Total Synthesis and Determination of the Absolute Configuration of Coscinosulfate. A New Selective Inhibitor of Cdc25 Protein Phosphatase§

Stéphane Poigny,† Samia Nouri,† Angèle Chiaroni,‡ Michèle Guyot,† and Mohammad Samadi*,†

Laboratoire de Chimie des Substances Naturelles, associé au CNRS, Muséum National d'Histoire Naturelle, 63, rue Buffon, F-75005 Paris, France, and Institut de Chimie des Substances Naturelles, CNRS, 1 Avenue de la terrasse, 91198 Gif-sur-Yvette, France

samadi@mnhn.fr

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The first total synthesis of coscinosulfate **1**, a metabolite isolated from a sea sponge, starting from (+)-sclareolide **3** is described. The convergent synthesis strategy relies on the coupling of sulfone **21** with the bromide **26**. The sulfone fragment **21** was obtained by successive asymmetric aldol reaction with aldehyde **2** to introduce the stereocenters at C-12 and C-13, followed by one-carbon homologation via Horner−Wadsworth−Emmons olefination. The selective sulfatation at C-12 was accomplished through the quinone intermediate **31** obtained by selective oxidation of hydroquinone **30**; this, when followed by reduction, furnished the desired coscinosulfate **1**. X-ray analysis of the intermediate aldehyde **18** confirmed the proposed stucture.

Cdc25 is a dual specificity family of the protein tyrosine phosphatase involved in the regulatory activation of cyclin dependent kinases (CDKs) by dephosphorylations of a threonine and a tyrosine of the subunit of the CDKs. Human cells contain three Cdc25 genes named cdc25A, cdc25B, and cdc25C. Cdc25A is thought to activate CDK2/cyclin E and thereby trigger the G1/S transition of the cell cycle. Cdc25B appears to play a role in both G1 and G2 phases, while cdc25C specifically dephosphorylates CDK1/cyclin B, thereby triggering the G2/M transition. Cdc25A and cdc25B are known to be oncogenic and overexpressed in a number of tumor cell lines. Cdc25 phosphatases constitute attractive screening targets to identify new antimitotic compounds of potential therapeutic interest, and several synthetic and natural compounds were found to be inhibitors of these enzymes.[1]

Coscinosulfate **1**, a sesterterpene sulfate, was recently isolated in our group from the marine sponge *Coscinoderma mathewsi* (New Caledonia).[2] It exhibits a selective inhibition of the cdc25A protein phosphatase,[3] with an IC_{50} of 3 μM.

The same structure was proposed for halisulfate-1 isolated from the marine sponge Halicondriidea by Kernan and Faulkner et al.,[4] for which the optical rotation ($[\alpha]_D$ −27) was of the opposite sign to that of coscinosulfate **1** ($[\alpha]_D$ +5). The stereochemistry at C-13 and C-12 for halisulfate-1 was postulated as 12*R**,13*R** based on the small coupling constant $J_{12,13} < 1$ Hz. In contrast, coscinosulfate **1** presents a large coupling constant ($J_{12,13} = 11$ Hz), and the relative configuration at C-12 and C-13 has been assigned as 12*R*,13*R* through Mosher ester analysis of the free secondary alcohol.[3]

Given these conflicting data, and as a part of our program directed toward the synthesis of bioactive marine natural products, we undertook the synthesis of **1**. Our strategy for the synthesis of **1** is presented in the retrosynthetic plan shown in Scheme 1. Accordingly, the sesterterpene sulfate **1** was dissected into two fragments A and B, which could be joined by alkylation and subsequent reductive desulfonylation, followed by selective sulfatation of the secondary alcohol at C-12. The sulfone fragment A could be prepared by successive stereocontrolled aldol reactions, to introduce the C-12 and C-13 stereocenters, and one carbon homologation via Horner−Wadsworth−Emmons (HWE) olefination. In turn, aldehyde **2** could be derived from the (3a*R*)-(+)-sclareolide **3** bearing the chiral centers at C-5, C-9, and C-10 required for the drimane skeleton.

As outlined below, herein we report the concise synthesis of this sesterterpene sulfate which enabled us to confirm the absolute configuration of the naturally occurring **1**.

The readily available **3** was converted to diol **4**,[5] which was followed by selective protection of the primary alcohol to give compound **5** in 99% yield over two steps (Scheme 2). Dehydration of alcohol **6** afforded, in quantitative yield, an inseparable mixture of *exo*- and *endo*-olefins **6** ($\Delta^{8,22}$ $\Delta^{7,8}$ $\Delta^{8,9}$) in a 80:15:5 ratio (coscinosulfate numbering). Selective allylic oxidation[6] produced an alcohol (**7**) as the sole isomer in 62% yield over two steps. In the described conditions only the *exo*-olefin undergoes

* To whom correspondence should be addressed. Tel: 33-1-40-79-31-44. Fax: 33-1-40-79-31-35. E-mail: Samadi@mnhn.fr.

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† Laboratoire de Chimie.

‡ Institut de Chimie des Substances Naturelles.

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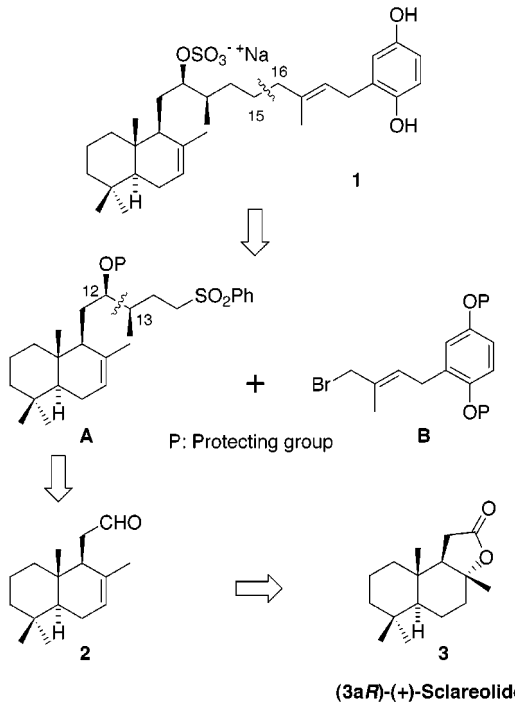
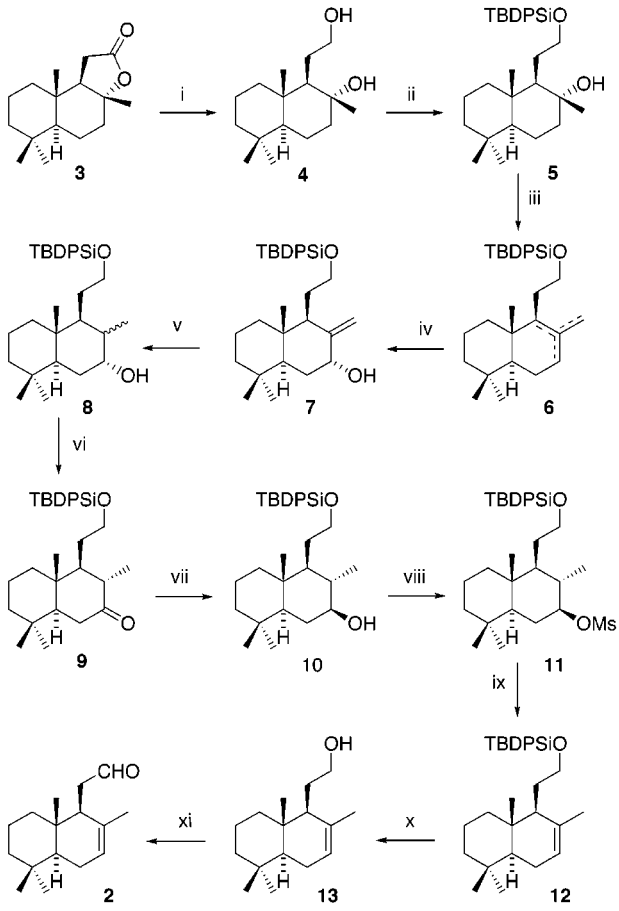
Scheme 1



Scheme 2



i: 1 equiv $LiAlH_4$, THF, 0 °C (100%); ii: 1.05 equiveTBDPSiCl, 3 equiv imidazol, DMF, rt (99%); iii: 2.5 equive $SOCl_2$, 1 equive 4-DMAP, pyridine, -50 to 0 °C, 1 h; iv: SeO_2 (cat), tBuOOH, CH_2Cl_2, rt, 48 h (62% for 2 steps); v: Pd/C , EtOH, rt (80% for **8** and 17% for **12**); vi: a. 2 equiv PCC, CH_2Cl_2 , 12 h; b. 1 equiv MeO^- + Na, MeOH, rt, 24 h (88% over 2 steps); vii: 3 equiv $NaBH_4$, 1.1 equiv $CeCl_3$, MeOH, -50 °C, 1 h; viii: 3 equiv MsCl, 6 equiv Et_3N, 0.1 equiv 4-DMAP, CH_2Cl_2, rt, 24 h; ix: 5 equiv LiBr, 5 equiv Li_2CO_3, DMF, 150 °C, 1 h (89% for 3 steps); x: 3 equiv TBAF, THF, reflux, 1 h (98%); xi: 4 equiv SO_3.Py, 6.5 Et_3N, DMSO, rt, 1 h (96%).

allylic oxidation to produce the corresponding allylic alcohol, whereas the *endo*-olefins remain unreacted and can be easily separated. Catalytic hydrogenation furnished the saturated alcohol (**8)** (80%) as a mixture of isomers, along with the *endo*-olefin (**12)** (17%). Oxidation of **8** followed by treatment with NaOMe in MeOH gave ketone **9** in 88% yield (over two steps). Ketone **9** was transformed into the *endo*-olefin **12** as follows. Luche reduction[7] of ketone **9** gave alcohol **10**, which after mesylation furnished mesylate **11**, and in situ bromination and debromination gave pure**12** in 89% yield over three steps. To us, the sequence of reactions described above seemed to be the only alternative to obtain pure **12** without contamination either with the *exo*- or with the tetrasubstituted *endo*-olefins. Deprotection of TBDPS's ether afforded compound **13**[8] (98%), and oxidation of the resulting primary alcohol furnished **2** in 96% yield.

At this stage, the desired **2** was submitted to asymmetric aldol reaction to introduce the C-12 and C-13 stereocenters. Thus, stereoselective aldol coupling of the Evans oxazolidinone **14**[9] with **2** furnished the syn adduct (**15)** in 87% yield (Scheme 3). Transamidation[10] of **15** gave **16** (98%), which was followed by protection of the secondary alcohol to afford **17** in 98% yield. Reduction of the amide moiety[11] gave aldehyde **18** in almost quantitative yield. Single-crystal X-ray analysis of **18** confirmed the structure of this advanced intermediate (Figure 1). HWE olefination of **18** with $(EtO)_2OPCH_2SO_2Ph$ (**19)**[12] gave the trans olefin **20** (70%), and subsequent selective reduction[13] of the activated double bond provided the saturated sulfone **21** (fragment A) in 92% yield.

The remaining right side chain fragment B, the allyl bromide, was prepared as follows: protection of **22** [14] gave **23** (97%) (Scheme 4). Allylic oxidation of **23** gave aldehyde **24** and alcohol **25** in a ratio of 3:1, and reduction of the crude mixture provided the alcohol **25** in 54% yield over two steps. Bromination using CBr_4 and PPh_3 on polymer support gave allyl bromide **26** in 99% yield.[15]

Coupling of sulfone **21** through its lithium anion in the presence of bromide **26** gave the intermediate **27** as a mixture of isomers (Scheme 5). Reductive desulfonylation[16] of the phenyl sulfone moiety furnished the addition

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(8) The *endo*-olefin **13** has been previously prepared in 12 steps starting from *S*-carvon in 15% overall yields. See: Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10095.

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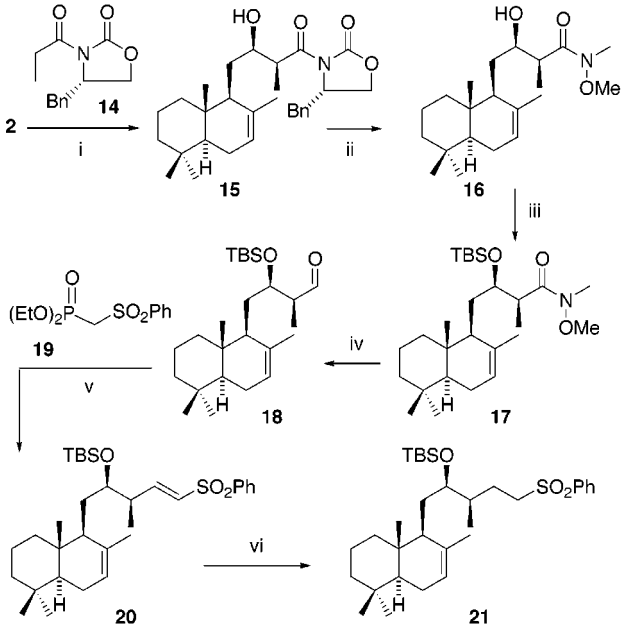
(15) Bromination of **25** using CBr_4 and PPh_3 and further purification over silica gel gave **26** in 50% yield. For this reason, PPh_3 was replaced by PPh_3 on polymer support to avoid the purification step.

Scheme 3



i: 1.1 equiv, of **14**, 1.2 equiv Bu_2BOTf, 1.5 equiv Et_3N, CH_2Cl_2, -78 to 0 °C, 2 h (87%); ii: 2 equiv $MeONHCH_3$, 2 equiv $AlMe_3$, CH_2Cl_2, 0 °C to rt, 24 h (98%); iii: 1.1 equiv TBSOTf, 2 equiv 2,6-lutidine, CH_2Cl_2, -78 to 0 °C, 1 h (98%); iv: 3 equiv DIBAL-H, CH_2Cl_2, -78 °C, 30 min (99%); v: 1.5 equiv $(EtO)_2OPCH_2SO_2Ph$, 1.5 equiv NaH, THF, 0 °C, 2 h (70%); vi: 4 equiv $NaBH_4$, 0.2 equiv $NiCl_2$, MeOH, 0 °C, 3 h (92%).

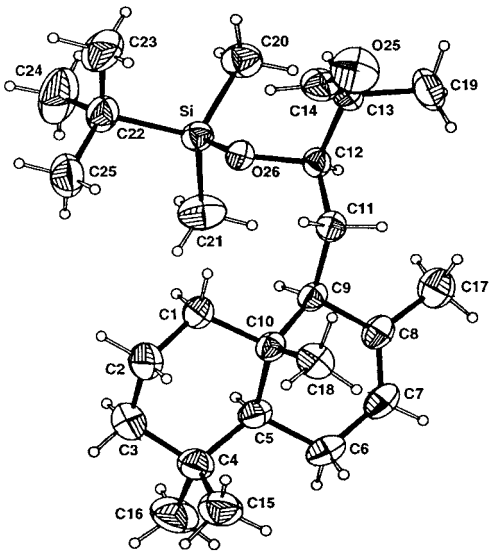


Figure 1. Ortep drawing of **18**. Displacement ellipsoids are shown at the 30% probability level.

product **28** in 70% yield over two steps. Deprotection of TBS ether gave **29** in 93% yield. Catalytic transfer hydrogenolysis of **29** (Pd/C 10%) in the presence of ammonium formate as hydrogen donor caused the removal of the aromatic benzyl ethers and the reduction of the double bond ($\Delta^{17,18}$) on the side chain, whereas with the use of cyclohexadiene as hydrogen donor only one benzyl group was removed. We found that the freshly prepared lithium naphthalenide selectively removed the benzyl ethers of **29** to afford triol **30** in 83% yield.

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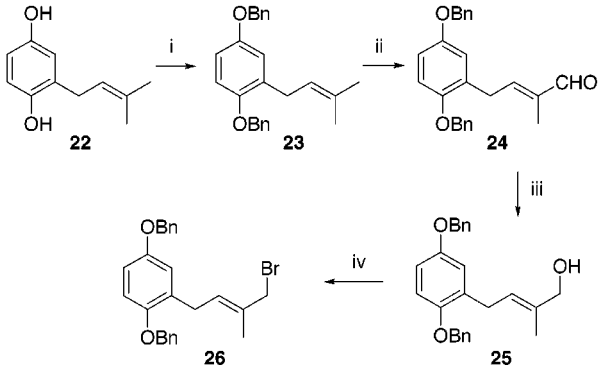
Scheme 4



i: 2.5 equiv NaH, 3 equiv BnBr, DMF, rt, 24 h (97%); ii: 0.02equiv SeO2, 3.6 equiv tBuOOH, 0.1 equiv salisalic acid, CH_2Cl_2, rt, 48 h; ii: 1 equiv NaBH4, MeOH, 0 °C, 30 min (54% over 2 steps); iv: 1.3 equiv CBr4,1.5 equiv P-$C_6H_4PPh_3$, 0 °C, 4 h (99%).

Finally, selective oxidation of the hydroquinone moiety of **30** afforded the quinone **31** and in situ sulfatation of the secondary alcohol followed by reduction of the quinone intermediate **32** provided coscinosulfate **1** in 58% yield over three steps. The synthetic material was found to be identical to the natural coscinosulfate as judged by ^1H NMR, mass spectrometry (MS), and high-resolution mass spectrometry (HRMS). Comparison of optical rotation confirmed that the synthetic and natural compounds possess the same absolute stereochemistry (synthetic $[\alpha]_D$ +4.8 (*c* 0.25, MeOH); natural $[\alpha]_D$ +5 (*c* 1.4, MeOH)). The synthesis of coscinosulfate **1** described above requires 24 steps from readily available sclareolide **3**.

In conclusion, we have described the first total synthesis of coscinosulfate **1**, which allowed us to establish its absolute stereochemistry. The present strategy could be applied to the synthesis of other isomers, at C-12 and C-13 through a stereocontrolled aldol reaction step using an appropriate oxazolidinone auxiliary,[17] for the determination of the absolute stereochemistry of other compounds in the series, such as halisulfate-1.

Experimental Section

All the reactions were carried out under an argon atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Mass spectra were recorded on a Kratos MS 50 instrument at 70 eV (EI) or a Nermag 10-10 (CI, NH_3). IR spectra were recorded on a Nicholet (impact 400D) FT-IR. All reagents were obtained from commercial suppliers and used without further purification. THF was freshly distilled from sodium benzophenone. Methylene chloride and triethylamine were distilled from CaH_2. DMSO was dried and stored over 4 Å molecular sieves. Flash chromatography was carried out using silica gel 60F254 (Merck) with mixtures of ethyl acetate and hexane as eluent unless specified otherwise. TLC analyses were performed on thin-layer analytical plates 60F254 (Merck).

(8a*S*,1*R*,2*R*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethylperhydro-2-naphthalenol (4). To a solution of (3a*R*)-(+)-scalareolide **3** (34.23 mmol, 8.57 g) in dry THF (100 mL) at 0 °C was added $LiAlH_4$ (34.23 mmol, 1.3 g) in portions. The

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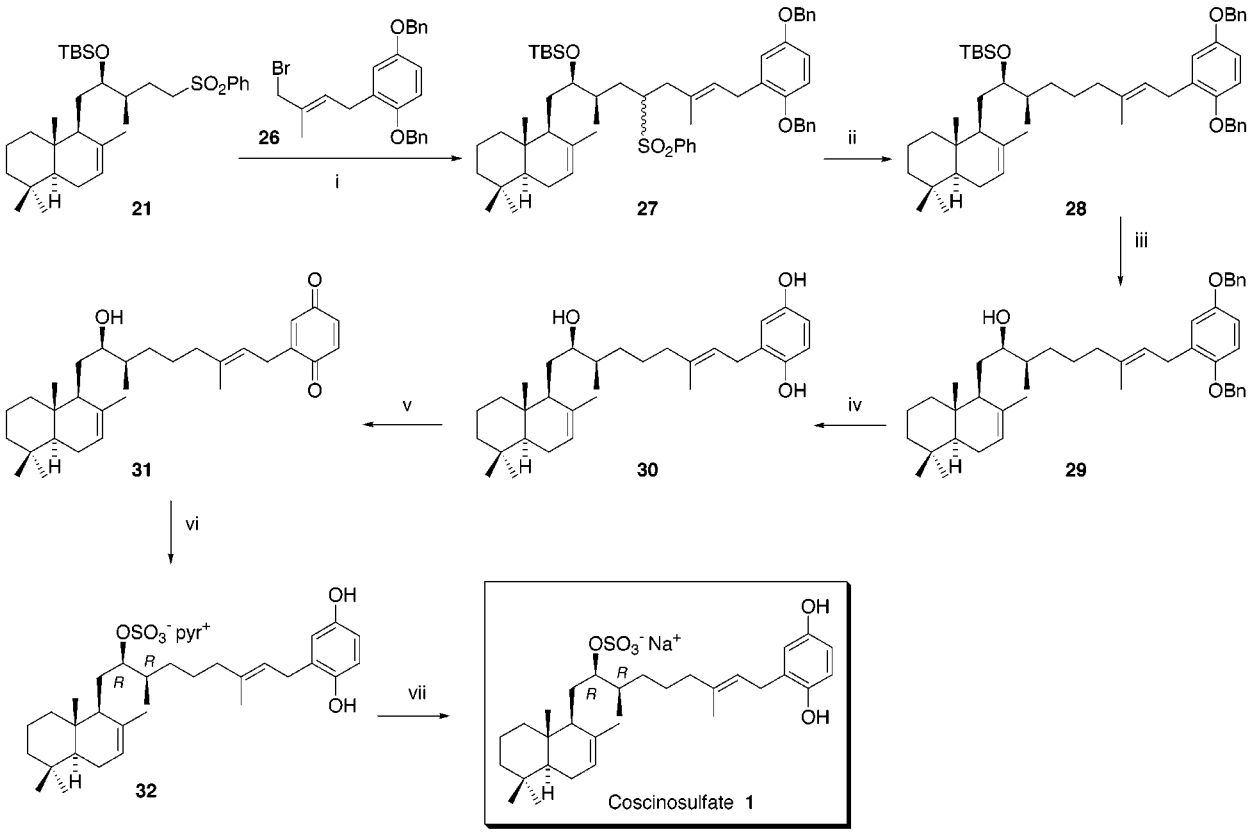
Scheme 5



i: 3 equiv LDA, 1.2 equiv **26**, THF, 78 to 0 °C, 4 h; ii: 20 equiv Na-Hg, MeOH, rt, 24 h (70% for 2 steps), iii: 5 equiv TBAF, THF, reflux, 48 h (93%), iv: 10 equiv Li-naphalenide, THF, -78 °C, 1 h (83%); v: 1.1 equiv $PhI(OAc)_2$, $ClCH_2CH_2Cl$, rt, 1 h; vi: SO_3.Py, $ClCH_2CH_2Cl$, reflux, 2 h; vii. 20 equiv $NaBH_4$, rt, 30 min (58% for 3 steps).

mixture was stirred at this temperature for 1 h. The reaction was quenched with EtOAc (5 mL), and the solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL), washed with 1 N aqueous HCl (100 mL), water, and brine (100 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give compound **4** (8.69 g, 100%) as a white solid: mp 128−129 °C, lit.[8] 130 °C; MS *m*/*z* (EI) 254 $[M]^+$; IR (KBr) 3390, 2950, 2847, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (m, 1H), 3.45 (m, 1H), 2.50 (s large, 2H), 1.85 (dt, 1H), 1.15 (s, 3H), 0.86 (s, 3H), 0.79 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 72.5, 63.6, 59.1, 55.9, 43.6, 41.7, 39.6, 39.3, 33.2, 33.1, 27.6, 24.2, 21.5, 20.3, 18.5, 15.0.

(4a*S*,8a*S*,1*R*,2*R*)-1-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-2,5,5,8a-tetramethylperhydro-2-naphthalenol (5). To a solution of diol **4** (13.4 mmol, 3.4 g) and imidazol (40 mmol, 2.73 g) in dry *N*,*N*-dimethylformamide (DMF) (30 mL) was added TBDPSiCl (3.61 mL, 1.05 equiv). The mixture was stirred at room temperature for 1 h. The DMF was removed in vacuo. The residue was dissolved in ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography using hexanes/EtOAc (90:10) gave compound **5** (6.52 g, 99%) as a colorless oil: R_f 0.49 (hexanes/EtOAc, 90:10); $[\alpha]^{20}_D$ +24 (*c* 2.05, $CHCl_3$); MS *m*/*z* (CI) 510 $(M + NH_4)^+$;^1H NMR ($CDCl_3$) δ 7.70 (m, 4H), 7.40 (m, 6H), 3.77 (m, 1H), 3.52 (td, J = 9.9, 4.5 Hz, 1H), 3.19 (s, 1H, O*H*), 1.92 (dt, J = 12.4, 3.0 Hz, 1H), 1.14 (s, 3H), 1.07 (s, 9H), 0.86 (s, 3H), 0.76 (s, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.7, 135.6, 133.1, 133.0, 129.7, 129.6, 127.6, 72.2, 65.7, 58.3, 55.9, 43.9, 41.8, 39.2, 38.7, 33.3, 33.1, 27.5, 26.8, 24.3, 21.4, 20.4, 19.0, 18.3, 15.2; HRMS (CI) calcd for $C_{32}H_{52}O_2NSi$ $[M + NH_4]^+$ 510.3767, found 510.3793.

(4a*S*,8a*S*,2*R*,4*R*)-4-(2-[*tert*-Butyldiphenylsilyloxy]ethyl)-4a,8,8,trimethyl-3-methyleneperhydro-2-naphthalenol (7). To a cooled (−50 °C) solution of **5** (10.16 mmol, 5 g) and 4-DMAP (10.1 mmol, 1.23 g) in dry pyridine (60 mL) was added $SOCl_2$ (26.3 mmol, 1.84 mL) in a dropwise manner. The reaction was stirred at this temperature for 1 h and then warmed to 0 °C. The reaction was quenched with some ice, and the pyridine was removed in vacuo. The residue was dissolved in ether, washed successively with water, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. Solvent was evaporated under reduced pressure to give compound **6** (4.72 g, 98%) as a colorless oil, which was used without further purification in the next step. To a suspension of SeO_2 (0.2 mmol, 22 mg) and salicylic acid (1 mmol, 138 mg) in dry CH_2Cl_2 (30 mL) was added *tert*-butylhydroperoxide (80%, 35.6 mmol, 4.5 mL), and then the mixture was stirred at room temperature for 10 min. A solution of olefins **6** (4.72 g, 9.96 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and the mixture was stirred at room temperature for 48 h. Toluene (50 mL) was added, and the solvents were evaporated in vacuo. The residue was diluted with ether, washed with 10% aqueous KOH, water, and brine, dried over $MgSO_4$, and concentrated. Purification over silica gel using hexanes/EtOAc (95:5) gave alcohol **7** (3.09 g, 62% from **5**) as a colorless oil: R_f 0.20 (hexanes/EtOAc, 95:5); $[\alpha]^{20}_D$ −12.9 (*c* 1.11, $CHCl_3$); MS *m*/*z* (CI) 508 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4H), 7.36 (m, 6H), 4.83 (s, 1H), 4.42 (s, 1H), 4.22 (bs, 1H), 3.71 (m, 1H), 3.55 (dt, J = 9.9 Hz, 7.6 Hz, 1H), 2.14 (m, 1H), 1.05 (s, 9H), 1.04 (s, 3H), 0.85 (s, 3H), 0.76 (s, 3H), 0.60 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 149.6, 135.6, 134.8, 134.0, 133.9, 129.5, 127.5, 109.5, 73.9, 63.2, 47.4, 46.6, 42.0, 39.4, 38.6, 33.2, 33.0, 30.6, 26.9, 26.6, 21.5, 19.3, 19.1, 13.4; HRMS (CI) calcd for $C_{32}H_{50}O_2NSi$ $[M + NH_4]^+$ 508.3600, found 508.3611.

(3*S*,4*S*,8a*S*,4a*R*)-4-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-3,4a,8,8-tetramethylperhydro-2-naphthalenone (9). A so-

lution of alcohol **7** (3.47 mmol, 1.7 g) and 10% Pd/C (170 mg) in EtOH (30 mL) was stirred at room temperature under 1 atm of hydrogen for 12 h. The reaction was filtered through Celite, and the filtrate was concentrated in vacuo. Purification over silica gel using hexanes gave olefin **12** (279 mg, 17%). Further elution using hexanes/EtOAc (95:5) gave alcohol **8** (1.37 g, 80%) as a colorless oil, which was dissolved in dry CH_2Cl_2 (15 mL) followed by addition of PCC (5.48 mmol, 1.18 g) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. CH_2Cl_2 was evaporated in vacuo, and the residue was triturated with ether, filtered, and solvent evaporated under reduced pressure. The mixture of ketones thus obtained was dissolved in anhydrous MeOH (20 mL), sodium methylate (2.74 mmol, 148 mg) was added, and the reaction was stirred overnight at room temperature. Methanol was evaporated under reduced pressure, and the residue was dissolved in ether, washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography using hexanes/EtOAc (95:5) gave ketone **9** (1.196 g, 88%) as a white solid: R_f 0.17 (hexanes/EtOAc, 96:4); mp 64 °C; $[\alpha]^{20}_D$ −3.8 (*c* 1.04, $CHCl_3$); MS *m*/*z* (CI) 491 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.66 (m, 4H), 7.39 (m, 6H), 3.65−3.47 (m, 2H), 2.39−2.10 (m, 3H), 1.84 (m, 1H), 1.05 (s, 9H), 0.95 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.82 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.4, 135.6, 133.7, 129.6, 127.6, 64.6, 54.0, 53.6, 47.7, 41.7, 38.9, 38.4, 37.9, 33.5, 32.7, 32.5, 26.9, 21.1, 19.1, 18.3, 13.4, 12.6; HRMS (CI) calcd for $C_{32}H_{47}O_2Si$ $[M + H]^+$ 491.3333, found 491.3345.

(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-[2′-*tert*-butyldiphenylsilyloxy)ethyl]-naphthalene (10). To a solution of ketone **9** (2.08 mmol, 1.02 g) in MeOH (20 mL) was added $CeCl_3 \cdot 7H_2O$ (2.28 mmol, 850 mg). The suspension was stirred at room temperature for 10 min and cooled to −50 °C. $NaBH_4$ (6.24 mmol, 237 mg) was added in small portions. The reaction was stirred at −20 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and concentrated. The residue was dissolved in ether, washed successively with saturated NH_4Cl, water, and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give alcohol **10** as a colorless oil, which was dissolved in dry CH_2Cl_2 (20 mL). To this were successively added 4-DMAP (0.2 mmol, 25 mg), Et_3N (12.48 mmol, 1.73 mL), and MsCl (6.24 mmol, 0.482 mL). The reaction was stirred at room temperature for 12 h. The CH_2Cl_2 was evaporated under reduced pressure, and the residue was extracted with ether, washed successively with water and brine, dried over $MgSO_4$, and concentrated. The crude mesylate **11** was dissolved in anhydrous DMF (10 mL) followed by the addition of lithium bromide (10.4 mmol, 894 mg) and lithium carbonate (10.4 mmol, 769 mg). The reaction was heated at 150 °C for 1 h and cooled to room temperature. Water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification over silica gel using hexane and then hexanes/EtOAc (98:2) gave **12** (878 mg, 89%) as a colorless oil: R_f 0.71 (hexanes/EtOAc, 98:2); $[\alpha]^{20}_D$ −12.1 (*c* 1.55, $CHCl_3$); MS *m*/*z* (CI) 475 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.68 (dd, 2H), 7.38 (m, 3H), 5.33 (bs, 1H), 3.77 (m, 1H), 3.59 (m, 1H), 1.49 (br s, 3H), 1.05 (s, 9H), 0.85 (s, 3H), 0.83 (s, 3H), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.6, 135.0, 134.0, 129.5, 127.6, 122.1, 65.4, 50.4, 50.1, 42.3, 39.0, 36.4, 33.1, 32.9, 30.1, 26.9, 23.7, 21.9, 21.8, 19.1, 18.7, 13.5; HRSM (CI) calcd for $C_{32}H_{47}OSi$ $[M + H]^+$ 475.3396, found 475.3385.

(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthalenethanol (13). To a solution of silyl ether **12** (2.32 mmol, 1.1 g) in dry THF (10 mL) was added TBAF (7 mmol, 7 mL, 1 M in THF). The reaction was heated at reflux for 1 h and concentrated. The residue was extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Purification over silica gel using hexanes/EtOAc (8:2) gave compound **13** (537 mg, 98%) as a colorless oil: R_f 0.27 (hexanes/EtOAc, 7:3); $[\alpha]_D$ −11.5 (*c* 0.74, $CHCl_3$), lit.[12] $[\alpha]^{20}_D$ −11.8 (*c* 0.9, $CHCl_3$); MS *m*/*z* (CI) 237 (MH^+); ^{1}H NMR ($CDCl_3$) δ 5.41 (bs, 1H), 3.78 (m, 1H), 3.56 (dt, J = 9.5, 8.2 Hz, 1H), 1.67 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 134.5, 122.7, 64.4, 50.7, 50.1, 42.2, 39.2, 36.4, 33.1, 32.9, 30.4, 23.8, 22.0, 21.8, 18.7, 13.5; HRMS (CI) calcd for $C_{16}H_{29}O$ $[M + H]^+$ 237.2218, found 237.2215.

(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthalenethanal (2). To a solution of alcohol **13** (3.2 mmol, 755 mg) in anhydrous DMSO (15 mL) was added Et_3N (20.8 mmol, 2.9 mL) followed by SO_3·pyridine (12.8 mmol, 2.04 g). The reaction was stirred at room temperature for 1 h and then cooled in an ice bath. A 15 mL portion of 10% aqueous $KHSO_4$ was added dropwise, and the solution was stirred vigorously for 15 min. The mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified over silica gel using hexanes/EtOAc (98:2, then 95:5) to give aldehyde **3** (719 mg, 96%) as a colorless oil: R_f 0.49 (hexanes/EtOAc, 95:5); $[\alpha]^{20}_D$ −33.6 (*c* 1.11, $CHCl_3$); MS *m*/*z* (CI) 235 $(M + H)^+$; IR (neat) 2922, 2842, 2714, 1726, 1650, 1447, 1386, 1146, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.81 (t, J = 1,5 Hz, 1H), 5.43 (dd, J = 1.9, 1.6 Hz, 1H), 2.49 (m, 1H), 2.37 (m, 2H), 1.48 (t, J = 1.4 Hz, 3H), 0.85 (s, 3H), 0.84 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.4, 132.8, 123.3, 49.8, 48.5, 42.3, 42.0, 39.5, 35.9, 33.1, 32.9, 23.6, 22.5, 21.8, 18.7, 14.1; HRMS (CI) calcd for $C_{16}H_{27}O$ $[M + H]^+$ 235.2062, found 235.2056.

(2*S*,3*R*)-1-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-3-hydroxy-2-methyl-4-[(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]butan-1-one (15). To a cooled (0 °C) solution of oxazolidinone **14** (8.18 mmol, 1.906 g) in dry CH_2Cl_2 (15 mL) was added Bu_2BOTf (8.9 mmol, 8.9 mL, 1 M in CH_2Cl_2) dropwise, followed by Et_3N (11.14 mmol, 1.55 mL). After being stirred at 0 °C for 15 min, the solution was cooled to −78 °C, and aldehyde **2** (1.74 g, 7.43 mmol) in dry CH_2Cl_2 (15 mL) was added. The reaction was stirred at −78 °C for 1 h, warmed to 0 °C over 1 h, and stirred at 0 °C for 2 h. The reaction was quenched by the addition of phosphate buffer (pH = 7, 20 mL) followed by MeOH (20 mL). After 5 min, a solution of 20 mL of 30% aqueous H_2O_2/MeOH (1:3) was added in a dropwise manner. The reaction mixture was stirred vigorously at 0 °C for 1 h. Solvents were removed under reduced pressure, and product was extracted with ether. The residue was purified on silica gel to give **15** (3.02 g, 87%) as a colorless oil: R_f 0.38 (hexanes/EtOAc, 8:2); $[\alpha]^{20}_D$ +41.5 (*c* 0.39, $CHCl_3$); MS *m*/*z* (CI) 468 (MH^+); ^{1}H NMR ($CDCl_3$) δ 7.36−7.19 (m, 5H), 5.40 (bd s, 1H), 4.71 (m, 1H), 4.26−4.04 (m, 2H), 3.78 (m, 1H), 3.24 (dd, J = 13.4, 3.3 Hz, 1H), 2.8 (dd, J = 13, 0.4, 9.4 Hz, 1H), 1.67 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.1, 152.9, 134.9, 129.4, 128.9, 127.3, 122.5, 71.6, 66.0, 60.3, 54.9, 49.9, 49.8, 43.3, 42.1, 39.0, 37.6, 36.3, 33.1, 32.9, 31.9, 23.8, 22.4, 21.8, 18.7, 13.5, 11.1; HRMS (CI) calcd for $C_{29}H_{42}O_4N$ $[M + H]^+$ 468.3114, found 468.3109.

(2*S*,3*R*)-3-Hydroxy-2-methyl-4-[(1*S*,4a*S*,8a*S*)-1,4,-4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]butan-1-[-*N*-methyl-*N*′-methoxy-amide] (16). A solution of $AlMe_3$ (2.0 M in toluene, 6.1 mmol, 6.1 mL) was added dropwise at 0 °C to a solution of MeONHMe·HCl (6.1 mmol, 0.6 g) in dry CH_2Cl_2 (10 mL). After the mixture was stirred at room temperature for 1 h, the reaction mixture was cooled to −50 °C, and a solution of **15** (1.4 g, 3.0 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C, quenched with 1 M aqueous tartaric acid, and stirred vigorously for 1 h. The mixture was extracted with CH_2Cl_2 (3×), washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified over silica gel using hexanes/EtOAc (8:2, then 7:3) to give amide **16** (1.03 g, 98%) as a colorless oil: R_f 0.14 (hexanes/EtOAc, 8:2); $[\alpha]^{20}_D$ −2.3 (*c* 0.31; $CHCl_3$); MS *m*/*z* (CI) 352 (MH^+); ^{1}H NMR ($CDCl_3$) δ 5.40 (bs, 1H), 3.95 (m, 1H), 3.69 (s, 3H), 3.41 (bs, 1H, O*H*), 3.19 (s, 3H), 2.87 (m, 1H), 1.66 (s, 3H), 1.20 (d, J = 7.2 Hz, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.1, 135.1, 122.7, 71.8, 61.6, 60.3, 50.1, 49.9, 42.2, 39.9, 39.0, 36.3, 33.2, 33.0, 32.3, 31.9, 23.9, 22.5, 21.9, 18.8, 13.6, 10.6; HRMS (CI) calcd for $C_{21}H_{38}O_3N$ $[M + H]^+$ 352.2852, found 352.2854.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-[(1*S*,-4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]butan-1-[-*N*-methyl-*N*′-methoxy-amide]

(17). To a cooled (−78 °C) solution of amide **16** (2.48 mmol, 870 mg) in dry CH_2Cl_2 (10 mL) was added 2,6-lutidine (600 μL, 2 equiv), followed by TBDMSOTf (630 μL, 1.1 equiv). The mixture was stirred at −78 °C for 1 h and warmed to −10 °C. The reaction was quenched with MeOH (1 mL), and the solvent was evaporated under reduced pressure. The residue was extracted with ether, washed with 0.5 N aqueous HCl, water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel using hexanes/EtOAc (9:1) gave **17** (1.13 g, 98%) as a colorless oil: R_f 0.27 (hexanes/EtOAc, 9:1); $[\alpha]^{20}_D$ +3.9 (*c* 0.49, $CHCl_3$); MS *m*/*z* (CI) 466 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 5.35 (bs, 1H), 4.01 (m, 1H), 3.63 (s, 3H), 3.12 (s, 3H), 2.81 (m, 1H), 1.66 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.82 (s, 3H), 0.81 (s, 3H), 0.67 (s, 3H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.1, 135.6, 122.4, 73.7, 61.3, 50.5, 48.3, 43.3, 42.5, 39.0, 36.5, 34.3, 33.1, 32.1, 26.3, 25.6, 23.9, 23.0, 21.9, 18.8, 18.3, 13.9, −2.0, −3.9; HRMS (CI) calcd for $C_{27}H_{52}O_3NSi$ $[M + H]^+$ 466.3716, found 466.3708.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-[(1*S*,-4a*S*,8a*S*)1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]butanal (18). To a cooled solution of amide **17** (1.12 g, 2.41 mmol) in dry THF (10 mL) was added DIBALH (1 M in THF, 7.23 mmol, 7.23 mL) in a dropwise manner. The reaction was stirred at −78 °C for 30 min and quenched with saturated aqueous sodium potassium tartrate (10 mL). The mixture was stirred vigorously at room temperature for 1 h. The reaction was extracted with ether (3×), washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel using hexanes/EtOAc (98:2, then 95:5) gave aldehyde **18** (970 mg, 99%) as white crystals: R_f 0.72 (EtOAc/hexanes); mp 114−116 °C (pentane); $[\alpha]^{20}_D$ +73.6 (*c* 0.63, $CHCl_3$); MS *m*/*z* (CI) 407 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H), 5.38 (m large, 1H), 4.08 (m, 1H), 2.58 (m, 1H), 1.62 (bs, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.83 (s, 3H), 0.67 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.5, 134.5, 123.1, 73.8, 53.1, 50.4, 49.1, 42.4, 39.1, 36.6, 33.1, 33.0, 31.3, 29.7, 25.9, 23.9, 22.7, 21.8, 18.7, 13.5, 9.1, −1.8, −2.5; HRMS (CI) calcd for $C_{25}H_{47}O_2Si$ $[M + H]^+$ 407.3345, found 407.3352.

Crystal Data for 18. Colorless needle (0.06 × 0.20 × 0.66 mm). C_{25} H_{46} O_2 Si, M_w = 406.71. Orthorhombic system, space group $P2_12_12_1$, Z = 4, a = 6.701(5) Å, b = 17.617(8) Å, c = 22.128(30) Å, V = 2612.2 Å^3, d_c = 1.034 g cm^{-3}, $F(000)$ = 904, λ(Cu Kα) = 1.5418 Å, μ = 0.90 mm; 5280 data measured on a Nonius-CAD4 diffractometer upto θ = 68° (−8 ≤ h ≤ 8, k = 0−21, l = 0−26) reduced to 4603 unique reflections (R_{int} = 0.078) of which 3572 were considered as observed with $I \geq 2.0\ \sigma(I)$; semiempirical absorption corrections. Absolute configuration deduced from the differences of Bijvoët pairs. Structure solved with program *SHELXS86*[18] and refined with program *SHELXL93*.[19] Refinement converged to $R_1(F)$ = 0.0497 for the 3572 observed F_o and $wR_2(F^2)$ = 0.1353 for all the 4603 data with goodness of fit S = 1.018. In the final difference map, the residual electron density was found to be between −0.17 and 0.20 e Å^{-3}. Further details on the crystal structure may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK).

(2*S*,3*R*)-3-Methyl-5-phenylsulfonyl-1-[(*1S*,4a*S*,8a*S*)-1,4,-4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]pentan-2-(*tert*-butyldimethylsilyl oxy) (21). To a suspension of NaH (3.27 mmol, 78 mg) in dry THF (5 mL) was added $(EtO)_2OPCH_2SO_2Ph$ (**19**) (3.27 mmol, 954 mg) in dry THF (4 mL) at 0 °C. The mixture was stirred at this temperature for 30 min. To this was added a solution of aldehyde **18** (2.182 mmol, 886 mg) in dry THF, and the reaction was stirred at room temperature for 2 h. The mixture was extracted twice with ether, washed with brine, and dried over $MgSO_4$. Flash chromatography on silica gel using hexanes/EtOAc (95:5 and 9:1) gave sulfone **20** (834 mg, 70%) as a colorless oil, which was used in the next step without further characterization: R_f 0.44 (hexanes/EtOAc, 9:1). To a solution of sulfone **20** (1.34 mmol, 730 mg) in MeOH (10 mL) was added $NiCl_2 \cdot xH_2O$ (0.268 mmol, 35 mg) at 0 °C. The mixture was stirred for 10 min, and then $NaBH_4$ (4 mmol, 152 mg) was added. After being stirred at 0 °C for 3 h, the reaction mixture was diluted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. Chromatography on silica gel using hexanes/EtOAc (90:10) gave sulfone **21** (673 mg, 92%) as a colorless oil: R_f 0.44 (hexanes/EtOAc, 9:1); $[\alpha]^{20}_D$ +20.5 (*c* 1.0, $CHCl_3$); MS *m*/*z* (CI) 547 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.89−7.50 (m, 5H), 5.34 (bs, 1H), 3.64 (m, J = 14, 2.7 Hz, 1H), 3.12 (m, 2H), 1.57 (bs, 3H), 0.86 (d, J = 8.3 Hz, 3H), 0.84 (s, 3H), 0.82 (s, 3H), 0.75 (s, 9H), 0.62 (s, 3H), −0.01 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.0, 134.8, 133.5, 129.1, 128.0, 122.7, 75.9, 55.5, 50.4, 48.7, 42.4, 39.2, 38.9, 36.5, 33.1, 32.9, 29.6, 28.1, 25.9, 23.9, 23.7, 22.6, 21.7, 18.7, 16.3, 13.5, −1.9, −2.4; HRMS (CI) calcd for $C_{32}H_{55}O_3SSi$ $[M + H]^+$ 547.3641, found 547.3646.

1,4-Dibenzyloxy-2-(3-methyl-2-butenyl)benzene (23). To a solution of **22** (14.04 mmol, 2.5 g), in anhydrous DMF (42 mL) at 0 °C, was added NaH (35.1 mmol, 1.4 g in oil) in small portions. The mixture was stirred for 15 min, and then benzyl bromide (42 mmol, 5 mL) was added dropwise. The solution was stirred at room temperature overnight, and ethanol (1 mL) was added at 0 °C. The DMF was evaporated under reduced pressure, and the residue was extracted twice with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography using hexanes/EtOAc (98:2) gave **23** (4.88 g, 97%) as a colorless oil: R_f 0.68 (hexanes/EtOAc, 95:5); MS *m*/*z* (CI) 359 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.42−7.27 (m, 10H), 6.88−6.69 (m, 3H), 5.29 (t large, J = 7.3 Hz, 1H), 4.97 (d, J = 7,6 Hz, 4H), 3.35 (d, J = 7.3 Hz, 2H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.0, 150.8, 137.6, 137.4, 132.7, 131.9, 128.5, 128.4, 127.8, 127.6, 127.5, 127.2, 122.2, 117.0, 115.8, 112.7, 111.7, 70.7, 70.5, 28.6, 25.8, 17.7; HRMS calcd for $C_{25}H_{27}O_2$ $[M + H]^+$ 359.2010, found 359.2012.

(*E*)-4-(2,5-Dibenzyloxy)-2-methyl-2-buten-1-ol (25). A solution of **23** (12.1 mmol, 4.33 g) in dry CH_2Cl_2 (25 mL) was added dropwise to a solution of SeO_2 (0.242 mmol, 27 mg), salicylic acid (1.21 mmol, 167 mg), and *t*-BuOOH (80%, 43.56 mmol, 5.48 mL) in 25 mL of CH_2Cl_2. The mixture was stirred for 48 h at room temperature. Toluene (50 mL) was added. The solvents were evaporated in vacuo. The residue was diluted with ether, washed with 10% aqueous KOH, water, and brine, dried over $MgSO_4$, and concentrated. The crude mixture of aldehyde **24** and alcohol **25** thus obtained was dissolved in MeOH (50 mL) and cooled to 0 °C. To this was added $NaBH_4$ (12.1 mmol, 460 mg) in small portions. The reaction was stirred for 30 min, quenched carefully by the addition of acetone (5 mL), and concentrated. The residue was dissolved in ether, washed successively with saturated NH_4Cl, water, and brine, dried over $MgSO_4$, and concentrated. Purification over silica gel using hexanes/EtOAc (8:2) gave alcohol **25** (2.45 g, 54%) as a colorless oil: R_f 0.3; MS *m*/*z* (CI) 375 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.41−7.26 (m, 10H), 6.8−6.7 (m, 3H), 5.54 (t, J = 6.3 Hz, 1H), 4.97 (d, 4H), 3.96 (bs, 2H), 3.38 (d, J = 7.3 Hz, 2H), 1.66 (s, 3H), 1.57 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 152.9, 150.8, 137.4, 137.3, 135.8, 131.0, 128.4, 128.3, 127.8, 127.7, 127.4, 127.2, 123.7, 117.0, 112.7, 111.9, 70.6, 70.4, 68.7, 28.3, 13.6; HRMS calcd for $C_{25}H_{27}O_3$ $[M + H]^+$ 375.1960, found 375.1969.

2-[(*E*)-4-Bromo-3-methyl-2-butenyl]-1,4-dibenzyloxybenzene (26). To a solution of alcohol **25** (4 mmol, 1.5 g) in dry CH_2Cl_2 (10 mL) was successively added CBr_4 (5.18 mmol, 1.72 g) and triphenylphosphine polymer bound (6 mmol, 2 g) at 0 °C. The suspension was stirred at this temperature for 4 h and then filtered. Solvent was evaporated under reduced pressure, and the excess of CBr_4 was removed in high vacuum to give the pure bromide **26** (1.73 g, 99%) as a colorless oil: R_f 0.46 (hexanes/EtOAc, 95:5); MS *m*/*z* (CI) 453 $(MH + CH_4)^+$; ^{1}H NMR ($CDCl_3$) δ 7.43−7.28 (m, 10H), 6.83−6.73 (m, 3H), 5.74 (t, J = 7.2 Hz, 1H), 5.00 (d, J = 5.6 Hz, 4H), 3.98 (bs, 2H), 3.37 (d, J = 7.4 Hz, 2H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$)

(18) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467−473.
(19) Sheldrick, G. M. *SHELXL93*: *Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1993.

δ 152.9, 150.8, 137.4, 137.3, 132.9, 130.1, 129.1, 128.5, 127.8, 127.7, 127.5, 127.2, 116.9, 112.8, 112.4, 70.7, 70.5, 41.5, 29.1, 14.7; HRMS (CI) calcd for $C_{26}H_{30}O_2Br$ $[MH + CH_4]^+$ 453.1429, found 453.1435.

(2*R*,3*R*,7*E*)-9-(2,5-Dibenzyloxyphenyl)-3,7-dimethyl-1-[(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]-7-nonen-2-(*tert*-butyldimethylsilyloxy) (28). To a solution of sulfone **21** (0.37 mmol, 200 mg) and bromide **26** (0.444 mmol, 194 mg) in dry THF (3 mL) at −78 °C was added LDA (1.11 mmol, freshly prepared from *n*-BuLi (1.6 M) in hexane and diisopropylamine) in a dropwise manner. The reaction was stirred at this temperature for 2 h, warmed to 0 °C, and stirred for 2 h. The reaction was extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Purification over silica gel using hexanes/EtOAc (95:5, then 90:10) gave **27** (254 mg, 76%), which was used in the next step without further characterization. To a solution of **27** (0.281 mmol, 254 mg) in dry MeOH (12 mL) was added 20 equiv of sodium−mercury amalgam (Na−Hg, 10%). The suspension was stirred overnight at room temperature and then filtered, and the solvent was evaporated under reduced pressure. Flash chromatography on silica gel using hexanes/EtOAc (95:5) gave **28** (198 mg, 70% from **21**) as a colorless oil: R_f 0.55 (hexanes/EtOAc, 95:5); $[\alpha]^{20}_D$ +14.8 (*c* 2.04, $CHCl_3$); MS *m*/*z* (EI) 762 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.45−7.31 (m, 10H), 6.86−6.71 (m, 3H), 5.39 (bs, 1H), 5.32 (t, J = 7.2 Hz, 1H), 5.01 (d, J = 9.3 Hz, 4H), 3.69 (dt, J = 2.5, 10.3 Hz, 1H-12), 3.37 (d, J = 7.2 Hz, 2H), 1.66 (s, 3H), 1.65 (s, 3H), 0.90 (s, 9H), 0.88 (s, 3H), 0.87 (s, 3H), 0.86 (d, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.0, 150.9, 137.7, 137.4, 137.0, 135.7, 132.0, 128.5, 128.4, 127.8, 127.6, 127.5, 127.2, 122.4, 121.7, 116.9, 112.8, 111.7, 76.6, 70.7, 70.5, 50.5, 49.2, 42.5, 40.3, 40.1, 39.0, 36.6, 33.2, 33.0, 30.1, 28.9, 28.5, 26.7, 26.1, 24.0, 22.8, 21.9, 18.8, 18.1, 16.2, 15.9, 13.6, −1.9, −2.5; HRMS (EI) calcd for $C_{51}H_{74}O_3Si$ (M^+) 762.5407, found 762.5418.

(2*R*,3*R*,7*E*)-9-(2,5-Dibenzyloxyphenyl)-3,7-dimethyl-1-[(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]-7-nonen-2-ol (29). To a solution of silyl ether **28** (0.293 mmol, 224 mg) in dry THF (5 mL) was added a solution of TBAF (1 M) in THF (1.465 mmol, 1.46 mL). The reaction was heated at reflux for 48 h. The solvent was evaporated under reduced pressure and extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified over silica gel using hexanes/EtOAc (9:1) to give **29** (177 mg, 93%) as a colorless oil: R_f. 0.37 (hexanes/EtOAc, 9:1); $[\alpha]^{20}_D$ +10.7 (*c* 0.67; $CHCl_3$); MS *m*/*z* (CI) 649 (MH^+); ^{1}H NMR ($CDCl_3$) δ 7.44−7.28 (m, 10H), 6.86−6.71 (m, 3H), 5.41 (bs, 1H), 5.33 (t, J = 7.3 Hz, 1H), 5.01 (d, J = 7.3 Hz, 4H), 3.62 (m, 1H-12), 3.38 (d, J = 7.3 Hz, 2H), 1.65 (s, 2 × 3H), 0.93 (s, 3H), 0.89 (d, 3H), 0.87 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.9, 150.8, 137.6, 137.3, 136.6, 135.1, 131.9, 128.5, 128.4, 127.8, 127.6, 127.4, 127.1, 122.5, 122.0, 116.9, 112.6, 111.6, 75.3, 70.6, 70.4, 50.6, 50.0, 42.2, 39.9, 39.4, 39.2, 36.2, 33.1, 32.9, 32.5, 28.4, 25.8, 23.8, 22.3, 21.8, 18.7, 16.0, 13.9, 13.6; HRMS calcd for $C_{45}H_{61}O_3$ (MH^+) 649.4620, found 649.4611.

(2*R*,3*R*,7*E*)-9-(2,5-Dihydroxyphenyl)-3,7-dimethyl-1-[(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthalenyl]-7-nonen-2-ol (30). A freshly prepared solution of lithium naphthalenide (2.31 mmol, 2.31 mL, 1 M in THF) was added dropwise to a solution of **29** (0.231 mmol, 150 mg) in dry THF (3 mL) at −78 °C. The reaction was stirred at this temperature for 1 h, quenched with saturated NH_4Cl, and extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to give triol **30** (90 mg, 83%) as a colorless oil: R_f 0.26 (hexanes/EtOAc, 75:25); $[\alpha]^{20}_D$ +1.3 (*c* 1.51, $CHCl_3$); MS *m*/*z* (CI) 469 (MH^+); ^{1}H NMR ($CDCl_3$) δ 6.66−6.53 (m, 3H), 6.35 (bs, 1H, O*H*), 5.40 (bs, 1H), 5.30 (t, J = 7.0 Hz, 1H), 5.27 (bs, 1H, O*H*), 3.68 (m, 1H-12), 3.28 (d, J = 7.4 Hz, 2H), 1.66 (s, 3H), 1.62 (bs, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.87 (s, 3H); 0.85 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.8, 147.4, 137.8, 134.8, 128.2, 122.7, 121.9, 116.1, 113.4, 76.2, 50.6, 49.9, 42.1, 39.6; 39.2, 39.1, 36.2, 33.0, 32.9, 32.5, 32.4, 28.4, 25.0, 23.8, 22.3, 21.8, 18.7, 15.7, 13.6, 13.3; HRMS (CI) calcd for $C_{31}H_{49}O_3$ [MH^+] 469.3681, found 469.3685.

Coscinosulfate 1. To a solution of triol **30** (0.021 mmol, 10 mg) in dry 1,2-dichloroethane (1 mL) was added $PhI(OAc)_2$ (0.023 mmol, 8 mg). The reaction was stirred at room temperature for 1 h. To this was added SO_3·pyridine (0.0965 mmol, 15.3 mg). The mixture was stirred for 2 h at reflux. The solvent was evaporated under reduced pressure, and the residue was dissolved in MeOH (3 mL) followed by careful addition of $NaBH_4$ (0.386 mmol, 15 mg) in portions. The reaction was stirred at room temperature for 30 min and concentrated in vacuo. The residue thus obtained was extracted with butanol-1, washed with water, and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified over C-18 reverse phase using CH_3CN/H_2O (4:6) as eluent to give **1** (7 mg, 58%) as a white solid: R_f 0.28 (CH_2Cl_2/MeOH, 8:2); mp 127−129 °C, lit. 129−130 °C; $[\alpha]^{20}_D$ +4.8 (*c* 0.25, MeOH), natural coscinosulfate $[\alpha]^{20}_D$ +5 (*c* 1.4, MeOH); MS *m*/*z* (FAB) 593 ($M + Na^+$); ^{1}H NMR (CD_3OH) δ 6.57 (d, J = 8.54, 1H, H-6′), 6.55 (d, J = 2.98, 1H, H-3′), 6.42 (dd, J = 8.54, J = 2.98, 1H, H-4′), 5.36 (bs, 1H, H-7), 5.32 (t, J = 7.35, 1H, H-18), 4.5 (dd, J = 11.15, J = 1.61, 1H, H-12), 3.23 (d, J = 7.33, 1H, H-19), 1.71 (s, 3H, CH_3-22), 1.70 (s, 3H, CH_3-25), 0.94 (d, J = 7.01, 3H, CH_3-24), 0.89 (s, 3H, CH_3-21), 0.85 (s, 3H, CH_3-20), 0.75 (s, 3H, CH_3-23); ^{13}C NMR 150.9, 147.9, 136.7, 135.4, 128.8, 123.2, 121.6, 116.4, 115.8, 113.2, 82.1, 50.3, 48.3, 42.5, 39.5, 38.8, 38.3, 36.9, 36.7, 33.2, 32.8, 28.3, 25.7, 27.2, 24.5, 22.4, 21.2, 19.3, 15.7, 13.6, 13.2; HRMS (FAB) calcd for $C_{31}H_{47}SO_5Na_2$ [$M + Na^+$] 593.2883, found 593.2887.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **5**, **7**, **9**, **12**, **13**, **15**, **16**, **17**, **18**, **21**, **25**, **26**, **28**, **29**, and **30** and X-ray crystallographic data for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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