Enantioselective Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopherol (Vitamin E) Based on Enzymatic Function[1)]

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Syntheses of (*S*)-chroman-2-carboxaldehyde congener 1 and (*S*)-chiral isoprene unit 3 were achieved based on the enzymatic acetylation of (±)-chroman-2-methanol 6 and (±)-(2,3)-*anti*-2-methyl-3-(*p*-methoxyphenyl)-1,3-propane diol 12, respectively. Synthesis of the side-chain part corresponding to (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol 27 was achieved by the coupling reaction of (*S*)-3 and (*R*)-3,7-dimethyloctyl iodide 4. The Wittig reaction of (3*R*,7*R*)-phosphonium salt 2 derived from (3*R*,7*R*)-27 and (*S*)-1 gave the olefin 28 which was subjected to catalytic hydrogenation to afford (2*R*,4′*R*,8′*R*)-α-tocopherol.

Key words enantioselective acetylation; lipase; total synthesis; Vitamin E; (2*R*,4′*R*,8′*R*)-α-tocopherol

α-Tocopherol, a potent antioxidant and radical scavenger in chemical and biological systems, has increasingly been receiving attention in clinical and nutritional applications in human health. Therefore, attempts have been made to develop an efficient and stereocontrolled synthesis of the natural form of α-Tocopherol.[2)] In terms of synthetic strategy, we considered the final carbon–carbon bond formation stage of our approach as involving a Wittig coupling of the chiral chroman-2-carboxaldehyde congener (*S*)-**1** with the 15-carbon phosphonium salt (3*R*,7*R*)-**2**. The chiral chroman part would be obtained based on the enantioselective acetylation of the racemic chroman diol (±)-**6**. The synthetic strategy for the side-chain moiety corresponding to the phosphonium salt (3*R*,7*R*)-**2** was based on the use of the chiral isoprene unit (*S*)-**3** in which the phenylsulfonyl group represents a reactive function capable of coupling with a ten-carbon synthon such as (3*R*)-3,7-dimethyloctyl iodide **4**.[3)] In this paper, we wish to describe the syntheses of the chiral chroman aldehyde (*S*)-**1** and chiral isoprene unit (*S*)-**3** based on enzymatic acetylation and their application to the total synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol.

1) Synthesis of the Chiral Chroman Aldehyde (*S*)-1 Reduction of the commercially available (±)-chroman-2-carboxylic acid **5** with $LiAlH_4$ was reported to give the (±)-chroman-2-methanol **6** in 42% yield.[1)] In order to improve the yield of (±)-**6**, the following four synthetic steps were undertaken to afford (±)-**6** in 81% overall yield from (±)-**5**.

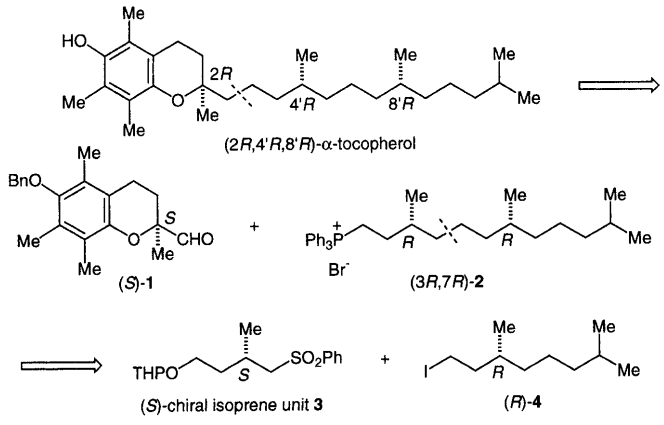


Chart 1

Esterification of (±)-**5** with CH_2N_2 provided the corresponding methyl ester (±)-**7** (98% yield), which was treated with benzyl bromide (BnBr) and K_2CO_3 in acetone to give the benzyl ether (±)-**8** (93% yield). Reduction of (±)-**8** afforded an alcohol (±)-**9** (99% yield) which was subjected to catalytic hydrogenation to provide the desired (±)-**6** in 90% yield.

From a screening experiment for (±)-**6** using several kinds of commercially available lipases, lipase PL-266 from *Alcaligenes* sp. was found to be effective and the result is shown in Table 1. When vinyl acetate was employed as the acylating reagent (entry 1), (*S*)-acetate **10** (67% ee) and (*R*)-unchanged **6** (>99% ee) were obtained in 58% and 39% yields, respectively. Deprotection of (*S*)-**10** (67% ee) with $LiAlH_4$ gave the (*S*)-**6** (67% ee), which was repeatedly subjected to enzymatic acetylation to provide (*S*)-**10** (77% yield, >99% ee) and (*R*)-**6** (18% yield, 74% ee). The enantiomeric excess (ee) of the

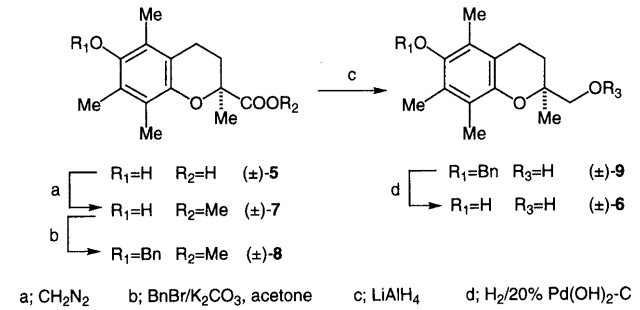
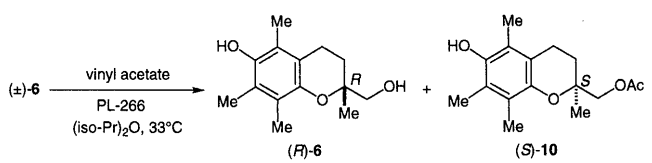


Chart 2

Table 1



Entry	Substrate (mg)	Time (h)	Products (%, % ee)	
1	(±)-**6** (788)	6	(*R*)-**6** (39, >99)	(*S*)-**10** (58, 67)
2	(*S*)-**6** (67% ee, 422)[a)]	4	(*R*)-**6** (18, 74)	(*S*)-**10** (77, >99)

a) (*S*)-**6** (67% ee) was obtained by the reduction of (*S*)-**10** (67% ee) with $LiAlH_4$.

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(*R*)-unchanged **6** was determined by HPLC analysis on a Chiralcell OD column (250 mm×4.6 mm), while that of (*S*)-acetate **10** was confirmed by HPLC analysis of the corresponding diol (*S*)-**6** derived from the enzymatic product (*S*)-**10**. The absolute stereochemistry of the unchanged **6** was determined to be *R*-configuration by the fact that spectral data of the unchanged **6** ($[\alpha]_D$ +2.0 (c=1.0, CH_2Cl_2) corresponding to >99% ee) were identical with those of the authentic (*S*)-**6**[4] ($[\alpha]_D$ −2.36 (c=1.49, CH_2Cl_2) corresponding to 98% ee) except for the sign of $[\alpha]_D$. Thus, the absolute configuration of (+)-**6** was determined to be *R* and that of the acetate **10** was confirmed to be *S*. Thus obtained (*S*)-**10** was subjected to benzylation with benzyl bromide in the presence of CsF to afford the corresponding benzyl ether (*S*)-**11** (87% yield), which was reduced with $LiAlH_4$ to provide the alcohol (*S*)-**9** (94% yield). Swern oxidation of (*S*)-**9** yielded the corresponding aldehyde (*S*)-**1** ($[\alpha]_D$ +12.6 (c=0.99, $CHCl_3$)) in 95% yield.

2) Synthesis of the Chiral Isoprene Unit (*S*)-3 The optically active (2,3)-*anti*-2-methyl-3-(*p*-methoxyphenyl)-1,3-propane diol **12** involving two stereogenic centers was selected as the target molecule corresponding to the chiral isoprene unit (*S*)-**3** because the *p*-methoxyphenyl group is convertible into a carboxylic acid or its congeners and the benzylic oxygen functional group can be reduced to give a useful chiral synthon possessing one stereogenic center. The Reformatsky reaction of *p*-anisaldehyde and methyl 2-bromopropionate was reported to afford (±)-*syn*-**13** (56% yield) and (±)-*anti*-**14** (42% yield).[5] Treatment of (±)-*syn*-**13** with methane sulfonic acid ($MeSO_3H$) afforded the α,β-unsaturated ester **15** in 95% yield, which was subjected to $LiAlH_4$ reduction to provide the allyl alcohol **16** (90% yield). The stereochemistry of **16** was confirmed by the nuclear Overhauser effect (NOE) observed as shown in Fig 1. Hydroboration reaction of **16** gave the (±)-*anti*-1,3-diol **12** with high *anti*-diastereoselectivity (*anti*/*syn*=61 : 1) and subsequent crystallization provided a single isomer (±)-**12** in 89% overall yield. The ratio of *anti*/*syn* was determined by Chiracel OD column (250 mm×4.6 mm, eluent, *n*-hexane/EtOH/iso-PrOH=300 : 10 : 5; detection, UV at 254 nm; flow rate, 1 ml/1 min, (±)-*anti*-**12**; 21.1 and 21.9 min, (±)-*syn*-**12**; 24.6 and 25.9 min). $LiAlH_4$ reduction of (±)-*anti*-**14** also yielded (±)-**12** in 96% yield.

Initially, (±)-**12** was subjected to a screening experiment using several kinds of commercially available lipases. Among them, lipase Amano P from *Pseudomonas* sp. was found to give the monoacetates (2*R*,3*R*)-**17** (57% yield, 65% ee) and (2*R*,3*R*)-**18** (3% yield, 80% ee), and the unchanged (2*S*,3*S*)-**12** (39% yield, $[\alpha]_D$ −39.8 (c=1.05, $CHCl_3$) corresponding to >99% ee) in the presence of vinyl acetate as an acyl donor as shown in Table 2.

Deprotection of (2*R*,3*R*)-**17** (65% ee) with K_2CO_3 in MeOH gave the (2*R*,3*R*)-**12** (65% ee), which was repeatedly subjected to enzymatic acetylation to afford the monoacetates (2*R*,3*R*)-**17** (76% yield, $[\alpha]_D$ +20.9 (c=1.23, $CHCl_3$) corresponding to 97% ee)) and (2*R*,3*R*)-**18** (3% yield, $[\alpha]_D$ +77.6 (c=1.08, $CHCl_3$) corresponding to 94% ee)) and the unchanged (2*S*,3*S*)-**12** (17% yield, 85% ee). The ee of the enzymatic reaction products was determined by HPLC analysis on a Chiralcell AD or OJ column (250 mm×4.6 mm). Acetylation of (2*R*,3*R*)-**17** (97% ee) followed by recrystallization gave the optically pure diacetate (2*R*,3*R*)-**19** ($[\alpha]_D$ +67.6 (c=1.06, $CHCl_3$)) in 83% overall yield. In order to confirm the absolute structure of the present (+)-**19**, (+)-**19** was successfully converted to the mono alcohol **21**. Catalytic hydrogenolysis of (+)-**19** provided a monoacetate (+)-**20** (77% yield, $[\alpha]_D$ +11.3 (c=1.08, $CHCl_3$)), which was treated with K_2CO_3 in MeOH to afford the alcohol (−)-**21** in 96% overall yield. The spectral data ($[\alpha]_D$ −11.9 (c=1.02, $CHCl_3$)) of **21** were identical with those ($[\alpha]_D$ −8.1 (c=0.64,

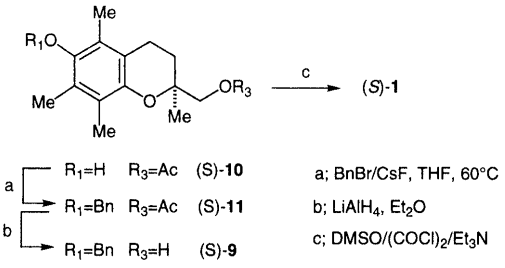


Chart 3

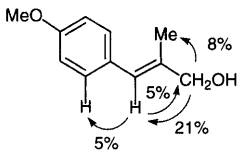


Fig. 1

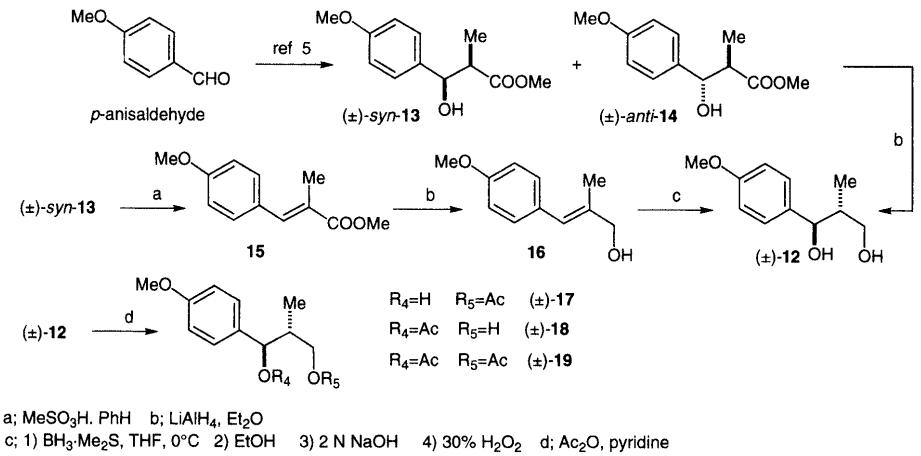
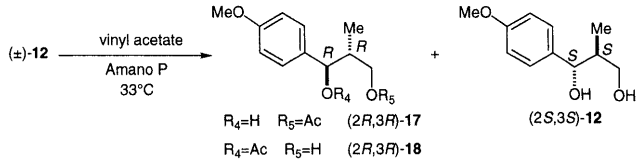


Chart 4

Table 2



Entry	Substrate (g)	Time (h)	Products (%, % ee)		
1	(±)-**12** (12, 38)	1	(2*R*,3*R*)-**17** (57, 65)	(2*R*,3*R*)-**18** (3, 80)	(2*S*,3*S*)-**12** (39, >99)
2	(2*R*,3*R*)-**12** (65% ee, 6.19)[a]	0.5	(2*R*,3*R*)-**17** (76, 97)	(2*R*,3*R*)-**18** (3, 94)	(2*S*,3*S*)-**12** (17, 85)

a) (2*R*,3*R*)-**12** (65% ee) was obtained by treatment of (2*R*,3*R*)-**17** (65% ee) with K_2CO_3 in MeOH.

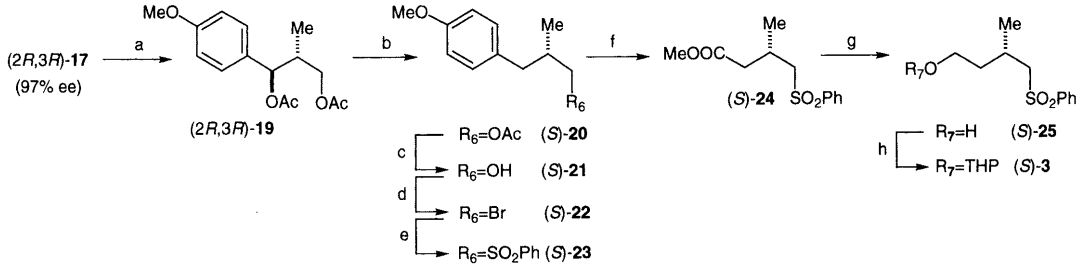


Chart 5

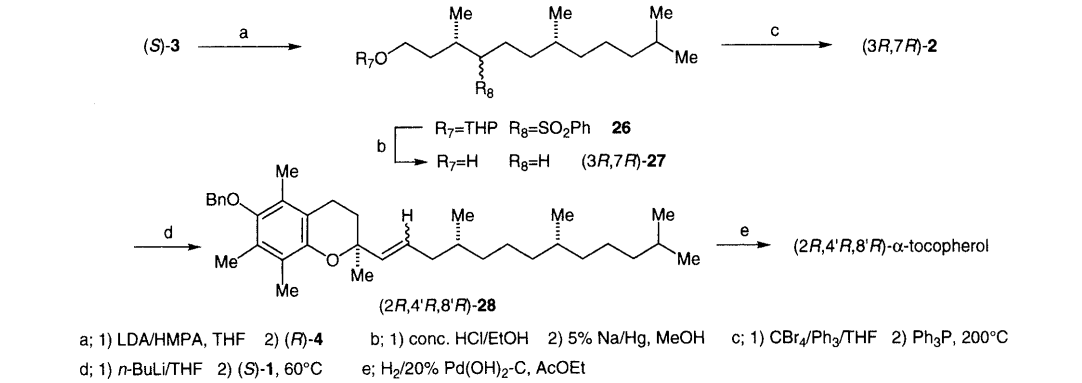


Chart 6

$CHCl_3$)) of the reported for (*S*)-alcohol **21**.[3] Thus, the absolute configurations of (+)-**17** (97% ee) were determined to be 2*R*, 3*R* and those of (−)-**12** (>99% ee) were confirmed to be 2*S*, 3*S*. The absolute configurations of (+)-**18** were determined to be 2*R*, 3*R* by the fact that HPLC analysis pattern of the diol **12** derived from (+)-**18** was found to be opposite in comparison with that of (2*S*,3*S*)-**12** (97% ee). By applying the reported procedure,[3] thus obtained (*S*)-**21** was converted into the desired tetrahydropyranyl (THP) ether (*S*)-**3** in 53% overall yield (5 steps) as shown in Chart 5 and the overall yield (53%) was improved in comparison with the reported one (39%).[3]

3) Total Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopherol The anion of (*S*)-**3** generated by treatment with lithium diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) was subjected to alkylation with the iodide (*R*)-**4**[3] to give the coupling product **26** in 42% yield. Deprotection of the THP group in **26** with acid followed by reduction with Na/Hg in MeOH provided (3*S*,7*S*)-phytol **27** ($[\alpha]_D$ +3.4 (c=1.49, $CHCl_3$)) in 88% overall yield. Bromination of (3*S*,7*S*)-**27** followed by treatment with triphenylphosphine (Ph_3P) gave the phosphonium salt (3*R*,7*R*)-**2**, which was subjected to the Wittig reaction with the (*S*)-chroman aldehyde **1** to afford a mixture of *Z*- and *E*-olefin **28** (*Z*/*E*=14 : 1) in 35% overall yield. Catalytic hydrogenation of **28** provided (2*R*,4′*R*,8′*R*)-α-Tocopherol ($[\alpha]_D$ −2.7 (c=0.59, benzene)) in 86% yield, whose spectral data were identical with those ($[\alpha]_D$ −3.0 (benzene))[6] of natural α-tocopherol.

In conclusion, chiral introductions at the 2*R* and 4′*R* positions in the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (vitamin E) were achieved based on the enzymatic acetylation of (±)-chroman-2-methanol **6** and (±)-(2,3)-*anti*-2-methyl-3-(*p*-methoxyphenyl)-1,3-propane diol **12**, respectively.

Experimental

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL EX 400 spectrometer. Spectra were taken with 5—10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. The mass spectra, FAB and

EI, were obtained with a JEOL JMS-600 and a JEOL JMS-AM II 50 spectrometer, respectively. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl 6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate (±)-7 A solution of (±)-**5** (2.004 g, 8 mmol) in Et_2O (50 ml) was treated with a solution of CH_2N_2 in Et_2O to give a crude product, which was chromatographed on silica gel (70 g, *n*-hexane : AcOEt=10 : 1) to afford colorless powder (±)-**7** (2.082 g, 98% yield). Recrystallization of (±)-**7** from *n*-hexane–AcOEt provided colorless prism (±)-**7**. (±)-**7**: mp 74 °C. MS (EI) *m/z*; 264 (M^+). IR (KBr): 3527, 1737 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.60 (3H, s), 1.86 (1H, ddd, *J*=6, 10.5, 13 Hz), 2.06 (3H, s), 2.15 (3H, s), 2.18 (3H, s), 2.42 (1H, ddd, *J*=3.5, 6.6, 13 Hz), 2.50 (1H, ddd, *J*=6, 10.5, 17 Hz), 2.64 (1H, ddd, *J*=3.5, 6.5, 17 Hz), 3.67 (3H, s), 4.29 (1H, s).

Methyl 6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carboxylate (±)-8 A mixture of (±)-**7** (1.903 g, 7.2 mmol), benzyl bromide (2.6 ml, 21.9 mmol) and K_2CO_3 (1.49 g, 10.8 mmol) in acetone (50 ml) was refluxed for 12 h with stirring and the reaction mixture was filtered. The filtrate was evaporated, diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (70 g, *n*-hexane : AcOEt=20 : 1) to provide colorless powder (±)-**8** (2.371 g, 93% yield). Recrystallization of (±)-**8** from *n*-hexane–AcOEt afforded colorless needles (±)-**8**. (±)-**8**: mp 86.5—87 °C. *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found C, 74.42; H, 7.49. MS (EI) *m/z*; 354 (M^+). IR (KBr): 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.63 (3H, s), 1.86—1.94 (1H, m), 2.14 (3H, s), 2.19 (3H, s), 2.24 (3H, s), 2.42—2.56 (2H, m), 2.61—2.69 (2H, m), 4.70 (2H, s), 7.35 (1H, d, *J*=7 Hz), 7.41 (2H, t, *J*=7 Hz), 7.50 (2H, d, *J*=7 Hz).

6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methanol (±)-9 A solution of (±)-**8** (2.246 g, 6.34 mmol) in dry Et_2O (30 ml) was added to a suspension of $LiAlH_4$ (0.36 g, 9.49 mmol) in dry Et_2O (10 ml) at 0 °C and the whole mixture was stirred for 30 min. It was diluted with aqueous 2 M HCl and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of organic solvent gave a crude product which was chromatographed on silica gel (40 g, *n*-hexane : AcOEt=5 : 1) to afford colorless powder (±)-**9** (2.056 g, 99% yield). Recrystallization of (±)-**9** from *n*-hexane gave colorless prism (±)-**9**. (±)-**9**: mp 62 °C. *Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found C, 77.10; H, 8.15. MS (EI) *m/z*; 326 (M^+). IR (KBr): 3260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.23 (3H, s), 1.73—1.77 (1H, m), 1.94—2.06 (2H, m), 2.10 (3H, s), 2.17 (3H, s), 2.22 (3H, s), 2.61—2.72 (1H, m), 3.58—3.67 (2H, m), 4.70 (2H, s), 7.34 (1H, t, *J*=7 Hz), 7.40 (2H, t, *J*=7 Hz), 7.50 (2H, d, *J*=7 Hz).

6-Hydroxy-2,5,7,8-tetramethylchroman-2-methanol (±)-6 A solution of (±)-**9** (235 mg, 0.72 mmol) in AcOEt (10 ml) was hydrogenated at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$–C (0.1 g). After hydrogen absorption had ceased, the catalyst was filtered off with the aid of Celite and the filtrate was evaporated. The residue was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=4 : 1) to afford colorless powder (±)-**6** (153 mg, 90% yield). Recrystallization of (±)-**6** from AcOEt provided colorless powder (±)-**6**. (±)-**6**: mp 106.5 °C. *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found C, 70.95; H, 8.61. MS (EI) *m/z*; 236 (M^+). IR (KBr): 3421 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.22 (3H, s), 1.73 (1H, ddd, *J*=4.5, 7, 14 Hz), 1.99 (1H, ddd, *J*=7, 9.5, 17 Hz), 2.11 (3H, s), 2.12 (3H, s), 2.16 (3H, s), 2.59—2.73 (2H, m), 3.59 (1H, d, *J*=11 Hz), 3.64 (1H, d, *J*=11 Hz). The racemate (±)-**6** was analyzed to provide well separated peaks (44.9, 57.0 min) corresponding to the enantiomers using Chiralcel OD (4.6 mm×250 mm) under the following analytical conditions (eluent, *n*-hexane/EtOH=40 : 1; detection, UV at 254 nm; flow rate, 1 ml/1 min). On the other hand, the retention time (t_R) of authentic (*S*)-**6** was found to be 57.0 min under the same analytical conditions as (±)-**6**.

Enantioselective Acetylation of (±)-6 with Lipase PL-266 1) A suspension of of (±)-**6** (788 mg, 3.34 mmol), lipase (0.79 g) and vinyl acetate (0.79 g) in iso-Pr_2O (200 ml) was incubated at 33 °C for 6 h. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (30 g) to give acetate (*S*)-**10** (538 mg, 58% yield, 67% ee) from *n*-hexane : AcOEt (10 : 1) eluent and alcohol (*R*)-**6** (307 mg, 39% yield, >99% ee) from *n*-hexane : AcOEt (5 : 1) eluent, respectively. A part of (*R*)-**6** was recrystallized from AcOEt to give colorless prism (*R*)-**6**. (*R*)-**6**: mp 89—89.5 °C. $[\alpha]_D^{24}$ +2.0 (*c*=1.0, CH_2Cl_2). Spectral data (IR and ^{1}H-NMR) were identical with those of (±)-**6**. (*S*)-**10**: MS (EI) *m/z*: 278 (M^+). IR (KBr): 3512, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.28 (3H, s), 1.79 (1H, dt, *J*=7, 12.5 Hz), 1.93 (1H, dt, *J*=7, 12.5 Hz), 2.09 (3H, s), 2.11 (3H, s), 2.15 (3H, s), 2.63 (2H, t, *J*=7 Hz), 4.08 (1H, d, *J*=11 Hz), 4.14 (1H, d, *J*=11 Hz). 2) A suspension of (*S*)-**10** (67% ee, 499 mg, 1.79 mmol) and $LiAlH_4$ (102 mg, 2.69 mmol) in dry Et_2O (20 ml) was stirred at 0 °C for 1.5 h. The reaction mixture was worked up in the same way as for the preparations of (±)-**9** and (±)-**6** to give (*S*)-**6** (67% ee, 423 mg, t_R=44.9 min (16.5%), t_R=57.0 min (83.5%)). A suspension of (*S*)-**6** (422 mg, 67% ee, 1.79 mmol), lipase (0.42 g) and vinyl acetate (0.42 g) in iso-Pr_2O (60 ml) was incubated at 33 °C for 4 h. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (30 g) to give acetate (*S*)-**10** (383 mg, 77% yield, >99% ee) from *n*-hexane : AcOEt (10 : 1) eluent and alcohol (*R*)-**6** (76 mg, 18% yield, 74% ee) from *n*-hexane : AcOEt (5 : 1) eluent, respectively. A part of (*S*)-**10** was recrystallized from *n*-hexane–AcOEt to give colorless plates (*S*)-**10**. (*S*)-**10**: mp 89 °C. *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 69.04; H, 7.97. Found C, 68.77; H, 7.99. $[\alpha]_D^{22}$ +1.9 (*c*=1.03, $CHCl_3$).

(*S*)-2-Acetoxymethyl-6-benzyloxy-2,5,7,8-tetramethylchromane 11 A mixture of (*S*)-**10** (303 mg, 1.09 mmol), benzyl bromide (0.57 ml, 4.8 mmol) and CsF (743 mg, 4.89 mmol) in tetrahydrofuran (THF) (5 ml) was stirred for 12 h at 60 °C. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to provide a crude oil which was chromatographed on silica gel (30 g, *n*-hexane : AcOEt=20 : 1) to afford homogeneous oil (*S*)-**11** (371 mg, 87% yield). Crystallization of (*S*)-**11** from *n*-hexane provided colorless plates (*S*)-**11**. (*S*)-**11**: mp 39 °C. *Anal.* Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found C, 74.99; H, 7.75. $[\alpha]_D^{22}$ +4.0 (*c*=0.94, $CHCl_3$). MS (EI) *m/z*; 368 (M^+). IR (KBr): 1729 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.30 (3H, s), 1.81 (1H, dt, *J*=7, 12.5 Hz), 1.95 (1H, dt, *J*=7, 12.5 Hz), 2.09 (6H, s), 2.16 (3H, s), 2.22 (3H, s), 2.62 (2H, t, *J*=7 Hz), 4.09 (1H, d, *J*=11 Hz), 4.15 (1H, d, *J*=11 Hz), 4.69 (2H, s), 7.33 (1H, t, *J*=7 Hz), 7.40 (2H, t, *J*=7 Hz), 7.49 (2H, t, *J*=7 Hz).

(*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-methanol 9 A solution of (*S*)-**11** (370 mg, 1.01 mmol) in dry Et_2O (3 ml) was added to a suspension of $LiAlH_4$ (60 mg, 1.56 mmol) in dry Et_2O (2 ml) at 0 °C and the whole mixture was stirred for 30 min at room temperature. It was diluted with aqueous 2 M HCl and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of organic solvent gave a crude product which was chromatographed on silica gel (12 g, *n*-hexane : AcOEt=5 : 1) to afford (*S*)-**9** (310 mg, 94% yield). (*S*)-**9**: $[\alpha]_D^{23}$ +12.6 (*c*=0.99, $CHCl_3$). Spectral data (IR and ^{1}H-NMR) were identical with those of (±)-**9**.

(*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carboxaldehyde 1 To a solution of dimethyl sulfoxide (DMSO, 198 mg, 2.54 mmol) in CH_2Cl_2 (2 ml) was added oxalyl chloride (0.11 ml, 1.32 mmol) at −78 °C and the reaction mixture was stirred for 30 min. A solution of (*S*)-**9** (100 mg, 0.31 mmol) in CH_2Cl_2 (2 ml) was added to the above reaction mixture and the whole was stirred for 30 min. Et_3N (0.7 ml) was added to the above reaction mixture and the whole was stirred at −78 °C for 30 min and at 0 °C for 30 min. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to provide a crude oil which was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=10 : 1) to afford a homogeneous oil (*S*)-**1** (95 mg, 95% yield). Crystallization of (*S*)-**1** from *n*-hexane provided colorless plates (*S*)-**1**. (*S*)-**1**: mp 56 °C. *Anal.* Calcd for $C_{21}H_{24}O_3$: C, 77.45; H, 7.46. Found C, 77.42; H, 7.54. $[\alpha]_D^{23}$ +12.6 (*c*=0.99, $CHCl_3$). MS (EI) *m/z*; 324 (M^+). IR (KBr): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.40 (3H, s), 1.79—1.87 (1H, m), 2.12 (3H, s), 2.20 (3H, s), 2.24 (3H, s), 2.25—2.30 (1H, m), 2.49—2.64 (2H, m), 4.66 (1H, d, *J*=10 Hz), 4.70 (1H, d, *J*=10 Hz), 7.34 (1H, t, *J*=7 Hz), 7.39 (2H, t, *J*=7 Hz), 7.48 (2H, d, *J*=7 Hz), 9.63 (1H, s).

Methyl 2-Methyl-3-(*p*-methoxyphenyl)-(2*E*)-propenoate 16 A mixture of (±)-*syn*-**13** (269 mg, 1.20 mmol) and methanesufonic acid (141 mg, 1.47 mmol) in $CHCl_3$ (4 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to provide a crude oil which was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=20 : 1) to afford homogeneous oil **15** (237 mg, 95% yield). **15**: *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found C, 69.75; H, 7.00. MS (EI) *m/z*; 206 (M^+). IR (neat): 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:2.13 (3H, d, *J*=1.5 Hz), 3.81 (3H, s), 3.83 (3H, s), 6.92 (2H, d, *J*=9 Hz), 7.38 (2H, d, *J*=9 Hz), 7.60 (1H, br s).

2-Methyl-3-(*p*-methoxyphenyl)-(2*E*)-propenol 16 A solution of **15** (3.566 g, 1.20 mmol) in THF (11 ml) was added to a suspension of $LiAlH_4$ (0.8 g, 21.1 mmol) in THF (10 ml) at 0 °C. The whole mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with H_2O and

extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to provide a crude oil which was chromatographed on silica gel (105 g, *n*-hexane : AcOEt=4 : 1) to afford homogeneous oil **16** (2.792 g, 90% yield). Crystallization of **16** from *n*-hexane gave a colorless plate **16**. **16**: mp 62 °C. *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found C, 74.04; H, 7.88. FAB-MS *m/z*; 178 (M^+). IR (KBr): 3349 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (3H, d, *J*=1.5 Hz), 3.80 (3H, s), 4.16 (2H, s), 6.45 (1H, br s), 6.87 (2H, d, *J*=8.5 Hz), 7.21 (2H, d, *J*=8.5 Hz).

(±)-(2,3)-*anti*-2-Methyl-3-(*p*-methoxyphenyl)-1,3-propane Diol 12 Borane–methyl sulfide complex (2 M solution in THF, 10 ml, 20 mmol) was added to a solution of **16** (1.028 g, 5.77 mmol) in THF (3 ml) at 0 °C and the whole was stirred for 2 h at room temperature. EtOH (3 ml), 2 M aqueous NaOH (1 ml) and 30% aqueous H_2O_2 (1.5 ml) were gradually added to the above reaction mixture and the whole was diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to provide a crude oil which was chromatographed on silica gel (35 g, *n*-hexane : AcOEt=1 : 1) to afford 61 : 1 mixture of (±)-(2,3)-*anti*-diol **12** (1.008 g, 89% yield). The ratio of *syn*/*anti* was determined by Chiracel OD column (250 mm×4.6 mm) under the following analytical conditions (eluent, *n*-hexane/EtOH/iso-PrOH=300 : 10 : 5; detection, UV at 254 nm; flow rate, 1 ml/1 min, (±)-*anti*-**12**; 21.1 and 21.9 min, (±)-*syn*-**12**; 24.6 and 25.9 min). Crystallization of **12** from *n*-hexane–AcOEt gave a colorless plate *anti*-**12**. *anti*-**12**: mp 110 °C. *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found C, 67.06; H, 8.22. MS (EI) *m/z*; 196 (M^+). IR (KBr): 3328 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, d, *J*=7 Hz), 1.97—2.07 (1H, m), 3.17 (1H, br s), 3.28 (1H, br s), 3.66—3.74 (2H, m), 3.81 (3H, s), 4.46 (1H, d, *J*=8.5 Hz), 6.88 (2H, d, *J*=8.5 Hz), 7.24 (2H, d, *J*=8.5 Hz).

(±)-(2,3)-*anti*-2-Methyl-3-(*p*-methoxyphenyl)-1,3-propane Diol 12 A solution of **14** (6.261 g, 27.9 mmol) in Et_2O (20 ml) was added to a suspension of $LiAlH_4$ (1.6 g, 42.2 mmol) in Et_2O (130 ml) at 0 °C. The whole mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with 2 M aqueous HCl and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to provide a crude oil which was chromatographed on silica gel (100 g, *n*-hexane : AcOEt=1 : 1) to afford (±)-(2,3)-*anti*-diol **12** (5.252 g, 95% yield). Crystallization of **12** from *n*-hexane–AcOEt gave a colorless plate *anti*-**12**.

Acetylation of (±)-(2,3)-*anti*-2-Methyl-3-(*p*-methoxyphenyl)-1,3-propane Diol 12 A solution of (±)-**12** (331 mg, 1.69 mmol) and Ac_2O (177 mg, 1.73 mmol) in pyridine (5 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with aqueous 2 M HCl, saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of organic solvent gave a crude oil which was chromatographed on silica gel (20 g) to afford (±)-**19** (67 mg, 15% yield) from *n*-hexane : AcOEt=10 : 1 eluent, (±)-**17** as a homogeneous oil (208 mg, 52% yield) and (±)-**18** (10 mg, 2% yield) from *n*-hexane : AcOEt=5 : 1 eluent in elution order, and (±)-**12** (67 mg, 20% recovery) from *n*-hexane : AcOEt=2 : 1 eluent. Crystallization of (±)-**18** from *n*-hexane gave a colorless powder (±)-**18**. Crystallization of (±)-**19** from *n*-hexane provided colorless needles (±)-**19**. (±)-**17**: MS (EI) *m/z* 238 (M^+). IR (neat) 3460, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, *J*=7 Hz), 2.08 (3H, s), 2.11—2.19 (1H, m), 3.80 (3H, s), 4.07 (1H, dd, *J*=4.5, 11 Hz), 4.16 (1H, dd, *J*=5.5, 11 Hz), 4.44 (1H, dd, *J*=3, 8 Hz), 6.88 (2H, d, *J*=8.5 Hz), 7.23 (2H, d, *J*=8.5 Hz). The racemate (±)-**17** was analyzed to provide well separated peaks (28 and 31 min) corresponding to the enantiomers using Chiralcel AD (250 mm×4.6 mm) under the following analytical conditions (eluent, *n*-hexane/EtOH=20 : 1; detection, UV at 254 nm; flow rate, 1 ml/1 min). (±)-**18**: mp 72 °C. MS (EI) *m/z* 238 (M^+). IR (KBr) 3427, 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, *J*=6.5 Hz), 2.06 (3H, s), 2.08—2.17 (1H, m), 3.58 (1H, dd, *J*=4.5, 11 Hz), 3.62 (1H, dd, *J*=4.5, 11 Hz), 3.80 (3H, s), 5.63 (1H, d, *J*=9 Hz), 6.87 (2H, d, *J*=9 Hz), 7.25 (2H, d, *J*=9 Hz). (±)-**19**: mp 66 °C. *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found C, 64.17; H, 7.32. FAB-MS *m/z* 280 (M^+). IR (KBr) 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, *J*=7 Hz), 2.04 (3H, s), 2.07 (3H, s), 2.29—2.37 (1H, m), 3.79 (3H, s), 4.04 (1H, dd, *J*=5, 11 Hz), 4.12 (1H, dd, *J*=6, 11 Hz), 5.60 (1H, d, *J*=8.5 Hz), 6.87 (2H, d, *J*=9 Hz), 7.23 (2H, d, *J*=9 Hz). The racemate (±)-**20** was analyzed to provide well separated peaks (11 and 13 min) corresponding to the enantiomers using Chiralcel AD (4.6 mm×250 mm) under the following analytical conditions (eluent, *n*-hexane/EtOH=50 : 1; detection, UV at 254 nm; flow rate, 1 ml/1 min).

Enantioselective Acetylation of (±)-12 with Lipase Amano P 1) A suspension of (±)-**12** (*ca.* 6 g), lipase (3 g) and vinyl acetate (225 ml) was incubated at 33 °C for 1 h. This scale experiment was carried out two times (total amount (12.38 g) of (±)-**12**). After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (300 g) to give (2*R*,3*R*)-**17** (7.882 g, 57% yield) as a colorless oil from *n*-hexane : AcOEt=4 : 1 eluent, (2*R*,3*R*)-**18** (405 mg, 3% yield, 80% ee) from *n*-hexane : AcOEt=2 : 1 eluent and (2*S*,3*S*)-**12** (4.412 g, 39% yield) from *n*-hexane : AcOEt=1 : 1 eluent. (2*R*,3*R*)-**17**: *Anal.* Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found C, 65.27; H, 7.65. 65% ee, t_R=31 min (82.5%) and t_R=28 min (17.5%). (2*R*,3*R*)-**18**: 80% ee. $[\alpha]_D^{22}$ +66.3 (*c*=1.04, $CHCl_3$). (2*S*,3*S*)-**12**: >99% ee, t_R=36 min (>99%) and t_R=32 min (<0%). $[\alpha]_D^{25}$ −39.8 (*c*=1.05, $CHCl_3$). 2) A suspension of (2*R*,3*R*)-**17** (65% ee, 7.882 g, 33.1 mmol) and K_2CO_3 (5.5 g, 39.9 mmol) in MeOH (100 ml) was stirred for 1.5 h at room temperature. The reaction mixture was evaporated, diluted with saturated brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (100 g) to give (2*R*,3*R*)-**12** (6.19 g, 95% yield) from *n*-hexane : AcOEt=1 : 1 eluent. A suspension of (2*R*,3*R*)-**12** (6.19 g, 31.5 mmol), lipase (3.8 g) and vinyl acetate (250 ml) was incubated at 33 °C for 30 min. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (150 g) to give (2*R*,3*R*)-**17** (5.743 g, 76% yield), (2*R*,3*R*)-**18** (257 mg, 3% yield) from *n*-hexane : AcOEt=4 : 1 eluent in elution order and (2*S*,3*S*)-**12** (1.020 g, 17% yield) from *n*-hexane : AcOEt=1 : 1 eluent. (2*R*,3*R*)-**18**: 94% ee. $[\alpha]_D^{22}$ +77.6 (*c*=1.08, $CHCl_3$). (2*R*,3*R*)-**18**: 97% ee. (2*S*,3*S*)-**12**: 85% ee. 3) A suspension of (2*R*,3*R*)-**18** (80% ee, 60 mg, Table 2, entry 1) and K_2CO_3 (46 mg) in MeOH (2 ml) was stirred for 3 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (10 g) to give (2*R*,3R)-**12** (40 mg) from *n*-hexane : AcOEt=1 : 1 eluent. The ee of the present (2*R*,3*R*)-**12** was estimated by HPLC analysis. 4) A suspension of (2*R*,3*R*)-**18** (94% ee, 61 mg, Table 2, entry 2) and K_2CO_3 (46 mg) in MeOH (2 ml) was stirred for 3 h at room temperature. The reaction mixture was worked up in the same way as for 3) to give (2*R*,3*R*)-**12** (41 mg) from *n*-hexane : AcOEt=1 : 1 eluent. The ee of the present (2*R*,3*R*)-**12** was estimated by HPLC analysis.

(2*R*,3*R*)-(1,3)-Diacetoxy-2-methyl-3-*p*-methoxyphenylpropane 19 A solution of (2*R*,3*R*)-**17** (97% ee, 5.194 g, 21.8 mmol), Ac_2O (12.66 g, 124 mmol) and 4-dimethylaminopyridine (DMAP, 133 mg, 1.1 mmol) in pyridine (20 ml) was stirred for 30 min at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with aqueous 2 M HCl, saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave crude crystal which was recrystallized from *n*-hexane–AcOEt to give optically pure (2*R*,3*R*)-**19** (5.27 g, 83% yield). (2*R*,3*R*)-**19**: mp 66 °C. $[\alpha]_D^{30}$ +67.6 (*c*=1.06, $CHCl_3$).

(2*S*)-1-Acetoxy-2-methyl-3-*p*-methoxyphenylpropane 20 A solution of (2*R*,3*R*)-**19** (1.006 g, 3.59 mmol) in MeOH (10 ml) was hydrogenated at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$–C (0.2 g). After hydrogen absorption had ceased, the catalyst was filtered off with the aid of Celite and the filtrate was evaporated. The residue was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=5 : 1) to afford a colorless oil (2*S*)-**20** (612 mg, 77% yield). (2*S*)-**20**: *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found C, 69.87; H, 8.38. MS (EI) *m/z*; 222 (M^+). $[\alpha]_D^{24}$ +11.3 (*c*=1.08, $CHCl_3$). IR (neat): 1738 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, *J*=7 Hz), 2.06 (3H, s), 2.02—2.08 (1H, m), 2.39 (1H, dd, *J*=8, 13.5 Hz), 2.66 (1H, dd, *J*=6, 13.5 Hz), 3.78 (3H, s), 3.88 (1H, dd, *J*=6.5, 11 Hz), 3.95 (1H, dd, *J*=6, 11 Hz), 6.82 (2H, d, *J*=8.5 Hz),. 7.06 (2H, d, *J*=8.5 Hz).

(2*S*)-2-Methyl-3-*p*-methoxyphenylpropanol 21 A suspension of (2*S*)-**20** (233 mg, 1.05 mmol) and K_2CO_3 (210 mg, 1.5 mmol) in MeOH (5 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (10 g) to give (2*S*)-**21** as a homogeneous oil (182 mg, 96% yield) from *n*-hexane : AcOEt=5 : 1 eluent. (2*S*)-**21**: $[\alpha]_D^{25}$ −11.9 (*c*=1.02, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.10; H, 9.13. Spectral data (IR and ^{1}H-NMR) were identical with those of reported (2*S*)-**21**.[3]

(2*S*)-1-Bromo-2-methyl-3-*p*-methoxyphenylpropanol 22 Triphenylphosphine (Ph_3P, 295 mg, 1.12 mmol) and CBr_4 (372 mg, 1.12 mmol) were added to a solution of (2*S*)-**21** (126 mg, 0.7 mmol) in THF (2 ml) and the resulting solution was stirred for 15 min at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (15 g) to give (2*S*)-**22** as a homogeneous oil (168 mg, 98% yield) from *n*-hexane : AcOEt=5 : 1 eluent. (2*S*)-

22: $[\alpha]_D^{23}$ +28.3 (c=1.21, $CHCl_3$). Spectral data (IR and ^{1}H-NMR) were identical with those of reported (2*S*)-**22**.[3]

(2*S*)-2-Methyl-3-(*p*-methoxyphenyl)-1-phenylsulfonylpropane 23 A mixture of (2*S*)-**22** (1.543 g, 6.34 mmol) and sodium benzenesulfinate ($PhSO_2Na \cdot 2H_2O$, 5.03 g, 25.1 mmol) in dimethylforamide (DMF, 30 ml) was heated at 100 °C for 1 h with stirring, then diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (30 g) to give (2*S*)-**23** as a homogeneous oil (1.548 g, 80% yield) from *n*-hexane : AcOEt=5 : 1 eluent. Spectral data (IR, ^{1}H-NMR) were identical with those of reported (2*S*)-**23**.[3]

Methyl (3*S*)-3-Methyl-4-phenylsulfonylbutanoate 24 Ozone was passed through a solution of (2*S*)-**23** (1.517 g, 4.98 mmol) in AcOEt (20 ml) at −78 °C for 2.5 h, then 30% aqueous H_2O_2 (10 ml) was added to the ozonolyzed product. The reaction mixture was stirred for 10 min at room temperature, then diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to afford a crude product which was treated with CH_2N_2 in Et_2O to provide an oily product. This was subjected to chromatographic separation on silica gel (50 g) to give (2*S*)-**24** as a homogeneous oil (1.063 g, 83% overall yield) from *n*-hexane : AcOEt=5 : 1 eluent. Spectral data (IR, ^{1}H-NMR) were identical with those of reported (3*S*)-**24**.[3]

(3*S*)-3-Methyl-4-phenylsulfonylbutanol 25 $LiBH_4$ (157 mg, 7.21 mmol) was added to a solution of (2*S*)-**24** (1.063 g, 4.15 mmol) in THF (20 ml) at 0 °C and the whole was stirred for 12 h at 60 °C. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (30 g) to give (3*S*)-**26** as a homogeneous oil (812 mg, 86% yield) from *n*-hexane : AcOEt=1 : 2 eluent. Spectral data (IR, ^{1}H-NMR) were identical with those of reported (3*S*)-**25**.[3]

(3*S*)-3-Methyl-4-phenylsulfonylbutyltetrahydropyranyl Ether 3 A mixture of (2*S*)-**25** (109 mg, 0.47 mmol), 3,4-dihydropyran (DHP) (108 mg, 1.28 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 11 mg, 0.043 mmol) in CH_2Cl_2 (2 ml) was stirred for 12 h at room temperature. The reaction mixture was washed with aqueous $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. The organic layer was evaporated to afford a crude product which was chromatographed on silica gel (15 g) to give (3*S*)-**3** as a homogeneous oil (142 mg, 95% yield) from *n*-hexane : AcOEt=4 : 1 eluent. Spectral data (IR, ^{1}H-NMR) were identical with those of reported (3*S*)-**3**.[3]

(3*R*,7*R*)-3,7,11-Trimethyldodecan-1-ol 27 1) *n*-Butyllithium (*n*-BuLi, 1.6 M in hexane, 10 ml, 16 mmol) was added to a stirred solution of diisopropylamine (2 ml) in THF (7 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 30 min at the same temperature. The resulting LDA-THF solution was added to a solution of (3*S*)-**3** (820 mg, 2.63 mmol) in THF (2 ml) at −78 °C and then HMPA (2 ml) was added. The whole was stirred for 30 min at −78 °C, then a solution of (3*R*)-3,7-dimethyloctyl iodide **4** (523 mg, 1.95 mmol) in THF (3 ml) was added at the same temperature. The reaction mixture was stirred for 30 min at −20 °C and for 30 min at room temperature, then diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (50 g, *n*-hexane : AcOEt=10 : 1) to afford **26** as a homogeneous oil (374 mg, 42% overall yield). 2) A mixture of **26** (374 mg) and concentrated HCl (4 drops) in EtOH (10 ml) was stirred for 12 h at room temperature. The reaction mixture was condensed and diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated with brine and dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (15 g, *n*-hexane : AcOEt=3 : 1) to afford a homogeneous oil (292 mg, 95% yield). 3) 5% Na/Hg (1.688 g, 0.377 mmol) was added to a solution of the above mentioned oil (125 mg, 0.34 mmol) described in 2) in MeOH (5 ml) and the mixture was refluxed for 2.5 h with stirring, then diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=10 : 1) to afford (3*R*,7*R*)-**27** as a homogeneous oil (72 mg, 93% yield). Spectral data (IR, ^{1}H-NMR) were identical with those of reported (3*R*,7*R*)-**27**.[3]

(2*R*,4′*R*,8′*R*)-1′,2′-Dehydro-α-tocopheryl Benzyl Ether 28 1) Triphenylphosphine (Ph_3P, 352 mg, 1.35 mmol) and CBr_4 (445 mg, 1.34 mmol) were added to a solution of (3*R*,7*R*)-**27** (100 mg, 0.44 mmol) in THF (2 ml) and the resulting solution was stirred for 15 min at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (10 g) to give (3*R*,7*R*)-3,7,11-trimethyldodecanyl bromide ($[\alpha]_D^{22}$ −3.1 (c=1.62, *n*-hexane)) as a homogeneous oil (129 mg, quantitative yield) from *n*-hexane eluent. 2) A mixture of (3*R*,7*R*)-3,7,11-trimethyldodecanyl bromide (72 mg, 0.25 mmol) and Ph_3P (72 mg, 0.27 mmol) was heated at 200 °C for 6 h with stirring and the generated phosphonium salt **2** was dissolved in THF (2 ml) after cooling. *n*-BuLi (1.6 M in hexane, 0.14 ml, 0.22 mmol) was added to the above THF-solution at −78 °C under an argon atmosphere and the whole was stirred for 30 min at the same temperature. A solution of chroman aldehyde (*S*)-**1** (81 mg, 0.25 mmol) in THF (2 ml) was added to the above phosphine-ylide at −78 °C. The whole was stirred at −78 °C for 30 min, at 0 °C for 30 min and heated at 60 °C for 2.5 h. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (10 g) to give a mixture of *Z*- and *E*-(2*R*,4′*R*,8′*R*)-**28** (*Z*/*E*=14 : 1) as a homogeneous oil (45 mg, 35% yield based on (3*R*,7*R*)-**27**)) from *n*-hexane : AcOEt=100 : 1 eluent. (2*R*,4′*R*,8′*R*)-**28**: MS (EI) *m*/*z* 518 (M^+). *Z*-**28**: ^{1}H-NMR ($CDCl_3$) δ: 5.32—5.48 (2H, m, olefinic H). *E*-**28**: ^{1}H-NMR ($CDCl_3$) δ: 5.00 (1H, ddd, J=1.4, 10.7, 17.3 Hz), 5.79 (1H, dd, J=10.7, 17.3 Hz).

(2*R*,4′*R*,8′*R*)-α-Tocopherol A solution of (2*R*,4′*R*,8′*R*)-**28** (43 mg, 0.08 mmol) in AcOEt (2 ml) was hydrogenated at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$–C (16 mg). After hydrogen absorption had ceased, the catalyst was filtered off with the aid of Celite and the filtrate was evaporated. The residue was chromatographed on silica gel (10 g, *n*-hexane : AcOEt=50 : 1) to afford (2*R*,4′*R*,8′*R*)-α-Tocopherol as a homogeneous oil (31 mg, 86% yield). (2*R*,4′*R*,8′*R*)-α-tocopherol: *Anal.* Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found C, 80.77; H, 11.93. $[\alpha]_D^{27}$ −2.7 (c=0.59, benzene). MS (EI) *m*/*z*; 430 (M^+). IR (neat): 3460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—0.87 (12H, m), 1.01—1.63 (24H, m), 1.71—1.84 (2H, m), 2.11 (6H, s), 2.15 (3H, s), 2.59 (2H, t, J=7 Hz), 4.20 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 11.7 (q), 12.3 (q), 12.7 (q), 20.1 (q), 20.2 (q), 21.2 (t), 21.5 (t), 23.1 (q), 23.2 (q), 23.4 (q), 24.9 (t), 25.3 (t), 28.4 (d), 32.0 (t), 33.1 (d), 33.2 (d), 37.7 (t), 37.8 (t), 37.9 (t), 38.0 (t), 39.8 (t), 40.2 (t), 74.8 (s), 117.6 (s), 118.7 (s), 121.2 (s), 122.8 (s), 144.7 (s), 145.7 (s). Spectral data (IR, MS (EI), ^{1}H-NMR and ^{13}C-NMR) were identical with those of (±)-α-Tocopherol.

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References and Notes

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