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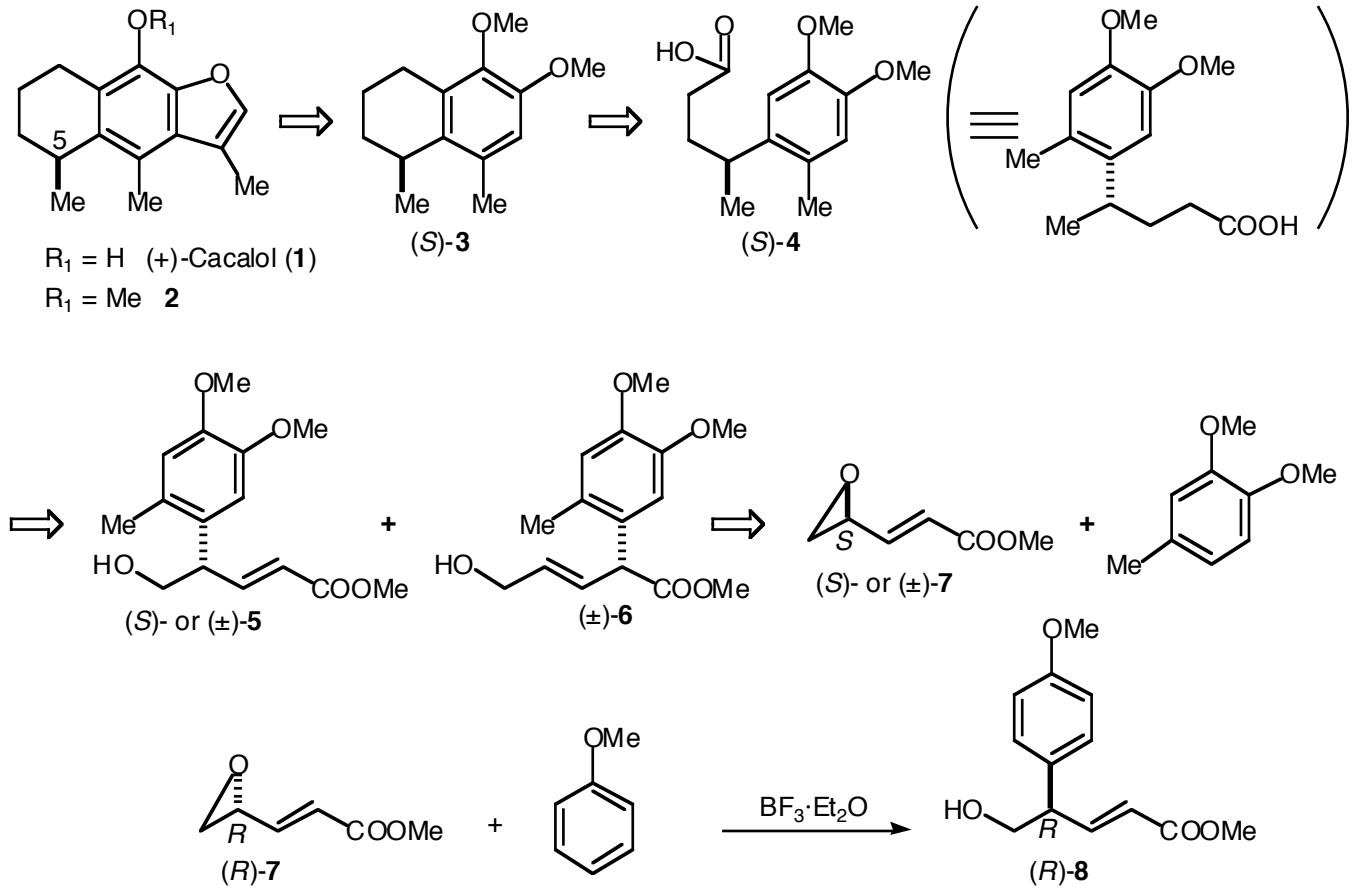
THE FIRST SYNTHESIS OF (*S*)-(+)-CACALOL

Shin Tanikawa, Machiko Ono, and Hiroyuki Akita*

School of Pharmaceutical Sciences, Toho University
2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan

Abstract- The first synthesis of (*S*)-(+)-cacalol (**1**) was achieved by a combination of the $BF_3 \cdot Et_2O$–mediated reaction of (*S*)-4,5-epoxy-(2*E*)-pentenoate (**7**) with 3,4-dimethoxytoluene to give (*S*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (**5**) and consecutive conversion of (*S*)-**5** into (*S*)-**1**.

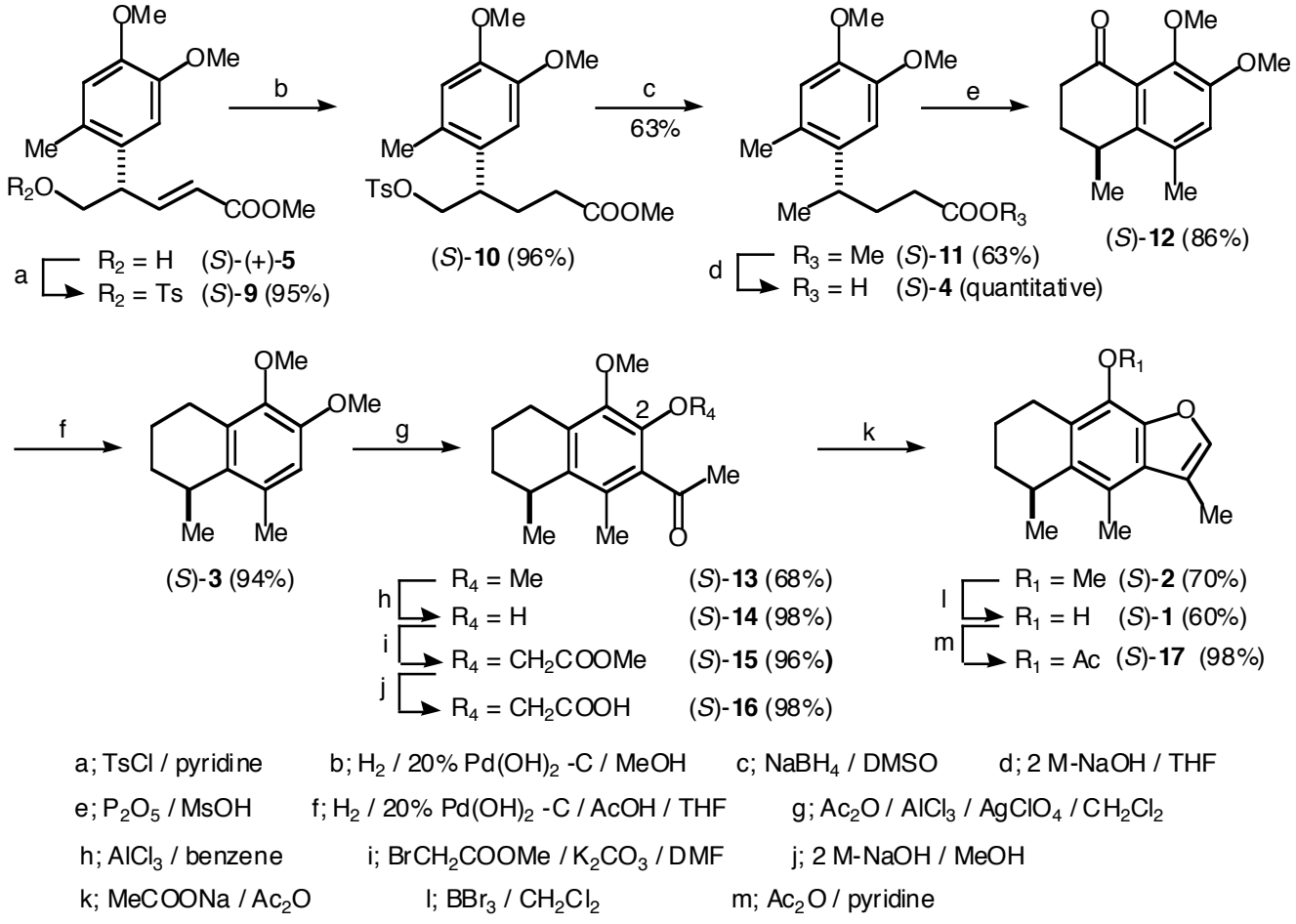
Cacalol (**1**) is one of the major components isolated from the root of *Cacalia decomposita*, a compositae widely distributed in the northern part of Mexico. Extracts from the root have been used for the treatment of diabetes and other diseases,[1] and were recently reported to possess antihyperglycemic activity.[2] Through a series of revisions,[3] the structure of cacalol (**1**) was established to be 5,6,7,8-tetrahydro-3,4,5-trimethylnaphto[2,3-*b*]furan-9-ol by unambiguous synthesis.[4] The absolute stereochemistry of C(5)-position of **1** was confirmed to be (*S*)-configuration by means of X-Ray analysis of its methyl ether (**2**)[5] and chemical correlation.[6] The furotetralin ring structure of **1** appeared to give reasonable opportunity to develop analogue from the standpoint of a medicinal chemistry effort and total synthesis of (±)-**1** was undertaken. Several syntheses of (±)-**1** have been reported,[7] however, the chiral synthesis of (*S*)-**1** was not reported so far. We now describe the first synthesis of (*S*)-(+)-**1**. (Scheme 1)
Our retrosynthetic strategy of (*S*)-**1** is illustrated in Scheme 1 and involves asymmetric synthesis of chiral tetralin intermediate ((*S*)-**3**) which could be obtained based on the intramolecular Friedel-Crafts acylation strategy from (*S*)-4-arylpentanoic acid (**4**). This chiral carboxylic acid ((*S*)-**4**) could be derived from (*S*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (**5**). On the other hand, we previously reported the reaction of (±)-4,5-epoxy-(2*E*)-pentenoate (**7**) and 3,4-dimethoxytoluene in the presence of $BF_3 \cdot Et_2O$ to give (±)-**5** (46% yield) as a major product and (±)-2-aryl-5-hydroxy-(2*E*)-penenoate (**6**) (18% yield) as a minor product.[8] When the optically active (*S*)-**7** instead of (±)-**7** is applied in the above-mentioned reaction, optically active (*S*)-**5** is presumably obtained. Because the reaction of (*R*)-**7** and anisole afforded (*R*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (**8**) (47% yield) along with the nucleophilic inversion at C(4)-position.[9] In order to confirm this assumption, $BF_3 \cdot Et_2O$-mediated reaction of (*S*)-**7** possessing 93% enantiomeric excess (ee)[9] and 3,4-dimethoxytoluene was carried out, and the obtained mixture of **5** and **6** was subjected



Scheme 1

to oxidation with MnO_2 followed by chromatographic separation to provide (+)-**5** (46% yield, $[\alpha]_D$ +22.7° (c=0.33, $CHCl_3$)) as a major product. The ee of (+)-**5** was estimated to be 93% ee by mean of HPLC analysis using chiral column (CHIRALCEL OD). The absolute stereochemistry at C(4)-position of (+)-**5** was determined to be *S*-configuration because (+)-**5** was finally converted into the natural product (*S*)-**1** at later mentioned in this text. (Scheme 2)

Tosylation of (*S*)-**5** gave the corresponding tosylate ((*S*)-**9**) (95% yield, $[\alpha]_D$ +3.4° (c=0.29, $CHCl_3$)), which was subjected to a catalytic hydrogenation to afford (*S*)-**10** ($[\alpha]_D$ +7.1° (c=0.31, $CHCl_3$)) in 96% yield. $NaBH_4$ reduction of (*S*)-**10** gave the (*S*)-4-arylpentanoate (**11**) ($[\alpha]_D$ +19.3° (c=0.71, $CHCl_3$)) in 63% yield, which was subjected to alkaline hydrolysis to provide the corresponding carboxylic acid ((*S*)-**4**) ($[\alpha]_D$ +17.3° (c=0.23, $CHCl_3$)) in quantitative yield. Treatment of (*S*)-**4** and P_2O_5 in methanesulfonic acid (MsOH) provided (*S*)-4,5-dimethyl-1-tetralone derivative (**12**) ($[\alpha]_D$ +34.9° (c=0.64, $CHCl_3$)) in 86% yield, which was subjected to a catalytic hydrogenolysis to afford (*S*)-4,5-dimethyl-5,6,7,8-tetrahydronaphthalene derivative (**3**) ($[\alpha]_D$ –8.8° (c=0.81, $CHCl_3$)) in 94% yield. By applying the Mukaiyama's Friedel-Crafts acylation method, [10] (*S*)-**3** was converted to (*S*)-3-acetyl-4,5-dimethyl-5,6,7,8-tetrahydronaphthalene derivative (**13**) ($[\alpha]_D$ –12.6° (c=0.29, $CHCl_3$)) in 68% yield. $AlCl_3$-Mediated selective demethylation at the *ortho*-substituted methoxyl group of benzoyl moiety by our method [11] was applied to (*S*)-**13** to provide the selective C(2)-demethylation product ((*S*)-**14**) (98% yield),



Scheme 2

which was crystallized from *n*-hexane/AcOEt to yield enantiomerically pure (*S*)-**14** (45% yield, $[\alpha]_D$ –11.3° (c=0.24, $CHCl_3$)). Methoxycarbonylmethylation of phenolic hydroxyl group of (*S*)-**14** was achieved by treatment with bromoacetate and K_2CO_3 to give (*S*)-**15** ($[\alpha]_D$ –11.0° (c=0.28, $CHCl_3$)) in 96% yield. Alkaline hydrolysis of (*S*)-**15** afforded the corresponding carboxylic acid ((*S*)-**16**) ($[\alpha]_D$ –11.5° (c=0.20, $CHCl_3$)) in 98% yield, which was treated with $AcONa/Ac_2O$ to provide the furotetralin derivative ((*S*)-**2**) ($[\alpha]_D$ +6.7° (c=0.10, $CHCl_3$)) in 70% yield. Finally, demethylation of (*S*)-**2** using boron tribromide (BBr_3) gave the synthetic cacalol ((*S*)-**1**) ($[\alpha]_D$ +12.5° (c=0.12, $CHCl_3$)) in 60% yield, whose spectral data were identical with those ($[\alpha]_D$ +10° ($CHCl_3$),[1] and ^{1}H-NMR[2]) of the natural (*S*)-**1**. Moreover, the physical data ($[\alpha]_D$ –4.9° (c=0.14, $CHCl_3$), and ^{1}H-NMR) of the acetylated product ((*S*)-**17**) were also identical with those ($[\alpha]_D$ -9° ($CHCl_3$),[1] and ^{1}H-NMR[4b] for (±)-**17**) of the reported (*S*)-**17**. Conversion of (+)-**5** into (*S*)-cacalol (**1**) was achieved and thence, the absolute chemistry at C(4)-position of (+)-**5** was unequivocally determined to be *S*-configuration.

In conclusion, the first synthesis of optical active (*S*)-cacalol (**1**) was achieved by a combination of the $BF_3{\cdot}Et_2O$-mediated reaction of (*S*)-4,5-epoxy-(2*E*)-pentenoate (**7**) with 3,4-dimethoxytoluene to give (*S*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (**5**) and consecutive conversion of (*S*)-**5** into (*S*)-**1**.

EXPERIMENTAL

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded by a JEOL AL 400 spectrometer (Tokyo, Japan). Spectra were taken with 5-10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. The fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-600H (matrix; Dithiothreitol : □-Thioglycerol = 1:1 mixture) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrophotometer. The HPLC system was composed of a detector (UV detector SSC-5200, Senshu), pump (SSC-3210, Senshu) and integrator (chromatocorder SIC 21). HPLC analysis conditions were as follows; column: CHIRALCEL OD and CHIRALPAC AD, Detection: UV at 254 nm, Flow rate; 1 mL/min. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

(*S*)-Methyl 4-(2'-methyl-4',5'-dimethoxyphenyl)-5-hydroxy-(2*E*)-pentenoate (5)

To a solution of (*S*)-**7** (93% ee, 8.0 g, 62.7 mmol)[9] and 3,4-dimethoxytoluene (14.3 g, 94.0 mmol) in CH_2Cl_2 (100 mL) was added $BF_3{\cdot}Et_2O$ (8.9 g, 62.7 mmol) at -78°C, and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (300 g, *n*-hexane:AcOEt = 1:1) to afford a mixture (11.2 g, 64 %) of (*S*)-**5** and **6** as a pale yellow oil. To a solution of a mixture (11.2 g) of (*S*)-**5** and **6** in CH_2Cl_2 (300 mL) was added MnO_2 (69.4 g, 799 mmol) and the whole mixture was vigorously stirred for 6 h at rt. After the precipitate was removed by filtration with the aid of Celite, it was washed with AcOEt. The filtrate was evaporated to give a residue, which was chromatographed on silica gel (300 g, *n*-hexane:AcOEt = 2:1) to afford (*S*)-**5** (8.05 g, 46%) as yellow oil. The NMR spectral data of (*S*)-**5** were identical with those of the reported (±)-**5**.[8] (*S*)-**5**: $[\alpha]_D^{29}$ +22.7° (c=0.33, $CHCl_3$) corresponding to 93% ee, CHIRALCEL OD, eluent, *n*-hexane:EtOH:*iso*-PrOH = 60:1:1, t_R=47.7 min (96.5%), t_R=60.0 min (3.5%)).

(*S*)-Methyl 4-(2'-methyl-4',5'-dimethoxyphenyl)-5-tosyloxy-(2*E*)-pentenoate (9)

To a solution of (*S*)-**5** (93% ee, 7.3 g, 26.1 mmol) in CH_2Cl_2 (15 mL) and pyridine (10 mL) was added TsCl (5.5 g, 28.7 mmol) at 0°C and the mixture was stirred for 3 h at 0°C. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 2M aqueous HCl, 7% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The organic layer was evaporated to give a residue which was chromatographed on silica gel (100 g, *n*-hexane:AcOEt = 4:1) to afford the corresponding tosylate (**9**) (10.8 g, 95%) as yellow oil. (*S*)-**9**: $[\alpha]_D^{27}$ +3.4° (c=0.29, $CHCl_3$), IR (neat): 1722 cm^{-1}; NMR: 2.15 (3H, s), 2.39 (3H, s), 3.67 (3H, s), 3.70 (3H, s), 3.80 (3H, s), 3.97 (1H, br q, *J*=6.5 Hz), 4.14 (1H, dd, *J*=9.9, 6.5 Hz), 4.22 (1H, dd, *J*=9.9, 7.9 Hz), 5.73 (1H, dd, *J*=15.9, 1.6 Hz), 6.38 (1H, s), 6.61

(1H, s), 6.92 (1H, dd, *J*=15.9, 6.5 Hz), 7.25 (2H, d, *J*=8.5 Hz), 7.63 (2H, dd, *J*=8.5 Hz). Anal. Calcd for $C_{22}H_{26}O_7S$: C, 60.81; H, 6.03. Found: C, 60.57; H, 6.10. FAB MS *m/z*: 434 (M^+).

(*S*)-Methyl 4-(2'-methyl-4',5'-dimethoxyphenyl)-5-tosyloxypentanoate (10)

A mixture of (*S*)-**9** (4.1 g, 9.5 mmol), 20% $Pd(OH)_2$-C (0.4 g) in MeOH (40 mL) was vigorously stirred under H_2 atmosphere (1 atm) for 4 h at rt. After the catalyst was removed by filtration passed through a pad of Celite and washed with AcOEt, the filtrate was concentrated *in vacuo* to give a residue, which was chromatographed on silica gel (80 g, *n*-hexane:AcOEt = 2:1) to afford (*S*)-(**10**) (4.0 g, 96%) as pale yellow oil. (*S*)-**10**: $[\alpha]_D^{25}$ +7.1° (c=0.31, $CHCl_3$), IR (neat): 1734 cm^{-1}; NMR: 1.76-1.88 (1H, m), 2.03-2.16 (3H, m), 2.15 (3H, s), 2.40 (3H, s), 3.16-3.26 (1H, m), 3.60 (3H, s), 3.71 (3H, s), 3.82 (3H, s), 3.98 (1H, dd, *J*=9.8, 6.5 Hz), 4.05 (1H, dd, *J*=9.8, 7.1 Hz), 6.42 (1H, s), 6.59 (1H, s), 7.23 (2H, d, *J*=8.5 Hz), 7.59 (2H, dd, *J*=8.5 Hz). Anal. Calcd for $C_{22}H_{28}O_7S$: C, 60.53; H, 6.47. Found: C, 60.34; H, 6.60. FAB MS *m/z*: 436 (M^+).

(*S*)-Methyl 4-(2'-methyl-4',5'-dimethoxyphenyl)pentanoate (11)

To a solution of (*S*)-**10** (0.29 g, 0.66 mmol) in DMSO (5 mL) was added $NaBH_4$ (0.05 g, 1.32 mmol) at rt. After the mixture was stirred for 1 h at 50°C and for 1 h at 80°C, the reaction mixture was allowed to cool. Small amounts of acetone, ether, and 7% aqueous $NaHCO_3$ were added to the reaction mixture, and the mixture was stirred for 30 min at rt, then extracted with ether. The organic layer was washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 4:1) to afford (*S*)-**11** (0.11 g, 63%) as a colorless oil. (*S*)-**11**: $[\alpha]_D^{27}$ +19.3° (c=0.71, $CHCl_3$), IR (neat): 1736 cm^{-1}; NMR: 1.18 (3H, d, *J*=7.2 Hz), 1.87 (2H, q, *J*=7.2 Hz), 2.16-2.22 (2H, m), 2.21 (3H, s), 2.93 (1H, sextet, *J*=7.2 Hz), 3.60 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 6.61 (1H, s), 6.66 (1H, s). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.59; H, 8.55. FAB MS *m/z*: 266 (M^+).

(*S*)-4-(2'-Methyl-4',5'-dimethoxyphenyl)pentanoic acid (4)

To a solution of (*S*)-**11** (2.71 g, 10.2 mmol) in THF (40 mL) and MeOH (10 mL) were added 2M aqueous NaOH (10 mL, 20 mmol) and the mixture was stirred for 2 h at rt. The reaction mixture was acidified with 2M aqueous HCl, and concentrated *in vacuo*. The aqueous residue was extracted with AcOEt and the organic layer was washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 1:1) to afford (*S*)-**4** (2.58 g, quantitative yield) as a pale yellow oil. (*S*)-**4**: $[\alpha]_D^{25}$ +17.3° (c=0.23, $CHCl_3$), IR (neat): 1710, 3504 cm^{-1}; NMR: 1.19 (3H, d, *J*=7.2 Hz), 1.88 (2H, q, *J*=7.2 Hz), 2.19-2.26 (2H, m), 2.22 (3H, s), 2.95 (1H, sextet, *J*=7.2 Hz), 3.82 (3H, s), 3.83 (3H, s), 6.62 (1H, s), 6.66 (1H, s). Anal. Calcd for $C_{14}H_{20}O_4 \cdot 1/2H_2O$: C, 64.45; H, 8.10. Found: C, 64.37; H, 7.97. FAB MS *m/z*: 252 (M^+).

(*S*)-7,8-Dimethoxy-4,5-dimethyl-1-tetralone (12)

To a solution of (*S*)-**4** (5.3 g, 21.0 mmol) in methanesulfoic acid (MsOH; 50 mL) was added P_2O_5 (14.9 g, 104.8 mmol) at 0°C over a 5 min period and the reaction mixture was stirred for 1.5 h at rt. The reaction mixture was poured into ice and neutralized with 2M aqueous NaOH, and extracted with AcOEt. The organic layer was washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (100 g, *n*-hexane:AcOEt = 5:1) to afford (*S*)-**12** (4.2 g, 86 %) as yellow oil. (*S*)-**12**: $[\alpha]_D^{25}$ +34.9° (c=0.64, $CHCl_3$), IR (neat): 1683 cm^{-1}; NMR: 1.17 (3H, d, *J*=7.1 Hz), 1.88-1.93 (1H, m), 2.07-2.20 (1H, m), 2.28 (3H, s), 2.52 (1H, dd, *J*=18.3, 6.0 Hz), 2.75 (1H, ddd, *J*=18.3, 13.8, 6.0 Hz), 3.10-3.19 (1H, m), 3.80 (3H, s), 3.81 (3H, s), 6.87 (1H, s). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.35; H, 7.69. FAB MS *m/z*: 235 (M^++1).

(*S*)-1,2-Dimethoxy-4,5-dimethyl-5,6,7,8-tetrahydronaphthalene (3)

A mixture of (*S*)-**12** (4.2 g, 18.0 mmol), 20% $Pd(OH)_2$-C (0.8 g) and acetic acid (24 mL) in THF (72 mL) was vigorously stirred under H_2 atmosphere (1 atm) for 1.5 h at rt. After the catalyst was removed by filtration passed through a pad of Celite and washed with AcOEt, the filtrate was washed with 7% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (100 g, *n*-hexane:AcOEt = 9:1) to afford (*S*)-(**3**) (3.7 g, 94%) as yellow oil. (*S*)-**3**: $[\alpha]_D^{24}$ –8.8° (c=0.81, $CHCl_3$), IR (neat): 1597 cm^{-1}; NMR: 1.16 (3H, d, *J*=7.0 Hz), 1.67-1.90 (4H, m), 2.29 (3H, s), 2.55 (1H, ddd, *J*=17.9, 10.4, 7.4 Hz), 2.90-3.08 (2H, m), 3.77 (3H, s), 3.82 (3H, s), 6.61 (1H, s). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.84; H, 9.31. FAB MS *m/z*: 220 (M^+).

(*S*)-3-Acetyl-1,2-dimethoxy-4,5-dimethyl-5,6,7,8-tetrahydronaphthalene (13)

$AlCl_3$ (0.18 g, 1.37 mmol) and $AgClO_4$ (0.29 g, 1.37 mmol) in CH_2Cl_2 (20 mL) were stirred for 30 min at rt. A solution of (*S*)-**3** (0.28 g, 1.25 mmol) and Ac_2O (0.64 g, 6.24 mmol) in CH_2Cl_2 (15 mL) was added to the above mentioned reaction mixture and whole mixture was stirred for 2 h at rt. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 10:1) to afford (*S*)-**13** (0.22 g, 68%) as yellow oil. (*S*)-**13**: $[\alpha]_D^{24}$ –12.6° (c=0.29, $CHCl_3$), IR (neat): 1702 cm^{-1}; NMR: 1.12 (3H, d, *J*=7.0 Hz), 1.60-1.84 (4H, m), 2.10 (3H, s), 2.42-2.57 (1H, m), 2.47 (3H, s), 2.85-2.94 (1H, m), 2.97-3.06 (1H, m), 3.78 (3H, s), 3.79 (3H, s). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.75; H, 8.61. FAB MS *m/z*: 263 (M^++1).

(*S*)-3-Acetyl-4,5-dimethyl-2-hydroxy-1-methoxy--5,6,7,8-tetrahydronaphthalene (14)

To a solution of (*S*)-**13** (0.22 g, 0.84 mmol) in benzene (10 mL) was added $AlCl_3$ (0.34 g, 2.53 mmol) at rt and whole mixture was stirred for 1.5 h at the same temperature. The reaction mixture was poured into ice and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 10:1) to afford (*S*)-**14** (0.20 g, 98%) as a pale yellow crystal. An ee of (*S*)-**14** was estimated to be 93% based on HPLC analysis (CHIRALCEL AD, eluent, *n*-hexane:EtOH = 100:1, t_R=27.0 min (96.5%), t_R=23.5 min (3.5%)). Recrystallization of (*S*)-**14** (0.29 g) from *n*-hexane:AcOEt gave a colorless prisms (*S*)-**14** (0.13g, 45%). (*S*)-**14**: mp 155-158°C; $[\alpha]_D^{25}$ –11.3° (c=0.24, $CHCl_3$), IR (KBr): 1677, 3315 cm^{-1}; NMR: 1.12 (3H, d, *J*=7.0 Hz), 1.62-1.88 (4H, m), 2.26 (3H, s), 2.47-2.64 (1H, m), 2.56 (3H, s), 2.92 (1H, dd, *J*=17.7, 5.6 Hz), 3.01-3.09 (1H, m), 3.76 (3H, s), 8.06 (1H, s). Anal. Calcd for $C_{15}H_{20}O_3 \cdot 1/2H_2O$: C, 70.01; H, 8.23. Found: C, 70.32; H, 8.08. FAB MS *m/z*: 249 (M^++1).

Methyl ((*S*)-3-acetyl-4,5-dimethyl-1-methoxy-5,6,7,8-tetrahydronaphthalen-2-yloxy)acetate (15)

To a mixture of (*S*)-**14** (0.18 g, 0.74 mmol) and K_2CO_3 (0.15 g, 1.11 mmol) in DMF (15 mL) was added methyl bromoacetate (0.17 g, 1.11 mmol) at rt and whole mixture was stirred for 2.5 h at 50°C. The reaction mixture was allowed to cool, and diluted with H_2O, extracted with AcOEt. The organic layer was washed with saturated aqueous NH_4Cl, brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 10:1) to afford (*S*)-**15** (0.23 g, 96%) as a colorless oil. (*S*)-**15**: $[\alpha]_D^{25}$ –11.0° (c=0.28, $CHCl_3$), IR (neat): 1701, 1766 cm^{-1}; NMR: 1.11 (3H, d, *J*=7.0 Hz), 1.61-1.85 (4H, m), 2.11 (3H, s), 2.44-2.56 (1H, m), 2.52 (3H, s), 2.83-2.92 (1H, m), 2.97-3.07 (1H, m), 3.75 (3H, s), 3.76 (3H, s), 4.52 (1H, d, *J*=15.9 Hz), 4.57 (1H, d, *J*=15.9 Hz). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.16; H, 7.65. FAB MS *m/z*: 320 (M^+).

(*S*)-3-Acetyl-4,5-dimethyl-1-methoxy-5,6,7,8-tetrahydronaphthalen-2-yloxy)acetic acid (16)

To a solution of (*S*)-**15** (0.11 g, 0.34 mmol) in a mixed solvent (THF (5 mL) and MeOH (5 mL)) was added 2M aqueous NaOH (2 mL, 4 mmol) and whole mixture was stirred for 1.5 h at rt. The reaction mixture was acidified with 2M aqueous HCl, and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt:AcOH = 200:100:3) to afford (*S*)-**16** (0.10 g, 98%) as a colorless oil. (*S*)-**16**: $[\alpha]_D^{22}$ –11.5° (c=0.20, $CHCl_3$), IR (neat): 1699, 1737 cm^{-1}; NMR: 1.08 (3H, d, *J*=7.0 Hz), 1.50-1.82 (4H, m), 2.08 (3H, s), 2.41-2.55 (1H, m), 2.47 (3H, s), 2.85 (1H, br d, *J*=17.0 Hz), 2.92-3.04 (1H, m), 3.73 (3H, s), 4.57 (2H, s). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.14; H, 7.39. FAB MS *m/z*: 307 (M^++1).

(*S*)-9-Methoxy-5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan (2)

To a solution of (*S*)-**16** (0.088 g, 0.29 mmol) in Ac_2O (5 mL) was added sodium acetate (0.35 g, 4.31 mmol) at rt and whole mixture was stirred for 1.5 h at 100°C. The reaction mixture was poured into ice and extracted with AcOEt. The organic layer was washed with 7% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 10:1) to afford (*S*)-**2** (0.049 g, 70%) as a pale yellow oil. (*S*)-**2**: $[\alpha]_D^{25}$ +6.7° (c=0.10, $CHCl_3$), IR (neat): 2927 cm^{-1}; NMR: 1.19 (3H, d, *J*=7.1 Hz), 1.72-1.92 (4H, m), 2.37 (3H, s), 2.54 (3H, s), 2.62 (1H, ddd, *J*=17.7, 11.0, 7.3 Hz), 3.02 (1H, dd, *J*=17.7, 4.3 Hz), 3.18-3.26 (1H, m), 4.03 (3H, s), 7.23 (1H, s). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.80; H, 8.71. FAB MS *m/z*: 244 (M^+).

(*S*)-(+)-Cacalol (1)

To a solution of (*S*)-**2** (0.083 g, 0.34 mmol) in CH_2Cl_2 (4 mL) was added 1.0 M BBr_3 in CH_2Cl_2 (0.34 mL, 0.34 mmol) at –78°C and whole mixture was stirred for 0.5 h at -78°C and for 1 h at 0°C. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 9:1) to afford (*S*)-**1** (0.047 g, 60%) as a yellow oil. (*S*)-**1**: $[\alpha]_D^{27}$ +12.5° (c=0.12, $CHCl_3$), NMR: 1.20 (3H, d, *J*=7.1 Hz), 1.73-1.97 (4H, m), 2.38 (3H, s), 2.53 (3H, s), 2.63 (1H, ddd, *J*=17.9, 11.4, 7.5 Hz), 2.99 (1H, dd, *J*=17.9, 5.0 Hz), 3.19-3.28 (1H, m), 5.15 (1H, br s), 7.24 (1H, s).

(*S*)-5,6,7,8-Tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan-9-yl acetate (17)

To a solution of (*S*)-**1** (0.012 g, 0.05 mmol) in pyridine (1 mL) was added Ac_2O (0.008 g, 0.08 mmol) at 0°C and whole mixture was stirred for 3 h at rt. The reaction mixture was diluted with AcOEt and the organic layer was washed with 2M aqueous HCl, 7% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt = 10:1) to afford (*S*)-**17** (0.014 g, 98%) as a colorless crystal. Recrystallization of (*S*)-**17** from *n*-hexane-acetone gave a colorless prism (*S*)-**17**. (*S*)-**17**: mp 105-106°C; $[\alpha]_D^{24}$ –4.9° (c=0.14, $CHCl_3$), IR (KBr): 1768 cm^{-1}; NMR: 1.20 (3H, d, *J*=7.1 Hz), 1.76-1.96 (4H, m), 2.38 (3H, s), 2.40 (3H, s), 2.50-2.63 (1H, m), 2.57 (3H, s), 2.85 (1H, dd, *J*=17.4, 5.3 Hz), 3.21-3.30 (1H, m), 7.24 (1H, s). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.66; H, 7.43. FAB MS *m/z*: 273 (M^++1).

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