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Syntheses of (+)- and (−)-Dihydropinidine and (+)- and (−)-Epidihydropinidine by Using Yeast Reduction of Methyl (2-oxocyclohexyl)acetate

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(+) and (−)-Dihydropinidine and (+)- and (−)-epidihydropinidine were synthesized from hydroxy esters 1 and 2 which had been prepared by yeast reduction of methyl (2-oxocyclohexyl)acetate. The enantiomeric excess at the C-1 positions of 1 and 2 were both determined as more than 99% ee.

Key words: dihydropinidine; epidihydropinidine; yeast reduction

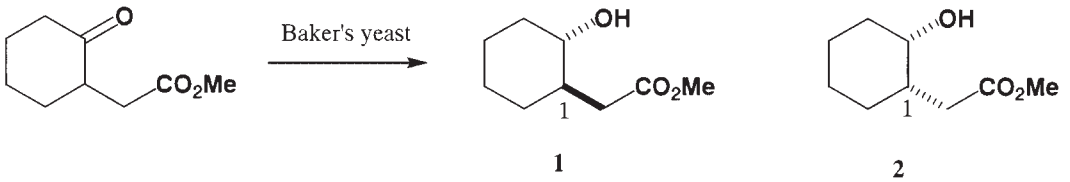
Yeast reduction of methyl (2-oxocyclohexyl)acetate, which gives hydroxy ester **1** (98% ee) and **2** (97%ee), has been previously reported (Fig. 1).[1)] The purpose of this work is to recheck the enantiomeric excess at the C-1 positions of **1** and **2** and to apply these yeast-mediated reduction products to the syntheses of natural products. Ring opening of **1** and **2** would give useful chiral synthons.

(+)- and (−)-Dihydropinidine (**3**) and (+)- and (−)-epidihydropinidine (**4**) were selected as the target compounds. Dihydropinidine was isolated from the Mexican bean beetle, *Epilachna varivestis*,[2)] and epidihydropinidine was isolated from *Pinus engelmannii*.[3)] Many reports of syntheses of (+)- and (−)-dihydropinidine have been published, due to biological activity (necrotoxic, hemolytic, phytotoxic, insecticidal, antibacterial, and antifungal)[4)] of 2,6-disubstituted piperidine. Two of these employed the enzymatic pathway.[5,6)] T. Momose *et al.* have obtained enantiomerically pure starting materials to (+)- and (−)-dihydropinidine.[5)] R. Chênevert *et al.* have obtained only (+)-dihydropinidine from the enantiomerically pure starting material.[6)] In both these reports, lipase has been employed to produce enantiomerically pure material. In the case of epidihydropinidine, only two synthetic pathways to (+)-epidihydropinidine have been reported.[7,8)] However, these seems to have been no synthetic research of (−)-epidihydropinidine. This article describes the syntheses of (+)- and (−)-dihydropinidine and (+)- and (−)-epidihydropinidine by using yeast reduction of methyl (2-oxocyclohexyl)acetate. This is a first approach to get both the (+) and (−) isomers of dihydropinidine and epidihydropinidine from one racemic compound by employing baker's yeast. This is also the first synthetic report on (−)-epidihydropinidine.

The synthetic plan is shown in Scheme 1. The piperidine ring of (−)-**3** and (+)-**4** would be formed by S_N2 cyclization of **5** and **7**, respectively. Compounds **6** and **8** could be respectively transformed to **5** and **7** *via* stereoselective α-hydroxylation followed by S_N2 conversion to an amino group. Both compounds **6** and **8** would be obtained from lactone **9** by ring opening and C–C bond elongation. Lactone **9** could be obtained from yeast-mediated reduction product **1**, and (+)-dihydropinidine (**3**) and (−)-epidihydropinidine (**4**) could be synthesized from yeast-mediated reductive product **2**. The C-1 positions of **1** and **2** would be respectively converted to the C-6 positions of **3** and **4**. This means that the values for the enantiomeric excess at the C-6 positions of **3** and **4** would depend on that at the C-1 positions of **1** and **2**. The chiral center at the C-2 positions of **3** and **4** would be introduced by using Evans's chiral auxiliaries.[9)]

Results and Discussion

Hydroxy ester **1** was subjected to $LiAlH_4$ reduction followed by protection of the resulting primary hydroxy



1 **2**

Fig. 1.

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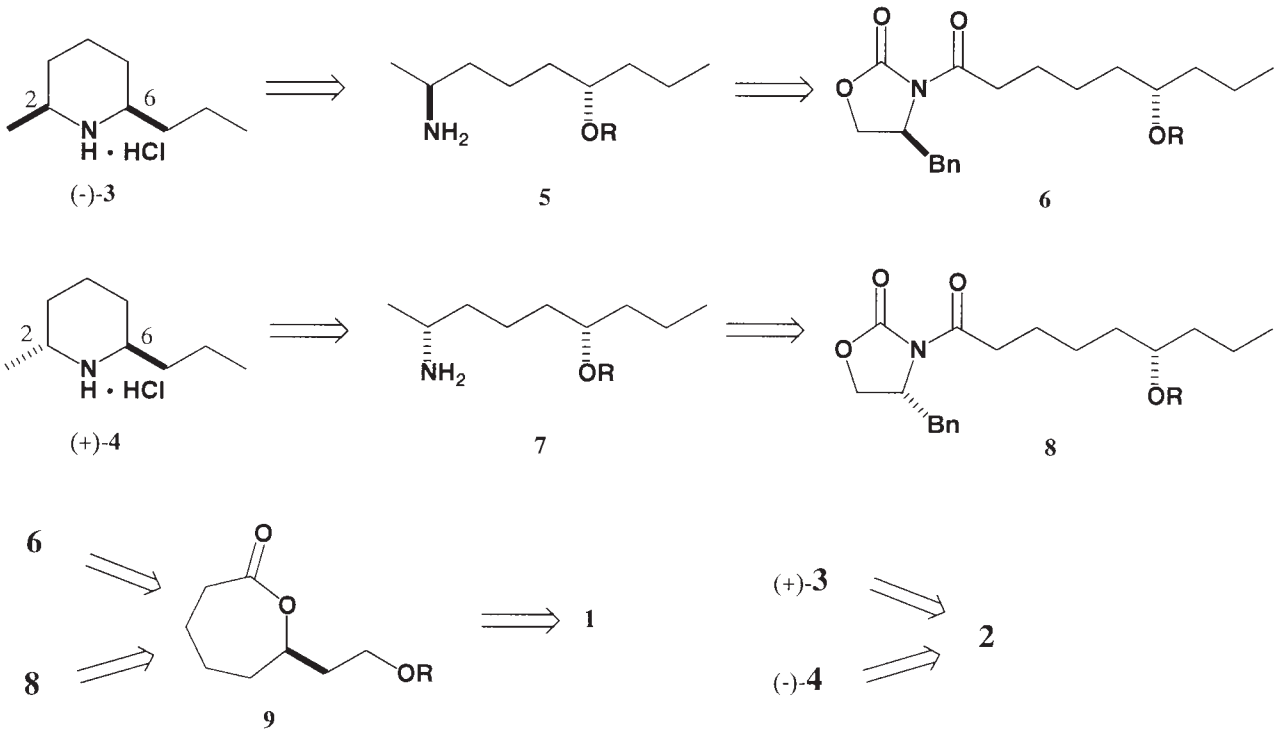


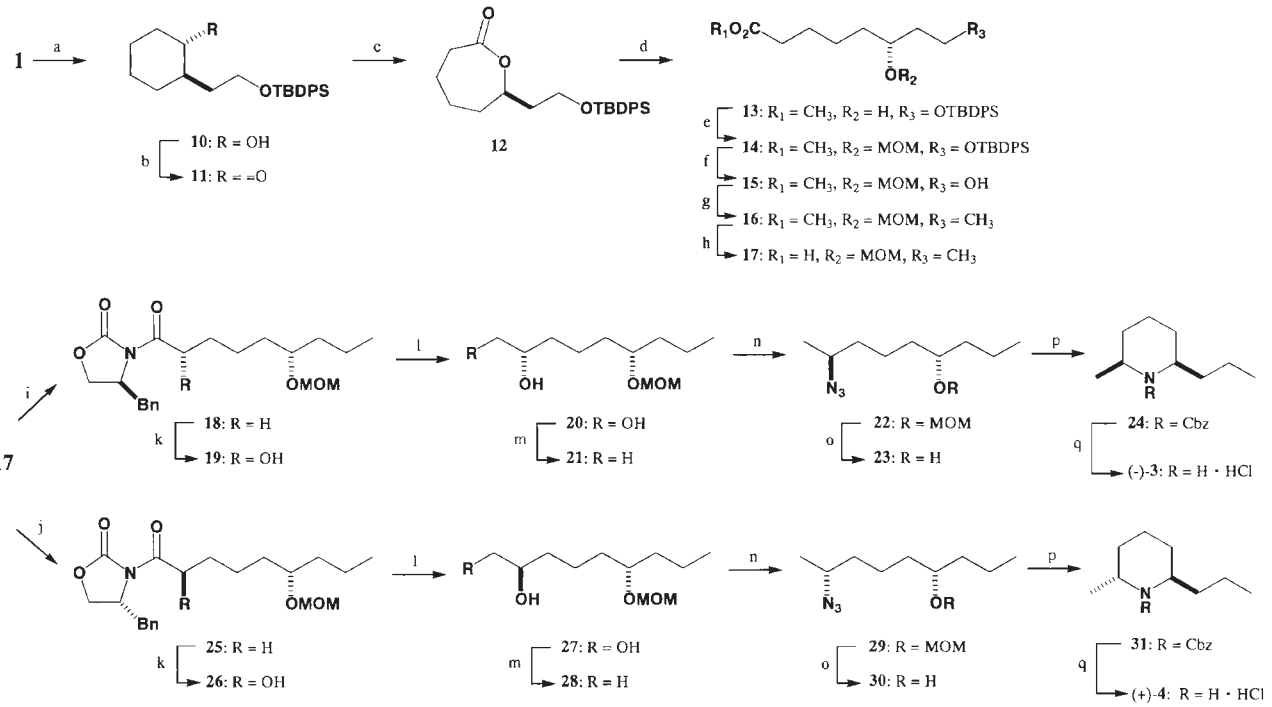
Scheme 1. Retrosynthetic Analyses of Optically Active Dihydropinidine and Epidihydropinidine.

group as a TBDPS ether by using TBDPSCl and imidazole (53% yield, 2 steps). After PCC oxidation of cyclohexanol derivative **10** (95% yield), resulting ketone **11** was converted to lactone **12** by Baeyer-Villiger oxidation, employing MCPBA in a phosphate buffer at pH 8 and $CHCl_3$,[10] in 98% yield.

The enantiomeric excess was determined after methanolysis of this lactone **12**. (*R*)-Hydroxy ester **13** was reacted with (−)-menthyl chloroformate, and the product was determined as being of more than 99% de by an HPLC analysis. On the other hand, corresponding (*S*)-hydroxy ester **13**, which had been transformed from yeast-mediated reduction product **2** by the same process, was also determined as being of more than 99% de. It became clear that the enantiomeric excess at the C-1 positions of yeast-mediated reduction products **1** and **2** were more than 99% ee, and that Baeyer-Villiger oxidation had proceeded with complete retention of the configuration.

After protecting of the secondary hydroxy group as an MOM ether by using MOMCl and *N*,*N*-diisopropylethylamine in 95% yield, the silyl group was removed by $(n\text{-Bu})_4NF$ to give alcohol **15** in 94% yield. After conversion to a tosylate (95% yield), C–C bond elongation was accomplished by employing Me_2CuLi, giving **16** in 78% yield. Hydrolysis of **16** (98% yield) followed by introduction of the *S* or *R* Evans's chiral auxiliary[11] gave **18** in 93% yield and **25** in 97% yield, respectively. The α-hydroxylation of **18** and **25** by using MoOPH[12] stereoselectively proceeded to give **19** (43% yield, 17% recovered) and **26** (45% yield, 18% recovered), respectively. In both reactions, **18** and **25** were recovered. The auxiliaries were reductively removed by using $LiBH_4$ to give glycols **20** (79% yield) and **27** (84% yield), respectively. These glycols were converted to monotosylates by using TsCl and pyridine, which were subsequently treated with $LiAlH_4$ to give **21** (66% yield, 2 steps) and **28** (73% yield, 2 steps), respectively. After the secondary hydroxy groups had been converted to mesylates by using MsCl and Et_3N, the resulting mesylates were treated with NaN_3 to give azides **22** (85% yield, 2 steps) and **29** (91% yield, 2 steps), respectively. To remove the MOM ethers, **22** and **29** were each treated with a diluted aqueous HCl solution, giving alcohol **23** (95% yield) and **30** (95% yield), respectively. After their conversion to mesylates, S_N2 cyclization was performed by treatment with Ph_3P in heated aqueous THF. The crude products were respectively transformed to Cbz-form **24** (42% yield, 3 steps) and **31** (44% yield, 3 steps) by using CbzCl in an aqueous K_2CO_3 solution and THF for purification. Finally, removal of the Cbz groups by H_2 and $Pd(OH)_2$/C followed by treatment with an aqueous HCl solution gave (−)-**3** (78% yield) and (+)-**4** (98% yield), respectively. By the same synthetic process, (+)-**3** and (−)-**4** were respectively synthesized from yeast-mediated reduction product **2** (Scheme 2).

The enantiomeric excess at the C-1 positions of yeast-mediated reduction products **1** and **2** were determined as more than 99% ee. (+)- and (−)-Dihydropinidine (**3**) and (+)- and (−)-epidihydropinidine (**4**) were synthesized from **1** and **2**, (−)-epidihydropinidine being synthesized for the first time. It was found that all four optically active compounds (+)-**3**, (−)-**3**, (+)-**4** and (−)-



Scheme 2. Syntheses of (−)-**3** and (+)-**4**.

(a) (1) $LiAlH_4$, ether, 0°C, 1 h; (2) TBDPSCl, imidazole, r.t., 2 h (53%, 2 steps). (b) PCC, MS 4A, CH_2Cl_2, r.t., 15 h (95%). (c) MCPBA, phosphate buffer pH 8, $CHCl_3$, r.t., 14 h (98%). (d) K_2CO_3, MeOH, r.t., 1 h (98%). (e) MOMCl, *N*,*N*-(*iso*-Pr)$_2$NEt, CH_2Cl_2, r.t., 15 h (95%). (f) (*n*-Bu)$_4$NF, THF, r.t., 2 h (94%). (g) (1) *p*-TsCl, pyridine, CH_2Cl_2, r.t., 12 h (95%); (2) Me_2CuLi, ether, −40°C, 2.5 h (78%). (h) 6 M aq. KOH, EtOH, r.t., 2 h (98%). (i) Et_3N, PivCl, lithium salt of (*S*)-4-benzyl-2-oxazolidinone, 0°C, 30 min (93%). (j) Et_3N, PivCl, lithium salt of (*R*)-4-benzyl-2-oxazolidinone, 0°C, 30 min (97%). (k) LDA, MoOPH, THF, −70°C, 2 h (**19**: 43%, **26**: 45%). (l) $LiBH_4$, MeOH, THF, 0°C, 2 h (**20**: 79%, **27**: 84%). (m) (1) *p*-TsCl, pyridine, CH_2Cl_2, 0°C, 5 h; (2) $LiAlH_4$, THF, r.t., 2 h (**21**: 66%, 2 steps, **28**: 73%, 2 steps). (n) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 1.5 h; (2) NaN_3, DMF, 100°C, 1 h (**22**: 85%, 2 steps, **29**: 91%, 2 steps). (o) 6 M aq. HCl solution, THF, r.t., 2 h (**23**: 95%, **30**: 95%). (p) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 1.5 h; (2) Ph_3P, aq. THF, 50°C, 60 h, and then 1 M aq. HCl solution; (**3**) CbzCl, 2 M aq. K_2CO_3 solution, THF, r.t., 15 h (**24**: 42%, 3 steps, **31**: 44%, 3 steps). (q) H_2, 20% $Pd(OH)_2$/C, EtOAc, ambient temperature, 1.5 h, and then 1 M aq. HCl solution ((−)-**3**: 78%, (+)-**4**: 98%).

4 could be synthesized from one racemic methyl (2-oxocyclohexyl)acetate by using yeast reduction. The utilization of yeast-mediated reduction products **1** and **2** is shown for the first time.

Experimental

Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer, FABMS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a HORIBA SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). HPLC analyses were performed with Shimadzu LC-6AD and SPD-6AV instruments.

*(1S,2R)-2-[2-(tert-Butyldiphenylsilyloxy)ethyl]cyclohexanol (**10**).* To an ice-cooled suspension of $LiAlH_4$ (2.04 g, 0.054 mol) in ether (20 ml) was added a solution of *trans*-hydroxy ester **1** (10.1 g, 0.059 mol) in ether (50 ml). After stirring at 0°C for 1 h, sat. aq. $MgSO_4$ solution and K_2CO_3 were added. The mixture was stirred for 30 min before filtration. The filtrate was concentrated to give crude diol. A reaction solution of crude diol, *tert*-butyldiphenylsilyl chloride (15.3 ml, 0.059 mol) and imidazole (8.01 g, 0.12 mol) in DMF (2 ml) was stirred at room temperature for 2 h before additions of sat. aq. $NaHCO_3$ solution and ethyl acetate. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After the organic solution was concentrated, the residue was applied to silica gel column chromatography (5% EtOAc in hexane) to give silyl ether **10** (11.7 g, 0.031 mol, 53%) as a colorless oil, $[\alpha]^{20}_D = +21$ (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3388, 2932, 1429, 1113, 1078, 1009; δ_H ($CDCl_3$) 0.90–1.06 (2H, m), 1.06 (9H, s, *tert*-Bu), 1.10–1.28 (3H, m), 1.35 (1H, m), 1.50 (1H, m), 1.55–1.67 (1H, m), 1.70–1.84 (2H, m), 2.01 (1H, m), 3.26 (1H, m, 1-H), 3.45 (1H, s, OH), 3.68–3.79 (2H, m, CH_2OTBDPS), 7.37–7.45 (6H, m, ArH), 7.67–7.69 (4H, m, ArH); δ_C ($CDCl_3$) 19.1, 24.9, 25.7, 26.8, 32.2, 35.1, 37.3, 44.3, 63.3, 74.7, 127.7, 129.7, 133.2, 135.6. *Anal.* Found: C, 75.09; H, 9.05. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96%.

*(1S,2S)-2-[2-(tert-Butyldiphenylsilyloxy)ethyl]cyclohexanol (1S,2S)-(**10**).* By the same method as that described for the preparation of (1*S*,2*R*)-**10**, the title

compound was obtained from *cis*-hydroxy ester **2** as a colorless oil in 80% yield. $[\alpha]^{20}_D = +6.1$ (*c* 1.6, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3400, 2934, 1429, 1111, 1075, 909, 824 cm^{-1}. NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.20–1.30 (1H, m), 1.32–1.47 (3H, m), 1.48–1.57 (2H, m), 1.58–1.74 (4H, m), 1.75–1.82 (1H, m), 2.21 (1H, s, OH), 3.68 (1H, m, C*H*HOTBDPS), 3.74 (1H, m, CH*H*OTBDPS), 3.89 (1H, m, 1-H), 7.37–7.45 (6H, m, ArH), 7.66–7.68 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.1, 20.7, 25.1, 26.8, 27.1, 32.7, 34.8, 39.0, 62.4, 69.1, 127.7, 129.7, 133.5, 133.6, 135.56, 135.59. *Anal*. Found C, 75.13; H, 9.26. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96%.

*(R)-2-[2-(tert-Butyldiphenylsilyloxy)ethyl]cyclohexanone (**11**).* A reaction mixture of alcohol **10** (23.5 g, 0.061 mol), PCC (14.6 g, 0.068 mol), and MS 4A (0.5 g) in CH_2Cl_2 (300 ml) was stirred at room temperature for 15 h before addition of ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (2% EtOAc in hexane) to give cyclohexanone derivative **11** (22.1 g, 0.058 mol, 95%) as a colorless oil, $[\alpha]^{20}_D = +1.0$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3021, 2934, 1705, 1429, 1217, 1113 cm^{-1}. NMR δ_H ($CDCl_3$): 1.04 (9H, s, *tert*-Bu), 1.25–1.43 (2H, m), 1.60–1.68 (2H, m), 1.81 (1H, m), 1.98–2.10 (2H, m), 2.14 (1H, m), 2.26 (1H, m, 6-*H*H), 2.36 (1H, m, 6-H*H*), 2.52 (1H, m, 2-H), 3.70 (2H, t, *J* 6.1, Hz, CH_2OTBDPS), 7.35–7.43 (6H, m, ArH), 7.63–7.66 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 25.1, 26.9, 28.1, 32.1, 34.0, 42.1, 47.1, 61.7, 127.6, 129.6, 133.9, 134.0, 135.5, 213.1. *Anal*. Found: C, 75.71; H, 8.84. Calcd. for $C_{24}H_{32}O_2Si$: C, 75.74; H, 8.48%. (*S*)-**11**, $[\alpha]^{20}_D = -0.9$ (*c* 3.3, $CHCl_3$).

*(R)-8-(tert-Butyldiphenylsilyloxy)octan-6-olide (**12**).* A reaction mixture of (*R*)-ketone **11** (20.4 g, 0.054 mol) and MCPBA (16.4 g, 70%, 0.067 mol) in $CHCl_3$ (200 ml) and phosphate buffer pH 8 (200 ml) was stirred at room temperature for 14 h. After filtration, the filtrate was washed with sat. aq. sodium thiosulfate solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). The organic solution was evaporated, and then the residue was applied to silica gel column chromatography (5% EtOAc/hexane) to give lactone **12** (21.0 g, 0.053 mol, 98%) as colorless crystals, mp 60–61°C (petroleum ether), $[\alpha]^{20}_D = -40$ (*c* 0.9, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3000, 2934, 1721, 1429, 1329, 1287, 1258, 1177, 1148, 1113, 1082, 1014 cm^{-1}. NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.52–1.68 (3H, m), 1.77 (1H, m), 1.87–1.98 (4H, m), 2.54 (1H, m, 2-*H*H), 2.65 (1H, m, 2-H*H*), 3.75 (1H, ddd, *J* 10.5, 4.9, 4.9 Hz, 8-*H*H), 3.87 (1H, ddd, *J* 10.5, 8.6, 4.4 Hz, 8-H*H*), 4.54 (1H, m, 6-H), 7.36–7.44 (6H, m, ArH), 7.63–7.65 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 23.0, 26.9, 28.3, 34.5, 34.8, 39.0, 59.8, 77.0, 127.69, 127.72, 129.7, 133.5, 133.7, 135.5, 175.6. *Anal*. Found C, 73.02; H, 8.29. Calcd. for $C_{24}H_{32}O_3Si$: C, 72.68; H, 8.13%. (*S*)-(**12**), $[\alpha]^{20}_D = +40$ (*c* 1.1, $CHCl_3$).

*(R)-Methyl 8-tert-butyldiphenylsilyloxy-6-hydroxyoctanoate (**13**).* A reaction mixture of (*R*)-lactone **12** (22.7 g, 0.057 mol) and K_2CO_3 (7.91 g, 0.057 mol) in MeOH (150 ml) was stirred at room temperature for 1 h before concentration. The residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After the organic solution was evaporated, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/5) to give (*R*)-methyl ester **13** (23.8 g, 0.056 mol, 98%) as a colorless oil, $[\alpha]^{20}_D = +7.2$ (*c* 2.3, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2934. 1732, 1429, 1113, 1078 cm^{-1}. NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.34–1.55 (4H, m), 1.60–1.75 (4H, m), 2.33 (2H, t, *J* 7.6 Hz, 2-H_2), 3.26 (1H, s, OH), 3.66 (3H, s, OCH_3), 3.80–3.92 (3H, m, 6-H, 8-H_2), 7.38–7.46 (6H, m, ArH), 7.66–7.68 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.0, 25.0, 25.2, 26.8, 34.1, 37.1, 38.3, 51.5, 63.6, 71.6, 127.8, 129.8, 132.9, 133.0, 135.5, 135.6, 174.2. *Anal*. Found: C, 70.28; H, 8.76. Calcd. for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47%. (*S*)-**13**, $[\alpha]^{20}_D = -7.2$ (*c* 1.8, $CHCl_3$).

*Determination of the optical purity of the (R)- and (S)-methyl esters (**13**).* To an ice-cooled solution of (*R*)-**13** (28 mg, 0.065 mmol) in pyridine (50 μl) was added (−)-menthyl chloroformate (20.9 μl, 0.098 mmol). After the reaction mixture was stirred at room temperature for 1 h, H_2O and EtOAc were added. The organic solution was separated, washed with 0.5 M aq. HCl solution and sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). The organic solution was concentrated. The residue was applied to HPLC (Merck, LiChrospher Si 60, 2% EtOAc in hexane, 2.0 ml/min, detected at 270 nm), retention time: 22 min, more than 99% de. Reaction product of (*S*)-**13** with (−)-menthyl chloroformate: 19 min, more than 99% de.

*(R)-Methyl 8-tert-butyldiphenylsilyloxy-6-methoxymethoxyoctanoate (**14**).* A reaction mixture of (*R*)-alcohol **13** (23.8 g, 0.056 mol), (*iso*-Pr)$_2$EtN (38.7 ml, 0.22 mol), and MOMCl (8.43 ml, 0.11 mol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 15 h before additions of MeOH and H_2O. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). The organic solution was evaporated, and then the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/7) to give (*R*)-MOM ether **14** (25.1 g, 0.053 mol, 95%) as a colorless oil, $[\alpha]^{20}_D = +1.7$ (*c* 1.2, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3021, 1732, 1429, 1217, 1111, 1036 cm^{-1}. NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.29–1.42 (2H, m), 1.48–1.53 (2H, m), 1.55–1.66 (2H, m), 1.70–1.75 (2H, m), 2.30 (2H, t, *J* 7.6 Hz, 2-H_2), 3.31 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.71–3.79 (3H, m, 6-H, 8-H_2), 4.58 (1H, d, *J* 6.8 Hz, OC*H*HOCH$_3$), 4.61 (1H, d, *J* 6.8 Hz, OCH*H*OCH$_3$), 7.36–7.44 (6H, m, ArH), 7.64–7.67 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 24.8, 25.1, 26.9, 34.0, 34.4, 37.3, 51.4,

55.5, 60.6, 74.7, 95.7, 127.6, 129.6, 133.9, 135.6, 174.1. *Anal*. Found: C, 68.62; H, 8.42. Calcd. for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53%. (*S*)-**14**, $[\alpha]^{20}_D = -1.6$ (*c* 2.0, $CHCl_3$).

*(R)-Methyl 8-hydroxy-6-methoxymethoxyoctanoate (**15**).* To an ice-cooled solution of silyl ether **14** (24.0 g, 0.051 mol) in THF (150 ml) was added $(n\text{-Bu})_4NF$ (0.056 ml, 1 M in THF, 0.056 mol). The reaction solution was stirred at room temperature for 2 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After the mixture was concentrated, the residue was applied to silica gel column chromatography (10% EtOAc in hexane) to give alcohol **15** (11.3 g, 0.048 mol, 94%) as a colorless oil; $[\alpha]^{20}_D = -50$ (*c* 1.6, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2950, 1732, 1439, 1208, 1150, 1100, 1071, 1032 cm^{-1}. NMR δ_H ($CDCl_3$): 1.31–1.41 (2H, m), 1.49–1.72 (4H, m), 1.65–1.74 (2H, m), 2.32 (2H, t, *J* 7.3 Hz, 2-H_2), 2.43 (1H, br. s, OH), 3.40 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.71–3.79 (3H, m, 6-H, 8-H_2), 4.65 (1H, d, *J* 6.8 Hz, OC*H*HOCH$_3$), 4.68 (1H, d, *J* 6.8 Hz, OCH*H*OCH$_3$). NMR δ_C ($CDCl_3$): 24.7, 25.0, 33.9, 34.3, 36.6, 51.5, 55.7, 59.8, 76.2, 95.9, 174.0. *Anal*. Found: C, 56.06; H, 9.47. Calcd. for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46%. (*S*)-**15**, $[\alpha]^{20}_D = +50$ (*c* 2.6, $CHCl_3$).

*(S)-Methyl 6-methoxymethoxynonanoate (**16**).* A reaction mixture of (*R*)-alcohol **15** (4.55 g, 0.019 mol), *p*-TsCl (3.70 g, 0.019 mol) and pyridine (3.14 ml, 0.039 mol) in CH_2Cl_2 (8 ml) was stirred at room temperature for 12 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). The organic solution was evaporated, and then the residue was applied to silica gel column chromatography (10% EtOAc in hexane) to give unstable tosylate (7.15 g, 0.018 mol, 95%) as a colorless oil. To a suspension of CuI (14.0 g, 0.074 mol) in ether (15 ml) was added MeLi (66.9 ml, 2.2 M in ether, 0.15 mol) at −40°C. After the mixture was stirred at −40°C for 2 h, tosylate (7.15 g, 0.018 mol) in ether (20 ml) was added. The reaction mixture was stirred at −40°C for 2.5 h, and then sat. aq. NH_4Cl solution and ether were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was purified with silica gel column chromatography (10% EtOAc in hexane) to recover tosylate (1.56 g, 0.0040 mol, 22%) and give (*S*)-**16** (3.21 g, 0.014 mol, 78%) as a colorless oil; $[\alpha]^{20}_D = -4.9$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2936, 1732, 1466, 1458, 1439, 1213, 1169, 1148, 1100, 1038. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.1 Hz, 9-H_3), 1.30–1.53 (8H, m), 1.60–1.68 (2H, m), 2.32 (2H, t, *J* 7.3 Hz, 2-H_2), 3.37 (3H, s, OCH_3), 3.53 (1H, m, 6-H), 3.67 (3H, s, OCH_3), 4.64 (2H, s, OCH_2OCH$_3$). NMR δ_C ($CDCl_3$): 14.2, 18.5, 24.8, 25.1, 33.9, 34.0, 36.5, 51.4, 55.5, 77.1, 95.4, 174.1. *Anal*. Found: C, 61.80; H, 10.47. Calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41%. (*R*)-**16**, $[\alpha]^{20}_D = +4.9$ (*c* 1.6, $CHCl_3$).

*(S)-6-Methoxymethoxynonanoic acid (**17**).* A reaction solution of (*S*)-ester **16** (10.1 g, 0.043 mol) in 6 M aq. KOH solution (100 ml) and EtOH (100 ml) was stirred at room temperature for 2 h before additions of $CHCl_3$ and 6 M aq. HCl solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After the organic solution was evaporated, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/2) to give carboxylic acid **17** (9.17 g, 0.042 mol, 98%) as a colorless oil; $[\alpha]^{20}_D = -3.9$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3613, 2936, 1709, 1146, 1100, 1038. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.3 Hz, 9-H_3), 1.35–1.54 (8H, m), 1.61–1.69 (2H, m), 2.36 (2H, t, *J* 7.3 Hz, 2-H_2), 3.38 (3H, s, OCH_3), 3.54 (1H, m, 6-H), 4.65 (2H, s, OCH_2OCH$_3$). NMR δ_C ($CDCl_3$): 14.2, 18.5, 24.7, 24.8, 33.9, 36.5, 55.5, 77.1, 95.4, 179.4. FABMS *m/z*: 217 (M^+-1, 10), 157 (100), 137 (70). HRMS (FAB) *m/z* (M^+-1): Calcd. for $C_{11}H_{21}O_4$, 217.1439; found, 217.1441. (*R*)-**17**, $[\alpha]^{20}_D = +3.8$ (*c* 1.9, $CHCl_3$).

*(4S)-4-Benzyl-3-[(S)-6-methoxymethoxynonanoyl]-2-oxazolidinone (**18**).* To a solution of (*S*)-carboxylic acid **17** (6.57 g, 0.030 mol) and Et_3N (4.41 ml, 0.032 mol) in THF (150 ml) was added PivCl (3.89 ml, 0.032 mol) at −70°C. The mixture was stirred at 0°C for 1 h before cooling to −70°C. To this mixture was added lithium salt of (*S*)-4-benzyl-2-oxazolidinone, which was prepared with (*S*)-4-benzyl-2-oxazolidinone (5.60 g, 0.032 mol) and *n*-BuLi (20.1 ml, 1.6 M in hexane, 0.032 mol) in THF (150 ml) at −70°C for 30 min. After the resulting reaction mixture was stirred at 0°C for 30 min, sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). The organic solution was evaporated, and then the residue was applied to silica gel column chromatography (10% EtOAc in hexane) to give acyl oxazolidinone **18** (10.7 g, 0.028 mol, 93%) as colorless crystals, mp 60–61°C (*iso*-Pr_2O); $[\alpha]^{20}_D = +35$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2934, 1782, 1700, 1385, 1352, 1210, 1200, 1150, 1098, 1038 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, s, *J* 7.1 Hz, CH_3), 1.30–1.58 (8H, m), 1.62–1.74 (2H, m), 2.77 (1H, dd, *J* 13.4, 9.5 Hz, PhC*H*H), 2.85–3.00 (2H, m, O=CCH_2), 3.34 (1H, dd, *J* 13.4, 3.1 Hz, PhCH*H*), 3.38 (3H, s, OCH_3), 3.55 (1H, m, CHOMOM), 4.16 (1H, dd, *J* 8.8, 3.4 Hz, 5-*H*H), 4.20 (1H, dd, *J* 8.8, 8.8 Hz, 5-H*H*), 4.65 (2H, s, OCH_2OCH$_3$), 4.64–4.70 (1H, m, 4-H), 7.20–7.21 (2H, m, ArH), 7.27–7.29 (1H, m, ArH), 7.31–7.35 (2H, m, ArH). NMR δ_C ($CDCl_3$): 14.3, 18.5, 24.4, 24.8, 34.1, 35.5, 36.6, 37.9, 55.5, 66.2, 77.1, 77.2, 95.4, 127.3, 128.9, 129.4, 135.3, 153.4, 173.2. *Anal*. Found: C, 66.75; H, 8.19; N, 3.44. Calcd. for $C_{21}H_{31}O_5N$: C, 66.82; H, 8.28; N, 3.71%. (4*R*)-[(*R*)]-(**18**), $[\alpha]^{20}_D = -35$ (*c* 1.9, $CHCl_3$).

*(4S)-4-Benzyl-3-[(2S,6S)-2-hydroxy-6-methoxymethoxynonanoyl]-2-oxazolidinone (**19**).* To a solution of (4*S*)-[(*S*)]-**18** (10.7 g, 0.028 mol) in THF (300 ml) was added KHMDS (84.9 ml, 0.5 M in toluene, 0.042 mol) at −70°C. After stirring at −70°C for 30 min, MoOPH (18.5 g, 0.043 mol) was added. The reaction mixture was stirred at −70°C for 2 h, and then sat. aq. Na_2SO_3 solution was added. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). After evaporation, the residue was applied to silica gel column chromatography (10% EtOAc in hexane) to give (4*S*)-[(2*S*,6*S*)]-**19** (4.72 g, 0.012 mol, 43%) as a colorless oil; $[\alpha]^{20}_D = +32$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$)/cm^{-1} 3500, 2934, 1788, 1694, 1385, 1352, 1298, 1213, 1198, 1150, 1111, 1098, 1038, 912 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.3 Hz, CH_3), 1.30–1.70 (9H, m), 1.82 (1H, m), 2.84 (1H, dd, *J* 13.7, 9.3 Hz, PhC*H*H), 3.31 (1H, dd, *J* 13.7, 3.2 Hz, PhCH*H*), 3.38 (3H, s, OCH_3), 3.47 (1H, d, *J* 8.3 Hz, OH), 3.55 (1H, m, CHOMOM), 4.25 (1H, dd, *J* 9.3, 2.9 Hz, 5-*H*H), 4.28 (1H, dd, *J* 9.3, 9.3 Hz, 5-H*H*), 4.65 (2H, s, O*CH*$_2$OCH$_3$), 4.65–4.69 (1H, m, 4-H), 5.00 (1H, m, O=CC*H*OH), 7.20–7.22 (2H, m, ArH), 7.29–7.31 (1H, m, ArH), 7.33–7.36 (2H, m, ArH). NMR δ_C ($CDCl_3$): 14.2, 18.5, 21.1, 33.9, 34.3, 36.6, 37.5, 55.5, 66.9, 70.6, 70.8, 77.2, 95.5, 127.5, 129.0, 129.4, 134.8, 153.2, 174.9. *Anal*. Found: C, 64.04; H, 7.91; N, 3.63. Calcd. for $C_{21}H_{31}O_6N$: C, 64.10; H, 7.94; N, 3.56%. (4*R*)-[(2*R*,6*R*)]-**19**, $[\alpha]^{20}_D = -32$ (*c* 1.5, $CHCl_3$).

*(2S,6S)-6-Methoxymethoxynonane-1,2-diol (**20**).* To an ice-cooled solution of (4*S*)-[(2*S*,6*S*)]-acyl oxazolidinone **19** (3.01 g, 7.65 mmol) and MeOH (1.24 ml, 30.6 mmol) in THF (80 ml) was added $LiBH_4$ (0.83 g, 38.1 mmol). The resulting mixture was stirred at 0°C for 2 h before addition of sat. aq. NH_4Cl solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration of the solvent, the residue was applied to silica gel column chromatography (EtOAc/toluene = 1/4) to give (2*S*,6*S*)-glycol **20** (1.34 g, 6.08 mmol, 79%) as a colorless oil; $[\alpha]^{20}_D = +6.8$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2936, 1460, 1148, 1134, 1096, 1038 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.3 Hz, 9-H_3), 1.25–1.56 (10H, m), 2.36 (1H, br. s, OH), 2.49 (1H, br. s, OH), 3.38 (3H, s, OCH_3), 3.44 (1H, dd, *J* 10.7, 7.3 Hz, 1-*H*H), 3.55 (1H, m, 6-H), 3.65 (1H, dd, *J* 10.7, 2.9 Hz, 1-H*H*), 3.70 (1H, m, 2-H), 4.65 (2H, s, O*CH*$_2$OCH$_3$). NMR δ_C ($CDCl_3$): 14.2, 18.5, 21.1, 33.2, 34.2, 36.6, 55.5, 66.7, 72.1, 95.5. *Anal*. Found: C, 59.69; H, 11.01. Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98%. (2*R*,6*R*)-**20**, $[\alpha]^{20}_D = -6.9$ (*c* 1.9, $CHCl_3$).

*(2R,6S)-6-Methoxymethoxy-2-nonanol (**21**).* To an ice-cooled solution of (2*S*,6*S*)-glycol **20** (1.34 g, 6.08 mmol) and pyridine (0.98 ml, 12.1 mmol) in CH_2Cl_2 (1 ml) was added *p*-TsCl (1.16 g, 6.08 mmol). The reaction mixture was stirred at 0°C for 5 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). After evaporation, the residue was applied to silica gel column chromatography (5% EtOAc in toluene) to give unstable tosylate (1.62 g, 4.33 mmol, 71%) as a colorless oil. To an ice-cooled suspension of $LiAlH_4$ (0.32 g, 8.43 mmol) in THF (10 ml) was added tosylate (1.60 g, 4.27 mmol) in THF (20 ml). The reaction mixture was stirred at room temperature for 2 h before additions of sat. aq. $MgSO_4$ and K_2CO_3. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (10% EtOAc in hexane) to give (2*R*,6*S*)-**21** (0.81 g, 3.96 mmol, 93%) as a colorless oil; $[\alpha]^{20}_D = -8.1$ (*c* 0.7, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2936, 1458, 1379, 1142, 1098, 1038. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.3 Hz, 9-H_3), 1.19 (3H, d, *J* 5.9 Hz, 1-H_3), 1.26–1.56 (10H, m), 1.60–1.79 (1H, br., OH), 3.38 (3H, s, OCH_3), 3.55 (1H, m, 6-H), 3.81 (1H, m, 2-H), 4.65 (2H, s, O*CH*$_2$OCH$_3$). NMR δ_C ($CDCl_3$): 14.2, 18.5, 21.3, 23.5, 34.2, 36.5, 39.4, 55.5, 68.0, 77.3, 95.4. FABMS *m/z*: 205 (M^++1, 100), 198 (50). HRMS (FAB) *m/z* (M^++1): Calcd. for $C_{11}H_{25}O_3$, 205.1804; found, 205.1801. (2*S*,6*R*)-**21**, $[\alpha]^{20}_D = +8.0$ (*c* 1.4, $CHCl_3$).

*(2S,6S)-2-Azido-6-methoxymethoxynonane (**22**).* To a solution of (2*R*,6*S*)-alcohol **21** (0.81 g, 3.96 mmol) and Et_3N (0.61 ml, 4.38 mmol) in CH_2Cl_2 (5 ml) was added MsCl (0.34 ml, 4.39 mmol). The reaction mixture was stirred at room temperature for 1.5 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was purified with silica gel column chromatography (EtOAc/hexane = 1/4) to give unstable mesylate (1.00 g, 3.54 mmol, 89%) as a colorless oil. A reaction solution of mesylate (1.00 g, 3.54 mmol) and NaN_3 (0.46 g, 7.08 mmol) in DMF (1 ml) was stirred at 100°C for 1 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). The solvent was evaporated. The residue was applied to silica gel column chromatography (5% EtOAc in hexane) to give (2*S*,6*S*)-azide **22** (0.78 g, 3.40 mmol, 96%) as a colorless oil; $[\alpha]^{20}_D = +30$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2936, 2103, 1458, 1381, 1262, 1238, 1144, 1096, 1038 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 6.8 Hz, 9-H_3), 1.25 (3H, d, *J* 6.3 Hz, 1-H_3), 1.26–1.60 (10H, m), 3.38 (3H, s, OCH_3), 3.42 (1H, m, 2-H), 3.52 (1H, m, 6-H), 4.65 (2H, s, O*CH*$_2$OCH$_3$). NMR δ_C ($CDCl_3$): 14.2, 18.5, 19.4, 21.9, 34.1, 36.4, 36.6, 55.5, 58.0, 77.1, 95.5. *Anal*. Found: C, 57.65; H, 10.12; N, 18.21. Calcd. for $C_{11}H_{23}O_2N_3$: C, 57.61; H, 10.11; N, 18.32%. (2*R*,6*R*)-**22**, $[\alpha]^{20}_D = -30$ (*c* 1.7, $CHCl_3$).

*(4S,8S)-8-Azido-4-nonanol (**23**).* To a solution of (2*S*,6*S*)-**22** (0.78 g, 3.40 mmol) in THF (17 ml) was added 6 M aq. HCl solution (17 ml). The reaction solution was stirred at room temperature for 2 h before

additions of H_2O and EtOAc. The organic solution was separated, washed with $NaHCO_3$ and brine, and dried (Na_2SO_4). After the solvent was concentrated, the residue was purified with silica gel column chromatography (5% EtOAc in hexane) to give (4*S*,8*S*)-alcohol **23** (0.60 g, 3.24 mmol, 95%) as a colorless oil; $[\alpha]^{20}_D = +39$ (*c* 0.8, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3125, 2934, 2105, 1458, 1381, 1329, 1262, 1238, 1119, 1021 cm^{-1}. NMR δ_H ($CDCl_3$): 0.93 (3H, t, *J* 7.1 Hz, 1-H_3), 1.26 (3H, d, *J* 6.4 Hz, 9-H_3), 1.30–1.58 (10H, m), 1.60 (1H, s, OH), 3.44 (1H, m, 8-H), 3.61 (1H, m, 4-H). NMR δ_C ($CDCl_3$): 14.1, 18.8, 19.4, 22.3, 36.2, 37.1, 39.7, 58.0, 71.5. *Anal*. Found: C, 58.30; H, 10.40; N, 22.58. Calcd. for $C_9H_{19}ON_3$: C, 58.35; H, 10.34; N, 22.68%. (4*R*,8*R*)-**23**, $[\alpha]^{20}_D = -39$ (*c* 1.7, $CHCl_3$).

*(2S,6R)-1-Benzyloxycarbonyl-2-methyl-6-propylpiperidine (**24**).* To an ice-cooled solution of (4*S*,8*S*)-alcohol **23** (0.60 g, 3.24 mmol) and Et_3N (0.50 ml, 3.59 mmol) in CH_2Cl_2 (2 ml) was added MsCl (0.28 ml, 3.62 mmol). After the reaction mixture was stirred at room temperature for 1.5 h, H_2O and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/7) to give unstable mesylate (0.82 g, 3.11 mmol, 96%) as a colorless oil. A reaction solution of mesylate (0.82 g, 3.11 mmol), Ph_3P (0.90 g, 3.43 mmol), and H_2O (0.4 ml) in THF (40 ml) was stirred at 50°C for 60 h before additions of 1 M aq. HCl solution and ether. To the aqueous solution was added 3 M aq. NaOH solution. The resulting alkaline aqueous solution was extracted with ether, and then the ether solution was treated with 1 M aq. HCl solution. The acidic aqueous solution was concentrated. To an ice-cooled mixture of the residue in THF (5 ml) and 2 M aq. K_2CO_3 solution (4 ml) was added CbzCl (0.57 ml, 3.99 mmol). The reaction mixture was stirred at room temperature for 15 h before additions of 10% aq. $NaHSO_4$ solution and EtOAc. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). After concentration, the residue was purified with silica gel column chromatography (2% EtOAc in hexane) to give (2*S*,6*R*)-**24** (0.38 g, 1.38 mmol, 44% yield from mesylate) as a colorless oil; $[\alpha]^{20}_D = +11$ (*c* 0.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2941, 1678, 1416, 1343, 1314, 1275, 1103, 909 cm^{-1}. NMR δ_H ($CDCl_3$): 0.89 (3H, t, *J* 7.3 Hz, $(CH_2)_2CH_3$), 1.20 (3H, d, *J* 6.8 Hz, CH_3), 1.20–1.38 (3H, m), 1.40–1.75 (7H, m), 4.16 (1H, m, 2-H), 4.39 (1H, m, 6-H), 5.13 (2H, s, $PhCH_2O$), 7.29–7.36 (5H, m, ArH). NMR δ_C ($CDCl_3$): 14.1, 20.6, 27.4, 30.3, 37.3, 46.1, 50.5, 66.8, 127.8, 128.4, 137.2, 155.9. FABMS *m/z*: 276 (M^++1, 100), 232 (50). HRMS (FAB) *m/z* (M^++1): Calcd. for $C_{17}H_{26}O_2N$, 276.1962; found, 276.1964. (2*R*,6*S*)-**24**, $[\alpha]^{20}_D = -11$ (*c* 1.5, $CHCl_3$).

*(2S,6R)-Dihydropinidine hydrochloride (**3**).* A reaction mixture of (2*S*,6*R*)-**24** (0.34 g, 1.23 mmol) and 20% $Pd(OH)_2/C$ (350 mg) in EtOAc (10 ml) was stirred under H_2 gas at the ambient temperature for 1.5 h before filtration. To the filtrate was added 1 M aq. HCl solution and ether. The acidic aqueous solution was separated and concentrated to give (2*S*,6*R*)-**3** (0.17 g, 0.96 mmol, 78%) as colorless crystals, mp 239–240°C (EtOH-EtOAc); $[\alpha]^{20}_D = -13$ (*c* 0.075, EtOH), lit,[13] mp 245°C, $[\alpha]^{20}_D = -12.71$ (*c* 1.14, EtOH). NMR data was agreed with that of literature. (2*R*,6*S*)-**3**, $[\alpha]^{20}_D = +13$ (*c* 1.12, EtOH) [lit,[9] $[\alpha]^{20}_D = +14.2$ (*c* 1.05, EtOH)].

*(R)-4-Benzyl-3-[(S)-6-methoxymethoxynonanoyl]-2-oxazolidinone (**25**).* 97% yield. $[\alpha]^{20}_D = -49$ (*c* 1.5, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2905, 1782, 1701, 1385, 1352, 1233, 1198, 1098, 1038 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.1 Hz, CH_3), 1.31–1.58 (8H, m), 1.68–1.76 (2H, m), 2.77 (1H, dd, *J* 13.2, 9.5 Hz, PhC*H*H), 2.91 (1H, ddd, *J* 16.6, 8.3, 6.4 Hz, O=CCH*H*), 2.99 (1H, ddd, *J* 16.6, 8.3, 6.4 Hz, O=CC*H*H), 3.30 (1H, dd, *J* 13.2, 3.4 Hz, PhCH*H*), 3.38 (3H, s, OCH_3), 3.56 (1H, m, CHOMOM), 4.16 (1H, dd, *J* 9.3, 2.9 Hz, 5-*H*H), 4.20 (1H, dd, *J* 9.3, 9.3 Hz, 5-H*H*), 4.65 (2H, s, OCH_2OCH_3), 4.64–4.70 (1H, m, 4-H), 7.20–7.21 (2H, m, ArH), 7.25–7.29 (1H, m, ArH), 7.32–7.35 (2H, m, ArH). NMR δ_C ($CDCl_3$) 14.2, 18.5, 24.4, 24.8, 34.1, 35.5, 36.6, 37.9, 55.1, 55.5, 66.1, 77.1, 95.4, 127.3, 128.9, 129.4, 135.3, 153.4, 173.2. *Anal*. Found: C, 66.91; H, 8.12; N, 3.66. Calcd. for $C_{21}H_{31}O_5N$: C, 66.82; H, 8.28; N, 3.71%. (*S*)-[(*R*)]-**25**, $[\alpha]^{20}_D = +49$ (*c* 1.2, $CHCl_3$).

*(R)-4-Benzyl-3-[(2R,6S)-2-hydroxy-6-methoxymethoxynonanoyl]-2-oxazolidinone (**26**).* 45% yield. $[\alpha]^{20}_D = -40$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3546, 2947, 1788, 1696, 1387, 1352, 1111, 1038, 909 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.1 Hz, CH_3), 1.30–1.65 (9H, m), 1.81 (1H, m), 2.84 (1H, dd, *J* 13.7, 9.3 Hz, PhC*H*H), 3.31 (1H, dd, *J* 13.7, 3.2 Hz, PhCH*H*), 3.38 (3H, s, OCH_3), 3.48 (1H, d, *J* 7.8 Hz, OH), 3.55 (1H, m, CHOMOM), 4.25 (1H, dd, *J* 9.3, 2.9 Hz, 5-*H*H), 4.28 (1H, dd, *J* 9.3, 9.3 Hz, 5-H*H*), 4.65 (2H, s, OCH_2OCH_3), 4.60–4.69 (1H, m, 4-H), 4.99 (1H, m, C*H*OH), 7.20–7.22 (2H, m, ArH), 7.28–7.29 (1H, m, ArH), 7.31–7.36 (2H, m, ArH). NMR δ_C ($CDCl_3$): 14.2, 18.5, 21.0, 33.8, 34.2, 36.6, 37.5, 55.47, 55.50, 66.9, 70.7, 77.1, 95.4, 127.5, 129.0, 129.4, 134.8, 153.2, 174.9. *Anal*. Found: C, 63.92; H, 8.23; N, 3.40. Calcd. for $C_{21}H_{31}O_6N$: C, 64.10; H, 7.94; N, 3.56%. (*S*)-[(2*S*,6*R*)]-**26**, $[\alpha]^{20}_D = +40$ (*c* 1.6, $CHCl_3$).

*(2R,6S)-6-Methoxymethoxynonane-1,2-diol (**27**).* 84% yield. $[\alpha]^{20}_D = +4.8$ (*c* 1.7, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3450, 2936, 1462, 1238, 1150, 1096, 1038, 911 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.1 Hz, CH_3), 1.30–1.57 (10H, m), 2.62 (1H, br. s, OH), 2.77 (1H, br. s, OH), 3.38 (3H, s, OCH_3), 3.43 (1H, dd, *J* 11.2, 7.8 Hz, 1-*H*H), 3.54 (1H, m, 6-H), 3.63 (1H, dd, *J* 11.2, 2.9 Hz,

1-H*H*), 3.70 (1H, m, 2-H), 4.65 (2H, s, OCH_2OCH_3). NMR δ_C ($CDCl_3$): 14.2, 18.5, 21.2, 33.1, 34.2, 36.6, 55.5, 66.7, 72.0, 77.3, 95.4. FABMS *m/z*: 221 (M^++1, 13), 207 (15), 189 (13), 171 (12), 159 (23), 147 (38). HRMS (FAB) *m/z* (M^++1): Calcd. for $C_{11}H_{25}O_4$, 221.1752; found, 221.1749. (2*S*,6*R*)-**27**, $[\alpha]^{20}_D = -4.7$ (*c* 1.7, $CHCl_3$)

*(2S,6S)-6-Methoxymethoxy-2-nonanol (**28**).* 73% yield (2 steps). $[\alpha]^{20}_D = +5.9$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2949, 1460, 1379, 1240, 1144, 1096, 1038, 912 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 6.8 Hz, 9-CH_3), 1.19 (3H, d, *J* 5.9 Hz, 1-CH_3), 1.28–1.58 (10H, m), 3.38 (3H, s, OCH_3), 3.54 (1H, m, 6-H), 3.80 (1H, m, 2-H), 4.65 (2H, s, OCH_2OCH_3). NMR δ_C ($CDCl_3$): 14.2, 18.5, 21.5, 23.5, 34.2, 36.6, 39.4, 55.5, 67.9, 77.2, 95.4. FABMS *m/z*: 205 (M^++1, 35), 154 (98), 143 (95), 136 (100). HRMS (FAB) *m/z* (M^++1): Calcd. for $C_{11}H_{25}O_3$, 205.1804; found, 205.1807. (2*R*,6*R*)-**28**, $[\alpha]^{20}_D = -5.8$ (*c* 1.6, $CHCl_3$).

*(2R,6S)-2-Azido-6-methoxymethoxynonane (**29**).* 91% yield (2 steps). $[\alpha]^{20}_D = -27$ (*c* 1.4, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2936, 2103, 1466, 1381, 1242, 1144, 1096, 1038, 912 cm^{-1}. NMR δ_H ($CDCl_3$): 0.92 (3H, t, *J* 7.1 Hz, 9-CH_3), 1.25 (3H, d, *J* 6.3 Hz, 1-CH_3), 1.32–1.56 (10H, m), 3.38 (3H, s, OCH_3), 3.44 (1H, m, 2-H), 3.54 (1H, m, 6-H), 4.65 (2H, m, OCH_2OCH_3). NMR δ_C ($CDCl_3$) 14.2, 18.5, 19.4, 21.8, 34.0, 36.3, 36.5, 55.5, 57.9, 77.1, 95.4. *Anal*. Found: C, 57.62; H,9.77; N, 18.40. Calcd. for $C_{11}H_{23}O_2N_3$: C, 57.61; H, 10.11; N, 18.32%. (2*S*,6*R*)-**29**, $[\alpha]^{20}_D = +27$ (*c* 1.6, $CHCl_3$)

*(4S,8R)-8-Azido-4-nonanol (**30**).* 95% yield. $[\alpha]^{20}_D = -30$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2934, 2105, 1458, 1381, 1244 cm^{-1}. NMR δ_H ($CDCl_3$): 0.93 (3H, t, *J* 6.8 Hz, 1-CH_3), 1.26 (3H, d, *J* 6.8 Hz, 9-CH_3), 1.30–1.64 (10H, m), 3.44 (1H, m, 8-H), 3.61 (1H, m, 4-H). NMR δ_C ($CDCl_3$): 14.1, 18.8, 19.4, 22.2, 36.2, 37.1, 39.7, 57.9, 71.4. *Anal*. Found: C, 58.24; H, 10.47; N, 22.69. Calcd. for $C_9H_{19}ON_3$: C, 58.35; H, 10.34; N, 22.68%. (4*R*,8*S*)-**30**, $[\alpha]^{20}_D = +30$ (*c* 1.5, $CHCl_3$).

*(2R,6R)-1-Benzyloxycarbonyl-2-methyl-6-propylpiperidine (**31**).* 44% yield (3 steps). $[\alpha]^{20}_D = -34$ (*c* 1.3, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2959, 1680, 1412, 1320, 1100 cm^{-1}. NMR δ_H ($CDCl_3$): 0.89 (3H, t, *J* 7.3 Hz, $(CH_2)_2CH_3$), 1.27 (3H, d, *J* 6.8 Hz, CH_3), 1.30–1.37 (1H, m), 1.43–1.57 (3H, m), 1.60–1.69 (4H, m), 1.76–1.90 (2H, m), 3.90 (1H, m, 2-H), 3.98 (1H, m, 6-H), 5.10 (1H, d, *J* 12.5 Hz, PhC*H*H), 5.16 (1H, d, *J* 12.5 Hz, PhCH*H*), 7.29–7.36 (5H, m, ArH). NMR δ_C ($CDCl_3$): 13.9, 14.0, 20.1, 20.8, 23.4, 27.0, 36.3, 47.4, 51.9, 66.5, 127.7, 127.8, 128.4, 137.2, 155.8. FABMS *m/z*: 276 (M^++1, 63), 91 (100). HRMS (FAB) *m/z* (M^++1): Calcd. for $C_{17}H_{26}O_2N$, 276.1964; found: 276.1965. (2*S*,6*S*)-**31**, $[\alpha]^{20}_D = +34$ (*c* 1.8, $CHCl_3$).

*(2R,6R)-Epidihydropinidine (**4**).* 98% yield, mp 162–163°C (2-propanol-EtOAc); $[\alpha]^{20}_D = +5.1$ (*c* 0.4, EtOH), lit[7] mp 164.5–165.5°C, $[\alpha]^{20}_D = +4.7$ (EtOH). The NMR data agreed with those of the literature. (2*S*,6*S*)-**4**, $[\alpha]^{20}_D = -5.1$ (*c* 1.14, EtOH).

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