Synthesis and Absolute Configuration of (−)-Subersic Acid, a Sponge-Derived, Terpenoidal Inhibitor of Human 15-Lipoxygenase[‡]

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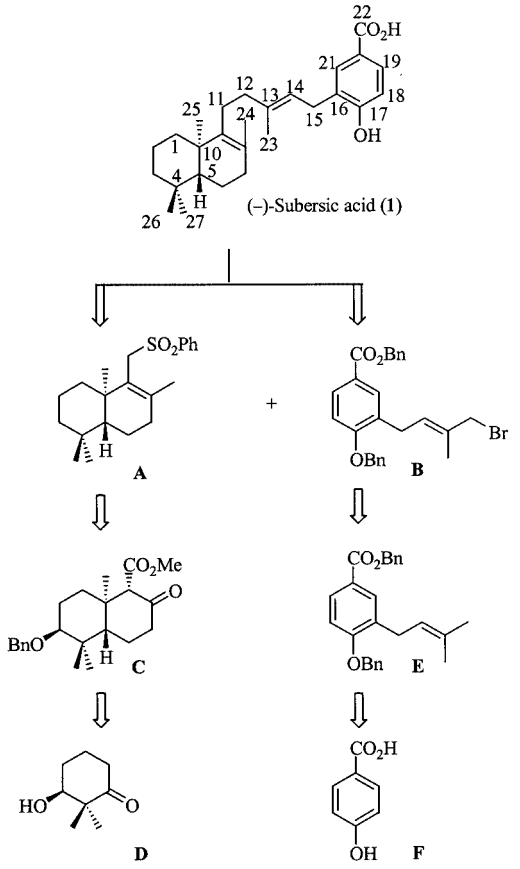
(–)-Subersic acid (**1**), a new derivative of *p*-hydroxybenzoic acid in which the *m*-position is substituted with a bicyclic diterpenoid, was synthesized from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone and *p*-hydroxybenzoic acid. The stereochemistry of this sponge-derived inhibitor of human 15-lipoxygenase was established as (5*R*,10*R*)-**1**.

Introduction

In 2001, Crews and co-workers isolated (−)-subersic acid (**1**, Scheme 1) from the Papua New Guinean sponge *Suberea* sp. as an inhibitor of human 15-lipoxygenase.[1] The compound's structure **1** was proposed on the basis of extensive NMR analysis, and its (5*R*,10*R*) absolute stereochemistry was suggested by the positive molar rotation of **1**.[1] We became interested in synthesizing (−)-**1** so as to verify its proposed structure, including its stereochemistry. Scheme 1 shows our synthetic plan for (−)-subersic acid: the target molecule **1** was to be constructed by alkylation of the sesquiterpene part **A** with the *m*-prenylated *p*-hydroxybenzoic acid part **B**. The sesquiterpene part **A** was to be synthesized from the known β-oxo ester **C**,[2] which has been prepared from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone (**D**).[3] The *p*-hydroxybenzoic acid derivative **B** was to be synthesized from *p*-hydroxybenzoic acid **F** via its *m*-prenylated derivative **E**. This paper describes the successful execution of the above plan to give (5*R*,10*R*)-(−)-subersic acid (**1**).



Scheme 1. Structure and retrosynthetic analysis of (−)-subersic acid; the numbering system used for **1** is that by Crews[1]

Results and Discussion

The synthesis of the β-oxo ester (+)-**10** is summarized in Scheme 2. The starting ketone **2** (= **D**) was converted into **5** (= **C**) by Mori and Koga's method.[2] Namely, ring-closure of unsaturated β-oxo ester **3** by treatment with tin(IV) chloride in wet dichloromethane gave a mixture of **4** and **5**, which could be separated by silica gel chromatography to give **5** in 7% overall yield based on **2** (nine steps). Acetalization of the oxo ester **5** under Noyori conditions[4] provided ethylene acetal (+)-**6**, the benzyl protective group of which was removed by hydrogenolysis to furnish crystalline (−)-

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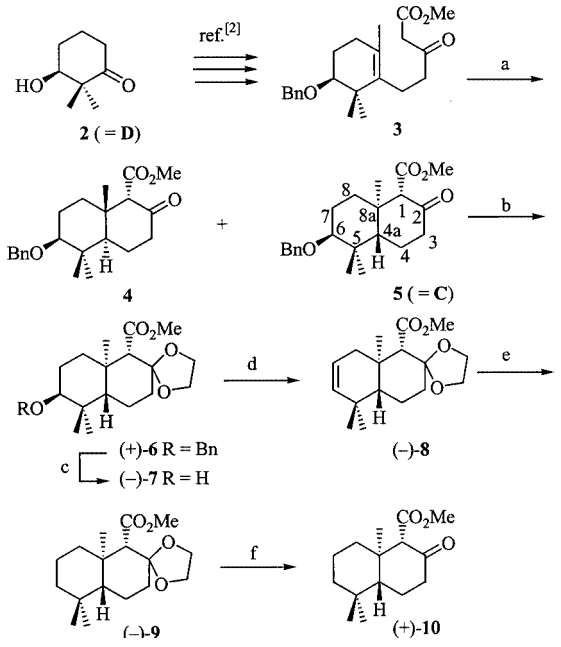
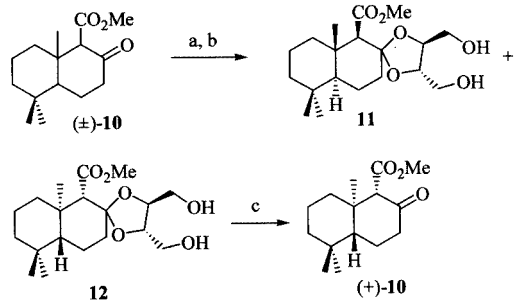
7. Dehydration of **7** with trifluoromethanesulfonyl (triflyl = Tf) chloride and 4-(dimethylamino)pyridine (DMAP) in dichloromethane[5] yielded olefin (−)-**8**. Hydrogenation of (−)-**8** in the presence of palladium/charcoal gave (−)-**9**, which was treated with hydrochloric acid to give β-oxo ester (+)-**10** in 50% overall yield based on **5** (five steps).



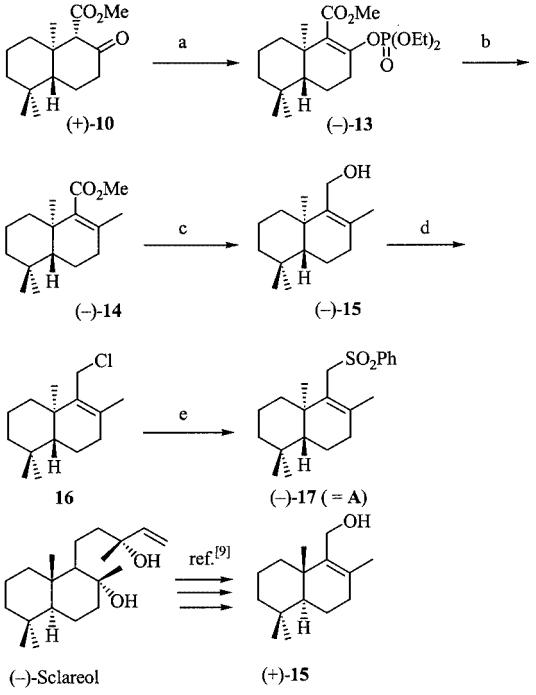
Scheme 2. Synthesis of (+)-**10** from **2**; reagents: (a) $SnCl_4$, wet CH_2Cl_2 (7% of **5** from **2**, nine steps); (b) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2 (76%); (c) H_2, 10% Pd/C, EtOAc (80%); (d) TfCl, DMAP, CH_2Cl_2 (90%); (e) H_2, 10% Pd/C, EtOAc (quant.); (f) 6 M HCl, THF (91%)

Katsumura and co-workers, however, recently reported an alternative procedure for the preparation of (+)-**10** (Scheme 3).[6] They converted (±)-**10**[7] into a diastereomeric mixture of acetals **11** and **12**, which could be separated by silica gel chromatography. Acid hydrolysis of **12** afforded (+)-**10**. This is indeed a short, six-step procedure to secure (+)-**10** from geraniol, but chromatographic separation of **11** and **12** was found to be rather tedious in our hands. In spite of the linear and multi-step nature of our route, our synthesis readily provided a substantial amount of pure (+)-**10**, because the separation of **4** and **5** was easier than that of **11** and **12**.

Scheme 4 shows the conversion of (+)-**10** into (−)-**17** (= **A**). By the known procedure recorded for conversion of (±)-**10** to (±)-**15**,[8] (+)-**10** furnished crystalline alcohol (−)-**15**, $[\alpha]_D^{24} = -115$ ($c = 0.13$, $CHCl_3$), via (−)-**13** and (−)-**14**. The known (+)-**15**, previously prepared from naturally occurring (−)-sclareol, was reported to have the specific rotation value $[\alpha]_D^{18} = +113$ ($c = 0.14$, $CHCl_3$).[9] Treatment of (−)-**15** with methanesulfonyl (mesyl = Ms) chloride and lithium chloride in DMF gave the unstable chloride **16**, which was used immediately for the next step to give the desired phenyl sulfone (−)-**17** (= sesquiterpene part **A**) as crystals.



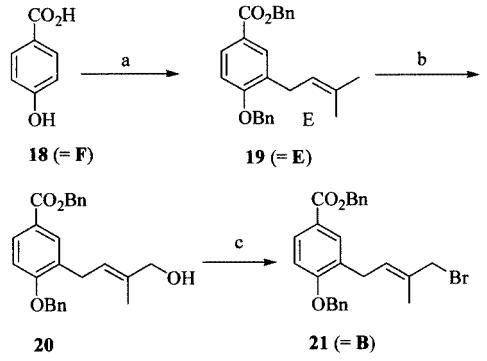
Scheme 3. Preparation of (+)-**10** from (±)-**10**; reagents: (a) (2*S*,3*S*)-1,2,3,4-butanetetraol 1,4-dibenzyl ether; (b) H_2, 10% Pd/C, EtOAc; then SiO_2 chromatography [33% of **11** and 30% of **12** from (±)-**10**]; (c) 5% H_2SO_4, MeOH, heat (91%)



Scheme 4. Synthesis of (−)-**17**; reagents: (a) NaH, $(EtO)_2POCl$, THF (89%); (b) Me_2CuLi, THF (87%); (c) $(iBu)_2AlH$, CH_2Cl_2 (95%); (d) MsCl, LiCl, DMF; (e) $PhSO_2Na$, DMF (70% based on **15**)

The prenylated *p*-hydroxybenzoic acid derivative **21** (= **B**) was synthesized as summarized in Scheme 5. *p*-Hydroxybenzoic acid (**18** = **F**) was dissolved in aqueous sodium hydroxide, and prenyl bromide was added to the solution to effect prenylation.[10] The crude product was treated in DMF with benzyl bromide and potassium carbonate to give the benzyl-protected prenylation product **19** (= **E**) in 9.5% yield after chromatographic purification. Although the yield of **19** was quite low, **19** could be obtained readily, because the crystalline by-product (benzyl *p*-benzyloxybenzoate) in this step could be removed simply by filtration. Oxidation of **19** with selenium dioxide and *tert*-butyl hydroperoxide afforded a mixture of the starting material **19**, alcohol **20**, and the corresponding aldehyde. This mixture was reduced with sodium borohydride, and the product was puri-

fied by silica gel chromatography to furnish pure **20** in 45% yield. The alcohol **20** gave the corresponding bromide **21** (= **B**) as crystals upon treatment with methanesulfonic anhydride and lithium bromide in the presence of DMAP and collidine in DMF.

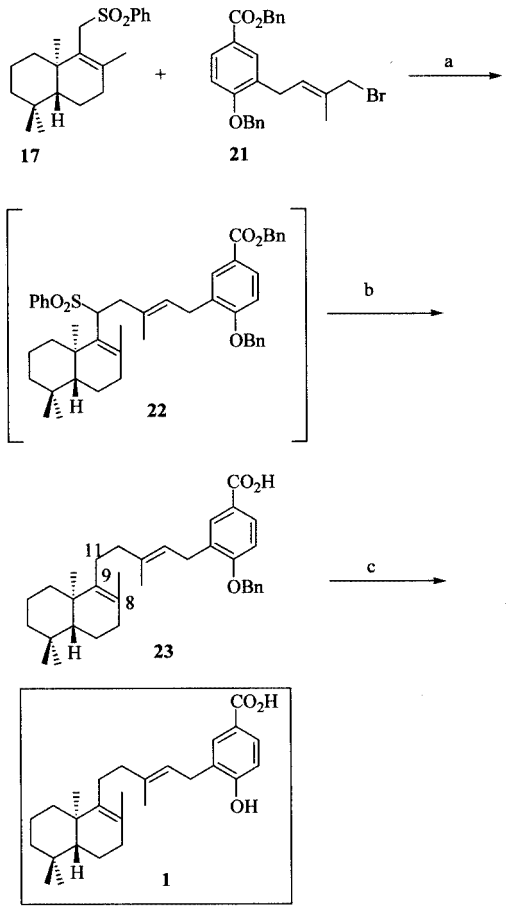


Scheme 5. Synthesis of **21**; reagents: (a) i) $Me_2C{=}CHCH_2Br$, NaOH, H_2O; ii) BnBr, K_2CO_3, DMF (9.5%); (b) i) SeO_2, $tBuO_2H$, CH_2Cl_2, ii) $NaBH_4$, THF/H_2O (45%); (c) Ms_2O, LiBr, DMAP, *s*-collidine, DMF (87%)

Scheme 6 shows the final stage of the synthesis to give (−)-subersic acid (**1**). A carbanion was generated from the phenyl sulfone **17** in THF by treatment with *n*-butyllithium in the presence of HMPA. It was then alkylated with the bromide **21** to give the coupling product **22** as a diastereomeric mixture.[11] Reductive removal of the phenylsulfonyl group of **22** was achieved by use of 5% sodium amalgam (126 equiv.) in the presence of disodium hydrogen phosphate (20 equiv.) in THF/MeOH (1:5) to give **23**, in 35% yield based on **17** and as fine needles after chromatographic purification and recrystallization. Unfortunately, the crystals of **23** were not suitable for X-ray analysis. NMR analysis of the mother liquor after collection of **23** revealed the presence of a by-product, which seemed to be a $\Delta^{9(11)}$-double bond isomer of **23** generated by the migration of the $\Delta^{8(9)}$-double bond in the course of the reductive removal of the phenylsulfonyl group.

The concluding step of the synthesis was the removal of the benzyl protective group of **23**. Treatment of **23** with a freshly prepared 1.0 M solution of lithium naphthalenide (4 equiv.) in THF furnished (−)-subersic acid (**1**) as a slightly unstable, amorphous solid. Its chromatographic purification, TLC separation, dissolution in $CDCl_3$ for NMR measurement, irradiation with UV or visible light, and even concentration of its solution in vacuo all increased the amount of impurities in the synthetic sample. The ^1H NMR and ^{13}C NMR spectra of our synthetic **1** were identical with those of the natural (−)-subersic acid.[1]

Our synthetic (5*R*,10*R*)-subersic acid (**1**) was levorotatory: $[\alpha]_D^{24} = -52.2$ (c = 0.52, $CHCl_3$). Since the natural **1** was also levorotatory {$[\alpha]_D = -46$ (c = 0.5, $CHCl_3$)}, our synthetic **1** must possess the same absolute configuration as that of the natural product. It was therefore concluded that (−)-subersic acid was indeed (5*R*,10*R*)-**1**, as proposed by



Scheme 6. Synthesis of (−)-subersic acid (**1**); reagents: (a) *n*BuLi, THF/HMPA; (b) 5% Na/Hg, Na_2HPO_4, MeOH/THF (35% based on **17**); (c) Li, naphthalene, THF (75%); the numbering system used for **23** follows that for **1** by Crews;[1] the IUPAC names of **1** and **23** are given in the Exp. Sect.

Crews.[1] The overall yield of (−)-**1** was 6.7% based on **5** (13 steps).

Experimental Section

General: Boiling and melting points: Uncorrected values. Melting points: Yanaco MP-S3, Büchi B-540. n_D: Atago DNT-1. $[\alpha]_D$: Jasco DIP-370, Jasco DIP-1000, Jasco DIP-1010. IR: Jasco IRA-102, Jasco FT/IR-460 plus, Perkin−Elmer FT-IR 1640. ^1H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 400, Bruker DPX 300, Bruker DPX 500 (TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ as an internal standard). ^{13}C NMR: Jeol JNM-LA 400 (100 MHz), Bruker DPX 300(75 MHz), Bruker DPX 500(125 MHz) ($CDCl_3$ at $\delta_C = 77.0$ as an internal standard). MS: Jeol JMS-AX 505HA, Jeol SX-102A. CC: Merck Kieselgel 60 Art 1.07734 or Kanto Chemical silica gel 60N (spherical neutral). TLC: 0.25 mm Merck silica gel plates (60F-254).

Methyl (1*S*,4a*S*,6*S*,8a*R*)-6-Benzyloxy-2,2-ethylenedioxy-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate (6): TMSOTf (0.73 mL, 4 mmol) was added at −78 °C under argon to a stirred solution of **5** (14.2 g, 39.6 mmol) and 1,2-bis(trimethylsilyloxy)ethane (12.4 g, 59.8 mmol) in CH_2Cl_2 (60 mL). The resulting mixture was stirred at −78 °C for 4 h and at 0 °C for 16 h, and was then poured into

water (150 mL), and extracted with Et_2O (2 × 500 mL). The combined organic phases were washed with a saturated aqueous sodium hydrogen carbonate solution and brine (each 1 × 150 mL), dried with magnesium sulfate, and concentrated in vacuo to give 20 g of a crude red oil. This was purified by silica gel chromatography (600 g, EtOAc/*n*-hexane, 1:6, then 1:4) to give **6** (12.1 g, 76%) as a pale yellow oil: n_D^{22} = 1.5171. $[\alpha]_D^{23}$ = +2.44 (*c* = 1.16, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 1740 (s, C=O), 1195 (m, C−O−C), 1155 (m, C−O−C), 1125 (m, C−O−C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.05−1.25 (m, 2 H, CH_2), 1.25 (s, 3 H, CH_3), 1.35−1.87 (m, 7 H), 2.60 (s, 1 H, $CHCO_2CH_3$), 3.06 (s, 1 H, $CHOCH_2Ph$), 3.63 (s, 3 H, CO_2CH_3), 3.73 (dd, *J* = 13.4 Hz, 6.0 Hz, 1 H, OCH_2CH_2O), 3.84 (dd, *J* = 13.4 Hz, 6.0 Hz, 1 H, OCH_2CH_2O), 3.92 (dd, *J* = 13.4 Hz, 6.0 Hz, 1 H, OCH_2CH_2O), 4.07 (dd, *J* = 13.4 Hz, 6.0 Hz, 1 H, OCH_2CH_2O), 4.34 (d, *J* = 8.4 Hz, 1 H, OCH_2Ph), 4.62 (d, *J* = 8.4 Hz,1 H, OCH_2Ph), 7.26−7.37 (m, 5 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 19.4, 20.3, 22.2, 28.8, 32.8, 37.5, 37.9, 38.8, 48.2, 51.0, 62.2, 64.0, 65.5, 70.8, 83.0, 109.3, 127.2, 127.4, 128.2, 139.3, 171.4 ppm. $C_{24}H_{34}O_5$ (402.5): calcd. C 71.61, H 8.51; found C 71.63, H 8.79.

Methyl (1*S*,4a*S*,6*S*,8a*R*)-2,2-Ethylenedioxy-6-hydroxy-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate (7): A suspension of Pd on carbon (10%, 1.2 g) in a solution of **6** (12 g, 30 mmol) in EtOAc (100 mL) was stirred under H_2 at room temperature for 11 h. The mixture was filtered and the filtrate was concentrated in vacuo to give 11.4 g of crude **7** as a colorless solid. It was recrystallized to give a first crop of **7** (4.9 g) as colorless needles. The mother liquor was concentrated and was purified by silica gel chromatography (300 g, EtOAc/*n*-hexane, 1:2) to give further **7** (2.5 g) as a colorless solid. The total amount of **7** was 7.4 g (80%). M.p. 162.0−163.0 °C (EtOAc/*n*-hexane). $[\alpha]_D^{24}$ = −14.0 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3430 cm^{-1} (s, OH), 1735 (s, C=O), 1195 (m, C−O−C), 1155 (m, C−O−C), 1125 (m, C−O−C). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 5-CH_3), 0.97 (s, 3 H, 5-CH_3), 1.11 (dt, *J* = 13.2 Hz, 3.1 Hz, 1 H), 1.24 (s, 3 H, 8a-CH_3), 1.40−1.50 (m, 2 H), 1.52−1.65 (m, 3 H), 1.71 (dt, *J* = 13.4 Hz, 3.4 Hz, 1 H), 1.86 (dt, *J* = 12.9 Hz, 2.9 Hz,1 H), 1.98 (dddd, 14.4 Hz, 14.4 Hz, 3.4 Hz, 3.4 Hz, 1 H, 7eq−*H*), 2.60 (s, 1 H, $CHCO_2CH_3$), 3.44 (seemingly s, 1 H, $CHOH$), 3.63 (s, 3 H, CO_2CH_3), 3.74 (dd, *J* = 13.4 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 3.87 (dd, *J* = 13.4 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 3.93 (dd, *J* = 13.4 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 4.08 (dd, *J* = 13.4 Hz, 6.3 Hz, 1 H, OCH_2CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 19.6, 22.0, 25.1, 28.4, 32.4, 37.4, 37.6, 38.8, 47.5, 51.0, 62.3, 64.0, 65.6, 75.7, 109.2, 171.3 ppm. $C_{17}H_{28}O_5$ (312.4): calcd. C 65.36, H 9.03; found C 65.43, H 9.17.

Methyl (1*S*,4a*S*,8a*R*)-2,2-Ethylenedioxy-5,5,8a-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (8): Trifluoromethanesulfonyl chloride (0.23 mL, 2.15 mmol) was added at 0 °C under argon to a stirred solution of **7** (268 mg, 0.86 mmol) and DMAP (630 mg, 5.15 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was stirred at room temperature for 2 h, and diluted with Et_2O (100 mL). The diethyl ether solution was washed with water (150 mL), 10% aqueous citric acid solution, saturated aqueous sodium hydrogen carbonate solution, and brine (each 1 × 20 mL), and dried with magnesium sulfate. The combined aqueous phase was reextracted with EtOAc (2 × 50 mL). The organic phase was dried with magnesium sulfate. All of the organic phase was combined, filtered and concentrated in vacuo to give 330 mg of a crude solid. This was purified by silica gel chromatography (twice: 40 g, EtOAc/*n*-hexane, 1:4; 40 g, Et_2O/*n*-hexane, 1:20 to 1:12 to 1:8) to give **8** (227 mg, 90%) as a colorless solid, which was recrystallized from *n*-hexane to give an analytical sample as colorless needles. M.p. 105.0−106.5 °C. $[\alpha]_D^{24}$ = −27.4 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 1735 cm^{-1}(s, C=O), 1195 (m, C−O−C), 1155 (m, C−O−C), 1125 (m, C−O−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, 5-CH_3), 0.98 (s, 3 H, 5-CH_3), 1.21 (s, 3 H, 8a-CH_3), 1.26 (dd, *J* = 9.0 Hz, 6.0 Hz, 1 H, 4a-*H*), 1.37−1.52 (m, 1 H, 4_{ax}-*H*), 1.57−1.74 (m, 3 H, 4_{eq}-*H*, 3_{ax}-*H*, 8_{ax}-*H*), 1.86 (dt, *J* = 12.6 Hz, 3.0 Hz, 1 H, 3_{eq}-*H*), 1.96 (d, *J* = 17 Hz, 1 H, 8_{eq}-*H*), 2.55 (s, 1 H, $CHCO_2CH_3$), 3.65 (s, 3 H, CO_2CH_3), 3.78 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 3.87 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 3.95 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 4.11 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 5.37 (dd, *J* = 9.9 Hz, 2.4 Hz, 1 H, 6-*H*), 5.41 (ddd, *J* = 9.9 Hz, 5.4 Hz, 0.9 Hz, 1 H, 7-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 20.9, 22.8, 31.8, 34.6, 37.0, 38.0, 39.6, 50.5, 51.1, 61.4, 64.1, 65.6, 76.6, 109.0, 120.6, 137.9, 171.1 ppm. $C_{17}H_{26}O_4$ (294.4): calcd. C 69.36, H 8.90; found C 69.32, H 8.99.

Methyl (1*S*,4a*R*,8a*R*)-2,2-Ethylenedioxy-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate (9): A suspension of Pd on carbon (10%, 0.6 g) in a solution of **8** (5.9 g, 20 mmol) in EtOAc (120 mL) was stirred under H_2 at room temperature for 19 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give 5.98 g of crude **9** as a colorless solid. It was purified by silica gel chromatography (200 g, EtOAc/*n*-hexane, 1:4) to give **9** as a colorless solid (5.95 g, quant.), which was recrystallized from EtOAc/*n*-hexane to give an analytical sample as colorless needles. M.p. 151.0−152.0 °C. $[\alpha]_D^{24}$ = −30.4 (*c* = 0.99, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 1735 cm^{-1} (s, C=O), 1195 (m, C−O−C), 1145 (s, C−O−C), 1120 (m, C−O−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3), 0.92 (dd, *J* = 11.4 Hz, 2.4 Hz, 1 H), 1.10−1.25 (m, 2 H), 1.23 (s, 3 H, CH_3), 1.30−1.72 (m, 7 H), 1.86 (dt, *J* = 12 Hz, 2.4 Hz, 1 H), 2.51 (s, 1 H, $CHCO_2CH_3$), 3.634, 3.637 [each (s), total 3 H, CO_2CH_3], 3.74 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 3.85 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 3.94 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O), 4.08 (dd, *J* = 12.6 Hz, 6.3 Hz, 1 H, OCH_2CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 18.4, 20.0, 21.5, 33.2, 33.6, 37.6, 39.1, 39.7, 41.9, 51.0, 54.7, 62.7, 63.9, 65.5, 109.2, 171.3 ppm. $C_{17}H_{28}O_4$ (296.4): calcd. C 68.89, H 9.52; found C 68.93, H 9.71.

Methyl (1*S*,4a*R*,8a*R*)-5,5,8a-Trimethyl-2-oxodecahydronaphthalene-1-carboxylate (10): A solution of **9** (3.0 g, 10 mmol) in THF (30 mL) and HCl (6 M, 10 mL) was stirred at room temperature for 24 h. The mixture was poured into saturated aqueous sodium hydrogen carbonate solution (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried with sodium sulfate, and concentrated in vacuo to give 2.62 g of the crude product as colorless granules. It was recrystallized from Et_2O/*n*-hexane to give a first crop of **10** (1.13 g). The mother liquor was concentrated and was purified by silica gel chromatography (200 g, EtOAc/*n*-hexane, 1:50 to 1:30 to 1:6) to give further **10** (1.17 g) as a colorless solid. The total amount of **10** was 2.30 g (91%). M.p. 104.6−105.1 °C (Et_2O/*n*-hexane). $[\alpha]_D^{24}$ = +57.3 (*c* = 1.01, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 1745 cm^{-1} (s, C=O), 1700 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.20−1.32 (m, 2 H), 1.40−1.75 (m, 5 H), 1.79 (dd, *J* = 12.9 Hz, 5.4 Hz, 1 H), 1.98−2.09 (m, 1 H), 2.33 (dt, *J* = 14.5 Hz, 7.6 Hz, 1 H), 2.51 (ddd, *J* = 14.6 Hz, 5.4 Hz, 1.8 Hz, 1 H), 3.21 (s, 1 H, $CHCO_2CH_3$), 3.67 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 18.5, 21.6, 22.9, 33.4, 33.5, 39.1, 41.2, 41.8, 41.9, 51.3, 53.1, 69.9, 168.6, 205.4 ppm. $C_{15}H_{24}O_3$ (252.3): calcd. C 71.39, H 9.59; found C 71.02, H 9.39.

Methyl (4a*R*,8a*R*)-2-Diethoxyphosphoryloxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (13): A suspension of sodium hydride in mineral oil (60%, 340 mg, 8.5 mmol) was rinsed twice with 2-mL portions of dry *n*-hexane to remove the mineral oil. Dry THF (10 mL) was added, and a solution of **10** in dry THF (25 mL) was added dropwise, at 0 °C under argon, to the resulting suspension. The resulting mixture was heated at reflux for 1 h, and diethyl chlorophosphate (1.35 g, 7.8 mmol) was added at 0 °C. After the mixture had been stirred at room temperature for 1 h, additional sodium hydride (90 mg, 2.3 mmol) and diethyl chlorophosphate (390 mg, 2.3 mmol) were added. The mixture was stirred for 1 h at room temperature, poured into water (100 mL), and extracted with Et_2O (2 ×150 mL). The combined organic extracts were washed with brine (1 × 100 mL), dried with sodium sulfate, and concentrated in vacuo to give 3.0 g of the crude product as a pale yellow oil. The crude product was purified by silica gel chromatography (150 g, EtOAc/*n*-hexane, 1:2 and then 1:1 as eluents) to give **13** (2.47 g, 89%) as a pale yellow oil. n_D^{28} =1.4821. $[\alpha]_D^{24}$ = −62.7 (*c* = 1.09, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 1730 cm^{-1} (s, C=O), 1680 (w, C=C), 1275 (s, P=O), 1030 (s, C−O). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, 5-C*H*$_3$), 0.90 (s, 3 H, 5-C*H*$_3$), 1.17−1.27 (m, 2 H), 1.29 (s, 3 H, 8-C*H*$_3$), 1.29−1.38 (m, 7 H, C*H*$_3$CH$_2$O, C*H*$_2$), 1.38−1.87 (m, 6 H), 2.36−2.61 (m, 2 H, 3-*H*), 3.72 (s, 3 H, CO_2CH_3), 4.04−4.21 (m, 4 H, CH_3CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =15.9, 16.0, 18.3, 18.5, 20.60, 20.63, 21.3, 28.2, 33.0, 36.4, 37.0, 41.4, 50.0, 51.3, 64.20, 64.25, 64.29, 64.3, 128.7, 128.8, 146.2, 146.3, 167.6 ppm. $C_{19}H_{33}O_6P$ (388.4): calcd. C 58.75, H 8.56; found C 58.36, H 8.58.

Methyl (4a*R*,8a*R*)-2,5,5,8a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (14): A solution of methyllithium (1.10 M in Et_2O, 67 mL, 74 mmol) was added dropwise at −65 °C under argon to a stirred suspension of dry CuI (7.0 g, 37 mmol) in dry Et_2O (150 mL), and the mixture was stirred at −20 °C for 1 h. A solution of **13** (2.27 g, 6.10 mmol) in dry Et_2O (50 mL) was then added dropwise at −65 °C to the cooled mixture. The mixture was stirred at −10 °C for 6 h and then poured into a saturated ammonium chloride solution (100 mL), insoluble material was filtered off, and the filtrate was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with a saturated aqueous sodium hydrogen carbonate solution and brine (each 1 × 200 mL), dried with magnesium sulfate, and concentrated in vacuo to give 1.54 g of a crude yellow oil. This was purified by silica gel chromatography (150 g, EtOAc/*n*-hexane, 1:10) to give **14** (1.32 g, 87%) as colorless oil. n_D^{28} =1.4985. $[\alpha]_D^{24}$ = −94.8 (*c* = 1.07, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 1715 cm^{-1} (s, C=O), 1660 (w, C=C), 1265 (s, C−O), 1200 (s, C−O), 1070 (s, C−O). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, 5-C*H*$_3$), 0.90 (s, 3 H, 5-C*H*$_3$), 1.15−1.35 (m, 3 H), 1.21 (s, 3 H, 8a-C*H*$_3$), 1.40−1.65 (m, 5 H), 1.63 (s, 3 H, 2-C*H*$_3$), 1.65−1.75 (m, 1 H), 2.10 (dd, *J* = 8.8 Hz, 4.4 Hz, 2 H, 3-*H*), 3.72 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =18.5, 18.7, 20.4, 20.8, 21.4, 32.1, 33.1, 36.7, 36.9, 41.7, 50.4, 51.0, 132.4, 138.6, 170.9 ppm. $C_{16}H_{26}O_2$ (250.4) calcd. C 76.75, H 10.47; found C 76.46, H 10.21.

[(4a*R*,8a*R*)-2,5,5,8a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methanol (15): A solution of DIBAL in *n*-hexane (0.95 M, 12.6 mL, 12 mmol) was added dropwise under argon at −65 °C to a cooled and stirred solution of **14** (1.2 g, 4.6 mmol) in CH_2Cl_2 (24 mL). After stirring at −65 °C for 2 h, the mixture was quenched by addition of an aqueous solution (100 mL) of potassium sodium tartrate (6.4 g). The mixture was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with brine (1 × 150 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (200 g, EtOAc/*n*-hexane, 1:10, then 1:1 as eluents) to give **15** as colorless rods (0.97 g, 95%). This was recrystallized from *n*-pentane to give an analytical sample as colorless needles. M.p. 119.0−120.1 °C. $[\alpha]_D^{24}$ = −115 (*c* = 0.13, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3360 cm^{-1} (s, OH), 1660 (w, C=C), 1000 (s, C=C), 985 (s, C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, 5-C*H*$_3$), 0.89 (s, 3 H, 5-C*H*$_3$), 0.96 (s, 3 H, 8a-C*H*$_3$), 1.05−1.68 (m, 8 H), 1.72(s, 3 H, 2-C*H*$_3$), 1.89 (br. d, *J* = 12.4 Hz, 1 H, 4a-*H*), 1.97−2.15 (m, 2 H, 3-*H*), 4.04 (d, *J* = 11.5 Hz, 1 H, C*H*$_2$OH), 4.19 (d, *J* = 11.5 Hz, 1 H, C*H*$_2$OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 18.9, 19.3, 20.7, 21.6, 33.2, 33.7, 36.8, 38.0, 41.6, 51.7, 58.3, 132.4, 141.0 ppm. $C_{15}H_{26}O$ (222.4): calcd. C 81.02, H 11.79; found C 80.92, H 11.64.

(4a*R*,8a*R*)-8-Benzenesulfonylmethyl-4,4,7,8a-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (17): Methanesulfonyl chloride (1.46 mL, 18.9 mmol) was added dropwise under argon at 0 °C to a stirred solution of **15** (2.10 g, 9.44 mmol), collidine (2.5 mL, 18.9 mmol), and LiCl (800 mg, 18.9 mmol) in DMF (21 mL). After stirring at 5 °C for 46 h, the mixture was diluted with Et_2O (100 mL), and washed with water (100 mL). The aqueous phase was reextracted with additional Et_2O (100 mL). The combined organic extracts were washed with saturated aqueous sodium carbonate solution and brine (each 1× 100 mL), dried with magnesium sulfate, filtered, and concentrated to give 2.56 g of crude **16** as an orange oil, which was used in the next step without further purification. Sodium phenylsulfinate (5.66 g, 28 mmol) was added under argon at room temperature to a stirred solution of crude **16** (2.56 g) in DMF (20 mL). The mixture was stirred at room temperature for 48 h, poured into water (100 mL), and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium carbonate solution and brine (each 1× 100 mL), dried with sodium sulfate, filtered, and concentrated in vacuo to give 5.88 g of an yellow oil. This was purified by silica gel chromatography (300 g, EtOAc/*n*-hexane, 1:15 as an eluent) to give **17** (2.3 g, 70% in two steps from **15**) as colorless rods. M.p. 97.5−98.1 °C (Et_2O/*n*-hexane). $[\alpha]_D^{24}$ = −75.0 (*c* = 1.03, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 1585 cm^{-1} (w), 1305 (s), 1145 (s), 1085 (m), 725 (s). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, 4-C*H*$_3$), 0.89 (s, 3 H, 4-C*H*$_3$), 1.02 (s, 3 H, 8a-C*H*$_3$), 1.05−1.25 (m, 2 H), 1.25−1.60 (m, 5 H), 1.64 (s, 3 H, 7-C*H*$_3$), 1.65−1.75 (m, 2 H), 2.05−2.20 (m, 2 H), 3.85 (d, *J* = 14.4 Hz, 1 H, $PhSO_2CH_2$), 4.00 (d, *J* = 14.4 Hz, 1 H, $PhSO_2CH_2$), 7.70−7.60 (m, 3 H, Ph-*H*), 7.93 (dd, *J* = 7.4 Hz, 1.4 Hz, 2 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =18.2, 18.7, 19.0, 20.5, 20.7, 21.5, 21.7, 33.2, 33.4, 33.7, 37.5, 37.9, 41.5, 50.8, 56.9, 127.8, 129.2, 129.5, 133.2, 138.1, 141.7 ppm. $C_{21}H_{30}O_2S$ (346.5): calcd. C 72.79, H 8.73; found C 72.50, H 8.48.

Benzyl 3-(3′-Methyl-2′-butenyl)-4-benzyloxybenzoate (19): 3-Methyl-2-butenyl bromide (32 g, 203 mmol) was added dropwise at room temperature to a stirred solution of *p*-hydroxybenzoic acid (28 g, 203 mmol) in aqueous NaOH solution (16 g in 364 mL water). The mixture was stirred at room temperature for 24 h, cooled to 0 °C, acidified with conc. HCl (35 mL), and extracted with EtOAc (3 × 250 mL). The combined extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was used for the next step without further purification. Benzyl bromide (72 g, 406 mmol) was added portionwise to a suspension of the crude alkylation product and K_2CO_3 (56 g, 406 mmol) in DMF (200 mL). The resulting mixture was stirred at room temperature for 15 h, poured into a mixture of water (300 mL) and Et_2O (300 mL), and filtered. The organic phase of

the filtrate was separated, washed with 5% HCl and brine (each 50 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo to give a gummy solid. This was rinsed with Et_2O/*n*-hexane and filtered. The filtrate was concentrated to give purer reaction product as a gummy solid. This was rinsed with Et_2O/*n*-hexane and filtered again. The filtrate was concentrated to give further, purer product (30 g) as an yellow oil. This was purified by silica gel chromatography (twice; 1.2 kg, EtOAc/*n*-hexane, 1:50 to 1:25 then 1.0 kg, EtOAc/*n*-hexane, 1:60 to 1:25) to give 7.5 g (9.5%) of **19** as a pale yellow oil. n_D^{24} =1.5171. IR (film): $\tilde{\nu}_{max}$ = 1715 cm^{-1} (s, C=O), 1605 (s, C=C), 1500 (s, C=C), 1455 (s, C=C), 1260 (s, C−O−C), 1025 (m, C−O−C). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 3.38 (d, 2 H, *J* = 7.4 Hz, $CHCH_2Ar$), 5.14 (s, 2 H, $PhCH_2$), 5.30 (t, *J* = 7.4 Hz, 1 H, $CHCH_2Ar$), 5.33 (s, 2 H, $ArCH_2$), 6.89 (d, 1 H, *J* = 8.2 Hz, Ph-*H*), 7.31−7.46 (m, 10 H, Ph-*H*), 7.89 (d, 1 H, *J* = 2.3 Hz, Ph-*H*), 7.90 (dd, 1 H, *J* = 8.2 Hz, 2.3 Hz, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 25.8, 28.7, 66.2, 69.9, 110.7, 121.7, 122.2, 127.1, 127.9, 128.0, 128.4, 128.5, 129.4, 130.4, 131.1, 133.0, 136.4, 136.5, 160.2, 166.4 ppm. $C_{26}H_{26}O_3$ (386.5): calcd. C 80.80, H 6.78; found C 80.84, H 7.05.

Benzyl 3-(3′-Hydroxymethyl-2′-butenyl)-4-benzyloxybenzoate (20): A solution of **19** (7.1 g, 20 mmol) in CH_2Cl_2 (35 mL) was added dropwise at room temperature over 0.5 h to a stirred suspension of SeO_2 (220 mg, 2.0 mmol) in a solution of *t*BuO_2H (80%, 6.7 mL, 59 mmol) in CH_2Cl_2 (35 mL). The mixture was stirred at room temperature for 71 h and concentrated in vacuo to a half volume. Na_2SO_3 (8.0 g, 63 mmol) and water (100 mL) were added to the concentrated mixture. The resulting mixture was extracted with Et_2O (2 ×150 mL). The combined organic extracts were washed with aqueous saturated sodium hydrogen carbonate and brine (each 1 × 150 mL), dried with sodium sulfate, and concentrated in vacuo to give 7.9 g of a crude yellow oil. This was used in the next step without further purification. $NaBH_4$ (757 mg, 20 mmol) was added portionwise at 0 °C to a solution of the crude oil (7.9 g) in THF/water (35 mL/35 mL), and the mixture was stirred at 0 °C for an additional 1 h. The mixture was allowed to warm to room temperature and stirred for an additional 1.5 h, and was then acidified with 2 M HCl and extracted with Et_2O (2 × 150 mL). The combined organic phases were washed with brine (1 × 200 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (150 g, EtOAc/*n*-hexane, 1:2) to give 3.6 g (45% in two steps) of **20** as a colorless solid, which was recrystallized from EtOAc/*n*-hexane to give an analytical sample as colorless needles. M.p. 64.5−66.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3315 cm^{-1} (s, OH), 3230 (s, OH), 1715 (s, C=O), 1605 (s, C=C), 1505 (s, C=C), 1270 (s, C−O−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 3 H, CH_3), 3.43 (d, 2 H, *J* = 7.2 Hz, $CHCH_2Ar$), 4.01 (s, 2 H, $HOCH_2$), 5.13 (s, 2 H, $PhCH_2$), 5.32 (s, 2 H, $PhCH_2$), 5.57(t, *J* = 7.2 Hz, 1 H, $CHCH_2Ar$), 6.91 (d, 1 H, *J* = 8.7 Hz, Ph-*H*), 7.30−7.46 (m, 10 H, Ph-*H*), 7.87 (d, 1 H, *J* = 2.1 Hz, Ph-*H*), 7.92 (dd, 1 H, *J* = 8.7 Hz, 2.1 Hz, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 28.4, 66.3, 68.7, 70.0, 110.8, 122.3, 123.3, 127.2, 128.0, 128.04, 128.07, 128.5, 128.6, 129.7, 131.2, 136.1, 136.3, 136.4, 160.3, 166.3 ppm. $C_{26}H_{26}O_4$ (402.5): calcd. C 77.59, H 6.51; found C 77.39, H 6.79.

Benzyl 3-(3′-Bromomethyl-2′-butenyl)-4-benzyloxybenzoate (21): Methanesulfonic anhydride (2.7 g, 15 mmol) was added in one portion at 0 °C under argon to a suspension of LiBr (1.3 g, 15 mmol) in a solution of **20** (1.5 g, 3.7 mmol), collidine (2.0 mL, 15 mmol), and DMAP (50 mg) in DMF (15 mL). After stirring at 0 °C under argon for 24 h, the mixture was diluted with water (100 mL), and extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with brine (3 × 100 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo to give 2.22 g of a crude product. This was purified by silica gel chromatography (150 g, EtOAc/*n*-hexane, 1:2) to give 1.50 g (87% in two steps) of **21** as a pale yellow gum. This solidified and was recrystallized from EtOAc/*n*-hexane to give an analytical sample as colorless needles. M.p. 60.0−61.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1710 cm^{-1} (s, C=O), 1605 (s, C=C), 1500 (s, C=C), 1260 (s, C−O−C), 1120 (s, C−O−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, CH_3), 3.42 (d, 2 H, *J* = 7.2 Hz, $CHCH_2Ar$), 3.97 (s, 2 H, $BrCH_2$), 5.13 (s, 2 H, $PhCH_2$), 5.33 (s, 2 H, $PhCH_2$), 5.75 (t, *J* = 7.2 Hz, 1 H, $CHCH_2Ar$), 6.91 (d, 1 H, *J* = 8.4 Hz, Ph-*H*), 7.30−7.46 (m, 10 H, Ph-*H*), 7.86(d, 1 H, *J* = 1.8 Hz, Ph-*H*), 7.93 (dd, 1 H, *J* = 8.4 Hz, 1.8 Hz, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 29.2, 41.4, 66.4. 70.1, 110.9, 122.4, 127.3, 128.11, 128.13, 128.55, 128.60, 128.64, 128.81, 130.0, 131.2, 133.2, 136.3, 160.3, 166.2 ppm. $C_{26}H_{25}BrO_4$ (465.4): calcd. C 67.10, H 5.41; found C 67.14, H 5.57.

4-Benzyloxy-3-{(2′*E*)-3′-methyl-5′-[(4a"*R*,8a"*R*)-2",5",5",8a"-tetramethyl-3",4",4a",5",6",7",8",8a"-octahydronaphthyl]-2′-pentenyl}benzoic Acid (23): *n*BuLi (1.59 M in *n*-hexane, 2.5 mL, 3.95 mmol) was added dropwise at −65 °C to a stirred solution of **17** (920 mg, 2.65 mmol) and HMPA (4.5 mL, 26 mmol) in dry THF (20 mL). After the mixture had been stirred for 0.5 h at −65 °C, a solution of **21** (1.5 g, 3.2 mmol) in THF (20 mL) was added dropwise by cannula. The mixture was stirred for 2.5 h at −65 °C, quenched with aqueous saturated NH_4Cl solution (50 mL), allowed to warm to room temperature, further stirred for 0.5 h, and extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with aqueous saturated $NaHCO_3$ and brine (each 1 × 80 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (200 g, EtOAc/*n*-hexane, 1:8 as eluent) to give 1.71 g of **22** as a colorless, amorphous solid, which was used in the next step without further characterization.: HRMS (FAB+): calcd. $[M + H]^+$ ($C_{47}H_{55}O_5S$) 731.3770, found 731.3787 (error +2.3 ppm/+1.7 mmu). 5% Na/Hg (62 g, 294 mmol) was added portionwise at 0 °C to a stirred suspension of the solid **22** (1.71 g) and Na_2HPO_4 (6.7 g, 47 mmol) in THF/MeOH (17 mL/86 mL). The suspension was stirred at 0 °C for 0.5 h and at room temperature for 16.5 h, and was then filtered. The residue on the filter was washed with MeOH (200 mL). All of the filtered organic solution was combined and concentrated in vacuo. The residue on the filter was washed with aqueous NaOH solution (25%, 350 mL) and water (350 mL). All of the filtered aqueous phases was combined with the concentrated organic phase, stirred for 0.5 h at room temperature, and acidified with HCl (6 N, 400 mL). The resulting solution was extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried with sodium sulfate, filtered, and concentrated in vacuo to give 1.54 g of crude **23** as pale yellow solid. This was purified by silica gel chromatography (250 g, EtOAc/*n*-hexane, 1:4 as an eluent) to give purer **23** (0.86 g). The obtained solid was recrystallized from EtOAc/*n*-hexane to give a first (430 mg) and second crop (38 mg) of pure **23** as fine needles. The total amount of **23** was 468 mg (35% in two steps). M.p. 136.6−142.7 °C. $[\alpha]_D^{24}$ = −46.1 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3600−2700 cm^{-1}(s, OH), 1682 (s, C=O), 1604 (s, C=C), 1502 (m), 1237 (s), 1019 (m, C−O). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, 5"-CH_3), 0.88 (s, 3 H, 5"-CH_3), 0.94 (s, 3 H, 8a"-CH_3), 1.05−1.75 (m, 8 H), 1.58 (s, 3 H, 2"-CH_3), 1.69 (s, 3 H, 3′-CH_3), 1.75−2.20 (m, 7 H), 3.40 (d, *J* = 7.2 Hz, 2 H, $CHCH_2Ar$), 5.17 (s, 2 H, OCH_2Bn), 5.34 (t, *J* = 7.2 Hz, 1 H, $CHCH_2Ar$), 6.93 (d, *J* = 8.6 Hz, 1 H, 5-*H*), 7.33−7.44 (m, 5 H, Ph-*H*), 7.92 (br. s,

1 H, 2-*H*), 7.93 (dd, *J* = 8.6 Hz, 2.2 Hz, 1 H, 6-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =16.2, 19.1, 19.5, 20.1, 21.7, 27.2, 28.7, 33.3, 33.7, 37.0, 39.1, 40.5, 41.9, 51.9, 70.0, 110.8, 120.9, 121.4, 125.8, 127.2, 128.0, 128.6, 130.2, 130.7, 131.7, 136.5, 137.8, 140.5, 160.9, 171.3 ppm. $C_{34}H_{44}O_3$ (500.7): calcd. C 81.56, H 8.86; found C 81.28, H 8.87.

4-Hydroxy-3-{(2′*E*)-3′-methyl-5′-[(4a"*R*,8a"*R*)-2",5",5",8a"-tetramethyl-3",4",4a",5",6",7",8",8a"-octahydronaphthyl]-2′-pentenyl}-benzoic Acid (1) [(5*R*,10*R*)-(−)-Subersic Acid]: A freshly prepared solution of lithium naphthalenide (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise under argon at −78 °C to a stirred solution of **23** (135 mg, 0.27 mmol) in dry THF (2 mL). The mixture was stirred at −78 °C for 0.5 h, quenched with saturated NH_4Cl (5 mL), allowed to warm to room temperature with stirring over 0.5 h, and made alkaline with aqueous NaOH solution (25%, 7.5 mL), and the aqueous layer was washed with Et_2O. The separated aqueous phase was acidified with HCl (6 M) and extracted with Et_2O (2 × 50 mL). The combined organic phase was washed with brine (2 × 50 mL), dried with sodium sulfate, filtered, and concentrated in vacuo to give 145 mg of crude **1** as an yellow oil. This was purified by silica gel chromatography (twice; 30 g, EtOAc/*n*-hexane, 1:2.5, then 30 g, CH_2Cl_2/MeOH, 1:100 to 1:50 to 1:25 as eluents) to give 103 mg of purer **1** as a colorless amorphous solid. It was purified again by silica gel chromatography (70 g, EtOAc/*n*-hexane, 1:2.5 as an eluent) to give 83 mg (75% from **23**, 13% in 8 steps from **10**, 6.7% in 13 steps from **5**) of **1** as white amorphous foam. $[\alpha]_D^{24} = -52.2$ (*c* = 0.52, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3600−2300 cm^{-1} (br, OH), 1688 (shoulder, C=O), 1681 (s, C=O), 1603 (s, C=C), 1498 (s, C=C), 1274 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, 5a"-CH_3), 0.88 (s, 3 H, 5a"-CH_3), 0.94 (s, 3 H, 8a"-CH_3), 1.14−1.20 (m, 3 H, 8"-*H*, 6"-*H*, 4a"-*H*), 1.35−1.52 (m, 3 H, 6"-*H*, 7" -*H*, 4"-*H*), 1.53−1.67 (m, 2 H, 4"-*H*, 7"-*H*), 1.58 (s, 3 H, 2"-CH_3), 1.75−1.84(m, 1 H, 8"-*H*), 1.83 (s, 3 H, 3′-CH_3), 1.88−2.17 (m, 6 H, 3′-*H,* 5"-*H*, 4"-*H*), 3.41 (d, *J* = 7.0 Hz, 2 H, 1′-*H*), 5.34 (t, *J* = 7.0 Hz, 1 H, 2′-*H*), 6.85 (d, *J* = 9.0 Hz, 1 H, 5-*H*), 7.89 (dd, *J* = 9.0 Hz, 2 Hz, 1 H, 6-*H*), 7.90 (s, 1 H, 2-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (3′-*C*H_3), 19.1 (C-4"), 19.1 (C-7"), 19.6 (2"-*C*H_3), 20.1 (8a"-*C*H_3), 21.7 (5"-*C*H_3), 27.0 (C-5′), 29.6 (C-1′), 33.33 (5"-*C*H_3), 33.34 (C-5"), 33.6 (C-3"), 37.0 (C-8"), 39.0 (C-8a"), 40.4 (C-4′), 41.8 (C-6"), 51.9 (C-4a"), 115.7 (C-5), 120.1 (C-2′), 121.7 (C-1), 126.1 (C-2"), 126.8 (C-3), 130.5 (C-6), 132.6 (C-2), 140.1 (C-1"), 140.6 (C-3′), 159.5 (C-4), 171.6 (1-*C*O_2). HRMS (FAB−): calcd. $[M - H]^-$ ($C_{27}H_{37}O_3$) 409.2743, found 409.2733 (error −2.5 ppm/−1.0 mmu). HRMS (FAB+): calcd. $[M + Na]^+$ ($C_{27}H_{38}O_3Na$) 433.2719, found 433.2718 (error −0.1 ppm/+0.0 mmu). The spectroscopic data of our synthetic **1** are identical with those reported for natural **1**.[1]

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