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

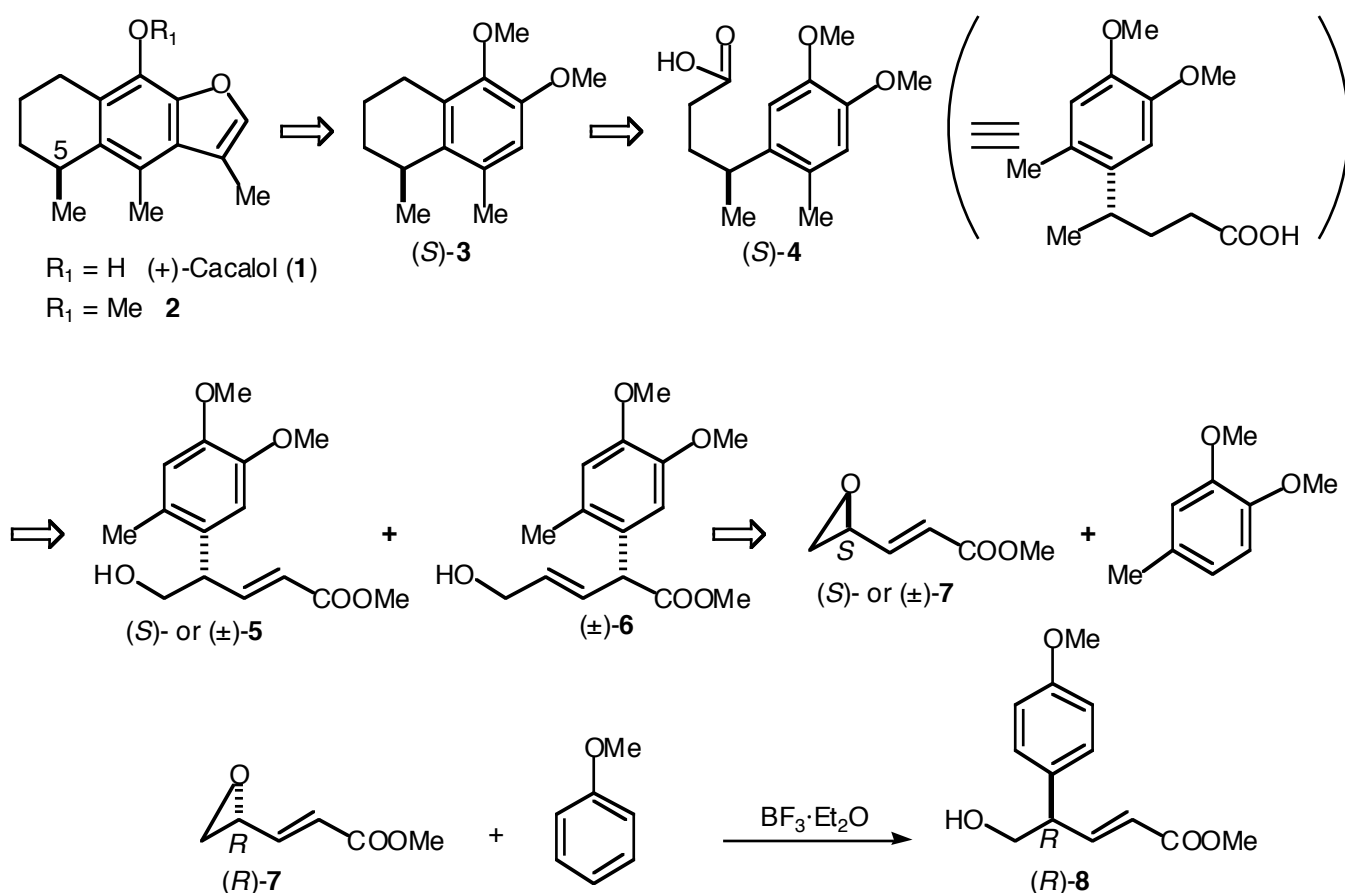
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**Abstract-** The first synthesis of (*S*)-(+)-cacalol (**1**) was achieved by a combination of the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated reaction of (*S*)-4,5-epoxy-(2*E*)-pentenoate (**7**) with 3,4-dimethoxytoluene to give (*S*)-4-aryl-5-hydroxy-(2*E*)-pentenoate (**5**) and consecutive conversion of (*S*)-**5** into (*S*)-**1**.

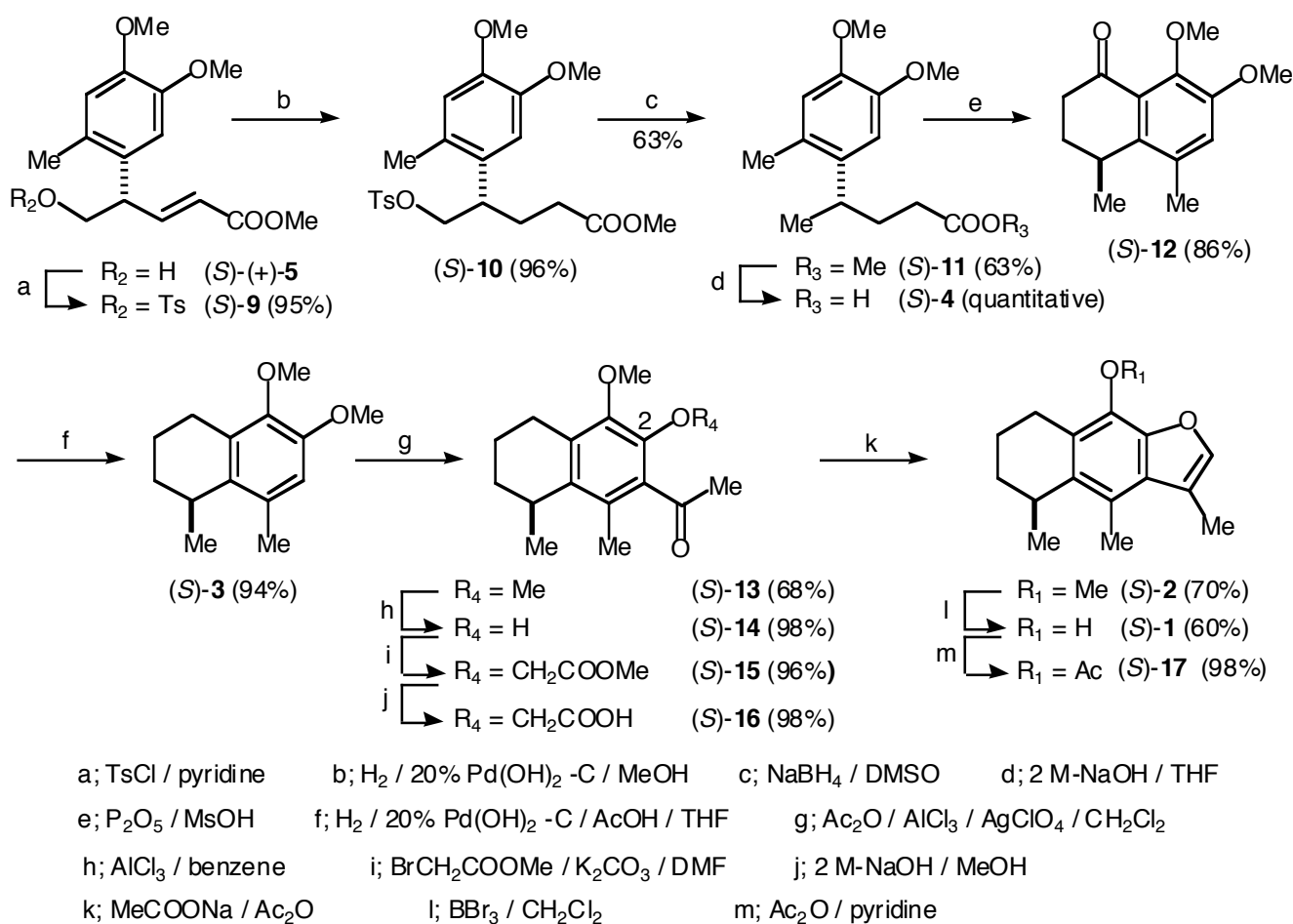
Cacalol (**1**) is one of the major components isolated from the root of *Cacalia decomposita*, a compositae widely distributed in the northern part of Mexico. Extracts from the root have been used for the treatment of diabetes and other diseases,<sup>1</sup> and were recently reported to possess antihyperglycemic activity.<sup>2</sup> Through a series of revisions,<sup>3</sup> 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.<sup>4</sup> 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**)<sup>5</sup> and chemical correlation.<sup>6</sup> 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 ( $\pm$ )-**1** was undertaken. Several syntheses of ( $\pm$ )-**1** have been reported,<sup>7</sup> 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 ( $\pm$ )-4,5-epoxy-(2*E*)-pentenoate (**7**) and 3,4-dimethoxytoluene in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to give ( $\pm$ )-**5** (46% yield) as a major product and ( $\pm$ )-2-aryl-5-hydroxy-(2*E*)-penenoate (**6**) (18% yield) as a minor product.<sup>8</sup> When the optically active (*S*)-**7** instead of ( $\pm$ )-**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.<sup>9</sup> In order to confirm this assumption,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated reaction of (*S*)-**7** possessing 93% enantiomeric excess (ee)<sup>9</sup> and 3,4-dimethoxytoluene was carried out, and the obtained mixture of **5** and **6** was subjected



Scheme 1

to oxidation with MnO<sub>2</sub> followed by chromatographic separation to provide (+)-5 (46% yield, [α]<sub>D</sub><sup>20</sup> +22.7° (c=0.33, CHCl<sub>3</sub>)) 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, [α]<sub>D</sub><sup>20</sup> +3.4° (c=0.29, CHCl<sub>3</sub>)), which was subjected to a catalytic hydrogenation to afford (*S*)-10 ([α]<sub>D</sub><sup>20</sup> +7.1° (c=0.31, CHCl<sub>3</sub>)) in 96% yield. NaBH<sub>4</sub> reduction of (*S*)-10 gave the (*S*)-4-arylpentanoate (11) ([α]<sub>D</sub><sup>20</sup> +19.3° (c=0.71, CHCl<sub>3</sub>)) in 63% yield, which was subjected to alkaline hydrolysis to provide the corresponding carboxylic acid ((*S*)-4) ([α]<sub>D</sub><sup>20</sup> +17.3° (c=0.23, CHCl<sub>3</sub>)) in quantitative yield. Treatment of (*S*)-4 and P<sub>2</sub>O<sub>5</sub> in methanesulfonic acid (MsOH) provided (*S*)-4,5-dimethyl-1-tetralone derivative (12) ([α]<sub>D</sub><sup>20</sup> +34.9° (c=0.64, CHCl<sub>3</sub>)) in 86% yield, which was subjected to a catalytic hydrogenolysis to afford (*S*)-4,5-dimethyl-5,6,7,8-tetrahydronaphthalene derivative (3) ([α]<sub>D</sub><sup>20</sup> -8.8° (c=0.81, CHCl<sub>3</sub>)) in 94% yield. By applying the Mukaiyama's Friedel-Crafts acylation method,<sup>10</sup> (*S*)-3 was converted to (*S*)-3-acetyl-4,5-dimethyl-5,6,7,8-tetrahydronaphthalene derivative (13) ([α]<sub>D</sub><sup>20</sup> -12.6° (c=0.29, CHCl<sub>3</sub>)) in 68% yield. AlCl<sub>3</sub>-Mediated selective demethylation at the *ortho*-substituted methoxyl group of benzoyl moiety by our method<sup>11</sup> 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,  $[\alpha]_{\text{D}} -11.3^\circ$  ( $c=0.24$ ,  $\text{CHCl}_3$ )). Methoxycarbonylmethylation of phenolic hydroxyl group of (*S*)-**14** was achieved by treatment with bromoacetate and  $\text{K}_2\text{CO}_3$  to give (*S*)-**15** ( $[\alpha]_{\text{D}} -11.0^\circ$  ( $c=0.28$ ,  $\text{CHCl}_3$ )) in 96% yield. Alkaline hydrolysis of (*S*)-**15** afforded the corresponding carboxylic acid ((*S*)-**16**) ( $[\alpha]_{\text{D}} -11.5^\circ$  ( $c=0.20$ ,  $\text{CHCl}_3$ )) in 98% yield, which was treated with  $\text{AcONa}/\text{Ac}_2\text{O}$  to provide the furotetralin derivative ((*S*)-**2**) ( $[\alpha]_{\text{D}} +6.7^\circ$  ( $c=0.10$ ,  $\text{CHCl}_3$ )) in 70% yield. Finally, demethylation of (*S*)-**2** using boron tribromide ( $\text{BBr}_3$ ) gave the synthetic cacalol ((*S*)-**1**) ( $[\alpha]_{\text{D}} +12.5^\circ$  ( $c=0.12$ ,  $\text{CHCl}_3$ )) in 60% yield, whose spectral data were identical with those ( $[\alpha]_{\text{D}} +10^\circ$  ( $\text{CHCl}_3$ ),<sup>1</sup> and  $^1\text{H-NMR}$ <sup>2</sup>) of the natural (*S*)-**1**. Moreover, the physical data ( $[\alpha]_{\text{D}} -4.9^\circ$  ( $c=0.14$ ,  $\text{CHCl}_3$ ), and  $^1\text{H-NMR}$ ) of the acetylated product ((*S*)-**17**) were also identical with those ( $[\alpha]_{\text{D}} -9^\circ$  ( $\text{CHCl}_3$ ),<sup>1</sup> and  $^1\text{H-NMR}$ <sup>4b</sup>) for ( $\pm$ )-**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  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated reaction of (*S*)-4,5-epoxy-(2*E*)-pentoate (**7**) with 3,4-dimethoxytoluene to give (*S*)-4-aryl-5-hydroxy-(2*E*)-pentoate (**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.  $^1\text{H-NMR}$  spectra were recorded by a JEOL AL 400 spectrometer (Tokyo, Japan). Spectra were taken with 5-10% (w/v) solution in  $\text{CDCl}_3$  with  $\text{Me}_4\text{Si}$  as an internal reference. The fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-600H (matrix; Dithiothreitol :  $\beta$ -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)<sup>9</sup> and 3,4-dimethoxytoluene (14.3 g, 94.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (8.9 g, 62.7 mmol) at  $-78^\circ\text{C}$ , 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  $\text{MgSO}_4$  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  $\text{CH}_2\text{Cl}_2$  (300 mL) was added  $\text{MnO}_2$  (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 ( $\pm$ )-**5**.<sup>8</sup> (*S*)-**5**:  $[\alpha]_{\text{D}}^{29} +22.7^\circ$  ( $c=0.33$ ,  $\text{CHCl}_3$ ) corresponding to 93% ee, CHIRALCEL OD, eluent, *n*-hexane:EtOH:*iso*-PrOH = 60:1:1,  $t_{\text{R}}=47.7$  min (96.5%),  $t_{\text{R}}=60.0$  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  $\text{CH}_2\text{Cl}_2$  (15 mL) and pyridine (10 mL) was added TsCl (5.5 g, 28.7 mmol) at  $0^\circ\text{C}$  and the mixture was stirred for 3 h at  $0^\circ\text{C}$ . The reaction mixture was diluted with  $\text{H}_2\text{O}$  and extracted with AcOEt. The organic layer was washed with 2M aqueous HCl, 7% aqueous  $\text{NaHCO}_3$  and brine, and dried over  $\text{MgSO}_4$ . 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**:  $[\alpha]_{\text{D}}^{27} +3.4^\circ$  ( $c=0.29$ ,  $\text{CHCl}_3$ ), IR (neat):  $1722\text{ cm}^{-1}$ ; 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)<sub>2</sub>-C (0.4 g) in MeOH (40 mL) was vigorously stirred under H<sub>2</sub> 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**:  $[\alpha]_D^{25} +7.1^\circ$  ( $c=0.31, CHCl_3$ ), 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<sub>4</sub> (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<sub>3</sub> 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<sub>4</sub>. 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**:  $[\alpha]_D^{27} +19.3^\circ$  ( $c=0.71, CHCl_3$ ), 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<sub>4</sub>. 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**:  $[\alpha]_D^{25} +17.3^\circ$  ( $c=0.23, CHCl_3$ ), 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<sub>2</sub>O<sub>5</sub> (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<sub>4</sub>. 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**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +34.9° (c=0.64, CHCl<sub>3</sub>), IR (neat): 1683 cm<sup>-1</sup>; 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<sub>14</sub>H<sub>18</sub>O<sub>3</sub>: C, 71.77; H, 7.74. Found: C, 71.35; H, 7.69. FAB MS *m/z*: 235 (M<sup>+</sup>+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)<sub>2</sub>-C (0.8 g) and acetic acid (24 mL) in THF (72 mL) was vigorously stirred under H<sub>2</sub> 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<sub>3</sub> and brine, dried over MgSO<sub>4</sub>. 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**: [ $\alpha$ ]<sub>D</sub><sup>24</sup> -8.8° (c=0.81, CHCl<sub>3</sub>), IR (neat): 1597 cm<sup>-1</sup>; 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<sub>14</sub>H<sub>20</sub>O<sub>2</sub>: C, 76.33; H, 9.15. Found: C, 76.84; H, 9.31. FAB MS *m/z*: 220 (M<sup>+</sup>).

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

AlCl<sub>3</sub> (0.18 g, 1.37 mmol) and AgClO<sub>4</sub> (0.29 g, 1.37 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were stirred for 30 min at rt. A solution of (*S*)-**3** (0.28 g, 1.25 mmol) and Ac<sub>2</sub>O (0.64 g, 6.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> and extracted with AcOEt. The organic layer was washed with brine and dried over MgSO<sub>4</sub>. 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**: [ $\alpha$ ]<sub>D</sub><sup>24</sup> -12.6° (c=0.29, CHCl<sub>3</sub>), IR (neat): 1702 cm<sup>-1</sup>; 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<sub>16</sub>H<sub>22</sub>O<sub>3</sub>: C, 73.25; H, 8.45. Found: C, 72.75; H, 8.61. FAB MS *m/z*: 263 (M<sup>+</sup>+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<sub>3</sub> (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<sub>4</sub>. 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*<sub>R</sub>=27.0 min (96.5%), *t*<sub>R</sub>=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; [α]<sub>D</sub><sup>25</sup> -11.3° (c=0.24, CHCl<sub>3</sub>), IR (KBr): 1677, 3315 cm<sup>-1</sup>; 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<sub>15</sub>H<sub>20</sub>O<sub>3</sub>·1/2H<sub>2</sub>O: C, 70.01; H, 8.23. Found: C, 70.32; H, 8.08. FAB MS *m/z*: 249 (M<sup>+</sup>+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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O, extracted with AcOEt. The organic layer was washed with saturated aqueous NH<sub>4</sub>Cl, brine and dried over MgSO<sub>4</sub>. 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**: [α]<sub>D</sub><sup>25</sup> -11.0° (c=0.28, CHCl<sub>3</sub>), IR (neat): 1701, 1766 cm<sup>-1</sup>; 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<sub>18</sub>H<sub>24</sub>O<sub>5</sub>: C, 67.48; H, 7.55. Found: C, 67.16; H, 7.65. FAB MS *m/z*: 320 (M<sup>+</sup>).

**(*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<sub>4</sub>. 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**: [α]<sub>D</sub><sup>22</sup> -11.5° (c=0.20, CHCl<sub>3</sub>), IR (neat): 1699, 1737 cm<sup>-1</sup>; 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<sub>17</sub>H<sub>22</sub>O<sub>5</sub>: C, 66.65; H, 7.24. Found: C, 66.14; H, 7.39. FAB MS *m/z*: 307 (M<sup>+</sup>+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<sub>2</sub>O (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<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. 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**: [α]<sub>D</sub><sup>25</sup> +6.7° (c=0.10, CHCl<sub>3</sub>), IR (neat): 2927 cm<sup>-1</sup>; 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<sub>16</sub>H<sub>20</sub>O<sub>2</sub>: C, 78.65; H, 8.25. Found: C, 78.80; H, 8.71. FAB MS *m/z*: 244 (M<sup>+</sup>).

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

To a solution of (*S*)-**2** (0.083 g, 0.34 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added 1.0 M BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>Cl and extracted with AcOEt. The organic layer was washed with brine and dried over MgSO<sub>4</sub>. 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**: [α]<sub>D</sub><sup>27</sup> +12.5° (c=0.12, CHCl<sub>3</sub>), 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<sub>2</sub>O (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<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. 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; [α]<sub>D</sub><sup>24</sup> -4.9° (c=0.14, CHCl<sub>3</sub>), IR (KBr): 1768 cm<sup>-1</sup>; 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<sub>17</sub>H<sub>20</sub>O<sub>3</sub>: C, 74.97; H, 7.40. Found: C, 74.66; H, 7.43. FAB MS *m/z*: 273 (M<sup>+</sup>+1).

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