Chiral Synthesis of Methyl (2*R*)-[(3*S*,4*S*)-3-Isopropenyl-2-oxoazetidin-4-yl]propanoate and Its Utilization in the Synthesis of 1β-Methylcarbapenem Antibiotics

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Chiral and stereoselective synthesis of methyl (2*R*)-[(3*S*,4*S*)-3-isopropenyl-2-oxoazetidin-2-yl]propanoate (14), a 3,4-*cis*-β-lactam, was achieved starting from (−)-carvone.

Keywords (−)-carvone; 3,4-*cis*-β-lactam; Marshall's bond cleavage reaction; 1β-methylthienamycin; 1β-methylcarpetimycin

Recently we have established[1] a stereoselective synthesis of a key 1β-methylthienamycin intermediate having the *trans* stereochemical relationship between the 3 and 4 positions of the azetidin-2-one from (−)-carvone as shown in Chart 1, *via* 1,5-bond cleavage reaction of the acetoxymethylenecyclopentanone (**2**) derived from the cyclopentanone (**1**), and the stereoselective reduction of **3** to construct a 3,4-*trans*-β-lactam (**4**).

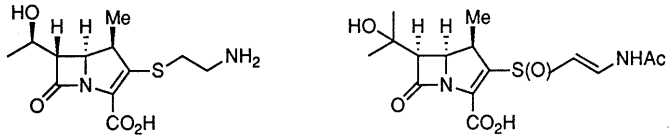

Fig. 1

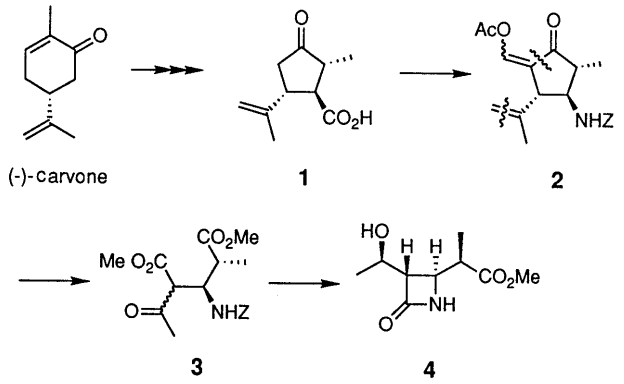

Chart 1

As part of our continuing program on the synthesis of β-lactam antibiotics utilizing (−)-carvone as a chiral precursor, we have focused our attention on the synthesis of a thermodynamically unstable 3,4-*cis*-β-lactam having an isopropenyl group at the 3-position, since the manipulation of the isopropenyl group would be expected to give a potential intermediate for 1β-methylcarpetimycin antibiotics.[2] We describe herein the stereoselective synthesis of methyl (2*R*)-[(3*S*,4*S*)-3-isopropenyl-2-oxoazetidin-4-yl]propanoate starting from (−)-carvone.

The cyclopentanone (**1**),[3] easily derived from (−)-carvone, was converted to its *tert*-butyl ester (**5**) by treatment with dicyclohexylcarbodiimide (DCC) in *tert*-butyl alcohol in the presence of *N*,*N*-dimethylamminopyridine (DMAP). Dithioacetalization of the ester (**5**) was achieved *via* two steps in a usual manner[4] to afford the ketone (**6**) in 63.2% yield. The 1,5-bond cleavage reaction of the ketone (**6**) according to Marshall's procedure[5] gave the acid (**7**), which without purification, was esterified with methanol and DCC to provide the ester (**8**) in 63.3% yield. The selective removal of the *tert*-butyl group of the diester (**8**) on exposure to trifluoroacetic acid in dichloromethane furnished the acid (**9**). Introduction of an amino function was achieved by treatment of the acid (**9**) with diphenylphosphoryl azide,[6] followed by heating with β-trimethylsilylethanol to give the carbamate (**10**) in 40.5% yield. The thioacetal group of the carbamate (**10**) was then converted to the carboxylic acid through two steps involving a dethioacetalization with methyl iodide in aqueous acetonitrile and subsequent oxidation of the resulting aldehyde (**11**) with sodium chlorite[7] in the

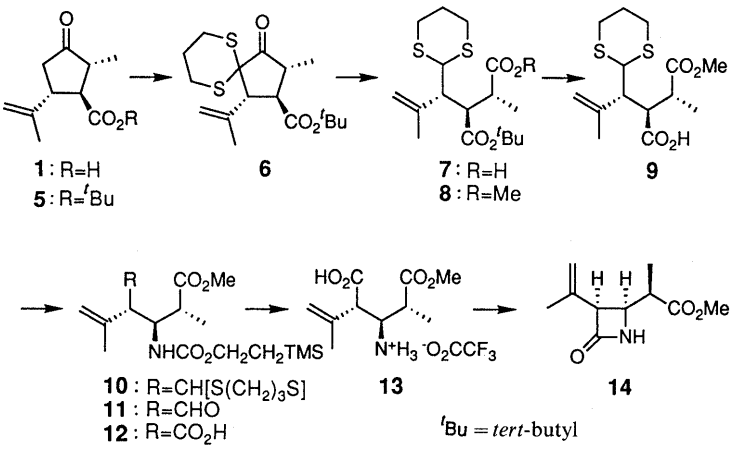

Chart 2

presence of 2-methyl-2-butene in *tert*-butyl alcohol to provide the acid (**12**). Deprotection of the amino group of the acid (**12**) with trifluoroacetic acid afforded the salt (**13**), which, on exposure to propylene oxide in isopropyl alcohol followed by treatment with methanesulfonyl chloride and sodium bicarbonate (powder),[8] furnished the β-lactam (**14**) in 60.5% yield from **12**. The relative stereochemistry at the 3 and 4 positions of the β-lactam (**14**) was easily deduced to be *cis* on the basis of its nuclear magnetic resonance (NMR) spectrum exhibiting C_4-proton (at δ 4.05) and C_3-proton (at δ 3.95) signals with the coupling constant of 5.5 Hz.

Since the desired 3,4-*cis*-β-lactam was thus synthesized stereoselectively, we investigated the utilization of **14** for the synthesis of the key intermediate for 1β-methylthienamycin-type antibiotics. Ozonolysis of the β-lactam (**14**), followed by reductive work-up with dimethyl sulfide gave the ketone (**15**), with epimerization at the 3-position, which was identical with an authentic specimen.[1a] Since the stereoselective reduction of **15** to **4** with L-Selectride has already been achieved by us,[1a] the above procedures constitute a new formal synthesis.

We next turned our attention to the synthesis of the 3,4-*cis*-β-lactam bearing a carpetimycin-type substituent at the 3-position as follows. The β-lactam (**14**) was first protected with *tert*-butyldimethylsilyl chloride to give the *N*-silylated compound (**16**). Although difficulties were initially encountered in the conversion of the isopropenyl group to the hydroxyisopropyl group, *e.g.* attempted addition of water by treatment with mercuric acetate or epoxide formation with peracids followed by reduction in appropriate solvents under various reaction conditions failed, treatment of **16** with iodine in aqueous dioxane at ambient temperature afforded the iodohydrin (**17**) in 87.5% yield as a mixture of diastereomers. This mixture was used in the following reaction without determination of the stereochemistry, because the stereogenic center was removed in a later step of the synthesis. Reductive dehalogenation of **17** with lithium borohydride[9] in methanol–ether brought about reduction of the ester function to provide the alcohol (**18**) in 85.9% yield. Deprotection of **18** with hydrochloric acid in methanol afforded the diol (**19**). Although attempts to oxidize **19** to the corresponding carboxylic acid have all failed so far, compound **19** seems to be a potential intermediate for 1β-methylcarpetimycin-type antibiotics.

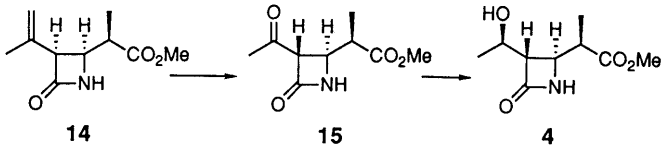

Chart 3

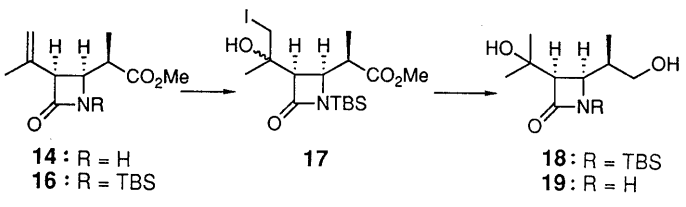

Chart 4

Experimental

Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported in ppm on the δ scale from internal tetramethylsilane. *J* values are given in Hz. Mass spectra (MS) were measured with a JEOL JMS D-300 spectrometer.

***tert*-Butyl (1*S*,2*R*,5*R*)-5-Isopropenyl-2-methyl-3-oxocyclopentane-1-carboxylate (5)** A stirred solution of the acid (**1**) (20 g, 0.11 mol) in *tert*-butyl alcohol (100 ml) was treated with DMAP (3 g, 25 mmol) and DCC (27 g, 0.13 mol), and the resulting mixture was further stirred at ambient temperature for 2 h. Evaporation of the solvent gave a residue, which was dissolved in ethyl acetate, and the insoluble material was filtered off. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (19 : 1, v/v) afforded the ester (**5**) (20.8 g, 79.5%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1720, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6.1 Hz, Me), 1.46 (9H, s, *tert*-Bu), 1.76 (3H, s, Me), 2.12 (1H, dd, J=11.6, 18.3 Hz, C_4-H), 2.44—2.62 (3H, m, C_1-H, C_2-H and C_4-H), 3.00 (1H, ddd, J=7.9, 11.0, 11.6 Hz, C_5-H), 4.84 (2H, m, C=CH_2). MS *m/z*: 238 (M^+). Calcd for $C_{14}H_{22}O_3$ requires 238.1568. Found: 238.1567. $[\alpha]_D$ −86.4° (*c*=12.9, $CHCl_3$).

***tert*-Butyl (1*R*,2*R*,5*R*)-5-Isopropenyl-2-methyl-3-oxo-4-(trimethylenedithio)cyclopentanecarboxylate (6)** Potassium *tert*-butoxide (480 mg, 4.2 mmol) was added in small portions to a stirred solution of the ester (**5**) (100 mg, 0.42 mmol) and methyl formate (622 mg, 8.4 mmol) in ether (5 ml) at 0 °C. After the stirring had been continued for 1 h, acetic acid (277 mg, 4.62 mmol) was added dropwise to the solution, and the resulting mixture was diluted with ethyl acetate (50 ml). The organic layer was washed with water, dried over Na_2SO_4 and concentrated to give a residue, which was dissolved in methanol (3 ml). To this solution, potassium acetate (206 mg, 2.1 mmol) and trimethylenedithiotosylate (192 mg, 0.46 mmol) were added, and the mixture was heated at reflux for 2 h. Evaporation of the solvent gave a residue, which was taken up in ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (40 : 1, v/v) afforded the thioacetal (**6**) (90.8 mg, 63.2%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.7 Hz, Me), 1.44 (9H, s, *tert*-Bu), 1.86 and 2.17 (each 1H, each m, CH_2), 2.00 (3H, s, Me), 2.50, 2.51, 3.21, and 3.98 (each 1H, each m, 2×SCH_2), 2.65 (1H, dq, J=11.0, 6.7 Hz, C_2-H), 2.87 (1H, d, J=11.6 Hz, C_5-H), 2.95 (1H, dd, J=11.0, 11.6 Hz, C_1-H), 4.93 and 5.11 (each 1H, each s, C=CH_2). MS *m/z*: 342 (M^+). Calcd for $C_{17}H_{26}O_3S_2$ requires 342.1322. Found: 342.1322. $[\alpha]_D$ +32.6° (*c*=7.4, $CHCl_3$).

4-*tert*-Butyl Methyl (3*R*,4*R*,5*R*)-2-Methyl-3-trimethylenedithiomethyl-1-hexene-4,5-dicarboxylate (8) A mixture of the ester (**6**) (100 mg, 0.29 mmol), powdered potassium hydroxide (58 mg, 0.87 mmol) and *tert*-butyl alcohol was heated at 60 °C for 2 h. After addition of water, *tert*-butyl alcohol was evaporated off under reduced pressure to leave an aqueous layer, which was washed with ether. The aqueous layer was acidified to pH 3 with concentrated HCl and extracted with chloroform–methanol (20 : 1, v/v). The organic layer was dried over Na_2SO_4 and evaporated to give the acid (**7**) which, without isolation, was dissolved in methanol (2 ml). To this solution, DCC (90 mg, 0.44 mmol) and DMAP (3.5 mg, 0.03 mmol) were added, and the resulting mixture was stirred at room temperature for 1 h. Evaporation of the solvent gave a residue, which was taken up in ethyl acetate, and the organic layer was filtered through a sintered glass funnel to remove insoluble materials. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (11 : 1, v/v) afforded the diester (**8**) (69.2 mg, 63.3%) as colorless plates, mp 68—70 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6.7 Hz, Me), 1.40 (9H, s, *tert*-Bu), 1.89 (3H, s, Me), 1.87 and 2.10 (each 1H, m, CH_2), 2.81—2.93 (5H, m, 2×SCH_2 and C_3-H), 3.01 (1H, dq, J=5.5, 6.7 Hz, C_5-H), 3.35 (1H, dd, J=5.5, 10.4 Hz, C_4-H), 3.72 (3H, s, OMe), 4.18 (1H, d, J=6.1 Hz, SCHS), 4.89 and 4.98 (each 1H, each s, C=CH_2). MS *m/z*: 374 (M^+). $C_{18}H_{30}O_4S_2$ requires 374.1585. Found: 374.1590. $[\alpha]_D$ +8.4° (*c*=7.1, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{30}O_4S_2$: C, 57.75; H, 8.02. Found: C, 57.51; H, 8.20.

(3*R*,4*R*,5*R*)-5-Methoxycarbonyl-2-methyl-3-trimethylenedithiomethyl-1-hexene-4-carboxylic Acid (9) Trifluoroacetic acid (5 ml) was added dropwise to a stirred solution of the diester (**8**) (9.68 g, 25.9 mmol) in dichloromethane (50 ml) at ambient temperature and the resulting

mixture was further stirred for 30 min. Evaporation of the solvent gave the acid (**9**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=7.3 Hz, Me), 1.83 (3H, s, Me), 1.89—2.13 (2H, m, CH_2), 2.82—2.93 (5H, m, 2×SCH_2 and C_3-H), 3.05 (1H, dq, J=7.3, 7.3 Hz, C_5-H), 3.52 (1H, dd, J=7.3, 7.3 Hz, C_4-H), 3.73 (3H, s, OMe), 4.22 (1H, d, J=6.7 Hz, SCHS), 4.88, 4.99 (each 1H, each s, C=CH_2), 7.80 (1H, br s, CO_2H). MS m/z: 318 (M^+). $C_{14}H_{22}O_4S_2$ requires 318.0960. Found: 318.0962. Compound **9** was used in the next reaction without purification.

Methyl (2*R*,3*R*,4*S*)-2,5-Dimethyl-4-trimethylenedithiomethyl-3-trimethylsilylethyloxycarbonylamino-5-hexenoate (10) Diphenylphosphoryl azide (7.8 g, 28.3 mmol) was slowly added to a stirred solution of the above crude acid (**9**) in toluene (100 ml) in the presence of triethylamine (3.9 g, 38.7 mmol) at room temperature, and the resulting mixture was further stirred for 2 h. After addition of 2-(trimethylsilyl)ethanol (12.2 g, 103 mmol), the solution was refluxed for 1 h, and washed with 2% NaOH solution and brine. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (5 : 1, v/v) afforded the carbamate (**10**) (4.42 g, 40.5% from **8**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1740, 1640. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (9H, s, 3×SiMe), 0.96 (2H, t, J=7.9 Hz, $SiCH_2$), 1.19 (3H, d, J=6.7 Hz, Me), 1.83 (3H, s, Me), 1.85—2.13 (2H, m, CH_2), 2.64 (1H, dd, J=5.5, 8.6 Hz, C_4-H), 2.72—2.90 (5H, m, 2×SCH_2 and C_2-H), 3.71 (3H, s, OMe), 4.07 (1H, d, J=8.6 Hz, SCHS), 4.13 (2H, t, J=7.9 Hz, OCH_2), 4.55—4.69 (2H, m, C_3-H and NH), 4.85 and 5.04 (each 1H, each s, C=CH_2). MS m/z: 433 (M^+). $C_{19}H_{35}NO_4SiS_2$ requires 433.1777. Found: 433.1778. $[\alpha]_D$ +13.1° (c=5.6, $CHCl_3$).

Methyl (2*R*,3*S*,4*S*)-4-Formyl-2,5-dimethyl-3-trimethylsilylethyloxycarbonylamino-5-hexenoate (11) Methyl iodide (3.65 g, 25.7 mmol) was added to a stirred mixture of the carbamate (**10**) (3.32 g, 7.67 mmol), Na_2HPO_4 (11 g, 77.5 mmol) and acetonitrile–water (30 ml, 10 : 1, v/v) and the resulting mixture was further stirred at room temperature for 12 h. After addition of water (100 ml), the mixture was extracted with ether and the ethereal layer was washed with water, dried over Na_2SO_4 and evaporated to give the aldehyde (**11**). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (9H, s, 3×SiMe), 0.95 (2H, t, J=8.5 Hz, $SiCH_2$), 1.14 (3H, d, J=7.3 Hz, Me), 1.76 (3H, s, Me), 2.72 (1H, dq, J=7.3, 7.3 Hz, C_2-H), 3.27 (1H, d, J=6.7 Hz, C_4-H), 3.68 (3H, s, OMe), 4.12 (2H, d, J=8.5 Hz, OCH_2), 4.58—4.73 (2H, m, C_3-H and NH), 4.94 and 5.17 (each 1H, each s, C=CH_2), 9.55 (1H, s, CHO), which, without purification, was used in the next reaction.

(3*S*,4*R*,5*R*)-5-Methoxycarbonyl-2-methyl-4-trimethylsilylethyloxycarbonylamino-1-hexene-3-carboxylic Acid (12) A solution of sodium chlorite (6.9 g, 76 mmol), Na_2HPO_4 (3.45 g) and NaH_2PO_4 (3.45 g) in water (69 ml) was slowly added to a stirred solution of the above aldehyde (**11**) and 2-methyl-2-butene (33 ml) in *tert*-butyl alcohol (150 ml) at room temperature, and the resulting mixture was further stirred for 1 h. After dilution with water (50 ml), most of the solvent was evaporated off to leave an aqueous layer, which was acidified with concentrated HCl and extracted with chloroform–methanol (20 : 1, v/v). The extract was washed with brine, dried over Na_2SO_4 and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with chloroform–ethyl acetate (9 : 1, v/v) afforded the acid (**12**) (1.92 g, 69.7% from **10**) as a colorless gum. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1720, 1640. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (9H, s, 3×SiMe), 0.94 (2H, t, J=7.9 Hz, $SiCH_2$), 1.14 (3H, d, J=7.3 Hz, Me), 1.80 (3H, s, Me), 2.80 (1H, dq, J=3.6, 7.3 Hz, C_5-H), 3.30 (1H, d, J=9.8 Hz, C_3-H), 3.69 (3H, s, OMe), 4.10 (2H, d, J=7.9 Hz, OCH_2), 4.57—4.71 (2H, m, C_4-H and NH), 5.01 and 5.04 (each 1H, each s, C=CH_2). MS m/z: 344 (M^+−15). $C_{15}H_{26}NO_6Si$ requires 344.1529. Found: 344.1530. $[\alpha]_D$ −58.9° (c=15.7, $CHCl_3$).

(3*S*,4*R*,5*R*)-3-Carboxy-5-methoxycarbonyl-2-methyl-1-hexen-4-ylammonium Trifluoroacetate (13) A solution of the acid (**12**) (47.6 mg, 0.13 mmol) in trifluoroacetic acid (0.2 ml) was stirred at ambient temperature for 10 min and the solvent was evaporated off to give the salt (**13**), ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=7.3 Hz, Me), 1.85 (3H, s, Me), 3.00 (4H, br s, CO_2H and N^+H_3), 3.01 (1H, dq, J=3.6, 7.3 Hz, C_5-H), 3.50 (1H, d, J=9.2 Hz, C_3-H), 3.76 (3H, s, Me), 3.98 (1H, dd, J=3.6, 9.2 Hz, C_4-H), 5.19 and 5.23 (each 1H, each s, C=CH_2), which, without purification, was subjected to the next reaction.

Methyl (2*R*)-[(3*S*,4*S*)-3-Isopropenyl-2-oxoazetidin-4-yl]propanoate (14) Propylene oxide (0.4 g, 6.86 ml) was added to a stirred solution of the salt (**13**) in isopropyl alcohol (1 ml), and the resulting mixture was heated at 50 °C for 10 min. To this solution, $NaHCO_3$ powder (100 mg, 1.19 mmol) and methanesulfonyl chloride (22.8 mg, 0.20 mmol) were added and the mixture was further heated at 50 °C for 1 h. The mixture was cooled and then filtered through a Celite pad to remove insoluble materials, and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1 : 1, v/v) afforded the β-lactam (**14**) (15.8 mg, 60.5% from **12**) as colorless needles, mp 103—104 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1760, 1740. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.3 Hz, Me), 1.72 (3H, s, Me), 2.65 (1H, dq, J=9.2, 7.3 Hz, C_2-H), 3.67 (3H, s, Me), 3.95 (1H, d, J=5.5 Hz, C_3-H), 4.05 (1H, dd, J=5.5, 9.2 Hz, C_4-H), 5.14 and 5.15 (each 1H, each s, C=CH_2), 6.08 (1H, br, NH). *Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.95; H, 7.81; N, 6.97. $[\alpha]_D$ +7.1° (c=0.3, $CHCl_3$).

Methyl (2*R*)-[(3*S*,4*S*)-3-Acetyl-2-oxoazetidin-4-yl]propanoate (15) A stream of ozone was bubbled through a solution of the β-lactam (**14**) (12.9 mg, 0.07 mmol) in dichloromethane (2 ml) at −78 °C until a persistent blue color was observed. The reaction mixture was flushed with argon and treated with dimethyl sulfide (40 mg, 0.65 mmol) at −78 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and further stirred for 1 h. After evaporation of the solvent the residue was purified by column chromatography on silica gel using hexane–ethyl acetate (1 : 1, v/v) as the eluant to give the β-lactam (**15**), which was identical with an authentic specimen.[1a]

Methyl (2*R*)-[(3*S*,4*S*)-1-*tert*-Butyldimethylsilyl-3-isopropenyl-2-oxoazetidin-4-yl]propanoate (16) A solution of the β-lactam (**14**) (10 mg, 0.05 mmol), triethylamine (39 mg, 0.38 mmol) and *tert*-butyldimethylsilyl chloride (46 mg, 0.31 mmol) in DMF (0.5 ml) was stirred at room temperature for 4 h under an argon atmosphere. To this solution was added water (2 ml), and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (9 : 1, v/v) afforded the silyl compound (**16**) (15.8 mg, 100%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.16 and 0.28 (each 3H, each s, 2×SiMe), 0.98 (9H, s, *tert*-Bu), 1.24 (3H, d, J=7.3 Hz, Me), 1.74 (3H, s, Me), 2.67 (1H, dq, J=6.1, 7.3 Hz, C_2-H), 3.66 (3H, s, OMe), 4.06 (1H, d, J=6.1 Hz, C_3-H), 4.21 (1H, dd, J=6.1, 6.1 Hz, C_4-H), 5.02 and 5.12 (each 1H, each s, C=CH_2). MS m/z: 296 (M^+−15). $C_{15}H_{26}NO_3Si$ requires 296.1680. Found: 296.1673. $[\alpha]_D$ +29° (c=0.8, $CHCl_3$).

Methyl (2*R*)-[(3*R*,4*S*)-1-*tert*-Butyldimethylsilyl-3-[1-hydroxy-1-(iodomethyl)ethyl]-2-oxoazetidin-4-yl]propanoate (17) A solution of iodine (108 mg, 0.43 mmol), Na_2HPO_4 (75 mg) and NaH_2PO_4 (75 mg) in water (1.5 ml) was added to a stirred solution of the β-lactam (**16**) (66 mg, 0.21 mmol) in dioxane (3 ml) at ambient temperature, then saturated aqueous $Na_2S_2O_3$ was added and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (6 : 1, v/v) afforded the iodohydrin (**17**) (84.5 mg, 87.5%) as a mixture of diastereomers. ^{1}H-NMR ($CDCl_3$) δ: 0.14, 0.20, 0.27 and 0.29 (total 6H, m, 2×SiMe), 0.97 and 0.98 (total 9H, each s, *tert*-Bu), 1.30—1.34 (total 6H, m, 2×Me), 1.98 and 2.03 (total 1H, each br s, OH), 3.10—3.34 (total 1H, m, C_2-H), 3.40—4.03 (total 3H, m, ICH_2 and C_3-H), 3.71 and 3.72 (total 3H, each s, OMe), 4.23—4.43 (total 1H, m, C_4-H). MS m/z: 440 (M^+−15). $C_{15}H_{27}NO_4ISi$ requires 440.0753. Found: 440.0754.

(3*R*,4*R*)-1-*tert*-Butyldimethylsilyl-3-(1-hydroxy-1-methylethyl)-4-[2-hydroxy-(1*R*)-methylethyl]azetidin-2-one (18) Lithium borohydride (2.1 mg, 0.10 mmol) and methanol (3.4 mg, 0.11 mmol) were added to a stirred solution of the iodohydrin (**17**) (9.5 mg, 0.02 mmol) in ether (1 ml) and the resulting mixture was heated at reflux. To this refluxing solution, methanol (5 mg) was added at intervals for a total of 15 min over a period of 2 h. The cooled solution was treated with saturated aqueous ammonium chloride and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (2 : 3, v/v) furnished the alcohol (**18**) (5.4 mg, 85.9%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.19 and 0.30 (each 3H, each s, 2×SiMe), 0.98 (9H, s, *tert*-Bu), 1.05 (3H, d, J=7.3 Hz, Me), 1.39 and 1.49 (each 3H, each s, 2×Me), 1.87 (2H, br s, 2×OH), 2.56 (1H, m, C_1-H), 3.47 (1H, d, J=6.1 Hz, C_3-H), 3.53 (1H, dd, J=7.9, 10.4 Hz, OCH_2), 3.73 (1H, dd, J=4.9, 10.4 Hz, OCH_2), 3.96 (1H, dd, J=4.9, 6.1 Hz, C_4-H). MS m/z: 286 (M^+−15). $C_{14}H_{28}NO_3Si$ requires 286.1837. Found: 286.1834. $[\alpha]_D$ −9.9° (c=0.5, $CHCl_3$).

(3*R*,4*R*)-3-(1-Hydroxy-1-methylethyl)-4-[2-hydroxy-(1*R*)-methylethyl]-azetidin-2-one (19) A solution of the alcohol (**18**) (52.1 mg, 0.17 mmol) and concentrated HCl (0.2 ml) in methanol (1 ml) was stirred at room

temperature for 6 h. After neutralization with saturated aqueous sodium bicarbonate, the mixture was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–methanol (19 : 1, v/v) gave the β-lactam (**19**) (14.3 mg, 44.2%) as colorless needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=6.7 Hz, Me), 1.47 (6H, s, 2 × Me), 2.13 (2H, br s, 2 × OH), 2.62 (1H, m, C_1-H), 3.41 (1H, dd, J=2.4, 5.5 Hz, C_3-H), 3.47 (1H, dd, J=8.6, 10.4 Hz, OCH_2), 3.69 (1H, dd, J=5.5, 9.8 Hz, C_4-H), 3.74 (1H, dd, J=4.3, 10.4 Hz, OCH_2), 5.85 (1H, br, NH). FABMS: 188 ($M^+ + 1$).

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