Enantio- and Diastereoselective Synthesis of *N*-[(1*R*,2*R*,3*R*,4*R*)-2,3-Diacetoxy-4-(acetoxymethyl)cyclopentyl]acetamide, a Synthetic Key Intermediate of (+)-Cyclaradine

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Enantio- and diastereoselective synthesis of *N*-[(1*R*,2*R*,3*R*,4*R*)-2,3-diacetoxy-4-(acetoxymethyl)cyclopentyl]-acetamide 1, a synthetic key intermediate of (+)-cyclaradine, has been achieved by using enzyme-catalyzed asymmetric hydrolysis and subsequent modification of a functional group.

Key words (+)-cyclaradine; enantio- and diastereoselective synthesis; enantiomerically pure form

Carbocyclic nucleosides have been the focus of extensive study in the fields of organic and medicinal chemistry.[1,2] As an application of our synthetic methodology for carbocyclic nucleosides, here we wish to report a facile synthesis of *N*-[(1*R*,2*R*,3*R*,4*R*)-2,3-diacetoxy-4-(acetoxymethyl)cyclopentyl]acetamide **1**, a synthetic key intermediate of an *anti*-HSV (herpes simplex virus)—active carbocyclic analogue of ara-A, (+)-cyclaradine,[1] in an enantio- and diastereoselective manner.

The synthetic route to (+)-cyclaradine is shown in Chart 1. The preparation of the *meso*-substrates (**2a**, **2b**) and the enzymatic process of chiral induction were established in our previous synthetic study of (−)-aristeromycin[3]; the enantiomers, (−)-**3** (71% yield) and (+)-**3** (81% yield), could each be obtained in a pure form by *Pseudomonas fluorescens* lipase[4] (PFL)-catalyzed hydrolysis of **2a** and transesterification of **2b**, respectively. Compound (−)-**3** was selected as an advantageous starting material to construct **1** from the viewpoint of absolute stereochemistry.

Acidic hydrolysis of the acetonide function in (−)-**3** afforded the corresponding triol **4** in 90% yield. A regioselective protection of the C3-hydroxy group in **4** was achieved by reaction with 1, 3-dichlorotetraisopropyldisiloxane (TIPDS dichloride) in pyridine to produce cyclic bis(siloxy)ether **5a** (96%). An inversion of the stereochemistry at C11 of **5a** as the next step was expected to be difficult because of steric hindrance around the C11-position. As expected, the usual Mitsunobu reaction of **5a** did not afford the desired product. To overcome this problem, several substrates **5**—**8** were prepared from **5a** in the usual manner (see Experimental) to research the two types of inversion reaction, Mitsunobu reaction for (11*S*)-hydroxy derivatives **5a**—**7a** and Ikegami's method for (11*S*)-methanesulfonyloxy derivatives **5b**—**7b** and **8**. Among these reactions tested, the desired inversion succeeded only in the case of using compound **6b** under Ikegami's reaction conditions to afford compound **9** in 65% yield. The structure of **9** was confirmed by spectroscopic analyses, including ^{1}H,^{1}H-nuclear Overhasuser effect correlation spectroscopy (NOESY) and correlation spectroscopy (COSY) NMR spectra. A nuclear Overhauser effect (NOE) correlation between C9α-H (δ 1.76—1.71) and C11α-H (δ 4.04—3.99) was observed. In the ^{1}H-NMR spectrum, signals at δ 4.30 (1H, dd, J=8.3, 11.2 Hz) and δ 4.04 (1H, dd, J=5.3, 11.2 Hz) suggested the presence of an acetoxymethyl group at the C10-position. This product might be obtained by usual inversion and subsequent acetyl migration to a primary alcohol. The other reactions of compounds **5b**, **6a**, **7b** and **8** resulted in complex mixtures, except for the case of using compound **7a** under Mitsunobu's reaction condition, which gave the cyclic acetal **10** (56%).[5]

Conversion of **9** to the target **1** was successfully completed *via* the sequence shown in Chart 3. That is to say, protection of the C11-hydroxy group of **9** as an ethoxyethyl ether **11** (96%) and subsequent solvolysis of the C10-acetoxymethyl function afforded the primary alcohol **12** (81%). Ruthenium-catalyzed oxidation of **12** into carboxylic acid **13** (73%) and further Curtius rearrangement by using diphenyl phosphorazidate (DPPA) afforded the carbamate **14** (40% yield), which possesses the correct stereochemistry and functional groups required for **1**. Subsequent deprotection of **14** was achieved by a two-step sequence (i. KOH/MeOH, ii. HCl), and further acetylation gave the target molecule **1** $[\alpha]_D$ +31.3°

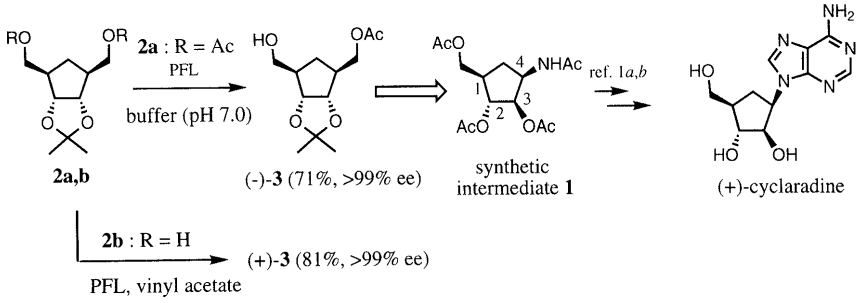

Chart 1. Synthetic Route to **1**

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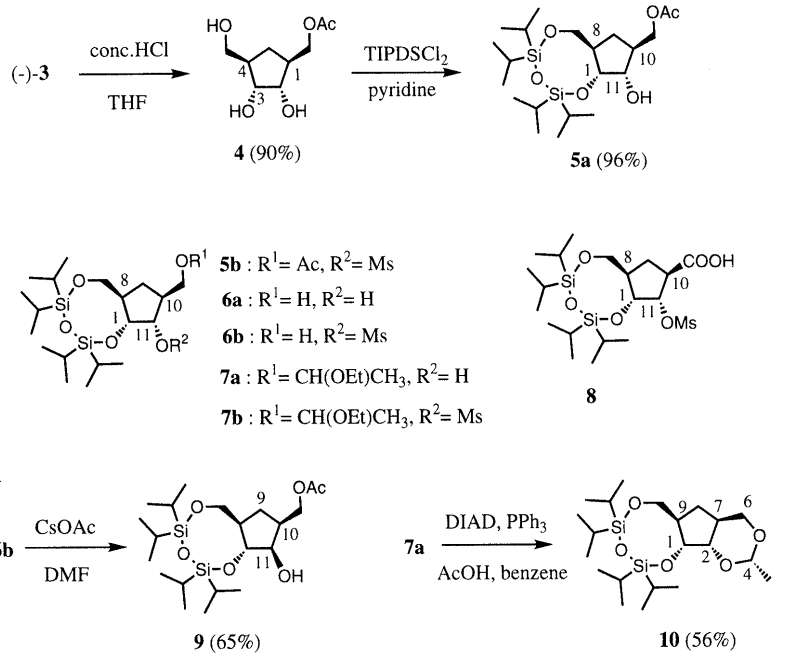

Chart 2. Inversion of Stereochemistry at the C9-Position

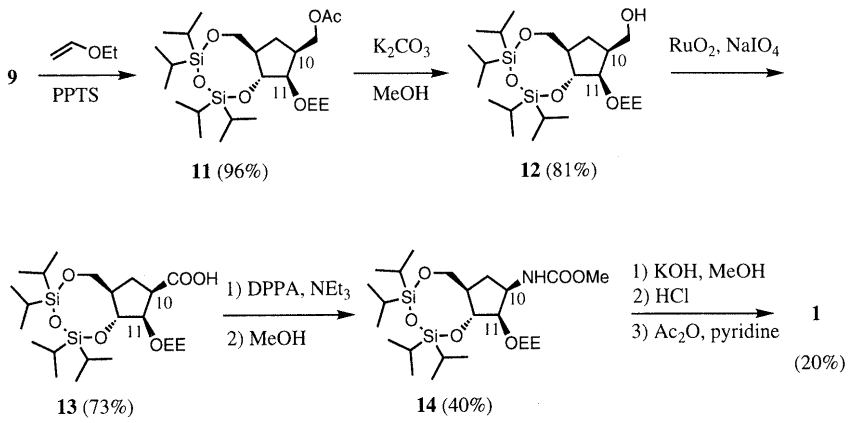

Chart 3

($c=0.23$, $CHCl_3$) in 20% yield from **14**. Spectroscopic data agreed with those reported by Tadano *et al.*, and the specific rotation was $[\alpha]_D$ +28.8° ($c=0.86$, $CHCl_3$).[1a)]

Experimental

IR spectra were measured on a JASCO A-100 IR spectrophotometer. ^1H- and ^{13}C-NMR spectra were measured with a JEOL JNM-GX 270 or Varian Unity-500P spectrometer. MS were taken on a JEOL SX-102A or JMS-600W/600H spectrometer. Specific rotations were measured on a JASCO DIP-360 polarimeter. Tetrahydrofuran (THF) was dried and distilled from sodium-benzophenone ketyl prior to use. CH_2Cl_2 was dried and distilled from calcium hydride prior to use. Melting points were obtained without correction. For column chromatography, silica gel (Merk, Kiselgel 60, 70—30 mesh) was used. The preparation of **2** and **3** was reported in our previous paper.[3)]

(1*S*,2*S*,3*R*,4*R*)-(2,3-Dihydroxy-4-hydroxymethylcyclopent-1-yl)methyl Acetate (4) Aqueous 10% HCl (10 ml) was added dropwise to a stirred solution of (−)-**3** (500 mg, 2.0 mmol) in THF (10 ml) at 0 °C. After having been stirred for 3 h at room temperature, the reaction mixture was diluted with aqueous 5% $NaHCO_3$. After removal of THF *in vacuo*, the residue was extracted with EtOAc and the extracts were dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% MeOH in $CHCl_3$ afforded **4** (378 mg, 90%) as a colorless oil, $[\alpha]_D^{25}$ −0.47° ($c=1.2$, $CHCl_3$). IR (neat) cm^{-1}: 3380 (OH), 1730 (C=O). ^1H-NMR ($CDCl_3$) δ: 4.09 (dd, $J=2.5$, 6.1 Hz, 2H, C$\underline{H}_2$OAc), 3.85 (m, 3H, C$\underline{H}_a$OH, H-2, H-3), 3.56 (dd, $J=7.9$, 10.6 Hz, 1H, C$\underline{H}_b$OH), 2.23 (m, 3H, H-1, H-4, OH), 2.07 (s, 3H, CH_3COO), 1.95 (m, 1H, H-5β), 0.85 (m, 1H, H-5α), FAB-MS m/z: 205 (M^++H). HR-MS (FAB) m/z: Calcd for $C_9H_{17}O_5$ (M^++H 205.1076); Found 205.1088.

(1*R*,8*R*,10*S*,11*S*)-[11-Hydroxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methyl Acetate (5a) TIPDS dichloride (1.79 ml, 5.58 mmol) was added dropwise to a stirred solution of **4** (950 mg, 6.45 mmol) in pyridine (20 ml). After having been stirred for 3 h at room temperature, the reaction mixture was evaporated. The residue was diluted with brine, and extracted with EtOAc. The extracts were washed with aqueous 10% HCl, aqueous 5% $NaHCO_3$, and brine and then dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 3% EtOAc in hexane afforded **5a** (1.98 g, 96%) as a colorless oil, $[\alpha]_D^{25}$ −11.2° ($c=0.67$, $CHCl_3$). IR (neat) cm^{-1}: 3500 (OH), 1740 (C=O), 1240, 1110, 1080, 1030 (SiO). ^1H-NMR ($CDCl_3$) δ: 4.08 (dd, $J=5.8$, 11.1 Hz, 1H, H-8), 4.02 (m, 2H, C$\underline{H}_2$OAc), 3.93 (dd, $J=3.7$, 11.7 Hz, 1H, SiOC$\underline{H}_a$), 3.80 (ddd, $J=2.9$, 5.8 Hz, 1H, H-9), 3.72 (dd, $J=4.5$, 11.8 Hz, 1H, SiOC$\underline{H}_b$), 2.65 (d, $J=2.5$ Hz, 1H, OH), 2.21 (m, 2H, H-1, H-10), 2.04 (s, 3H, CH_3COO), 1.81 (m, 1H, H-11β), 1.14 (m, 1H, H-11α), 1.06 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$). FAB-MS m/z: 447 (M^++H). HR-MS (FAB) m/z: Calcd for $C_{21}H_{43}O_6Si_2$ (M^++H 447.2598); Found 447.2591.

(1*R*,8*R*,10*S*,11*S*)-[11-Methanesulfonyloxy-3,3,5,5,-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methyl Acetate (5b) Et_3N (0.15 ml, 1.07 mmol) and methanesulfonyl chloride (0.73 ml, 0.940 mmol) were added dropwise to a stirred solution of **5a** (288 mg,

0.645 mmol) in CH_2Cl_2 (3 ml). After having been stirred for 15 h at room temperature, the reaction mixture was diluted with brine and extracted with CH_2Cl_2. The extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 15% EtOAc in hexane afforded **5b** (330 mg, 98%) as colorless crystals, mp 34—35 °C. $[\alpha]_D^{24}$ +19.3° (c=1.17, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1740 (C=O), 1350, 1170 (SO_3), 1080, 1040 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.88 (d, J=4.6 Hz, 1H, H-9), 4.11 (dd, J=5.0, 11.4 Hz, 1H, C$\underline{H}_a$OAc), 3.98 (dd, J=4.7, 11.0 Hz, 1H, H-8), 3.94 (dm, J=11.9 Hz, 1H, SiOCH_a), 3.93 (dd, J=7.7, 11.4 Hz, 1H, C$\underline{H}_b$OAc), 3.76 (dm, J=11.4 Hz, 1H, SiOCH_b), 3.05 (s, 3H, SO_2CH_3), 2.55 (m, 1H, H-10), 2.16 (m, 1H, H-1), 2.05 (s, 3H, CH_3COO), 1.84 (m, 1H, H-11α), 1.33 (m, 1H, H-11β), 1.05 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$). FAB-MS m/z: 481 (M^+−Ac), 429 (M^+−OMs).

(1*R*,8*R*,10*S*,11*S*)-[11-Hydroxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methanol (6a) K_2CO_3 (14.9 mg, 0.11 mmol) was added to a stirred solution of **5a** (93 mg, 0.216 mmol) in MeOH (1 ml). After having been stirred for 1 h at room temperature, the reaction mixture was diluted with aqueous NH_4Cl. After removal of the solvent *in vacuo*, the residue was extracted with EtOAc. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded **6a** (85.8 mg, 98%) as colorless crystals, mp 85—87 °C, $[\alpha]_D^{25}$ −18.2° (c=0.58, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3500 (OH), 1120, 1040 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.05 (dd, J=5.8, 7.7 Hz, 1H, H-8), 3.93 (dd, J=3.7, 11.7 Hz, 1H, SiOCH_a), 3.82 (m, 1H, H-9), 3.68 (dd, J=5.4, 11.7 Hz, 1H, SiOCH_b), 3.64 (m, 1H, C$\underline{H}_a$OH), 3.59 (dd, J=4.6, 7.3 Hz, 1H, C$\underline{H}_b$OH), 2.74 (d, J=3.6 Hz, 1H, OH), 2.24—2.05 (m, 2H, H-1, H-10), 1.83—1.63 (m, 1H, H-11α), 1.06 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$), 1.00 (m, 1H, H-11β). FAB-MS m/z: 405 (M^++H).

(1*R*,8*R*,10*S*,11*S*)-[11-Methanesulfonyloxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methanol (6b) Compound **6b** was prepared from **5b** in a similar manner to that described for the preparation of **6a**, in 72% yield.

6b: A colorless oil, $[\alpha]_D^{24}$ +6.9° (c=1.08, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1330, 1160 (SO_3), 1030 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.94 (d, J=4.6 Hz, 1H, H-9), 4.01 (dd, J=4.8, 10.6 Hz, 1H, H-8), 3.95 (dd, J=3.0, 11.9 Hz, 1H, SiOCH_a), 3.77 (d, J=11.9 Hz, 1H, SiOCH_b), 3.60 (m, 2H, C$\underline{H}_2$OH), 3.07 (s, 3H, SO_2CH_3), 2.43 (m, 1H, H-10), 2.16 (m, 1H, H-1), 1.82 (m, 1H, H-11α), 1.32 (m, 1H, H-11β), 1.05 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$). FAB-MS m/z: 483 (M^++H), 387 (M^+−OMs). HR-MS (FAB) m/z: Calcd for $C_{20}H_{43}O_7SSi_2$ (M^++H 483.2267); Found 483.2260.

(1*R*,8*R*,10*S*,11*S*)-10-(1-Ethoxyethyl)oxymethyl-11-hydroxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undecane (7a) Ethyl vinyl ether (0.05 ml, 0.556 mmol) was added dropwise to a stirred solution of **6a** (112.3 mg, 0.278 mmol) and pyridinium-*p*-toluenesulfonate (PPTS, 14 mg, 0.056 mmol) in CH_2Cl_2 (10 ml). After having been stirred at 50 °C for 4 h, the reaction mixture was diluted with aqueous 5% $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 2% EtOAc in hexane afforded **7a** (128.4 mg, 97%) as a colorless oil, IR (neat) cm^{-1}: 3550 (OH), 1140 (OCO), 1110, 1020, 1000 (SiO). ^{1}H-NMR ($CDCl_3$) 4.69 (q, J=5.2 Hz, 0.5H, OC$\underline{H}$(Me)OEt), 4.67 (q, J=5.2 Hz, 0.5H, OC$\underline{H}$(Me)OEt), 4.02 (dd, J=5.6, 8.9 Hz, 1H), 3.93 (dd, J=3.4, 11.7 Hz, 1H), 3.83 (m, 1H), 3.73 (dd, J=4.3, 11.5 Hz, 1H), 3.69—3.39 (m, 3H), 3.36 (dd, J=5.3, 9.4 Hz, 1H), 2.63 (m, 1H, OH), 2.16 (m, 2H), 1.80 (dt, J=8.1, 12.5 Hz, 1H), 1.59—1.24 (m, 3H), 1.19 (m, 3H), 1.14—0.83 (m, 29H, SiC$\underline{H}$($C\underline{H}_3$)$_2$, H-11β). FAB-MS m/z: 404 (M^++H−CH(Me)OEt).

(1*R*,8*R*,10*S*,11*S*)-10-(1-Ethoxyethyl)oxymethyl-11-methanesulfonyloxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undecane (7b) Compound **7b** was prepared from **7a** in a similar manner to that described for the preparation of **6b**.

7b: A colorless oil, IR (neat) cm^{-1}: 1350, 1170 (SO_3), 1120, 1080, 1040 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.91 (t, J=3.8 Hz, 1H, C$\underline{H}$OMs), 4.67 (dd, J=5.4, 8.1 Hz, 3/4H, OC$\underline{H}$(Me)OEt), 4.73—4.60 (m, 1/4H ,OC$\underline{H}$(Me)-OEt), 4.02 (dd, J=2.3, 4.6 Hz, 1/4H), 3.99—3.96 (m, 1/4H), 3.94 (dd, J=2.8, 11.7 Hz, 3/4H), 3.77 (dm, J=11.7 Hz, 3/4H), 3.69—3.34 (m, 19/4H), 3.24 (dd, J=5.9, 9.6 Hz, 1/4H), 3.07 (s, 3H, SO_2CH_3), 2.44 (m, 1H), 2.15 (m, 1H), 1.78 (ddd, J=7.3, 9.7, 12.5 Hz, 1H), 1.47 (tdd, J=2.2, 7.9, 13.7 Hz, 1H), 1.27 (m, 3H), 1.17 (m, 3H), 1.09—0.88 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$). FAB-MS m/z: 554 (M]), 459 (M^+−OMs).

(1*R*,8*R*,10*S*,11*S*)-11-Methanesulfonyloxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undecane-10-carboxylic Acid (8) $NaIO_4$ (676 mg, 3.16 mmol), benzyltriethylammonium chloride (1.4 mg, 0.006 mmol) and RuO_2 (0.8 mg, 0.006 mmol) were successively added to a stirred solution of **6b** (304.1 mg, 0.631 mmol) in $CHCl_3$ (15 ml) and phosphate buffer (pH 7, 15 ml). This mixture was stirred for 8 h at room temperature, then 2-propanol (2 ml) was added. The whole was filtered through a Celite pad. The filtrate was evaporated and the residue was extracted with $CHCl_3$. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 15% EtOAc in hexane afforded **8** (219 mg, 70%) as a colorless oil, IR (neat) cm^{-1}: 3420 (OH), 1690 (C=O), 1340, 1170 (SO_3), 1030 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 5.21 (d, J=4.3 Hz, 1H, C$\underline{H}$OMs), 4.12 (m, 1H, H-8), 3.94 (dd, J=2.3, 11.9 Hz, 1H, SiOCH_a), 3.79 (dd, J=11.9 Hz, 1H, SiOCH_b), 3.10 (s, 3H, SO_2CH_3), 2.18 (m, 2H, H-1, H-10), 1.86 (m, 1H, H-11α), 1.29 (m, 1H, H-11β), 1.06 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$).

(1*R*,8*R*,10*S*,11*R*)-[11-Hydroxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methyl Acetate (9) CsOAc (454 mg, 2.36 mmol) was added to a stirred solution of **6b** (248 mg, 0.473 mmol) in *N*,*N*-dimethylformamide (DMF) (25 ml). After having been stirred at 100 °C for 12 h, the reaction mixture was diluted with brine, and extracted with EtOAc. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in hexane afforded **9** (454 mg, 65%) as a colorless oil, $[\alpha]_D^{24}$ +26.6° (c=0.66, $CHCl_3$). IR (neat) cm^{-1}: 3430 (OH), 1730 (C=O), 1250, 1110, 1050, 1020 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.30 (dd, J=8.2, 11.2 Hz, 1H, C$\underline{H}_a$OAc), 4.04 (dd, J=5.3, 11.2 Hz, 1H, C$\underline{H}_b$OAc), 4.04—3.99 (m, 2H, H-8, H-9), 3.93 (dd, J=3.2, 11.4 Hz, 1H, SiOCH_a), 3.66 (dd, J=6.9, 11.7 Hz, 1H, SiOCH_b), 2.36—2.34 (m, 1H, H-10), 2.21 (d, J=3.9 Hz, 1H, OH), 2.06 (s, 3H, CH_3COO), 2.00—1.92 (m, 1H, H-1), 1.76—1.71 (m, 1H, H-11α), 1.35—1.26 (m, 1H, H-11β), 1.09—1.02 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$). FAB-MS m/z: 447 (M^++H), 403 (M^+−Ac). HR-MS (FAB) m/z: Calcd for $C_{21}H_{43}O_6Si_2$ (M^++H 447.2598); Found 447.2587.

(1*R*,2*S*,4*S*,7*S*,9*R*)-4-Methyl-3,5,11,13,15-pentaoxa-12,14-disila-12,12,14,14-tetrakis(1-methylethyl)tricyclo[7.6.0.02,7]pentadecane (10) Diisopropyl diazodicarboxylate (DIAD, 0.07 ml, 0.366 mmol) was added dropwise to a stirred solution of Ph_3P (113.6 mg, 0.366 mmol) in benzene (0.5 ml) at 5 °C. This mixture was stirred for 30 min at 5 °C, then a solution of **7a** (44.7 mg, 0.093 mmol) in benzene (0.8 ml) and AcOH (0.02 ml, 0.372 mmol) were added. The whole was refluxed for 8 h, then diluted with brine, and extracted with EtOAc. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 15% EtOAc in hexane afforded **10** (22.5 mg, 56%) as a colorless oil, IR (neat) cm^{-1}: 1440, 1160 (OCO), 1110, 1080, 1040 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.69 (q, J=5.4 Hz, 1H, H-4), 4.40 (dd, J=1.2, 5.8 Hz, 1H, H-6α), 4.30 (dd, J=4.6, 10.6 Hz, 1H, H-1), 3.88 (dd, J=4.6, 11.5 Hz, 1H, SiOCH_a), 3.46 (t, J=11.9 Hz, 1H, SiOCH_b), 3.42 (t, J=10.6 Hz, 1H, H-2), 3.01 (dd, J=5.9, 11.2 Hz, 1H, H-6β), 2.34—2.05 (m, 2H, H-9, H-7), 1.75 (ddd, J=5.7, 8.4, 12.2 Hz, 1H, H-8α), 1.38 (d, J=5.4 Hz, 3H, OCHC$\underline{H}_3$), 1.18—0.83 (m, 28H, SiC$\underline{H}$(CH_3)$_2$), 0.44 (td, J=9.6, 12.2 Hz, 1H, H-8β).

(1*R*,8*R*,10*S*,11*R*)-[11-(1-Ethoxyethyl)oxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methyl Acetate (11) Compound **11** was prepared from **9** in a similar manner to that described for the preparation of **7a**, in 96% yield.

11: A colorless oil, IR (neat) cm^{-1}: 1730 (C=O), 1120 (OCO), 1071, 1020 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.80 (q, J=5.3 Hz, 0.5H, OC$\underline{H}$(Me)OEt), 4.72 (q, J=5.3 Hz, 0.5H, OC$\underline{H}$(Me)OEt), 4.25—4.17 (m, 1H), 4.14—4.06 (m, 2H), 4.04—3.90 (m, 2H), 3.68—3.44 (m, 3H), 2.48—2.39 (m, 1H), 2.04 (s, 1.5H, CH_3COO), 2.04 (s, 1.5H, CH_3COO), 2.04—1.96 (m, 1H, H-1), 1.89—1.81 (m, 1H, H-11α), 1.29 (d, J=5.3 Hz, 1.5H, OCHC$\underline{H}_3$), 1.28 (d, J=5.3 Hz, 1.5H, OCHC$\underline{H}_3$), 1.26—1.20 (m, 1H, H-11β), 1.21—1.16 (m, 3H, OCH_2CH_3), 1.18—1.00 (m, 28H, SiC$\underline{H}$($C\underline{H}_3$)$_2$). FAB-MS m/z: 430 (M^++H−OCH(Me)OEt), 429 (M^+−OCH(Me)OEt). *Anal.* Calcd for $C_{25}H_{50}O_7Si_2$: C, 57.83; H, 9.73. Found: C, 57.88; H, 9.72.

(1*R*,8*R*,10*S*,11*R*)-[11-(1-Ethoxyethyl)oxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undec-10-yl]methanol (12) Compound **12** was prepared from **11** in a similar manner to that described for the preparation of **6b**, in 81% yield.

12: A colorless oil, IR (neat) cm^{-1}: 3450 (OH), 1130 (OCO), 1080, 1020 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.82 (q, J=5.3 Hz, 0.5H, OC<u>H</u>(Me)OEt), 4.74 (q, J=5.3 Hz, 0.5H, OC<u>H</u>(Me)OEt), 4.17—4.07 (m, 1H), 4.02—3.89 (m, 2H), 3.77—3.44 (m, 5H), 3.37—2.28 (m, 1.5H), 1.95—1.64 (m, 2H), 1.50—1.38 (m, 0.5H), 1.34 (d, J=5.3 Hz, 1.5H, OCHC<u>H</u>$_3$), 1.32 (d, J=5.0 Hz, 1.5H, OCHC<u>H</u>$_3$), 1.25—1.17 (m, 3H, OCH$_2$C<u>H</u>$_3$), 1.11—1.00 (m, 28H, SiC<u>H</u>(C<u>H</u>$_3$)$_2$). FAB-MS m/z: 477 (M^++H), 476 (M^+), 387 (M^+−OCH(Me)OEt). HR-MS (FAB) m/z: Calcd for $C_{23}H_{48}O_6Si_2$ (M^+ 476.2989); Found 476.2995.

(1*R*,8*R*,10*R*,11*R*)-[11-(1-Ethoxyethyl)oxy-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undecane-10-carboxylic Acid (13) Compound **13** was prepared from **12** in a similar manner to that described for the preparation of **8**, in 73% yield.

13: A colorless oil, IR (neat) cm^{-1}: 3100 (OH), 1700 (C=O), 1120 (OCO), 1060, 1020, 990 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 4.86 (q, J=5.3 Hz, 0.5H, OC<u>H</u>(Me)OEt), 4.81 (q, J=5.1 Hz, 0.5H, OC<u>H</u>(Me)OEt), 4.30—4.19 (m, 1H), 4.11—4.01 (m, 1H), 3.96—3.89 (m, 1H), 3.79—3.49 (m, 3H), 3.11—3.03 (m, 1H, H-10), 2.07—1.83 (m, 3H, H-1, H-11), 1.36 (d, J=5.3 Hz, 1.5H, OCHC<u>H</u>$_3$), 1.27 (d, J=5.6 Hz, 1.5H, OCHC<u>H</u>$_3$), 1.29—1.16 (m, 3H, OCH$_2$C<u>H</u>$_3$), 1.07—0.98 (m, 28H, SiC<u>H</u>(C<u>H</u>$_3$)$_2$). FAB-MS m/z: 491 (M^++H), 402 (M^++H−OCH(Me)OEt), 401 (M^+−OCH(Me)OEt). HR-MS (FAB) m/z: Calcd for $C_{23}H_{47}O_7Si_2$ (M^++H 491.2860); Found 491.2869.

(1*R*,8*R*,10*R*,11*R*)-11-(1-Ethoxyethyl)oxy-10-methoxycarbonylamino-3,3,5,5-tetrakis(1-methylethyl)-2,4,6-trioxa-3,5-disilabicyclo[6.3.0]undecane (14) DPPA (0.047 ml, 0.208 mmol) and Et_3N (0.029 ml, 0.006 mmol) in benzene (5 ml) were added to a stirred solution of **13** (85 mg, 0.173 mmol) in benzene (5 ml). The reaction mixture was refluxed for 3 h, MeOH (2 ml) was added, and the whole was refluxed for 20 h at 100 °C. After removal of the solvent, the residue was diluted with EtOAc and washed with aqueous 5% NH_4Cl, aqueous 5% $NaHCO_3$, and brine, successively. The organic layer was dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 1% EtOAc in hexane afforded **14** (36 mg, 40%) as a colorless oil, IR (neat) cm^{-1}: 3450, 3250 (NH), 1730 (C=O), 1130 (OCO), 1080, 1020 (SiO). ^{1}H-NMR ($CDCl_3$) δ: 5.44 (br s, 0.5H, NH), 5.06 (br s, 0.5H, NH), 4.77—4.70 (m, 1H, OC<u>H</u>(Me)OEt), 4.25—3.98 (m, 2H), 3.95—3.90 (m, 2H), 3.71—3.56 (m, 2H), 3.66 (s, 3H, OCH_3), 3.55—3.43 (m, 1H), 2.17—2.11 (m, 1H), 2.04—1.98 (m, 1H), 1.45—1.40 (m, 1H), 1.31 (d, J=5.3 Hz, 1.5H, OCHC<u>H</u>$_3$), 1.31 (d, J=5.3 Hz, 1.5H, OCHC<u>H</u>$_3$), 1.26—1.18 (m, 3H, OCH$_2$C<u>H</u>$_3$), 1.09—0.98 (m, 28H, SiC<u>H</u>(C<u>H</u>$_3$)$_2$). FAB-MS m/z: 520 (M^++H), 519 (M^+), 430 (M^+−OCH(Me)OEt). HR-MS (FAB) m/z: Calcd for $C_{24}H_{49}O_7NSi_2$ (M^+ 519.3047); Found 519.3042.

(1*R*,2*R*,3*R*,4*R*)-4-Acetamido-2,3-diacetoxy-1-cyclopentanemethyl Acetate (1) KOH (306 mg, 5.45 mmol) in water (1.8 ml) was added to a stirred solution of **14** (19.5 mg, 0.037 mmol) in MeOH (1.5 ml). After having been refluxed at 100 °C for 5 h, the reaction mixture was acidified with aqueous 10% HCl, and evaporated to dryness. The residue was diluted with CH_2Cl_2 (3 ml). Pyridine (0.5 ml), Ac_2O (0.2 ml, 2.1 mmol) and *N*,*N*-dimethylaminopyridine (DMAP, 2.6 mg, 0.021 mmol) were added to this solution. The whole was stirred for 6 h at room temperature, then diluted with aqueous 5% $NaHCO_3$, and extracted with CH_2Cl_2. The extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 5% EtOH in toluene afforded **1** (2.4 mg, 20%) as colorless needles, mp 124—125 °C. (lit[1a] 125.5—126.5 °C). $[\alpha]_D^{29}$ +31.3° (c=0.23, $CHCl_3$). IR (KBr) cm^{-1}: 3280 (NH), 1730 (OC=O), 1650 (NC=O). ^{1}H-NMR ($CDCl_3$) δ: 5.60 (d, J=7.7 Hz, 1H, NH), 5.09 (dd, J=2.2, 5.2 Hz, 1H, H-3), 4.92 (dd, J=2.4, 4.7 Hz, 1H, H-2), 4.62—4.56 (m, 1H, H-4), 4.18—4.08 (m, 2H, C<u>H</u>$_2$OAc), 2.39—2.31 (m, 1H, H-5α), 2.29—2.26 (m, 1H, H-1), 2.12 (s, 3H, CH_3COO), 2.06 (s, 6H, CH_3COO), 1.99 (s, 3H, C<u>H</u>$_3$CONH), 1.47—1.41 (m, 1H, H-5β). FAB-MS m/z: 364 (M^++H), 363 (M^+).

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References and Notes

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4) PFL has been reclassified as *P. cepacia* lipase (PCL, Amano PS). However, we use the former name for the sake of uniformity with previous results.

5) This reaction might be caused by the acetic acid employed. The stereochemistry of **10** was confirmed by ^{1}H,^{1}H-NOESY and COSY NMR spectra. NOE correlations between C4-H (δ 4.69), C2-H (δ 3.42) and C6β-H (δ 3.01) were observed, which suggested that the orientation of methyl group at C-4 position is equatorial in the chair form of the six-membered ring (C2—C7).