The Reaction of (4*R*,5*R*)- and (4*S*,5*S*)-4,5-Epoxy-2(*E*)-Hexenoates and Secondary Amines

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A reaction of methyl (4*R*,5*R*)-4,5-epoxy-2(*E*)-hexenoate 1 with *N*-benzylmethylamine gave a diastereomerically pure methyl (4*R*,5*R*)-4,5-epoxy-(3*S*)-*N*-benzylmethylamino hexanoate 6 and methyl (4*S*,5*R*)-4-*N*-benzylmethylamino-5-hydroxy-2(*E*)-hexenoate 7. The former was chemoenzymatically converted to (−)-osmundalactone 11, which is an aglycone of osmundalin. On the other hand, the directly conjugated addition of dimethylamine to methyl (4*S*,5*S*)-4,5-epoxy-2(*E*)-hexenoate 1 followed by treatment with MeOH at 40 °C exclusively provided methyl (4*R*,5*S*)-4-dimethylamino-5-hydroxy-2(*E*)-hexenoate 16, which was converted into L-(−)-forosamine 18.

Key words Michael addition; secondary amine; osmundalactone; forosamine

In the preceding paper, we reported the syntheses of each optically pure stereoisomer of 4,5-epoxy-2(*E*)-hexenoates (4*R*,5*R*)-**1** and (4*S*,5*S*)-**1** based on a chemoenzymatic method from an achiral precursor, methyl sorbate.[1] As a part of the useful application of (4*S*,5*S*)-**1** to the syntheses of amino sugars or related compounds, formal total syntheses of D-acosamine **2** and D-ristosamine **3** from (4*S*,5*S*)-**1** were achieved.[2] The reaction of (4*S*,5*S*)-**1** with 4 eq of benzylamine gave the 1,4-addition products (3*R*,4*S*,5*S*)-**4** (53%) and (3*S*,4*S*,5*S*)-**5** (32%). The intramolecular nucleophilic attack by an ester carbonyl group upon the epoxy ring of the substrates, (3*R*,4*S*,5*S*)-**4** and (3*S*,4*S*,5*S*)-**5** resulted in the formal total syntheses of D-acosamine **2** and D-ristosamine **3**, respectively. In the course of our continuing interest in the reaction of 4,5-epoxy-2(*E*)-hexenoates (4*S*,5*S*)-**1** with amine, the reaction of (4*S*,5*S*)-**1** with a secondary amine aroused our interest.

The reaction of (±)-**1** with 2 eq of *N*-methylbenzylamine at 40 °C for 4 d gave a diastereomerically pure (±)-**6** (68%) and (±)-**7** (22%), while this reaction in the presence of MeOH provided (±)-**6** (30%) and (±)-**7** (66%). In case of the latter, a solvent effect appeared and the product ratio of (±)-**6** and (±)-**7** was reversed. In order to determine the structure of (±)-**6**, two possible authentic samples were prepared. The reaction of (±)-3,4-*syn* **4** and (±)-3,4-*anti* **5** with an excess of methyl iodide at 0 °C provided the *N*-methylated amines (±)-3,4-*syn* **6** (48%) and (±)-3,4-*anti* **8** (33%), respectively. Physical data of the present (±)-**6** were identical with those of authentic (±)-3,4-*syn* **6**. For the purpose of determining the structure of (±)-**7**, compound (±)-**7** was converted into the acetate (±)-**9** (88%) and the acetal (±)-**10** (47%) by applying the Evans method.[3] A chemical shift due to the C_5-H of (±)-**9** appeared in the lower field (δ 5.21, dq, J=6, 9 Hz) in comparison with that (δ 4.11, quintet, J=6 Hz) of (±)-**7**, thus the hydroxyl group was located at the C_5-position. The *anti*-stereochemistry of (±)-**7** was confirmed by the following experimental fact. Nuclear Overhauser effect (NOE) experiments of (±)-**10** were shown in Fig. 1, and the coupling constants of the C_3-axial and C_4-axial protons, and the C_4-axial and C_5-axial protons were 10 Hz and 10 Hz, respectively, clearly indicating that the starting (±)-**7** possessed 4,5-*anti*-configurations. Then, the formation of diastereomerically pure (±)-**6** and 4,5-*anti* **7** was explained by the following experiments.

When a solution of (±)-**6** in MeOH was allowed to stand at 40 °C for a long time (4 d), the rearranged (±)-**7** was obtained in 54% yield along with the starting (±)-**6** (30%). The same reaction was carried out for a short time (2 d), after which (±)-**7** (43%) and the intermediary (±)-**1** (16%) were obtained along with the starting (±)-**6** (21%). A solution of (±)-**7** in MeOH was exposed at 40 °C for 4 d, no change of (±)-**7** was observed. On the other hand, exposure of the syn-

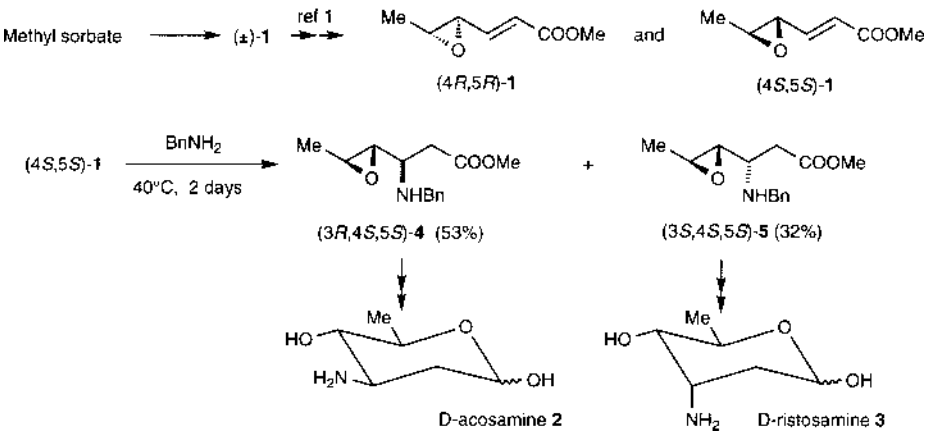

Chart 1

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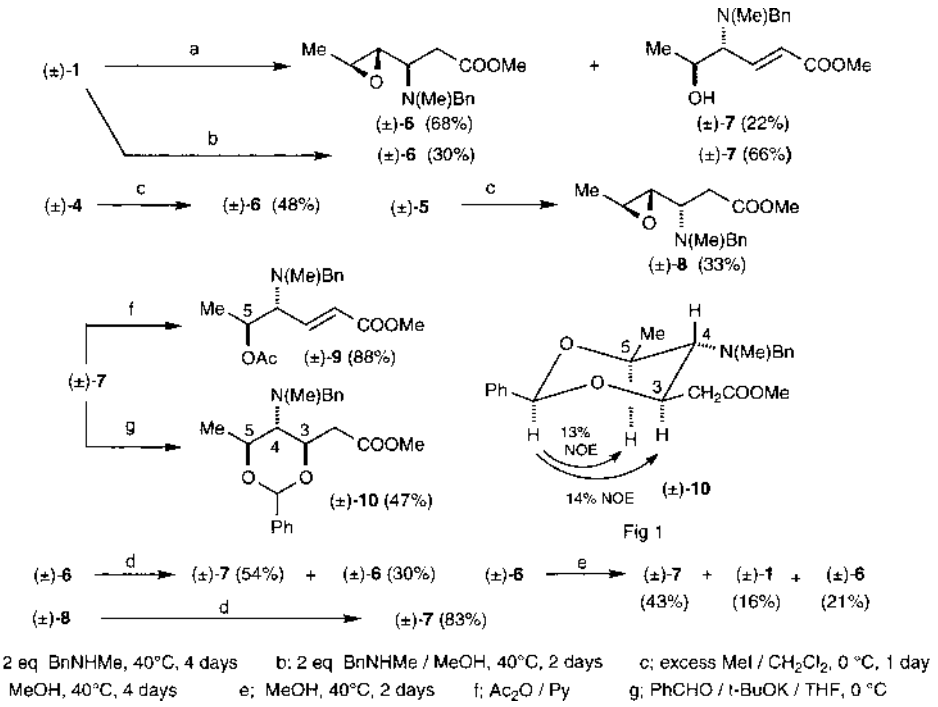

Chart 2

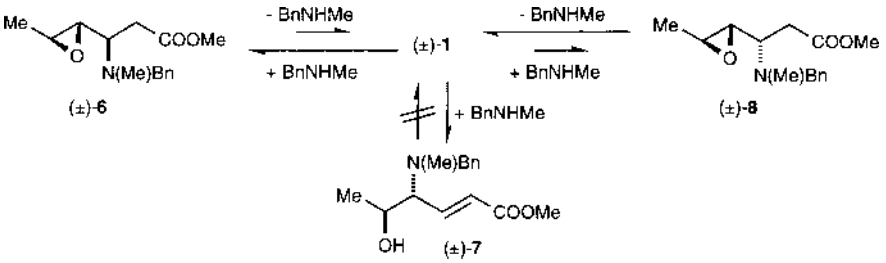

Chart 3

thetic (±)-**8** in MeOH at 40 °C for 4 d gave (±)-**7** exclusively in 83% yield. These experimental results could be explained by the thermodynamic stability of (±)-**6** and (±)-**8**. Based on inspection of the stability of (±)-**6** and (±)-**8** using Dreiding stereomodels, (±)-**8** was presumably more unstable than (±)-**6**. Because, in case of (±)-**8**, steric repulsion between the C_5-methyl group and C_3-substituent appeared to be larger than that of (±)-**6**. Consequently, the rate of conversion of the unstable (±)-**8** into (±)-**1** is presumably faster than that of the conversion of (±)-**6** into (±)-**1**. According to the above mentioned conversion experiments, the intermediary product resulting from exposure of (±)-**6** in MeOH for 2 d and (±)-**8** in MeOH for 4 d are the retro-Michael reaction product, 4,5-epoxy-2(*E*)-hexenoate ((±)-**1**). From these experimental results, the epoxy ester ((±)-**1**) is generated from (±)-**6** or/and (±)-**8**, and the liberated *N*-methylbenzylamine again attacks at the C_4-position of (±)-**1** in the manner of *anti*-stereochemistry to afford the (4,5)-*anti* **7** corresponding to the thermodynamically controlled product. On the whole, the reaction of (±)-**1** with *N*-methylbenzylamine is explained as follows: At first, a competitive attack by the nucleophile at the C_3- and C_4-positions of (±)-**1** presumably occurs to afford (±)-**6**, (±)-**8** and the 4,5-*anti* **7**. Then, more unstable (±)-**8** could be converted into (±)-**1**, and the partial conversion of (±)-**6** into (±)-**1** probably occurs. Finally, the reaction of (±)-**1** with *N*-methylbenzylamine gave 3,4-*syn* **6** corresponding to the kinetically controlled product and 4,5-*anti* **7** corresponding to the thermodynamically controlled product. The difference in the product ratio of (±)-**6** and (±)-**7** between the absence of MeOH and the presence of MeOH is explained by the solvent effect. Methanol presumably accelerates the rate of the retro-Michael process to afford (±)-**1**, then the thermodynamically favored (±)-**7** could be obtained from (±)-**1** as a major product.

This reaction was effectively applied to the synthesis of osmundalactone **11**, which is an aglycone of osmundalin isolated from *Osmunda japonica* THUNBERG (Akaboshi zenmai), which acts as a feeding inhibitor for the larvae of butterfly *Eurema hecabe mandrarina*.[4a,b] The reaction of (+)-(4*R*,5*R*)-**1** with *N*-methylbenzylamine gave (+)-(3*S*,4*R*,5*R*)-**6** (65%, $[\alpha]_D$ +17.3° (c=0.98, $CHCl_3$)) and (+)-(4*S*,5*R*)-**7** (25%, $[\alpha]_D$ +52.2° (c=1.01, $CHCl_3$)). Treatment of (+)-**6** with trifluoromethanesulfonic acid (CF_3SO_3H) exclusively provided δ-lactone ((+)-(3*S*,4*R*,5*S*)-**12**) (72% $[\alpha]_D$ +53.2° (c=0.76, $CHCl_3$)), which was then subjected to acetylation[5] with Ac_2O–AcOH (2 : 1) to afford an acetate (−)-(4*R*,5*S*)-**13**

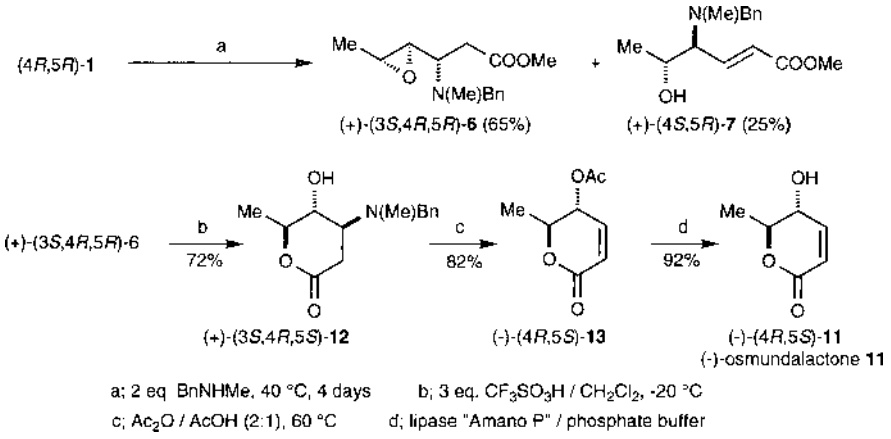

Chart 4

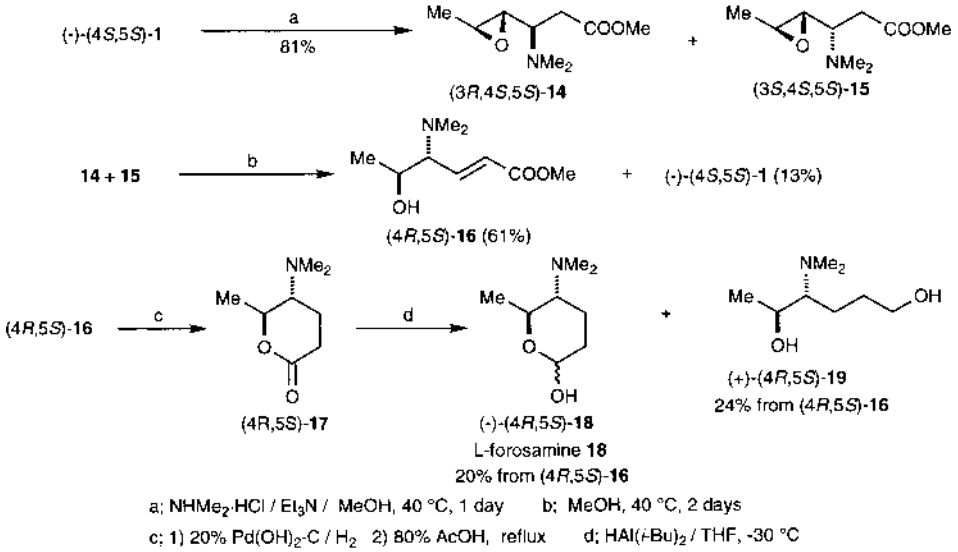

Chart 5

(82%, $[\alpha]_D$ −169.8° (c=0.73, $CHCl_3$)) with the elimination of *N*-methylbenzylamine. In this case, the liberated *N*-methylbenzylamine was acetylated in 98% yield and did not work as a nucleophilic reagent against the 2*H*-pyran-2-one moiety of the generated substrate (−)-**13**. The physical data ($[\alpha]_D$ and NMR) of (−)-**13** were identical with those ($[\alpha]_D$ −172° (c=2.8, $CHCl_3$) and NMR) of the reported (−)-**13**.[4a] Finally, the acetate ((−)-**13**) was exposed to enzymatic hydrolysis using the lipase "Amano P" from *Pseudomonas* sp. and converted to the hydroxy δ-lactone ((−)-(4*R*,5*S*)-**11**) (92%, $[\alpha]_D$ −69.0° (c=0.46, H_2O)) whose physical data ($[\alpha]_D$ and NMR) were identical with those ($[\alpha]_D$ −70.6° (c=2.0, H_2O)) of the natural (−)-osmundalactone **11**.[4a]

Then, the reaction of (−)-(4*S*,5*S*)-**1** with dimethylamine was carried out. The reaction of (−)-(4*S*,5*S*)-**1** with dimethylamine hydrochloride (2 eq)–triethylamine (2 eq) in MeOH gave a 1.7 : 1 diastereomeric mixture of (3*R*,4*S*,5*S*)-**14** and (3*S*,4*S*,5*S*)-**15** in 81% yield. This mixture was again exposed to MeOH at 40 °C for 2 d to provide the rearranged (−)-(4*R*,5*S*)-**16** (61%, $[\alpha]_D$ −115.9° (c=1.02, $CHCl_3$)) and (4*S*,5*S*)-**1** (13%) along with the starting mixture (25% recovery) of **14** and **15**. This phenomenon was also understood by the same explanation as the preparation of (±)-**7** from (±)-**1**. Hydrogenation of (−)-(4*R*,5*S*)-**16**, followed by treatment with 80% AcOH, gave the δ-lactone ((4*R*,5*S*)-**17**) which was reduced with diisobutylaluminum hydride (DIBAH) to provide an amino sugar L-(−)-(4*R*,5*S*)-**18** (20% from (−)-**16**, $[\alpha]_D$ −85.7° (c=0.78, MeOH)) and a diol (+)-(4*R*,5*S*)-**19** (24% from (−)-**16**, $[\alpha]_D$ +10.7° (c=0.93, MeOH)). The physical data of the synthesized L-(−)-**18** were consistent with those ($[\alpha]_D$ +86.1° (c=0.9, MeOH) and NMR) of D-forosamine **18**.[6]

In conclusion, in the reaction of 4,5-epoxy-2(*E*)-hexenoate **1** with a secondary amine, the 1,4-conjugated addition of secondary amine to the α,β-unsaturated ester moiety may occur to provide a diastereomeric mixture of (4,5)-epoxy-3-*N*-substituted amino esters. From this mixture, the product distribution between a 4,5-*anti*-2(*E*)-hexenoate such as **7** or **16** and an enantiomerically pure 4,5-epoxy-3-*N*-substituted amino ester such as **6** was found to depend upon the reaction condition and the nature of the secondary amine used.

Experimental

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by Distortionless Enhancement by Polarization

Transfer (DEPT) pulse sequence. The fast atom bombardment mass spectra (FAB-MS) was obtained with a JEOL JMS-DX 303 spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl 3β-Benzylamino-4β,5β-epoxyhexanoate (±)-4 and Methyl 3α-Benzylamino-4β,5β-epoxyhexanoate (±)-5 A mixture of (±)-**1** (3.11 g, 21.9 mmol) and $BnNH_2$ (9.39 g, 88 mmol) was allowed to stand for 2 d at 40 °C. The reaction mixture was directly chromatographed on silica gel (200 g, *n*-hexane : AcOEt=2 : 1) to afford (±)-**4** (2.95 g, 53%) as a colorless oil and (±)-**5** (1.91 g, 32%) as a colorless oil in eluate order. (±)-**4**: the spectral data (IR and NMR) of (±)-**4** were identical with those of the reported (3*R*,4*S*,5*S*)-**4**: FAB-MS *m*/*z*: 250 (M^++1). (±)-**5**: the spectral data (IR and NMR) of (±)-**5** were identical with those of the reported (3*S*,4*S*,5*S*)-**5**: FAB-MS *m*/*z*: 250 (M^++1).

Methyl 3β-*N*-Benzylmethylamino-4β,5β-epoxyhexanoate (±)-6 and Methyl (4α,5β)-4-*N*-Benzylmethylamino-5-hydroxy-2(*E*)-hexenoate (±)-7 i) A mixture of (±)-**1** (1.00 g, 7 mmol) and *N*-benzylmethylamine (1.71 g, 14 mmol) was allowed to stand for 4 d at 40 °C. The reaction mixture was directly chromatographed on silica gel (60 g) to afford (±)-**1** (0.08 g, 8%), (±)-**6** (1.259 g, 68%) as a colorless oil from *n*-hexane : AcOEt=9 : 1 eluate and (±)-**7** (0.37 g, 22%) as a colorless oil from *n*-hexane : AcOEt=4 : 1 eluate. (±)-**6**: IR (neat): 1736 cm^{-1}; NMR: δ 1.31 (3H, d, *J*=5 Hz), 2.31 (3H, s), 2.42 (1H, dd, *J*=7, 14 Hz), 2.61 (1H, dd, *J*=7, 14 Hz), 2.82—2.88 (2H, m), 3.08 (1H, dt, *J*=7, 7 Hz), 3.69 (3H, s), 3.71, 3.75 (each 1H, d, *J*=12 Hz), 7.21—7.36 (5H, m). FAB-MS *m*/*z*: 264 (M^++1). (±)-**7**: IR (neat): 3439, 1723 cm^{-1}; NMR: δ 1.20 (3H, d, *J*=6 Hz), 2.22 (3H, s), 2.88 (1H, dd, *J*=6, 10 Hz), 3.49, 3.67 (each 1H, d, *J*=13 Hz), 3.77 (3H, s), 4.11 (1H, dq, *J*=6, 6 Hz), 5.98 (1H, d, *J*=16 Hz), 7.01 (1H, dd, *J*=10, 16 Hz), 7.23—7.34 (5H, m). FAB-MS *m*/*z*: 264 (M^++1). ii) To a solution of (±)-**1** (1.42 g, 10 mmol) in MeOH (5 ml) was added *N*-benzylmethylamine (2.69 g, 22 mmol), and the whole mixture was allowed to stand for 2 d at 40 °C. The reaction mixture was evaporated and the residue was directly chromatographed on silica gel (60 g, *n*-hexane : AcOEt=9 : 1) to afford (±)-**6** (0.789 g, 30%) as a colorless oil and (±)-**7** (1.735 g, 66%) as a colorless oil in eluate order.

Methylation of (±)-4 and (±)-5 i) To a solution of (±)-**4** (0.14 g, 0.6 mmol) in CH_2Cl_2 (1 ml) was added methyl iodide (1 ml), and the whole mixture was allowed to stand for 12 h at 0 °C. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g) to give (±)-**6** (0.07 g, 48%) from *n*-hexane : AcOEt=9 : 1 eluate and (±)-**4** (0.03 g, 23%) from *n*-hexane : AcOEt=1 : 1 eluate. The spectral data (IR and NMR) of (±)-**6** were identical with those of the previous (±)-**6**. ii) To a solution of (±)-**5** (0.12 g, 0.5 mmol) in CH_2Cl_2 (1 ml) was added methyl iodide (1 ml), and the whole mixture was allowed to stand for 12 h at 0 °C. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g) to give (±)-**8** (0.04 g, 33%) from *n*-hexane : AcOEt=9 : 1 eluate and (±)-**5** (0.05 g, 46%) from *n*-hexane : AcOEt=1 : 1 eluate. (±)-**8**: IR (neat): 1736 cm^{-1}; NMR: δ 1.33 (3H, d, *J*=5 Hz), 2.28 (3H, s), 2.49 (1H, dd, *J*=6, 15 Hz), 2.64 (1H, dd, *J*=8, 15 Hz), 2.80—2.84 (2H, m), 3.08 (1H, dt, *J*=6, 8 Hz), 3.64, 3.71 (each 1H, d, *J*=14 Hz), 3.71 (3H, s), 7.22—7.33 (5H, m). *Anal*. Found: C, 68.41; H, 8.04; N, 5.32. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32%. FAB-MS *m*/*z*: 264 (M^++1).

Acetylation of (±)-7 A solution of (±)-**7** (1.11 g, 4.2 mmol) and Ac_2O (0.53 g, 5.2 mmol) in pyridine (10 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. The organic layer was evaporated to give a residue which was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=9 : 1) to afford (±)-**9** (1.13 g, 88%) as a homogeneous oil. (±)-**9**: IR (neat): 1737 cm^{-1}; NMR: δ 1.32 (3H, d, *J*=6 Hz), 1.97 (3H, s), 2.24 (3H, s), 3.06 (1H, t, *J*=9 Hz), 3.48, 3.66 (each 1H, d, *J*=13 Hz), 3.78 (3H, s), 5.21 (1H, dq, *J*=6, 9 Hz), 5.91 (1H, d, *J*=16 Hz), 6.95 (1H, dd, *J*=9, 16 Hz), 7.23—7.34 (5H, m). *Anal*. Found: C, 66.67; H, 7.90; N, 4.49. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59%. FAB-MS *m*/*z*: 306 (M^++1).

Acetal Formation from (±)-7 To a solution of (±)-**7** (0.22 g, 0.8 mmol) in Tetrahydrofuran (THF) (2 ml) was added benzaldehyde (0.3 g, 2.7 mmol) and potassium *tert*-butoxide (0.15 g, 1.2 mmol) at 0 °C, and the whole mixture was stirred for 15 min at 0 °C. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=20 : 1) to give (±)-**10** (0.145 g, 47%) as a homogeneous oil. (±)-**10**: IR (neat): 1739 cm^{-1}; NMR: δ 1.47 (3H, d, *J*=6 Hz), 2.32 (3H, s), 2.42 (1H, t, *J*=10 Hz), 2.57 (1H, dd, *J*=8, 16 Hz), 3.09 (1H, dd, *J*=4, 16 Hz), 3.69 (3H, s), 3.79, 3.85 (each 1H, d, *J*=14 Hz), 4.10 (1H, dq, *J*=6, 10 Hz), 4.37 (1H, ddd, *J*=4, 8, 10 Hz), 5.54 (1H, s), 7.23—7.48 (10H, m). *Anal*. Found: C, 71.56; H, 7.77; N, 3.69. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79%. FAB-MS *m*/*z*: 370 (M^++1).

Treatment of (±)-6 with MeOH i) A solution of (±)-**6** (0.1 g, 0.4 mmol) in MeOH (2 ml) was allowed to stand for 4 d at 40 °C. The reaction mixture was worked up in the same way as for the preparation of (±)-**6** and (±)-**7** from (±)-**1** to afford (±)-**6** (0.03 g, 30%) and (±)-**7** (0.054 g, 54%). ii) A solution of (±)-**6** (0.1 g, 0.4 mmol) in MeOH (2 ml) was allowed to stand for 2 d at 40 °C. The reaction mixture was worked up in the same way as for i) to afford (±)-**1** (0.009 g, 16%), (±)-**6** (0.021 g, 21%) and (±)-**7** (0.044 g, 43%).

Treatment of (±)-8 with MeOH A solution of (±)-**8** (0.14 g, 0.5 mmol) in MeOH (2 ml) was allowed to stand for 4 d at 40 °C. The reaction mixture was worked up in the same way as for the preparation of (±)-**7** from (±)-**1** to afford (±)-**7** (0.116 g, 83%).

Methyl (3*S*)-*N*-Benzylmethylamino-(4*R*,5*R*)-epoxyhexanoate 6 and Methyl (4*S*,5*R*)-4-*N*-Benzylmethylamino-5-hydroxy-2(*E*)-hexenoate 7 A mixture of (4*R*,5*R*)-**1** (1.00 g, 7 mmol) and *N*-benzylmethylamine (1.71 g, 14 mmol) was allowed to stand for 4 d at 40 °C. The reaction mixture was directly chromatographed on silica gel (60 g) to afford (3*S*,4*R*,5*R*)-**6** (1.203 g, 65%) as a colorless oil from *n*-hexane : AcOEt=9 : 1 eluate and (4*S*,5*R*)-**7** (0.463 g, 25%) as a colorless oil from *n*-hexane : AcOEt=4 : 1 eluate. (3*S*,4*R*,5*R*)-**6**: Spectral data (IR, NMR) of (3*S*,4*R*,5*R*)-**6** were identical with those of the reported (±)-**6**. $[\alpha]_D^{25}$ +17.3° (*c*=0.98, $CHCl_3$); *Anal*. Found: C, 68.47; H, 8.52; N, 5.07. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32%. (4*S*,5*R*)-**7**: Spectral data (IR and NMR) of (4*S*,5*R*)-**7** were identical with those of the reported (±)-**7**. $[\alpha]_D^{24}$ +52.2° (*c*=1.01, $CHCl_3$); HR-MS (FAB-MS); *m*/*z*: 264.1551 (M^++1), Calcd for $C_{15}H_{22}NO_3$: 264.1600.

Treatment of (3*S*,4*R*,5*R*)-6 with CF_3SO_3H To a solution of (3*S*,4*R*,5*R*)-**6** (0.42 g, 1.6 mmol) in CH_2Cl_2 (40 ml) was added trifluoromethanesulfonic acid (0.4 ml) at −20 °C, and the whole mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with cooled 7% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=3 : 1) to give (3*S*,4*R*,5*S*)-**12** (0.286 g, 72%) as a homogeneous oil. (3*S*,4*R*,5*S*)-**12**: $[\alpha]_D^{24}$ +53.2° (*c*=0.76, $CHCl_3$); IR (neat): 3376, 1713 cm^{-1}; NMR: δ 1.48 (3H, d, *J*=5 Hz), 2.25 (3H, s), 2.60 (1H, dd, *J*=11, 18 Hz), 2.77 (1H, dd, *J*=6, 18 Hz), 3.01 (1H, dt, *J*=6, 10 Hz), 3.44 (1H, t, *J*=10 Hz), 3.50, 3.72 (each 1H, d, *J*=13 Hz), 4.10 (1H, dq, *J*=6, 10 Hz), 7.26—7.37 (5H, m). FAB-MS *m*/*z*: 250 (M^++1). HR-MS (FAB-MS); *m*/*z*: 250.1454 (M^++1), Calcd for $C_{14}H_{20}NO_3$: 250.1443.

Acetylation of (3*S*,4*R*,5*S*)-12 A solution of (3*S*,4*R*,5*S*)-**12** (0.26 g, 1 mmol) and Ac_2O (4 ml) in AcOH (2 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with toluene and evaporated. To the residue was added 7% aqueous $NaHCO_3$, and the whole was extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue which was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=4 : 1) to afford (4*R*,5*S*)-**13** (0.145 g, 82%) as a homogeneous oil. (4*R*,5*S*)-**13**: $[\alpha]_D^{27}$ −169.8° (*c*=0.73, $CHCl_3$); IR (neat): 1739 cm^{-1}; NMR: δ 1.44 (3H, d, *J*=6 Hz), 2.14 (3H, s), 4.60 (1H, dq, *J*=7, 7 Hz), 5.28 (1H, ddd, *J*=1, 3, 7 Hz), 6.11 (1H, dd, *J*=1, 10 Hz), 6.78 (1H, dd, *J*=3, 10 Hz). *Anal*. Found: C, 56.31; H, 6.13. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92%. FAB-MS *m*/*z*: 171 (M^++1).

(−)-Osmundalactone 11 A mixture of (4*R*,5*S*)-**13** (0.09 g, 0.5 mmol) and lipase Amano P (0.1 g) in 0.1 M phosphate buffer solution (20 ml) was stirred for 2 d at 30 °C. The reaction mixture was extracted with AcOEt and the organic layer was dried over $MgSO_4$. The organic layer was evaporated to give a residue which was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=1 : 1) to afford (−)-**11** (0.062 g, 92%). Crystallization of (−)-**11** from benzene gave a colorless crystal (−)-**11**. (−)-**11**: mp 81—82 °C (lit. mp 82—82.5 °C)[4a]; $[\alpha]_D^{22}$ −69.0° (*c*=0.46, H_2O) (lit. $[\alpha]_D^{22}$ −70.6° (*c*=2.0, H_2O))[4a]; IR (neat): 3410, 1710 cm^{-1}; NMR: δ 1.49 (3H, d, *J*=6 Hz), 4.25 (1H, dt, *J*=2, 9 Hz), 4.39 (1H, dq, *J*=6, 9 Hz), 5.97 (1H, dd, *J*=2, 10 Hz), 6.88 (1H, dd, *J*=2, 10 Hz). *Anal*. Found: C, 56.14; H, 6.37. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29%. FAB-MS *m*/*z*: 129 (M^++1).

Methyl (4*R*,5*S*)-4-Dimethylamino-5-hydroxy-2(*E*)-hexenoate 16 To a solution of (4*S*,5*S*)-**1** (0.81 g, 5.7 mmol) in MeOH (16 ml) were added di-

methylamine hydrochloride (0.93 g, 11.4 mmol) and triethylamine (1.15 g, 11.4 mmol), and the whole mixture was allowed to stand for 1 d at 40 °C. The reaction mixture was evaporated to give a residue which was chromatographed on silica gel (20 g, $CHCl_3$: MeOH=50 : 1) to afford a mixture (0.846 g, 81%) of (3*R*,4S,5S)-**14** and (3*S*,4*S*,5*S*)-**15** as an oil. This mixture in MeOH (16 ml) again stood for 2 d at 50 °C. The reaction mixture was evaporated to give a residue which was again chromatographed on silica gel (30 g) to afford (4*S*,5*S*)-**1** (0.084 g, 13%) from $CHCl_3$ eluate and (4*R*,5*S*)-**16** (0.516 g, 61%) as a colorless oil from $CHCl_3$: MeOH=50 : 1 eluate. NMR data of (4*S*,5*S*)-**1** were identical with those of (±)-**1**. (4*R*,5*S*)-**16**: $[\alpha]_D^{20}$ −115.9° (*c*=1.02, $CHCl_3$); IR (neat): 3430, 1724 cm^{-1}; NMR: δ 1.09 (3H, d, *J*=6 Hz), 2.28 (6H, s), 2.55 (1H, dd, *J*=4, 10 Hz), 3.76 (3H, s), 4.08 (1H, dq, *J*=4, 6 Hz), 5.93 (1H, d, *J*=16 Hz), 6.91 (1H, dd, *J*=10, 16 Hz). *Anal*. Found: C, 57.34; H, 9.18; N, 7.52. Calcd for $C_9H_{17}NO_3$: C, 57.74; H, 9.15; N, 7.48%. FAB-MS *m*/*z*: 188 (M^++1).

Conversion of (4*R*,5*S*)-16 into L-(−)-Forosamine 18 i) A solution of (4*R*,5*S*)-**16** (0.47 g, 2.5 mmol) in MeOH (10 ml) was hydrogenated at an ordinary temperature and pressure over 20% $Pd(OH)_2$–C (0.08 g). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated to give a residue. A solution of the crude residue in 80% aqueous AcOH (10 ml) was refluxed for 2.5 h and the reaction mixture was diluted with benzene. The organic layer was evaporated to give a residue which was chromatographed on silica gel (15 g, $CHCl_3$: MeOH=4 : 1) to afford a δ-lactone (4*R*,5*S*)-**17** (0.32 g) as an oil. ii) To a solution of (4*R*,5*S*)-**17** (0.31 g) in THF (8 ml) was added a 1.5 M solution of DIBAH (5.9 ml, 8.8 mmol) in toluene at −30 °C, and the whole mixture was stirred for 1 h at the same temperature. Aqueous MeOH (MeOH : H_2O=3 : 1, 8 ml) was added to the reaction mixture at −30 °C and the whole mixture was filtered off with the aid of Celite. The precipitate was washed with acetone. The washing was combined with the filtrate and the combined organic layer was evaporated to give a residue, which was chromatographed on silica gel (10 g) to afford L-(−)-forosamine **18** (0.08 g, 20% yield from (4*R*,5*S*)-**16**) as an oil from $CHCl_3$: MeOH=9 : 1 eluate and (4*R*,5*S*)-**19** (0.1 g, 24% yield from (4*R*,5*S*)-**16**) as an oil from $CHCl_3$: MeOH=4 : 1 eluate. L-(−)-forosamine **18**: $[\alpha]_D^{24}$ −85.7° (*c*=0.78, MeOH) (lit. D-(+)-**18**: $[\alpha]_D^{25}$ +86.1° (*c*=0.9, MeOH))[6]; IR (neat): 3388, 2937 cm^{-1}; NMR: δ 1.20, 1.28 (each 3H, d, *J*=6.5 Hz), 1.40—2.05 (8H, m), 2.20—2.35 (2H, m), 2.21, 2.24 (each 6H, s), 3.66—3.72 (1H, m), 3.56, 4.38 (each 1H, dq, *J*=6.6, 9 Hz), 4.71 (1H, dd, *J*=1.2, 9 Hz), 5.19 (1H, t, *J*=2 Hz). *Anal*. Found: C, 60.72; H, 10.90; N, 8.57. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80%. (4*R*,5*S*)-**19**: $[\alpha]_D^{24}$ +10.7° (*c*=0.93, MeOH); IR (KBr): 3357, 2936 cm^{-1}; NMR: δ 1.19 (3H, d, *J*=6 Hz), 1.53-1.86 (4H, m), 2.28—2.32 (1H, m), 2.38 (6H, s), 3.51—3.57, 3.64—3.69 (each 1H, m), 4.10 (1H, dq, *J*=2, 6 Hz). *Anal*. Found: C, 59.96; H, 12.01; N, 8.79. Calcd for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69%.

References and Notes

1) Ono M., Saotome C., Akita H., *Tetrahedron:Asymmetry*, **7**, 2595—2602 (1996).
2) Saotome C., Ono M., Akita H., *Tetrahedron:Asymmetry*, **11**, 4137—4151 (2000).
3) Evans D. A., Gauchet-Prunet J. A., *J. Org. Chem*., **58**, 2446—2453 (1993).
4) Isolation and bioactivity: *a*) Hollenbeak K. H., Kuehne M. E., *Tetrahedron*, **30**, 2307—2316 (1974); *b*) Numata A., Hokimoto K., Takemura T., Katsuno T., Yamamoto K., *Chem. Pharm. Bull*., **32**, 2815—2820 (1984); Synthesis of (±)-**11**: *c*) Torssell K., Tyagi M. P., *Acta Chem. Scand*., *B*, **31**, 297—301 (1977); *d*) Yamagiwa S., Sato H., Hoshi N., Kosugi H., Uda H., *J. Chem. Soc*., *Perkin Trans. I*, **1979**, 570—583. Synthesis of (−)-**11**: *e*) Murayama T., Sugiyama T., Yamashita K., *Agric. Biol. Chem*., **50**, 2347—2351 (1986); *f*) Noshita T., Sugiyama T., Kitazumi Y., Oritani T., *Tetrahedron Lett*., **35**, 8259—8262 (1994).
5) As a preliminary experiment, the acetylation of (±)-**12** with Ac_2O–pyridine gave the corresponding acetate (95%) which was treated with Ac_2O/AcOH (2 : 1) to afford (±)-**13** (87%) and *N*-methylbenzylamine acetate (68%).
6) Dyong I., Knollmann R., Jersch N., *Angew. Chem*., *Int. Ed. Engl*., **15**, 302—302 (1976).