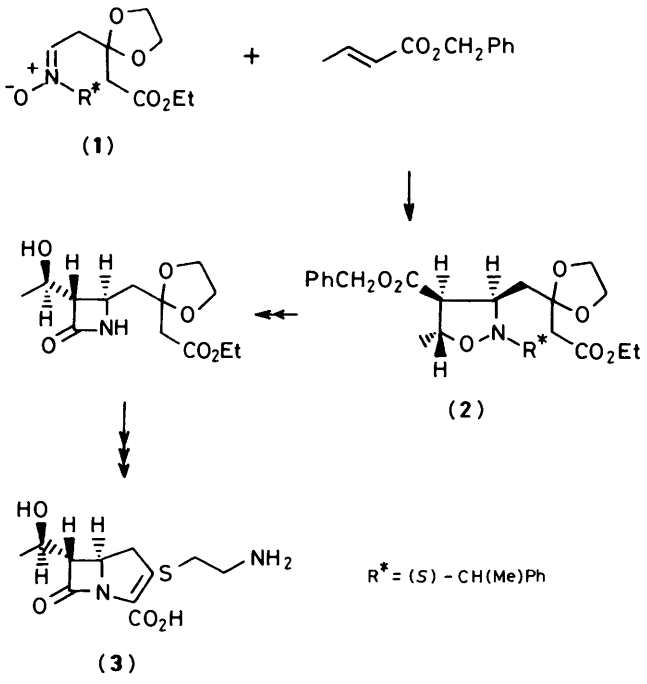
Chiral Synthesis of 3-[(*R*)-1-Hydroxyethyl]-4-oxoazetidin-2-yl Acetate using an Asymmetric 1,3-Dipolar Cycloaddition Reaction†

Tetsuji Kametani,* Shih-Der Chu, and Toshio Honda
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo, 142, Japan

3-[(*R*)-1-Hydroxyethyl]-4-oxoazetidin-2-yl acetate (**4**; R = H), a key intermediate for the preparation of penem and carbapenem antibiotics was synthesized in an optically active form using a 1,3-dipolar cycloaddition reaction of a chiral nitrone (**6**) as a key step.

1,3-Dipolar cycloaddition reactions[1] have been known to play an important role in organic synthesis and recently much attention has focused on chiral induction using chiral 1,3-dipoles such as chiral nitrones.[2]

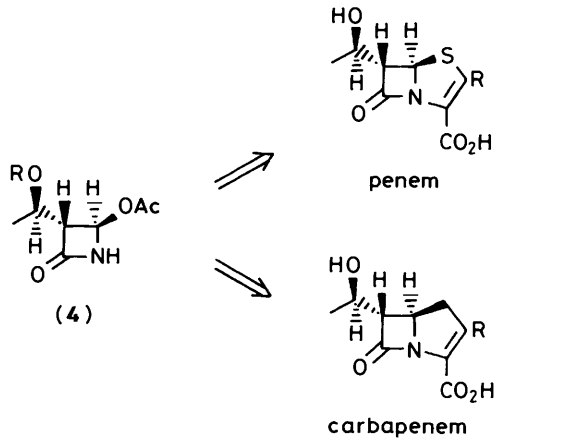
We have already published[3] an enantioselective synthesis of thienamycin (**3**), a carbapenem antibiotic, by applying the above synthetic strategy; the chiral amine was used to prepare the chiral nitrone (**1**) and its 1,3-dipolar cycloaddition reaction with benzyl but-2-enoate afforded the chiral isoxazolidine (**2**) stereoselectively, in high enantiomeric excess, which was converted into thienamycin as shown in Scheme 1.



Scheme 1.

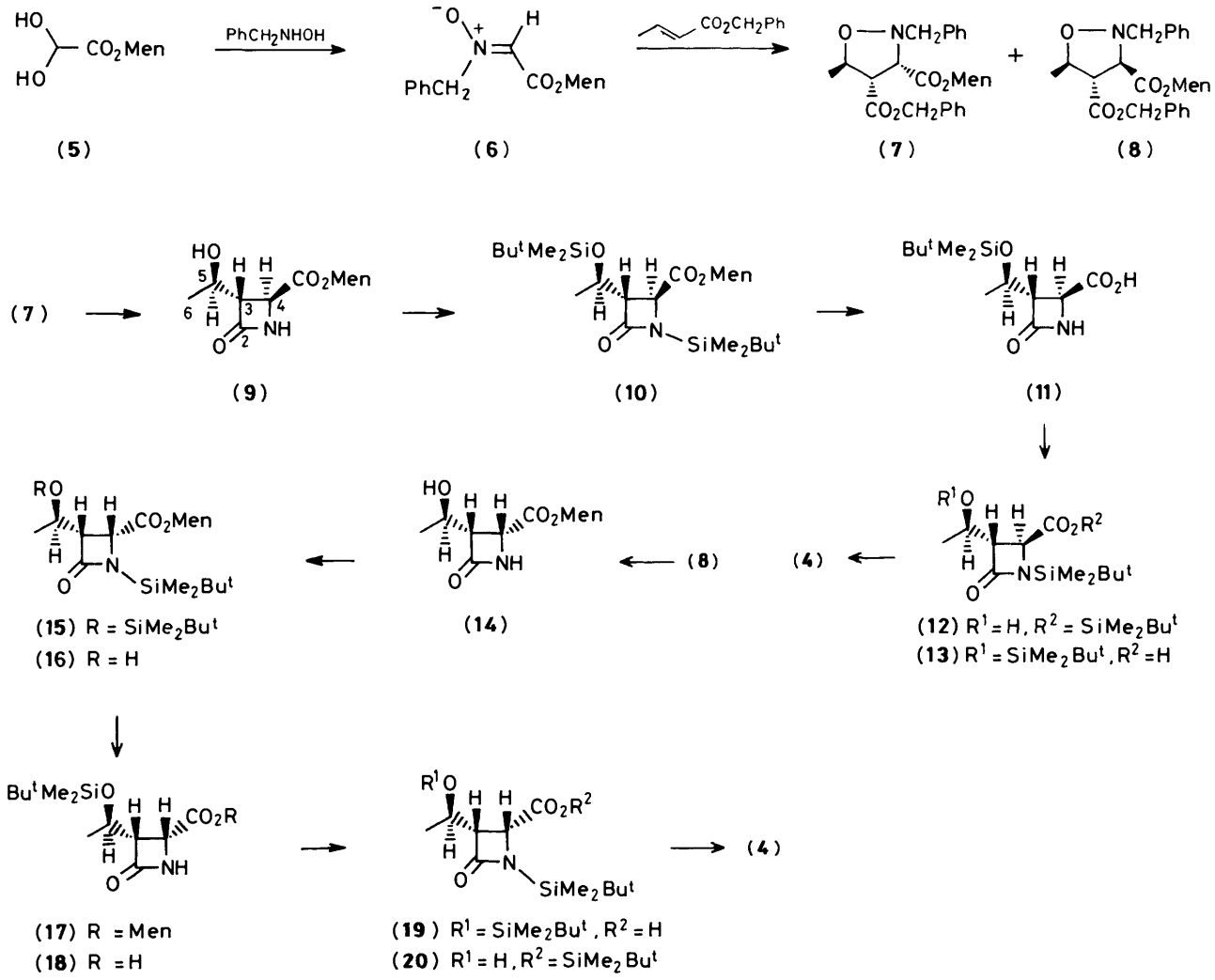
As part of our continuing effort to synthesize nonclassical β-lactam antibiotics, we became interested in the preparation of an optically active 3-(1-hydroxyethyl)-4-oxoazetidin-2-yl acetate derivative (**4**; R = H), a versatile starting material for the synthesis of penem[4] and carbapenem[5] antibiotics by further application of an asymmetric 1,3-dipolar cycloaddition reaction. A number of enantiospecific syntheses of (**4**) have already appeared by elaboration of a chiral natural source such as 6-aminopenicillanic acid,[6] (+)-aspartic acid,[7] and β-hydroxybutyrate,[8] and by an asymmetric [2 + 2]cycloaddition reaction[9] (Scheme 2).

† Part of this work has been published in *Heterocycles*, 1987, **25**, 241.



Scheme 2.

Thus, the chiral nitrone (**6**), derived from the reaction of (−)-menthyl glyoxylate hydrate (**5**)[10] with benzylhydroxylamine in refluxing benzene, was subjected to a 1,3-dipolar cycloaddition reaction with benzyl but-2-enoate to afford the isoxazolidines (**7**) and (**8**) in 30 and 29.5% yields, respectively, as the major two products (Scheme 3). Preparation of nitrones from glyoxylate esters and various hydroxylamines have been reported by Inoue[11] who claimed that these nitrones in solution existed as a mixture of *E*- and *Z*-isomers depending on the solvent.[12] Although ordinarily aldonitrones appeared in the more stable *Z*-configuration,[13] it is also known[14] that such compounds undergo thermal interconversion and that the *E*-nitrone undergoes cycloaddition faster than the *Z*-isomer. The nitrone (**6**) exhibited the methylene protons at the benzylic position at δ 5.58 in its n.m.r. spectrum, in accord with the reported value for the *E*-isomer.[11] Therefore, the formation of the isoxazolidines (**7**) and (**8**) can be rationalised by assuming the transition states depicted in Figure. Ring cleavage and debenzylation reactions of (**7**) by catalytic reduction over platinum oxide in methanol under an atmosphere of hydrogen at ambient temperature gave the β-amino acid, which without isolation was treated with *N*,*N*-dicyclohexylcarbodi-imide (DCC) in acetonitrile to bring about β-lactam formation affording the azetidinone (**9**) in 39% yield. Although the absolute configuration of (**9**) could not be determined at this stage, the relative stereochemistry was assigned as 3,4-*trans*- and 3,5-*trans* on the basis of its n.m.r. spectrum which had the 6-Me group at δ 1.31 as a doublet with *J* values of 6.3 Hz, 3-H at δ 3.27 as a doublet of double doublets with *J* values of 1, 2.8, and 5.6 Hz, and 4-H at δ 4.29 as a doublet with a *J* value of 2.8 Hz. After silylation of the hydroxy and amide groups of the azetidinone (**9**) with dimethyl-t-butylsilyl chloride in *N*,*N*-dimethylformamide in the presence of triethylamine, the menthyl ester of the bis-silylated compound (**10**) was



Scheme 3.

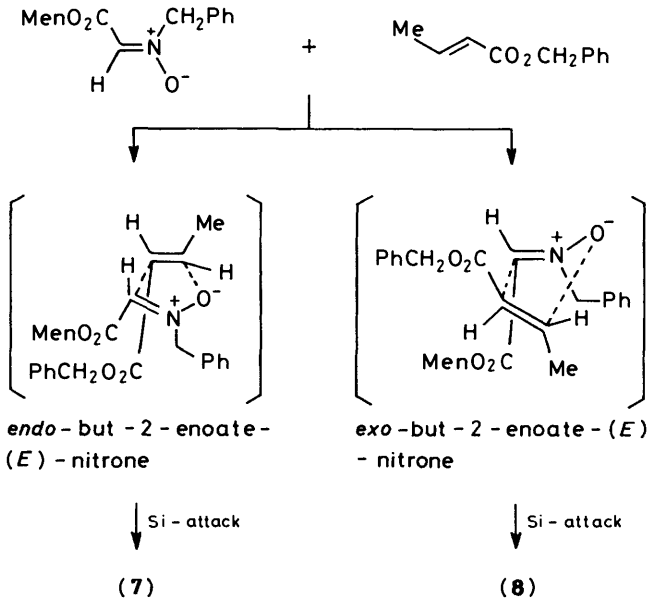


Figure.

hydrolysed with 1M aqueous sodium hydroxide to give the acid (**11**) in 80.5% yield. The *N*-silyl group was removed during the above conversion.

An acetoxy group at the C-4 position of the azetidinone was introduced by oxidative acetoxylation with lead tetra-acetate; the amide group of (**11**) was again protected with dimethyl-t-butylsilyl chloride in *N*,*N*-dimethylformamide in the presence of triethylamine to give the silyl ester (**12**) in 94% yield. Interestingly, the migration of the silyl group from the hydroxy to the carbonyl group occurred during the silylation reaction. Position transfer of the silyl group of (**12**) by treatment with acetic acid in tetrahydrofuran (THF) regenerated the free acid (**13**), in 82% yield. Finally, the acid (**13**) was converted into the desired 3-(1-hydroxyethyl)-4-oxoazetidin-2-yl acetate derivative (**4**; R = H) [m.p. 105 °C (lit.,[6] 104—106 °C), $[\alpha]_D^{25}$ + 49.31° (lit.,[6] +48.8°)], by oxidative acetoxylation in 70% yield. Since the physicochemical properties including specific optical rotation value were identical with those reported, the absolute stereochemistry was deduced to be 3*R* and 4*R* unambiguously.

The other isoxazolidine (**8**) was also subjected to a catalytic hydrogenation reaction over platinum oxide in methanol under an atmosphere of hydrogen, and subsequent β-lactam ring construction of the resulting amino acid with DCC in acetonitrile afforded the 3,4-*cis*-azetidin-2-one (**14**) (35%) in two-steps. The stereochemistry of (**14**) was determined on the basis of the

n.m.r. spectrum to be 3,4-*cis*. Silylation of compound (**14**) with an excess of dimethyl-t-butylsilyl chloride gave the *N,O*-bis-silylated compound (**15**) and the *N*-silylated compound (**16**) in 56 and 23% yields, respectively. The latter compound was readily transformed into the former by further silylation. Hydrolysis of compound (**15**) with 1M aqueous sodium hydroxide was carried out as for the preparation of the acid (**11**) to give the acid (**18**) and the *N*-desilylated compound (**17**) in 43 and 48% yields respectively. The latter compound was converted into the acid (**18**) by recycling the above silylation and hydrolysis process. The acid (**18**) was then silylated with dimethyl-t-butylsilyl chloride in THF in the presence of triethylamine to give the acid (**19**) and the silyl ester (**20**) in 62 and 13.5% yield, respectively. Oxidative acetoxylation of compound (**19**) with lead tetra-acetate provided the desired azetidinone (**4**) [m.p. 82—84 °C, $[\alpha]_D^{25}$ +16.27° ($CHCl_3$)]. The reason for the observed low specific optical rotation of compound (**4**), derived from (**8**) was rationalised by assuming that the isoxazolidine (**8**) was accompanied with its enantiomer in the chromatographical separation of the 1,3-dipolar cycloadducts; the azetidinone (**4**) derived from (**7**) exhibited a reasonably high specific optical rotation.

Since the acid (**11**) has already been converted[3] into thienamycin, this synthesis constitutes a formal synthesis of (+)-thienamycin.

Experimental

N.m.r. spectra were measured with JEOL JNM-FX-100 or JEOL PMX-60 spectrometer with tetramethylsilane as an internal standard, i.r. spectra (for solutions in chloroform) with a Hitachi 260-10 spectrophotometer, and mass spectra with a JEOL JMS-D-300 spectrometer. M.p.s were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were taken with JASCO DIP-181 or DIP-360 instruments.

Preparation of the Chiral Nitrone (**6**).—A solution of (−)-menthyl glyoxylate hydrate (**5**) (6.9 g) and benzylhydroxylamine (3.69 g) in benzene (100 ml) was heated under reflux in Dean-Stark equipment for 1.5 h. Evaporation of the solvent gave a solid, which was recrystallised from ether to afford the *nitrone* (**6**) (7.63 g, 80.7%) as pale yellow needles, m.p. 104 °C (Found: C, 72.0; H, 8.8; N, 4.5. $C_{19}H_{27}NO_3$ requires C, 71.9; H, 8.55; N, 4.4%); $\nu_{max.}(CHCl_3)$ 1 715 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 4.50—4.93 (1 H, m, CO_2CH), 5.58 (2 H, s, NCH_2Ar), 7.00 (1 H, s, CH=N), and 7.27 (5 H, br s, ArH); *m/z* 318 (M^+ + 1) and 317 (M^+).

(3S,4S,5R)- *and* (3R,4S,5R)-2-*Benzyl*-4-*benzyloxycarbonyl*-3-*menthyloxycarbonyl*-5-*methylisoxazolidine* (**7**) *and* (**8**).—A solution of the nitrone (**6**) (7.6 g) and benzyl but-2-enoate (10.6 g) in dry benzene (80 ml) was heated at reflux for 5 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ether (95:5 v/v) afforded the 3*R*,4*S*,5*R*-isoxazolidine (**8**) (4.37 g, 29.5%) as an oil; $\nu_{max.}(CHCl_3)$ 1 730 cm^{-1} (C=O); δ_H(100 MHz, $CDCl_3$) 1.43 (3 H, d, *J* 6.1 Hz, 5-Me), 3.52 (1 H, m, 4-H), 4.02 (1 H, d, *J* 4.6 Hz, 3-H), 4.09 (2 H, s, NCH_2Ar), 4.53 (1 H, dq, *J* 6.1 and 8.3 Hz, 5-H), 5.18 (2 H, s, CO_2CH_2Ph), and 7.30 (10 H, br s, 2 × ArH) (Found: M^+, 493.2836. $C_{30}H_{39}NO_5$ requires *M*, 493.2828); $[\alpha]_D^{25}$ −44.0° (*c* 0.1, $CHCl_3$). Further elution with the same solvent system provided the diastereoisomer as a solid, which was recrystallised from hexane to give 3*S*,4*S*,5*R*-isoxazolidine (**7**) (4.45 g, 30%) as needles, m.p. 95 °C (Found: C, 73.0; H, 8.0; N, 2.8. $C_{30}H_{39}NO_5$ requires C, 73.0; H, 7.95; N, 2.85%); $\nu_{max.}(CHCl_3)$ 1 740 cm^{-1} (C=O); δ_H(100 MHz, $CDCl_3$) 1.35 (3 H, d, *J* 6.1 Hz, 5-Me), 3.16 (1 H, dd, *J* 8.3 and 8.5 Hz, 4-H), 3.75 (1 H, d, *J* 8.5 Hz, 3-H), 4.03 (1 H, d, *J* 14.2 Hz, HC*H*HPh), 4.20 (1 H, d, *J* 14.2 Hz, NCH*H*Ph), 4.41 (1 H, dq, *J* 6.1 and 8.3 Hz, 5-H), 5.12 (2 H, s, CO_2CH_2Ph), and 7.32 (10 H, br s, 2 × ArH); *m/z* 493 (M^+); $[\alpha]_D^{25}$ −76.42° (*c* 1.086, $CHCl_3$).

(3S,4S)-3-[(R)-1′-*Hydroxyethyl*]-4-(−)-*menthyloxycarbonylazetidin*-2-*one* (**9**).—A mixture of the isoxazolidine (**7**) (1.24 g), platinum oxide (150 mg), and methanol (50 ml) was stirred for 20 h under an atmosphere of hydrogen at ambient temperature. The insoluble material was filtered off through Celite and the filtrate was concentrated to leave a residue which, without purification, was dissolved in acetonitrile (80 ml). To the above solution was added DCC (0.6 g) and the resulting mixture was warmed at 60 °C for 3 h with stirring. The precipitated materials was filtered off, and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with benzene–acetone (10:1, v/v) afforded the β-lactam (**9**) (298 mg, 39%) as an oil; $\nu_{max.}(CHCl_3)$ 3 400 (NH), 1 765, and 1 730 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 1.31 (3 H, d, *J* 6.3 Hz, 1′-Me), 2.75 (1 H, br s, OH), 3.27 (1 H, ddd, *J* 0.8, 2.8, and 8.6 Hz, 3-H), 4.29 (1 H, d, *J* 2.8 Hz, 4-H), 4.33 (1 H, m, 1′-H), 4.76 (1 H, dt, *J* 4.2 and 10.5 Hz, CO_2CH), and 6.45 (1 H, br s, NH) (Found: M^+ + 1, 298.2030. $C_{16}H_{28}NO_4$ requires *M* + 1, 298.2018); $[\alpha]_D^{25}$ −55.48° (*c* 1.77, $CHCl_3$).

(3S,4S)-4-(−)-*Menthyloxycarbonyl*-1-*dimethyl-t-butylsilyl*-3-[(R)-1-(*dimethyl-t-butylsilyloxy*)*ethyl*]*azetidin*-2-*one*. (**10**).—A solution of the 3*S*,4*S*-azetidinone (**9**) (296 mg), dimethyl-t-butyl silyl chloride (500 mg), and triethylamine (354 mg) in dry *N,N*-dimethylformamide (10 ml) was stirred at ambient temperature for 16 h. After dilution with benzene, the organic layer was washed with water, dried (Na_2SO_4), and concentrated to leave the residue, which was subjected to silica gel column chromatography. Elution with benzene–acetone (99:1, v/v) gave the bis-silylated compound (**10**) (415 mg, 80%) as an oil; $\nu_{max.}(CHCl_3)$ 1 730 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 0.09 (3 H, s, Me), 0.10 (3 H, s, Me), 0.16 (3 H, s, Me), 0.26 (3 H, s, Me), 0.91 (9 H, s, Bu^t), 1.00 (9 H, s, Bu^t), 1.20 (3 H, d, *J* 6.3 Hz, 1′-Me), 3.16 (1 H, dd, *J* 2.9 and 4.2 Hz, 3-H), 4.14 (1 H, d, *J* 2.9, Hz, 4-H), 4.23 (1 H, dq, *J* 4.2 and 6.3 Hz, 1′-H), and 4.76 (1 H, dt, *J* 4.2 and 10.5 Hz, CO_2CH) (Found: M^+ + 1, 526.3719. $C_{28}H_{56}NO_4Si_2$ requires *M* + 1, 526.3746); $[\alpha]_D^{25}$ −59.32° (*c* 1.57, $CHCl_3$).

(3S,4S)-3-[(R)-1′-(*Dimethyl-t-butylsilyloxy*)*ethyl*]-4-*oxoazetidine*-2-*carboxylic Acid* (**11**).—1M Aqueous sodium hydroxide was added to a stirred solution of the bis-silylated azetidinone (**10**) (270 mg) in THF–methanol (2:1, v/v) (12 ml) (0.56 ml) at room temperature and the resulting solution was stirred further at the same temperature. After treatment with 1M hydrochloric acid, the solvent was evaporated off to give the residue, which was extracted with ether. The ethereal layer was extracted with 1M aqueous sodium hydroxide (0.9 ml) and the aqueous layer was treated with 1M hydrochloric acid (1 ml). The resultant acidic solution was again extracted with ether, and the extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a solid, which was recrystallised from ether to afford the *acid* (**11**) (113 mg, 80.5%) as needles, m.p. 134 °C (Found: C, 52.75; H, 8.75; N, 5.2. $C_{12}H_{23}NO_4Si$ requires C, 52.7; H, 8.5; N, 5.1%); $\nu_{max.}(CHCl_3)$ 3 405 (NH), 1 765, and 1 735 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 0.08 (3 H, s, Me), 0.09 (3 H, s, Me), 0.89 (9 H, s, Bu^t), 1.33 (3 H, d, *J* 6.3 Hz, 1′-Me), 3.55 (1 H, m, 3-H), 4.28 (1 H, m, 1′-H), 4.36 (1 H, d, *J* 2.3 Hz, 4-H), 6.61 (1 H, br s, NH), and 7.35 (1 H, br s, CO_2H); *m/z* 274 (M^+ + 1); $[\alpha]_D^{25}$ −21.0° (*c* 0.2, $CHCl_3$).

(3S,4S)-3-[(R)-1′-*Hydroxyethyl*]-1-*dimethyl-t-butylsilyl*-4-*dimethyl-t-butylsilyloxycarbonylazetidin*-2-*one* (**12**).—A solution of the acid (**11**) (90 mg), dimethyl-t-butylsilyl chloride (149

mg), and triethylamine (100 mg) in *N,N*-dimethylformamide (4 ml) was stirred at ambient temperature for 18 h. After dilution with benzene, the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded the silyl ester (**12**) (120 mg, 94.1%) as an oil; $\nu_{max.}(CHCl_3)$ 3 550 (OH), 1 740, and 1 725 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 6.3 Hz, 1′-Me), 3.07 (1 H, br s, OH), 3.25 (1 H, dd, *J* 2.6 and 4.0 Hz, 3-H), 4.12 (1 H, d, *J* 2.6 Hz, 4-H), and 4.27 (1 H, m, 1′-H) (Found: $M^+ + 1$, 388.2320. $C_{18}H_{38}NO_4Si_2$ requires $M + 1$, 388.2338), which was used in the next reaction without further purification.

(3S,4S)-1-*Dimethyl-t-butylsilyl*-3-[(R)-1′-(*dimethylbutylsilyloxy*)*ethyl*]-4-*oxoazetidine*-2-*carboxylic Acid* (**13**).—A solution of the silyl ester (**12**) (100 mg) in THF (3 ml) containing 2.5M aqueous acetic acid (1 ml) was stirred at ambient temperature for 6 h. After neutralisation with 5% aqueous sodium hydrogen carbonate, the mixture was concentrated to leave the residue, which was extracted with ether. The ethereal layer was treated with 1M hydrochloric acid (0.1 ml), washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a powder, which was recrystallized from ether to afford the acid (**13**) (98 mg, 81.6%) as needles, m.p. 132—133 °C; $\nu_{max.}(CHCl_3)$ 1 745 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 0.07 (3 H, s, Me), 0.09 (3 H, s, Me), 0.18 (3 H, s, Me), 0.26 (3 H, s, Me), 0.89 (9 H, s, Bu^t), 0.97 (9 H, s, Bu^t), 1.22 (3 H, d, *J* 6.1 Hz, 1′-Me), 3.26 (1 H, dd, *J* 2.8 and 4.3 Hz, 3-H), 4.17 (1 H, d, *J* 2.8 Hz, 4-H), 4.24 (1 H, m, 1′-H), and 8.40 (1 H, br s, CO_2H) (Found: M^+ + Bu^t, 330.1550. $C_{14}H_{28}NO_4Si_2$ requires M − Bu^t, 330.1557); $[\alpha]_D^{25}$ −53.70° (*c* 0.108, $CHCl_3$).

(3R,4R)-3-[(R)-1′-*Dimethyl-t-butylsilyloxy*)*ethyl*]-4-*oxoazetidin*-2-*yl Acetate* (**4**; R = Bu^{t}Me$_2$Si).—Lead tetra-acetate (83 mg) was added to a stirred solution of the acid (**13**) (60 mg) and potassium acetate (15.2 mg) in *N,N*-dimethylformamide (2 ml) at 40 °C and the resulting mixture was stirred at the same temperature for a further 1 h. To the mixture was added ethylene glycol (0.5 ml), brine, and ethyl acetate, and the resulting mixture was filtered through Celite. The filtrate was extracted with ethyl acetate and the extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a white powder, which was recrystallised from ether to afford the desired acetate (**4**) (31 mg, 69.6%) as needles, 105 °C; $[\alpha]_D^{25}$ + 49.31° (*c* 0.073, $CHCl_3$). The spectroscopic data of (**4**) were identical with those reported.[6]

(3S,4R)-3-[(R)-1′-*Hydroxyethyl*]-4-(−)-*menthyloxycarbonylazetidin*-2-*one* (**14**).—A mixture of the isoxazolidine (**8**) (1.2 g), platinum oxide (150 mg) and methanol (50 ml) was stirred at ambient temperature under an atmosphere of hydrogen for 50 h. The insoluble material was filtered off through Celite and the filtrate was concentrated to leave a residue which was dissolved in acetonitrile (80 ml), then treated with DCC (0.6 g) at 60 °C for 3 h. Work-up as described above for the preparation of (**9**) gave the azetidinone (**14**) (253 mg, 35%) as an oil; $\nu_{max.}(CHCl_3)$ 3 420 (NH), 1 775, and 1 730 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 1.39 (3 H, d, *J* 6.1 Hz, 1′-Me), 3.05 (1 H, br s, OH), 3.52 (1 H, ddd, *J* 1.0, 5.6, and 8.6 Hz, 3-H), 4.02 (1 H, dq, *J* 6.1 and 8.6 Hz, 1′-H), 4.32 (1 H, d, *J* 5.6 Hz, 4-H), 4.81 (1 H, dt, *J* 4.2 and 10.5 Hz, CO_2CH), and 6.35 (1 H, br s, NH); *m/z* 297 (M^+).

(3S,4R)-3-[(R)-1′-(*Dimethyl-t-butylsilyloxy*)*ethyl*] *and* 3-[(R)-1′-*Hydroxyethyl*]-4-(−)-*menthyloxycarbonyl*-1-*dimethyl-t-butylsilylazetidin*-2-*one* (**15**) *and* (**16**).—A solution of the azetidinone (**14**) (250 mg), dimethyl-t-butylsilyl chloride (505 mg) and triethylamine (340 mg) in dry *N,N*-dimethylformamide (10 ml) was stirred at ambient temperature for 24 h. After dilution of the solution with benzene, the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with benzene–acetone (99:1, v/v) afforded the bis-silylated azetidinone (**15**) (247 mg, 56%) as an oil; $\nu_{max.}(CHCl_3)$ 1 740 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 0.05 (3 H, s, Me), 0.06 (3 H, s, Me), 0.12 (3 H, s, Me), 0.30 (3 H, s, Me), 0.87 (9 H, s, Bu^t), 0.97 (9 H, s, Bu^t), 1.30 (3 H, d, *J* 6.3 Hz, 1′-Me), 3.60 (1 H, dd, *J* 4.8 and 5.9 Hz, 3-H), 4.12 (1 H, d, *J* 5.9 Hz, 4-H), and 4.27 (1 H, dq, *J* 4.8 and 6.3 Hz, 1′-H) (Found: M^+ − Bu^t, 468.2966. $C_{24}H_{46}NO_4Si_2$ requires M − Bu^t, 468.2965); $[\alpha]_D^{25}$ −30.99° (*c* 1.2, $CHCl_3$). Further elution with benzene–acetone (97:3, v/v) gave the monosilylated azetidinone (**16**) (80 mg, 23%) as an oil; $\nu_{max.}(CHCl_3)$ 3 550 (OH) and 1 735 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 0.15 (3 H, s, Me), 0.29 (3 H, s, Me), 0.95 (9 H, s, Bu^t), 1.38 (3 H, d, *J* 6.1 Hz, 1′-Me), 3.51 (1 H, dd, *J* 5.8 and 9 Hz, 3-H), 4.11 (1 H, m, 1′-H), 4.18 (1 H, d, *J* 5.8 Hz, 4-H), and 4.76 (1 H, dt, *J* 4.2 and 10.5 Hz, CO_2CH); *m/z* 412 ($M^+ + 1$); $[\alpha]_D^{25}$ −32.31° (*c* 1.9, $CHCl_3$).

(3S,4R)-3-[(R)-1′-(*Dimethyl-t-butylsilyloxy*)*ethyl*]-4-*oxoazetidine*-2-*carboxylic Acid* (**18**).—1M Aqueous sodium hydroxide was added to a stirred solution of the azetidinone (**15**) (180 mg) in THF–methanol (2:1, v/v) (10 ml), and the resulting mixture was stirred at ambient temperature for 8 h. Work-up as described for the preparation of (**11**) afforded the 3*S*,4*R*-carboxylic acid (**18**) (40 mg, 43%) as an oil; $\nu_{max.}(CHCl_3)$ 3 405 (NH), 1 768, and 1 720 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$), 0.06 (3 H, s, Me), 0.12 (3 H, s, Me), 0.86 (9 H, s, Bu^t), 1.35 (3 H, d, *J* 6.3 Hz, 1′-Me), 3.55 (1 H, dd, *J* 2.9 and 5.7 Hz, 3-H), 4.28 (1 H, m, 1′-H), 4.30 (1 H, d, *J* 5.7 Hz, 4-H), 6.80 (1 H, br s, NH), and 9.89 (1 H, br s, CO_2H) (Found: $M^+ + 1$, 274.1462. $C_{12}H_{24}NO_4Si$ requires $M + 1$, 274.1472); $[\alpha]_D^{25}$ +2.22 (*c* 0.36, $CHCl_3$), and the menthyl ester (**17**) (67 mg, 48%) which, without purification, was further silylated with dimethyl-t-butylsilyl chloride and triethylamine in *N,N*-dimethylformamide to give (**15**) in quantitative yield.

(3S,4R)-3-[(R)-1′-*Hydroxyethyl*]-1-*dimethyl-t-butylsilyl*-4-*dimethyl-t-butylsilyloxycarbonylazetidin*-2-*one* (**20**) *and* (3S,4R)-1-*Dimethyl-t-butylsilyl*-3-[(R)-1′-(*dimethyl-t-butylsilyloxy*)*ethyl*]-4-*oxoazetidine*-2-*carboxylic Acid* (**19**).—A solution of the acid (**18**) (70 mg), dimethyl-t-butylsilyl chloride (116 mg) and triethylamine (78 mg) in dry *N,N* dimethylformamide (4 ml) was stirred at ambient temperature for 24 h. The mixture was diluted with benzene and the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a semi-solid, which was crystallised from hexane to give the silyl ester (**20**) (13 mg, 13.5%) as needles, m.p. 147 °C (Found: C, 55.75; H, 9.75; N, 3.8. $C_{18}H_{33}NO_4Si_2$ requires C, 55.75; H, 9.6; N, 3.6%); $\nu_{max.}(CHCl_3)$ 1 740 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 0.08 (6 H, s, 2 × Me), 0.16 (3 H, s, Me), 0.31 (3 H, s, Me), 0.89 (9 H, s, Bu^t), 0.98 (3 H, s, Bu^t), 1.33 (3 H, d, *J* 6.2 Hz, 1′-Me), 3.60 (1 H, dd, *J* 5.6 and 5.8 Hz, 3-H), 4.22 (1 H, d, *J* 5.6 Hz, 4-H), and 4.40 (1 H, dq, *J* 5.8 and 6.2 Hz, 1′-H); *m/z* 330 (M^+ − Bu^t). From the mother liquor, the acid (**19**) (61 mg, 62%) was isolated as an oil; $\nu_{max.}(CHCl_3)$ 1 740 cm^{-1} (C=O); δ_H(100 MHz; $CDCl_3$) 1.40 (3 H, d, *J* 6.3 Hz, 1′-Me), 3.64 (1 H, dd, *J* 4.2 and 5.6 Hz, 3-H), 4.20 (1 H, d, *J* 5.6 Hz, 4-H), 4.27 (1 H, dd, *J* 4.2 and 6.3 Hz, 1′-H), and 8.15 (1 H, br s, CO_2H) (Found: M^+ + Bu^t, 330.1566. $C_{14}H_{28}NO_4Si_2$ requires M − Bu^t, 330,1558).

(3R,4R)-3-[(R)-(*Dimethyl-t-butylsilyloxy*)*ethyl*]-4-*oxoazetidin*-2-*yl Acetate* (**4**; R = Bu^{t}Me$_2$Si).—Following the procedure described above for the preparation of compound (**4**) from (**13**), the azetidinone (**4**) (29 mg, 65.1%) was prepared from (**19**) (60 mg) by treatment with potassium acetate (15.2 mg) and

lead tetra-acetate (83 mg) in *N*,*N*-dimethylformamide (2 ml), as needles, m.p. 82—84 °C; $[\alpha]_D^{25}$ +16.27° (*c* 0.086, $CHCl_3$).

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