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SYNTHESIS OF MONOCERIN, AN ANTIFUNGAL, INSECTICIDAL AND PHYTOTOXIC HEPTAKETIDE METABOLITE OF EXSEROHILUM MONOCERAS†

KENJI MORI* and HIDEO TAKAISHI††

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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Abstract — Both the naturally occurring enantiomer and the racemate of monocerin [**1a**, (2S,3aR,9bR)-2,3,3a,9b-tetrahydro-6-hydroxy-7,8-dimethoxy-2-propyl-5H-furo[3,2-c][2]benzopyran-5-one] were synthesized for the first time.

Introduction and Retrosynthetic Analysis. Monocerin (**1a**) was first isolated by Aldridge and Turner as an antifungal metabolite from culture filtrates of Exerohilum monoceras Drechsler (= Drechslera monocerus = Helminthosporium monoceras), which protect wheat against powdery mildew (Erisyphe graminis).[1] Subsequently, Grove and Pople indentified **1a** as an insecticidal constituent of the entomogenous fungus Fusarium larvarum Fukel.[2]

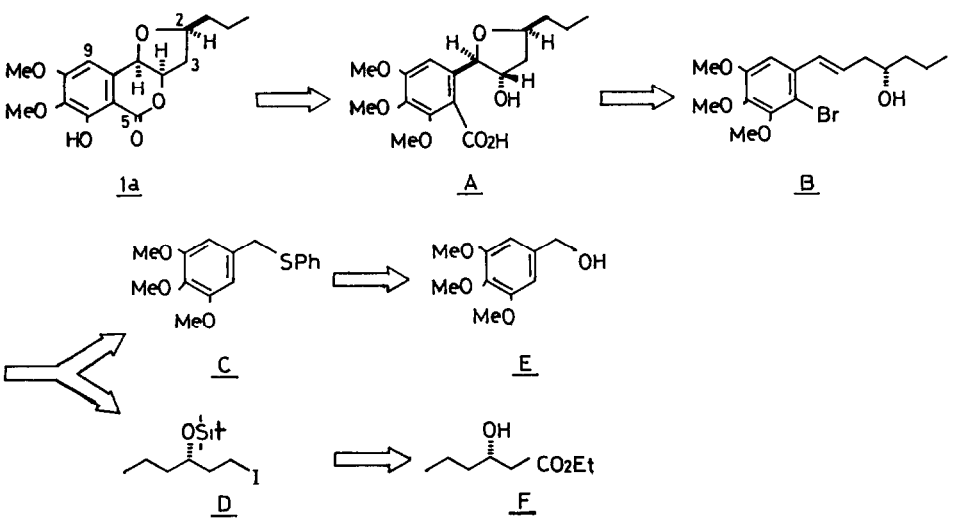

Fig. 1. Retrosynthetic analysis of monocerin

† Synthetic Microbial Chemistry —XXII. Part XXI, K. Mori and A. Kamada, Liebigs Ann. Chem., in the press.
†† Research Fellow on leave from Nihon Noyaku Co., Ltd. (1987-1989).

Phytotoxic property of **1a** was later reported by Robeson and Strobel, who identified **1a** as a phytotoxin produced by Exserohilum turcicum Pass.[3] The stereochemistry of monocerin as depicted in **1a** was proposed on the basis of chiroptical and ^{1}H NMR studies.[2,4] Biosynthetic studies of **1a** revealed it to be of heptaketide origin.[4] Herein we describe the first synthesis of both the racemate and the naturally occurring enantiomer of monocerin.

Our retrosynthetic analysis of monocerin (**1a**) is shown in Fig.1. The lactone ring of **1a** is to be constructed by cyclizing **A** under the Mitsunobu condition[5] with an inversion at C-4. The hydroxy acid **A** can be derived from **B** by oxidatively cyclizing the side-chain and also introducing a carboxyl group to the aromatic ring. Two building blocks **C** and **D** are to be assembled to give **B**. The aromatic building block **C** is readily available from 3,4,5-trimethoxybenzyl alcohol **E**, while ethyl 3-hydroxyhexanoate **F** can be employed for the preparation of **D**. The natural enantiomer of monocerin (**1a**) can accordingly be prepared by starting from (S)-**F**.

Synthesis of (±)-Monocerin. The retrosynthetic analysis as described above was put into practice first for the synthesis of (±)-monocerin as shown in Fig.2. 3,4,5-Trimethoxybenzyl alcohol (**2**) was converted to the corresponding chloride **3** by treatment with thionyl chloride in ether. Reaction of **3** with sodium thiophenoxide in DMF furnished **4** (=**C**) in 83 % yield from **2**. Another building block (±)-**8** (=**D**) was prepared from ethyl 3-oxohexanoate (**5**). Reduction of **5** with sodium borohydride gave a hydroxy ester (±)-**6a**, which was converted to the corresponding t-butyldimethylsilyl ether (±)-**6b**. Treatment of (±)-**6b** with lithium borohydride in the presence of a small amount of lithium triethylborohydride gave alcohol (±)-**7a**. The corresponding tosylate (±)-**7b** was treated with sodium iodide to give the desired building block (±)-**8** in 59% overall yield from **5**.

Alkylation of the sulfur-stabilized carbanion derived from **4** with (±)-**8** furnished **9** in 92% yield. At this stage, we thought it appropriate to substitute one of the two aromatic hydrogens of the tetrasubstituted benzene ring with a bromine atom to facilitate the later introduction of a carboxyl group to the aromatic ring. Reaction of bromine with **9** or the sulfoxide derived from **9** was examined under various different conditions. The condition finally adopted was to treat **9** with 4.7 eq of bromine in the presence of a large excess (60-70 eq) of sodium acetate in acetic acid to give **10a**. Substitution of the phenylthio group with an acetoxyl group under that condition was not unexpected, because Kwart and Miller had recorded a similar reaction (**a** + **b** + **c**).[6] In our case, the intermediary bromide (**9**, Br instead of SPh) could not be isolated, because an excess of sodium acetate was present in the reaction mixture. Without purification **10a** was saponified with methanolic sodium hydroxide to give **10b** in 85% yield from **9**. The corresponding mesylate **10c** was treated with DBU to give an olefin (±)-**11a** in 80% yield, whose E-geometry was supported by its ^{1}H NMR analysis.

There were two possible routes to continue the synthesis: whether to introduce the carboxyl group prior to the closure of the tetrahydrofuran ring or vice versa. As the earlier introduction of the carboxyl group turned out to be disastrous at the stage of the tetrahydrofuran ring-formation, we decided to execute the cyclization first. After removing the t-butyldimethylsilyl protective group of (±)-**11a**, the resulting (±)-**11b** (=**B**) was successively treated with m-chloroperbenzoic acid and boron trifluoride etherate to give a diastereomeric mixture of (±)-**12** in 80% yield. Metallation of (±)-**12** was achieved by treating its THF solution with 2.3 eq of n-butyllithium. The resulting dianion reacted with carbon dioxide gas to give a diastereomeric mixture of the desired product (±)-**13** together with 17% of (±)-**14**. The by-product (±)-**14** could be recycled to give back (±)-**12** in three steps in 82% overall yield by successive acetylation, bromination and hydrolysis.

The ring-closure of a diastereomeric mixture of (±)-**13** under the Mitsunobu condition[5]

yielded a separable mixture of an oily and a crystalline δ-lactones. The more polar and crystalline lactone obtained in 31% overall yield from (±)-12 was shown to be (±)-monocerin methyl ether (1b) by comparing its ^{1}H NMR spectrum with the published data of the methyl ether derived from the natural product.[1] The yield of the oily C-2 epimer (±)-15b was 38% from (±)-12. Finally, partial demethylation of (±)-1b with boron tribromide gave (±)-monocerin (1a), m.p. 78.5-80.0°C, in 84% yield. Its ^{1}H NMR spectrum was

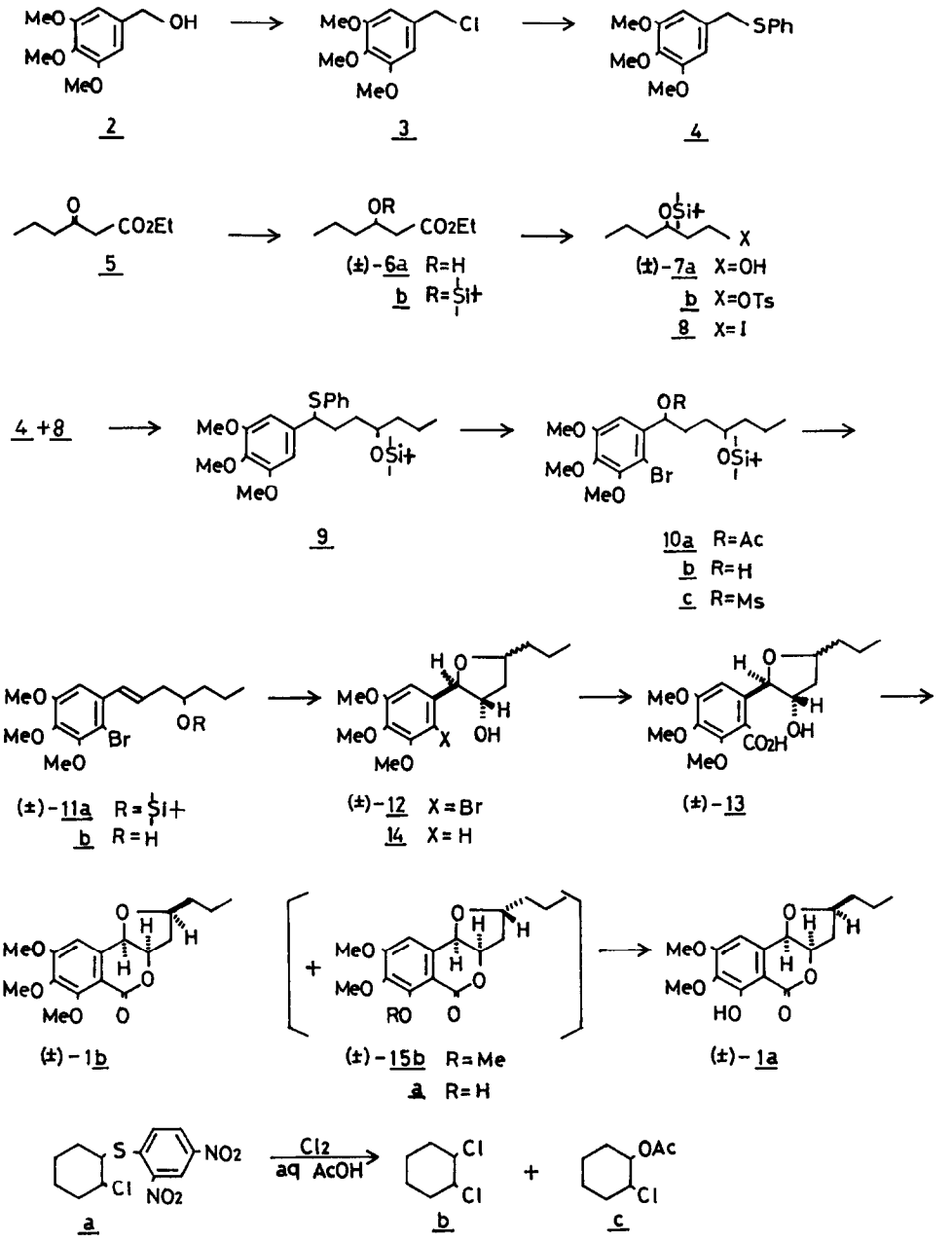

Fig. 2. Synthesis of (±)-monocerin

identical with that of the natural product. Similarly, partial demethylation of (±)-15b yielded (±)-2-epimonocerin (15a). The overall yield of (±)-1a from 2 was 9.4% in 12 steps, and that from 5 was 7.4% in 15 steps.

Synthesis of (+)-Monocerin. For the synthesis of the natural (2S,3aR,9bR)-(+)-enantiomer of monocerin (1a), the (S)-enantiomer of ethyl 3-hydroxyhexanoate (6a) was necessary. Fig.3 shows our synthetic route leading to (+)-1a starting from (S)-6a.

Our first attempt to prepare (S)-6a was the reduction of octyl 3-oxohexanoate with baker's yeast.[cf.7] However, octyl 3-hydroxyhexanoate obtained in 36% yield by the yeast reduction of the β-keto ester was shown to be of only 54% e.e. The attempt was therefore abandoned.

Our second and successful attempt was the conversion of (S)-norvaline (16) into (S)-6a. The α-amino acid (S)-16 furnished epoxide (S)-20 in 36% overall yield via hydroxy acid (S)-17, diol (S)-18 and acetoxy bromides 19 and 19' in the same manner as reported previously for other amino acids.[8] Treatment of (S)-20 with sodium cyanide in 40% aqueous ethanol yielded β-hydroxy acid (S)-21a.[8,9] Although (S)-18 of 94% e.e. was employed in this transformation, the resulting (S)-21a was of only 76% e.e., indicating the occurrence of the partial racemization in this step. The acid (S)-21a was therefore purified by recrystallizing its dibenzylamine salt (S)-21b according to Tai and his co-workers.[10] The acid (S)-21a was liberated by acidifying (S)-21b, and esterified with ethanol to give (S)-6a in 45% overall yield from (S)-20. The enantiomeric purity of (S)-6a was estimated as 98% e.e. by the HPLC analysis of its (R)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester).[11]

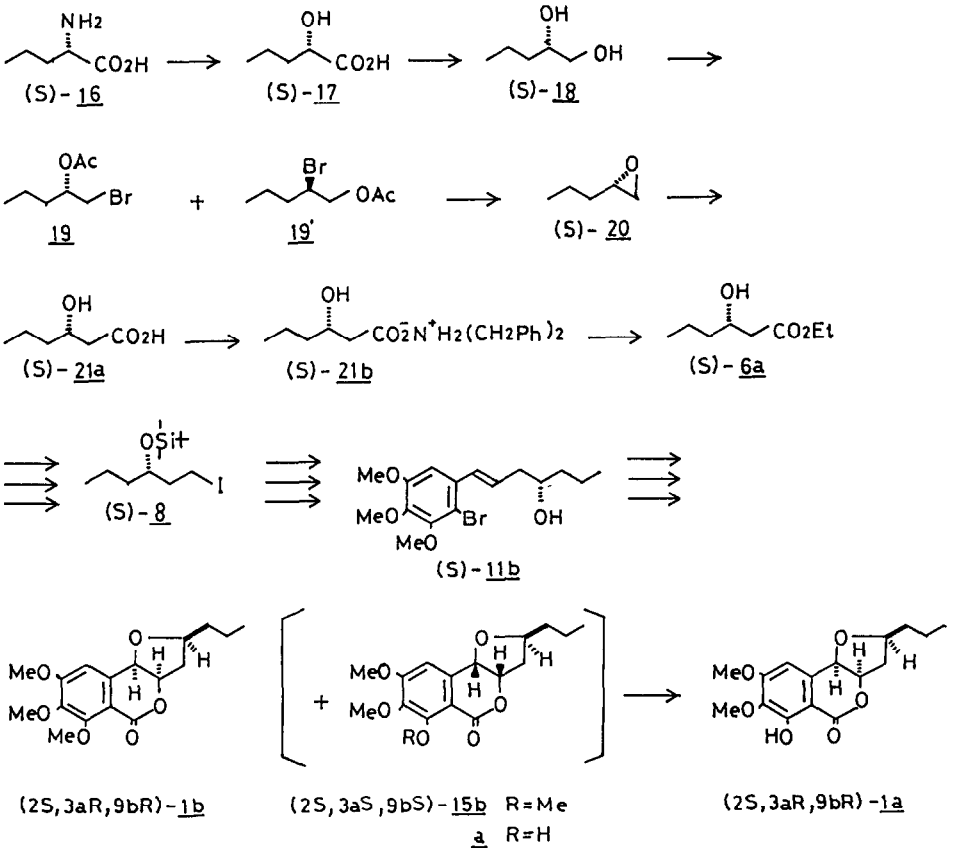

Fig. 3. Synthesis of (+)-monocerin

With (S)-6a in hands, the remaining synthetic steps to (+)-monocerin (1a) were executed without accident via (S)-8 and (S)-11b as shown in Fig.3. Both optically active 15b and 1b were obtained as oils. Finally, partial demethylation of (2S,3aR,9bR)-1b yielded (2S,3aR,9bR)-(+)-1a. The synthetic monocerin (1a) was identical in every respect (m.p., $[\alpha]_D$, IR and ^1H NMR) with an authentic sample provided for us by Dr. D. C. Aldridge. The overall yield of (+)-1a was 6.6% in 14 steps from (S)-6a or 7.9% in 12 steps from 2.

In conclusion the synthesis of (±)- and (+)-monocerin was achieved for the first time.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on Jasco A-102 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JNM FX-100 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Merck Kieselgel 60 Art. 7734 were used for SiO_2 column chromatography.

Phenyl 3,4,5-trimethoxybenzyl sulfide 4. A soln of 3,4,5-trimethoxybenzyl alcohol (25 g, 126 mmol) and thionyl chloride (23 g, 193 mmol) in dry ether (300 ml) was stirred for 3 h under reflux, and concentrated in vacuo. The residue 3 was added to a soln of the sodium salt of benzenethiol [prepared from benzenethiol (17 g, 154 mmol) and sodium hydride (ca. 60 %, 5.1 g, 128 mmol)] in dry DMF (100 ml) at room temp. The mixture was stirred for 2 h at room temp, poured into water (300 ml) and extracted with ether. The extract was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from n-hexane-ethyl acetate (4:1) to give 30.3 g (83%) of 4 as plates, m.p. 76.5-77.0°C; vmax ($CHCl_3$ soln) 1585 (s), 1495 (s), 1450 (s), 1235 (s), 1120 (s) cm^{-1}; δ (60MHz, $CDCl_3$) 3.71 (6H, s), 3.75 (3H, s), 3.96 (2H, s), 6.40 (2H, s), 7.20 (5H, m). (Found: C, 65.94; H, 6.25. Calc for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25%).

Ethyl (±)-3-hydroxyhexanoate 6a. To a stirred and cooled soln of 5 (26 g, 164 mmol) in 95% ethanol (300 ml) was added dropwise a suspension of sodium borohydride (3.0 g, 793 mmol) in 95% ethanol (100 ml) over 30 min at 0-10°C. To this was added sat NH_4Cl soln (100 ml) and the mixture was neutralized with 2N HCl. The mixture was concentrated in vacuo and extracted with ether (150 ml x 2). The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 22.2 g (85%) of 6a, b.p. 73.0-75.0°C/6 Torr (lit.[12] b.p. 83-85°C/10 Torr); n_D^{17} 1.4230; vmax 3460 (br.s), 1730 (s), 1180 (s) cm^{-1}; δ (60MHz, CCl_4) 0.70-1.10 (3H, m), 1.23 (3H, t, J=7 Hz), 1.20-1.60 (4H, m), 2.36 (2H, d, J=6 Hz), 3.16 (1H, d, J=4 Hz), 3.65-4.10 (1H, m), 4.05 (2H, q, J=7 Hz).

Ethyl (±)-3-t-butyldimethylsilyloxyhexanoate 6b. To a mixture of t-butyldimethylchlorosilane (14.0 g, 92.9 mmol) and imidazole (9.2 g, 135 mmol) was added a soln of 6a (9.8 g, 61.3 mmol) in dry DMF (80 ml). The mixture was stirred for 15 h at room temp. The mixture was poured into ice-water (200 ml), and extracted with ether (100 ml x 2). The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 14.6 g (87%) of 6b, b.p. 83.0-87.0°C/3 Torr; n_D^{18} 1.4283; vmax 1745 (s), 1260 (s), 1185 (s) cm^{-1}; δ (60MHz, CCl_4) 0.03 (6H, s), 0.84 (9H, s), 0.70-1.00 (3H, m), 1.20 (3H, t, J=7 Hz), 1.15-1.50 (4H, m), 2.27 (2H, d, J=6 Hz), 4.02 (2H, q, J=7 Hz), 3.90-4.20 (1H, m). (Found: C, 61.18; H, 10.92. Calc for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02%).

(±)-3-t-Butyldimethylsilyloxy-1-hexanol 7a. To a suspension of lithium borohydride (1.1 g, 50.5 mmol) in dry ether (120 ml) was added a soln of (±)-6b (12.0 g, 43.8 mmol) in dry ether (20 ml) at room temp under Ar. Then to the mixture was added lithium triethylborohydride (1M in THF; 4.1 ml, 4.1 mmol) and the mixture was stirred for 3 h under reflux. After cooling, sat NH_4Cl soln (20 ml) was added to the mixture and the stirring was continued for 30 min at room temp. Then the mixture was poured into sat NH_4Cl soln (100 ml) and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 9.3 g (92%) of 7a, b.p. 82.5-83.5°C/2 Torr; n_D^{21} 1.4354; vmax 3350 (br.s), 1260 (s), 1070 (s), 1040 (s) cm^{-1}; δ (60MHz, CCl_4) 0.05 (6H, s), 0.88 (9H, s), 0.70-1.10 (3H, m), 1.10-1.80 (7H, m), 3.55 (2H, t, J=6 Hz), 3.50-3.95 (1H, m). (Found: C, 61.80; H, 11.69. Calc for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14%).

(±)-3-t-Butyldimethylsilyloxy-1-iodohexane 8. To a soln of (±)-7a (9.0 g, 38.7 mmol) in dry pyridine (12 ml) was added a soln of p-toluenesulfonyl chloride (8.85 g, 46.4 mmol) in dry pyridine (20 ml) at 0-5°C. After stirring for 3 h at 0-5°C, the mixture was poured into sat NH_4Cl soln (200 ml), and extracted with ether. The extract was washed with sat $CuSO_4$ soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo to give crude (±)-7b, vmax 1360 (s), 1175 (s) cm^{-1}. The residue was dissolved in acetone (300 ml). To this soln was added NaI (54 g, 360 mmol) and $NaHCO_3$ (30.3 g, 361 mmol). The mixture was stirred for 2 h under reflux. It was then concentrated in vacuo, poured into water (300 ml) and extracted with ether. The extract was washed with 10% $Na_2S_2O_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with n-hexane gave 11.3 g (85%) of 8 as a colorless oil, n_D^{25} 1.4700; vmax 1220 (m) 1070 (s) cm^{-1}; δ (60MHz, CCl_4) 0.07 (6H, s), 0.86 (9H, s), 0.73-1.10 (3H, m), 1.10-1.53 (4H, m), 1.73-2.12 (2H, m),

3.12 (2H, t, J=7 Hz) 3.46~3.85 (1H, m). (Found: C, 42.11; H, 7.90. Calc for $C_{12}H_{27}IO_2Si$: C, 42.10; H, 7.95%).

A diastereomeric mixture of 1-(4-t-butyldimethylsilyloxy-1-phenylthioheptyl)-3,4,5-trimethoxybenzene 9. To a soln of 4 (9.6 g, 33.0 mmol) in dry THF (300 ml) was added n-BuLi (1.59 M in n-hexane; 30 ml, 47.7 mmol) over 1 h at -20~-10°C under Ar. After stirring for 1 h at -20°C, to this mixture was added a soln of (±)-6 (11.0 g, 32.1 mmol) in dry THF (50 ml) over 1 h at -20~-10°C. The mixture was stirred for 2 h at -20°C, poured into ice-water (500 ml) and extracted with ether. The extract was washed with brine and concentrated in vacuo. The residue was chromatographed over SiO_2 (200 g). Elution with n-hexane-ethyl acetate (10:1) gave 15.3 g (92%) of 9 as a colorless oil, n_D^{25} 1.5198; νmax 1590 (s), 1510 (s), 1460 (s), 1240 (s), 1130 (s), 835 (s), 775 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.05 (6H, s), 0.87, 0.88 (total 9H, each s), 0.65~1.00 (3H, m), 1.10~1.55 (6H, m), 1.78~2.07 (2H, m), 3.50~3.80 (1H, m) 3.80 (6H, s), 3.84 (3H, s), 3.99 (1H, t, J=7 Hz), 6.37, 6.38 (total 2H, each s), 7.23 (5H, m). (Found: C, 66.63; H, 8.79. Calc for $C_{28}H_{44}O_4SSi$: C, 66.63; H, 8.72%).

A diastereomeric mixture of 1-(2-bromo-3,4,5-trimethoxyphenyl)-4-t-butyldimethylsilyloxy-1-heptanol 10b. To a vigorously stirred suspension of 9 (10.0 g, 19.8 mmol) and anhydrous sodium acetate (70 g, 833 mmol) in acetic acid (300 ml) was added a soln of bromine (15.5 g, 97 mmol) in acetic acid (15 ml) over 10 min at room temp. The mixture was vigorously stirred for 2 h, poured into ice-cooled 2N KOH (500 ml) and neutralized with 2N KOH. Then the mixture was extracted with ether. The extract was washed with 10% $Na_2S_2O_3$ soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo. To this residue was added a soln of NaOH (5 g, 125 mmol) in methanol (150 ml) at room temp. After stirring for 1 h, the mixture was concentrated in vacuo. The residue was poured into water (300 ml) and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with n-hexane-ethyl acetate (10:1~5:1) gave 8.3 g (85%) of 10b as a colorless oil, n_D^{25} 1.4952; νmax 3450 (br.s), 1570 (m), 1485 (s), 1240 (s), 1110 (s), 835 (s), 775 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.05, 0.10 (total 6H, each s), 0.90, 0.93 (total 9H, each s), 0.78~1.00 (3H, m), 1.25~1.85 (9H, m), 3.65~3.90 (1H, m), 3.90, 3.91 (total 9H, each s), 4.91~5.12 (1H, m), 6.97, 7.02 (total 1H, each s). (Found: C, 53.40; H, 7.86. Calc for $C_{22}H_{39}BrO_5Si$: C, 53.75; H, 8.00%).

(±)-2-Bromo-1-[(E)-4-t-butyldimethylsilyloxy-1-heptenyl]-3,4,5-trimethoxybenzene (±)-11a. To a stirred soln of 10b (3.85 g, 7.83 mmol) and triethylamine (1.0 g, 9.9 mmol) in dry THF (50 ml) was added dropwise methanesulfonyl chloride (1.0 g, 8.73 mmol) over 20 min at 0°C. After stirring for 2 h at 0°C, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in benzene (100 ml). To this soln was added DBU (1.8 g, 11.8 mmol), and the mixture was stirred for 2 h under reflux. The mixture was concentrated in vacuo, and the residue was passed through SiO_2 (50 g) to give 2.96 g (80%) of crude (±)-11a as an oil, n_D^{25} 1.5166; νmax 1660 (s), 1480 (s), 1250 (s), 1110 (s), 965 (m) cm^{-1}; δ (100MHz, $CDCl_3$) 0.08 (6H, s), 0.92 (9H, s), 0.80~1.00 (3H, m), 1.30~1.52 (4H, m), 2.39 (2H, t, J=7 Hz), 3.70~3.90 (1H, m), 3.89 (3H, s), 3.90 (6H, s), 6.13 (1H, dt, J=16, 7 Hz), 6.72 (1H, d, J=16 Hz), 6.85 (1H, s); HPLC analysis (Column, Senshu Pack®-Silica-1251-N 4.6 x 250 mm; Solvent, n-hexane-ethyl acetate (100:3); 1.5 ml/min; Detection at 254 nm) Rt 11.3 min (97.4%). This was employed in the next step without further purification.

(±)-(E)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-1-hepten-4-ol (±)-11b. To a soln of (±)-11a (17.5 g, 37.0 mmol) in THF (300 ml) was added tetra-n-butylammonium fluoride (1 M in THF; 50.0 ml, 50.0 mmol) at room temp. The mixture was stirred for 20 h at room temp. It was then concentrated in vacuo. The residue was diluted with water and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (300 g). Elution with n-hexane-ethyl acetate (4:1) gave 11.6 g (87%) of (±)-11b as a colorless oil, n_D^{20} 1.5420; νmax 3450 (br.s), 1555 (s), 1475 (s), 1240 (s), 1105 (s), 1005 (s), 965 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.85~1.05 (3H, m), 1.40~1.60 (4H, m), 1.71 (1H, d, J=5 Hz), 2.30~2.53 (2H, m), 3.64~3.90 (1H, m), 3.91 (9H, s), 6.13 (1H, dt, J=16, 7 Hz), 6.78 (1H, d, J=16 Hz), 6.85 (1H, s); HPLC analysis (Column, Senshu Pack®-Silica-1251-N 4.6 x 250 mm; Solvent, n-hexane-ethyl acetate (4:1); 1.5 ml/min; Detection at 254 nm) Rt 41.0 min (single peak). (Found: C, 53.45; H, 6.20. Calc for $C_{16}H_{23}BrO_4$: C, 53.49, H, 6.45%).

A diastereomeric mixture of 2-(2-bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol (±)-12. To a stirred soln of (±)-11b (6.82 g, 19.0 mmol) in dry dichloromethane (100 ml) was added m-CPBA (80%, 5.0 g, 23.2 mmol) at 0 °C. The mixture was stirred overnight at room temp. Then BF_3 Et_2O (0.2 ml) was added to the mixture. The mixture was stirred for 30 min at room temp. It was then diluted with ether, washed with sat $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with n-hexane-ethyl acetate (4:1) gave 5.73 g (80%) of (±)-12 as a colorless oil, n_D^{20} 1.5368; νmax 3450 (br.s), 1565 (m), 1475 (s), 1460 (s), 1105 (s), 1010 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.88~1.10 (3H, m), 1.28~2.00 (5H, m), 1.88 (1H, br.s), 2.10~2.43 (1H, m), 3.88 (6H, s), 3.90 (3H, s), 4.25~4.47 (2H, m), 5.06,5.16 (total 1H, br.s, d, J=3 Hz), 6.82, 6.95 (total 1H, each s). (Found: C, 50.83; H, 6.02. Calc for $C_{16}H_{23}BrO_5$: C, 51.21; H, 6.18%).

(2S*,3aR*,9bR*)-2,3,3a,9b-Tetrahydro-6,7,8-trimethoxy-2-propyl-5H-furo[3,2-c][2]benzopyran-5-one (±)-15b and its isomer (±)-15b. To a stirred soln of (±)-12 (1.27 g, 3.38 mmol) in dry THF (70 ml) was added n-BuLi (1.54 M in n-hexane; 5.0 ml, 7.7 mmol) over 45 min at -60°C. After stirring for 1 h at -60°C, CO_2 gas dried with conc H_2SO_4 was bubbled into the mixture for 1 h at -60°C. The mixture was warmed gradually to room temp and concentrated in vacuo. The residue was diluted with 2N NaOH (100 ml) and extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated in vacuo to give 180 mg (17 %) of (±)-14, νmax 3450 (br.s), 1590 (s), 1500 (s), 1455 (s), 1230 (s), 1115 (s) cm^{-1}; δ (60MHz, $CDCl_3$) 0.75~1.15 (3H, m), 1.15~2.05 (5H, m), 2.05 (1H, br.s), 2.20~2.60 (1H, m), 3.76 (3H, s), 3.80 (6H, s), 4.00~4.40 (2H, m), 4.60 (1H, d, J=5.5 Hz), 6.57 (2H, s). The aqueous layer was acidified with 2N HCl, and extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated in vacuo to give 1.21 g of crude (±)-13, νmax 3400 (br.s), 1700 (s) cm^{-1}. To the stirred soln of (±)-13 (1.21 g, 3.55 mmol) and Ph_3P (1.00 g, 3.81 mmol) in dry THF (20 ml) was added dropwise diethyl azodicaboxylate (0.70 g, 4.02 mmol) over 20 min at 0°C. Then the mixture was stirred for 3 h at room temp and concentrated in vacuo. The residue was diluted with n-hexane-ethyl acetate (2:1) and filtered. The filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (60 g). The earlier fractions eluted with n-hexane-ethyl acetate (3:1~2:1) gave 430 mg (38 %) of (±)-15b as a colorless oil, n_D^{20} 1.5324; νmax 1720 (s), 1595 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.95 (3H, t, J=7 Hz), 1.15~1.70 (4H, m), 1.93 (1H, ddd, J=4, 9, 13 Hz), 2.58 (1H, ddd, J=1, 6, 13 Hz), 3.88 (3H, s), 3.97 (6H, s), 4.30~4.53 (1H, m), 4.76 (1H, d, J=3 Hz), 5.03 (1H, br.t, J=3.5 Hz), 6.78 (1H, s). (Found: C, 63.64; H,6.85. Calc for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%). The later fractions eluted with n-hexane-ethyl acetate (3:1~2:1) gave 350 mg (31%) of (±)-15b. A portion of (±)-15b was recrystallized from n-hexane-ethyl acetate (2:1) to give pure (±)-15b as prisms, m.p. 98.0~99.0°C; νmax 1720 (s), 1600 (s), 1370 (s), 1255 (s), 1115 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.90 (3H, t, J=7 Hz), 1.15~1.85 (4H, m), 2.15 (1H, ddd,

J=1.5, 6, 14 Hz), 2.52 (1H, ddd, J=6, 8, 14 Hz), 3.89 (3H, s), 3.95 (3H, s), 3.98 (3H, s), 4.03~4.25 (1H, m), 4.50 (1H, d, J=3 Hz), 4.94 (1H, ddd, J=1.5, 3, 6 Hz), 6.79 (1H, s). (Found: C, 63.52; H, 6.75. Calc for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88 %). TLC (Merck Kieselgel 60 F_{254} Art. 5715 n-hexane-ethyl acetate = 1:1): Rf values: (±)-15b, 0.45; (±)-1b, 0.34.

(±)-Monocerin (±)-1a. To a stirred soln of (±)-1b (750 mg, 2.33 mmol) in dry dichloromethane (20 ml) was added dropwise boron tribromide (1.27 M in dichoromethane; 2.0 ml, 2.54 mmol) at -20°C. The stirring was continued for 30 min at -20°C. Sat $NaHCO_3$ soln (10 ml) was added to the mixture, and it was stirred for 30 min at room temp. The mixture was acidified with 2N HCl, and extracted with chloroform. The chloroform soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (15 g). Elution with n-hexane-ethyl acetate (3:1~2:1) gave (±)-1b (97 mg, 13% recovery) and 523 mg [84% yield based on consumed (±)-1b] of (±)-1a. A portion of (±)-1a was recrystallized from n-hexane-ethyl acetate (2:1) to give pure (±)-1a as prisms, m.p. 78.5~80.0°C, νmax 3470 (m), 2980 (s), 2960 (s), 2900 (s), 1660 (s), 1620 (m), 1580 (m), 1525 (s), 1455 (s), 1400 (s), 1380 (s), 1280 (s), 1120 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.92 (3H, t, J=7 Hz), 1.10~1.85 (4H, m), 2.13 (1H, ddd, J=1.5, 6, 14 Hz), 2.60 (1H, ddd, J=6, 8, 14 Hz), 3.91 (3H, s), 3.98 (3H, s), 4.00~4.30 (1H, m), 4.53 (1H, d, J=3 Hz), 5.04 (1H, ddd, J=1.5, 3, 6 Hz), 6.60 (1H, s), 11.30 (1H, s). (Found: C, 62.53; H, 6.39. Calc for $C_{16}H_{20}O_5$: C,62.33; H, 6.54%).

(2R*,3aR*,9bR*)-2,3,3a,9b-Tetrahydro-6-hydroxy-7,8-dimethoxy-2-propyl-5H-furo[3,2-c][2]benzopyran-5-one [2-epimonocerin, (±)-15a]. In the same manner as described for the preparation of (±)-1a, (±)-15b (17 mg, 0.053 mmol) yielded 14 mg (86%) of 15a. It was recrystallized from n-hexane-ethyl acetate (3:1) to give pure 15a as prisms, m.p. 75.0~77.0°C; νmax 3400 (br.w), 1665 (s), 1275 (s), 1125 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.95 (3H, t, J=7 Hz), 1.15~1.80 (4H, m), 1.98 (1H, ddd, J=4, 9, 13 Hz), 2.58 (1H, ddd, J=1, 6, 13 Hz), 3.90 (3H, s), 3.96 (3H, s), 4.15~4.47 (1H, m), 4.80 (1H, d, J=3 Hz), 5.15 (1H, br.t, J=3.5 Hz), 6.58 (1H, s), 11.25 (1H, s). (Found: C, 62.33; H, 6.46. Calc for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54%).

(S)-2-Hydroxypentanoic acid 17. To a stirred soln of (S)-16 (10 g, 85.4 mmol) in 1N H_2SO_4 (100 ml) was added dropwise a soln of $NaNO_2$ (14 g, 217 mmol) in water (20 ml) over 3 h at 0~5°C. The mixture was stirred overnight, concentrated in vacuo and extracted with ether. The extract was dried ($MgSO_4$) and concentrated in vacuo to give 8.3 g (82%) of crude 17, νmax 3400 (br.s), 1725 (s) cm^{-1}. This was employed in the next step without further purification.

(S)-1,2-Pentanediol 18. To a stirred suspension of LAH (3.6 g, 95 mmol) in dry ether (200 ml) was added dropwise a soln of 17 (8.3 g, 70.3 mmol) in dry ether (30 ml) at 0~10°C. The excess LAH was destroyed by the addition of water (3.6 ml), 2N NaOH (4 ml) and water (8 ml) to the stirred and ice-cooled mixture. After stirring for 3 h at room temp, the mixture was filtered and the filter-cake was washed with acetone. The combined filtrate and washings were dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled using a Vigreux column to give 4.82 g (66%) of 18 as a colorless oil, b.p. 83.0~84.5°C/7 Torr (lit.[13] b.p. 96~99°C/11 Torr); n_D^{18} 1.4356; $[\alpha]_D^{16}$ +1.0° (c=1.43, $CHCl_3$); νmax 3350 (br.s), 1060 (br.s) cm^{-1}; δ (60MHz, $CDCl_3$) 0.70~1.20 (3H, m), 1.20~1.70 (4H, m), 3.20~3.70 (1H, m), 3.50 (2H, d, J=4 Hz), 3.68 (2H, s).

(S)-1,2-Epoxypentane 20. To ice-coold 18 (8.0 g, 76.8 mmol) was added 30% soln of HBr in acetic acid (40 ml). The mixture was stirred for 1 h at room temp, poured into ice-water (300 ml) and neutralized with K_2CO_3. The mixture was extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, and concentrated in vacuo. To the residual 19 and 19' [νmax 1740 (s), 1230 (s) cm^{-1}] was added 50% KOH soln (60 ml). The mixture was stirred and heated at 120°C. The distillate (b.p. ~70°C) was collected in a flask cooled with ice-water. It was distilled over KOH pellets to give 4.38 g (66%) of 20 as a colorless oil, b.p. 83~86°C; n_D^{21} 1.3932; $[\alpha]_D^{21}$ -12.0° (c=1.89, $CHCl_3$); νmax 3050 (m), 1255 (m), 1110 (s), 940 (s), 830 (s) cm^{-1}; δ (60MHz, CCl_4) 0.92 (3H, m), 1.10~1.60 (4H, m), 2.14~2.28 (1H, m) 2.42~2.75 (2H, m); MS: m/z 86.0711 (M^+); Calc for $C_5H_{10}O$: 86.0732.

Ethyl (S)-3-hydroxyhexanoate (S)-6a. A soln of (S)-20 (8.3 g, 96.4 mmol) and NaCN (16.0 g, 326 mmol) in 40% aqueous ethanol (200 ml) was stirred for 19 h under reflux. The mixture was concentrated in vacuo, acidified with 2N HCl, and extracted with ether. The extract was dried ($MgSO_4$) and concentrated in vacuo. To the residue (21a) was added acetonitrile (500 ml) and dibenzylamine (19.0 g, 96.3 mmol). The mixture was stirred for 1 h under reflux and left to stand overnight. The precipitates were collected on a filter and recrystallized from acetonitrile to give 15.0 g (45%) of 21b. The filtrate was concentrated in vacuo and recrystallized three times from acetonitrile to give 3.3 g (10%) of 21b as leaflets, m.p. 101.0~103.0°C; $[\alpha]_D^{19}$ + 2.3° (c=1.19, MeOH); νmax 3400 (br.s), 2800 (m), 2700 (m), 2600 (m), 2450 (m), 2350 (m), 1550 (s), 1530 (s), 1380 (s) cm^{-1}; δ (100MHz, $CDCl_3$) 0.80~1.02 (3H, m), 1.15~1.55 (4H, m), 2.20~2.50 (2H, m), 3.75~3.90 (1H, m), 3.90 (4H, s), 6.15 (4H, s), 7.35 (10H, m). The salt 21b (18.3 g, 55.5 mmol) was added to 2N HCl (100 ml). The mixture was extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated in vacuo to give crude 21a, νmax 3400 (br.s), 1710 (s)cm^{-1}. The crude 21a was esterified in the usual manner to give 6.9 g (45% from 20) of (S)-6a, b.p. 94.0~95.0°C/20 Torr (lit.[12] b.p. 83~85°C/10 Torr); n_D^{19} 1.4258; $[\alpha]_D^{19}$ +29.1° (c=0.71, $CHCl_3$) [lit.[14] $[\alpha]_D$ +24° (c=1, $CHCl_3$)]; νmax 3450 (br.s), 1725 (s), 1170 (s) cm^{-1}; δ (60MHz, CCl_4) 0.70~1.10 (3H, m), 1.23 (3H, t, J=7 Hz), 1.20~1.60 (4H, m), 2.32 (2H, d, J=6 Hz), 3.00 (1H, br.s), 3.60~4.10 (1H, m), 4.05 (2H, q, J=7 Hz). This was emproyed in the next step without further purification.

Ethyl (S)-3-t-butyldimethylsilyloxyhexanoate (S)-6b. In the same manner as described for the preparation of (±)-6b, (S)-6a (4.5 g, 28.1 mmol) yielded 6.4 g (83%) of (S)-6b, b.p. 101~103°C/5 Torr; n_D^{20} 1.4276; $[\alpha]_D^{20}$ +18.5° (c=1.09, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-6b. (Found: C, 61.13; H, 10.77. Calc for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02%).

(S)-3-t-Butyldimethylsilyloxy-1-hexanol (S)-7a. In the same manner as described for the preparation of (±)-7a, (S)-6b (6.2 g 22.6 mmol) yielded 5.0 g (95%) of (S)-7a, b.p. 91.0~93.0°C/4 Torr; n_D^{20} 1.4374; $[\alpha]_D^{20}$ +19.3° (c=0.67, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-7a. MS: m/z 232.1844 (M^+). Calc for $C_{12}H_{28}O_2Si$: 232.1859.

(S)-3-t-Butyldimethylsilyloxy-1-iodohexane (S)-8. In the same manner as described for the preparation of (±)-8, (S)-7a (2.58 g, 11.1 mmol) yielded 3.34 g (88%) of (S)-8, n_D^{19} 1.4730; $[\alpha]_D^{19}$ +35.0° (c=0.96, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-8. (Found: C, 42.36; H, 7.87. Calc for $C_{12}H_{27}IO_2Si$: C, 42.10; H, 7.95%).

A diastereomeric mixture of 1-[(4S)-4-t-butyldimethylsilyloxy-1-phenylthioheptyl]-3,4,5-trimethoxybenzene (S)-9. In the same manner as described for the preparation of (±)-9, (S)-8 (6.07 g, 17.7 mmol) yielded 7.65 g (86%) of (S)-9, n_D^{19} 1.5246; $[\alpha]_D^{19}$ -4.5° (c=0.49, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-9. (Found: C, 66.79; H, 8.76.

Calc for $C_{28}H_{44}O_4SSi$: C, 66.63; H, 8.72%).

A diastereomeric mixture of (4S)-1-(2-bromo-3,4,5-trimethoxyphenyl)-4-t-butyldimethylsilyloxy-1-heptanol (S)-10b. In the same manner as described for the preparation of (±)-10b, (S)-9 (3.0 g, 5.9 mmol) yielded 2.2 g, (75%) of (S)-10b, n_D^{19} 1.5014; $[\alpha]_D^{19}$ -10.0° (c=0.20, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-10b. (Found: C, 53.51; H, 7.97. Calc for $C_{22}H_{39}BrO_5Si$: C, 53.75; H, 8.00%).

2-Bromo-1-[(1E,4S)-4-t-butyldimethylsilyloxy-1-heptenyl]-3,4,5-trimethoxybenzene (S)-11a. In the same manner as described for the prepartion of (±)-11a, (S)-10b (1.30 g, 2.64 mmol) yielded 943 mg (75%) of (S)-11a, n_D^{16} 1.5176; $[\alpha]_D^{16}$ -7.7° (c=0.60, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-11a. This was employed in the next step without further purification.

(1E,4S)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-1-hepten-4-ol (S)-11b. In the same manner as described for the preparation of (±)-11b, (S)-11a (643 mg, 1.36 mmol) yielded 398 mg (81%) of (S)-11b, n_D^{14} 1.5608; $[\alpha]_D^{14}$ +4.1° (c=0.24, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-11b. (Found: C, 53.04; H, 6.32. Calc for $C_{16}H_{23}BrO_4$: C, 53.49; H, 6.45%).

A diastereomeric mixture of (2R,3S,5S)-2-(2-bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol and (2S,3R,5S)-2-(2-bromo-3,4,5-trimethoxyphenyl)-5-propyltetrahydrofuran-3-ol (S)-12. In the same manner as described for the preparation of (±)-12, (S)-11b (880 mg, 2.45 mmol) yielded 760 mg (85%) of (S)-12, n_D^{19} 1.5406; $[\alpha]_D^{19}$ -9.4° (c=0.53, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-12. (Found: C, 51.24; H, 6.11. Calc for $C_{16}H_{23}BrO_5$: C, 51.21; H, 6.18%).

(2S,3aR,9bR)-2,3,3a,9b,-Tetrahydro-6,7,8-trimethoxy-2-propyl-5H-furo[3,2-c][2]benzopyran-5-one 1b and (2S,3aS,9bS)-2,3,3a,9b,-tetrahydro-6,7,8-trimethoxy-2-propyl-5H-furo[3,2-c][2]benzopyran-5-one 15b. In the same manner as described for the preparation of (±)-1b and (±)-15b, (S)-12 (700 mg, 1.92 mmol) yielded 237 mg (37%) of 15b and 200 mg (33%) of 1b.

15b: n_D^{20} 1.5328; $[\alpha]_D^{20}$ -17.5° (c=0.13, $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (±)-15b. (Found: C, 62.99; H, 6.86. Calc for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%).

1b: n_D^{21} 1.5306; $[\alpha]_D^{21}$ +22.8° (c=2.76, $CHCl_3$); vmax 1720 (s), 1595 (s) cm^{-1}. Its ^1H NMR spectrum was identical with that of (±)-1b. (Found: C, 63.71; H, 6.86. Calc for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88%).

(+)-Monocerin 1a. In the same maner as described for the preparation of (±)-1a, 1b (200 mg, 0.62 mmol) yielded 56 mg (28% recovery) of 1b and 98 mg (71% yield based on consumed 1b) of 1a. A portion of 1a was recrystallized from n-hexane-ethyl acetate (3:1) to give pure 1a as plates, m.p. 54.0~55.5°C (natural 53.0~55.0°C, mixed m.p. 53.0~55.5°C, lit.[1]: 58~59°C); $[\alpha]_D^{16}$ +60.3° (c=0.18, MeOH) [natural $[\alpha]_D^{16}$ +58.8° (c=0.37, MeOH), lit.[1]: $[\alpha]_D^{24}$ +53° (c=0.85, MeOH)]; vmax 3450 (br.s), 2990 (s), 2960 (s), 2900 (s), 1670 (s), 1625 (m), 1590 (m), 1525 (s), 1465 (s), 1450 (w), 1430 (m), 1400 (s), 1380 (s), 1340 (m), 1285 (s), 1125 (s), 1040 (m), 1020 (m), 885 (m), 805 (m) cm^{-1}; δ (100MHz, $CDCl_3$) 0.92 (3H, t, J=7 Hz), 1.10~1.85 (4H, m), 2.13 (1H, ddd, J=1.5, 6, 14 Hz), 2.60 (1H, ddd, J=6, 8, 14 Hz), 3.91 (3H, s), 3.98 (3H, s), 4.00~4.30 (1H, m), 4.53 (1H, d, J=3 Hz), 5.04 (1H, ddd, J=1.5, 3, 6 Hz), 6.60 (1H, s), 11.30 (1H, s). Its ^1H NMR spectrum was identical with that of (±)-1a. Its IR and ^1H NMR spectra were coincided with those of an authentic sample. (Found: C, 62.25; H, 6.29. Calc for $C_{16}H_{20}O_6$: C, 62.33; H,6.54%).

Determination of enantiomeric purity of 18. The bis-(R)-MTPA ester of 18 was prepared in the usual manner[11], and analyzed by HPLC (Column, Senshu Pack®-Silica-1251-N 4.6 x 250 mm; solvent, n-hexane-THF-MeOH (120:10:1), 1.2 ml/min; Detection at 254 nm): Rt 23.1 min [(R)-18 with (R)-MTPA], 24.2 min [(S)-18 with (R)-MTPA]. The enantiomeric purity of (S)-18 was 94.1% e.e.

Determination of enantiomeric purity of (S)-6a. The (R)-MTPA ester of (S)-6a was prepared in the usual manner[11], and analyzed by HPLC (Column, Senshu Pack®-Silica-1251-N 4.6 x 250 mm; Solvent, n-hexane-THF (60:1), 1.2 ml/min; Detection at 254 nm): Rt 17.4 min [(R)-6a with (R)-MTPA], 18.6 min [(S)-6a with (R)-MTPA]. The enantiomeric purity of (S)-6a was 97.5% e.e.

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