Biosci. Biotechnol. Biochem., **70** (3), 712–717, 2006

Synthesis of a Glandular Secretion of the Civet Cat, (2*S*,6*S*)-(6-Methyltetrahydropyran-2-yl)acetic Acid and Its Enantiomer, by Using the Yeast-Reduction Product and Recovered Substrate from Yeast Reduction

Shunji MORI, Shoko IWAMOTO, and Satoshi YAMAUCHI†

Faculty of Agriculture, Ehime University, 3-5-7 Tarumi, Matsuyama, Ehime 790-8566, Japan

Received October 25, 2005; Accepted November 4, 2005

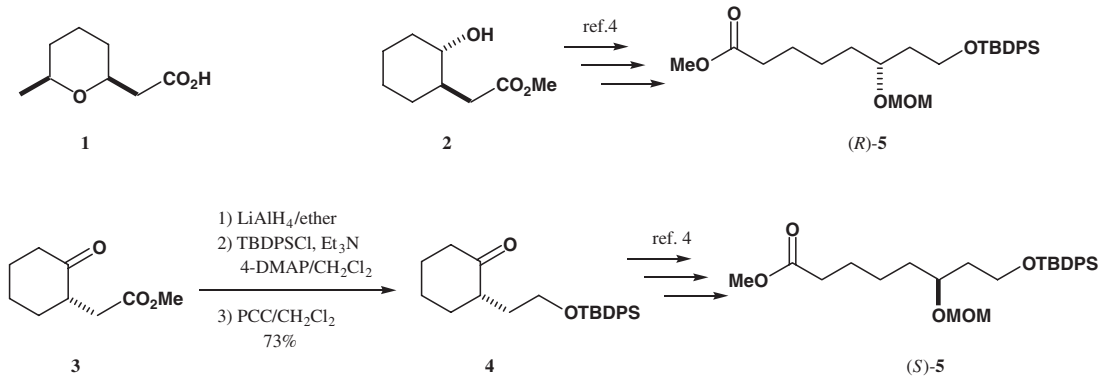
A glandular secretion of the civet cat, (2*S*,6*S*)-(6-methyltetrahydropyran-2-yl)acetic acid 1 and its enantiomer, were synthesized from the yeast-reduction product and recovered substrate from yeast reduction.

Key words: yeast reduction; glandular secretion; civet cat; (2*S*,6*S*)-(6-methyltetrahydropyran-2-yl)acetic acid

(2*S*,6*S*)-(6-Methyltetrahydropyran-2-yl)acetic acid **1** is a glandular secretion of the civet cat.[1] Two syntheses of **1** using an enzyme-catalyzed reaction have been reported. One of them employed porcine pancreatic lipase to give a synthetic intermediate of 58% ee,[2] and the another used *Thermoanaerobium brockii* alcohol dehydrogenase to obtain a synthetic intermediate of 98% ee.[3] In this study, compound (*R*)-**5**, which has been derived from yeast-reduction product **2** in more than 99% ee,[4] was selected as the starting material. This report describes a new synthetic route to (2*S*,6*S*)-**1** by using a biological transformation material to give higher optical purity than that with the previous enzymatic transformation. The synthesis of (2*R*,6*R*)-**1** from (*S*)-**5** is also described. (*S*)-**5** was prepared from recovered substrate **3**[5] from the yeast reduction *via* ketone **4** (Scheme 1).

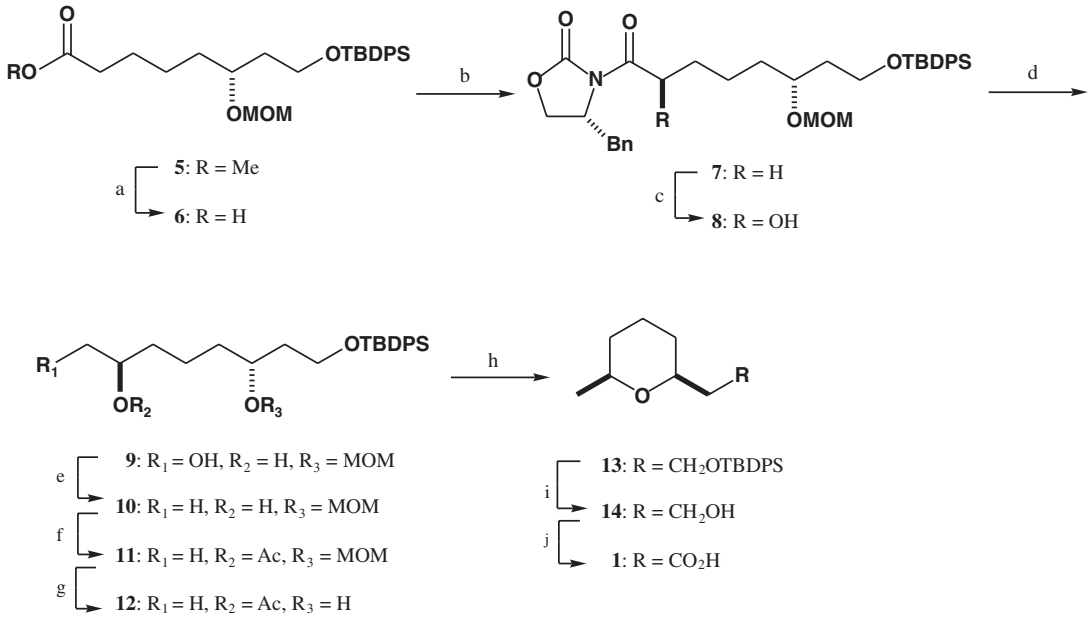
Results and Discussion

The starting materials, (*R*)-**5** and (*S*)-**5**, were respectively prepared from **2** and **3** to more than 99% ee (Scheme 1).[4,5] After hydrolyzing (*R*)-**5** (97% yield), resulting carboxylic acid **6** was treated with pivaloyl chloride, triethylamine, and the lithium salt of (*R*)-4-benzyl-2-oxazolidinone to introduce Evans's chiral auxiliary in 95% yield (Scheme 2). Stereoselective α-hydroxylation[6] to **7** by MoOPH[7] gave α-hydroxy compound **8** as a single stereoisomer in 53% yield. Acyl oxazolidinone **7** was recovered (26%) in this hydroxylation reaction. Removal of the chiral auxiliary by $LiBH_4$ reduction gave glycol **9** in 89% yield. The undesired 2*S* isomer of **9** was not produced. This undesired 2*S* isomer of **9** was prepared from carboxylic acid **6** by employing (*S*)-4-benzyl-2-oxazolidinone. The NMR spectra of **9** were different from those of the 2*S* isomer of **9**. After reducing to **10** *via* the tosylate (76% yield, 2 steps), the hydroxy group was protected as an acetate in the pyridine-acetic anhydride system in 99%



Scheme 1.

† To whom correspondence should be addressed. Fax: +81-89-977-4364; E-mail: syamauch@agr.ehime-u.ac.jp



Scheme 2. Synthesis of **1**.

(a) 6 M aq. KOH–EtOH (1/1), 0 °C, 1 h (97%); (b) Et_3N, PivCl, lithium salt of (*R*)-4-benzyl-2-oxazolidinone, 0 °C, 1 h; (c) KHMDS, MoOPH, THF, −70 °C, 2 h (53%); (d) $LiBH_4$, MeOH, THF, 0 °C, 2 h (89%); (e) (1) *p*-TsCl, pyridine, CH_2Cl_2, 0 °C, 5 h (85%); (2) $LiAlH_4$, THF, r.t., 1 h (89%); (f) Ac_2O–pyridine (1/1), 4-DMAP, r.t., 1 h (99%); (g) TMSBr, CH_2Cl_2, −10 °C, 2 h (88%); (h) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 1 h; (2) K_2CO_3, MeOH, r.t., 16 h; (3) K_2CO_3, DMF, 100 °C, 12 h (57%, 3 steps); (i) $(n\text{-Bu})_4NF$, THF, r.t., 2 h (80%); (j) Jones reagent, acetone, 0 °C, 2 h (84%).

yield. Selective removal of the methoxymethyl group was achieved by treating with trimethylsilyl bromide[8] to give alcohol **12** in 88% yield. Removal of methoxymethyl group under the protic acid condition was accompanied by desilylation. Cyclization to tetrahydropyran derivative **13** was achieved by successive mesylation, methanolysis and treatment with K_2CO_3 in heated DMF in 57% yield through 3 steps. Partial cyclization was observed during this methanolysis. Desilylation by using tetrabutylammonium fluoride gave (2*S*,6*S*)-alcohol **14**. The NMR datum agreed with that of the literature.[2] Desilylation under the acidic condition gave a small amount of unknown by-products. (2*R*,6*R*)-Alcohol **14** was also obtained from **3** by employing same process. To determine the optical purity, (2*S*,6*S*)- and (2*R*,6*R*)-**14** were each treated with (*S*)-Mosher's reagent. An HPLC analysis of the resulting products with a chiral column determined the optical purity of (2*S*,6*S*)- and (2*R*,6*R*)-**14** to be more than 99% ee, respectively. This alcohol **14** was oxidized[2,9–11] to **1** in 67% yield. The NMR datum agreed with that of the literature.[12]

The synthetic process involving biological transformation can be carried out under mild conditions, and the stereoselectivity is sometimes high. However, only two reports have been presented for the synthesis of glandular secretion (2*S*,6*S*)-**1** of the civet cat. In this experiment, compound (2*S*,6*S*)-**1** and its enantiomer were synthesized by using the yeast-reduction product and its recovered substrate from yeast reduction. This new synthetic method employing enzyme-catalyzed product gave higher optical purity than previously reported enzymatic transformation. The use of recovered substrate **3** was also demonstrated.

Experimental

NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer, 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.

*(S)-2-[2-(tert-Butyldiphenylsilyloxy)ethyl]cyclohexanone (**4**).* To an ice-cooled suspension of $LiAlH_4$ (5.35 g, 0.14 mol) in ether (200 ml) was added a solution of (*S*)-ketoester **3**[5] (26.3 g, 0.15 mol) in ether (150 ml). The resulting reaction mixture was stirred at room temperature for 1 h before additions of sat. aq. $MgSO_4$ and K_2CO_3. After stirring at room temperature for 30 min, the mixture was filtered. The filtrate was concentrated to give crude diol. To an ice-cooled solution of the crude diol, Et_3N (25.1 ml, 18.2 g, 0.18 mol), and 4-DMAP (0.73 g, 0.006 mol) in CH_2Cl_2 (50 ml) was added *tert*-$BuPh_2SiCl$ (39.0 ml, 41.2 g, 0.15 mol). After the resulting reaction mixture was stirred at room temperature for 1 h, H_2O and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude silyloxy alcohol. A reaction mixture of the crude silyloxy alcohol and PCC (36.6 g, 0.17 mol), and MS 4A (0.5 g) in CH_2Cl_2 (250 ml) was

stirred at room temperature for 16 h before addition of ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (2% EtOAc/hexane) to give ketone **4** (41.9 g, 0.11 mol, 73%) as a colorless oil. NMR spectra were agreed with that of literature.[4] $[\alpha]^{20}_D = +0.8$ (*c* 2.4, $CHCl_3$), $[\alpha]^{20}_D = -0.9$ (*c* 3.3, $CHCl_3$) in the literature.[4]

*(R)-8-(tert-Butyldiphenylsilyloxy)-6-(methoxymethoxy)-octanoic acid (**6**).* A reaction solution of ester **5** (23.3 g, 49.3 mmol) in EtOH (200 ml) and 6 M aq. KOH solution (200 ml) was stirred at 0 °C for 1 h before addition of $CHCl_3$. After acidification with 6 M aq. HCl solution, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave carboxylic acid **6** (22.0 g, 48.0 mmol, 97%) as a colorless oil. $[\alpha]^{20}_D = -1.6$ (*c* 1.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.39 (2H, m), 1.51 (2H, m), 1.63 (2H, m), 1.73 (2H, m), 2.34 (2H, t, *J* 7.3 Hz, 2-H_2), 3.31 (3H, s, OCH_2OCH_3), 3.73–3.77 (3H, m, 6-H, 8-H_2), 4.58 (1H, d, *J* 6.8 Hz, OC*H*HOMe), 4.61 (1H, d, *J* 6.8 Hz, OCH*H*OMe), 7.36–7.42 (6H, m, ArH), 7.64–7.67 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 24.7, 24.8, 26.9, 33.9, 34.4, 37.3, 55.5, 60.6, 74.7, 95.7, 127.6, 129.6, 133.9, 135.6, 179.0. IR ν_{max} ($CHCl_3$): 2934, 1709, 1111, 1036, 909 cm^{-1}. *Anal*. Found: C, 68.18; H, 87.54. Calcd. for $C_{26}H_{38}O_5Si$: C, 68.09; H, 8.35%. (*S*)-**6**, $[\alpha]^{20}_D = +1.6$ (*c* 1.2, $CHCl_3$).

*(R)-4-Benzyl-3-[(R)-8-(tert-butyldiphenylsilyloxy)-6-(methoxymethoxy)octanoyl]-2-oxazolidinone (**7**).* To a solution of carboxylic acid **6** (10.2 g, 22.2 mmol) in THF (200 ml) was added Et_3N (3.25 ml, 2.36 g, 23.3 mmol) and PivCl (2.87 ml, 2.81 g, 23.3 mmol) at −75 °C, and then the resulting mixture was stirred at 0 °C for 1 h before cooling to −75 °C. To the resulting mixture was added a solution of lithium salt of (*R*)-4-benzyl-2-oxazolidinone (4.13 g, 23.3 mmol) in THF (100 ml) at −75 °C. After the resulting reaction mixture was stirred at 0 °C for 1 h, sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave acyl oxazolidinone **7** (13.0 g, 21.0 mmol, 95%) as a colorless oil. $[\alpha]^{20}_D = -27$ (*c* 1.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.41–1.47 (2H, m), 1.55 (2H, m), 1.65–1.77 (2H, m), 1.74 (2H, m), 2.76 (1H, dd, *J* 13.4, 9.5 Hz, ArC*H*H), 2.86–3.02 (2H, m, $CH_2C{=}O$), 3.30 (1H, dd, *J* 13.4, 2.9 Hz, ArCH*H*), 3.31 (3H, s, OCH_2OCH_3), 3.73–3.81 (3H, m, CHOMOM, CH_2OTBDPS), 4.11–4.21 (2H, m, 5-H_2), 4.59 (1H, d, *J* 6.8 Hz, OC*H*HOMe), 4.62 (1H, d, *J* 6.8 Hz, OCH*H*OMe), 4.67 (1H, m, 4-H), 7.19–7.21 (3H, m, ArH), 7.25–7.43 (8H, m, ArH), 7.65–7.68 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.1, 24.4, 24.8, 26.8, 34.5, 35.5, 37.4, 37.9, 55.1, 55.5, 60.6, 66.1, 74.7, 95.7, 127.3, 127.6, 128.9, 129.4, 129.6, 133.9, 135.3, 135.5, 153.4, 173.1. IR ν_{max} ($CHCl_3$): 2932, 1782, 1701, 1387, 1246, 1111, 1036, 909 cm^{-1}. *Anal*. Found: C, 70.33; H, 8.05; N, 2.20. Calcd. for $C_{36}H_{47}O_6NSi$: C, 69.97; H, 7.67; N, 2.27%. (*S*)-[(*S*)]-**7**, $[\alpha]^{20}_D = +27$ (*c* 2.9, $CHCl_3$).

*(R)-4-Benzyl-3-[(2R,6R)-8-(tert-butyldiphenylsilyloxy)-2-hydroxy-6-(methoxymethoxy)octanoyl]-2-oxazolidinone (**8**).* To a solution of KHMDS (72.6 ml, 0.5 M in toluene, 36.3 mmol) in THF (150 ml) was added a solution of acyl oxazolidinone **7** (15.0 g, 24.2 mmol) in THF (100 ml). After the mixture was stirred at −75 °C for 30 min, MoOPH (15.8 g, 36.4 mmol) was added. The reaction mixture was stirred at −75 °C for 2 h, and then sat. aq. Na_2SO_3 solution and EtOAc were 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). Concentration followed by silica gel column chromatography (EtOAc/toluene = 1/9) gave alcohol **8** (8.11 g, 12.8 mmol, 53%) as a colorless oil. Acyl oxazolidinone **7** (3.74 g, 6.05 mmol, 26%) was recovered. $[\alpha]^{20}_D = -31$ (*c* 1.8, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.49–1.62 (5H, m), 1.72–1.85 (3H, m), 2.84 (1H, dd, *J* 13.4, 9.5 Hz, ArC*H*H), 3.30 (1H, dd, *J* 13.4, 3.4 Hz, ArCH*H*), 3.31 (3H, s, OCH_2OCH_3), 3.46 (1H, d, *J* 7.8 Hz, OH), 3.70–3.80 (3H, m, CHOMOM, CH_2OTBDPS), 4.23–4.27 (2H, m, 5-H_2), 4.58 (1H, d, *J* 6.8 Hz, OC*H*HOMe), 4.61 (1H, d, *J* 6.8 Hz, OCH*H*OMe), 4.65 (1H, m, 4-H), 4.97 (1H, m, C*H*OH), 7.18–7.21 (3H, m, ArH), 7.25–7.41 (8H, m, ArH), 7.64–7.67 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 21.0, 26.9, 34.2, 34.4, 37.4, 37.5, 55.48, 55.50, 60.6, 66.9, 70.7, 74.7, 95.8, 127.50, 127.61, 129.0, 129.4, 129.6, 133.9, 134.8, 135.5, 153.2, 174.9. IR ν_{max} ($CHCl_3$): 3530, 1788, 1694, 1389, 1352, 1298, 1113, 1036, 911 cm^{-1}. *Anal*. Found: C, 68.46; H, 7.95; N, 2.21. Calcd. for $C_{36}H_{47}O_7NSi$: C, 68.22; H, 7.47; N, 2.21%. (*S*)-[(2*S*,6*S*)]-**8**, $[\alpha]^{20}_D = +31$ (*c* 1.2, $CHCl_3$).

*(2R,6R)-8-(tert-Butyldiphenylsilyloxy)-6-(methoxymethoxy)-1,2-octanediol (**9**).* To an ice-cooled solution of acyl oxazolidinone **8** (7.04 g, 11.1 mmol) and MeOH (1.80 ml, 44.4 mmol) in THF (50 ml) was added $LiBH_4$ (1.21 g, 55.6 mmol). The reaction solution was stirred at 0 °C 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). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/1) gave glycol **9** (4.57 g, 9.92 mmol, 89%) as a colorless oil. $[\alpha]^{20}_D = +2.8$ (*c* 1.8, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.42–1.52 (6H, m), 1.73 (2H, m), 2.22 (1H, br. s, OH), 2.41 (1H, br. s, OH), 3.31 (3H, s, OCH_2OCH_3), 3.42 (1H, dd, *J* 10.7, 7.8 Hz, 1-*H*H), 3.66 (1H, dd, *J* 10.7, 11.2 Hz, 1-H*H*), 3.70 (1H, m, 2-H), 3.71–3.79 (3H, m, 6-H, 8-H_2), 4.59 (1H, d, *J* 6.6 Hz, OC*H*HOMe), 4.62 (1H, d, *J* 6.6 Hz, OCH*H*OMe), 7.36–7.44 (6H, m, ArH), 7.64–7.67 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 21.2, 26.8, 33.1, 34.6, 37.4, 55.5, 60.5, 66.8, 72.0, 74.9, 95.8, 127.6, 129.6,

133.83, 133.85, 135.5. IR ν_{max} ($CHCl_3$): 3425, 2934, 1111, 1092, 1036 cm^{-1}. *Anal*. Found: C, 67.69; H, 8.80. Calcd. for $C_{26}H_{40}O_5Si$: C, 67.79; H, 8.75%. (2*S*,6*S*)-**9**: $[\alpha]^{20}_D = -2.7$ (*c* 2.1, $CHCl_3$). (2*S*,6*R*)-**9**: NMR δ_H ($CDCl_3$): 1.05 (9H, s), 1.35–1.60 (5H, m), 1.69–1.77 (3H, m), 2.07 (1H, br. s), 2.22 (1H, br. s), 3.32 (3H, s), 3.43 (1H, m), 3.62–3.73 (3H, m), 3.73–3.78 (2H, m), 4.59 (1H, d, *J* 6.8 Hz), 4.62 (1H, d, *J* 6.8 Hz), 7.35–7.42 (6H, m), 7.63–7.66 (4H, m). NMR δ_C ($CDCl_3$): 19.1, 20.9, 26.7, 33.0, 34.4, 37.2, 55.3, 60.4, 66.6, 71.9, 74.7, 95.7, 127.5, 129.4, 133.69, 133.71, 135.4.

*(2S,6R)-8-(tert-Butyldiphenylsilyloxy)-6-(methoxymethoxy)-2-octanol (**10**).* To an ice-cooled solution of glycol **9** (4.77 g, 10.4 mmol) and pyridine (1.68 ml, 1.65 g, 20.8 mmol) in CH_2Cl_2 (5 ml) was added *p*-TsCl (1.97 g, 10.3 mmol). The reaction solution 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). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave unstable tosylate (5.44 g, 8.85 mmol, 85%) as a colorless oil. To an ice-cooled suspension of $LiAlH_4$ (0.64 g, 16.9 mmol) in THF (20 ml) was added a solution of tosylate (5.44 g, 8.85 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 1 h before additions of sat. aq. $MgSO_4$ solution and K_2CO_3. The mixture was stirred for 30 min, and then filtered. After the filtrate was concentrated, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/5) to give alcohol **10** (3.52 g, 7.92 mmol, 89%) as a colorless oil. $[\alpha]^{20}_D = +3.8$ (*c* 2.4, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.18 (3H, d, *J* 6.2 Hz, 1-H_3), 1.20–1.58 (6H, m), 1.74 (2H, m), 3.32 (3H, s, OCH_2OCH_3), 3.74–3.80 (4H, m, 2-H, 6-H, 8-H_2), 4.59 (1H, d, *J* 6.8 Hz, OC*H*HOMe), 4.62 (1H, d, *J* 6.8 Hz, OCH*H*OMe), 7.36–7.42 (6H, m, ArH), 7.64–7.67 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 21.4, 23.5, 26.8, 34.6, 37.4, 39.3, 55.5, 60.6, 67.9, 74.9, 95.7, 127.6, 129.6, 133.87, 133.89, 135.5. IR ν_{max} ($CHCl_3$): 3505, 2934, 1111, 1094, 1036 cm^{-1}. *Anal*. Found: C, 70.20; H, 9.06. Calcd. for $C_{26}H_{40}O_4Si$: C, 70.23; H, 9.07%. (2*R*,6*S*)-**10**, $[\alpha]^{20}_D = -3.7$ (*c* 1.2, $CHCl_3$).

*(2S,6R)-8-(tert-Butyldiphenylsilyloxy)-6-(methoxymethoxy)oct-2-yl acetate (**11**).* A reaction solution of alcohol **10** (3.45 g, 7.76 mmol) and 4-DMAP (10 mg, 0.082 mmol) in pyridine (3.5 ml) and acetic anhydride (3.5 ml) was stirred at room temperature for 1 h before addition of ice. The mixture was extracted with EtOAc. The extract was washed with 1 M aq. HCl solution and sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave acetate **11** (3.74 g, 7.68 mmol, 99%) as a colorless oil. $[\alpha]^{20}_D = -4.7$ (*c* 1.7, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.20 (3H, d, *J* 5.9 Hz, 1-H_3), 1.36 (2H, m), 1.41–1.60 (2H, m), 1.49 (2H, m), 1.73 (2H, m), 2.02 (3H, s, Ac), 3.31 (3H, s, OCH_2OCH_3), 3.70–3.79 (3H, m, 6-H, 8-H_2), 4.58 (1H, d, *J* 6.8 Hz, C*H*HOMe), 4.61 (1H, d, *J* 6.8 Hz, CH*H*OMe), 4.88 (1H, m, 2-H), 7.35–7.43 (6H, m, ArH), 7.64–7.67 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 19.9, 21.1, 21.4, 26.8, 34.5, 36.0, 37.3, 55.5, 60.6, 70.9, 74.6, 95.7, 127.6, 129.6, 133.9, 135.5, 170.7. IR ν_{max} ($CHCl_3$): 2934, 1727, 1375, 1258, 1111, 1036 cm^{-1}. *Anal*. Found: C, 69.38; H, 8.70. Calcd. for $C_{28}H_{42}O_5Si$: C, 69.10; H, 8.70%. (2*R*,6*S*)-**11**, $[\alpha]^{20}_D = +4.5$ (*c* 1.4, $CHCl_3$).

*(2S,6R)-8-(tert-Butyldiphenylsilyloxy)-6-hydroxyoct-2-yl acetate (**12**).* To a solution of MOM ether **11** (4.23 g, 8.69 mmol) in CH_2Cl_2 (85 ml) was added TMSBr (1.14 ml, 1.32 g, 8.64 mmol) at −10 °C, and then the reaction solution was stirred at −10 °C for 2 h. After addition of sat. aq. $NaHCO_3$ solution, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/5) gave hydroxy acetate **12** (3.38 g, 7.64 mmol, 88%) as a colorless oil. $[\alpha]^{20}_D = +3.8$ (*c* 1.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.05 (9H, s, *tert*-Bu), 1.21 (3H, d, *J* 6.4 Hz, 1-H_3), 1.33–1.55 (4H, m), 1.56–1.76 (4H, m), 2.02 (3H, s, Ac), 3.28 (1H, br. s, OH), 3.82–3.89 (3H, m, 6-H, 8-H_2), 4.90 (1H, m, 2-H), 7.38–7.46 (6H, m, ArH), 7.66–7.68 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.0, 19.9, 21.4, 21.5, 26.8, 35.9, 37.3, 38.4, 63.6, 71.0, 71.7, 127.8, 129.83, 129.84, 132.9, 133.0, 135.5, 170.8, IR ν_{max} ($CHCl_3$): 3524, 2934, 1725, 1375, 1258, 1113, 1082 cm^{-1}. *Anal*. Found: C, 70.63; H, 8.77. Calcd. for $C_{26}H_{38}O_4Si$: C, 70.55; H, 8.65%. (2*S*,6*S*)-**12**, $[\alpha]^{20}_D = -3.7$ (*c* 1.4, $CHCl_3$).

*(2S,6S)-2-(tert-Butyldiphenylsilyloxyethyl)-6-methyltetrahydropyran (**13**).* To an ice-cooled solution of hydroxy acetate **12** (3.38 g, 7.64 mmol) and Et_3N (1.17 ml, 0.85 g, 8.39 mmol) in CH_2Cl_2 (3.5 ml) was added MsCl (0.65 ml, 0.96 g, 8.40 mmol). The reaction mixture was stirred at room temperature for 1 h before additions of sat. aq. $NaHCO_3$ solution and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, a mixture of the residue and K_2CO_3 (1.06 g, 7.67 mmol) in MeOH (10 ml) was stirred at room temperature for 16 h before concentration. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, a mixture of the residue and K_2CO_3 (1.06 g, 7.67 mmol) in DMF (3.5 ml) was stirred at 100 °C for 12 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (2% EtOAc in hexane) gave tetrahydropyran derivative **13** (1.68 g, 4.39 mmol, 57%) as a colorless oil. $[\alpha]^{20}_D = +16$ (*c* 1.4, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.04 (9H, s, *tert*-Bu), 1.15 (3H, d, *J* 5.9 Hz, CH_3), 1.44–1.57 (5H, m), 1.65–1.81 (3H, m), 3.41 (1H, m, 6-H), 3.53

(1H, m, 2-H), 3.72 (1H, m, C*H*HOTBDPS), 3.85 (1H, m, CH*H*OTBDPS), 7.35–7.43 (6H, m, ArH), 7.66–7.73 (4H, m, ArH). NMR δ_C ($CDCl_3$): 19.2, 22.2, 23.8, 26.8, 31.5, 33.4, 39.4, 60.3, 73.7, 74.3, 127.53, 127.55, 129.4, 134.1, 135.5. IR ν_{max} ($CHCl_3$): 3023, 1215, 1111, 1082 cm^{-1}. *Anal*. Found C, 75.48; H, 9.04. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.97%. (2*R*,6*R*)-**13**, $[\alpha]^{20}_D = -16$ (*c* 1.1, $CHCl_3$).

*2-[(2S,6S)-(6-Methyltetrahydropyran-2-yl)]ethanol (**14**).* To an ice-cooled solution of silyl ether **13** (1.30 g, 3.40 mmol) in THF (2 ml) was added (n-Bu)$_4$NF (3.73 ml, 1 M in THF, 3.73 mmol). After the reaction solution was stirred at room temperature for 1 h, sat. aq. NH_4Cl solution and EtOAc were added. The organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was applied to silica gel column chromatography (ether/petroleum ether = 1/1) to give alcohol **14** (0.39 g, 2.70 mmol, 80%) as a colorless oil. $[\alpha]^{20}_D = +24.2$ (*c* 1.8, $CHCl_3$), $[\alpha]^{20}_D = +24.6$ in the literature.[11] The NMR data agreed with those of the literature.[2] (2*R*,6*R*)-**14**, $[\alpha]^{20}_D = -24.1$ (*c* 0.5, $CHCl_3$).

Determination of the optical purity. To an ice-cooled solution of (2*S*,6*S*)-alcohol **14** (24 mg, 0.17 mmol) and 4-DMAP (1 mg) in pyridine (0.5 ml) was added (*S*)-Mosher's acid chloride (37 µl, 51 mg, 0.20 mmol). The resulting reaction mixture was stirred at room temperature for 16 h before additions of CH_2Cl_2 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). After concentration, the residue was applied to a short silica gel column (EtOAc/hexane = 1/5) to give the (*S*)-Mosher ester of (2*S*,6*S*)-alcohol **14** in quantitative yield. NMR δ_H ($CDCl_3$): 1.10–1.20 (2H, m), 1.14 (3H, d, *J* 6.4 Hz), 1.42–1.57 (3H, m), 1.75–1.88 (3H, m), 3.26–3.38 (2H, m), 3.55 (3H, s), 4.39 (1H, m), 4.48 (1H, m), 7.40–7.42 (3H, m), 7.51–7.53 (2H, m). NMR δ_C ($CDCl_3$): 22.0, 23.5, 31.2, 33.1, 35.0, 55.3, 63.4, 73.80, 73.83, 127.2, 127.3, 128.3, 128.4, 129.5, 129.6, 166.5. The HPLC analysis with an OD-H chiral column (0.2% 2-propanol/hexane, 1 ml/min, detected at 260 nm) gave a retention time of 7.8 min. (*S*)-Mosher ester of (2*R*,6*R*)-alcohol **14**: NMR δ_H ($CDCl_3$): 1.10–1.22 (2H, m), 1.15 (3H, d, *J* 6.4 Hz), 1.38–1.60 (3H, m), 1.75–1.86 (3H, m), 3.29–3.39 (2H, m), 3.56 (3H, s), 4.39–4.49 (2H, m), 7.39–7.41 (3H, m), 7.50–7.55 (2H, m); NMR δ_C ($CDCl_3$): 22.0, 23.5, 31.2, 33.1, 34.9, 55.3, 63.3, 73.7, 73.8, 127.2, 128.3, 129.5, 132.4, 166.5. An HPLC analysis with an OD-H chiral column (0.2% 2-propanol/hexane, 1 ml/min, detected at 260 nm) gave a retention time of 7.4 min.

*(2S,6S)-(6-Methyltetrahydropyran-2-yl)acetic acid (**1**).* To an ice-cooled solution of alcohol **14** (0.27 g, 1.87 mmol) in acetone (2 ml) was added Jones reagent until the color turned to orange. After the reaction mixture was stirred in ice-bath for 2 h, H_2O and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (50% ether in petroleum ether) gave carboxylic acid **1** (0.25 g, 1.58 mmol, 84%) as a colorless oil. $[\alpha]^{20}_D = +20.2$ (*c* 1.8, $CHCl_3$). $[\alpha]^{31}_D = +20.5$ (*c* 1.23, $CHCl_3$) in the lit.[12] The NMR data agreed with those in the literature.[12] (2*R*,6*R*)-**1**, $[\alpha]^{20}_D = -20.0$ (*c* 1.5, $CHCl_3$).

Acknowledgment

We measured the 400 MHz NMR data at INCS, Ehime University. We are grateful to Marutomo Co. for financial support.

References

1) Maurer, B., Grieder, A., and Thommen, W., (*cis*-6-Methyltetrahydropyran-2-yl)acetic acid, a novel compound from civet (*Viverra civetta*). *Helv. Chim. Acta*, **62**, 44–47 (1979).
2) Jones, J. B., and Hinks, R. S., Enzymes in organic synthesis 36. Synthesis of optically active civet constituent from an enzyme-generated chiral synthon. *Can. J. Chem.*, **65**, 704–707 (1987).
3) Keinan, E., Seth, K. K., and Lamed, R., Organic synthesis with enzymes 3. TBDADH-catalyzed reduction of chloro ketones. Total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid: a civet constituent. *J. Am.Chem. Soc.*, **108**, 3474–3480 (1986).
4) Yamauchi, S., Mori, S., Hirai, Y., and Kinoshita, Y., Syntheses of (+)- and (−)-dihydropinidine and (+)- and (−)-epidihydropinidine by using yeast reduction of methyl (2-oxocyclohexyl)acetate. *Biosci. Biotechnol. Biochem.*, **68**, 676–684 (2004).
5) Ganaha, M., Funabiki, Y., Motoki, M., Yamauchi, S., and Kinoshita, Y., Reduction of alkyl (2-oxocyclohexyl)acetates by baker's yeast. *Biosci. Biotechnol. Biochem.*, **62**, 181–184 (1998).
6) Evans, D. A., Morrisey, M. M., and Dorow, R. L., Asymmetric oxygenation of chiral imide enolates. A general approach to the synthesis of enantiomerically pure α-hydroxy carboxylic acid synthons. *J. Am. Chem. Soc.*, **107**, 4346–4348 (1985).
7) Vedejs, E., and Larsen, S., Hydroxylation of enolates with oxodiperoxymolybdenum(pyridine) (hexamethylphosphoric triamide), MoO_5·Py·HMPA (MoOPH): 3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one. *Org. Synth. Coll. Vol. VII*, 277–282 (1990).
8) Hanessian, S., Delorme, D., and Dufresne, Y., Mild cleavage of methoxymethyl (MOM) ethers with trimethylsilyl bromide. *Tetrahedron Lett.*, **25**, 2515–2518 (1984).
9) Mandai, T., Ueda, M., Kashiwagi, K., Kawada, M., and Tsuji, J., A highly steroselective synthetic method for *cis*-2-hydroxy-6-alkyltetrahydrofurans. *Tetrahedron Lett.*, **34**, 111–114 (1993).
10) Ishihara, K., Mori, A., and Yamamoto, H., Stereoselective reduction of acetals. A method for reductive generation of heterocyclic ring systems. *Tetrahedron*,

46, 4595–4612 (1990).
11) Masaki, Y., Serizawa, Y., Nagata, K., and Kaji, K., Enantiospecific synthesis of natural (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid, a constituent of civet. *Chem. Lett.*, 1601–1602 (1983).
12) Dixon, D. J., Ley, S. V., and Tate, E. W., Diastereoselective oxygen to carbon rearrangements of anomerically linked enol ethers and the total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid, a component of civet. *J. Chem. Soc., Perkin Trans. 1*, 2385–2394 (2000).