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A Short and Convenient Chemical Route to Optically Pure 2-Methyl Chromanmethanols. Total Asymmetric Synthesis of β-, γ-, and δ-Tocotrienols

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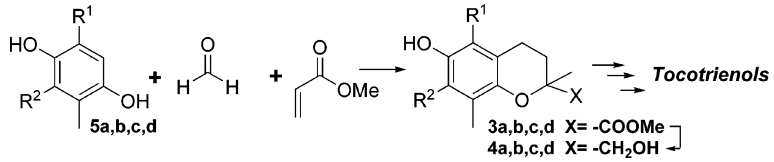

With use of inexpensive commercially available raw materials, chromanmethanol precursors to the natural β-, γ-, and δ-tocotrienols have been prepared in high yield. Enzymatic resolution afforded chiral chromanmethanols in high enantiomeric excess. Subsequent attachment of the farnesyl side chain was high yielding, thus allowing the preparation of asymmetric β-, γ-, and δ-tocotrienols in one final step wherein simultaneous deprotection of the phenol and removal of the sulfone group occurs. This chemistry provides the first synthesis of natural-series β-tocotrienol.

Introduction

Chromans and chromens have attracted the interest of many synthetic groups due to their occurrence in many biologically important compounds.[1] Among them, 2-methyl derivatives, including trolox, MDL-73404, and the natural products clusifoliol, daurichromenic acid, cordiachromene, and Vitamin E components consist of a particularly interesting subgroup.

From a synthetic point of view, setting the chirality at position 2 is the major issue. This has been addressed so far in several ways, including kinetic resolution,[2,3] enzymatic resolution,[4−11] and asymmetric synthesis.[12−24] However, in spite of the high efficiency of both Trost's[14−19] and Tietze's methods[22,24] for

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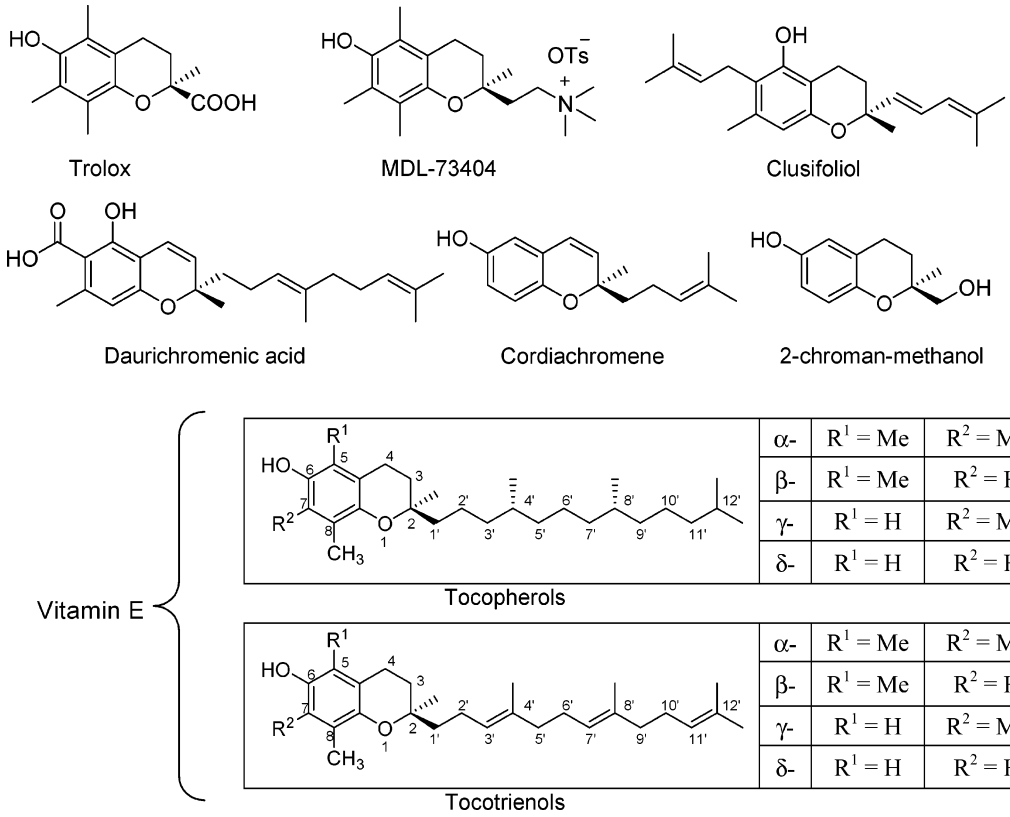
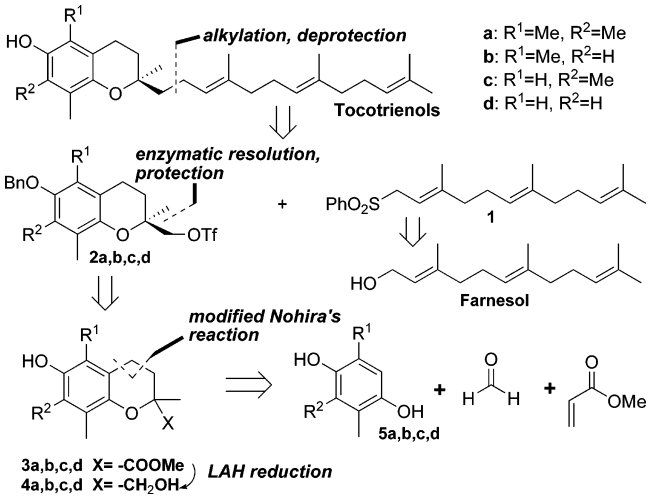


FIGURE 1. Typical chromanes and tocols.

synthesizing optically pure 2-methylchroman derivatives, the pioneering work of the Hoffman-La Roche[25] group and a recent chemoenzymatic synthesis[26] remain the only completed total asymmetric syntheses of any tocotrienols reported so far.[11,25−33]

We would like to report a new convenient chemical route toward chiral chromanols **4** via Trolox type esters **3** (Scheme 1), which may serve as key intermediates for the synthesis of members of the 2-methylchroman family. Our method is potentially scalable and fulfills the following requirements: (a) high availability of relatively inexpensive raw materials, (b) "fast-and-cheap-arrival" to a chiral chroman key intermediate,

SCHEME 1. Retrosynthetic Analysis for Tocotrienols[a]



[a] **a**, **b**, **c**, and **d** refer to α-, *β*-, *γ*-, and *δ*-tocotrienols, respectively.

(c) short synthetic scheme for its transformation to the target molecule, and (d) avoidance of significant isomerization during chemical manipulations. As an application, we report herein the first total synthesis of natural-series *β*-tocotrienol, as well as the synthesis of *γ*- and *δ*-tocotrienols.

Results and Discussion

According to Scheme 1, an efficient disconnection for the formation of tocotrienols would have led to commercially available farnesol and trolox-type esters **3**. Simple conversion to the respective sulfone (**1**) and triflate (**2**) derivatives and

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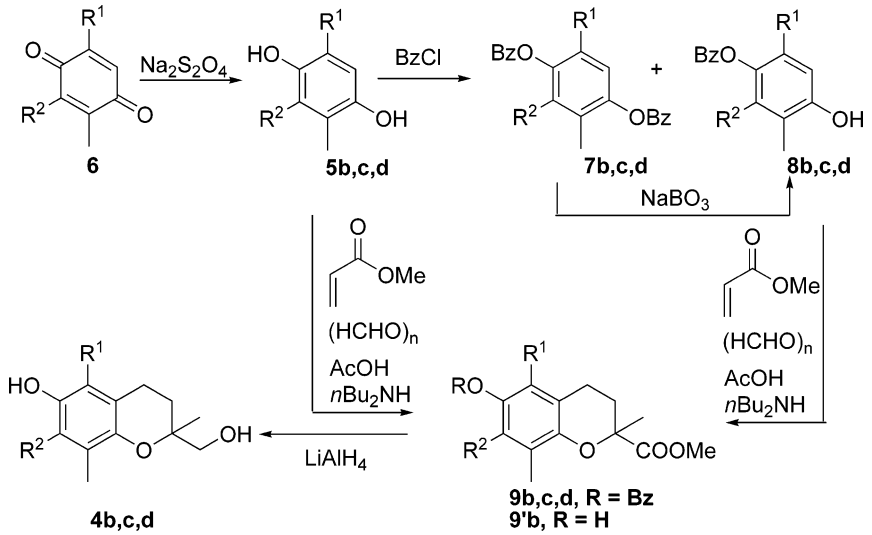
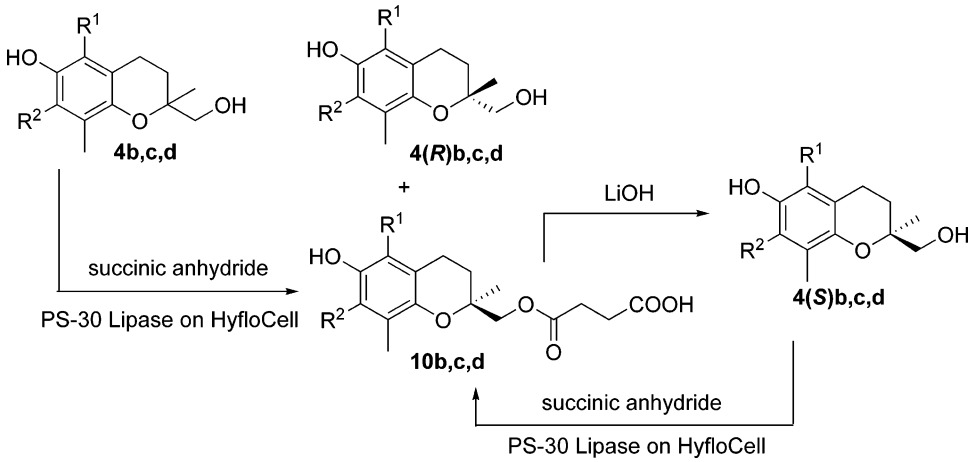
SCHEME 2. Synthesis of Chromanmethanols



SCHEME 3. Resolution of Chromanmethanols[a]



[a] 38−40% total yield, 95.9−97.5% ee after two cycles.

subsequent coupling under alkaline conditions followed by radical desulfonylation would furnish the targeted tocotrienols. Chiral **4** could in turn be derived from its racemates by applying a scalable enzymatic resolution protocol previously established by Hyatt et al.[7] Though there are several approaches toward (±)-**3** or (±)-**4**, we decided to try Nohira's protocol,[3] which has been applied only on unsubstituted hydroquinones. The advantage of this approach, if successful, would be the formation of (±)-**3** in one step, employing only commercially available chemicals. The required hydroquinones **5** are commercially available or can be easily and quantitatively derived by reduction of the appropriate cheaper quinones **6** with sodium dithionite[33] (Scheme 2).

Our synthesis commences with the acylation of **5** with benzoyl chloride, which afforded a 1:4 mixture of di- and monoprotected substrates. However, the dibenzoate byproducts **7** could be selectively hydrolyzed to monobenzoates **8** with use of sodium perborate[34] (the MeOH/MeONa protocol was less selective). Thus, **8** was derived in 70−78% total yield based on **5**. It should be noted that all chemical manipulations in the β, γ, and δ series gave similar results; therefore a range of yields is stated instead of exact numbers per case throughout this article.

The crucial condensation of substituted phenols **8** was then attempted. To our delight, condensation of all phenols with formaldehyde and methyl methacrylate under buffered conditions gave the chroman esters **9** in substantially higher yields than the reported one for the unsubstituted phenol (80−82% vs 30−32%).[3] All attempts to perform the above reaction on unprotected substrate (**5b**) gave significantly lower yields. Finally, esters **9** were converted quantitatively to the desired (±)-**4** alcohols upon simultaneous reduction of the ester group and the benzoyl group.

The resolution of racemic alcohols **4** was accomplished following the reported protocol for **4a** ($R^1 = R^2 =$ Me) as depicted in Scheme 3.[7,35] In a single run the resolution proceeded in 40−45% conversion and 70−87% ee. By repeating the same protocol once more, alcohol **4(*S*)** was obtained in high enantiomeric excess (95.9−97.5% ee) and 38−40% conversion based on racemic **4**.

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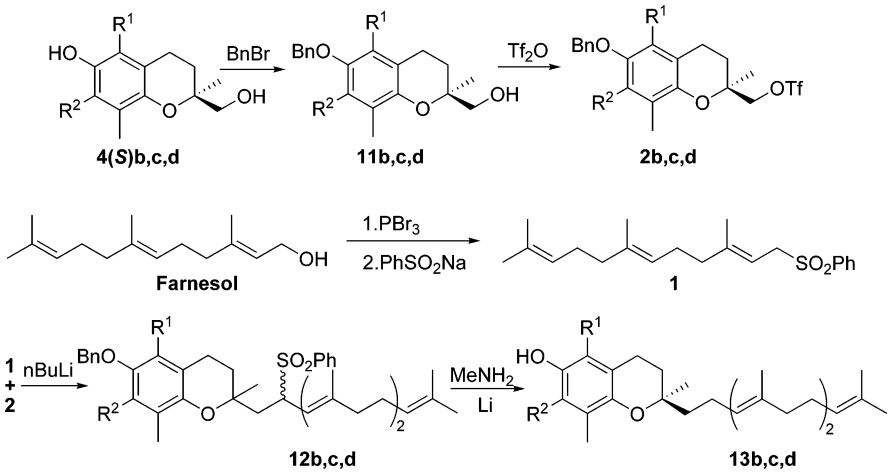
SCHEME 4. Completion of the Total Synthesis of Tocotrienols b, c, and d



While the optical purity of the resolved alcohols was confirmed by chiral column HPLC, the depicted absolute configuration was initially assumed based on analogy to reported data for the α-series[7] and had to be confirmed upon completion of the synthesis. In the event, the enzymatic resolution of **4b** had proceeded in the opposite sense to that of **4c** and **4d**, and provided the heretofore unknown *ent*-*β*-tocotrienol. Thus it was necessary to repeat the synthesis of *β*-tocotrienol by using the opposite enantiomer of **4b** in order to obtain the natural-series final product (vide infra).

Having accomplished the synthesis of the chiral chromanmethanols **4(*S*)b**,**c**,**d** in enantiomerically pure form, the preparations of the appropriate key intermediates **2b**,**c**,**d** and **1** were easy tasks. Indeed, selective benzylation of the phenol followed by sulfonylation of the primary hydroxyl group led to triflates **2b**,**c**,**d**. Farnesyl sulfone **1** was produced from commercially available farnesol via farnesyl bromide in high overall yield,[11] as shown in Scheme 4:

Triflates **2b**,**c**,**d** coupled smoothly with the anion of sulfone **1** to afford coupled intermediates **12b**,**c**,**d** (Scheme 4). Extensive experimentation on the deprotection of the phenol and the removal of the sulfone group was carried out on **12b**. We first used a dissolving-metal reduction method employing Li/naphthalene at −20 °C,[36] whereupon an inseparable mixture of *β*-tocotrienol together with double bond migration and/or *cis*−*trans* isomerization byproducts was obtained. In contrast, the Li/$MeNH_2$ reducing system at −78 °C gave much more promising results.[37] Simultaneous desulfonylation and debenzylation occurred and *β*-, *γ*-, and *δ*-tocotrienols were obtained as colorless liquids. In most runs isomerization was less than 5−8%, observed by ^{1}H NMR spectra.

The optical rotations of our synthetic tocotrienols were compared to those of authentic samples or literature reports. Surprisingly, all were comparable except **13b**, indicating that, only in this case, the enzymatic kinetic resolution gave opposite results. To confirm this hypothesis, the enantiomeric alcohol **4b** was transformed to the related tocotrienol, following the same reaction sequence. The measured optical rotation was this time in agreement with that of an authentic sample of *β*-tocotrienol confirming that the enzymatic resolution of alcohols **4** was dependent on the substitution of the aromatic ring. The final results are summarized in Table 1. The synthetic tocotrienols had NMR spectra identical with those of natural-source material in all cases.

TABLE 1. Comparison of the Optical Rotation between Reported (ref 31) and Synthetic Tocotrienols

		literature	synthetic
β-tocotrienol	**13b**	−1.1, *c* 2.7, $CHCl_3$	−0.9, *c* 0.16, $CHCl_3$
ent-*β*-tocotrienol	*ent*-**13b**		+1.0, *c* 03.0, $CHCl_3$
γ-tocotrienol	**13c**	−5.2, *c* 1.0, $CHCl_3$	−5.7, *c* 0.59, $CHCl_3$
δ-tocotrienol	**13d**	−2.2, *c* 1.0, $CHCl_3$	−1.3, *c* 0.38, $CHCl_3$

Experimental Section

General Procedure for the Preparation of 2,5-Dimethylhydroquinone Monobenzoate 8b, 2,3-Dimethylhydroquinone Monobenzoate 8c, and 20-Methylhydroquinone-4-monobenzoate 8d. A solution of benzoyl chloride (14.5 mmol) in benzene (40 mL) was added dropwise to a solution of hydroquinone **5b**, **5c**, or **5d** (14.5 mmol) in pyridine (10 mL) and benzene (20 mL) at 0 °C for 1 h. The reaction mixture was washed with a saturated aqueous solution of $CuSO_4$ (4 × 20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic phases were washed with brine (3 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (10% EtOAc in hexanes) to yield the monoprotected hydroquinone **8b**, **8c**, or **8d**, along with the diesters **7b**, **7c**, or **7d**, respectively.

2,5-Dimethylhydroquinone dibenzoate 7b: R_f 0.65 (30% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) *δ* 8.22 (4 H, d, *J* = 7.3 Hz), 7.67−7.62 (2 H, m), 7.55−7.49 (4 H, m), 7.06 (2 H, br s), 2.21 (6 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) *δ* 184.9, 146.9, 133.6, 130.2, 129.4, 129.0, 128.6, 124.3, 16.0. IR (neat) *ν* 3036, 2926, 1738.

2,3-Dimethylhydroquinone dibenzoate 7c: R_f 0.80 (30% AcOEt in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) *δ* 8.16 (3 H, d, *J* = 7.1 Hz), 8.07 (1H, d, *J* = 7.1 Hz), 7.60−7.51 (2 H, m), 7.45−7.38 (5 H, m), 6.99 (1 H, s), 2.09 (6 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) *δ* 184.5, 164.7, 147.0, 137.0, 134.3, 133.4, 130.5, 130.3, 130.0, 129.2, 128.7, 128.5, 128.2, 128.1, 12.7. IR (neat) *ν* 3048, 2925, 1743.

Methylhydroquinone dibenzoate7d: R_f 0.62 (30% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 8.27 (4 H, m), 7.68 (2 H, m), 7.56 (4 H, m), 7.02 (3 H, m), 2.31 (3 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 165.0, 164.7, 148.4, 147.0, 133.6, 133.5, 131.7, 130.1, 129.5, 129.3, 128.6, 128.5, 124.0, 122.8, 120.0, 16.4. IR (neat) *ν* 3042, 2923, 1735.

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General Procedure for the Preparation of Monoprotected Hydroquinones 8b, 8c, and 8d from Diprotected Hydroquinones 7b, 7c, and 7d. Compounds **7b**, **7c**, or **7d** (6.4 mmol) and sodium perborate tetrahydrate (13 mmol) were stirred in methanol (10 mL) at 40 °C for 6 h. After completion of the reaction $NaBO_3$ was filtered off and washed with EtOAc (3 × 10 mL). The solvent was removed under reduced pressure and the crude products were purified by flash column chromatography (10% EtOAc in hexanes) to yield compounds **8b**, **8c**, or **8d**, respectively.

8b: Yield 70%. R_f 0.75 (30% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.00 (2 H, m), 7.47−7.39 (1 H, m), 7.33−7.26 (2 H, m), 6.63 (1 H, s), 6.33 (1 H, s), 5.28−5.00 (1 H, br s), 1.96 (3 H, s), 1.89 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 165.9, 151.7, 142.4, 133.6, 130.2, 129.4, 128.6, 128.2, 123.7, 122.7, 117.2, 109.6, 15.8, 15.4. IR (neat) ν 3437, 1716.

8c: Yield 73%. R_f 0.63 (30% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.20 (2 H, m), 7.64−7.58 (1 H, m), 7.52−7.46 (2 H, m), 6.79 (1 H, d, J = 8.7 Hz), 6.59 (1 H, d, J = 8.7 Hz), 4.89 (1 H, br s), 2.1 (3 H, s), 2.08 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 171.1, 165.7, 151.4, 142.8, 133.8, 133.5, 130.2, 129.5, 129.2, 128.6, 128.6, 128.5, 124.2, 120.1, 119.4, 113.0, 13.1, 13.0, 12.1. IR (neat) ν 3441, 1710.

8d: Yield 72%. R_f 0.50 (30% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.21 (2 H, d, J = 7.1 Hz), 7.64 (1 H, m), 7.51 (2 H, m), 6.98−6.81 (2 H, m), 6.69 (1 H, d, J = 8.6 Hz), 5.48 (1 H, br s), 2.22 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 166.2, 151.8, 143.8, 133.6, 130.1, 128.6, 128.5, 125.4, 123.6, 119.6, 115.6, 15.9. IR (neat) ν 3445, 1712.

General Procedure for the Preparation of Methyl 2,5,8-Trimethyl-6-benzoyloxychroman-2-carboxylate 9b, Methyl 2,7,8-Trimethyl-6-benzoyloxychroman-2-carboxylate 9c, and Methyl 2,8-Dimethyl-6-benzoyloxychroman-2-carboxylate 9d. Hydroquinone monobenzoyl ester **8b**, **8c**, or **8d** (13.2 mmol) was added to a mixture of methyl methacrylate (64.5 mmol) and paraformaldehyde (421 mg). The reaction mixture was stirred at 0 °C and dibutylamine (1.6 mmol) and acetic acid (6.6 mmol) were added. Then, the reaction mixture was refluxed for 23 h. The resulting mixture was then poured into a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (10% EtOAc in hexanes) to yield **9b**, **9c**, or **9d**, respectively, as white amorphous solid.

9b: Yield 82%. R_f 0.55 (20% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.11 (2 H, d, J = 7.7 Hz), 7.59−7.48 (1 H, m), 7.46−7.37 (2 H, m), 6.71 (1 H, s), 3.60 (3 H, s), 2.64−2.32 (2 H, m), 2.14 (3 H, s), 1.90 (3 H, s), 1.88−1.73 (2 H, m), 1.53 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 174.1, 165.4, 149.6, 142.0, 133.4, 130.1, 129.7, 128.5, 125.6, 124.6, 121.5, 119.8, 77.2, 52.4, 30.1, 25.4, 20.9, 15.9, 11.9. IR (KBr) ν 2934, 1757, 1732, 1601, 1479, 1450, 1268, 1230, 1102, 1066, 1024, 713. HRMS calcd for $C_{21}H_{22}O_5$ 354.1467; found 354.1439.

9c: Yield 80%. R_f 0.46 (20% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.20−8.16 (2 H, m), 7.63−7.56 (1 H, m), 7.51−7.44 (2 H, m), 6.65 (1 H, s), 3.68 (3 H, s), 2.70−2.64 (2 H, m), 2.41−2.32 (1 H, m), 2.20 (3 H, s), 2.07 (3H, s), 1.92−1.79 (1 H, s), 1.62 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 174.0, 165.5, 149.2, 142.4, 133.4, 130.1, 129.7, 128.5, 125.9, 118.9, 118.1, 78.0, 52.4, 30.2, 29.6, 28.4, 25.5, 12.8, 12.0. IR (KBr) ν 2927, 1740, 1476, 1450, 1233, 1188, 1102, 1027, 893, 712. HRMS calcd for $C_{21}H_{22}O_5$: 354.1467; found 354.1473.

9d: Yield 82%. R_f 0.61 (20% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (2 H, d, J = 7.7 Hz), 7.64 (1 H, m), 7.51 (2 H, m), 6.85 (1 H, d, J = 2.2 Hz), 6.74 (1 H, d, J = 2.2 Hz), 3.73 (3 H, s), 2.73 (2 H, m), 2.42 (1 H, m), 2.28 (3 H, s), 1.91 (1 H, m), 1.66 (3 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 165.7, 149.5, 143.5, 133.4, 130.1, 128.5, 127.4, 121.6, 120.8, 119.1, 78.2, 52.5, 30.3, 25.5, 22.8, 16.1. IR (KBr) ν 2936, 1758, 1738, 1600, 1476, 1451, 1267, 1228, 1110, 1067, 1026, 719. HRMS calcd for $C_{20}H_{20}O_5$ 340.1311, found 340.1326.

General Procedure for the Preparation of 2,5,8-Trimethyl-6-hydroxychroman-2-methanol 4b, 2,7,8-Trimethyl-6-hydroxychroman-2-methanol 4c, and 2,8-Dimethyl-6-hydroxychroman-2-methanol 4d. To a stirred solution of **9b**, **9c**, or **9d** (10.7 mmol) in Et_2O (10 mL) was added LAH (21 mmol) at 0 °C. When the reaction was completed, 1 N HCl was added dropwise and the mixture was stirred for 15 min. The reaction mixture was poured into water, neutralized with $NaHCO_3$, and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (20% EtOAc in hexanes) to yield **4b**, **4c,** or **4d**, respectively.

4b: Yield 98%. R_f 0.58 (50% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.46 (1 H, s), 4.56 (0.5 H, br s (OH)), 3.59 (2.5 H, AB_q, J = 11.4 Hz, $\Delta\nu$ = 15.9 Hz, also OH br s), 2.67−2.60 (2 H, m), 2.07 (6 H, br s), 2.03−1.91 (1 H, m), 1.75−1.65 (1 H, m), 1.19 (3H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 146.2, 144.9, 123.7, 120.2, 115.4, 109.4, 74.8, 69.1, 27.6, 20.3, 20.2, 15.8, 10.9. IR (neat) ν 3747, 3311, 2933, 1705, 1463, 1230. HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1250.

4c: Yield 99%. R_f 0.58 (50% EtOAc in hxanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.35 (1 H, s), 4.99 (1 H, br s), 3.60 (2 H, AB_q, J = 11.3 Hz, $\Delta\nu$ = 16.4 Hz), 2.80−2.56 (2 H, m), 2.11 (3 H, s), 2.06 (3H, s), 2.01−1.89 (1 H, m), 1.68−1.58 (1 H, m), 1.21 (3H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 146.9, 145.0, 128.2, 125.5, 121.8, 118.1, 112.3, 69.1, 29.5, 27.9, 21.9, 20.7, 12.0. IR (neat) ν 3745, 3290, 2930, 1715, 1453, 1210. HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1254.

4d: Yield 99%. R_f 0.48 (50% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.49 (1 H, s), 6.41 (1 H, s), 3.62 (2 H, AB_q, J = 11.4 Hz, $\Delta\nu$ = 16.1 Hz), 2.73 (2 H, m), 2.12 (3 H, s), 1.99 (1 H, m), 1.67 (1 H, m), 1.24 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 148.2, 145.3, 127.3, 123.0, 115.8, 112.6, 76.1, 69.4, 27.7, 22.0, 20.7, 16.1. IR (neat) ν 3737, 3350, 2923, 1708, 1465, 1280. HRMS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1112.

Immobilization of Lipase PS-30. Lipase PS-30 (3 g) and Hyflosupercell (10 g) were added to a buffered solution (10 mL) of Na_2HPO_4 (117.12 mg) and KH_2PO_4 (81.66 mg) in distilled water (30 mL, pH 7) and the mixture was shaken vigorously then dried under high vacuum for 24 h.

General Procedure for the Resolution of the Racemic Chromandiols 4b, 4c, and 4d (First Cycle). A mixture of compound **4a**, **4b,** or **4c** (2 g), hyflosupercell-supported PS-30 lipase (1.3 g), succinic anhydride (1.2 g), and *tert*-butyl methyl ether (33 mL) was stirred at room temperature for 5 h, at which time TLC analysis indicated formation of equal amounts of a polar product and unreacted alcohol. The mixture was diluted with ethyl acetate and acetone, filtered through a pad of Celite, and extracted 5 times with 5% aq sodium bicarbonate. After separation of the two phases, the aqueous layer was carefully acidified with 1 N aq HCl and extracted with ethyl acetate. The solution was dried and the solvent evaporated to give crude succinate **10b**, **10c**, or **10d** as white amorphous solids, which were used without further purification (yields of crude acids were 55−65%).

The acid **10b**, **10c**, or **10d** (1.4 mmol) was dissolved in methanol (8 mL) and THF (8 mL). An aqueous solution of 3 N LiOH (150 μL) was added at 0 °C and the mixture was stirred for 20 min. When the reaction was completed, it was poured into a saturated aqueous solution of ammonium chloride (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (30% EtOAc in hexanes) to yield enriched diols **4(*S*)b**, **4(*S*)c**, or **4(*S*)d**, respectively, as white amorphous solids (yields 90−95%, ee 70−87% (hplc)).

General Procedure for the Resolution of the Enriched Chromandiols 4(*S*)b, 4(*S*)c, and 4(*S*)d (Second Cycle). The enriched diols **4(*S*)b**, **4(*S*)c**, or **4(*S*)d** were subjected to the same protocol as before. The final yields after the two enzymic resolutions are listed below (maximium theoretical yield = 50%). All resolved compounds had spectroscopic data identical with those of the respective racemic diols.

4(*S*)b: Yield 38%. $[\alpha]^{20}_D$ −2.44 (*c* 0.41 in $CHCl_3$). HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1257.

4(*S*)c: Yield 40%. $[\alpha]^{20}_D$ +6.3 (*c* 0.98 in $CHCl_3$). HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1264.

4(*S*)d: Yield 38%. $[\alpha]^{20}_D$ +3.8 (*c* 0.7 in $CHCl_3$). HRMS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1103.

(It must be noted that the compound characterized above as **4-(*S*)b** was found, after completion of the tocotrienol synthesis, to actually be the enantiomeric **4(*R*)b** substance. Recovery of the opposite enantiomer from the enzymatic kinetic resolution gave the true (*S*) enantiomer, which afforded natural-series β-tocotrienol upon completion of the synthesis.)

General Procedure for the Preparation of 2,5,8-Trimethyl-6-benzyloxychroman-2-methanol 11b, 2,7,8-Trimethyl-6-benzyloxychroman-2-methanol 11c, and 2,8-Dimethyl-6-benzyloxychroman-2-methanol 11d. To a stirred solution of compound **4(*S*)b**, **4(*S*)c**, or **4(*S*)d** (1.8 mmol) in DMF (2 mL) were added benzyl bromide (2.68 mmol) and K_2CO_3 (2.68 mmol) at room temperature. When the reaction was completed (12 h), it was neutralized with water and 1 N HCl. It was extracted EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (10% EtOAc in hexanes) to yield **11b**, **11c**, or **11d**, respectively.

11b: Yield 72%. R_f 0.38 (20% EtOAc in hexanes). $[\alpha]^{20}_D$ −0.87 (*c* 0.46 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.26 (4.3 H, m), 6.69 (1 H, s), 5.00 (2 H, s), 3.65 (2.4 H, AB_q, J = 11.1 Hz, $\Delta\nu$ = 19.5 Hz), 2.72−2.66 (2 H, m), 2.18 (6 H, br s), 2.07−2.00 (1 H, m), 1.79−1.76 (1 H, m), 1.26 (3 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.7, 145.5, 137.9, 128.4, 127.6, 127.2, 123.3, 122.9, 120.5, 113.7, 75.1, 71.2, 69.3, 27.6, 20.4, 20.2, 16.2, 11.2. IR (KBr) ν 3300, 2940, 1705, 1440, 1160. HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1720.

11c: Yield 71%. R_f 0.42 (30% EtOAc in hexanes). $[\alpha]^{20}_D$ +0.81 (*c* 0.37 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56−7.27 (5 H, m), 6.53 (1 H, s), 4.99 (2 H, s), 3.64 (2 H, AB_q, J = 11.2 Hz, $\Delta\nu$ = 25.2 Hz), 2.86−2.80 (1 H, m), 2.75−2.69 (1H, m), 2.21 (3 H, s), 2.14 (3H. s), 2.04−1.89 (1 H, m), 1.72−1.67 (1 H, m), 1.26 (6 H, d, J = 4.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3, 160.7, 150.3, 145.4, 137.9, 128.4, 127.6, 127.2, 126.9, 125.9, 125.1, 118.8, 117.5, 110.2, 109.5, 74.5, 70.9, 69.4, 68.3, 66.6, 29.7, 29.2, 29.0, 28.0, 27.8, 22.2, 20.7, 12.3, 12.0. IR (KBr) ν 3350, 2950, 1718,-1260. HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1720.

11d: Yield 73%. R_f 0.54 (30% EtOAc in hexanes). $[\alpha]^{20}_D$ +2.5 (*c* 0.7 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.48−7.27 (5 H, m), 6.67 (1 H, d, J = 2.5 Hz), 6.55 (1 H, d, J = 2.5 Hz), 4.98 (2 H, s), 3.62 (2 H, AB_q, J = 11.3 Hz, $\Delta\nu$ = 16.2 Hz), 2.92−2.64 (2 H, m), 2.15 (3 H, br s), 2.07−1.92 (1 H, m), 1.75−1.62 (1 H, m), 1.25 (3 H, s). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 151.8, 145.6, 137.5, 128.5, 127.8, 127.4, 127.2, 121.0, 115.9, 112.2, 76.1, 70.5, 69.5, 27.7, 22.2, 20.7, 16.2. IR (KBr) ν 3320, 2935, 1708,1220. HRMS calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1559.

General Procedure for the Preparation of 2,5,8-Trimethyl-6-benzyloxychroman-2-methanol Triflate 2b, 2,7,8-Trimethyl-6-benzyloxychroman-2-methanol Triflate 2c, and 2,8-Dimethyl-6-benzyloxychroman-2-methanol Triflate 2d. To a stirred solution of compound **11b**, **11c**, or **11d** (1.3 mmol) in pyridine (2 mL) was added Tf_2O (1.3 mmol) at 0 °C and the mixture was stirred for 2 h. The reaction was quenched with 1 N HCl (2 mL) then extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (20% EtOAc in hexanes) to yield **2b**, **2c**, or **2d**, respectively, as white amorphous solids.

2b: Yield 96%. R_f 0.66 (20% EtOAc in hexanes). $[\alpha]^{20}_D$ −0.23 (*c* 0.51 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.30 (5 H, m), 6.68 (1 H, s), 4.99 (2 H, s), 4.47 (2.4 H, AB_q, J = 10.1 Hz, $\Delta\nu$ = 18.8 Hz), 2.70 (2.2 H, t, J = 6.9 Hz), 2.15 (6.6 H, br s), 2.03−1.96 (1 H, m), 1.89−1.83 (1 H, m), 1.37 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 144.8, 137.9, 128.4, 127.7, 127.3, 123.9, 122.9, 119.5, 117.4, 114.0, 79.6, 71.3, 29.7, 27.9, 21.1, 19.9, 16.0, 11.2. IR (KBr) ν 2936, 1482, 1413, 1245, 1235, 1210, 1151, 962. HRMS calcd for $C_{21}H_{23}F_3O_5S$ 444.1218, found 444.1249.

2c: Yield 95%. R_f 0.72 (30% EtOAc in hexanes). $[\alpha]^{20}_D$ +0.70 (*c* 0.52 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.25 (5 H, m), 6.49 (1 H, s), 4.97 (2 H, s), 4.44 (2 H, AB_q, J = 10.2 Hz, $\Delta\nu$ = 15.4 Hz), 2.76 (2 H, AB_q, J = 8.4 Hz, $\Delta\nu$ = 15.6 Hz), 2.18 (3 H, s), 2.11 (3 H, s), 2.00−1.80 (1 H, m), 1.78−1.70 (1 H, m), 1.37 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 144.5, 137.8, 128.4, 127.7, 127.1, 126.4, 125.5, 121.1, 116.5, 116.1, 109.8, 109.5, 79.6, 73.4, 70.8, 46.5, 29.7, 27.8, 21.7, 21.3. 12.1, 11.8. IR (KBr) ν 3744, 2925, 1542, 1459, 1207, 945. HRMS calcd for $C_{21}H_{23}F_3O_5S$ 444.1218, found 444.1239.

2d: Yield 95%. R_f 0.50 (20% EtOAc in hexanes). $[\alpha]^{20}_D$ +1.96 (*c* 0.97 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.32 (5 H, m), 6.72 (1 H, s), 6.57 (1 H, s), 5.01 (2 H, s), 4.49 (2 H, AB_q, J = 10.2 Hz, $\Delta\nu$ = 18.8 Hz), 2.90−2.73 (2 H, m), 2.19 (3 H, br s), 2.04−1.96 (1 H, m), 1.88−1.81 (1 H, m), 1.41 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 144.8, 137.4, 128.5, 127.8, 127.7, 127.4, 120.0, 116.3, 112.1, 79.5, 73.6, 70.5, 27.8, 21.8, 21.3, 16.0. IR (KBr) ν 2929, 2852, 1604, 1484, 1414, 1250, 1216, 1146, 975, 950, 623. Compound **2d** was unstable and repeatedly failed to give correct elemental analysis or HRMS. However, compounds **12d** and **13d**, prepared sequentially from **2d**, gave satisfactory analytical data.

General Procedure for the Preparation of 2′-Phenylsulfonyl-β-tocotrienyl Benzyl Ether 12b, 2-Phenylsulfonyl-γ-tocotrienyl Benzyl Ether 12c, and 2-Phenylsulfonyl-δ-tocotrienyl Benzyl Ether 12d. *n*-Butyllithium (1.6 M in hexanes, 1.2 mmol) was added dropwise to a stirred solution of *all-trans*-farnesyl benzyl sulfone **1**[11] (0.9 mmol) and HMPA (504 μL) in THF (3 mL) at −78 °C. The orange-colored anion was stirred for 45 min at −78 °C. Then a mixture of compound **2b**, **2c**, or **2d** (1.1 mmol) in THF (350 μL) was added and the mixture was slowly warmed to room temperature over a period of 2 h. The reaction mixture was then poured into a saturated solution of ammonium chloride (5 mL) and 1 N HCl (1 mL) was added. The mixture was then extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (10% acetone in hexanes) to yield **12b**, **12c**, or **12d**, respectively, as light yellow oil.

12b: Yield 62%. R_f 0.48 (20% EtOAc in hexanes). $[\alpha]^{20}_D$ −28.30 (*c* 1.29 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 + 7.79 (2 H, d, J = 7.7 Hz), 7.67−7.30 (8 H, m), 6.63 + 6.62 (1 H, s), 5.19−4.95 (5 H, m), 4.17 + 4.10 (1 H, t, J = 10.2 Hz), 2.67−2.50 (2 H, m), 2.18−1.55 (30 H, m), 1.32−1.16 (3 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.5, 149.4, 145.5, 145.3, 144.6, 144.0, 137.9, 137.7, 137.6, 135.4, 135.3, 133.2, 133.0, 131.1, 129.3, 128.8, 128.5, 128.4, 128.3, 128.2, 127.5, 127.4, 127.1, 124.1, 123.4, 123.4, 123.2, 122.8, 122.7, 119.8, 119.7, 118.9, 118.8, 113.7, 113.6, 73.7, 73.4, 71.2, 71.1, 61.4, 61.0, 39.7, 39.6, 39.5, 37.2, 37.1, 32.1, 31.7, 26.5, 25.9, 25.8, 25.5, 24.0, 23.9, 20.5, 20.3, 17.5, 16.5, 16.4, 16.0, 15.8, 14.0, 11.1, 11.0. IR (neat) ν 3075, 2921, 2852, 1588, 1486, 1308, 1235, 1090, 1030, 842. HRMS calcd for $C_{41}H_{56}NO_4S$ $[M + NH_4]^+$ 658.3930, found 658.3910.

12c: Yield 63%. R_f 0.44 (20% EtOAc in hexanes). $[\alpha]^{20}_D$ +27.87 (*c* 0.94 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 + 7.81 (2 H, d, J = 7.5 Hz), 7.65−7.34 (8 H, m), 6.50 + 6.45 (1 H, s),

5.20−4.99 (5 H, m), 4.19 + 4.11 (1 H, t, J = 9.5 Hz), 2.74−2.58 (2 H, m), 2.20−1.62 (30 H, m), 1.32−1.17 (3 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ150.1, 150.1, 145.0, 144.7, 144.1, 137.9, 137.7, 137.5, 135.5, 135.5, 133.3, 133.1, 131.3, 129.4, 128.9, 128.6, 128.5, 128.3, 128.2, 127.5, 127.5, 127.1, 125.8, 125.5, 124.8, 124.8, 124.1, 123.4, 123.4, 118.9, 118.8, 116.8, 116.8, 110.0, 110.0. IR (neat) ν 2972, 2923, 2857, 2362, 1484, 1447, 1426, 1382, 1302, 1230, 1145, 1100, 1085, 742, 691. HRMS calcd for $C_{41}H_{56}NO_4S$ $[M + NH_4]^+$ 658.3930, found 658.3890.

12d: Yield 60%. R_f 0.40 (20% EtOAc in hexanes). $[\alpha]^{20}_D$ +20.70 (*c* 0.99 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 + 7.82 (2 H, d, J = 7.2 Hz), 7.67−7.31 (8 H, m), 6.70−6.48 (2 H, m), 5.21−4.96 (5 H, m), 4.18 + 4.09 (1 H, t, J = 10.1 Hz), 2.78−2.54 (2 H, m), 2.19−1.57 (27 H, m), 1.32−1.14 (3 H, m). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 151.7, 151.6, 144.7, 144.1, 137.7, 137.6, 137.5, 135.6, 135.5, 133.3, 133.2, 131.3, 129.4, 129.0, 128.6, 128.6, 128.4, 128.3, 127.7, 127.4, 127.1, 126.8, 124.2, 123.4, 123.4, 120.3, 118.9, 118.9, 115.9, 115.8, 112.1, 112.0, 74.7, 74.5, 73.1, 70.4, 61.5, 61.0, 50.1, 39.8, 39.7, 39.6, 37.5, 37.2, 32.1, 31.7, 29.6, 28.0, 26.6, 26.0, 25.9, 25.6, 25.3, 24.2, 24.1, 22.4, 22.2, 21.9, 21.8, 21.3, 17.6, 16.5, 16.4, 16.2, 15.9, 13.4. IR (neat) ν 2972, 2921, 2853, 1603, 1480, 1450, 1304, 1224, 1147, 1086, 1058, 741, 696, 596. HRMS calcd for $C_{40}H_{54}NO_4S$ $[M + NH_4]^+$ 644.3774, found 644.3710.

General Procedure for the Preparation of β-Tocotrienol 13b, γ-Tocotrienol 13c, and δ-Tocotrienol 13d. Li (1.15 mmol) was added to a stirred solution of the sulfone **12b**, **12c**, or **12d** (0.28 mmol) in Et_2O (1.5 mL) and liquid $MeNH_2$ (1.5 mL) at −78 °C. The mixture was colored deep blue and changed to red as the reaction proceeded. After being stirred at −78 °C for 45 min, the reaction was quenched by the dropwise addition of MeOH until the color disappeared. The reaction mixture was allowed to warm at ambient temperature and stirred overnight to evaporate the amine. Then it was poured into a saturated solution of ammonium chloride (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (10% acetone in hexanes) to yield **13b**, **13c**, or **13d**, respectively, as colorless oils.

13b: Yield 72%. R_f 0.20 (10% acetone in hexanes). $[\alpha]^{20}_D$ −0.90 (*c* 0.16 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.45 (1 H, s), 5.17−5.00 (3 H, m), 4.15 (1 H, br s), 2.58 (2 H, t, J = 6.7 Hz), 2.13−1.94 (18 H, m), 1.78 (2 H, m), 1.65 (3 H, s), 1.56 (9 H, br s), 1.22 (3 H, s). ^{13}C NMR ($CDCl_3$, 145.9, 139.9, 135.0, 134.9, 131.2, 124.4, 124.4, 124.2, 123.4, 120.3, 119.2, 115.4, 74.2, 39.7, 39.6, 39.4, 31.5, 26. 8, 26.6, 25.7, 23.7, 22.2, 20.8, 17.7, 16.0, 15.9, 15.8, 10.9. IR (neat) ν 3370, 2945, 2935, 1616, 1450, 1233, 1110. HRMS calcd for $C_{28}H_{42}O_2$ 410.3185, found 410.3196.

13c: Yield 73%. R_f 0.20 (10% acetone in hexanes). $[\alpha]^{20}_D$ −5.7 (*c* 0.59 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (1 H, s), 6.39 (1H, s), 5.17−5.11 (3 H, m), 4.34 (1 H, s), 2.69 (2 H, t, J = 6.3 Hz), 2.19−1.97 (18 H, m), 1.83−1.72 (2 H, m), 1.70 (3 H, s), 1.62 (3 H, s), 1.61 (3H, s), 1.28 (3 H, s). ^{13}C NMR ($CDCl_3$), 146.2, 145.6, 145.5, 139.9, 131.2, 128.3, 125.7, 124.4, 124.3, 124.1, 121.6, 118.2, 112.7, 75.2, 39.8, 39.6, 31.4, 26.7. 26.6, 25.6, 24.3, 24.0, 22.2, 22.2, 17.6, 15.9, 15.8.11.8. IR (neat) ν 2966, 2972, 2854, 1446, 1374, 1227, 1087, 937, 849, 743. HRMS calcd for $C_{28}H_{42}O_2$ 410.3185, found 410.3207.

13d: Yield 75%. R_f 0.12 (10% acetone in hexanes). $[\alpha]^{20}_D$ −1.32 (*c* 0.38 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (1 H, d, J = 2.1 Hz), 6.40 (1 H, d, J = 2.1 Hz), 5.19−5.07 (3 H, m), 4.20 (1 H, br s), 2.71 (2 H, m), 2.15 (3 H, s), 2.11−1.95 (15 H, m), 1.86−1.72 (2 H, m), 1.70 (3 H, s), 1.62 (9 H, br s), 1.28 (3 H, s). IR (neat) ν 3389, 2965, 2932, 2856, 1606, 1473, 1378, 1259, 1221, 1098, 798. HRMS calcd for $C_{27}H_{40}O_2$ 396.3028, found 396.3042.

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Supporting Information Available: General experimental methods, HPLC traces for resolution of **4b**, and ^{1}H and ^{13}C NMR spectra of compounds **2**, **4**, **7**, **8**, **9**, **11**, **12**, and **13** for **b**, **c**, and **d** series. This material is available free of charge via the Internet at http://pubs.acs.org.

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