Synthesis of Phytyl- and Chroman-Derivatized Photoaffinity Labels Based on α-Tocopherol

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Photoaffinity analogues of α-tocopherol have been prepared by substituting photosensitive functional groups at either the terminus of an alkyl chain of varying length mimicking the phytyl tail or on C-3 of the chroman portion of tocopherol. The alkyl chain-modified compounds **2a**−**d** contain a hexyl to nonyl alkyl chain extending from C-2 of the chroman, terminating in a tetrafluoroazidobenzyloxy group. These compounds were prepared starting from the commercially available Trolox acid **4**, followed by esterification, protection, and reduction to the silyl-protected Trolox aldehyde **7**, which was coupled using Wittig chemistry to different ω-hydroxyphosphonium bromides. Reduction of the alkene product, coupling with *p*-azidotetrafluorobenzyl bromide, and deprotection of the phenolic silyl group gave compounds **2a**−**d** in excellent yields. Chroman-functionalized photoaffinity labels were synthesized starting from the protected tocopherol chromene **16b** which was a key intermediate for preparation of a 3-hydroxy derivative, either by reduction of epoxides produced directly with Jacobsen's catalysts or by treatment with NBS in wet DME to give two stereoisomeric bromohydrins which were cyclized and reduced to give the phenol-protected C-3 alcohols **19a**,**b**. These alcohols were then converted to diazoacetate esters, and the protecting group was removed to give 3-diazoacetoxy α-tocopherols **3a**,**b**.

The descriptor "vitamin E" refers to a family of differentially methylated chromanols and related tocotrienols rather than a single compound. While several of these compounds display equivalent or better antioxidant properties in vitro,[1] (2*R*,4′*R*,8′*R*)-α-tocopherol **1** (Figure 1) is the most biologically active. Indeed, it is now confidently accepted that α-tocopherol is the most important lipid soluble antioxidant in plasma.[2] While accounts of the effects of α-tocopherol's antioxidant properties continue to be explored and reported from both chemical[3] and medical[4] perspectives, within the past decade or less, increasing attention has been given to aspects of its biokinetics[5−9] and metabolism.[10−14] Essential components in the biokinetics of tocopherol transport and turnover are α-tocopherol transfer proteins (α-TTPs). Two very similar proteins of approximately 32 kDa have been identified, sequenced, and cloned from both human[15,16] and rat[17] liver. A novel cytosolic protein has recently been reported by Azzi and co-workers.[18] Smaller proteins (∼15 kDa) that bind tocopherol, possibly responsible for intracellular traffic of tocopherol, have also been found in rabbit[19,20] and beef heart.[21,22] A

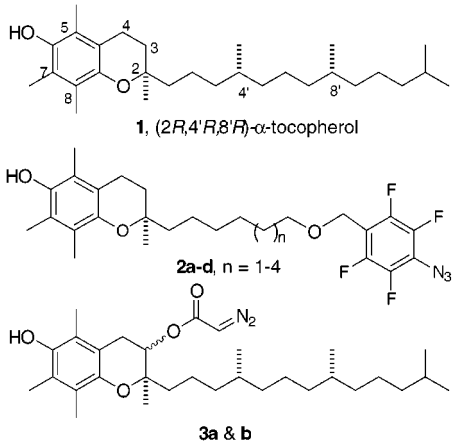

Figure 1. Structures of the natural isomer of α-tocopherol **1**, and six α-tocopherol photoaffinity labels, **2a**−**d** and **3a**,**b**.

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tocopherol binding or transfer protein has also been indicated to occur in salmon liver.[23]

Of equal interest is compelling evidence that α-tocopherol has some biological activities that are not dependent on its action as an antioxidant. Examples include the inhibition of protein kinase C (PKC),[24−28] an enzyme whose activity is strongly linked with the etiology of atherosclercosis,[4] and the modulation of other lipid-dependent enzyme activities such as phospholipase A_2,[29,30] phospholipase D,[31] a diacyl glycerol (DAG) kinase, and a CoA independent transacylase.[32,33] These new biological activities may involve direct tocopherol−protein contact or be mediated by tocopherol's effect on membrane structure and dynamics.[34,35]

Investigations of the role(s) of the α-TTP in liver, the occurrence of other proteins in nonliver tissues capable of binding α-tocopherol, and the modulation of enzyme activity by this vitamin would all benefit if molecular probes were available to confirm and identify those proteins that recognize α-tocopherol as a ligand. To this end we have designed analogues that incorporate photosensitive functional groups as the first examples of α-tocopherol photoaffinity labels. We recently reported our first results on the design and synthesis of such labels[36] and here report further details of our efforts.

Design of Photoaffinity Analogues. Studies on the distribution and chiral discrimination of deuterated (2*R*,4′*R*,8′*R*) and (2*S*,4′*R*,8′*R*)-α-tocopherols[37,38] have shown that the stereochemistry at C-2 dominates the biokinetics[39−44] such that the 2*R*-isomer is preferentially retained by the liver and then redistributed to tissues. In vitro studies of the human α-TTP-catalyzed transfer of ^{3}H-α-tocopherol from liposomes to crude membrane fractions show that *β*-, *γ*-, and *δ*-tocopherol, as well as α-tocopherol acetate, only partially inhibit transfer.[45] This illustrates that the free phenol as well as the three methyl groups at C-5, C-7, and C-8 are required for efficient recognition by the human α-TTP. Work with analogues of α-tocopherol where the phytyl side chain has been replaced by straight chain alkanes has demonstrated that the phytyl methyl substitutions are not mandatory for absorption and activity as antioxidants in rats.[46] This greatly simplifies the synthetic task of making a photoaffinity analogue since preparing a side chain with stereochemically pure methyl groups is considerably more complex. These observations restrict the location for attaching photosensitive groups to the terminus of the phytyl tail and to C-3 or C-4 of the chroman. With these considerations in mind, targets of structure **2** and **3** have been designed as potential photoaffinity ligands of α-tocopherol (Figure 1).

Structures **2a**−**d** have left the chromanol ring system completely unchanged, retaining the critical natural *R*-configuration at C-2. It is important to recognize that labels of type **2** where the side chains are seven or eight methylenes long (as in **2b** or **2c**) are excellent compromises on the structure of the natural ligand.[36] While the phytyl methyl groups have been abandoned, the terminal azidobenzyloxy group closely mimics the final isoprene unit. Indeed, calculations (MacSpartan v.1.17) at the AM1 level showed that the volume and surface area of the final isoprene unit (142.7 Å^3 and 156.3 Å^2) are very similar to that of the benzyl azide (144.2 Å^3 and 169.9 Å^2). The perfluorobenzyl azides were chosen since there is evidence[47] that the nitrene produced on photolysis is more likely to stay in its singlet state and be more reactive toward C−H bond insertion. This is important since the binding site of the α-TTPs is likely made up of a preponderance of hydrophobic amino acid residues.

Synthesis of 2a−d. Producing the proper stereochemistry at C-2 is straightforward for **2** as a short chain α-tocopherol analogue known as Trolox is commercially available (Scheme 1). To link the relatively hydrophilic ring system of Trolox with the hydrophobic tail necessary in the photoaffinity label the carboxylic acid of **4** is first transformed to the methyl ester **5**, and then the phenol is protected as the *tert*-butyldimethylsilyl (TBS) ether to give **6**. The ester group can be reduced selectively to the aldehyde oxidation level using diisobutylaluminum hydride (DIBAL)[48] to generate the (*S*)-Trolox aldehyde, **7**. The designation of the configuration at C-2 changes on going from the aldehyde, which is (*S*), to the long chain compounds which are (*R*). The side chain must incorporate a functional group that can be used to attach the photolabile group, and this has been accomplished by using the *ω*-hydroxyalkyl phosphonium bromides **8a**−**d**.[49,50] Treatment of **8a**−**d** with a strong base generated

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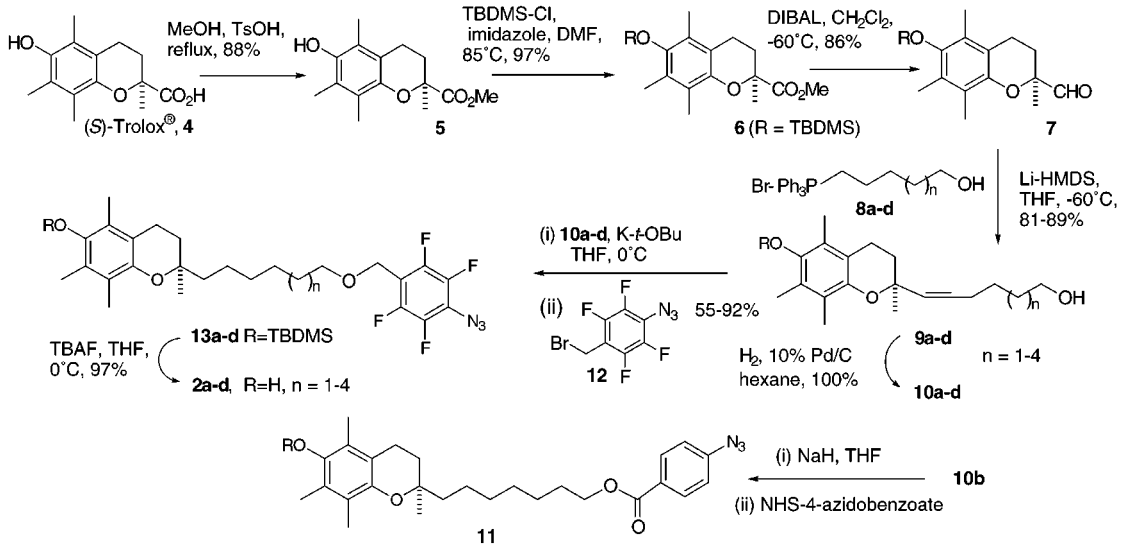
Scheme 1



the ylides which were coupled to the Trolox aldehyde **7** to form the alkenols **9a**−**d**. Yields of the alkenols were consistently 20−30% better using lithium hexamethyldisilylamide (Li-HMDS) rather than methyl or *n*-butyllithium.

Catalytic reduction of the alkenols **9a**−**d** provided saturated side chain analogues of α-tocopherol **10a**−**d** with an appropriate terminal functional group (hydroxyl) for linking to the photolabile group. The photolabile group was synthesized by treating 2,3,5,6-tetrafluoro-4-azidobenzyl alcohol[51] with PBr_3 in refluxing $CHCl_3$ to provide **12**. Several bases were explored for the benzylation of **10a**−**d**. Aqueous bases such as NaOH with phase tranfer catalysts are inappropriate because of the fast substitution of the benzyl bromide by hydroxyl. Sodium hydride in ethereal solvents served only to decompose the azide apparently by reduction to the aniline and several other products. The best yields for the benzylation were achieved utilizing 4 equiv of potassium *tert*-butoxide in THF at 0 °C. Inverting the coupling to the tetrafluorazidobenzyl alcohol and the long chain bromide (not shown) was not successful. Removal of the silyl groups from **13a**−**d** with tetrabutylammonium fluoride (TBAF) was easily accomplished.

As an alternative photoaffinity ligand, azidobenzoate **11** was also prepared by coupling the NHS-ester of 4-azidobenzoic acid to **10b**. Since the free phenols do not store well, only **13b** was desilylated to provide **2b**.

Synthesis of 3a and 3b. To prepare compounds **3a** and **3b**, functionalization at C-3 of tocopherol is required (Scheme 2). This was readily achieved by oxidation of (*R*,*R*,*R*)-α-tocopherol acetate **14** with DDQ in refluxing toluene[52] which gave the chromene acetate **15**. The phenol protecting group must be changed to be compatible with the next steps, and this was accomplished by hydrolyzing the acetate to **16a** with K_2CO_3 in MeOH followed by silylation with *tert*-butyldimethylsilyl triflate giving **16b**. Our intial wish had been to epoxidize the chromene **16b** enantioselectively using Jacobsen's catalysts (*R*,*R*)-(−) or (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride.[53,54]

During our intial attempts, **16b** was slow to react, and any epoxide that was produced was hydrolyzed to a diol that could be detected by mass spectroscopy, but even this represented only a fraction of the starting material—presumably the rest having decomposed. A modification of the original Jacobsen procedure has been described that uses the added ligand 4-(3-phenylpropyl)pyridine *N*-oxide (P_3NO).[55,56] Using this method we were successful in epoxidizing **16b**. Concurrent with these efforts chromene **16b** was treated with NBS in wet DME [57] to generate a near equal mixture of two halohydrins **17a** and **17b**. Fortunately, these were separable by chromatography on a gram scale. This allowed the facile production of the two epoxides **18a** and **18b** by NaH-promoted cyclization. The epoxides cannot be chromatographed on silica, as residual water easily hydrates the compounds to form the diols. This is not that unexpected given the reactivity noted for similar epoxides in the preparation of metabolites of precocenes.[58] Nonetheless, the products from cyclization were pure enough for characterization. Reduction of **18a** and **18b** with $LiAlH_4/AlCl_3$ in THF gave the alcohols **19a** and **19b**, respectively. The regiochemistry of ring opening by $LiAlH_4$ is in accord with that obsrved with simple chroman epoxides.[59]

The stereochemistry of the C-3 alcohols on **19a** and **19b** were assigned on the basis of NOE effects and correlation to identical products prepared using Jacobsen's catalysts. The single proton remaining on C-3 is either cis or trans to the methyl group at C-2 (Figure 2). Irradiation of the C-3 proton resonance at 3.85 ppm gave a large NOE effect for the C-2 methyl resonance at 1.23 ppm in **19a** but none

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Scheme 2

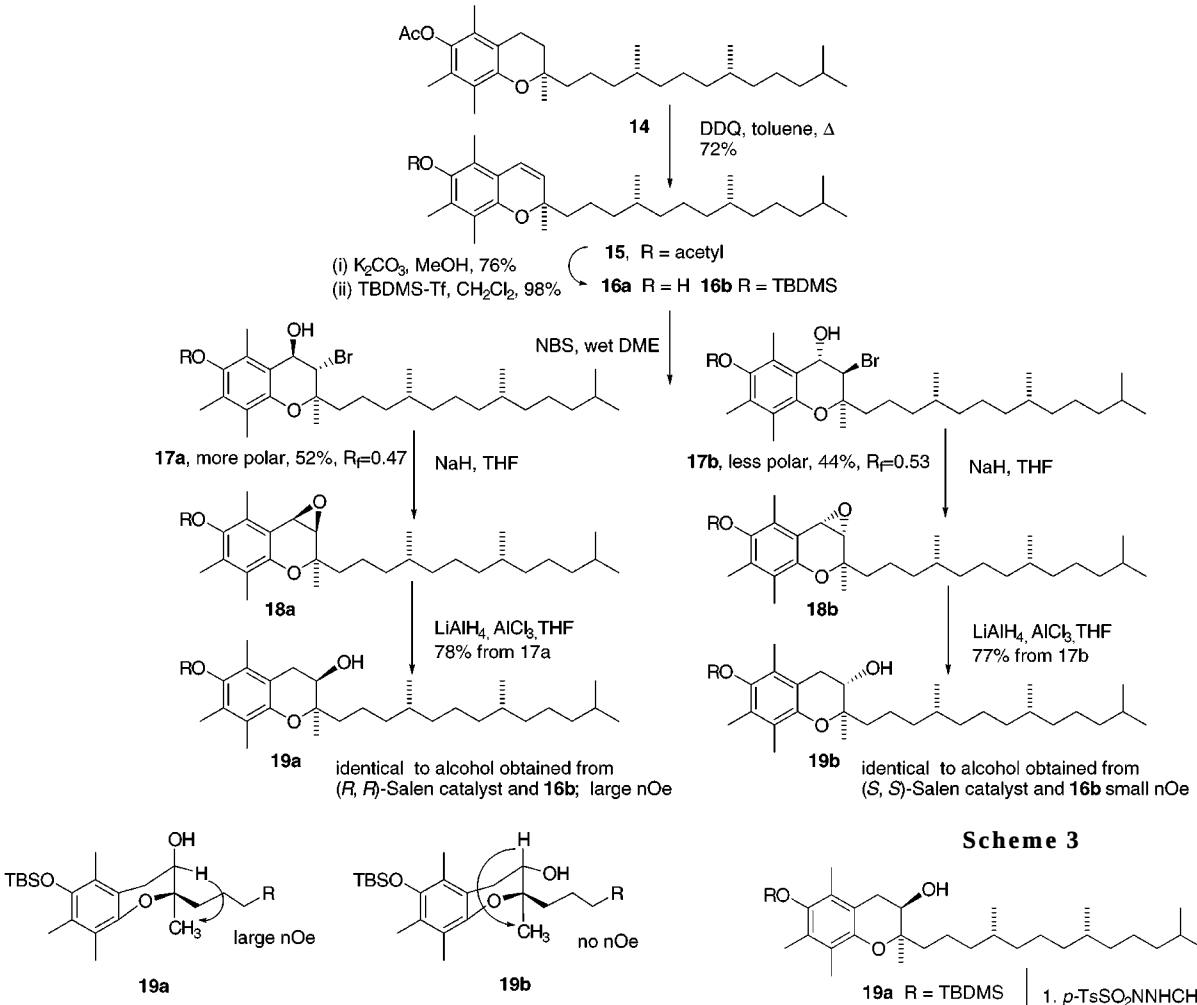
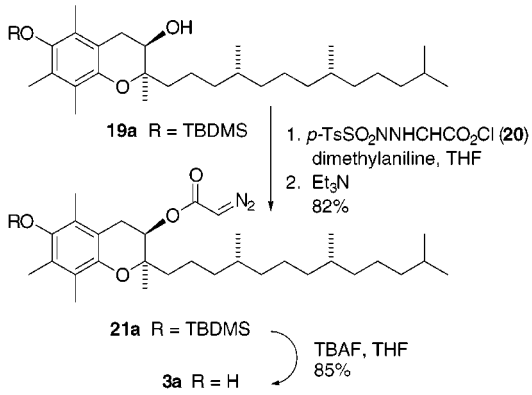


Figure 2. Illustration of the structural basis for the observed nuclear Overhauser effects for compounds **19a** and **19b**.

for **19b.** The alcohol **19a** could also be prepared by reduction of the epoxide **18a** obtained from the chromene **16b** using Jacobsen's (*R*,*R*)-Salen catalyst. The epoxide stereochemistry correlates to that observed from the enantioselective epoxidation of similar substrates.[60]

The two alcohols **19a** and **19b** were then transformed into the diazoacetates **3a** and **3b** using a modification of a published procedure.[61,62] (Scheme 3) In our hands, preparation of the glyoxylic acid *p*-toluenesulfonylhydrazone in 2.5 M aqueous HCl[61] did not provide any of the quoted hydrazone. Simply stirring a solution of glyoxylic acid and *p*-toluenesulfonyl hydrazide in THF and room temperature overnight gave good yields of pure hydrazone. Only small amounts of the byproduct *p*-toluenesulfinate ester[62] were observed in the transformation of **19a**,**b** to **21a**,**b**. Final removal of the TBDMS protecting group could be accomplished easily with 2 equiv of TBAF in THF. Larger amounts of TBAF or long times at room temperature provided mixtures of elimination products (~5−10% yield) and other polar material that has not yet been fully characterized.

Scheme 3



Conclusion

The design of photoaffinity labels described herein has also considered that for their eventual use they will need to be made radioactive. Using the methods described, the final photoaffinity labels **2a**−**d** could be prepared from alkenols **9a**−**d** by reduction with $^3H_2$ on a small scale and in "one-pot", lowering the risk of handling radioactive materials. Radiolabel introduction into compounds **3a** and **3b** would be most easily achieved by reduction of the epoxides **18a** and **18b** with (^{3}H)-$LiAlH_4$ or (^{3}H)-$NaBH_4$).

We are currently assessing the binding abilities of the photoaffinity labels against recombinant rat α-TTP expressed in *E. coli* and will report these results elsewhere.

Experimental Section

Materials and Solvents. All starting materials were obtained from Aldrich and were used without further purification. All nonaqueous reactions were conducted in oven-dried

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(120 °C) glassware under an argon atmosphere. Reagent-grade solvents were used for all extractions and workup procedures. Distilled water was used for all aqueous extractions and for all aqueous solutions. For reaction using sodium hydride (60% dispersion in mineral oil), the mineral oil was removed by washing with dried hexane and removed via a syringe. THF was dried by refluxing and distilling from sodium and benzophenone under dry nitrogen. *N*,*N*-Dimethylformamide (DMF) was refluxed and subsequently distilled from calcium hydride. Ethyl acetate (EtOAc), hexane, and dichloromethane (CH_2Cl_2) were distilled from calcium hydride. Dry methanol and ethanol were distilled from magnesium and catalytic amount of iodine.

General Methods. Chromatography was carried out on Aldrich silica gel (230−400 mesh) with the indicated solvent systems. Analytic thin-layer chromatography (TLC) was performed on 0.25 mm precoated silica gel plates (EM Science, Silica Gel 60 F-254). Visualization was achieved using a UV lamp at 254 nm or exposure to iodine vapor, or immersion in a solution of 4% H_2SO_4 in methanol followed by heating with a heat gun. Melting points were determined on a hot stage apparatus and are uncorrected. Optical rotations were obtained in the indicated solvent at ambient temperature. Low resolution mass spectra were obtained electron impact (EI) at 70 eV or fast atom bombardment (FAB) using *m*-nitrobenzyl alcohol as the matrix. ^{1}H NMR were recorded at 300 MHz and ^{13}C NMR at 75 MHz with deuterated chloroform as the solvent unless otherwise noted. Residual chloroform was used as the internal standard (7.26 ppm).

Methyl (2*S*)-6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2-carboxylate (5). *S*-Trolox **4** (1.00 g, 2.01 mmol) was refluxed in 100 mL of dry methanol and dichloromethane (1:1, v/v) containing 0.40 g of *p*-toluenesulfonic acid for 18 h. The cooled solution was poured into water, and the aqueous layer was extracted with chloroform. Recrystallization from methanol gave white crystals of **5** (0.94 g, 88%). mp 134.5−136 0 °C. TLC: $R_f = 0.85$ (CH_2Cl_2/MeOH = 10:1); $[\alpha]^{19}_D = -54.95$ (*c* 1.06, ethanol); ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H, OCH_3), 2.58 (m, 2H), 2.43 (m, 1H) 2.16 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 1.90 (m, 1H), 1.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 145.78, 144.97, 126.49, 124.14, 123.08, 117.88, 75.47, 69.67, 53.84, 28.27, 26.53, 20.95, 20.83, 19.03, 14.76. EI-MS (*m*/*z*, relative intensity) 264 (M^+, 100), 205 (98), 164 (58), 121 (7.5).

Methyl (2*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene-2-carboxylate (6). A solution of **5** (0.94 g, 3.57 mmol), *tert*-butyldimethylsilyl chloride (0.81 g, 5.4 mmol), and imidazole (1.01 g, 14.8 mmol) in dry dimethylformamide (10 mL) was stirred and heated in an oil bath under argon atmosphere at 85 °C for 5 h until none of the starting material **5** was detected by TLC. The reaction mixture was poured into water and then extracted with ethyl acetate. Evaporation yielded a light yellow oily liquid. The crude product was purified by column chromatography on silica gel using (CH_2Cl_2:hexane = 3:1). The yield of **6** was 1.32 g (97%). TLC: $R_f = 0.63$ (CH_2Cl_2:hexane = 5:1) $[\alpha]^{19}_D = -54.91$ (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 3.68 (s, 3H, OCH_3), 2.58 (m, 2H), 2.43 (m, 1H), 2.16 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 1.90 (m, 1H), 1.61 (s, 3H), 1.06 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) 145.78, 144.97, 126.49, 124.14, 123.04, 117.88,75.47, 69.67, 53.84, 28.27, 26.53, 20.95, 20.83, 19.03, 14.76, 13.86, 12.44, −2.93. MS [EI+]: 378 (M^+, 100), 321 (25), 319 (15), 278 (11), 261 (12), 221 (27), 131 (12).

(2*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene-2-carbaldehyde (7). A solution of **6** (5.40 g, 14.3 mmol) in dry hexane (60 mL) was cooled in an acetone/liquid nitrogen bath to −60 °C, and diisobutylaluminum hydride (DIBAL-H, 1.0 M in hexane, 15.5 mL) was added via a syringe over 1.5 h so as not to exceed −57 °C. After 1 h the reaction was quenched with 50 mL of methanol and 25 mL of water and then poured into water and extracted with hexane/ethyl acetate (2:1). Removal of the solvent afforded the crude product as white crystals. Purification by column chromotography using (CH_2Cl_2:hexane, 1:1 to 3:1) yielded 4.29 g of **7** (86%). TLC: $R_f = 0.54$ (CH_2Cl_2:hexane = 3:1); mp 71−72 °C (lit.[63] 66−69 °C); $[\alpha]^{19}_D = +11.53$ (*c* 1.15, $CHCl_3$) lit. +14.7 (*c* = 0.42, unknown solvent); ^{1}H NMR ($CDCl_3$), 9.66 (s, 1H), 2.56 (m, 2H), 2.30, (m, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 1.84 (m, 1H), 1.42 (s, 3H), 1.08 (s, 9H), 0.15 (s, 6H). ^{13}C NMR ($CDCl_3$), 205.19, 145.98, 145.55, 126.88, 124.28, 123.24, 118.02, 80.67, 28.34, 26.49, 22.00, 20.90, 19.01, 14.76, 13.78, 12.47, −2.92. MS [EI] 348 (M^+, 100), 319 (56), 293 (12), 221 (29).

Preparation of ω-Hydroxyalkyltriphenylphosphonium Bromides (8a−d). The syntheses of **8b**, **8c**, **8d** were conducted under identical conditions and give similar yields of products. During the preparation of **8a** (*n* = 5), K_2CO_3 was added[64] as an acid scavenger to the reaction mixture to avoid forming the bis-phosphonium salt. Other conditions are identical with other preparations.

6-Hydroxyhexyltriphenylphosphonium Bromide (8b). A solution of 6-bromo-1-hexanol[65] (5.11 g, 28.2 mmol) in 65 mL of absolute ethanol was added to 1 equiv of triphenylphosphine (7.39 g, 28.2 mmol) and heated at reflux overnight. The solvent was removed with a rotary evaporator, and the crude product was stirred vigorously at 100 °C with an equal volume of toluene. On cooling, the phosphonium salt crystallized and the toluene was decanted. The yield was 98.8% (12.6 g, 28.4 mmol). mp 148−149 °C. TLC of the salt (disolved in CH_3CN; 9:1 CH_3CN:H_2O as developer) showed one spot, $R_f = 0.55$. IR: 3350 (OH, strong and wide), 2325 (P−aryl stretch), 1440 with 1110 (P−Ph) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.90−7.69 (m, 15H), 3.95−3.43 (m, 4H), 2.58 (s, 1H), 1.86−1.23 (m, 8H); ^{13}C NMR ($CDCl_3$) 135.35, 134.17, 134.04, 130.96, 130.80, 119.42, 61.94, 32.31, 30.65, 29.92, 25.16, 22.74; FAB-MS 805 (2M + Br, 1.5), 363 (M^+, 100), 345 (2.6) 331 (2.7), 317 (1.8), 303 (1.5), 289 (6.4), 275 (4.8), 262 (9.6).

(*Z*)-6-(2*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-yl)-5-hexen-1-ol (9a). The syntheses of **9a**−**d** were conducted under identical conditions and gave similar yields of products. A suspension of the phosphonium salt **8a** (126.9 mg, 0.29 mmol) in dry THF (3 mL) at room temperature under argon was treated dropwise with a THF solution of LiHMDS (0.9 M in THF, 0.85 mL, 0.72 mmol) via a syringe. The red ylide was stirred for 1 h under argon, and then a solution of the **7** (100 mg, 0.29 mmol) in THF was added dropwise. The color changed from red to pale yellow. The resulting suspension was stirred for an additional 3 h until **7** could not be detected by TLC. The reaction was quenched with saturated NH_4Cl (10 mL) and water (10 mL) and then extracted with ethyl acetate. After solvent removal, trituration with cold hexane removed triphenylphosphine oxide. Concentration of the hexane solution and purification by column chromatography on silica gel using CH_2Cl_2:hexane (1:3 to 3:1) as eluent yielded 104.5 mg (86%) of **9a** as a colorless oil. TLC $R_f = 0.1$ (CH_2Cl_2:hexane = 5:1). ^{1}H NMR δ 5.31 (overlapping doublets, 2H, $J = 11$ Hz), 3.62 (t, 2H, $J = 6$ Hz), 2.57 (t, 2H, $J = 7$ Hz), 2.27 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H) 1.77 (m, 1H), 1.55 (t, 2H, $J = 7$ Hz), 1.50 (s, 3H), 1.32 (m, 4H), 1.06 (s, 9H), 0.14 (s, 6H). ^{13}C NMR 146.45, 144.60, 134.09, 132.32, 126.24, 123.95, 122.76, 118.24, 75.98, 63.31, 33.83, 32.90, 27.79, 27.64, 26.51, 25.74, 21.66, 19.01, 14.76, 13.82, 12.61, −2.93. EI-MS *m*/*z* 418 (M^+, 50.5), 278 (38.6), 221 (16.4), 119 (9.1), 84 (100).

6-(2*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)-1-hexanol (10a). The syntheses of **10a**−**d** were conducted under identical conditions and gave similar yields of products. To a solution of **9a** (0.225 g, 0.538 mmol) in ethyl acetate (10 mL) was added 70 mg of 10% Pd/C, and the reaction mixture was attached to a hydrogen balloon for 18 h. Filtering and evaporation afforded compound **10a** (0.226 g) as a colorless, oily liquid. The yield was 100%. The product was directly used for next step without any purification. ^{1}H NMR δ 3.65 (t, 2H, CH_2OH $J = 7$ Hz), 2.59 (t, 2H, $J = 7$ Hz), 2.11 (t, 9H, $J = 7$ Hz), 1.83 (m, 2H), 1.59(m, 4H), 1.37 (m, 6H), 1.26(s, 3H), 1.09(s, 9H), 0.16 (s, 6H);

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^{13}C NMR 146.29, 144.49, 126.26,123.93, 123.08, 117.89, 74.82, 63.36, 39.88, 33.13, 32.00, 30.34, 26.53, 26.14, 24.23, 23.99, 21.31, 19.02, 14.75, 13.82, 12.37, −2.92. EI-MS *m*/*z* 420 (M^+, 100), 404 (44.3), 390 (25.7) 279 (50.7), 221 (23.6).

6-{(2*R*)-2,5,7,8-Tetramethyl-6-[(trimethylsilyl)oxy]-3,4-dihydro-2*H*-chromene-2-yl}heptyl-4-azidobenzoate (11). To a suspension of sodium hydride (7.5 mg, 0.046 mmol) in dry THF (2 mL) was added **10b** (8.9 mg, 0.023 mmol) in THF (0.5 mL) at room temperature under argon. This mixture was stirred for 1 h before 12 mg of *N*-hydroxysuccinimidyl-4-azidobenzoate (0.046 mmol in THF) was added via a syringe. The resulting mixture was stirred overnight until no starting material **10b** was detected by TLC. The reaction mixture was diluted with ethyl acetate (5 mL) and washed with brine, and the solvent was removed under reduced pressure. This material was further purified by chromatography on silica gel (hexane:ethyl acetate = 20:1) to yield 7.3 mg (55%) of **11**. TLC R_f = 0.69 (hexane:ethyl acetate = 5:1); ^{1}H NMR δ 8.06 (d, 2H, J = 9 Hz), 7.06 (d, 2H, J = 9 Hz), 4.34 (t, 2H, J = 7 Hz), 2.56 (t, 2H, J = 7 Hz), 2.11 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.78 (m, 2H), 1.57−1.32 (br, 12H), 1.23 (s,3H), 1.06 (s, 9H), 0.13 (s, 6H); ^{13}C NMR 169.50, 146.31, 144.52, 132.89, 126.20, 123.85, 123.05, 119.69, 117.87, 74.82, 63.44, 39.99, 33.19, 31.98, 30.50, 29.77, 26.51, 26.07, 24.20, 23.93, 21.29, 19.00, 14.69, 13.76, 12.30, −2.94; EI-MS *m*/*z* 580 (M^+,13.0), 553 (63.8), 495 (30.0), 469 (17.4), 377 (19.3), 322 (41.0), 279 (24.7), 221 (24.2).

1-Azido-4-(bromomethyl)-2,3,5,6-tetrafluorobenzene (12). A solution of 4-azidotetrafluorobenzyl alcohol[51] (2.0 g, 9.05 mmol) in dry CH_2Cl_2 was cooled in an ice bath under argon atmosphere. Pyridine (0.73 mL) and PBr_3 (0.98 g, 3.6 mmol) were added to this stirred solution via a syringe over a period of 30 min. After 3 h at room-temperature, 2-propanol (15 mL) in CH_2Cl_2 (50 mL) was added followed after 15 min by an equal volume of 1 N $NaHCO_3$. Extraction with CH_2Cl_2 and evaporation yielded a light yellow solid. This crude compound was purified by chromatography on silica gel (CH_2Cl_2:hexane = 1:1 to 3:1) and provided 1.86 g (72%) of **12** as a light yellow crystalline compound. mp 53−55 °C. TLC R_f = 0.22 (hexane:EtOAc = 8:1); ^{1}H NMR δ 4.51 (s, 2H); ^{13}C NMR 147.07, 143.65, 142.68, 139.37, 139.14, 112.72, 16.81; EI-MS *m*/*z* 285 (M^+, 10.4), 283 (M^+, 10.6), 257 (19.4), 255 (19.7), 204 (100), 176 (67.0), 131 (58.6).

4-Azido-2,3,5,6-tetrafluorobenzyl 6-((2*R*)-6-{[*tert*-Butyl-(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)nonyl Ether (13d). The syntheses of **13a**−**d** were conducted under identical conditions. **10d** (25.0 mg, 0.054 mmol) was dissolved in dry THF (3 mL) in a two-necked round-bottomed flask fitted under argon and cooled in an ice bath to 0 °C. Potassium *tert*-butoxide (28 mg, 0.25 mmol) was added in 1 mL of THF. This mixture was stirred at 0 °C for another 40 min before adding a solution of 4-azidotetrafluorobenzyl bromide **12** (40 mg, 0.14 mmol) in 1 mL of dry THF via syringe over a 5 min period. Once addition was completed, the reaction mixture was stirred and allowed to warm to room temperature over a few hours. By this time no starting material **10d** was detected by TLC (hexane:EtOAc = 5:1). The reaction was diluted with CH_2Cl_2 (10 mL), washed, dried and evaporated to give a crude product which was purified by chromatography on silica gel (hexane:EtOAc = 25:1) and provided 33.11 mg (92%) of **13d**. TLC R_f = 0.79 (hexane:EtOAc = 5:1); ^{1}H NMR δ 4.58 (s, 2H), 3.49 (t, 2H,J = 7 Hz), 2.57 (t, 2H,J = 7 Hz), 2.11 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.81 (t, 2H, J = 7 Hz), 1.61−1.23 (br m, 16H), 1.24 (s, 3H), 1.06 (s, 9H), 0.13 (s, 6H); ^{13}C NMR 146.30, 144.45, 126.22, 123.84, 123.06, 117.89, 76.37, 74.86, 71.48, 59.96, 39.99, 31.94, 30.53, 29.93, 29.76, 26.51, 26.38, 24.20, 24.01, 21.30, 19.50, 19.00, 14.71, 13.79, 12.32, −2.95 EI-MS *m*/*z* 665 (M^+, 0.2), 576 (3.0), 319 (1.3), 278 (17.2), 227 (67.4), 176 (20.6). HREIMS calcd for $C_{35}H_{51}O_3N_3SiF_4$ (M^+) 665.3636, found 665.3663.

(2*R*)-2-{7-[4-Azido-2,3,5,6-tetrafluorobenzyl)oxy]heptyl}-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (2b). A solution of **13b** prepared above (5 mg, 0.0079 mmol) in dry THF (0.8 mL) was added dropwise via syringe to a stirred solution of TBAF (0.075 mL of a 1 M solution in 0.3 mL THF). The mixture was stirred overnight at room temperature until no starting material **13b** was detected by TLC. The reaction was diluted with ether, washed with water, and then dried and evaporated to afford a colorless oil. The crude product was chromatographed on silica gel (hexane:ethyl acetate = 20:1 to 10:1) and provided 4.00 mg (97%) of **2b**. TLC R_f = 0.47 (hexane:ethyl acetate = 10:1) $[\alpha]_D$ = +10.25 ($CHCl_3$, c = 0.55). ^{1}H NMR δ 4.58 (s, 2H), 3.49 (t, 2H, J = 7 Hz), 2.62 (t, J = 7 Hz), 2.24 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 1.80 (t, 2H, J = 7 Hz), 1.56 (m, 4H), 1.30 (m, 8H), 1.23 (s, 3H); ^{13}C NMR 145.5, 144.5, 122.6, 121.0, 118.5, 117.3, 74.4, 71.1, 59.5, 39.5, 31.5, 30.0, 29.5, 29.4, 25.9, 23.7, 23.5, 20.7, 12.2, 11.8, 11.3. ^{19}F NMR (188 MHz, vs C_6F_6 at −162.70 ppm): −144.21 (2F, dd, ^{19}F−^{13}C, J = 8 Hz, ^{19}F−^{19}F J_3 = 12 Hz), −152.98 (2F, dd, ^{19}F−^{13}C J = 8 Hz, ^{19}F−^{19}F J_3 = 12 Hz). EI-MS *m*/*z* 523 (M^+, 17), 497 (18), 320 (25), 205(14), 203 (15), 178 (100). HREIMS calcd for $C_{27}H_{33}F_4N_3O_3$ 523.2458, found 523.2376.

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-chromen-6-yl Acetate (15). Following the method reported by Mayer,[52] a solution of vitamin E acetate **14** (2.0 g, 4.24 mmol) in 40 mL of toluene was set to reflux for 30 min, and then a solution of DDQ (1.88 g, 8.28 mmol) in 50 mL of toluene was added dropwise via an addition funnel over 3 h. This mixture was refluxed and stirred overnight. TLC showed the product at the same position with starting material, but the starting material turned yellow and the product brown on charring with 4% H_2SO_4 in methanol. Chromatography on silica gel (hexane:ethyl acetate = 20:1) afforded a colorless oil. The yield of **15** was 1.44 g (72%). TLC R_f = 0.47 (hexane:ethyl acetate = 10:1); ^{1}H NMR δ 6.59 (d, 1H, J = 10 Hz), 5.62 (d, 1H, J = 10 Hz), 2.36 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 1.69 (m, 2H), 1.60 (m, 2H), 1.40 (s, 3H) 1.35−1.15 (br m, 17H), 0.95 (m, 12H); ^{13}C NMR 169.76, 148.94, 141.76, 130.03, 129.35, 123.02, 122.75, 120.25, 118.11, 77.80, 41.51, 39.84, 37.90, 37.76, 33.25, 33.15, 32.06, 28.42, 26.28, 25.27, 24.93, 23.16, 23.07, 20.84, 20.18, 20.08, 13.58, 12.00, 11.93; EI-MS *m*/*z* 470 (M^+, 4.3), 455 (4.4), 245 (100), 203 (19.0), 168 (1.9).

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-chromen-6-ol (16a). **15** (2.24 g, 4.76 mmol) was dissolved in 200 mL of dry methanol, and then K_2CO_3 (1.97 g, 14.27 mmol) was added. This mixture was stirred at room temperature under argon for 8 h, until no starting material (**15**) was detected by TLC. The solvent was evaporated under reduced pressure, and the product was further purified by column chromatography on silica gel using 50% dichloromethane in hexane as the eluent to afford 1.55 g (76%) of a colorless oil. TLC R_f = 0.58 (CH_2Cl_2:hexane = 5:1); ^{1}H NMR δ 6.56 (d, 1H, J = 10 Hz), 5.65 (d, 1H, J = 10 Hz), 4.21 (s, 1H), 2.20 (s, 3H), 2.1 (s, 3H), 2.14 (s, 3H), 1.63 (m, 4H), 1.29 (s, 3H), 1.35−1.05 (br m, 17H), 0.88 (m, 12H); ^{13}C NMR 145.64, 145.03, 130.53, 123.27, 122.72, 120.46, 118.19, 116.45, 76.99, 40.93, 39.78, 37.84, 37.74, 37.69, 33.21, 33.10, 28.38, 25.65, 25.20, 24.87, 23.13, 23.04, 21.75, 20.15, 20.05, 12.84, 12.01, 11.26; EI-MS *m*/*z* 428 (M^+, 5.8), 413 (5.6), 203 (100), 165 (2.7).

6-{[*tert*-Butyl(dimethyl)silyl]oxy}({(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2*H*-chromene (16b). To a stirred solution of **16a** (0.99 g, 2.31 mmol) in 30 mL of dry dichloromethane were added 0.900 g of 2,6-lutidine (5.78 mmol) and 0.950 g of *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.47 mmol) dropwise at room temperature under an argon atmosphere and then stirred for 3.5 h. The crude product was purified by chromatography on silica gel using 2% ethyl acetate in hexane as the eluent. The yield of **16b** was 1.23 g (98%). TLC R_f =0.86 (hexane:ethyl acetate = 10:1); ^{1}H NMR δ 6.55 (d, 1H, J = 10 Hz), 5.63 (d, 1H, J = 10 Hz), 2.17 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 1.66 (m, 4H), 1.37 (s, 3H) 1.52−1.22 (br, 17H), 1.08 (s, 9H), 0.88 (m, 12H), 0.16 (s, 6H); ^{13}C NMR 145.50, 145.23, 129.08, 128.42, 123.85, 122.90, 121.36, 118.34, 76.99, 40.93, 39.78, 37.84, 37.80, 37.74, 37.69, 33.21, 33.10, 28.38, 26.53, 25.65, 25.20, 24.87, 23.13, 23.04, 21.75, 20.15, 20.05, 12.84, 12.01, 11.26, −2.95; EI-MS *m*/*z* 542 (M^+, 10.2), 527 (5.8), 325 (20.5), 317 (100), 249 (8.6), 185 (39.3%). HREIMS calcd for $C_{35}H_{62}O_2Si$ 542.4519, found 542.4525.

(2*R*,3*R*,4*S*)-3-Bromo-6-{[*tert*-butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-4-ol (17a) and (2*R*,3*S*,4*R*)-3-bromo-6-{[*tert*-butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-4-ol (17b). **16b** (100 mg, 0.19 mmol) was dissolved in a mixture of DME:H_2O = 6:2.4 at O°C in an ice bath.[57] Then the NBS solution (49.27 mg, 0.2768 mmol in 2 mL of DME) was added to the well-stirred mixture and kept at 4 °C overnight, at which point no starting material **16b** was detected by TLC. Two spots were visible by TLC; R_f = 0.74 and 0.54 (CH_2Cl_2:hexane = 5:1). The DME was removed under reduced pressure, and the residue was extracted with ether and dried over Na_2SO_4. Purification by column chromatography yielded two compounds. These two product's ^{1}H NMR, ^{13}C, and MS are nearly identical, but the TLC R_f values are different. The total yield of both isomers **17a** and **17b** was 96%. TLC for **17a** R_f = 0.47 (CH_2Cl_2:hexane = 5:1) The yield was 63.0 mg (51.8%). ^{1}H NMR δ 5.05 (t, 1H, J = 6 Hz), 4.34 (d, 1H, J = 6 Hz), 2.25 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.82 (m, 2H), 1.60 (m, 2H), 1.53 (s, 3H), 1.29−1.14 (br, 17H), 1.06 (s, 9H), 0.88 (m, 12H), 0.15 (d, 6H, J = 10 Hz); ^{13}C NMR 146.35, 144.82, 129.73, 125.65, 123.68, 119.48, 79.54, 71.71, 64.42, 39.77, 37.80, 37.71, 37.68, 37.37, 33.53, 33.19, 32.98, 28.38, 26.50, 25.20, 24.75, 24.68, 23.12, 23.03, 20.71, 20.14, 19.92, 14.94, 14.84, 12.49, −2.67; EI-MS m/z 640 (M^+, 6.6), 638 (6.2), 558 (8.2), 540 (39.2), 397 (11.1), 317 (100).

17b: TLC R_f = 0.54 (CH_2Cl_2:hexane = 5:1). The yield was 53.9 mg (44.3%). ^{1}H NMR δ 5.05 (t, 1H, C-4 H, J = 6 Hz), 4.34 (d, 1H, J = 6 Hz), 2.25 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.82 (m, 2H), 1.60 (m, 2H), 1.53 (s, 3H), 1.29−1.14 (br, 17H), 1.06 (s, 9H), 0.88 (m, 12H), 0.15 (d, 6H, J = 10 Hz); ^{13}C NMR 146.35, 144.82, 129.73, 125.65, 123.68, 119.48, 79.54, 71.71, 64.42, 39.77, 37.80, 37.71, 37.68, 37.37, 33.53, 33.19, 32.98, 28.38, 26.50, 25.20, 24.75, 24.68, 23.12, 23.03, 20.71, 20.14, 19.92, 14.94, 14.84, 12.49, −2.67; EI-MS m/z 640 (M^+, 6.7), 638 (4.8), 558 (8.4), 540 (39.0), 397 (11.2), 317 (100). HREIMS for $C_{35}H_{63}BrO_3Si$ 638.3730 found 638.3773.

(1a*R*,2*R*,7b*R*)-2,4,5,7-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-1a,7b-dihydro-2*H*-oxireno[2,3-*c*]chromen-6-yl *tert*-Butyl(dimethyl)silyl Ether (18a). To the suspension of sodium hydride (12 mg, 0.225 mmol) in dry THF (1 mL) was added **17a** (36 mg, 0.056 mmol) in THF (0.5 mL) at 0 °C under argon. The resulting mixture was stirred at room temperature for 6 h. Precipitated NaBr was filtered, and the solvent removed under reduced pressure to yield the epoxide **18a** which was reduced directly in the next step without further purification. A small sample was retained for spectral analysis. TLC R_f = 0.60 (hexane:ethyl acetate = 10:1). ^{1}H NMR δ 4.09 (d, 1H, J = 6 Hz), 3.48 (d, 1H, J = 4 Hz), 2.31 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 1.70 (m, 2H), 1.55 (m, 2H), 1.36−1.09 (br, 17H), 1.10 (s, 3H), 1.06 (s, 9H), 0.88 (m, 12H), 0.14 (d, 6H, J = 5 Hz); ^{13}C NMR 145.76, 144.95, 129.74, 125.43, 124.87, 116.21, 77.00, 74.03, 62.42, 48.43, 39.91, 39.78, 37.92, 37.87, 37.70, 33.21, 33.15, 28.38, 26.49, 25.21, 24.93, 23.13, 23.04, 21.10, 20.44, 20.17, 20.10, 15.01, 13.09, 12.14, −2.90; EI-MS m/z 558 (M^+, 3.4), 280 (2.6), 245 (21.5), 203 (6.4), 151 (10.1), 137 (12.3), 125 (17.4), 97 (58.2).

(1a*S*,2*R*,7b*S*)-2,4,5,7-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-1a,7b-dihydro-2*H*-oxireno[2,3-*c*]chromen-6-yl *tert*-Butyl(dimethyl)silyl Ether (18b). The synthesis of **18b** was conducted under identical conditions with the synthesis of **18a**. TLC R_f = 0.60 (hexane;ethyl acetate = 10:1); ^{1}H NMR δ 4.09 (d, 1H, J = 6 Hz), 3.48 (d, 1H, J = 4 Hz), 2.31 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 1.70 (m, 2H), 1.55 (m, 2H), 1.36−1.09 (br, 17H), 1.10 (s, 3H), 1.06 (s, 9H), 0.88 (m, 12H), 0.14 (d, 6H, J = 5 Hz); ^{13}C NMR 145.76, 144.95, 129.74, 125.43, 124.87, 116.21, 77.00, 74.03, 62.42, 48.43, 39.91, 39.78, 37.92, 37.87, 37.70, 33.21, 33.15, 28.38, 26.49, 25.21, 24.93, 23.13, 23.04, 21.10, 20.44, 20.17, 20.10, 15.01, 13.09, 12.14, −2.90; EI-MS m/z 558 (M^+, 3.2), 280 (2.5), 245 (21.7), 203 (6.6), 151 (9.9), 137 (12.1), 125 (17.7), 97 (58.4).

Synthesis of 18a and 18b Using Jacobsen's Catalysts. A 12% solution of NaOCl (0.3 mL) was cooled in an ice bath to 0 °C. Jacobsen's catalyst either (*R*,*R*)-(−)- or (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride (10 mg) and 4-(3-phenylpropyl)pyridine *N*-oxide, (15 mg) were dissolved in dichloromethane (1.5 mL), and the mixture was added to the hypochlorite solution. The solution was stirred for 15 min at 0 °C, and then **16b** (50 mg, 0.092 mmol) in 0.5 mL of CH_2Cl_2 and the remaining hypochlorite solution (0.5 mL) were added over 30 min via syringe. The reaction was completed in 2 h at 0 °C. The mixture was filtered through a pad of Celite, washed once with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford 42.1 mg (85%) of the epoxide **18a**. The same yield was obtained for **18b**. All spectral data for the epoxides obtained by this method were identical to those obtained by cyclization of the bromohydrins **17a** and **17b.**

(2*R*,3*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-3-ol (19a). Lithium aluminum hydride (0.3 mL of a 1.0 M solution in THF) and aluminum chloride (15 mg) were suspended in dry THF (2 mL), and the suspension was stirred for 20 min under argon at 0 °C. A solution of 27.5 mg of **18a** in 1.0 mL of dry THF was then added dropwise at 0 °C. After 3 h, the reaction was quenched with water and extracted with ether. The product was purified by column chromatography (hexane:ethyl acetate, 10:1). The overall yield from **17a** to **19a** was 25.2 mg (78%). TLC R_f = 0.30 (hexane:ethyl acetate = 10:1); ^{1}H NMR δ 3.86 (overlapped dd, X of ABX, 1H, J_{XA} = 5 Hz, J_{XB} = 5 Hz), 2.86 (dd, A of ABX, J_{AB} = 17 Hz, J_{AX} = 5 Hz), 2.61 (dd, B of ABX, J_{BA} = 17 Hz, J_{BX} = 5 Hz), 2.12 (s, 6H, $2CH_3$), 2.07 (s, 3H, CH_3), 1.68 (s, 1H, C-3OH), 1.55 (m, 2H, CH_2), 1.50−1.10 (br, 17H), 1.21 (s, 3H), 1.07 (s, 9H), 0.90 (m, 12H), 0.14 (s, 6H); ^{13}C NMR 145.32, 145.01, 126.85, 124.58, 123.44, 116.07, 77.00, 69.56, 39.78, 37.88, 37.70, 35.48, 33.21, 33.12, 30.72, 28.39, 26.50, 25.22, 24.89, 23.14, 23.04, 21.33, 21.06, 20.16, 20.05, 14.73, 13.86, 12.44, −2.88; EI-MS m/z 560 (M^+, 100), 317 (14.7), 279 (14.1), 221 (6.4), 149 (8.8). HREIMS calcd for $C_{35}H_{64}O_3Si$ 560.4625, found 560.4644.

(2*R*,3*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-3-ol (19b). The synthesis of **19b** was conducted under identical conditions with the synthesis of **19a**. The overall yield from **19b** to **17b** was 24.1 mg (77%). TLC R_f = 0.30 (hexane:ethyl acetate = 10:1); ^{1}H NMR δ 3.85 (overlapped dd, X of ABX, 1H, J_{XA} = 5 Hz, J_{XB} = 5 Hz), 2.80 (dd, A of ABX, 1H, J_{AB} = 17 Hz, J_{AX} = 5 Hz), 2.68 (dd, B of ABX, 1H, J_{BA} = 17 Hz, J_{BX} = 5 Hz), 2.12 (s, 6H), 2.07 (s, 3H), 1.68 (s, 1H), 1.55 (m, 2H), 1.50−1.10 (br, 17H), 1.21 (s, 3H), 1.07 (s, 9H), 0.90 (m, 12H), 0.14 (s, 6H); ^{13}C NMR 145.32, 145.01, 126.85, 124.58, 123.44, 116.07, 77.00, 69.56, 39.78, 37.88, 37.70, 35.48, 33.21, 33.12, 30.72, 28.39, 26.50, 25.22, 24.89, 23.14, 23.04, 21.33, 21.06, 20.16, 20.05, 14.73, 13.86, 12.44, −2.88; EI-MS m/z 560 (M^+, 100), 317 (14.5), 279 (13.9), 221(6.5), 149 (8.9).

Glyoxylic Acid Chloride *p*-Toluenesulfonyl Hydrazone (20). A mixture of glyoxylic acid (2.5 g, 27.2 mmol) and *p*-toluenesulfonyl hydrazide (5.11 g, 27.18 mmol) in 30 mL of dry THF was stirred overnight at room temperature. The solvent was removed under reduced pressure, and then the residue was washed with cold water and air-dried for 2 days. The crude, dry hydrazone was recrystallized from a carbon tetrachloride−ethyl acetate mixture to give white crystals. The yield was 5.3 g (81%). mp 151−153 °C (lit.[61] 149.5−152 °C) ^{1}H NMR (DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.64 (d, 2H, J = 5 Hz), 7.53 (d, 2H, J = 5 Hz), 7.18 (s,1H), 2.39 (s, 3H); ^{13}C NMR (DMSO-d_6) 164.43, 144.90, 138.31, 136.55, 130.30, 127.96, 21.89; FAB-MS (NBA as matrix) m/z 727 (3M + 1, 2.1), 485 (2M + 1, 14.0), 243 (M + 1, 100), 225 (37.9), 139 (49.3), 91 (49.7).

Glyoxylic acid chloride *p*-toluenesulfonyl hydrazone **20** was prepared as described below but was not isolated for analytical characterization. A suspension of 81.0 mg (0.32 mmol) of glyoxylic acid *p*-toluenesulfonyl hydrazone in a solution of 3 mL of dry benzene and 0.5 mL of thionyl chloride (2 M in CH_2Cl_2, 1.0 mmol) was refluxed with stirring for 1.5 h under an argon atmosphere. The solvent was removed under reduced pressure, and then the residue was placed on a high vacuum

line for 2 h to remove residual thionyl chloride. This material was used immediately without purification.

(2*S*,3*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-3-yl 2-Diazoacetate (21a). The crude glyoxylic acid chloride *p*-toluenesulfonyl hydrazone **20** and **19a** (14.5 mg, 0.026 mmol) were disolved in dry CH_2Cl_2 in an ice bath under an argon atmosphere. Dimethylaniline (16 mg, 0.13 mmol) was added and stirred for 15 min prior to addition of Et_3N (25 mg, 0.26 mmol). The resulting dark orange solution was stirred for 10 min at 0 °C and then 20 min at room temperature. The CH_2Cl_2 solution was washed with saturated aqueous citric acid dried over Na_2SO_4 and evaporated. Column chromatography (hexane:ethyl acetate = 30:1 to 20:1) provided 13.5 mg (82.7%) of **21a** as a yellow oil. TLC R_f = 0.54 (hexane:ethyl acetate = 10:1); IR (film, cm^{-1}) 2112; ^1H NMR δ 5.16 (overlapped dd, X of ABX, 1H, J = 6 Hz), 4.82 (br s, 1H, CHN_2), 3.00 (dd, A of ABX, 1H, J_{AB} = 18 Hz, J_{AX} = 6 Hz), 2.65 (dd, B of ABX, 1H, J_{BA} = 18 Hz, J_{BX} = 8 Hz), 2.11 (2 × s, 6H), 2.07 (s, 3H), 1.55−1.10 (br m, 21H), 1.27 (s, 3H), 1.06 (s, 9H), 0.89−0.84 (m, 12H), 0.14 (s, 6H); ^{13}C NMR 167.07, 145.18, 144.97, 126.89, 124.07, 123.27, 115.92, 76.00, 72.72, 46.94, 39.78, 37.84, 37.77, 34.80, 33.21, 33.01, 28.38, 27.99, 26.49, 25.21, 24.83, 23.12, 23.03, 22.02, 20.76, 20.14, 19.94, 19.00, 14.74, 13.82, 12.44, −2.92; FAB-MS *m*/*z* 628 (M + 1, 15.7), 543 (12.4), 317 (33.7), 279 (12.2), 221 (8.4). HRFABMS calcd for $C_{37}H_{64}N_2O_4Si$ 628.4635, found 628.4647.

(2*S*,3*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-3-yl 2-Diazoacetate (21b). TLC R_f = 0.54 (hexane:ethyl acetate = 10:1); IR (film, cm^{-1}) 2112 (=N_2); ^1H NMR δ 5.15 (overlapped dd, X of ABX, 1H, J_{XA} = 6 Hz, J_{XB} = 6 Hz), 4.82 (br s, 1H, CH=N_2), 2.95 (dd, A of ABX, 1H, J_{AB}= 18 Hz, J_{AX} = 6 Hz), 2.62 (dd, B of ABX, 1H, J_{BA} = 18 Hz, J_{BX} = 6 Hz), 2.12 (2 × s, 6H), 2.07 (s, 3H), 1.55−1.10 (br m, 21H), 1.26 (s, 3H), 1.06 (s, 9H), 0.90 (m, 12H), 0.14 (s, 6H); ^{13}C NMR 166.77, 145.32, 145.01, 126.85, 124.58, 123.44, 116.07, 77.00, 69.56, 46.67, 39.78, 37.88, 37.70, 35.48, 33.21, 33.12, 30.72, 28.39, 26.50, 25.22, 24.89, 23.14, 23.04, 21.33, 21.06, 20.16, 20.05, 14.73, 13.86, 12.44, −3.32. FAB-MS *m*/*z* 628 (M + 1, 12.1), 543(13.3), 317 (32.0), 279 (13.7), 243 (13.7), 149 (9.3). HRFABMS calcd for $C_{37}H_{64}N_2O_4Si$ 628.4635, found 628.4656.

(2*S*,3*R*)-6-Hydroxy-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,-12-trimethyltridecyl]-3,4-dihydro-2*H*-chromen-3-yl 2-Diazoacetate (3a). A solution of **21a** (5 mg, 0.008 mmol) in 0.5 mL of dry THF was added to a well-stirred solution of TBAF (2 equiv, 16 μL of 1 M TBAF in THF) at 0 °C under argon. After 30 min the solution was warmed to room temperature for another 1.5 h when TLC (hexane:ethyl acetate = 5:1) showed that no starting material remained. The reaction was diluted with ethyl acetate washed with brine and concentrated. Chromatography (hexane:ethyl acetate = 30:1 to 5:1) yielded 3.5 mg (85%) of a pale yellow oil. TLC R_f = 0.21 (hexane:ethyl acetate = 5:1) IR (cm^{-1}) 2360; ^1H NMR δ 5.25 (overlapped dd, X of ABX, 1H, J_{XA} = 6 Hz, J_{XB} = 6 Hz), 4.23 (br s, 1H, CH=N_2), 3.05 (dd, A of ABX, 1H, J_{AB} = 17 Hz, J_{AX} = 6 Hz), 2.72 (dd, B of ABX, 1H, J_{BA}= 17 Hz, J_{BX} = 6 Hz), 2.18 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H), 1.21 (s, 3H) 1.52−1.07 (br m, 22H), 0.87 (m, 12H); ^{13}C NMR 161.59, 145.74, 145.33, 144.43, 123.31, 122.13, 118.92, 115.11, 76.98, 75.72, 74.25, 39.77, 37.84, 37.70, 33.20, 33.06, 30.10, 28.38, 27.45, 25.21, 24.84, 23.12, 23.03, 21.77, 20.74, 20.13, 19.93, 12.63, 12.29, 11.74; FABMS (no molecular ion) 446 (15.1), 429 (10.8), 203 (41.8), 189 (10.3), 177 (15.9), 165 (75.7).

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Supporting Information Available: ^1H NMR spectra for compounds **2b**, **3a**, **5**, **6**, **7**, **8a**−**d**, **9a**−**d**, **10a**−**d**, **11**, **13a**−**d**, **15**, **16a**,**b**, **17a**,**b**, **18a**,**b**, **19a**,**b**, **21a**,**b** and analytical data for **8a**,**c**,**d**, **9b**−**d**, **10b**−**d**, **13a**−**c**. . This material is available free of charge via the Internet at http://pubs.acs.org.

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