β-Lactam Antifungals. II.[1] Enantiocontrolled Synthesis of (2*R*,5*S*)-2-Hydroxymethyl-1-carbapenam, the Carba-Analog of a Clavam Antifungal

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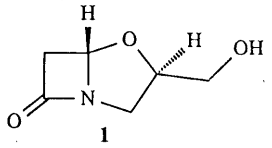
(2*R*,5*S*)-2-Hydroxymethyl-1-carbapenam (3), the carba-analog of an antifungal β-lactam (2*R*,5*S*)-2-(hydroxymethyl)clavam (1), was synthesized in an enantiocontrolled manner, starting from the coupling reaction of an optically active phthalimido-acetate (3*S*,4*S*)-4 and an allylsilane 7, followed by removal of the phthalimido group that was crucial for asymmetric induction. Hydroboration, protecting-group interconversion, and cyclization gave 3 stereoselectively.

Keywords carbapenam; synthesis; enantiocontrol; antifungal; oxapenam; allylsilane; phthalimide; isonitrile; hydroboration

(3*R*,5*S*)-3-Hydroxymethyl-4-oxa-1-azabicyclo[3.2.0]-heptan-7-one [(2*R*,5*S*)-2-(hydroxymethyl)clavam] (**1**) is an antifungal β-lactam that was isolated by Brown and Evans[2] from culture fluides of *Streptomyces clavuligerus*. It is reported to exhibit activity against a number of species of fungi. From a stereochemical point of view, it is interesting that this and related clavam antifungals possess the 5*S* absolute configuration (hereafter in this paper, the clavam numbering shown in A will be used), which is opposite to that of the corresponding positions of the natural β-lactam antibacterials, such as penicillin and cephalosporin, and the β-lactamase inhibitor clavulanic acid (**2**).[3]

The clavam **1** is structurally rather simple and therefore deserves attention as a new lead for a novel type of antifungal agent. As a part of a program directed toward the development of novel antifungal agents, we first synthesized **1** in an enantiocontrolled manner.[1] The clavam **1** synthesized, however, showed only moderate antifungal potency and its chemical instability required improvement. Consequently, structural modification of **1** was started. We reasoned, by analogy with clavulanic acid **2**, that the chemical instability of the clavam **1** was brought about by protonation at O1, which activates the β-lactam system, followed by the attack of a nucleophile on the C7 carbonyl to cleave the β-lactam ring, as shown in B. Consequently, we designed the 1-carba-analog of the natural product **1**, the title compound, (2*R*,5*S*)-2-hydroxymethyl-1-carbapenam (**3**), in the expectation that **3** might be chemically more stable than **1**, and exhibit higher biological activty. In the present paper, we report an enantiocontrolled synthesis of **3**.



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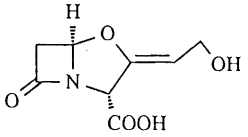

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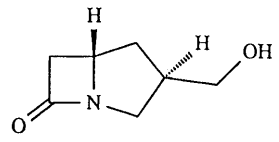

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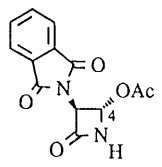

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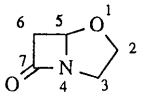
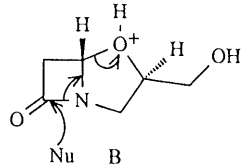


A clavam skeleton



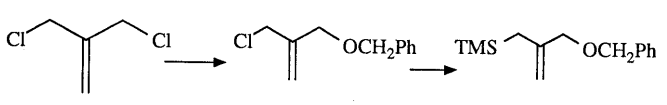
B

Chart 1

We recognized the importance of controlling the stereochemistry at C5 in the synthesis, because the absolute configuration at this position generally seems to determine whether bicyclic β-lactams were antibacterial or antifungal.[3] Toward this end, we selected the known, optically active phthalimido-acetate (3*S*,4*S*)-**4**,[1,4] which is readily available from 6-aminopenicillanic acid (6-APA), as a starting material for the synthesis. The bulky, subsequently removable phthalimido group in (3*S*,4*S*)-**4** was expected to control the stereochemistry upon C–C bond formation at the neighboring C4 position. For the remaining four-carbon segment, we selected the allylsilane **7**.

This allylsilane **7** was prepared in two steps from commercially available allylic dichloride **5**, as shown in Chart 2. Thus, the dichloride **5** was treated with sodium benzyloxide in tetrahydrofuran (THF) to afford a half-ether **6** in 66% yield, and **6** was converted to the allylsilane **7** in 77% yield *via* the Grignard reagent.

On the other hand, the optically active phthalimido-acetate (3*S*,4*S*)-**4** was converted by treatment with chlorotrimethylsilane and triethylamine to an *N*-silyl-β-lactam (3*S*,4*S*)-**8**. This lactam (3*S*,4*S*)-**8** reacted with the allylsilane **7** in 1,2-dichloroethane at 50 °C in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate[5] (TMSOTf) to afford, after aqueous work-up, the *trans* lactam (3*S*,4*S*)-**9** in 79% overall yield from (3*S*,4*S*)-**4** (Chart 3). The coupling constant between the C3 and C4 protons in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of (3*S*,4*S*)-**9** was 2 Hz. This result shows that the relative configuration of the C3 and C4



5 **6** **7**

Chart 2

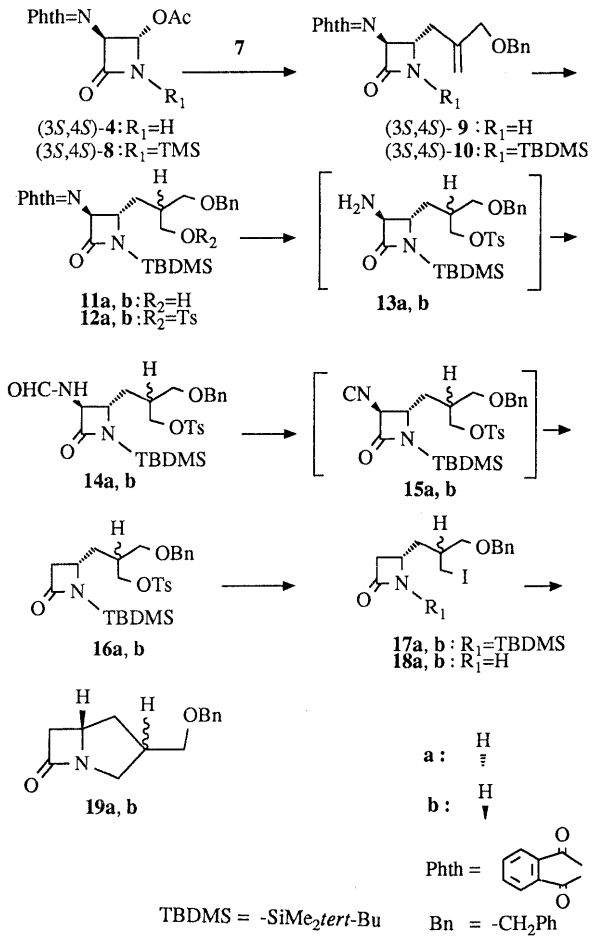


Chart 3

substituents is *trans*, and accordingly, the absolute configuration at C4 is *S*. The lactam nitrogen was silylated again using *tert*-butylchlorodimethylsilane and triethylamine in *N*,*N*-dimethylformamide (DMF), giving (3*S*,4*S*)-**10** in 94% yield. The olefin moiety in (3*S*,4*S*)-**10** was hydroborated using borane dimethylsulfide in THF, to afford, after oxidative work-up, a diastereomeric mixture of alcohols, which was separated by flash column chromatography to give the more polar isomer **11a** in 24% yield, and the less polar one **11b** in 43% yield. The absolute configuration of the chiral centers that were generated in **11a** and **11b** could not be determined at this stage, but it was later assigned to be as depicted in Chart 3.

In order to investigate the subsequent steps, the diastereomer **11a** was subjected to the following reaction first. This alcohol was tosylated by treatment with *p*-toluenesulfonyl chloride in pyridine to afford a tosylate **12a** in 99% yield. The phthaloyl group in **12a** was removed by reaction with methylhydrazine in dichloromethane to liberate an unstable amine **13a**, which, without isolation, was formylated to give a formamide **14a** in 73% overall yield from **12a**. The formamide **14a** was dehydrated using trichloromethyl chloroformate ("diphosgene") and triethylamine in dichloromethane to give an isocyanide **15a**, which was decyanated[6] by heating with tributylstannane and a catalytic amount of α,α′-azobisisobutyronitrile in benzene to give **16a** in 77% overall yield from **14a**. The tosyloxy group in **16a** was converted into the iodine atom in the conventional manner, quantitatively giving an iodide

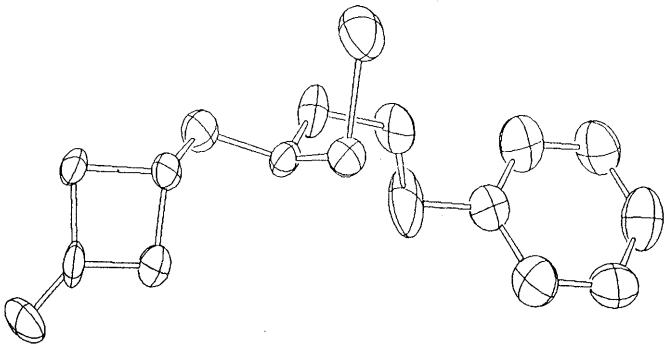


Fig. 1. Projection of the Structure of the Iodide **18a**

17a, which was desilylated by treatment with tetrabutylammonium fluoride to give a crystalline, *N*-unsubstituted β-lactam **18a** in quantitative yield.

Following exactly the same reaction sequence as described above, the diastereomeric alcohol **11b** was converted into the corresponding iodide **18b**.

At this stage, the diastereomer **18a** was subjected to X-ray diffraction analysis, and the relative configuration of the two chiral centers that exist in this diastereomer was determined (Fig. 1) to be *lk*. Taking into account that the absolute configuration at C4 in the azetidinone ring in **18a** is *S*, the configuration at the chiral center in the side chain was found to be *S*. Hence, the absolute configuration of **11a**, **b** through **18a**, **b** was found to be as depicted in Chart 3.

The iodides **18a**, **b** were separately treated with powdered potassium carbonate in DMF at room temperature to give the carbapenams **19a**, **b** in 64 and 82% yields, respectively. Then, the hydrogenolysis of the diastereomer **19a** to **3** was investigated. However, **19a** remained almost unchanged after being treated with 10% palladium–carbon catalyst under H_2 atmosphere even at 150 atm for 4 h; only a trace amount of the desired alcohol **3** was detected in the reaction mixture.[7]

Therefore, we next turned our attention to the preparation of the corresponding *tert*-butyldimethylsilyl ether **33**. This was achieved as follows (Chart 4).

The phthalimide (3*S*,4*S*)-**10** was converted, in a manner similar to that described for the preparation of **14a** from **12a**, into a formamide (3*S*,4*S*)-**21** in 64% yield. The formamido moiety was then removed, in the same manner as described above, *via* the isocyanide (3*S*,4*S*)-**22**, to give (*S*)-**23** in 82% yield. The olefin moiety in (*S*)-**23** was hydroborated as above, giving a diastereomeric mixture of alcohols, which was separated by flash column chromatography to give the more polar alcohol **24a** in 27% yield, and the less polar one **24b** in 34% yield. The configuration of the two alcohols **24a** and **24b** was determined to be as depicted, by leading these alcohols to the aforementioned tosylates **16a** and **16b**, respectively. Although the stereoselectivity in this hydroboration reaction was low, both diastereomers **24a** and **24b** could be converted into the sole, desired intermediate **30**.

Thus, the diastereomer **24a** was treated with isobutyryl chloride in pyridine to give an ester **25** in 90% yield, and this was hydrogenolyzed in ethanol using palladium black at 1 atm to give a half-alcohol **26**. Since this material was prone to suffer acyl migration upon standing for a long

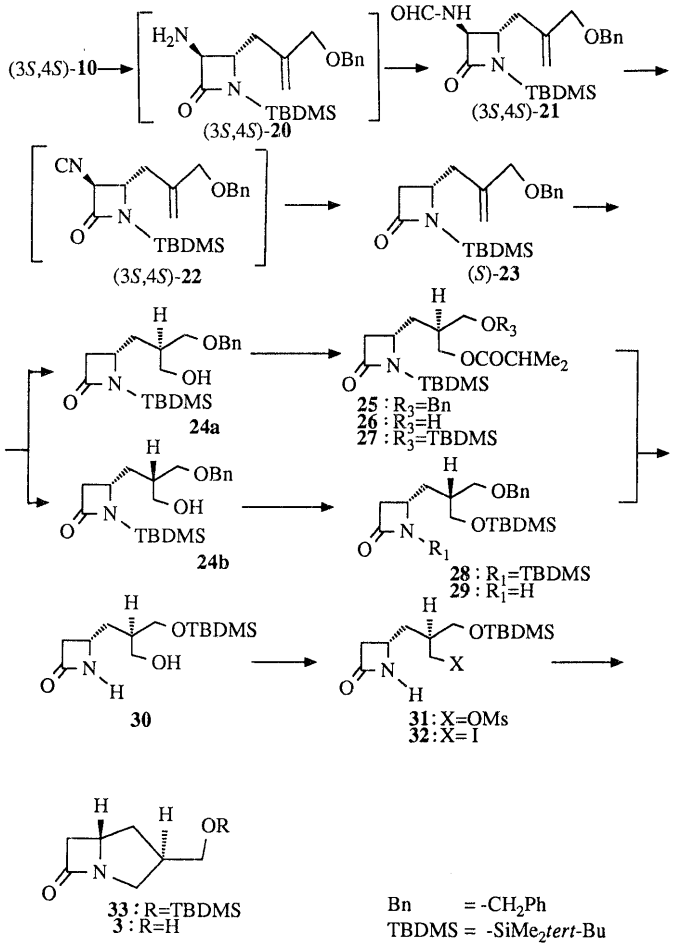


Chart 4

time, it was crucial to use palladium black instead of palladium–carbon, in order to shorten the reaction time. The product **26** was silylated immediately to give the silyl ether **27** in 71% overall yield from **25**. Upon treatment with sodium hydroxide in methanol–water, **27** was selectively *N*-desilylated and was converted into an alcohol **30** in 99% yield.

On the other hand, the other diastereomer **24b** was converted into a silyl ether **28** in 95% yield, and **28** was *N*-desilylated by sodium hydroxide into **29** in quantitative yield. Hydrogenolysis of **29** using 10% palladium–carbon catalyst gave the above-mentioned alcohol **30** in 97% yield.

The alcohol **30** thus obtained was mesylated to give **31** in 90% yield, and the latter was converted into an iodide **32** in 88% yield. The iodide **32** was cyclized, in a way similar to that described for **18a**, giving the desired carbapenam **33** in 72% yield.

Finally, the silyl protecting group was removed by treatment with tetrabutylammonium fluoride in THF which was buffered with acetic acid, liberating the title compound **3**, $[\alpha]_D^{25}$ $-191°$ ($c=1.20$, $CHCl_3$), as a colorless oil in 57% yield after chromatographic purification.

Contrary to our expectation, the carbapenam **3** turned out to be much more unstable than the oxapenam **1**. When left to stand in chloroform overnight, **3** decomposed almost completely to give insoluble, gummy precipitates. The difference of "ring strain" that is inherent in oxa- and carbapenam systems presumably overwhelmed the effect of protonation shown in B. The carbapenam derivative **3** exhibited no antifungal activity *in vitro*.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer, ^{1}H-NMR spectra on a Varian EM-360L spectrometer (60 MHz), or a JEOL GX-270 spectrometer (270 MHz) using tetramethylsilane as the internal standard, and mass spectra (MS) and high-resolution mass spectra (HRMS) on a JEOL JMS D300 spectrometer. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 0.25 mm (E. Merck), and spots were made visible by ultraviolet (UV) irradiation or by spraying with phosphomolybdic acid or with vanadic acid–sulfuric acid followed by heating. Preparative TLC was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 2 mm (E. Merck). Chromatography columns were prepared with silica gel (60—110 mesh, Kanto Chemical Co., Inc.), and flash chromatography columns were prepared with silica gel (230—400 mesh, E. Merck). The amount of silica gel used and the developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dddd, doublet of doublets of doublets of doublets; ddddd, doublet of doublets of doublets of doublets of doublets; dt, doublet of triplets; m, multiplet; br, broad; sh, shoulder.

3-Benzyloxy-2-chloromethyl-1-propene (6) Benzyl alcohol (9.80 g, 90.7 mmol) was slowly added to a stirred suspension of NaH (55% mineral oil suspension, 3.60 g, 82.5 mmol, washed with hexane) in THF (100 ml) at 0 °C. When hydrogen gas ceased to evolve, 3-chloro-2-chloromethyl-1-propene (**5**, 21.0 g, 16.8 mmol) was added. The mixture was refluxed for 6 h. After cooling, it was partitioned between hexane and water. The organic layer was dried and concentrated under reduced pressure giving an oily residue, which was purified by distillation to give **6** (11.8 g, 66%, bp 110—116 °C (3 mmHg)) as an oil. *Anal.* Calcd for $C_{11}H_{13}ClO$: C, 67.18; H, 6.66. Found: C, 67.40; H, 6.63. IR ($CHCl_3$): 1725, 1705, 1090, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.08 (4H, s-like), 4.47 (2H, s), 5.06 (2H, br s), 7.30 (5H, s). MS *m/z*: 197, 195 (M^+-1), 166, 131, 122, 107, 91 (100%).

(2-Benzyloxymethyl-2-propenyl)trimethylsilane (7) A solution of **6** (13.0 g, 66 mmol) and chlorotrimethylsilane (14.3 g, 132 mmol) in THF (80 ml) was added to a suspension of Mg (3.20 g, 132 mmol) in THF (50 ml) with stirring under an N_2 atmosphere at 80 °C (bath temperature) over a period of 15 min. The mixture was refluxed for an additional 1 h. After cooling, the mixture was partitioned between hexane and a diluted aqueous solution of $NaHCO_3$. The resulting precipitates were dissolved by adding NH_4Cl (solid). The organic layer was collected, washed with brine, and dried. Evaporation of the solvent under reduced pressure and distillation of the oily residue gave **7** (11.9 g, 77%, bp 125—126 °C (8 mmHg)) as an oil. *Anal.* Calcd for $C_{14}H_{22}OSi$: C, 71.73; H, 9.46. Found: C, 71.51; H, 9.42. IR ($CHCl_3$): 2950, 1455, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: -0.02 (9H, s), 1.53 (2H, s), 3.81 (2H, br s), 4.44 (2H, s), 4.66 (1H, br s), 4.86 (1H, br s), 7.30 (5H, s). MS *m/z*: 235 (M^++1), 221, 181, 179, 143, 131, 115, 105, 91 (100%).

(3*S*,4*S*)-4-Acetoxy-3-phthalimido-1-trimethylsilyl-2-azetidinone [(3*S*,4*S*)-8] A mixture of (3*S*,4*S*)-4-acetoxy-3-phthalimido-2-azetidinone[1,4] [(3*S*,4*S*)-**4**, mp 184—188 °C (dec.), $[\alpha]_D^{25}$ $-56.0°$ ($c=0.48$, acetone), 4.00 g, 14.6 mmol], triethylamine (1.60 g, 15.8 mmol), chlorotrimethylsilane (1.70 g, 15.6 mmol), and CH_2Cl_2 (130 ml) was stirred at 0 °C for 50 min. Then it was diluted with dry ether (400 ml) and allowed to warm to room temperature. The resulting precipitates were filtered off and the solvent was evaporated off to give (3*S*,4*S*)-**8** (4.98 g, 99%) as a solid, which was used for the next step without further purification.

(3*S*,4*S*)-4-(2-Benzyloxymethyl-2-propenyl)-3-phthalimido-2-azetidinone [(3*S*,4*S*)-9] A solution of (3*S*,4*S*)-**8** (4.98 g, 14.4 mmol), **7** (6.70 g, 30.0 mmol), and TMSOTf (0.5 g, 2.3 mmol) in 1,2-dichloroethane (30 ml) was heated at 45—50 °C for 5 h. After the mixture had been cooled to 0 °C, a saturated aqueous solution of $NaHCO_3$ was added, and the whole was stirred for 10 min. Then it was extracted with $CHCl_3$ (×3), and the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (150 g, AcOEt : hexane = 1 : 6, v/v) to afford (3*S*,4*S*)-**9** [4.32 g, 79% overall yield from (3*S*,4*S*)-**4**] as an oil. *Anal.* Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 69.98; H, 5.39; N, 7.29. IR ($CHCl_3$): 3420, 1780, 1760, 1720, 1390 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.3—2.7 (2H, m), 3.95 (2H, br s), 4.23 (1H, ddd, $J=7$, 6, 2 Hz), 4.46 (2H, s), 5.00 (1H, d, $J=2$ Hz), 5.02 (1H, br s), 5.15 (1H, br s), 6.4 (1H, br), 7.3 (5H, br s), 7.6—8.0 (4H,

m). MS *m/z*: 377 ($M^+ + 1$), 315, 286, 225, 160, 148, 95, 91, 80 (100%).

(3*S*,4*S*)-4-(2-Benzyloxymethyl-2-propenyl)-1-*tert*-butyldimethylsilyl-3-phthalimido-2-azetidinone [(3*S*,4*S*)-10] A solution of (3*S*,4*S*)-**9** (16.38 g, 43.6 mmol), triethylamine (6.91 g, 70.0 mmol), and *tert*-butylchlorodimethylsilane (10.30 g, 70.0 mmol) in DMF (220 ml) was stirred at room temperature for 10 h. The mixture was partitioned between PhH and a diluted aqueous solution of $NaHCO_3$. The organic layer was washed with water (×3) and brine (×1), successively. The extract was dried over Na_2SO_4, and the solvent was evaporated off to leave an oily residue, which was chromatographed (150 g, AcOEt : PhH = 1 : 12, v/v) to afford (3*S*,4*S*)-**10** (20.1 g, 94%) as an oil. *Anal.* Calcd for $C_{28}H_{34}N_2O_4Si$: C, 68.54; H, 6.98; N, 5.71. Found: C, 68.38; H, 7.05; N, 5.69. IR ($CHCl_3$): 2930, 1780, 1745, 1720, 1390, 1320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.34 (6H, s), 1.06 (9H, s), 2.38 (1H, d, J = 14 Hz), 2.83 (1H, dd, J = 14, 5 Hz), 3.90 (2H, br s), 4.1—4.5 (1H, m), 4.39 (2H, s), 4.9—5.2 (3H, m), 7.2—7.5 (5H, m), 7.6—8.1 (4H, m). MS *m/z*: 491 ($M^+ + 1$), 475, 433, 331, 231, 189 (100%).

(3*S*,4*S*)-4-[(*R*)-3-Benzyloxy-2-(hydroxymethyl)propyl]-1-*tert*-butyldimethylsilyl-3-phthalimido-2-azetidinone (11a) and Its Side-Chain Epimer (11b) A solution of $BH_3 \cdot SMe_2$ (2 M solution in THF, 0.88 ml, 1.76 mmol) was added to a solution of (3*S*,4*S*)-**10** (865 mg, 1.76 mmol) in THF (8 ml) at 0 °C with stirring. The mixture was stirred at 0 °C for 50 min, and then at room temperature for 1.5 h. At the end of this period, the mixture was diluted with THF (30 ml). A solution of H_2O_2 (35%, w/v, 1 ml, 0.01 mol) and NaOH (0.1 g, 2.5 mmol) in water (1 ml) was added to this at 0 °C with stirring. After being stirred at 0 °C for 50 min, the mixture was partitioned between AcOEt and water. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave an oily residue, which was purified by flash column chromatography (15 g, AcOEt : PhH = 1 : 9—2 : 8, v/v) to afford the less polar isomer **11b** (387 mg, 43%) and the more polar one **11a** (210 mg, 24%) as oils. The spectral data of these alcohols are as follows.

11a: IR ($CHCl_3$): 3500, 1780, 1745, 1720, 1392 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.33 (6H, s), 1.03 (9H, s), 1.5—2.2 (3H, m), 3.3—3.7 (3H, m), 3.9—4.3 (2H, m), 4.30 (2H, s), 4.96 (1H, d, J = 3 Hz), 7.1—7.3 (5H, m), 7.6—8.0 (4H, m). MS *m/z*: 509 ($M^+ + 1$), 493, 451, 212, 204, 186, 113, 91 (100%). HRMS Calcd for $C_{28}H_{37}N_2O_5Si$ ($M^+ + 1$): 509.2470. Found: 509.2473.

11b: IR ($CHCl_3$): 3500, 1780, 1748, 1720, 1392 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.31 (3H, s), 0.34 (3H, s), 1.03 (9H, s), 1.5—2.3 (3H, m), 3.3—3.7 (3H, m), 3.9—4.4 (2H, m), 4.50 (2H, s), 4.93 (1H, d, J = 3 Hz), 7.32 (5H, br s), 7.6—8.0 (4H, m). MS *m/z*: 509 ($M^+ + 1$), 493, 451, 292, 212, 204, 113, 91 (100%). HRMS Calcd for $C_{28}H_{37}N_2O_5Si$ ($M^+ + 1$): 509.2470. Found: 509.2475.

(3*S*,4*S*)-4-[(*S*)-2-Benzyloxymethyl-3-(*p*-toluenesulfonyloxy)propyl]-1-*tert*-butyldimethylsilyl-3-phthalimido-2-azetidinone (12a) *p*-Toluenesulfonyl chloride (1.00 g, 5.3 mmol) was added to a stirred solution of **11a** (1.00 g, 1.96 mmol) in pyridine (10 ml) at 0 °C, and stirring was continued for 5 h at room temperature. Then the solvent was evaporated off *in vacuo*, and the residue was partitioned between PhH and water. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by flash column chromatography (20 g, AcOEt : PhH = 1 : 9, v/v) to give **12a** (1.29 g, 99%) as an oil. IR ($CHCl_3$): 1780, 1740, 1720, 1390, 1172 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.30 (6H, s), 1.00 (9H, s), 1.2—2.2 (3H, m), 2.40 (3H, s), 3.0—3.5 (2H, m), 3.8—4.2 (3H, m), 4.16 (2H, s), 4.79 (1H, d, J = 3 Hz), 6.9—7.5 (7H, m), 7.5—8.0 (6H, m). MS *m/z*: 605 ($M^+ - C_4H_9$), 499, 469, 278, 222, 148, 131, 91 (100%). HRMS Calcd for $C_{31}H_{33}N_2O_7SSi$ ($M^+ - C_4H_9$): 605.1776. Found: 605.1765.

(3*S*,4*S*)-4-[(*R*)-2-Benzyloxymethyl-3-(*p*-toluenesulfonyloxy)propyl]-1-*tert*-butyldimethylsilyl-3-phthalimido-2-azetidinone (12b) Following a procedure similar to that described for the preparation of **12a**, **11b** (1.80 g, 3.54 mmol) was tosylated to give **12b** (2.10 g, 89%) as a foam. IR ($CHCl_3$): 1780, 1750, 1720, 1390, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.26 (3H, s), 0.31 (3H, s), 1.02 (9H, s), 1.5—2.5 (3H, m), 2.39 (3H, s), 2.38 (2H, d, J = 5 Hz), 3.8—4.3 (3H, m), 4.40 (2H, s), 4.90 (1H, d, J = 3 Hz), 7.23 (2H, d, J = 9 Hz), 7.30 (5H, s), 7.67 (2H, d, J = 9 Hz), 7.6—8.0 (4H, m). MS *m/z*: 605 ($M^+ - C_4H_9$), 499, 469, 451, 229, 212, 186, 91 (100%). HRMS Calcd for $C_{31}H_{33}N_2O_7SSi$ ($M^+ - C_4H_9$): 605.1776. Found: 605.1775.

(3*S*,4*S*)-4-[(*S*)-2-Benzyloxymethyl-3-(*p*-toluenesulfonyloxy)propyl]-1-*tert*-butyldimethylsilyl-3-formylamino-2-azetidinone (14a) Methylhydrazine (0.5 g, 11 mmol) was added to a solution of **12a** (1.00 g, 1.51 mmol) in CH_2Cl_2 (20 ml) at 0 °C with stirring. The mixture was stirred and allowed to warm to room temperature over a period of 3 h. Then it was diluted with CCl_4 (*ca.* 100 ml), and the solvent was evaporated off *in vacuo*, in order to remove excess methylhydrazine. The residue was dissolved in a mixture of CCl_4 (*ca.* 100 ml) and CH_2Cl_2 (*ca.* 20 ml) and the solvent was again evaporated off. After repeating this procedure two more times, the residue was dissolved again in CH_2Cl_2 (50 ml), and the mixture was stirred at room temperature for 12 h, during which time precipitates gradually emerged. To this slurry was added, at 0 °C, a solution of 1-formylimidazole, which had been obtained by mixing formic acid (206 mg, 4.5 mmol) and 1,1′-carbonyldiimidazole (726 mg, 4.5 mmol) in CH_2Cl_2 (1 ml). After 1 h, the mixture was partitioned between CH_2Cl_2 and a diluted aqueous solution of Na_2CO_3. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give an oily residue, which was purified by flash column chromatography (15 g, AcOEt : PhH = 1 : 3, v/v) to give **14a** (0.62 g, 73%) as an oil. IR ($CHCl_3$): 3420, 1740, 1685, 1360, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.30 (6H, s), 0.94 (9H, s), 1.2—2.2 (3H, m), 2.41 (3H, s), 3.38 (1H, d, J = 5 Hz), 3.4—4.5 (2H, m), 4.08 (1H, d, J = 6 Hz), 4.38 (2H, s), 6.3 (1H, br), 7.2—7.5 (7H, m), 7.82 (2H, d, J = 9 Hz), 8.15 (1H, br s). MS *m/z*: 561 ($M^+ + 1$), 503, 418, 358, 267, 229, 91 (100%). HRMS Calcd for $C_{28}H_{41}N_2O_6SSi$ ($M^+ + 1$): 561.2452. Found: 561.2454.

(3*S*,4*S*)-4-[(*R*)-2-Benzyloxymethyl-3-(*p*-toluenesulfonyloxy)propyl]-1-*tert*-butyldimethylsilyl-3-formylamino-2-azetidinone (14b) Following a procedure similar to that described for the preparation of **14a**, **12b** (2.10 g, 3.17 mmol) was dephthaloylated and then formylated, to give **14b** (1.00 g, 56%) as an oil. IR ($CHCl_3$): 3430, 1740, 1690, 1360, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.25 (3H, s), 0.26 (3H, s), 0.96 (9H, s), 1.53 (1H, ddd, J = 14, 12, 4 Hz), 1.96 (1H, ddd, J = 14, 9, 3 Hz), 2.3—2.5 (1H, m), 2.43 (3H, s), 3.37 (1H, d, J = 6 Hz), 3.67 (1H, dt, J = 12, 3 Hz), 4.04 (1H, dd, J = 10, 5 Hz), 4.08 (1H, dd, J = 10, 4 Hz), 4.38 (1H, d, J = 12 Hz), 4.41 (1H, d, J = 12 Hz), 4.43 (1H, dd, J = 7, 3 Hz), 6.0 (1H, br d, J = 7 Hz), 7.2—7.4 (7H, m), 7.76 (2H, d, J = 8 Hz), 8.13 (1H, d, J = 0.7 Hz). MS *m/z*: 560 ($M^+ + 1$), 503, 418, 358, 267, 229 (100%). HRMS Calcd for $C_{28}H_{40}N_2O_6SSi$: 560.2374. Found: 560.2369.

(*S*)-4-[(*S*)-2-Benzyloxymethyl-3-(*p*-toluenesulfonyloxy)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (16a) Trichloromethyl chloroformate (230 mg, 1.16 mmol) was added to a solution of **14a** (620 mg, 1.11 mmol) and triethylamine (570 mg, 5.6 mmol) in CH_2Cl_2 (32 ml) at −50 °C, and stirring was continued at −50 °C for 10 min. At the end of this period, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was stirred under ice-cooling for 5 min. The mixture was extracted with CH_2Cl_2, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude isocyanide **15a** (0.6 g) as a brown oil. This product was mixed with tributylstannane (650 mg, 2.23 mmol) and α,α′-azobisisobutyronitrile (23 mg, 0.14 mmol) in PhH (50 ml) under an atmosphere of argon, and the mixture was refluxed for 30 min. After cooling, the concentrated mixture was purified by flash column chromatography (15 g, AcOEt : hexane = 1 : 19, v/v) to give **16a** (443 mg, 77%) as a solid. Recrystallization from Et_2O–hexane gave an analytical sample as colorless needles, mp 79—80 °C. *Anal.* Calcd for $C_{27}H_{39}NO_5SSi$: C, 62.63; H, 7.59; N, 2.71; S, 6.19. Found: C, 62.58; H, 7.54; N, 2.63; S, 6.36. IR ($CHCl_3$): 1720, 1360, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.19 (6H, s), 0.95 (9H, s), 1.2—2.1 (3H, m), 2.41 (3H, s), 2.43 (1H, dd, J = 15, 3 Hz), 3.07 (1H, dd, J = 15, 5 Hz), 3.2—3.7 (1H, m), 3.40 (1H, d, J = 5 Hz), 4.03 (1H, d, J = 5 Hz), 4.40 (2H, s), 7.1—7.5 (7H, m), 7.81 (2H, d, J = 9 Hz). MS *m/z*: 517 (M^+), 460, 418, 229, 105 (100%).

(*S*)-4-[(*R*)-2-Benzyloxymethyl-3-(*p*-toluenesulfonyloxy)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (16b) Following a procedure similar to that described for the preparation of **16a**, **14b** (1.03 g, 1.84 mmol) was dehydrated and then decyanated to give **16b** (0.81 g, 85%) as an oil. IR ($CHCl_3$): 1725, 1360, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.20 (3H, s), 0.21 (3H, s), 0.94 (9H, s), 1.5—1.8 (1H, s), 1.8—2.0 (2H, m), 2.43 (3H, s), 2.54 (1H, dd, J = 15, 3 Hz), 3.07 (1H, dd, J = 15, 5 Hz), 3.33 (1H, dd, J = 10, 6 Hz), 3.36 (1H, dd, J = 10, 4 Hz), 3.56 (1H, dddd, J = 12, 5, 3, 3 Hz), 4.05 (1H, dd, J = 10, 5 Hz), 4.07 (1H, dd, J = 10, 5 Hz), 4.38 (2H, s), 7.2—7.4 (7H, m), 7.77 (2H, d, J = 9 Hz). MS *m/z*: 460 ($M^+ - C_4H_9$), 418, 229, 91 (100%). HRMS Calcd for $C_{23}H_{30}NO_5SSi$ ($M^+ - C_4H_9$): 460.1612. Found: 460.1631.

(*S*)-4-[(*S*)-3-Benzyloxy-2-(iodomethyl)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (17a) A mixture of **16a** (430 mg, 0.83 mmol), NaI (1.7 g, 11 mmol), and acetone (17 ml) was refluxed for 2 h. The mixture was partitioned between AcOEt and water, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by flash column chromatography (6 g, AcOEt : hexane = 1 : 9, v/v) to afford **17a** (398 mg, 100%) as an oil. IR ($CHCl_3$): 2950, 1725, 1315, 1192, 1090, 1000, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.22 (6H, s), 0.95 (9H, s), 1.2—2.2 (3H, m), 2.60 (1H, dd,

$J=15$, 3 Hz), 3.15 (1H, dd, $J=15$, 5 Hz), 3.0—3.7 (1H, m), 3.36 (2H, d, $J=5$ Hz), 3.46 (2H, d, $J=5$ Hz), 4.50 (2H, s), 7.33 (5H, s). MS *m/z*: 458 (M^+-CH_3), 416 ($M^+-C_4H_9$), 374, 203, 91 (100%). HRMS Calcd for $C_{19}H_{29}INO_2Si$ (M^+-CH_3): 458.1011. Found: 458.1020.

(*S*)-4-[(*R*)-3-Benzyloxy-2-(iodomethyl)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (17b) Following a procedure similar to that described for the preparation of **17a**, **16b** (90 mg, 0.174 mmol) was treated with NaI in acetone to give **17b** (70 mg, 85%) as an oil. IR ($CHCl_3$): 2950, 1725, 1310, 1195, 1100, 1000, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.25 (3H, s), 0.26 (3H, s), 0.96 (9H, s), 1.2—1.8 (2H, m), 1.8—2.0 (1H, m), 2.61 (1H, dd, $J=15$, 3 Hz), 3.13 (1H, dd, $J=15$, 5 Hz), 3.24 (1H, dd, $J=10$, 4 Hz), 3.31 (1H, dd, $J=10$, 7 Hz), 3.37 (1H, dd, $J=10$, 5 Hz), 3.47 (1H, dd, $J=10$, 4 Hz), 3.57 (1H, dddd, $J=11$, 6, 3, 3 Hz), 4.51 (2H, s), 7.2—7.5 (5H, m). MS *m/z*: 474 ($M^+ +1$), 458, 416, 374, 91 (100%). HRMS Calcd for $C_{20}H_{33}INO_2Si$ ($M^+ +1$): 474.1324. Found: 474.1319.

(*S*)-4-[(*S*)-3-Benzyloxy-2-(iodomethyl)propyl]-2-azetidinone (18a) A solution of **17a** (398 mg, 0.84 mmol), Bu_4NF (1.0 M solution in THF, 0.90 ml, 0.90 mmol), and AcOH (160 mg, 2.7 mmol) in THF (7 ml) was stirred at 0 °C for 1 h. The mixture was partitioned between AcOEt and a diluted aqueous solution of $NaHCO_3$, and the organic layer was washed with brine. The extract was dried over Na_2SO_4, and the solvent was evaporated off to leave an oily residue, which was purified by flash column chromatography (6 g, AcOEt : PhH = 3 : 1, v/v) to afford **18a** (302 mg, 100%) as a solid. Recrystallization from Et_2O–hexane gave an analytical sample as colorless needles, mp 76—77 °C. *Anal.* Calcd for $C_{14}H_{18}INO_2$: C, 46.81; H, 5.05; N, 3.90; I, 35.33. Found: C, 47.10; H, 5.22; N, 3.94; I, 35.60. IR ($CHCl_3$): 3400, 1745, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.8 (3H, m), 2.63 (1H, ddd, $J=15$, 3, 1 Hz), 3.09 (1H, ddd, $J=15$, 5, 2 Hz), 3.25 (1H, dd, $J=10$, 5 Hz), 3.36 (1H, dd, $J=10$, 5 Hz), 3.40 (1H, dd, $J=9$, 7 Hz), 3.45 (1H, dd, $J=9$, 4 Hz), 3.69 (1H, dddd, $J=11$, 6, 6, 3 Hz), 4.52 (2H, s), 5.9 (1H, br), 7.3—7.4 (5H, m). MS *m/z*: 360 ($M^+ +1$), 331, 314, 226, 204, 190, 126, 91 (100%).

(*S*)-4-[(*R*)-3-Benzyloxy-2-(iodomethyl)propyl]-2-azetidinone (18b) Following a procedure similar to that described for the preparation of **18a**, **17b** (64 mg, 0.13 mmol) was desilylated to give **18b** (47 mg, 97%) as an oil. IR ($CHCl_3$): 3420, 1750, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.8 (3H, m), 2.58 (1H, ddd, $J=15$, 2, 1 Hz), 3.08 (1H, ddd, $J=15$, 5, 2 Hz), 3.27 (1H, dd, $J=10$, 5 Hz), 3.36 (1H, dd, $J=10$, 5 Hz), 3.41 (1H, dd, $J=10$, 5 Hz), 3.48 (1H, dd, $J=10$, 5 Hz), 3.70 (1H, dddd, $J=7$, 7, 5, 2 Hz), 4.51 (2H, s), 5.9 (1H, br), 7.3—7.4 (5H, m). MS *m/z*: 360 ($M^+ +1$), 314, 190, 126, 91 (100%). HRMS Calcd for $C_{14}H_{19}INO_2$ ($M^+ +1$): 360.0460. Found: 360.0459.

(3*R*,5*S*)-3-Benzyloxymethyl-1-azabicyclo[3.2.0]heptan-7-one (19a) A mixture of **18a** (52 mg, 0.14 mmol), powdered K_2CO_3 (35 mg, 0.25 mmol), and DMF (0.9 ml) was vigorously stirred at room temperature for 18 h. The mixture was partitioned between PhH and a phosphate buffer solution (pH 7.0), and the organic layer was washed with water and brine. The extract was dried over Na_2SO_4 and the solvent was evaporated off to leave an oily residue, which was purified by preparative TLC (AcOEt : hexane = 2 : 3, v/v) to give **19a** (22.9 mg, 68%) as an oil. IR ($CHCl_3$): 1745, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (1H, ddd, $J=13$, 9, 7 Hz), 2.05 (1H, ddd, $J=13$, 7, 4 Hz), 2.58 (1H, dd, $J=16$, 2 Hz), 2.69 (1H, ddd, $J=12$, 5, 1 Hz), 2.82 (1H, m), 3.23 (1H, ddd, $J=16$, 5, 1 Hz), 3.40 (1H, dd, $J=9$, 6 Hz), 3.44 (1H, dd, $J=9$, 6 Hz), 3.74 (1H, dddd, $J=7$, 7, 5, 2 Hz), 3.79 (1H, dd, $J=12$, 7 Hz), 4.51 (2H, s), 7.2—7.4 (5H, m). MS *m/z*: 231 (M^+), 203, 189, 91 (100%). HRMS Calcd for $C_{14}H_{17}NO_2$: 231.1258. Found: 231.1266.

(3*S*,5*S*)-3-Benzyloxymethyl-1-azabicyclo[3.2.0]heptan-7-one (19b) Following a procedure similar to that described for the preparation of **19a**, **18b** (43 mg, 0.12 mmol) was cyclized to give **19b** (22.7 mg, 82%) as an oil. IR ($CHCl_3$): 1740, 1346 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (1H, ddd, $J=12$, 11, 9 Hz), 2.28 (1H, ddd, $J=12$, 6, 6 Hz), 2.60 (1H, dd, $J=15$, 2 Hz), 2.85 (1H, ddddd, $J=14$, 10, 8, 6, 6 Hz), 3.06 (1H, ddd, $J=11$, 8, 1 Hz), 3.20 (1H, ddd, $J=15$, 5, 1 Hz), 3.35 (1H, dd, $J=11$, 8 Hz), 3.46 (2H, d, $J=6$ Hz), 3.68 (1H, dddd, $J=9$, 6, 5, 2 Hz), 4.51 (2H, s), 7.2—7.5 (5H, m). MS *m/z*: 231 (M^+), 125, 107, 91 (100%). HRMS Calcd for $C_{14}H_{17}NO_2$: 231.1258. Found: 231.1263.

(3*S*,4*S*)-4-(2-Benzyloxymethyl-2-propenyl)-1-*tert*-butyldimethylsilyl-3-formylamino-2-azetidinone [(3*S*,4*S*)-21] Following a procedure similar to that described for the preparation of **14a**, (3*S*,4*S*)-**10** (20.1 g, 41 mmol) was dephthaloylated and then formylated to give (3*S*,4*S*)-**21** (7.62 g, 64%) as an oil. IR ($CHCl_3$): 3440, 1740, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.33 (6H, s), 1.05 (9H, s), 2.2—3.0 (2H, m), 3.93 (2H, br s), 4.0—4.5 (1H, m), 4.40 (2H, s), 4.7—5.2 (3H, m), 6.3 (1H, br), 7.1—7.5 (5H, m), 8.15 (1H, br s). MS *m/z*: 389 ($M^+ +1$), 331, 303, 246, 227, 186, 140, 123, 91 (100%). HRMS Calcd for $C_{21}H_{33}N_2O_3Si$ ($M^+ +1$): 389.2259. Found: 389.2263.

(*S*)-4-(2-Benzyloxymethyl-2-propenyl)-1-*tert*-butyldimethylsilyl-2-azetidinone [(*S*)-23] Following a procedure similar to that described for the preparation of **16a**, (3*S*,4*S*)-**21** (2.31 g, 6.0 mmol) was dehydrated and then decyanated to give (*S*)-**23** (1.66 g, 81%) as an oil. *Anal.* Calcd for $C_{20}H_{31}NO_2Si$: C, 69.52; H, 9.04, N, 4.05. Found: C, 69.29; H, 9.27; N, 4.09. IR ($CHCl_3$): 1720, 1460, 1330, 1255, 1188, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.23 (3H, s), 0.24 (3H, s), 0.96 (9H, s), 2.12 (1H, br dd, $J=14$, 11 Hz), 2.65 (1H, dd, $J=15$, 3 Hz), 2.73 (1H, br dd, $J=14$, 3 Hz), 3.11 (1H, dd, $J=15$, 5 Hz), 3.72 (1H, dddd, $J=11$, 5, 3, 3 Hz), 3.94 (2H, br s), 4.49 (2H, br s), 4.93 (1H, br s), 5.12 (1H, br s), 7.2—7.5 (5H, m). MS *m/z*: 346 ($M^+ +1$), 288, 246, 181, 142, 100, 91 (100%), 73.

(*S*)-4-[(*R*)-3-Benzyloxy-2-(hydroxymethyl)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (24a) and Its Side-Chain Epimer (24b) Following a procedure similar to that described for the preparation of **11a** and **11b**, (*S*)-**23** (119 mg, 0.34 mmol) was hydroborated to give a diastereomeric mixture of alcohols, which was separated by flash column chromatography (2 g, AcOEt : PhH = 1 : 4—2 : 3, v/v) to afford the less polar isomer **24b** (42 mg, 34%) and the more polar one **24a** (34 mg, 27%) as oils. The spectral data of these alcohols are as follows.

24a: IR ($CHCl_3$): 3400, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.21 (6H, s), 0.95 (9H, s), 1.46 (1H, ddd, $J=13$, 11, 4 Hz), 1.7—1.9 (1H, m), 1.96 (1H, ddd, $J=13$, 9, 3 Hz), 2.63 (1H, dd, $J=15$, 3 Hz), 3.13 (1H, dd, $J=15$, 5 Hz), 3.51 (1H, dd, $J=9$, 6 Hz), 3.5—3.8 (4H, m), 4.50 (1H, d, $J=11$ Hz), 4.53 (1H, d, $J=11$ Hz), 7.3—7.4 (5H, m). MS *m/z*: 364 ($M^+ +1$), 348, 322, 306, 264, 91 (100%). HRMS Calcd for $C_{20}H_{34}NO_3Si$ ($M^+ +1$): 346.2306. Found: 364.2303.

24b: IR ($CHCl_3$): 3400, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.22 (6H, s), 0.96 (9H, s), 1.37 (1H, ddd, $J=13$, 11, 4 Hz), 1.7—1.9 (1H, m), 1.99 (1H, ddd, $J=13$, 9, 4 Hz), 2.59 (1H, dd, $J=15$, 3 Hz), 3.13 (1H, dd, $J=15$, 5 Hz), 3.46 (1H, dd, $J=9$, 6 Hz), 3.5—3.7 (2H, m), 3.57 (1H, dd, $J=9$, 4 Hz), 3.72 (1H, dd, $J=7$, 3 Hz), 4.50 (1H, d, $J=12$ Hz), 4.53 (1H, d, $J=12$ Hz), 7.3—7.4 (5H, m). MS *m/z*: 364 ($M^+ +1$), 348, 306, 264, 91 (100%). HRMS Calcd for $C_{20}H_{34}NO_3Si$ ($M^+ +1$): 364.2306. Found: 364.2298.

Conversion of the Alcohols 24a, b to the Tosylates 16a, b Following a procedure similar to that described for the conversion of **11a** to **12a**, the alcohols **24a** and **24b** were tosylated separately to give the corresponding tosylates **16a** and **16b**, respectively. The products (yields: 85 and 87%) were identical with **16a** and **16b** obtained from **14a** and **14b**, respectively.

(*S*)-4-[(*S*)-2-Benzyloxymethyl-3-(isobutyryloxy)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (25) Isobutyryl chloride (87 mg, 0.82 mmol) was added to a stirred solution of **24a** (240 mg, 0.66 mmol) in pyridine (2.1 ml) at 0 °C, and stirring was continued at 0 °C for 1 h. Then a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was stirred for 10 min. The mixture was partitioned between Et_2O and water, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (2.5 g, AcOEt : PhH = 1 : 19, v/v) to afford **25** (257 mg, 90%) as an oil. IR ($CHCl_3$): 1730 (sh), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.21 (6H, s), 0.95 (9H, s), 1.15 (6H, d, $J=7$ Hz), 1.3—1.6 (1H, m), 1.9—2.1 (2H, m), 2.53 (1H, septet, $J=7$ Hz), 2.58 (1H, dd, $J=15$, 2 Hz), 3.13 (1H, dd, $J=15$, 5 Hz), 3.42 (2H, d, $J=4$ Hz), 3.5—3.7 (1H, m), 4.05 (1H, dd, $J=11$, 6 Hz), 4.07 (1H, dd, $J=11$, 6 Hz), 4.49 (2H, s), 7.2—7.4 (5H, m). MS *m/z*: 434 ($M^+ +1$), 418, 376, 334, 306, 264, 145, 91 (100%). HRMS Calcd for $C_{24}H_{40}NO_4Si$ ($M^+ +1$): 434.2724. Found: 434.2721.

(*S*)-1-*tert*-Butyldimethylsilyl-4-[(*R*)-2-(*tert*-butyldimethylsilyl)oxymethyl-3-(isobutyryloxy)propyl]-2-zaetidinone (27) A suspension of palladium black in water (*ca.* 0.2 ml) was added to a solution of **25** (26 mg, 0.060 mmol) in EtOH (2 ml), and the mixture was stirred at room temperature under an atmosphere of H_2 (1 atm) for 1 h. Then the mixture was filtered and the solvent was evaporated off to give an oily residue, which was immediately mixed with *tert*-butylchlorodimethylsilane (30 mg, 0.19 mmol) and imidazole (30 mg, 0.44 mmol) in DMF (1 ml) at 0 °C. The mixture was stirred at room temperature for 10 min, then a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with PhH. The extract was successively washed with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (0.5 g, AcOEt : PhH = 1 : 19, v/v) to afford **27** (17.5 mg, 64%) as an oil. IR ($CHCl_3$): 1720, 1470, 1255, 1190, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.23 (6H, s), 0.89 (9H, s), 0.95 (9H, s), 1.17 (6H, d, $J=7$ Hz), 1.37 (1H, ddd, $J=13$, 11, 4 Hz), 1.7—1.9 (1H, m), 2.03 (1H, ddd, $J=12$, 9, 3 Hz), 2.55 (1H,

septet, $J=7$ Hz), 2.59 (1H, dd, $J=15$, 3 Hz), 3.14 (1H, dd, $J=15$, 5 Hz), 3.59 (2H, d, $J=5$ Hz), 3.66 (1H, dddd, $J=11$, 5, 3, 3 Hz), 3.99 (1H, dd, $J=11$, 6 Hz), 4.01 (1H, dd, $J=11$, 7 Hz). MS *m/z*: 458 ($M^+ +1$), 442, 400, 358 (100%). HRMS Calcd for $C_{23}H_{48}NO_4Si_2$ ($M^+ +1$): 458.3119. Found: 458.3123.

(*S*)-4-[(*R*)-2-Benzyloxymethyl-3-(*tert*-butyldimethylsilyloxy)propyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (28) A solution of **24b** (0.48 g, 1.3 mmol), *tert*-butylchlorodimethylsilane (0.42 g, 2.8 mmol) and imidazole (0.196 g, 2.8 mmol) in DMF (12 ml) was stirred at 0 °C for 40 min. Then a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with PhH. The extract was successively washed with water and brine, and then dried over Na_2SO_4. Evaporation of solvent gave an oily residue, which was purified by column chromatography (10 g, AcOEt : PhH = 1 : 19, v/v) to give **28** (0.60 g, 95%) as an oil. IR ($CHCl_3$): 1725, 1255, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.22 (6H, s), 0.88 (9H, s), 0.95 (9H, s), 1.40 (1H, ddd, $J=13$, 11, 5 Hz), 1.7—1.8 (1H, m), 1.99 (1H, ddd, $J=14$, 9, 4 Hz), 2.61 (1H, dd, $J=15$, 3 Hz), 3.10 (1H, dd, $J=15$, 5 Hz), 3.34 (1H, dd, $J=9$, 7 Hz), 3.42 (1H, dd, $J=9$, 7 Hz), 3.60 (2H, d, $J=5$ Hz), 3.65 (1H, dddd, $J=14$, 5, 3, 3 Hz), 4.47 (2H, s), 7.2—7.4 (5H, m). MS *m/z*: 462 ($M^+ -CH_3$), 420 ($M^+ -C_4H_9$), 378, 91 (100%). HRMS Calcd for $C_{25}H_{44}NO_3Si_2$ ($M^+ -CH_3$): 462.2857. Found: 462.2858.

(*S*)-4-[(*R*)-2-Benzyloxymethyl-3-(*tert*-butyldimethylsilyloxy)propyl]-2-azetidinone (29) A solution of NaOH (0.1 g, 2.5 mmol) in water (1 ml) was added to a solution of **28** (0.60 g, 1.26 mmol) in MeOH (20 ml) at −15 °C with stirring. After being stirred at −15 °C for 13 h, the mixture was partitioned between Et_2O and water, and the organic layer was washed with a saturated aqueous solution of NH_4Cl and brine, successively. The extract was dried over Na_2SO_4, and the solvent was evaporated off, to leave an oily residue, which was purified by column chromatography to afford **29** (0.46 g, 100%) as an oil. IR ($CHCl_3$): 3425, 1750, 1190, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.5—2.0 (3H, m), 2.54 (1H, ddd, $J=15$, 3.5, 1.5 Hz), 3.05 (1H, ddd, $J=15$, 5, 2 Hz), 3.40 (1H, dd, $J=9$, 6 Hz), 3.45 (1H, dd, $J=9$, 5 Hz), 3.5—3.7 (2H, m), 3.6—3.8 (1H, m), 4.48 (2H, s), 5.9 (1H, br), 7.2—7.4 (5H, m). MS *m/z*: 348 ($M^+ -CH_3$), 335, 321, 306 ($M^+ -C_4H_9$), 264, 91 (100%). HRMS Calcd for $C_{19}H_{30}NO_3Si$ ($M^+ -CH_3$): 348.1993. Found: 348.1984.

(*S*)-4-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)propyl]-2-azetidinone (30) (a) A solution of **27** (22 mg, 0.048 mmol) and NaOH (10% in water, w/v, 0.1 ml, 0.25 mmol) in MeOH (1 ml) was stirred at 0 °C for 7 h. The mixture was partitioned between Et_2O and water, and the organic layer was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (0.5 g, AcOEt) to give **30** (13 mg, 99%) as an oil. IR ($CHCl_3$): 3400, 1750, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.5—1.9 (3H, m), 2.61 (1H, dd, $J=15$, 2 Hz), 3.11 (1H, dd, $J=15$, 5 Hz), 3.6—3.8 (5H, m), 5.9 (1H, br). MS *m/z*: 274 ($M^+ +1$), 216, 174 (100%). HRMS Calcd for $C_{13}H_{28}NO_3Si$ ($M^+ +1$): 274.1837. Found: 274.1819. (b) A mixture of **29** (59 mg, 0.16 mmol), 10% Pd/C (60 mg), and MeOH (0.8 ml) was stirred at room temperature under an atmosphere of H_2 (1 atm) for 17 h. Then it was filtered and the solvent was evaporated off to leave an oily residue, which was purified as described in (a) to give **30** (43 mg, 97%) as an oil.

(*S*)-4-[(*S*)-2-(*tert*-Butyldimethylsilyloxy)methyl-3-(methanesulfonyloxy)-propyl]-2-azetidinone (31) Methanesulfonyl chloride (50 mg, 0.44 mmol) was added to a solution of **30** (69 mg, 0.25 mmol) and triethylamine (78 mg, 0.77 mmol) in CH_2Cl_2 (1 ml) at 0 °C with stirring. After 10 min, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$, and the mixture was partitioned between Et_2O and water. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography to afford **31** (80 mg, 90%) as an oil. IR ($CHCl_3$): 3400, 1750, 1355, 1170, 830 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (9H, s), 1.71 (1H, dt, $J=14$, 7 Hz), 1.76 (1H, ddd, $J=14$, 7, 6 Hz), 1.97 (1H, triplet of quintets, $J=7$, 5 Hz), 2.60 (1H, ddd, $J=15$, 2, 1 Hz), 3.02 (3H, s), 3.13 (1H, ddd, $J=15$, 5, 2 Hz), 3.59 (1H, dd, $J=15$, 5 Hz), 3.66 (1H, dd, $J=10$, 5 Hz), 3.77 (1H, dddd, $J=7$, 6, 5, 2 Hz), 4.21 (1H, dd, $J=10$, 5 Hz), 4.25 (1H, dd, $J=10$, 5 Hz), 5.95 (1H, br). MS *m/z*: 310, 294 ($M^+ -C_4H_9$), 252 (100%). HRMS Calcd for $C_{10}H_{20}NO_5SSi$ ($M^+ -C_4H_9$): 294.0830. Found: 294.0835.

(*S*)-4-[(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(iodomethyl)propyl]-2-azetidinone (32) Following a procedure similar to that described for the preparation of **17a**, **31** (78 mg, 0.22 mmol) was treated with NaI in acetone to give **32** (75 mg, 88%) as an oil. IR ($CHCl_3$): 3420, 1755, 1100, 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.4—1.8 (3H, m), 2.65 (1H, ddd, $J=15$, 2, 1 Hz), 3.12 (1H, ddd, $J=15$, 5, 2 Hz), 3.21 (1H, dd, $J=10$, 5 Hz), 3.33 (1H, dd, $J=10$, 5 Hz), 3.52 (1H, dd, $J=10$, 6 Hz), 3.59 (1H, dd, $J=10$, 5 Hz), 3.72 (1H, dddd, $J=7$, 6, 5, 2 Hz), 5.9 (1H, br). MS *m/z*: 384 ($M^+ +1$). 326, 284 (100%). HRMS Calcd for $C_{13}H_{27}INO_2Si$ ($M^+ +1$): 384.0855. Found: 384.0851.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyl)oxymethyl-1-azabicyclo[3.2.0]heptan-7-one (33) Following a procedure similar to that described for the preparation of **19a**, **32** (261 mg, 0.68 mmol) was cyclized to give **33** (126 mg, 72%) as an oil. IR ($CHCl_3$): 1740, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 1.63 (1H, ddd, $J=13$, 8, 7 Hz), 2.04 (1H, ddd, $J=13$, 7, 4 Hz), 2.57 (1H, dd, $J=15$, 2 Hz), 2.6—2.8 (1H, m), 2.68 (1H, dd, $J=8$, 4 Hz), 3.23 (1H, ddd, $J=15$, 5, 1 Hz), 3.56 (1H, dd, $J=10$, 6 Hz), 3.57 (1H, dd, $J=10$, 6 Hz), 3.7—3.8 (2H, m). MS *m/z*: 256 ($M^+ +1$), 240, 237, 212, 193, 156 (100%). HRMS Calcd for $C_{13}H_{26}NO_2Si$ ($M^+ +1$): 256.1731. Found: 256.1735.

(3*R*,5*S*)-3-Hydroxymethyl-1-azabicyclo[3.2.0]heptan-7-one (3) A mixture of **33** (121 mg, 0.47 mmol), Bu_4NF (1.0 M solution in THF, 1.14 ml, 1.14 mmol), AcOH (41 mg, 0.68 mmol), and THF (0.7 ml) was stirred at room temperature for 3 h. Then, the mixture was charged on a column of silica gel (2 g, in PhH) and eluted with AcOEt (150 ml). The eluates were combined and the solvent was evaporated to leave an oily residue, which was chromatographed again on silica gel (2 g, AcOEt : PhH = 2 : 3, v/v) to afford **3** (58 mg, 57%) as an oil, $[\alpha]_D^{25}$ −191° ($c=1.20$, $CHCl_3$). IR ($CHCl_3$): 3450, 1740, 1340, 1300, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (1H, ddd, $J=13$, 8, 7 Hz), 2.07 (1H, ddd, $J=13$, 7, 4 Hz), 2.6—2.8 (2H, m), 2.61 (1H, dd, $J=16$, 2 Hz), 3.26 (1H, ddd, $J=16$, 5, 1 Hz), 3.5—3.75 (1H, m), 3.75—3.9 (2H, m). MS *m/z*: 141 (M^+), 124, 113, 99, 82, 80, 68, 67 (100%). HRMS Calcd for $C_7H_{11}NO_2$: 141.0789. Found: 141.0792.

References and Notes

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7) When a more active catalyst such as palladium black was used, we observed an abnormal ring cleavage reaction. The details will be reported elsewhere.