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Divinylcarbinol Desymmetrization Strategy: A Concise and Reliable Approach to Chiral Hydroxylated Fatty Acid Derivatives

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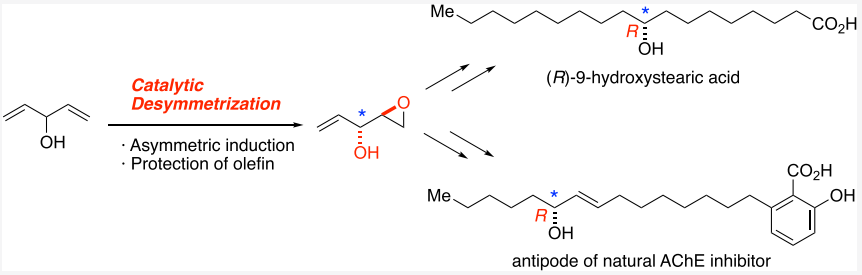

ABSTRACT: By the aid of the catalytic desymmetrization of divinylcarbinol as one-pot asymmetric induction and protection of olefin, asymmetric total syntheses of two chiral hydroxylated fatty acid derivatives were successfully achieved. The desired stereoisomers could be concisely prepared in mild conditions in a highly convergent manner. Thus, this novel strategy can help stereochemical elucidations of natural products, which have difficulties in spectroscopic stereochemical analyses due to their local symmetries in the vicinities of the stereogenic secondary hydroxyl units.

INTRODUCTION

Recently, several hydroxylated fatty acids and their variants have been reported as biologically active compounds (Figure 1). In 2012, 7′-multijuguinol (**1**) was isolated from senna multijuga as an acetylcholinesterase inhibitor.[1] However, it was a racemic mixture and the biologically active enantiomer was not determined. 9-Hydroxystearic acid (HSA) (**2**), which is a member of endogeneous lipid peroxidation byproducts, has been known as a sterically simple but competitive inhibitor of histone deacetylase 1 (HDAC-1) isoform in cancerogenesis of a human colon adenocarcinoma cell line, HT29.[2] As suggested by an in silico docking simulation study, (*R*)-**2** demonstrated higher HDAC-1 inhibitory activity than its antipode in vitro. By extensive studies on the stem bark of *Knema laurina* pursuing a neuroprotective constituent,[3a] (+)-2-hydroxy-6-(10′-hydroxypentadec-8′(*E*)-enyl)benzoic acid ((+)-**3**) was isolated as an acetylcholinesterase inhibitor.[3b] Apart from structurally similar gingkolic acids,[3c] this compound was found to be dextrorotary; however, its absolute configuration was not indicated.

In these contexts, the stereoselective synthesis of the secondary alcohols having quasi-symmetric long-chain substituents has been believed as important in the field of synthetic organic chemistry. While several reliable methods for asymmetric reduction of carbonyl compounds have been developed,[4] it would be obvious that such approach could not be easily applicable for the discrimination between two alkyl groups on quasi-symmetric carbonyl compounds. Hence, alternative strategies have been applied and several synthetic strategies have been performed (Scheme 1). For example, a synthesis of (−)-(*S*)-heptadec-1-en-6-ol, which is a precursor for (−)-5-hexadecanolide, a pheromone of the wasp *Vespa orientalis*, was established by the assistance of DIBALH·BHT complex and chiral auxiliary (Scheme 1a).[5a] Optically active (*R*)-**2** could be prepared by hydrolysis of methyl (*R*)-9-hydroxystearate obtained from *Dimorphoteca sinuata* seeds through an extraction of methyl dimorphecolate and successive hydrogenation (Scheme 1b).[2c,d] Although the enzymatic resolution of (±)-**2** was also examined, the enantiomeric excess reached only 55% ee (Scheme 1c).[5b] Recently, (*R*)-**2** and its acylated derivatives could be prepared through nucleophilic installation of fatty chains on enantioenriched (+)-(*S*)-epichlorohydrin ((+)-(*S*)-**4**) (Scheme 1d).[5c] However, the use of Grignard reagents as the nucleophiles would arise the issue on the functional group acceptance and narrow the product scope. Hence, there is still room for further improvement on a flexible, catalytic enantioselective approach for diverse chiral hydroxylated fatty acid derivatives.

Our new concept to pave an easily accessible way to such secondary alcohols is outlined in Scheme 1e. The divinylcarbinol **7**, which could be obtained from ethyl formate and vinyl

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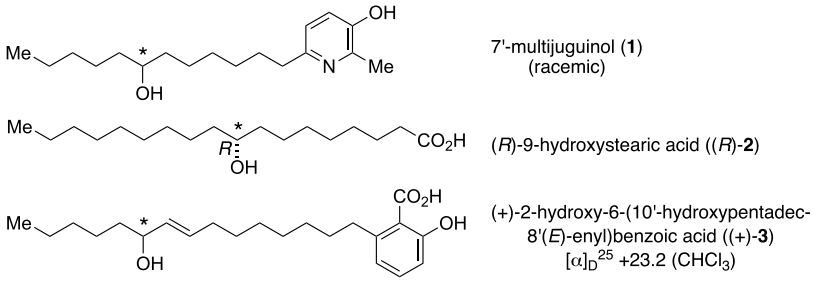

Figure 1. Natural chiral hydroxylated fatty acids and derivatives.

Grignard reagent in a large scale,[6] would be transformed into optically active epoxy ether **8** via the Sharpless asymmetric epoxidation (SAE),[7] and subsequent introduction of one long-chain unit onto the remained olefin could afford **9**. After deoxygenation of the epoxide **9**, another long-chain fragment would be installed on the olefin unmasked in **10** to give **11**. For the above synthetic strategy, catalytic desymmetrization of divinylcarbinol **7** has two major strong points as follows: (1) stereochemistry of generated chiral center can be reliable and, in principle, the high enantiomeric excess can be secured; (2) epoxide can be regarded as a small, one-atom protective group of the olefin[8] readily removable after the introduction of one long-chain unit. Therefore, we expected that the SAE of divinylcarbinol would realize one-pot "enantioselective protection of olefin".[9] Based on this strategy, we successfully accomplished a concise, convergent total synthesis of cryptchiral natural product containing local symmetry on secondary alcohol unit and revealed an absolute stereochemistry of a novel natural acetylcholine esterase inhibitor. Therefore, we will describe herein the details of our work.

RESULT AND DISCUSSION

To prove the concept, we initially applied our strategy to a concise synthesis of (*R*)-**2** (Scheme 2). SAE of divinylcarbinol with (−)-DIPT followed by TBDPS protection of the hydroxyl group afforded the epoxide **12** (≥99% ee).[7d,9] A cross-metathesis of **12** with 1-nonene provided **13** without undesired olefin isomerization in the presence of 1,4-benzoquinone,[10] and subsequent hydrogenation could afford **14**. Deoxygenation of **14** proceeded effectively with PPh_3/Zn[8b] to give **15**. Since the specific rotation of allyl alcohol **16**, which was obtained by desilylation of **15**, was comparable to the reported value for >99% ee sample,[11] its optical purity was proved to be maintained at a high level and no racemization proceeded through metathesis, hydrogenation, and deoxygenation sequence.

From intermediate **15**, we accomplished a total synthesis of (*R*)-**2**, as depicted in Scheme 3. The right-hand segment of (*R*)-**2**, methyl 7-heptenate (**20**) was prepared from dimethyl malonate in a satisfactory yield (55% for five steps). After alkylation with tosylate **17**, hydrolysis followed by decarboxylation afforded carboxylic acid **19**. Fischer esterification gave methyl 7-heptenate (**20**). With the right-hand fragment in hand, seven carbon units were introduced by cross-metathesis and subsequent hydrogenation to furnish **21**. Finally, desilylation followed by hydrolysis in one-pot procedure established **2**. For a definite stereochemical elucidation of cryptchiral **2** ($[\alpha]_D$ +0.4 in acetic acid),[12] the precursor **21** was delivered into **23**, known as (*R*)-*O*-acetylmandelate ester of **22**,[2c] and the reference ***rac*-22**/(*R*)-*O*-acetyl mandelic acid ester was also prepared from ***rac*-15**. Although the chemical shifts of methyl group on the ester moiety are known to appear at 3.671 ppm for the ester from (*R*)-**22** and 3.668 ppm for the ester from (*S*)-**22**, respectively, our derivative **23** shows a corresponding signal only at 3.671 ppm (shown in the SI). Thus, the absolute stereochemistry of **2** could be judged as "*R*" unambiguously and the optical purity was elucidated to be >98% ee. With these results, our concept was proved quite promising for the production of quasi-symmetric secondary alcohols.

With the concept proven in Schemes 2 and 3, we then focused on the stereochemical elucidation of naturally occurring AChE inhibitor **3** (Scheme 4) by asymmetric total synthesis starting from **12**. The right-hand fragment **25** was prepared from triflate **24**[13] and 7-octenol through a modified Larock's procedure.[14] The highly reactive Schrodi−Stewart−Grubbs catalyst[15] was found to be suitable for the cross-metathesis of epoxide **12** with volatile 1-pentene. A hydrogenation and deoxygenation sequence afforded known **26**[16] with a requisite alkyl chain. At this time, we confirmed again that the stereocenter induced by SAE was retained through the chemical transformations by comparison of optical rotations. Then, the right-hand fragment benzodioxinone **25** was coupled with **26** by cross-metathesis to give an inseparable mixture of geometric isomers (*trans*/*cis* = 9:1); however, these isomers could be separated after desilylation. Finally, hydrolysis of **27** under basic conditions followed by acidic workup gave the proposed structure of (***R***)-**3** ($[\alpha]_D^{25}$ −21.1 (*c* 0.080, $CHCl_3$)) in a good yield. The sign of $[\alpha]_D$, which is found to be antipodal to that for natural AChE inhibitor **3** ($[\alpha]_D$ +23.2 ($CHCl_3$)),[3b] revealed that the naturally occurring (+)-**3** has "*S*" absolute stereochemistry.

CONCLUSIONS

In conclusion, we could demonstrate a novel strategy for a flexible production of optically active secondary alcohols possessing quasi-symmetric alkyl side chains devising a divinylcarbinol as a conjunctive chiral module via SAE. Since our method provides a reliable stereoisomer and an adaptable synthetic route due to excellent functional group compatibility, this novel protocol can provide facile stereochemical elucidations of naturally occurring compounds with their concise asymmetric total syntheses. Furthermore, this strategy enables a highly convergent synthesis of biologically active fatty acid derivatives possessing chiral secondary hydroxyl group. Thus, structure−activity relationship studies on similar naturally occurring hydroxystearic acids such as 7-HSA and 8-HSA, whose precursors are less available from natural sources than 9-HSA,[17] can be accelerated by our strategy. Further applications to complex molecules are now ongoing in our laboratory.

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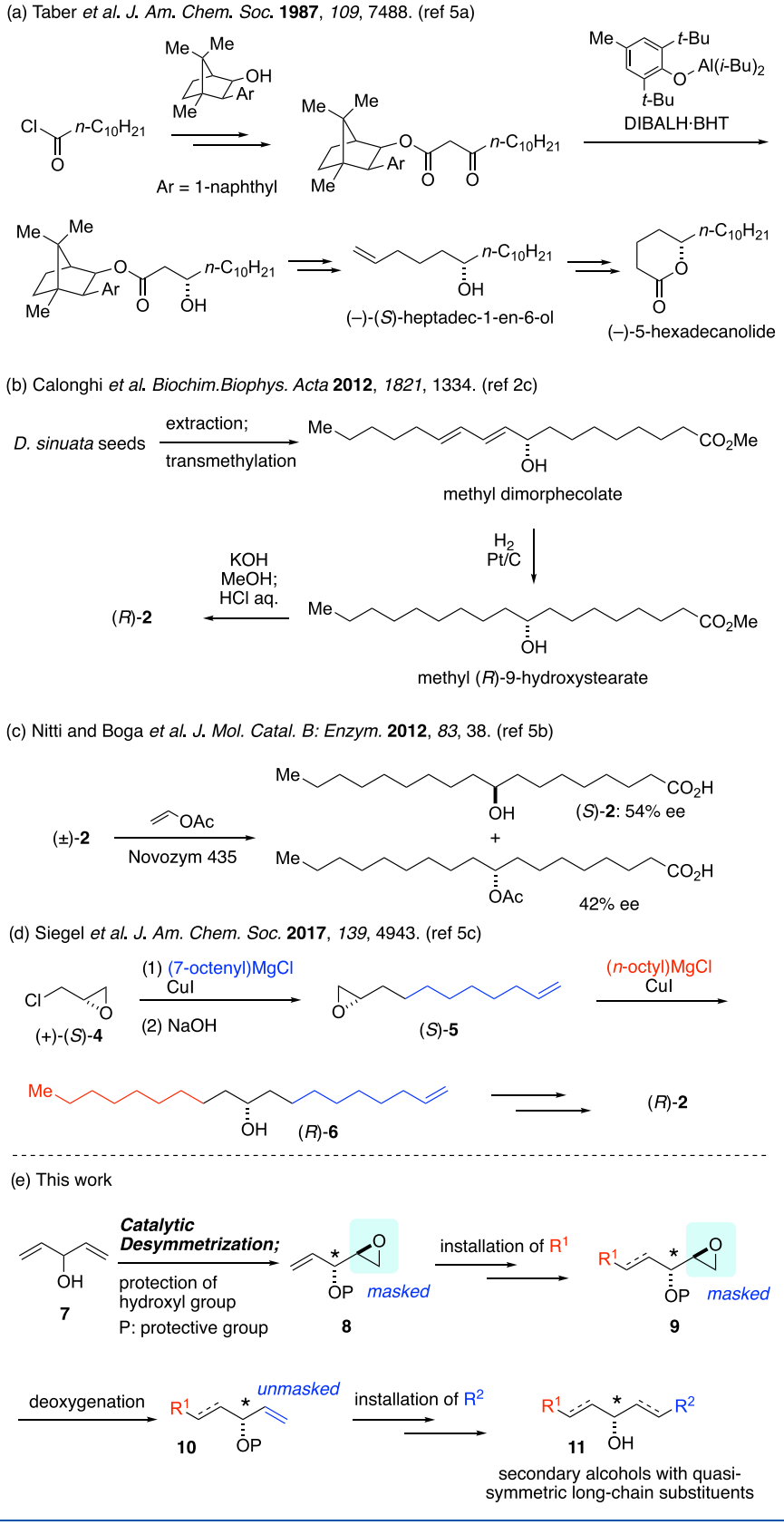
Scheme 1. Preparation of Chiral Hydroxylated Fatty Acids Having Local Symmetries in the Vicinity of the Hydroxyl Group



EXPERIMENTAL SECTION

General. All nonaqueous reactions were carried out under an Ar atmosphere unless otherwise noted. Reagents were purchased from commercial suppliers and used as received. Anhydrous solvents were prepared by distillation over CaH_2 or purchased from commercial suppliers. ^1H and ^{13}C NMR spectra were measured on a JEOL ECA 500 II, a JEOL ECX 400 or a Varian GEMINI 300 instrument, using tetramethylsilane (TMS) (0.00 ppm for ^1H), $CHCl_3$ (7.26 ppm for

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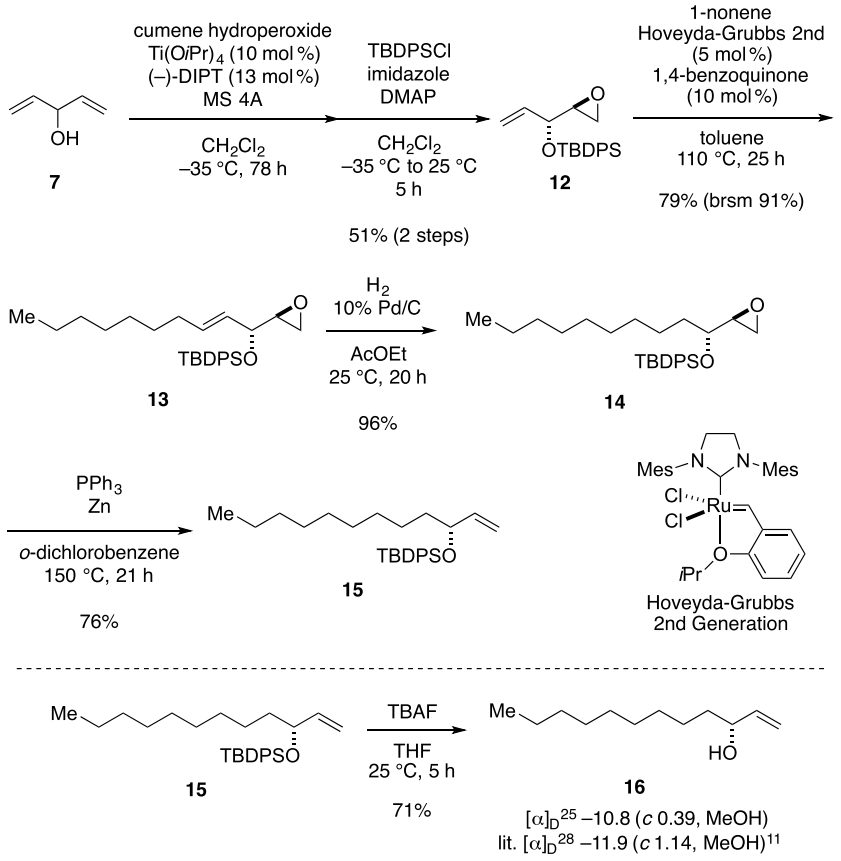
Scheme 2. Preparation of the Left-Hand Segment of (*R*)-2



^{1}H), or $CDCl_3$ (77.0 ppm for ^{13}C) as an internal reference. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. *J* values were in hertz. Mass spectra were measured on a JEOL JMS-GCmate II or a JEOL JMS-AX 505 HAD mass spectrometer, and the ionization method was electron impact (EI, 70 eV) and fast atom bombardment (FAB). A magnetic sector mass analyzer was used for high resolution mass spectrometry (HRMS) measurement. IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Optical rotations were measured on a JASCO P-2100 digital polarimeter. Column chromatography was carried out using Cica Silica Gel 60N (spherical, neutral, 40−50 μm). Preparative thin-layer chromatography was performed on precoated silica gel 60 F_{254} plates (Merck).

*1,4-Pentadien-3-ol (**7**).* To a stirred suspension of Mg turning (4.9 g, 200 mmol) in tetrahydrofuran (THF) (60 mL) were added potionwise I_2 (1.1 g, 4.33 mmol) and a solution of vinyl bromide (1.0 M in THF, 200 mL, 200 mmol) at 25 °C. After the mixture was refluxed for 1.5 h, to the above Grignard reagent was added dropwise ethyl formate (6.1 g, 82 mmol) at 0 °C. After the mixture was stirred for 1 h at 25 °C, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by vacuum distillation (45 °C/200 mmHg) to give divinylcarbinol (**7**) (5.4 g, 78%) as a colorless oil. R_f 0.41 (*n*-hexane/AcOEt = 95:5). The ^{1}H NMR spectrum was identical to that previously reported.[7e] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (2H, ddd, *J* = 17.2, 10.3, 5.7 Hz), 5.29 (2H, ddd, *J* = 17.2, 1.4, 1.4 Hz), 5.17 (2H, ddd, *J* = 10.3, 1.4, 1.4 Hz), 4.66−4.62 (1H, m), 1.63 (1H, br s).

*(2S,3R)-1,2-Epoxy-3-(tert-butyldiphenylsilyloxy)pent-4-ene (**12**).* According to a reported procedure for the antipode of **12**,[9] the Sharpless asymmetric epoxidation of divinylcarbinol[7d] followed by silylation was conducted. The epoxide **12** (1.72 g, 51% for two steps) was prepared from divinylcarbinol (**7**) (841 mg, 10.0 mmol). R_f 0.51 (*n*-hexane/AcOEt = 90:10). The ^{1}H NMR spectrum was identical to that previously reported for its antipode.[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.63 (4H, m), 7.45−7.35 (6H, m), 5.89 (1H, ddd, *J* = 17.1, 10.5, 6.6 Hz), 5.20 (1H, d, *J* = 17.1 Hz), 5.13 (1H, d, *J* = 10.5 Hz), 3.96−3.92 (1H, m), 2.91−2.87 (1H, m), 2.52−2.49 (1H, m), 2.18−2.16 (1H, m), 1.07 (9H, s). Separation of enantiomers by Chiral HPLC (DAICEL, CHIRALCEL OD-H, heptane/*i*PrOH, 5000:1, flow rate = 0.8 mL min^{-1}, $t_{2S,3R}$ = 12.7 min, $t_{2R,3S}$ = 14.4 min) provided the enantiomer ratio: (2*S*,3*R*):(2*R*,3*S*) ≥ 99:1 (≥98% ee). $[\alpha]_D^{23}$ −0.131 (*c* 1.85, $CHCl_3$). [lit. $[\alpha]_D^{23}$ +0.336 (*c* 1.95, $CHCl_3$) for ***ent*-12**].[9]

*(2S,3R)-1,2-Epoxy-3-(tert-butyldiphenylsilyloxy)dodec-4-ene (**13**).* To a stirred solution of the epoxide **12** (269 mg, 0.795 mmol) in toluene (3.7 mL) were added 1-nonene (197 mg, 1.56 mmol), 1,4-benzoquinone (9.3 mg, 0.086 mmol), and Hoveyda−Grubbs second-generation catalyst (24.0 mg, 0.038 mmol) at 25 °C. After the mixture was stirred for 25 h in refluxing toluene (using a heating block), the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: gradient from *n*-hexane only to *n*-hexane/AcOEt = 98:2) to afford olefin **13** (274 mg, 79%, brsm 91%, colorless oil) with recovered epoxide **12** (33.9 mg). R_f 0.54 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.64 (4H, m), 7.43−7.33 (6H, m), 5.49−5.41 (2H, m), 3.95−3.92 (1H, m), 2.93−2.88 (1H, m), 2.57−2.54 (1H, m), 2.30−2.27 (1H, m), 1.96−1.92 (2H, m), 1.32−1.22 (10H, m), 1.06 (9H, s), 0.88 (3H, t, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 133.9, 133.8, 129.7, 129.6, 128.5, 127.5, 127.4, 73.9, 54.7, 45.2, 32.1, 31.8, 29.14, 29.07, 28.9, 26.9, 22.7, 19.3, 14.1; IR (neat) 1590, 1112 cm^{-1}; MS (EI) *m*/*z* 436, (M$^+$); HRMS (EI) *m*/*z*: [M]$^+$ calcd for $C_{28}H_{40}O_2Si$ 436.2798; Found 436.2773; $[\alpha]_D^{22}$ −35.2 (*c* 0.18, $CHCl_3$).

*(2S,3R)-1,2-Epoxy-3-(tert-butyldiphenylsilyloxy)dodecane (**14**).* After a mixture of the olefin **13** (300 mg, 0.690 mmol) and 10% Pd/C (74.0 mg, 0.0695 mmol) in AcOEt was vigorously stirred under H_2 gas (balloon) for 20 h at 25 °C, the mixture was filtered through a

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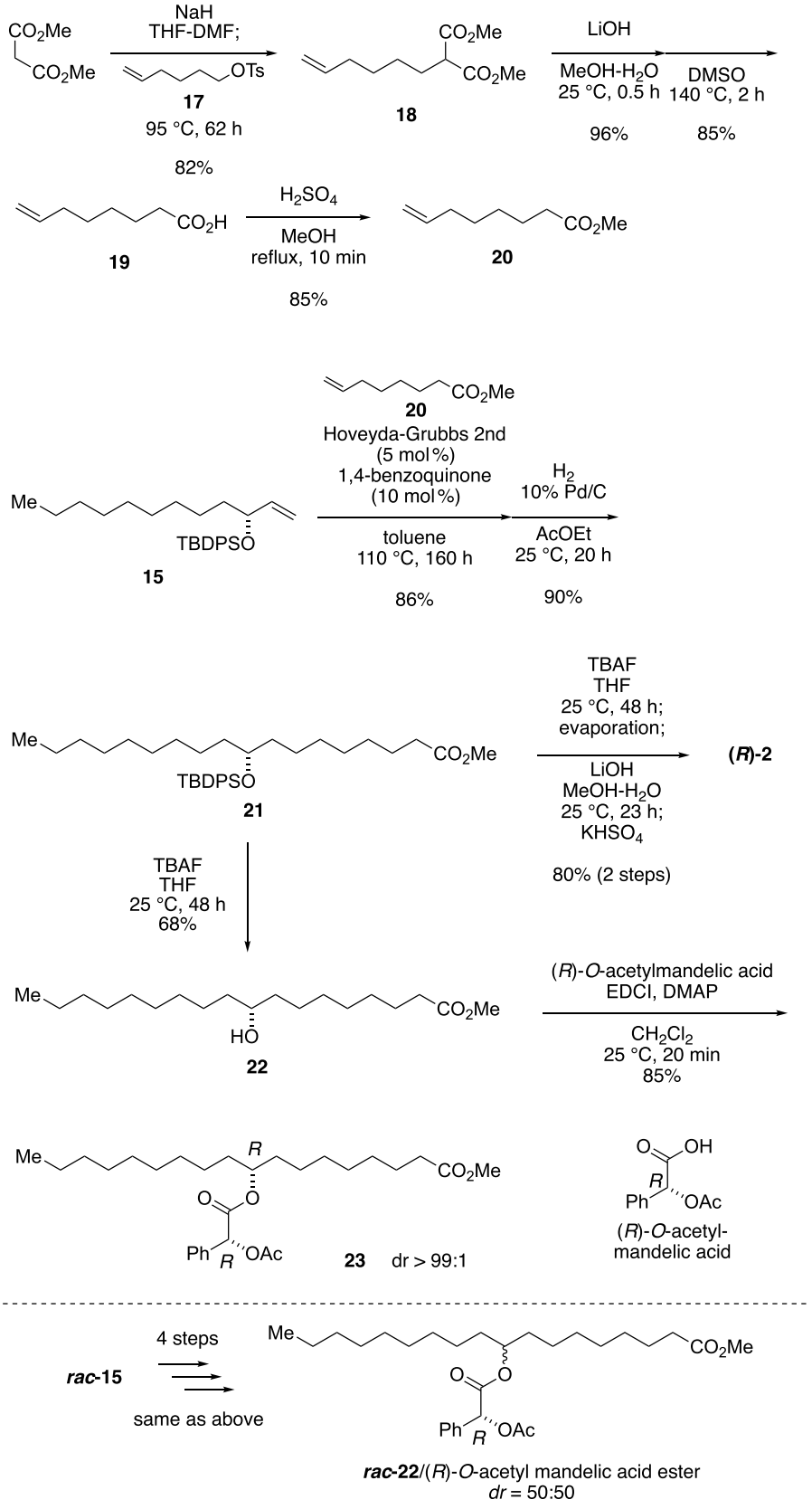
Scheme 3. Total Synthesis of (*R*)-2 and Preparation of *rac*-22/(*R*)-*O*-acetyl-mandelic Acid Ester



pad of Celite and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/AcOEt = 98:2) to afford epoxide **14** (289 mg, 96%) as a colorless oil. R_f 0.60 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.65 (4H, m), 7.44−7.34 (6H, m), 3.42−3.34 (1H, m), 2.89−2.87 (1H, m), 2.44 (1H, dd, J = 4.6, 4.6 Hz), 2.15−2.10 (1H, m), 1.61−1.50 (2H, m), 1.41−1.13 (14H, m), 1.05 (9H, s), 0.88 (3H, t, J = 6.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.90,

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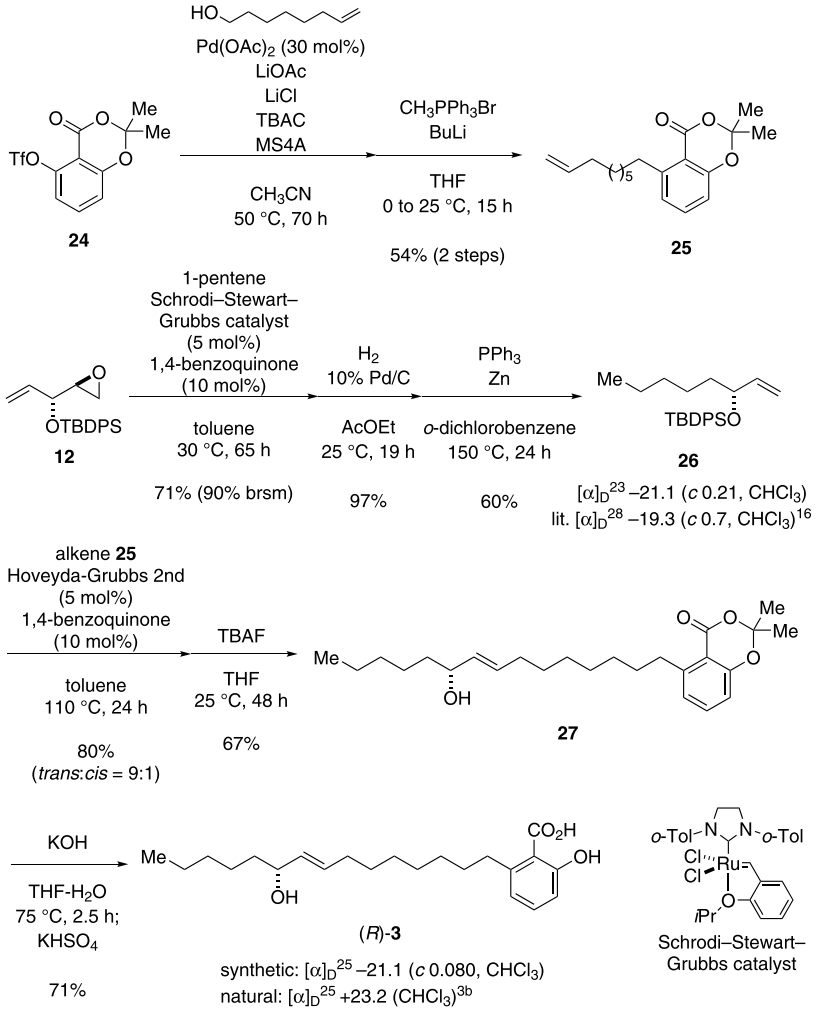
Scheme 4. Total Synthesis of (*R*)-3



135.86, 134.0, 133.9, 129.7, 129.6, 127.6, 127.5, 73.3, 54.3, 46.2, 35.3, 31.9, 29.7, 29.50, 29.48, 29.3, 29.2, 26.9, 24.3, 22.7, 19.4, 14.1; IR (neat) 1465, 1428, 1111 cm^{-1}; MS (EI) *m*/*z* 438, (M^+); HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_{28}H_{42}O_2Si$ 438.2954; Found 438.2987; $[\alpha]_D^{23}$ −20.3 (*c* 0.23, $CHCl_3$).

*(R)-3-(tert-Butyldiphenylsilyloxy)dodec-1-ene (**15**).* To a stirred solution of epoxide **14** (97.4 mg, 0.222 mmol) in *o*-dichlorobenzene (1.53 mL, degassed) were added Zn (229 mg, 3.50 mmol) and PPh_3 (946 mg, 3.61 mmol) at 25 °C. After the mixture was stirred for 21 h at 150 °C using a heating block, the mixture was filtered through a pad of Celite and diluted with CH_2Cl_2 and water. The aqueous phase was extracted with CH_2Cl_2, and combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: gradient from *n*-hexane only to *n*-hexane/AcOEt = 98:2) to afford the alkene **15** (71.5 mg, 76%) as a colorless oil. R_f 0.46 (*n*-hexane/AcOEt = 98:2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.64 (4H, m), 7.42−7.34 (6H, m), 5.76 (1H, ddd, *J* = 17.2, 10.8, 6.4 Hz), 4.97 (1H, d, *J* = 17.2 Hz), 4.94 (1H, d, *J* = 10.8 Hz), 4.15−4.05 (1H, m), 1.54−1.06 (25H, m), 0.88 (3H, t, *J* = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.0, 136.0, 135.9, 134.6, 134.3, 129.5, 129.4, 127.4, 127.3, 114.1, 74.7, 37.6, 31.9, 29.5, 29.3, 27.0, 24.4, 22.7, 19.4, 14.1; IR (neat) 1590, 1112 cm^{-1}; MS (EI) *m*/*z* 422 (M^+); HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_{28}H_{42}OSi$ 422.3005; Found 422.3003; $[\alpha]_D^{23}$ −23.0 (*c* 0.23, $CHCl_3$).

*(R)-Dodec-1-en-3-ol (**16**).* To a stirred solution of the silyl ether **15** (24.7 mg, 0.0584 mmol) in THF (0.1 mL) was added TBAF (1.0 M in THF, 0.14 mL, 0.14 mmol) at 25 °C. After the mixture was stirred for 5 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl and aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: toluene/AcOEt = 95:5) to give the alcohol **16** (7.7 mg, 71%) as a colorless oil. R_f 0.26 (toluene/AcOEt = 95:5). The ^1H NMR spectrum was identical to that previously reported.[11] ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, ddd, *J* = 18.8, 12.0, 6.4 Hz), 5.22 (1H, dd, *J* = 18.8, 1.2 Hz), 5.10 (1H, dd, *J* = 12.0, 1.2 Hz), 4.16−4.05 (1H, m), 1.58−1.22 (17H, m), 0.88 (3H, t, *J* = 6.4 Hz); $[\alpha]_D^{25}$ −10.8 (*c* 0.39, MeOH) [lit. $[\alpha]_D^{28}$ −11.9 (*c* 1.14, MeOH)][11]

*Hex-5-en-1-yl 4-methylbenzenesulfonate (**17**).* To a solution of 5-hexen-1-ol (3.00 g, 30.0 mmol) in CH_2Cl_2 (60 mL) were added Et_3N (3.93 g, 38.9 mmol), 4-dimethylaminopyridine (DMAP) (73.4 mg, 0.601 mmol), and TsCl (6.26 g, 32.8 mmol) at 0 °C. After the mixture was stirred for 17 h at 25 °C, the reaction was quenched with H_2O. The aqueous phase was extracted with CH_2Cl_2 and combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/AcOEt = 90:10) to afford the tosylate **17** (7.40 g, 97%) as a colorless oil. R_f 0.33 (*n*-hexane/AcOEt = 90:10). The ^1H NMR spectrum was identical to that previously reported.[18] ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 5.67−5.75 (1H, m), 4.95 (1H, d, *J* = 17.3 Hz), 4.94 (1H, d, *J* = 9.6 Hz), 4.03 (2H, t, *J* = 6.4 Hz), 2.45 (3H, s), 2.05−1.97 (2H, m), 1.69−1.62 (2H, m), 1.45−1.37 (2H, m).

*Dimethyl 2-hex-5-enylmalonate (**18**).* To a stirred suspension of NaH (60% dispersion in mineral oil, 572 mg, 23.8 mmol) in THF (17.7 mL) were added dropwise dimethylformamide (DMF) (17.7

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mL) and dimethyl malonate (7.11 g, 53.8 mmol) at 0 °C. After the mixture was stirred for 15 min at 0 °C and then for 30 min at 25 °C, to this suspension was added a solution of the tosylate **17** (3.30 g, 13.0 mmol) in THF at 0 °C. After the mixture was stirred for 62 h at 95 °C using an oil bath, the reaction was quenched with H_2O. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-pentane/Et_2O = 95:5) to afford the alkene **18** (2.29 g, 82%) as a colorless oil. R_f 0.32 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82−5.74 (1H, m), 4.99 (1H, d, J = 17.6 Hz), 4.94 (1H, d, J = 10.8 Hz), 3.74 (6H, s), 3.36 (1H, t, J = 7.2 Hz), 2.05 (2H, dt, J = 6.8, 6.8 Hz), 1.91 (2H, dt, J = 7.2, 7.2 Hz), 1.46−1.29 (4H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 138.1, 114.3, 51.9, 51.2, 33.1, 28.3, 28.1, 26.4; IR (neat) 1737, 1640 cm^{-1}; MS (EI) m/z 214 (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{18}O_4$ 214.1205; Found 214.1222.

*2-Hex-5-enylmalonic Acid (**I-1**).* To a stirred solution of the olefin **18** (1.93 g, 8.99 mmol) in MeOH (11 mL) and H_2O (11 mL) was added LiOH·H_2O (1.89 g, 45.0 mmol) at 25 °C. After the mixture was stirred for 4 h at the same temperature, the mixture was acidified (adjusted to pH 1) with $KHSO_4$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue (1.60 g, 95%, colorless solid) was used in the next reaction without further purification. R_f 0.14 (1% HCOOH (v/v) in toluene/AcOEt = 80:20). The ^{1}H NMR spectrum was identical to that previously reported.[19]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (2H, br s), 5.86−5.72 (1H, m), 5.04−4.93 (2H, m), 3.44 (1H, t, J = 7.4 Hz), 2.08−2.04 (2H, m), 1.99−1.92 (2H, m), 1.44−1.41 (4H, m).

*Oct-7-enoic Acid (**19**).* A solution of dicarboxylic acid **I-1** (1.44 g, 7.73 mmol) in dimethyl sulfoxide (DMSO) (27 mL) was stirred at 140 °C using an oil bath. After the mixture was stirred for 2 h, the reaction was quenched with saturated aqueous NH_4Cl at 25 °C. The aqueous phase was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: gradient from 1% HCOOH (v/v) in *n*-hexane/AcOEt = 90:10 to 1% HCOOH (v/v) in *n*-hexane/AcOEt = 50:50) to afford the carboxylic acid **19** (935 mg, 85%) as a pale yellow oil. R_f 0.74 (1% HCOOH (v/v) in *n*-hexane/AcOEt = 50:50). The ^{1}H NMR spectrum was identical to that previously reported.[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86−5.73 (1H, m), 5.00 (1H, d, J = 18.6 Hz), 4.95 (1H, d, J = 12.0 Hz), 2.36 (2H, t, J = 7.5 Hz), 2.09−2.02 (2H, m), 1.70−1.60 (2H, m), 1.47−1.33 (4H, m).

*Methyl oct-7-enoate (**20**).* To a stirred solution of the carboxylic acid **19** (930 mg, 6.55 mmol) in MeOH (22 mL) was added concn H_2SO_4 (0.30 mL, 5.24 mmol) at 25 °C. After the mixture was stirred for 10 min in refluxing MeOH (using an oil bath), the solution was concentrated in vacuo. The residue was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ and then brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. ^{1}H NMR spectrum of the residue (865 mg, 85%, pale yellow oil) was identical to that previously reported for the alkene **20**.[20] Thus, the residue was used in the next reaction without further purification. R_f 0.47 (*n*-hexane/AcOEt = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86−5.72 (1H, m), 5.00 (1H, d, J = 17.1 Hz), 4.94 (1H, d, J = 11.7 Hz), 3.67 (3H, s), 2.31 (2H, t, J = 5.1 Hz), 2.09−2.02 (2H, m), 1.68−1.58 (2H, m), 1.46−1.27 (4H, m).

*Methyl (R,E)-9-(tert-butyldiphenylsilyloxy)octadec-7-enoate (**I-2**).* According to the procedure described for **13**, the ester **I-2** (21.1 mg, 86%, colorless oil) was prepared from the alkene **15** (18.8 mg, 0.0445 mmol). R_f 0.50 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (4H, m), 7.42−7.31 (6H, m), 5.35 (1H, dd, J = 15.6, 6.0 Hz), 5.23−5.16 (1H, m), 4.07−4.02 (1H, m), 3.67 (3H, s), 2.28−2.20 (2H, m), 1.87−1.85 (1H, m), 1.58−1.04 (32H, m), 0.88 (3H, t, J = 6.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.2, 136.0, 135.9, 134.7, 133.1, 130.7, 129.4, 129.2, 127.3, 127.2, 74.7, 51.4, 38.0, 34.0, 31.9, 31.8, 29.52, 29.46, 29.3, 28.7, 28.6, 27.0, 24.7, 22.7, 19.3, 14.1; IR (neat) 1742, 1428, 1111 cm^{-1}; MS (EI) m/z 550, (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{35}H_{54}O_3Si$ 550.3842; Found 550.3815; $[\alpha]_D^{23}$ +11.4 (c 0.24, $CHCl_3$).

*Methyl (R)-9-(tert-butyldiphenylsilyloxy)stearate (**21**).* According to the procedure described for **14**, the silyl ether **21** (59.1 mg, 90%, colorless oil) was prepared from the ester **I-2** (65.2 mg, 0.118 mmol). R_f 0.50 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.66 (4H, m), 7.42−7.34 (6H, m), 3.70−3.67 (4H, m), 2.28 (2H, t, J = 7.8 Hz), 1.59−1.55 (2H, m), 1.41−1.04 (35H, m), 0.88 (3H, t, J = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.3, 135.9, 134.8, 129.3, 127.3, 73.2, 51.4, 36.3, 36.2, 34.1, 31.9, 29.7, 29.6, 29.5, 29.3, 29.14, 29.06, 27.1, 24.91, 24.87, 24.79, 22.7, 19.4, 14.1; IR (neat) 1742, 1463, 1428, 1111 cm^{-1}; MS (EI) m/z 552, (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{35}H_{56}O_3Si$ 552.3999; Found 552.4016; $[\alpha]_D^{22}$ +1.3 (c 0.59, $CHCl_3$).

*(R)-9-Hydroxystearic Acid [**(R)-2**].* To a stirred solution of the silyl ether **21** (24.7 mg, 0.0584 mmol) in THF (0.1 mL) was added TBAF (1.0 M in THF, 0.16 mL, 0.16 mmol) at 25 °C. After the mixture was stirred for 48 h at the same temperature, the reaction mixture was concentrated in vacuo. To a stirred solution of the above residue in MeOH (65 μL) and H_2O (65 μL) was added LiOH·H_2O (12.1 mg, 0.288 mmol) at 25 °C. After the mixture was stirred for 23 h at 25 °C, the reaction mixture was concentrated in vacuo. After the residue was diluted with CH_2Cl_2 and H_2O, the solution was acidified (adjusted to pH 1) by $KHSO_4$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: gradient from *n*-hexane/AcOEt = 99:1 to 1% HCOOH in *n*-hexane/AcOEt = 60:40) to give the hydroxy acid **(*R*)-2** (12.6 mg, 80%) as a colorless solid. R_f 0.53 (*n*-hexane/AcOEt = 50:50). The ^{1}H and ^{13}C NMR spectra were identical to those previously reported.[2c] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, br s), 3.61−3.55 (1H, m), 2.34 (2H, t, J = 7.6 Hz), 1.69−1.60 (2H, m), 1.54−1.20 (26H, m), 0.88 (3H, t, J = 6.8 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 179.4, 72.1, 37.4, 37.3, 34.0, 31.9, 29.7, 29.62, 29.57, 29.4, 29.3, 29.2, 28.9, 25.6, 25.5, 24.6, 22.7, 14.1. $[\alpha]_D^{22}$ −1.02 (c 0.63, $CHCl_3$).

*Methyl (R)-9-hydroxystearate (**22**).* According to the procedure described for **16**, the alcohol **22** (11.4 mg, 68%, colorless oil) was prepared from the silyl ether **21** (29.3 mg, 0.0530 mmol). R_f 0.33 (*n*-hexane/AcOEt = 80:20). The ^{1}H NMR spectrum was identical to that previously reported.[2c] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s), 3.61−3.55 (1H, m), 2.30 (2H, t, J = 7.6 Hz), 1.69−1.57 (2H, m), 1.50−1.22 (27H, m), 0.88 (3H, t, J = 6.6 Hz). $[\alpha]_D^{22}$ −0.04 (c 0.57, $CHCl_3$).

*Methyl (9R)-9-{[(2R)-2-(acetyloxy)-2-phenylacetyl]oxy}-octadecanoate (**23**).* To a stirred solution of the alcohol **22** (11.4 mg, 0.0360 mmol) in CH_2Cl_2 (0.18 mL) were added EDCI·HCl (21.4 mg, 0.112 mmol), DMAP (26.4 mmol, 0.216 mmol), and (−)-(*R*)-*O*-acetyl-mandelic acid (22.9 mg, 0.118 mmol) at 25 °C. After the mixture was stirred for 20 min at the same temperature, the reaction mixture was diluted with CH_2Cl_2 and washed subsequently with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by PTLC (*n*-hexane/AcOEt = 85:15) to afford the mandelate **23** (15.1 mg, 85%) as a colorless oil. R_f 0.38 (*n*-hexane/AcOEt = 85:15). The ^{1}H spectrum was identical to that previously reported.[2c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (2H, m), 7.38−7.27 (3H, m), 5.872 (1H, s), 4.89−4.82 (1H, m), 3.671 (3H, s), 2.27 (2H, t, J = 7.5 Hz), 2.20 (3H, s), 1.57−1.43 (4H, m), 1.38−0.87 (27H, m); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.3, 170.2, 168.7, 134.1, 129.1, 128.6, 127.6, 75.9, 74.7, 51.4, 34.1, 34.0, 33.8, 31.9, 29.4, 29.3, 29.0, 28.95, 28.89, 25.1, 24.8, 24.6, 22.7, 20.7, 14.1.

*Dodec-1-en-3-ol (**rac-16**).* To a stirred solution of decanal (1.00 g, 6.40 mmol) in Et_2O (14.5 mL) was added dropwise vinylmagnesium bromide (1.0 M in THF, 12.7 mL, 12.7 mmol) at 0 °C. After the mixture was stirred for 4.5 h at 25 °C, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O, and combined organic phases were washed with brine, dried

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over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/AcOEt = 90:10) to give the alcohol ***rac*-16** (593 mg, 50%) as a colorless oil. R_f 0.31 (*n*-hexane/AcOEt = 90:10). The ^{1}H spectrum was identical to that previously reported.[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (1H, ddd, J = 16.8, 10.2, 6.0 Hz), 5.22 (1H, d, J = 16.8 Hz), 5.10 (1H, d, J = 10.2 Hz), 4.14−4.06 (1H, m), 1.55−1.20 (17H, m), 0.88 (3H, t, J = 6.6 Hz).

*3-(tert-Butyldiphenylsilyloxy)dodec-1-ene (**rac-15**).* To a solution of the alcohol ***rac*-16** (114 mg, 0.618 mmol) in DMF (1.1 mL) were added imidazole (227 mg, 3.33 mmol), DMAP (14.0 mg, 0.115 mmol), and TBDPSCl (476 mg, 1.73 mmol) at 25 °C. After the mixture was stirred for 1 h at 50 °C using a heating block, the reaction was quenched with water. The aqueous phase was extracted with AcOEt, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane) to give the silyl ether ***rac*-15** (270 mg, 91%) as a colorless oil. R_f 0.44 (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.64 (4H, m), 7.41−7.32 (6H, m), 5.84−5.74 (1H, m), 4.97 (1H, d, J = 16.8 Hz), 4.94 (1H, d, J = 10.0 Hz), 4.14−4.11 (1H, m), 1.51−1.06 (25H, m), 0.88 (3H, t, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.0, 136.0, 135.9, 134.6, 134.3, 129.5, 129.4, 127.4, 127.3, 114.1, 74.7, 37.6, 31.9, 29.5, 29.3, 27.1, 24.4, 22.7, 19.4, 14.1; IR (neat) 1644, 1590, 1471 cm^{-1}; MS (EI) m/z 422, (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{28}H_{42}OSi$ 422.3005; Found 422.3001.

*Methyl (E)-9-(tert-butyldiphenylsilyloxy)octadec-7-enoate (**rac-I-2**).* According to the procedure described for **13**, the ester ***rac*-I-2** (58.9 mg, 88%, colorless oil) was prepared from the alkene ***rac*-15** (51.6 mg, 0.122 mmol). R_f 0.50 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (4H, m), 7.44−7.33 (6H, m), 5.35 (1H, dd, J = 15.4, 7.2 Hz), 5.23−5.16 (1H, m), 4.09−4.03 (1H, m), 3.66 (3H, s), 2.30−2.20 (2H, m), 1.89−1.82 (2H, m), 1.61−1.04 (31H, m), 0.88 (3H, t, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.2, 136.0, 135.9, 134.6, 133.1, 130.7, 129.4, 129.2, 127.3, 127.2, 74.7, 51.4, 38.0, 34.0, 31.9, 31.8, 29.52, 29.46, 29.3, 28.7, 28.6, 27.0, 24.80, 24.75, 22.7, 19.3, 14.1; IR (neat) 1742, 1428, 1111 cm^{-1}; MS (EI) m/z 550, (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{35}H_{54}O_3Si$ 550.3842; Found 550.3815.

*Methyl 9-(tert-butyldiphenylsilyloxy)stearate (**rac-21**).* According to the procedure described for **14**, the silyl ether ***rac*-21** (223 mg, quant., colorless oil) was prepared from the alkene ***rac*-I-2** (223 mg, 0.404 mmol). R_f 0.50 (*n*-hexane/AcOEt = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (4H, m), 7.41−7.34 (6H, m), 3.72−3.64 (4H, m), 2.28 (2H, t, J = 7.6 Hz), 1.57−1.51 (2H, m), 1.39−1.04 (35H, m), 0.88 (3H, t, J = 6.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.3, 136.0, 134.8, 129.3, 127.3, 73.2, 51.4, 36.3, 36.2, 34.1, 31.9, 29.7, 29.6, 29.53, 29.46, 29.3, 29.14, 29.06, 27.1, 24.91, 24.87, 24.79, 22.6, 19.4, 14.1; IR (neat) 1742, 1590, 1463, 1428, 1111 cm^{-1}; MS (EI) m/z 552, (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{35}H_{56}O_3Si$ 552.3999; Found 552.4034.

*Methyl 9-hydroxystearate (**rac-22**).* According to the procedure described for **16**, the alcohol ***rac*-22** (71.6 mg, 84%, colorless waxy solid) was prepared from the silyl ether ***rac*-21** (150 mg, 0.271 mmol). R_f 0.26 (*n*-hexane/AcOEt = 85:15). The ^{1}H spectrum was identical to that previously reported.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s), 3.61−3.52 (1H, m), 2.30 (2H, t, J = 7.2 Hz), 1.69−1.58 (2H, m), 1.49−1.23 (27H, m), 0.88 (3H, t, J = 6.4 Hz).

*Methyl (9R)-9-{[(2R)-2-(acetyloxy)-2-phenylacetyl]oxy}-octadecenoate and Methyl (9S)-9-{[(2R)-2-(acetyloxy)-2-phenylacetyl]oxy}octadecanoate (**rac-22**/(R)-O-Acetyl-Mandelic Acid Ester).* According to the procedure described for **23**, ***rac*-22**/(*R*)-*O*-acetyl-mandelic acid ester (12.8 mg, 75%, colorless oil) was prepared from the alcohol ***rac*-22** (11.0 mg, 0.0350 mmol). R_f 0.38 (*n*-hexane/AcOEt = 85:15). The ^{1}H spectrum was identical to the corresponding diastereomers previously reported.[2c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.46 (2H, m), 7.38−7.26 (3H, m), 5.873 (0.5H, s, for (***R*)-22** derivative), 5.869 (0.5H, s, for (***S*)-22** derivative), 4.89−4.82 (1H, m), 3.671 (1.5H, s, for (***R*)-22** derivative), 3.668 (1.5H, s, for (***S*)-22** derivative), 2.30 (1H, t, J = 7.5 Hz, for (***R*)-22** derivative), 2.27 (1H, t, J = 7.5 Hz, for (***S*)-22** derivative), 2.20 (3H, s), 1.67−1.45 (4H, m), 1.38−0.99 (24H, m), 0.885 (1.5H, t, J = 7.0 Hz, for (***R*)-22** derivative), 0.882 (1.5H, t, J = 7.0 Hz, for (***S*)-22** derivative).

*2,2-Dimethyl-5-hydroxy-4-oxo-benzo-1,4-dioxin (**I-3**).* To a stirred solution of 2,6-dihydroxybenzoic acid (5.00 g, 32.4 mmol), DMAP (198 mg, 1.62 mmol), and acetone (3.10 mL, 42.2 mmol) in dimethyl ether (DME) (11.5 mL) was added dropwise $SOCl_2$ (3.31 mL, 45.4 mmol) in DME at 0 °C. After the mixture was stirred for 2 h at 25 °C, the solvent was removed in vacuo. The residue was dissolved in a mixture of *n*-hexane-CH_2Cl_2 (1:1, v/v) and filtered through a pad of silica gel. The pad was washed with the mixture of *n*-hexane-CH_2Cl_2 (1:1, v/v), and the combined filtrates were concentrated in vacuo. The residue was purified repeatedly by recrystallization from *n*-hexane to give **I-3** (1.49 g, 24%) as a colorless solid. R_f 0.60 (*n*-hexane/AcOEt = 80:20). The ^{1}H NMR spectrum of the phenol **I-3** is identical to that previously reported.[13b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (1H, s), 7.42 (1H, dd, J = 8.3, 8.0 Hz), 6.64 (1H, d, J = 8.3 Hz), 6.44 (1H, d, J = 8.0 Hz), 1.75 (6H, s).

*2,2-Dimethyl-5-(trifluoromethanesulfonyl)-benzo[1,3]dioxin-4-one (**24**).* To a solution of **I-3** (1.49 g, 7.67 mmol) in pyridine (1.44 mL) was added dropwise Tf_2O (1.50 mL, 9.20 mmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, the reaction mixture was diluted with Et_2O and the reaction was quenched with 0.1 M aqueous HCl. The aqueous phase was extracted with AcOEt and the combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by recrystallization from CH_2Cl_2/AcOEt/*n*-hexane (1:1:3, v/v) to give the triflate **24** (1.95 g, 78%) as colorless needles. R_f 0.35 (*n*-hexane/AcOEt = 80:20). The ^{1}H NMR spectrum of the triflate **24** is identical to that previously reported.[13c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, dd, J = 8.9, 8.3 Hz), 7.06 (1H, d, J = 8.9 Hz), 7.00 (1H, d, J = 8.3 Hz), 1.77 (6H, s).

*2,2-Dimethyl-5-(non-8-en-1-yl)-4H-benzo[d][1,3]dioxin-4-one (**25**).* A mixture of $Pd(OAc)_2$ (105 mg, 0.468 mmol), LiOAc (492 mg, 7.46 mmol), LiCl (492 mg, 7.46 mmol), TBAC (1.75 g, 6.30 mmol), and MS4A (powdered, 1.23 g) in a round-bottom flask was dried by heating at 150 °C in an oil bath under reduced pressure. CH_3CN (30 mL), 7-octen-1-ol (238 mg, 1.86 mmol), and triflate **24** (508 mg, 1.56 mmol) were then added to the flask. After the mixture was stirred at 50 °C (using an oil bath) for 70 h, the reaction was quenched with water and CH_3CN was removed in vacuo. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude aldehyde **I-4**. **I-4**: R_f 0.14 (*n*-hexane/AcOEt = 75:25); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (1H, t, J = 1.5 Hz), 7.39 (1H, dd, J = 8.0, 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.80 (1H, d, J = 8.0 Hz), 3.09−3.06 (2H, m), 2.41 (2H, td, J = 7.5, 1.5 Hz), 1.70−1.56 (10H, m), 1.40−1.30 (6H, m).

To a stirred suspension of CH_3PPh_3Br (predried by heating in vacuo, 2.15 g, 6.02 mmol) in THF (28 mL) was added BuLi (1.6 M in *n*-hexane, 5.6 mL, 9.0 mmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, to the resultant yellow solution at −78 °C was added dropwise a solution of the above crude aldehyde **I-4** in THF (9 mL). After the mixture was stirred at 25 °C for 15 h, the reaction was quenched with saturated aqueous HCl at 0 °C. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/AcOEt = 95:5) to give the alkene **25** (253 mg, 54% for 2 steps) as a colorless oil. R_f 0.32 (*n*-hexane/AcOEt = 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (1H, dd, J = 8.5, 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.80 (1H, d, J = 8.0 Hz), 5.81 (1H, ddt, J = 15.5, 10.0, 7.5 Hz), 4.98 (1H, d, J = 15.5 Hz), 4.92 (1H, d, J = 10.0 Hz), 3.08 (2H, t, J = 7.8 Hz), 2.03 (2H, dt, J = 7.5, 7.5 Hz), 1.70 (6H, s), 1.59−1.56 (2H, m), 1.40−1.28 (8H, m); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.2, 157.1, 148.5, 139.2, 135.0, 125.1, 115.0, 114.1, 112.1, 104.9, 34.4, 33.8, 31.2, 29.6, 29.3, 29.1, 28.9, 25.6; IR (neat) 1739, 1606, 1582, 1477, 1211 cm^{-1}; MS

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(EI) m/z 302 (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{19}H_{26}O_3$ 302.1882; Found 302.1900.

*(2S,3R)-1,2-Epoxy-3-(tert-butyldiphenylsilyloxy)oct-4-ene (**I-5**).* According to the procedure described for **13**, the alkene **I-5** (40.2 mg, 71%, colorless oil) was prepared from **12** (50.2 mg, 0.148 mmol) and 1-pentene (210 mg, 3.00 mmol) in the presence of the Schrodi−Stewart−Grubbs catalyst (4.6 mg, 8.06 mmol). R_f 0.29 (*n*-hexane/AcOEt = 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.65 (4H, m), 7.42−7.33 (6H, m), 5.47−5.45 (2H, m), 3.94 (1H, dd, J = 5.2, 5.2 Hz), 2.92−2.90 (1H, m), 2.55 (1H, dd, J = 5.0, 4.0 Hz), 2.28 (1H, dd, J = 5.0, 3.0 Hz), 1.95−1.91 (2H, m), 1.33−1.29 (2H, m), 1.06 (9H, s), 0.85 (3H, t, J = 7.4 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.0, 135.9, 133.9, 133.7, 133.6, 129.7, 129.6, 128.7, 127.5, 127.4, 73.9, 54.7, 45.2, 34.2, 26.9, 22.1, 19.3, 13.6; IR (neat) 1428, 1112 cm^{-1}; MS (EI) m/z 323 (M^+−*t*Bu); HRMS (EI) m/z: $[M-t\text{Bu}]^+$ calcd for $C_{20}H_{23}O_2Si$ 323.1467; Found 323.1471; $[\alpha]_D^{25}$ −38.4 (*c* 1.00, $CHCl_3$).

*(2S,3R)-1,2-Epoxy-3-(tert-butyldiphenylsilyloxy)octane (**I-6**).* According to the procedure described for **14**, the epoxide **I-6** (12.6 mg, 97%, colorless oil) was prepared from **I-5** (12.9 mg, 0.0339 mmol). R_f 0.56 (*n*-hexane/toluene = 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.66 (4H, m), 7.44−7.36 (6H, m), 3.40−3.36 (1H, m), 2.87−2.85 (1H, m), 2.47−2.43 (1H, m), 2.15−2.12 (1H, m), 1.61−1.57 (2H, m), 1.42−1.33 (2H, m), 1.26−1.17 (4H, m), 1.05 (9H, s), 0.85 (3H, t, J = 6.5 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.90, 135.86, 134.0, 133.9, 129.7, 129.6, 127.6, 127.5, 73.3, 54.3, 46.3, 35.3, 31.9, 26.9, 24.0, 22.5, 19.4, 14.0; IR (neat) 1428, 1111 cm^{-1}; MS (EI) m/z 325 (M^+−*t*Bu); HRMS (EI) m/z: $[M-t\text{Bu}]^+$ calcd for $C_{20}H_{25}O_2Si$ 325.1624; Found 325.1616; $[\alpha]_D^{25}$ −20.2 (*c* 1.52, $CHCl_3$).

*(R)-3-(tert-Butyldiphenylsilyloxy)oct-1-ene (**26**).* According to the procedure described for **15**, the alkene **26** (9.4 mg, 60%, colorless oil) was prepared from **I-6** (16.3 mg, 0.0426 mmol). R_f 0.57 (*n*-hexane/AcOEt = 98:2). The ^{1}H NMR spectrum of the alkene **26** is identical to that previously reported.[16] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.65 (4H, m), 7.41−7.34 (6H, m), 5.79 (1H, ddd, J = 15.5, 9.0, 6.5 Hz), 4.97 (1H, d, J = 15.5 Hz), 4.94 (1H, d, J = 9.0 Hz), 4.15−4.11 (1H, m), 1.45−1.06 (17H, m), 0.81 (3H, t, J = 7.0 Hz); $[\alpha]_D^{23}$ −21.1 (*c* 0.21, $CHCl_3$) [lit. $[\alpha]_D^{28}$ −19.3 (*c* 0.7, $CHCl_3$)][16]

*2,2-Dimethyl-5-[(R,E)-10-(tert-butyldiphenylsilyloxy)pentadec-8-en-1-yl]-4H-benzo[d][1,3]dioxin-4-one and 2,2-Dimethyl-5-[(R,Z)-10-(tert-butyldiphenylsilyloxy)pentadec-8-en-1-yl]-4H-benzo[d][1,3]dioxin-4-one (**I-7**, trans/cis = 9:1).* According to the procedure described for **13**, the benzodioxinone **I-7** (21.6 mg, 80%, *trans*/*cis* = 9:1, colorless oil) was prepared from the alkene **26** (24.0 mg, 0.0655 mmol) and the alkene **25** (36.1 mg, 0.119 mmol) in the presence of the Hoveyda−Grubbs second-generation catalyst (2.2 mg, 0.00351 mmol). R_f 0.34 (*n*-hexane/AcOEt = 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.64 (4H, m), 7.40−7.30 (7H, m), 6.92 (1H, d, J = 7.5 Hz), 6.79 (1H, d, J = 8.0 Hz), 5.35 (1H, dd, J = 15.5, 7.0 Hz), 5.22 (1H, ddd, J = 15.5, 8.5, 7.0 Hz), 4.41−4.36 (0.1H, m), 4.07−4.02 (0.9H, m), 3.10−3.05 (2H, m), 2.06−2.04 (0.2H, m), 1.88−1.82 (1.8H, m), 1.70 (6H, s), 1.61−1.08 (18H, m), 1.03 (9H, s), 0.82 (3H, t, J = 6.4 Hz); ^{13}C{^{1}H} NMR (major isomer, 126 MHz, $CDCl_3$) δ 160.2, 157.1, 148.5, 136.0, 135.9, 135.0, 134.7, 134.6, 132.8, 131.2, 129.3, 129.2, 127.3, 127.2, 125.0, 115.0, 112.1, 104.9, 74.7, 38.0, 34.4, 32.0, 31.7, 31.2, 29.6, 29.3, 29.1, 27.1, 25.7, 24.5, 22.5, 19.3, 14.0; IR (neat): 1740, 1606, 1582, 1476, 1211 cm^{-1}; MS (EI) m/z 584 (M^+−*t*Bu); HRMS (EI) m/z: $[M]^+$ calcd for $C_{41}H_{56}O_4Si$ 640.3948; Found 640.3958; $[\alpha]_D^{22}$ +12.3 (*c* 1.30, $CHCl_3$).

*2,2-Dimethyl-5-[(R,E)-10-hydroxypentadec-8-en-1-yl]-4H-benzo-[d][1,3]dioxin-4-one (**27**).* According to the procedure described for **16**, the alcohol **27** (8.9 mg, 67%, colorless oil) was prepared from the silyl ether **I-7** (21.2 mg, 0.0331 mmol). R_f 0.31 (*n*-hexane/AcOEt = 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (1H, dd, J = 8.0, 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.80 (1H, d, J = 8.0 Hz), 5.65−5.59 (1H, m), 5.44 (1H, dd, J = 15.5, 7.5 Hz), 4.05−4.01 (1H, m), 3.08 (2H, t, J = 7.8 Hz), 2.04−1.99 (2H, m), 1.70 (6H, s), 1.61−1.25 (19H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.3, 157.1, 148.5, 135.1, 133.0, 132.2, 125.1, 115.1, 112.1, 104.9, 73.2, 37.3, 34.4, 32.1, 31.8, 29.6, 29.2, 29.0, 25.6, 25.2, 22.6, 14.0; IR (neat) 3438, 1739, 1606, 1582, 1478 cm^{-1}; MS (EI) m/z 402 (M^+); HRMS (EI) m/z: $[M]^+$ calcd for $C_{25}H_{38}O_4Si$ 402.2770; Found 402.2797; $[\alpha]_D^{25}$ +3.4 (*c* 0.16, $CHCl_3$).

*(−)-2-Hydroxy-6-[(R)-10′-hydroxypentadec-8′(E)-enyl]benzoic Acid [(**R**)-**3**].* To a stirred solution of the benzodioxinone **27** (2.5 mg, 6.21 μmol) in THF (7.9 μL) and H_2O (7.9 μL) was added KOH (4.6 mg, 82.0 μmol) at 25 °C. After the mixture was stirred for 2.5 h at 75 °C using a heating block, the reaction mixture was concentrated in vacuo. After the residue was diluted with CH_2Cl_2 and H_2O, the solution was acidified (adjusted to pH 1) by $KHSO_4$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by PTLC (eluent: 1% HCOOH in toluene/AcOEt = 70:30) to give the benzoic acid (***R***)-**3** (1.6 mg, 71%) as a colorless oil. R_f 0.55 (1% HCOOH in toluene/AcOEt = 60:40); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.6 (1H, br s), 7.30 (1H, dd, J = 10.0, 9.8 Hz), 6.83 (1H, d, J = 10.0 Hz), 6.72 (1H, d, J = 9.0 Hz), 5.71−5.65 (1H, m), 5.47 (1H, dd, J = 8.5 Hz), 4.23−4.17 (1H, m), 2.93−2.87 (2H, m), 2.57 (2H, br), 2.12−2.04 (2H, m), 1.65−1.28 (18H, m), 0.89 (3H, t, J = 8.0 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.5, 163.4, 147.5, 134.8, 133.1, 131.9, 122.6, 115.6, 111.0, 73.8, 37.3, 36.5, 31.8, 31.7, 31.3, 29.3, 28.6, 28.2, 27.8, 25.0, 22.6, 14.0; IR (neat) 3423, 1655, 1605, 1451 cm^{-1}; MS (EI) m/z 344 (M^+−18); HRMS (EI) m/z: $[M]^+$ calcd for $C_{22}H_{34}O_4$ 362.2457; Found 362.2495; $[\alpha]_D^{25}$ −21.1 (*c* 0.080, $CHCl_3$); [lit. $[\alpha]_D^{17}$ +23.2 ($CHCl_3$)][3b]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02821.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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