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Synthesis of the Sesquiterpenes Albicanol, Drimanol, and Drimanic Acid, and the Marine Sesquiterpene Hydroquinone Deoxyspongiaquinol

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A Ti^{III}-mediated radical cyclization cascade has been used for the synthesis of the sesquiterpenes (+)-albicanol, (+)-drimanol, and (+)-drimanic acid. Starting from *all-trans*-farnesol, (+)-albicanol could be prepared in seven steps in an overall yield of 14.9%. Furthermore, a highly diastereoselective hydrogenation of (+)-albicanol to give (+)-drimanol has been developed. We used the synthesized (+)-drimanic acid to achieve the first synthesis of the marine sesquiterpene hydroquinone deoxyspongiaquinol and the quinone deoxyspongiaquinone. Thus, this synthetic strategy gave access to five natural products.

Introduction

The sesquiterpenoid compounds (+)-albicanol (**1**), and (+)-drimanic acid (**2**) are valuable building blocks in the synthesis of various meroterpenes, especially marine sesquiterpene hydroquinones and quinones (Figure 1). The enantioselective synthesis of the above-mentioned natural building blocks is challenging, and the Ti^{III}-mediated radical cyclization cascade of Justicia et al.[1a] has been used for the synthesis of (+)-3β-hydroxyalbicanyl acetate.[1b–1e] This compound has been transformed into interesting natural products of the albicane and drimane family.

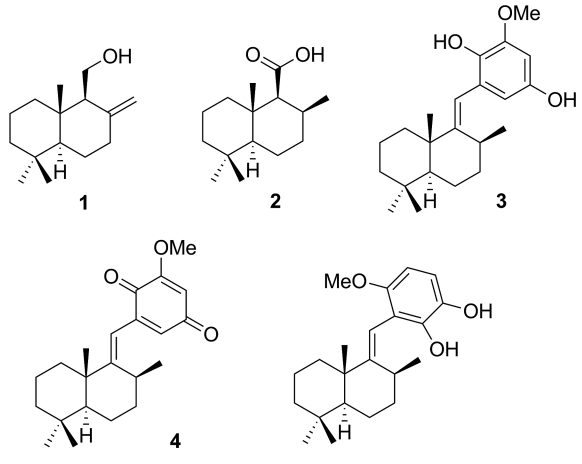

Figure 1. Structures of (+)-albicanol (**1**), (+)-drimanic acid (**2**), deoxyspongiaquinol (**3**), deoxyspongiaquinone (**4**), and wiedendiol B.

Various methods to obtain enantioenriched (+)-albicanol (**1**) are known that involve enzyme-based kinetic resolution[2a] or separation of diastereomers. To the best of our knowledge, only two asymmetric syntheses of **1** are known in the literature. The older approach by Ihara et al.[2b] gave (+)-albicanol (**1**) in 17 steps and 3.3% overall yield starting from the already enantioenriched Wieland–Miescher ketone. Another protocol starting from β-ionone was published by Henderson et al.,[2c] and used an auxiliary-based asymmetric Diels–Alder cycloaddition. In this approach, a chromatographic step was used to separate the albicanol diastereomeric mixture, and **1** could be obtained in 10 steps and 8.5% overall yield. Deoxyspongiaquinol (**3**), deoxyspongiaquinone (**4**; Figure 1), (*E*)-chlorodeoxyspongiaquinol, and (*E*)-chlorodeoxyspongiaquinone have been isolated from *Euryspongia* sp., a southern Australian marine sponge.[3] The absolute configurations of these four compounds could not be determined. The structure of sesquiterpene hydroquinone **3** is very similar to that of the pharmacologically active wiedendiol B. Therefore, interesting biological activities should be expected for deoxyspongiaquinol (**3**) and deoxyspongiaquinone (**4**). Wiedendiol B was isolated from the marine sponge *Xestospongia wiedemayeri*,[4a] and it inhibits the cholesteryl ester transfer protein (CETP).[4b] This is a plasma-neutral glycoprotein that mediates the net transfer of cholesteryl ester from high-density lipoprotein (HDL) into low-density lipoprotein (LDL). Since low levels of HDL and high levels of LDL are directly correlated with increased coronary artery diseases, CETP may play a role in the pathogenesis of atherosclerosis. The inhibition of CETP by compounds like wiedendiol B may be used to reduce the risks of coronary artery disease. Wiedendiol B shows a selective COX2 inhibition with an IC_{50} value between 0.7 and 7 μM, which is ten times more active than the reference compound indomethacine.[5]

The retrosynthesis of deoxyspongiaquinol (**3**) leads to drimanophenone **5**, which should be derived from (+)-drimanic acid (**2**) and protected aryl bromide **7** (Scheme 1).

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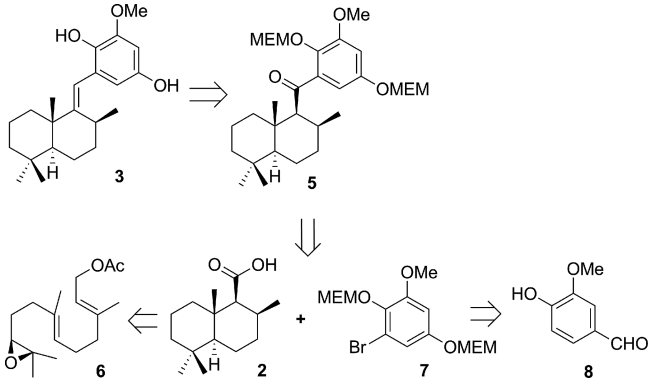
(+)-Drimanic acid (**2**) should be accessible from (–)-(*S*)-10,11-epoxyfarnesyl acetate (**6**). Compound **7** could be prepared starting from vanillin (**8**).

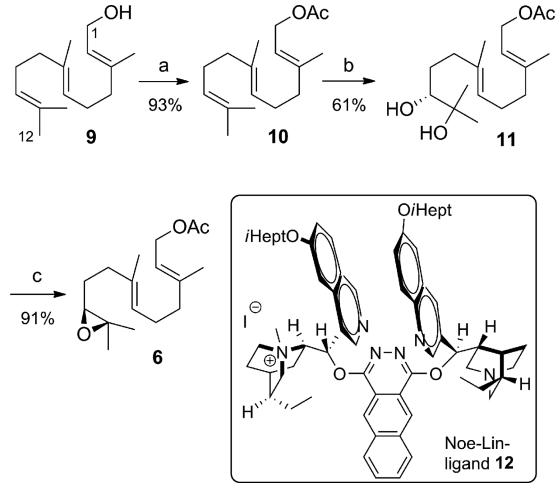


Scheme 1. Retrosynthesis of deoxyspongiaquinol (**3**).

Results and Discussion

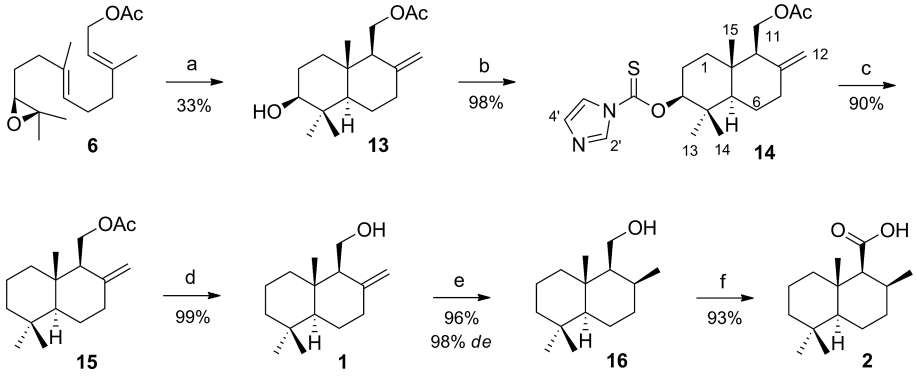
Acetylation of *all-trans*-farnesol (**9**) with Ac_2O and pyridine catalysed by DMAP [4-(dimethylamino)pyridine] gave *all-trans*-farnesyl acetate (**10**)[6] (Scheme 2). The asymmetric Sharpless dihydroxylation[7a] of *all-trans*-farnesyl acetate (**10**)[7b] with Noe–Lin-ligand **12**[7c] gave (*R*)-glycol **11** in 61% yield with an *ee* of 98%, as determined by ^1H NMR spectroscopic analysis of the Mosher ester derived from (+)-drimanol (**16**). Mesylation of the secondary alcohol of **11**, basic one-pot cyclization with K_2CO_3 in MeOH to give the epoxide, and subsequent acetylation gave compound **6** in a yield of 91%.[7d]

(–)-(10*S*,2*E*,6*E*)-10,11-Epoxyfarnesyl acetate (**6**) was subjected to a known bioinspired Ti^{III}-mediated cyclization cascade[8a–8c] to obtain (+)-3β-hydroxyalbicanyl acetate (**13**)[1a–1e] (Scheme 3). Reaction of **13** with TCDI (thiocarbonyl diimidazole) and DMAP gave thiocarbamate **14**. Our first attempts to get rid of the thiocarbamate moiety using standard Barton–McCombie conditions[9a–9c] were disappointing, and gave yields around 40%. Optimization of the



Scheme 2. Preparation of (–)-(10*S*,2*E*,6*E*)-10,11-epoxyfarnesyl acetate (**6**). Reagents and conditions: (a) Ac_2O, pyridine, DMAP [4-(dimethylamino)pyridine], CH_2Cl_2, room temp., 1 h, 93%; (b) $K_3[Fe(CN)_6]$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv.), **12** (1 mol-%), $K_2OsO_4{\cdot}2H_2O$ (0.5 mol-%), *t*BuOH/H_2O, 1:1, 0 °C, 19 h, 61%, 98% *ee*; (c) (1) $MeSO_2Cl$, pyridine, CH_2Cl_2, 0 °C, room temp. 12 h, then K_2CO_3, MeOH, room temp., 6 h, (2) Ac_2O, pyridine, DMAP, CH_2Cl_2, room temp., 2 h, 91%.

reaction conditions (e.g., temperature, concentration, stoichiometry) resulted in the formation of the desired (+)-albicanyl acetate (**15**) in very good yields. K_2CO_3-promoted methanolysis of the acetate moiety of **15** led to (+)-albicanol (**1**). In this way, (+)-albicanol (**1**) could be synthesized in seven steps starting from commercially available *all-trans*-farnesol (**9**) in an overall yield of 14.9%. Several investigations suggest that a homogeneous hydrogenation catalyst (Wilkinson's catalyst) with strongly oxophilic properties would lead to good diastereoselectivity in the conversion of (+)-albicanol (**1**) into (+)-drimanol (**16**).[10] Hydrogenation of (+)-albicanyl acetate (**15**) with Wilkinson's catalyst led to poor *de* values (72%), whereas hydrogenation of (+)-albicanol (**1**) with $(PPh_3)_3RuCl_2$ in an alcohol-free solvent gave a high selectivity (98% *de*) (Table 1). These facts



Scheme 3. Synthesis of (+)-albicanol (**1**), (+)-drimanol (**16**), and (+)-drimanic acid (**2**). Reagents and conditions: (a) Cp_2TiCl_2, Mn-dust, THF (tetrahydrofuran), room temp., 15–20 min, then 2,4,6-collidine, TMSCl (trimethylsilyl chloride), THF, **6**, room temp., 16 h, 33%; (b) TCDI (thiocarbonyl diimidazole), DMAP [4-(dimethylamino)pyridine], toluene, 80 °C, 21 h, 98%; (c) Bu_3SnH, AIBN (2,2′-azoisobutyronitrile), toluene, 125 °C, 30 min, 90%; (d) K_2CO_3, MeOH, room temp., 16 h, 99%; (e) $(PPh_3)_3RuCl_2$, H_2 100 bar, benzene, room temp., 16 h, 96%, 98% *de*; (f) (1) H_5IO_6, MeCN, room temp., 5 min, (2) PCC (pyridinium chlorochromate, 20 mol-%), 0 °C, 15 min, then room temp., 1 h, 93%.

led us to believe that coordination of **1** through its equatorially positioned CH_2OH group to the metal centre of the catalyst occurs to position the catalyst on the α face, and that this coordination is essential for a good diastereoselectivity. The β face of **1** is sterically hindered due to the axially orientated methyl groups CH_3-14 and CH_3-15. As a result of these investigations, we were able to obtain (+)-drimanol (**16**) with a *de* value of 98% in almost quantitative yield. PCC (pyridinium chlorochromate) catalysed oxidation[11] of **16** gave (+)-drimanic acid (**2**) after a single recrystallization from hexanes in 93% yield.

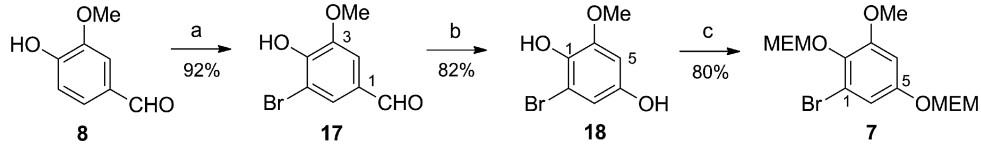
For the preparation of the aryl building block **7**, vanillin (**8**) was brominated with Br_2 to give 5-bromovanillin (**17**)[12] (Scheme 4). Dakin oxidation of **17** led to hydroquinone **18** in 82% yield after two recrystallizations from water and toluene.[12] Protection of both of the hydroxy groups of **18** with MEMCl (methoxyethoxymethyl chloride)[5] in the presence of NaH gave **7** in 80% yield. It is noteworthy that this protection had to be conducted in the consecutive manner as described in the Experimental section. Attempts to carry out this reaction in a single step led to significantly lower yields.

Table 1. Diastereoselectivities of the hydrogenation of (+)-albicanol (**1**) and (+)-albicanyl acetate (**15**).

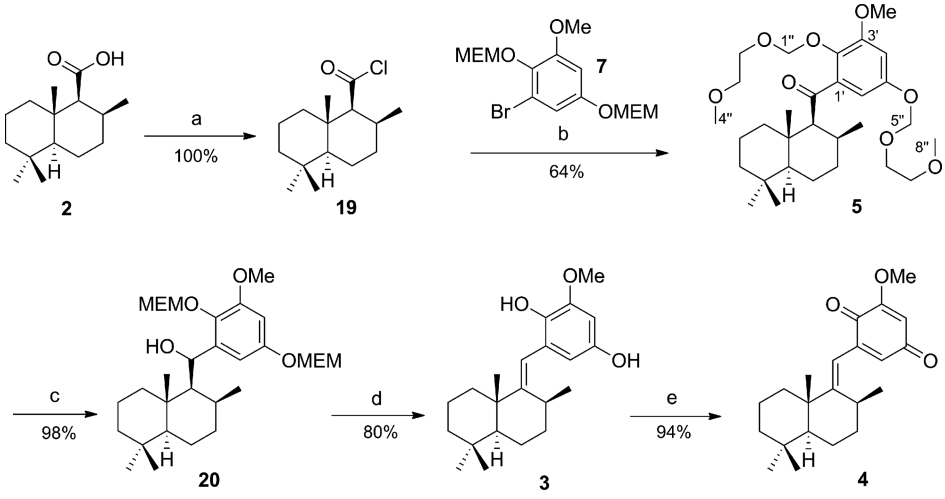
Substrate	Catalyst	Solvent	*de* [%][a]	Yield [%][b]
1	Pd/C	MeOH	73	98
1	$Pd(OH)_2/C$	C_6H_6	–[c]	–[c]
1	PtO_2	MeOH	79	98
1	$(PPh_3)_3RhCl$	C_6H_6/MeOH, 2:1	90	97
15	$(PPh_3)_3RhCl$	C_6H_6/MeOH, 2:1	72	98
1	$(PPh_3)_3RuCl_2$[d]	C_6H_6	98	97

[a] *de* values were estimated by GC analysis. [b] Yield for the sum of both epimers. [c] A complex mixture was obtained. [d] Hydrogenation was carried out at 100 bar H_2.

With the two desired compounds **2** and **7** in hand, we converted (+)-drimanic acid (**2**) into the corresponding acid chloride (i.e., **19**) by treatment with oxalyl chloride, and simultaneously lithiated aryl bromide **7** with *n*BuLi in Et_2O at –78 °C[13a] (Scheme 5). The reaction of these two compounds in Et_2O at low temperature gave drimanophenone **5** in 64% yield. Reduction with $LiEt_3BH$ in THF[13a] gave benzylic alcohol **20** as a single epimer. Attempts to dehydrate compound **20** to give the corresponding styrol by treatment with SO_3·pyridine[13a] led to a partial deprotection of the 2′-MEM moiety. After some investigation, we decided to dehydrate and deprotect compound **20** in a consecutive manner. We found that the deprotection was best carried out with a strong anhydrous Brønsted acid in EtOH. In this way, dehydration with SO_3·pyridine and subsequent complete deprotection of the crude product with anhydrous HCl in EtOH gave deoxyspongiaquinol (**3**) in 80% yield over two steps. To prevent oxidation, the reaction was carried out under inert gas. Hydroquinone **3** was oxidized with CAN [cerium(IV) ammonium nitrate][13b] to give deoxyspongiaquinone (**4**) in 94% yield.



Scheme 4. Preparation of protected aryl bromide **7**. Reagents and conditions: (a) Br_2, AcOH, room temp., 1 h, 92%; (b) H_2O_2 (3%), KOH (1 M), room temp., 1 h, 82%; (c) THF, 0 °C, NaH, 15 min, then MEMCl, 2 h, room temp., then NaH, 15 min, then MEMCl, 2 h, 80%.



Scheme 5. Synthesis of deoxyspongiaquinol (**3**) and deoxysponigiaquinone (**4**). Reagents and conditions: (a) $(COCl)_2$, DMF (dimethylformamide), CH_2Cl_2, 50 min, 100%; (b) **7**, *n*BuLi, Et_2O, –78 °C, 15 min, then **19** in Et_2O, –78 °C→ room temp., 1.5 h, 64%; (c) $LiEt_3BH$, Et_2O, 0 °C, 2 h, 98%; (d) (1) SO_3·pyridine, benzene, reflux, 2.5 h, (2) HCl (2 M in Et_2O), EtOH, room temp., 2.5 h, 80%; (e) CAN [cerium(IV) ammonium nitrate] (1.2 M in H_2O), MeCN, room temp., 15 min, 94%.

A comparison of the spectroscopic data (NMR, MS, IR) and the optical rotations of **3** and **4** with natural deoxyspongiaquinol and deoxyspongiaquinone showed good agreement. In this way, the absolute configuration of the both natural compounds could be established as 5*S*,8*S*,10*S*. The assignments of the ^{13}C NMR signals of C-13–C-15, C-2′, C-3′ and C-3, C-8, C-10–C-15, C-4′ and of the ^{1}H NMR signals of 13-H and 15-H of the natural deoxyspongiaquinol and deoxyspongiaquinone[3] were not in agreement with those of **3** and **4**. The NMR spectroscopic data of **3** and **4** were assigned by $^{1}H,^{1}H$-COSY (correlation spectroscopy), HSQC (heteronuclear single quantum coherence), and HMBC (heteronuclear multiple bond correlation) experiments.

Conclusions

A short, efficient, and stereoselective synthesis of the most common compounds of the albicane and drimane family, i.e., (+)-albicanol (**1**), (+)-drimanol (**16**), and (+)-drimanic acid (**2**), using the known titanocene-catalysed epoxyfarnesyl acetate cyclization cascade[1a–1e] (Scheme 3) is described. Furthermore a highly diastereoselective hydrogenation of (+)-albicanol (**1**) to give (+)-drimanol (**16**) exploiting the oxophilicity of $(PPh_3)_3RuCl_2$ was developed. (+)-Drimanic acid (**2**) was used for the first synthesis of the marine sesquiterpene hydroquinone deoxyspongiaquinol (**3**) and the quinone deoxyspongiaquinone (**4**). For the coupling reaction, aromatic bromide **7** was lithiated and treated with drimanoyl chloride (**19**; Scheme 5). Furthermore, the absolute configuration of natural deoxyspongiaquinol and deoxyspongiaquinone was determined as 5*S*,8*S*,10*S* by comparison of their optical rotations with those of **3** and **4**.

Experimental Section

General Remarks: All reactions were carried out in oven-dried glassware under an argon atmosphere using standard Schlenk techniques. THF and Et_2O were distilled from sodium/potassium alloy or sodium diphenyl ketyl. Toluene was distilled from $LiAlH_4$, and CH_2Cl_2 from P_2O_5. Solvents for chromatography were purchased technical grade, and were distilled before use. Thin-layer chromatography (TLC) was carried out on precoated Alugram® SIL G/UV_{254} plates from Macherey–Nagel. TLC spots were visualized by dipping the plate into molybdophosphoric acid (5% in ethanol) or cerium molybdate solution with subsequent heating. MPLC separations were conducted using a Büchi Sepacore® system with SepacoreControl software and a C-620 control unit. Mass spectra were recorded using a Finnigan MAT 95 (EI, 70 eV) mass spectrometer or a Bruker APEX IV (HRMS, ESI) Fourier transform ion cyclotron resonance mass spectrometer. IR spectra were recorded with a Perkin–Elmer FTIR spectrophotometer equipped with an ATR (attenuated total reflectance) sampling unit. NMR spectroscopic data were recorded under the conditions indicated, with Bruker Avance 300 and Bruker Avance-III-HD 500 spectrometers. Solvent signals were used as internal standard (^{1}H: δ = 7.26 ppm and ^{13}C: δ = 77.0 ppm for $CDCl_3$; ^{1}H: δ = 2.50 ppm and ^{13}C: δ = 39.5 ppm for $[D_6]$DMSO). All starting compounds were purchased from commercial suppliers, and were used as received. Reactions were monitored by TLC or gas chromatography using a TR-5MS column.

***all-trans*-Farnesyl Acetate (10):** *all-trans*-Farnesol (**9**; 10.12 g, 45.5 mmol) was dissolved in CH_2Cl_2 (250 mL) and pyridine (14.7 mL, 182 mmol) under an inert gas atmosphere at room temp., and then Ac_2O (12.9 mL, 136.5 mmol) and DMAP (278 mg, 2.28 mmol) were added. The mixture was stirred for 1 h, then saturated NH_4Cl solution (300 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2× 100 mL). The organic layers were combined, and the solvent was removed under reduced pressure. Toluene (2× 75 mL) was added to the residue, and this mixture was then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (150 mL), the resulting solution was passed through a plug of silica/$MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography [silica gel; hexanes/methyl *tert*-butyl ether (MTBE), 9:1] to give **10** (11.19 g, 42.3 mmol, 93%) as a colourless oil. R_f = 0.46 (hexanes/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.33 (tq, J = 7.1, 1.3 Hz, 1 H, 2-H), 5.08 (m, 1 H, 6-H), 5.07 (m, 1 H, 10-H), 4.57 (d, J = 7.1 Hz, 2 H, 1-H), 2.07 (m, 2 H, 5-H), 2.05 (m, 2 H, 4-H), 2.03 (s, 3 H, $COCH_3$), 2.00 (m, 2 H, 9-H), 1.97 (m, 2 H, 8-H), 1.69 (m, 3 H, 3-CH_3), 1.67 (m, 3 H, 12-H), 1.58 (m, 6 H, 7-CH_3, 11-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.0 (*C*OCH_3), 142.1 (C-3), 135.4 (C-7), 131.2 (C-11), 124.3 (C-10), 123.6 (C-6), 118.3 (C-2), 61.3 (C-1), 39.6 (C-8), 39.5 (C-4), 26.7 (C-9), 26.1 (C-5), 25.6 (C-12), 20.9 (CO*C*H_3), 17.6 (11-CH_3), 16.3 (3-CH_3), 15.9 (7-CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 264 (2) $[M]^+$, 204 (5), 189 (7), 161 (10), 136 (22), 123 (11), 121 (15), 107 (20), 93 (40), 81 (36), 69 (100), 55 (13).

(10*R*,2*E*,6*E*)-10,11-Dihydroxyfarnesyl Acetate (11): A mixture of K_2CO_3 (6.85 g, 49.6 mmol), $K_3[Fe(CN)_6]$ (16.3 g, 49.5 mmol), $MeSO_2NH_2$ (1.57 g, 16.5 mmol), Neo–Lin-ligand (**12**; 159 mg, 165 µmol, 1.0 mol-%), and $K_2OsO_4{\cdot}H_2O$ (30.4 mg, 82.6 µmol, 0.5 mol-%) was dissolved at room temp. in a mixture of H_2O/*t*BuOH (1:1; 165 mL). The mixture was stirred vigorously for 20 min at 0 °C, then *all-trans*-farnesyl acetate (**10**; 4.37 g, 16.5 mmol) was added to the suspension. The mixture was stirred for 19 h at 0 °C. Saturated Na_2SO_3 solution (80 mL) and saturated $Na_2S_2O_4$ solution (80 mL) were then added. The mixture was stirred for 1 h at room temp., then it was partitioned between EtOAc (250 mL) and H_2O (50 mL), and the aqueous layer was extracted with EtOAc (2× 30 mL). The combined organic extracts were treated with KOH solution (1 M, 100 mL) and saturated NaCl solution (100 mL), and dried with $MgSO_4$, and the solvents were evaporated. The residue was purified by flash chromatography (silica gel; hexanes/Me_2CO, 4:1→3:1) to give **11** (3.01 g, 10.1 mmol, 61%, 98% *ee*) as a colourless oil. R_f = 0.24 (hexanes/Me_2CO, 3:1). $[a]_D^{23}$ = +19.1 (c = 2.07, MeOH) {ref.[7c] $[a]_D^{23}$ = +20 (c = 0.72, MeOH)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.28 (tq, J = 7.0, 1.3 Hz, 1 H, 2-H), 5.10 (tq, J = 6.8, 1.2 Hz, 1 H, 6-H), 4.53 (d, J = 7.0 Hz, 2 H, 1-H), 3.27 (dd, J = 10.4, 2.0 Hz, 1 H, 10-H), 2.19 (m, 1 H, 8-H_A), 2.04 (m, 2 H, 5-H), 2.00 (m, 2 H, 4-H), 2.00 (s, 3 H, $COCH_3$), 1.98 (m, 1 H, 8-H_B), 1.64 (m, 3 H, 3-CH_3), 1.58 (m, 3 H, 7-CH_3), 1.52 (m, 1 H, 9-H_A), 1.34 (m, 1 H, 9-H_B), 1.14 (s, 3 H, 12-H), 1.10 (s, 3 H, 11-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.2 (*C*OCH_3), 141.9 (C-3), 135.2 (C-7), 124.1 (C-6), 118.3 (C-2), 77.9 (C-10), 72.9 (C-11), 61.9 (C-1), 39.3 (C-4), 36.6 (C-8), 29.6 (C-9), 26.2 (C-12), 25.9 (C-5), 23.1 (11-CH_3), 20.9 (CO*C*H_3), 16.3 (3-CH_3), 15.8 (7-CH_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 294 (10) $[M]^+$, 227 (8), 171 (20), 159 (40), 145 (95), 117 (100), 101 (44), 75 (71), 59 (23).

(–)-(10*S*,2*E*,6*E*)-10,11-Epoxyfarnesyl Acetate (6): Compound **11** (4.05 g, 13.6 mmol) was dissolved in CH_2Cl_2 (40 mL) and pyridine (16.4 mL, 203 mmol) under an inert gas atmosphere. The solution was cooled in an ice bath, and $MeSO_2Cl$ (1.68 mL, 21.7 mmol) was

added. The mixture was stirred for 3 h at 0 °C, then MeOH (180 mL) and finely powdered K_2CO_3 (7.50 g, 54.2 mmol) were added. The reaction mixture was stirred for 6 h at room temp., and then most of the volatiles were removed under reduced pressure. The residue was partitioned between MTBE (250 mL) and H_2O (100 mL), and the aqueous layer was extracted with MTBE (2× 50 mL). The combined organic extracts were dried with $MgSO_4$, and the solvents were evaporated to dryness.

The residue was dissolved in CH_2Cl_2 (12 mL) and pyridine (2.41 mL, 29.8 mmol) under an inert gas atmosphere at 0 °C, and Ac_2O (2.56 mL, 27.2 mmol), and DMAP (82.8 mg, 678 μmol, 5 mol-%) were added. The mixture was stirred for 2 h at room temp., then it was partitioned between CH_2Cl_2 (250 mL) and H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2× 50 mL). The combined organic extracts were dried with $MgSO_4$, and the solvents were evaporated. The crude product was purified by column chromatography (silica gel; hexanes/EtOAc, 9:1) to give **6** (3.45 g, 12.32 mmol, 91%) as a colourless oil. R_f = 0.40 (hexanes/EtOAc, 5:1). $[\alpha]_D^{23}$ = –5.0 (c = 0.77, MeOH) {ref.[1b] $[\alpha]_D$ = –2.8 (c = 1.0, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.27 (tq, J = 7.1, 1.3 Hz, 1 H, 2-H), 5.07 (tq, J = 6.9, 1.3 Hz, 1 H, 6-H), 4.50 (d, J = 7.1 Hz, 2 H, 1-H), 2.62 (t, J = 6.2 Hz, 1 H, 10-H), 2.06 (m, 2 H, 5-H), 2.05 (m, 2 H, 8-H), 2.00 (m, 2 H, 4-H), 1.97 (s, 3 H, $COCH_3$), 1.63 (m, 3 H, 3-CH_3), 1.55 (m, 5 H, 9-H, 7-CH_3), 1.22 (s, 3 H, 12-H), 1.18 (s, 3 H, 11-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.8 ($COCH_3$), 141.7 (C-3), 134.4 (C-7), 124.1 (C-6), 118.3 (C-2), 63.9 (C-10), 61.1 (C-1), 58.0 (C-11), 39.2 (C-4), 36.1 (C-8), 26.0 (C-5), 24.7 (C-12), 20.8 ($CO\mathit{C}H_3$), 18.6 (11-CH_3), 16.2 (3-CH_3), 15.8 (7-CH_3) ppm. MS (EI, 70 eV): m/z (%) = 280 (1) $[M]^+$, 220 (7), 202 (7), 187 (9), 177 (6), 159 (16), 153 (15), 134 (47), 119 (39), 107 (28), 93 (55), 81 (85), 71 (100), 55 (22).

(+)-3β-Hydroxyalbicanyl Acetate (13): A mixture of Mn dust (7.52 g, 137 mmol) and Cp_2TiCl_2 (852 mg, 3.42 mmol) was suspended in THF (260 mL) under an inert gas atmosphere at room temp. After 15–20 min, the colour of the reaction mixture had changed from reddish to grey-greenish. A solution of trimethylsilyl chloride (9.77 mL, 77.0 mmol) in THF (10 mL) and a solution of 2,4,6-collidine (15.9 mL, 120 mmol) in THF (5 mL) were added at the same time. After 5 min, compound **6** (4.80 g, 17.1 mmol) was added, and the mixture was stirred for 19 h. The excess Mn was dissolved by the addition of HCl (2 M, 20 mL). H_2O (200 mL) was added, and the reaction mixture was extracted with MTBE (1× 300 mL, 3× 100 mL). The combined organic extracts were passed through a plug of silica/$MgSO_4$, which was eluted with MTBE (100 mL), and the solvents were evaporated.

The resulting highly viscous, brownish oil was dissolved in MeCN (20 mL), and HF (40% in H_2O; 0.90 mL, 19.8 mmol) was added. After 1 h, $KHCO_3$ (3.0 g) and then H_2O (5 mL) were slowly added. The mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3× 25 mL). The solvent was removed, and the crude product was purified by flash chromatography (silica gel; hexanes/MTBE, 1:1) followed by MPLC (MN-Nucleodur® 100–12; hexanes/MTBE gradient 10–90%; flow rate 40 mL/min; column 460 × 26 mm) to give **13** (1.59 g, 5.65 mmol, 33%) as a colourless oil that quickly crystallized. R_f = 0.15 (hexanes/MTBE, 1:1), m.p. 91 °C (hexanes). $[\alpha]_D^{23}$ = +26.1 (c = 1.22, $CHCl_3$) {ref.[1b] $[\alpha]_D$ = +8.0 (c = 1.0, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.85 (d, J = 1.5 Hz, 1 H, 12-H_A), 4.52 (d, J = 1.5 Hz, 1 H, 12-H_B), 4.30 (dd, J = 11.3, 3.9 Hz, 1 H, 11-H_A), 4.16 (dd, J = 11.3, 8.9 Hz, 1 H, 11-H_B), 3.25 (dd, J = 11.4, 4.3 Hz, 1 H, 3-H), 2.40 (ddd, J = 13.2, 4.2, 2.4 Hz, 1 H, 7-H_{eq}), 2.01 (m, 1 H, 7-H_{ax}), 2.00 (m, 1 H, 9-H), 2.00 (s, 3 H, $COCH_3$), 1.74 (m, 1 H, 1-H_{eq}), 1.73 (m, 1 H, 6-H_{eq}), 1.68 (m, 1 H, 2-H_{ax}), 1.57 (m, 1 H, 2-H_{eq}), 1.38 (m, 1 H, 6-H_{ax}), 1.36 (m, 1 H, 1-H_{ax}), 1.10 (dd, J = 12.5, 2.7 Hz, 1 H, 5-H), 0.98 (s, 3 H, 13-H), 0.76 (s, 3 H, 14-H), 0.74 (s, 3 H, 15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.3 ($\mathit{C}OCH_3$), 146.1 (C-8), 107.5 (C-12), 78.5 (C-3), 61.4 (C-11), 54.4 (C-9), 54.2 (C-5), 39.1 (C-4), 38.6 (C-10), 37.4 (C-7), 36.9 (C-1), 28.3 (C-13), 27.6 (C-2), 23.6 (C-6), 21.4 ($CO\mathit{C}H_3$), 15.4 (C-14), 15.0 (C-15) ppm. MS (EI, 70 eV): m/z (%) = 280 (1) $[M]^+$, 220 (16), 202 (39), 187 (35), 159 (33), 152 (20), 135 (100), 119 (24), 107 (37), 93 (39), 81 (21), 79 (22).

(+)-3β-(1*H*-Imidazole-1-carbonothioyloxy)albicanyl Acetate (14): Compound **13** (127 mg, 0.45 mmol) and toluene (10 mL) were mixed in a tube equipped with a stirrer bar under an inert gas atmosphere. TCDI (218 mg, 1.22 mmol) and DMAP (61 mg, 0.50 mmol) were added. The tube was tightly sealed, and the mixture was stirred for 21 h at 80 °C. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The combined organic extracts were passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 1:1) to give **14** (173 mg, 443 μmol, 98%) as a colourless crystalline solid. R_f = 0.36 (hexanes/EtOAc, 1:1), m.p. 112 °C (hexanes). $[\alpha]_D^{23}$ = +63.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.29 (s, 1 H, 2′-H), 7.58 (d, J = 1.5 Hz, 1 H, 5′-H), 7.00 (d, J = 1.5 Hz, 1 H, 4′-H), 5.24 (dd, J = 11.9, 4.2 Hz, 1 H, 3-H), 4.87 (d, J = 1.5 Hz, 1 H, 12-H_A), 4.54 (d, J = 1.5 Hz, 1 H, 12-H_B), 4.29 (dd, J = 11.5, 4.3 Hz, 1 H, 11-H_A), 4.17 (dd, J = 11.5, 8.5 Hz, 1 H, 11-H_B), 2.42 (ddd, J = 13.1, 4.0, 2.3 Hz, 1 H, 7-H_{eq}), 2.06 (m, 1 H, 9-H), 2.04 (m, 3 H, 2-H, 7-H_{ax}), 2.00 (s, 3 H, $COCH_3$), 1.83 (ddd, J = 13.0, 3.5 Hz, 1 H, 1-H_{eq}), 1.74 (m, 1 H, 6-H_{eq}), 1.51 (m, 1 H, 1-H_{ax}), 1.39 (m, 1 H, 6-H_{ax}), 1.29 (dd, J = 12.4, 2.3 Hz, 1 H, 5-H), 0.98 (s, 3 H, 14-H), 0.94 (s, 3 H, 13-H), 0.80 (s, 3 H, 15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 183.8 (C=S), 171.0 ($\mathit{C}OCH_3$), 145.4 (C-8), 136.5 (C-2′), 130.6 (C-4′), 117.7 (C-5′), 108.0 (C-12), 90.7 (C-3), 61.1 (C-11), 54.2 (C-5), 54.1 (C-9), 38.7 (C-4), 38.4 (C-10), 37.0 (C-7), 36.2 (C-1), 28.2 (C-13), 23.0 (C-6), 22.7 (C-2), 20.1 ($CO\mathit{C}H_3$), 17.3 (C-14), 15.0 (C-15) ppm. MS (EI, 70 eV): m/z (%) = 390 (1) $[M]^+$, 330 (5), 219 (30), 203 (100), 187 (15), 161 (25), 159 (58), 147 (79), 133 (39), 119 (41), 105 (38), 81 (24), 69 (68), 43 (17), 41 (43). HRMS (ESI): calcd. for $C_{21}H_{31}O_3N_2S$ $[M + H]^+$ 391.2055; found 391.2039.

(+)-Albicanyl Acetate (15): Thiocarbamate **14** (1.00 g, 2.56 mmol), Bu_3SnH (2.03 mL, 7.68 mmol), and AIBN (84.1 mg, 512 μmol) were dissolved in toluene (375 mL) in a sealed pressure tube. The reaction mixture was immersed in an oil bath at 160 °C and stirred vigorously. After 10 min, the oil-bath temperature was dropped to 125 °C and the mixture was stirred for a further 20 min. The mixture was cooled to room temp. using a water bath, then all the volatiles were evaporated. The crude product was purified by column chromatography (silica gel; hexanes/MTBE, 9:1) to give **15** (611 mg, 2.31 mmol, 90%) as a colourless oil. R_f = 0.38 (hexanes/MTBE, 9:1). $[\alpha]_D^{23}$ = +29.9 (c = 2.03, $CHCl_3$) {ref.[14] $[\alpha]_D^{20}$ = +24 (c = 0.5, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.85 (d, J = 1.5 Hz, 1 H, 12-H_A), 4.51 (d, J = 1.5 Hz, 1 H, 12-H_B), 4.33 (dd, J = 11.3, 3.9 Hz, 1 H, 11-H_A), 4.18 (dd, J = 11.3, 9.1 Hz, 1 H, 11-H_B), 2.40 (ddd, J = 13.1, 4.2, 2.3 Hz, 1 H, 7-H_{eq}), 2.04 (m, 2 H, 7-H_{ax}, 9-H), 2.01 (s, 3 H, $COCH_3$), 1.73 (m, 1 H, 6-H_{eq}), 1.72 (m, 1 H, 1-H_{eq}), 1.52 (m, 2 H, 2-H), 1.40 (m, 1 H, 3-H_{eq}), 1.34 (m, 1 H, 6-H_{ax}), 1.23 (m, 1 H, 1-H_{ax}), 1.20 (m, 1 H, 3-H_{ax}), 1.12 (dd, J = 12.6, 2.7 Hz, 1 H, 5-H), 0.87 (s, 3 H, 13-H), 0.81 (s, 3 H, 14-H), 0.75 (s, 3 H, 15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.4 ($\mathit{C}OCH_3$), 146.8 (C-8), 107.1 (C-12), 61.6 (C-11), 55.1 (C-5), 54.7 (C-9), 41.9 (C-3), 39.0 (C-1, C-10), 37.6 (C-7), 33.6 (C-

13), 33.5 (C-4), 23.9 (C-6), 21.1 (C-14), 19.2 ($CO\mathit{C}H_3$), 18.7 (C-2), 15.1 (C-15) ppm. MS (EI, 70 eV): *m/z* (%) = 264 (1) $[M]^+$, 204 (33), 189 (28), 175 (7), 161 (14), 148 (13), 137 (90), 133 (28), 123 (45), 107 (45), 95 (64), 93 (64), 81 (80), 69 (79), 55 (54), 43 (100), 41 (70).

(+)-Albicanol (1): Albicanyl acetate (**15**; 600 mg, 2.27 mmol) was dissolved in MeOH (25 mL), and finely powdered K_2CO_3 (784 mg, 5.67 mmol) was added. The mixture was stirred at room temp. for 16 h, then it was partitioned between MTBE (100 mL) and H_2O (50 mL), and the aqueous layer was extracted with MTBE (2× 25 mL). The combined organic extracts were passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. Compound **1** (501 mg, 2.25 mmol, 99%) was obtained as a colourless oil that crystallized on standing for a longer time. R_f = 0.30 (hexanes/EtOAc, 3:1), m.p. 69 °C (hexanes). (ref.[14] m.p. 68–69 °C). $[\alpha]_D^{23}$ = +8.8 (*c* = 1.0, $CHCl_3$) {ref.[14] $[\alpha]_D$ = +13 (*c* = 0.6, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.93 (d, *J* = 1.5 Hz, 1 H, 12-H_A), 4.63 (d, *J* = 1.5 Hz, 1 H, 12-H_B), 3.83 (dd, *J* = 11.0, 3.9 Hz, 1 H, 11-H_A), 3.75 (dd, *J* = 11.0, 9.5 Hz, 1 H, 11-H_B), 2.41 (ddd, *J* = 13.0, 4.3, 2.4 Hz, 1 H, 7-H_{eq}), 2.02 (m, 1 H, 7-H_{ax}), 1.96 (m, 1 H, 9-H), 1.74 (m, 1 H, 6-H_{eq}), 1.66 (m, 1 H, 1-H_{eq}), 1.57 (m, 1 H, 2-H_{ax}), 1.49 (m, 1 H, 2-H_{eq}), 1.40 (m, 1 H, 3-H_{eq}), 1.33 (m, 1 H, 6-H_{ax}), 1.21 (m, 1 H, 1-H_{ax}), 1.19 (m, 1 H, 3-H_{ax}), 1.12 (dd, *J* = 12.5, 2.7 Hz, 1 H, 5-H), 0.87 (s, 3 H, 13-H), 0.79 (s, 3 H, 14-H), 0.71 (s, 3 H, 15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 147.8 (C-8), 106.3 (C-12), 59.2 (C-9), 58.7 (C-11), 55.1 (C-5), 42.0 (C-3), 39.0 (C-1), 38.9 (C-10), 37.8 (C-7), 33.6 (C-13), 33.4 (C-4), 24.1 (C-6), 21.7 (C-14), 19.2 (C-2), 15.2 (C-15) ppm. MS (EI, 70 eV): *m/z* (%) = 222 (19) $[M]^+$, 207 (17), 204 (15), 189 (19), 177 (15), 166 (11), 147 (7), 137 (100), 123 (44), 109 (37), 107 (34), 95 (60), 81 (64), 69 (55), 55 (44).

(+)-Drimanol (16): $(PPh_3)_3RuCl_2$ (21.5 mg, 22.5 μmol) was added to a solution of albicanol (**1**; 200 mg, 899 μmol) in benzene (15 mL). The mixture was hydrogenated at 100 bar hydrogen pressure in an autoclave for 16 h. The mixture was passed through a plug of silica, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel; hexanes/MTBE, 5:1) to give **16** (193 mg, 860 μmol, 96%) as a colourless crystalline solid, m.p. 105 °C (hexanes) [ref.[14] m.p. 100 °C (hexanes)]. $[\alpha]_D^{23}$ = +16.1 (*c* = 1.0, $CHCl_3$) {ref.[14] $[\alpha]_D$ = +15 (*c* = 0.5, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.84 (dd, *J* = 10.7, 4.5 Hz, 1 H, 11-H_A), 3.57 (dd, *J* = 10.7, 9.6 Hz, 1 H, 11-H_B), 2.14 (m, 1 H, 8-H), 1.68 (m, 1 H, 7-H_{eq}), 1.66 (m, 1 H, 1-H_{eq}), 1.60 (m, 1 H, 7-H_{ax}), 1.57 (m, 1 H, 2-H_{ax}), 1.46 (m, 1 H, 6-H_{eq}), 1.38 (m, 1 H, 2-H_{eq}), 1.36 (m, 2 H, 3-H_{eq}, 6-H_{ax}), 1.34 (m, 1 H, 9-H), 1.15 (m, 1 H, 3-H_{ax}), 1.00 (m, 1 H, 1-H_{ax}), 0.95 (d, *J* = 7.6 Hz, 3 H, 12-H), 0.85 (dd, *J* = 11.6, 2.7 Hz, 1 H, 5-H), 0.85 (s, 6 H, 13-H, 15-H), 0.80 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 60.9 (C-11), 56.5 (C-5), 55.7 (C-9), 41.9 (C-3), 39.9 (C-1), 37.5 (C-10), 34.4 (C-7), 33.5 (C-13), 33.2 (C-4), 28.5 (C-8), 21.6 (C-14), 18.4 (C-2), 17.5 (C-6), 17.0 (C-15), 15.6 (C-12) ppm. MS (EI, 70 eV): *m/z* (%) = 224 (33) $[M]^+$, 209 (47), 191 (14), 137 (15), 135 (12), 123 (100), 109 (41), 95 (45), 81 (47), 69 (46), 55 (36).

(+)-Drimanic Acid (2): (+)-Drimanol (**16**; 803 mg, 3.38 mmol) was added to a solution of H_5IO_6 (1.77 g, 7.77 mmol) in MeCN (50 mL) at room temp. After 5 min, the suspension was cooled to 0 °C, and PCC (146 mg, 676 μmol) was added in one portion. After 15 min, the cooling bath was removed. The reaction mixture was stirred at room temp. for approximately 1 h until TLC (hexanes/MTBE, 3:1) showed full conversion of the starting material. The orange suspension was partitioned between MTBE (200 mL) and half-saturated brine (150 mL), and the aqueous layer was extracted with MTBE (2× 50 mL). The combined organic phases were washed with $NaHSO_3$ solution, and passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The resulting almost colourless amorphous solid was crystallized from boiling hexanes to give **2** (750 mg, 3.15 mmol, 93%). R_f = 0.40 (hexanes/AcOH, 9:1), m.p. 132 °C (hexanes) [ref.[15] m.p. 135–136 °C (aqueous EtOH)]. $[\alpha]_D^{23}$ = +13.6 (*c* = 1.0, $CHCl_3$) {ref.[15] $[\alpha]_D$ = +14 (*c* = 1.70, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 11.68 (br. s, COOH), 2.33 (m, 1 H, 8-H), 2.28 (d, *J* = 4.6 Hz, 1 H, 9-H), 1.84 (m, 1 H, 1-H_{eq}), 1.67 (m, 2 H, 7-H), 1.64 (m, 1 H, 2-H_{ax}), 1.49 (m, 2 H, 6-H), 1.40 (m, 1 H, 3-H_{eq}), 1.38 (m, 1 H, 2-H_{eq}), 1.21 (s, 3 H, 15-H), 1.17 (m, 1 H, 3-H_{ax}), 1.10 (d, *J* = 7.3 Hz, 3 H, 12-H), 0.99 (m, 1 H, 1-H_{ax}), 0.86 (s, 3 H, 13-H), 0.84 (s, 3 H, 14-H), 0.81 (dd, *J* = 10.6, 3.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 180.6 (C-11), 59.4 (C-9), 55.9 (C-5), 42.1 (C-3), 39.5 (C-1), 37.2 (C-10), 34.0 (C-7), 33.4 (C-13), 33.2 (C-4), 31.5 (C-8), 21.6 (C-14), 18.1 (C-2), 17.3 (C-6), 17.2 (C-12), 16.1 (C-15) ppm. MS (EI, 70 eV): *m/z* (%) = 238 (18) $[M]^+$, 223 (82), 205 (6), 182 (25), 177 (15), 137 (12), 123 (100), 109 (39), 95 (34), 87 (30), 82 (31), 81 (30), 69 (42), 55 (27).

5-Bromovanillin (17): Vanillin (**8**; 34.17 g, 224.6 mmol) was dissolved in AcOH (70 mL), and Br_2 (39.12 g, 244.8 mmol) was added dropwise over 30 min. After a further 30 min the excess Br_2 was destroyed by the addition of saturated Na_2SO_3 solution, and the pale yellowish solid was obtained by filtration. The filter cake was washed with H_2O (2× 100 mL), and crystallized from EtOH to give **17** (47.69 g, 206.4 mmol, 92%) as colourless flaky crystals. R_f = 0.23 (hexanes/EtOAc, 2:1), m.p. 163 °C (EtOH) (ref.[12] m.p. 163–164 °C). ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 10.70 (br. s, 1 H, OH), 9.75 (s, 1 H, CHO), 7.69 (d, *J* = 1.8 Hz, 1 H, 6-H), 7.40 (d, *J* = 1.8 Hz, 1 H, 2-H), 3.90 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 190.3 (CHO), 149.8 (C-4), 148.6 (C-3), 128.9 (C-1), 128.7 (C-6), 109.6 (C-2), 109.2 (C-5), 56.3 (OCH_3) ppm. MS (EI, 70 eV): *m/z* (%) = 232 (95) $[M(^{81}Br)]^+$, 230 (100) $[M(^{79}Br)]^+$, 217 (5), 215 (5), 203 (7), 201 (8), 189 (13), 187 (14), 161 (8), 159 (9), 135 (7), 107 (8), 94 (8), 79 (17), 51 (21).

2-Bromo-6-methoxybenzene-1,4-diol (18): H_2O_2 solution (3% aq.; 214 mL, 195 mmol) was added to a solution of **17** (36.0 g, 156 mmol) in KOH (1 M aq.; 197 mL, 197 mmol). The reaction mixture was stirred with an overhead stirrer for 1 h, then MTBE (250 mL) was added, and the pH value was adjusted to 1 by the addition of concentrated HCl. The two layers were separated, the aqueous layer was extracted with MTBE (3× 100 mL), and the combined organic extracts were successively washed with saturated $Na_2S_2O_3$ solution (100 mL) and saturated NaCl solution (2× 100 mL). The solvent was removed under reduced pressure. The brownish red solid was crystallized from H_2O and then from toluene. After drying at 10^{-3} mbar, compound **18** (28.1 g, 128 mmol, 82%) was obtained as colourless needles. R_f = 0.23 (hexanes/EtOAc, 2:1), m.p. 141 °C (toluene) (ref.[12] m.p. 141 °C). ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 9.14 (s, 1 H, 4-OH), 8.53 (s, 1 H, 1-OH), 6.47 (d, *J* = 2.6 Hz, 1 H, 3-H), 6.41 (d, *J* = 2.6 Hz, 1 H, 5-H), 3.75 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 150.7 (C-4), 149.2 (C-6), 136.4 (C-1), 109.7 (C-3), 109.5 (C-2), 100.1 (C-5), 55.9 (OCH_3) ppm. MS (EI, 70 eV): *m/z* (%) = 220 (98) $[M(^{81}Br)]^+$, 218 (100) $[M(^{79}Br)]^+$, 205 (56), 203 (60), 177 (39), 175 (40), 95 (8), 69 (15), 53 (19).

1-Bromo-3-methoxy-2,5-bis[(2′-methoxyethoxy)methoxy]benzene (7): Hydroquinone **18** (5.00 g, 22.8 mmol) was dissolved in absolute THF (45 mL) under an inert gas atmosphere, and NaH (60% in mineral oil; 1.01 g, 25.3 mmol) was added at 0 °C. After 15 min,

MEMCl (2.91 mL, 25.1 mmol) was slowly added dropwise. After about 2 h, the greenish colour disappeared, and NaH (60% in mineral oil; 1.01 g, 25.3 mmol) was added. After 15 min, MEMCl (3.34 mL, 28.78 mmol) was added dropwise. The reaction was quenched after 2 h by the addition of saturated NH_4Cl solution (100 mL), and the mixture was extracted with EtOAc (3× 70 mL). The combined organic extracts were successively washed with $NaHCO_3$ solution (2× 50 mL), H_2O (2× 50 mL), and saturated NaCl solution (2× 50 mL), and passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The crude product was purified by flash chromatography (silica gel; hexanes/Me_2CO, 18:7) to give **7** (7.20 g, 18.2 mmol, 80%) as a colourless viscous oil. R_f = 0.26 (hexanes/Me_2CO, 18:7). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.81 (d, J = 2.7 Hz, 1 H, 6-H), 6.54 (d, J = 2.7 Hz, 1 H, 4-H), 5.14 (s, 2 H, 5′-H), 5.11 (s, 2 H, 1′-H), 3.98 (m, 2 H, 2′-H), 3.75 (m, 2 H, 6′-H), 3.74 (s, 3 H, OCH_3), 3.54 (m, 2 H, 3′-H), 3.51 (m, 2 H, 7′-H), 3.33 (s, 6 H, 4′-H, 8′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.1 (C-5), 153.6 (C-3), 138.0 (C-2), 117.5 (C-1), 111.6 (C-6), 101.3 (C-4), 100.3 (C-1′), 93.7 (C-5′), 71.6 (C-3′), 71.4 (C-7′), 69.0 (C-2′), 67.5 (C-6′), 58.8 (C-4′, C-8′), 55.8 (OCH_3) ppm. MS (EI, 70 eV): m/z (%) = 396 (1) $[M(^{81}Br)]^+$, 394 (1) $[M(^{79}Br)]^+$, 308 (1), 306 (1), 220 (2), 218 (3), 89 (78), 59 (100). HRMS (ESI): calcd. for $C_{15}H_{23}O_7BrNa$ $[M + Na]^+$ 417.0525; found 417.0509.

Drimanoyl Chloride (19): (+)-Drimanic acid (**2**; 866 mg, 3.63 mmol) was dissolved in absolute CH_2Cl_2 (45 mL) under an inert gas atmosphere, and oxalyl chloride (3.12 mL, 36.3 mmol) and DMF (2 μL, 26 μmol) were added. After 20 min, the evolution of gas ended, and the reaction mixture was stirred for a further 30 min. The volatile compounds were removed at 40 °C and 7 mbar to give **19** (933 mg, 3.63 mmol, 100%) pale yellowish waxy solid. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.79 (d, J = 4.7 Hz, 1 H, 9-H), 2.67 (m, 1 H, 8-H), 1.86 (m, 1 H, 1-H_{eq}), 1.72 (m, 2 H, 7-H), 1.62 (m, 1 H, 2-H_{ax}), 1.51 (m, 1 H, 6-H_{eq}), 1.41 (m, 2 H, 6-H_{ax}, 2-H_{eq}), 1.39 (m, 1 H, 3-H_{eq}), 1.19 (s, 3 H, 15-H), 1.16 (m, 1 H, 3-H_{ax}), 1.10 (d, J = 7.4 Hz, 3 H, 12-H), 1.05 (m, 1 H, 1-H_{ax}), 0.90 (s, 3 H, 13-H), 0.82 (s, 3 H, 14-H), 0.78 (dd, J = 10.6, 3.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.4 (C-11), 73.0 (C-9), 55.3 (C-5), 41.8 (C-3), 39.4 (C-1), 39.2 (C-10), 33.4 (C-7, C-13), 33.1 (C-4), 30.8 (C-8), 21.5 (C-14), 17.9 (C-2), 17.1 (C-6), 16.9 (C-12), 16.3 (C-15) ppm.

(–)-11-{3′-Methoxy-2′,5′-bis[(2′′-methoxyethoxy)methoxy]-phenyl}driman-11-one (5): Compound **7** (2.15 g, 5.44 mmol) was dissolved in Et_2O (17 mL) in a Schlenk flask equipped with an SmCo magnetic stirrer bar under an inert gas atmosphere, and the solution was cooled to –78 °C. *n*BuLi (2.1 M in hexanes; 2.54 mL, 5.27 mmol) was added over 5 min with vigorous stirring. The resulting highly viscous white suspension was stirred vigorously for a further 10 min. Then, a freshly prepared solution of drimanoyl chloride **19** (933 mg, 3.63 mmol) in absolute Et_2O (13 mL) was added, and the flask was rinsed with absolute Et_2O (2× 3 mL). After 5 min, the cooling bath was removed, and the reaction mixture was stirred at room temp. for 1.5 h. The mixture was then partitioned between MTBE (100 mL) and half-saturated NH_4Cl solution (50 mL). The aqueous layer was extracted with MTBE (2× 50 mL). The combined organic extracts were passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The pale yellowish crude product was purified by flash chromatography (hexanes/Me_2CO, 3:1) to give **5** (1.24 g, 2.33 mmol, 64%) as a colourless viscous oil. R_f = 0.32 (hexanes/Me_2CO, 3:1). $[\alpha]_D^{23}$ = –17.3 (c = 1.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.64 (d, J = 2.8 Hz, 1 H, 4′-H), 6.50 (d, J = 2.8 Hz, 1 H, 6′-H), 5.18 (d, J = 7.0 Hz, 1 H, 5′′-H_A), 5.15 (d, J = 7.0 Hz, 1 H, 5′′-H_B), 5.09 (d, J = 5.4 Hz, 1 H, 1′′-H_A), 5.04 (d, J = 5.4 Hz, 1 H, 1′′-H_B), 3.81 (m, 2 H, 2′′-H), 3.76 (m, 2 H, 6′′-H), 3.76 (s, 3 H, 3′-OCH_3), 3.51 (m, 2 H, 7′′-H), 3.49 (m, 2 H, 3′′-H), 3.32 (s, 3 H, 8′′-H), 3.31 (s, 3 H, 4′′-H), 3.05 (d, J = 4.2 Hz, 1 H, 9-H), 2.12 (m, 1 H, 8-H), 1.94 (m, 1 H, 1-H_{eq}), 1.62 (m, 1 H, 2-H_{ax}), 1.56 (m, 2 H, 7-H), 1.43 (m, 2 H, 6-H), 1.33 (m, 1 H, 3-H_{eq}), 1.31 (m, 1 H, 2-H_{eq}), 1.23 (s, 3 H, 15-H), 1.12 (m, 1 H, 3-H_{ax}), 0.96 (m, 1 H, 1-H_{ax}), 0.94 (d, J = 7.5 Hz, 3 H, 12-H), 0.81 (dd, J = 10.3, 2.3 Hz, 1 H, 5-H), 0.79 (s, 6 H, 13-H, 14-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 206.2 (C-11), 153.8 (C-5′), 153.0 (C-3′), 137.9 (C-1′), 136.9 (C-2′), 106.5 (C-6′), 103.0 (C-4′), 98.6 (C-1′′), 93.8 (C-5′′), 71.5 (C-3′′), 71.4 (C-7′′), 69.2 (C-2′′), 67.5 (C-6′′), 64.8 (C-9), 58.8 (C-4′′, C-8′′), 55.7 (3′-OCH_3), 56.0 (C-5), 42.0 (C-3), 39.0 (C-1), 38.1 (C-10), 34.1 (C-7), 33.4 (C-13), 33.1 (C-4), 30.4 (C-8), 21.5 (C-14), 18.0 (C-2), 17.3 (C-6), 17.1 (C-12), 16.5 (C-15) ppm. MS (EI, 70 eV): m/z (%) = 536 (20) $[M]^+$, 460 (6), 447 (22), 372 (11), 316 (15), 255 (31), 240 (14), 193 (24), 137 (15), 123 (21), 89 (100), 59 (100). HRMS (ESI): calcd. for $C_{30}H_{48}O_8Na$ $[M + Na]^+$ 559.3247; found 559.3230.

11-{3′-Methoxy-2′,5′-bis[(2′′-methoxyethoxy)methoxy]phenyl}-driman-11-ol (20): $LiEt_3BH$ (1 M in THF; 5.70 mL, 5.70 mmol) was added to a solution of (–)-drimanophenone **5** (608 mg, 1.14 mmol) in absolute Et_2O (100 mL) at 0 °C under an inert gas atmosphere. After 2 h, half-saturated NH_4Cl solution (50 mL) was added, and the aqueous layer was extracted with MTBE (3× 20 mL). The combined organic extracts were passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The residue was purified by column chromatography (hexanes/Me_2CO, 3:1) to give benzylic alcohol **20** (602 mg, 1.12 mmol, 98%) as a colourless oil. R_f = 0.28 (hexanes/Me_2CO, 3:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.64 (d, J = 2.8 Hz, 1 H, 6′-H), 6.52 (d, J = 2.8 Hz, 1 H, 4′-H), 5.23 (d, J = 6.8 Hz, 1 H, 5′′-H_A), 5.18 (d, J = 8.0 Hz, 1 H, 11-H), 5.18 (d, J = 6.8 Hz, 1 H, 5′′-H_B), 5.13 (s, 2 H, 1′′-H), 4.01 (m, 1 H, 2′′-H_A), 3.79 (m, 2 H, 6′′-H), 3.78 (s, 3 H, 3′-OCH_3), 3.77 (m, 1 H, 2′′-H_B), 3.55 (m, 4 H, 7′′-H, 3′′-H), 3.37 (s, 3 H, 8′′-H[a]), 3.33 (s, 3 H, 4′′-H[a]), 1.73 (dd, J = 9.6 Hz, 3.8 Hz, 1 H, 9-H), 1.58 (m, 1 H, 2-H_{ax}), 1.50 (m, 1 H, H-8), 1.43 (m, 1 H, 6-H_{eq}), 1.40 (m, 2 H, 7-H), 1.37 (m, 1 H, 2-H_{eq}), 1.34 (m, 1 H, 3-H_{eq}), 1.33 (m, 1 H, 6-H_{ax}), 1.28 (m, 1 H, 1-H_{eq}), 1.21 (m, 2 H, 1-H_{ax}, 3-H_{ax}), 1.10 (s, 3 H, 15-H), 0.94 (dd, J = 10.3 Hz, 2.3 Hz, 1 H, 5-H), 0.84 (s, 3 H, 13-H), 0.82 (s, 3 H, 14-H), 0.71 (d, J = 7.3 Hz, 3 H, 12-H) ppm. [a] assignments may be reversed. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.1 (C-5′), 152.1 (C-3′), 139.6 (C-1′), 138.2 (C-2′), 107.1 (C-6′), 100.4 (C-4′), 98.0 (C-1′′), 93.8 (C-5′′), 71.7 (C-3′′[b]), 71.6 (C-7′′[b]), 69.7 (C-11), 69.3 (C-2′′), 67.5 (C-6′′), 59.0 (C-4′′[c]), 58.9 (C-8′′[c]), 57.2 (C-9), 56.8 (C-5), 55.7 (3′-OCH_3), 42.1 (C-3), 41.5 (C-1), 40.0 (C-10), 35.2 (C-7), 33.9 (C-13), 33.5 (C-4), 30.7 (C-8), 21.7 (C-14), 18.6 (C-2), 17.4 (C-6), 17.2 (C-15), 16.3 (C-12) ppm. [b, c] assignments may be reversed. MS (EI, 70 eV): m/z (%) = 538 (5) $[M]^+$, 435 (95), 355 (7), 294 (28), 269 (57), 205 (26), 191 (16), 89 (100), 59 (100). HRMS (ESI): calcd. for $C_{30}H_{50}O_8Na$ $[M + Na]^+$ 561.3403; found 561.3398.

Deoxyspongiaquinol (3): Benzylic alcohol **20** (306 mg, 568 μmol) was dissolved in benzene (20 mL) under an inert gas atmosphere, and SO_3·pyridine (118 mg, 741 μmol) was added. The reaction mixture was heated under reflux for 2.5 h. Then it was cooled to room temp., and filtered through a plug of silica, which was rinsed with EtOAc (250 mL). The solvent was evaporated.

The elimination product (320 mg) was dissolved in absolute EtOH (20 mL) under an inert gas atmosphere and HCl (2 M in absolute Et_2O; 5 mL) was added. After 2.5 h, half-saturated $NaHCO_3$ solution (20 mL) was added, and the reaction mixture was partitioned

between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The combined organic extracts were passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The residue was purified by flash chromatography (silica gel; hexanes/Me_2CO, 3:1) to give **3** (156 mg, 453 μmol, 80%) as a pale yellowish solid. R_f = 0.24 (hexanes/Me_2CO, 3:1), m.p. 95 °C (hexanes). $[a]_D^{23}$ = +70.2 (*c* = 1.3, $CHCl_3$) {ref.[3] $[a]_D$ = +67 (*c* = 10.8, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.34 (d, *J* = 2.7 Hz, 1 H, 4′-H), 6.21 (d, *J* = 2.7 Hz, 1 H, 6′-H), 6.08 (s, 1 H, 11-H), 3.80 (s, 3 H, 3′-OCH_3), 2.94 (m, 1 H, 8-H), 1.80 (br. d, *J* = 12.2 Hz, 1 H, 1-H_{eq}), 1.68 (m, 1 H, 2-H_{ax}), 1.56 (m, 2 H, 6-H), 1.54 (m, 1 H, 2-H_{eq}), 1.52 (m, 1 H, 1-H_{ax}), 1.51 (m, 2 H, 7-H), 1.39 (m, 1 H, 3-H_{eq}), 1.19 (m, 1 H, 3-H_{ax}), 1.18 (s, 3 H, 15-H), 1.16 (d, *J* = 7.5 Hz, 3 H, 12-H), 1.02 (dd, *J* = 11.0, 2.7 Hz, 1 H, 5-H), 0.88 (s, 3 H, 14-H), 0.86 (s, 3 H, 13-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 159.4 (C-9), 148.1 (C-5′), 146.8 (C-3′), 136.7 (C-2′), 125.9 (C-1′), 113.5 (C-11), 107.6 (C-6′), 97.8 (C-4′), 55.9 (3′-OCH_3), 54.5 (C-5), 41.9 (C-3), 40.9 (C-10), 38.4 (C-1), 34.0 (C-7), 33.9 (C-4), 33.3 (C-13), 31.1 (C-8), 22.7 (C-12), 22.6 (C-15), 21.8 (C-14), 18.8 (C-2), 17.7 (C-6) ppm. IR: $\tilde{\nu}$ = 3349 (m), 2923 (s), 2854 (m), 1623 (w), 1596 (m), 1465 (s), 1436 (s), 1374 (m), 1308 (m), 1262 (m), 1205 (s), 1188 (s), 1146 (s), 1082 (s), 1026 (m), 939 (m), 799 (s), 738 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 344 (94) $[M]^+$, 206 (77), 191 (100), 175 (20), 153 (43), 135 (14), 109 (19), 95 (21), 58 (30). HRMS (ESI): calcd. for $C_{22}H_{33}O_3$ $[M + H]^+$ 345.2429; found 345.2413.

Deoxyspongiaquinone (4): CAN (1.2 M solution in H_2O; 433 μL, 508 μmol) was slowly added to a solution of deoxyspongiaquinol (50.0 mg, 145 μmol) in MeCN (2 mL). The colourless solution immediately turned an intense yellow. After 15 min, the mixture was partitioned between MTBE (25 mL) and half-saturated brine (10 mL), and the aqueous layer was extracted with MTBE (2× 10 mL). The combined organic phases were washed with brine, and passed through a plug of silica/$MgSO_4$, and the solvents were evaporated. The orange residue was purified by flash chromatography (silica gel; hexanes/Me_2CO, 3:1) to give **4** (46.8 mg, 137 μmol, 94%) as a yellow-orange solid. R_f = 0.46 (hexanes/Me_2CO, 3:1), m.p. 90–100 °C (hexanes, decomposition). $[a]_D^{23}$ = +189.9 (*c* = 1.0, $CHCl_3$) {ref.[3] $[a]_D$ = +164 (*c* = 7.48, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.47 (m, 1 H, 6′-H), 6.08 (s, 1 H, 11-H), 5.88 (d, *J* = 2.3 Hz, 1 H, 4′-H), 3.80 (s, 3 H, 3′-OCH_3), 2.94 (m, 1 H, 8-H), 1.74 (br. d, *J* = 11.5 Hz, 1 H, 1-H_{eq}), 1.61 (m, 1 H, 2-H_{ax}), 1.60 (m, 1 H, 7-H_{eq}), 1.57 (m, 2 H, 6-H), 1.53 (m, 1 H, 2-H_{eq}), 1.50 (m, 1 H, 1-H_{ax}), 1.49 (m, 1 H, 7-H_{ax}), 1.38 (m, 1 H, 3-H_{eq}), 1.25 (d, *J* = 7.6 Hz, 3 H, 12-H), 1.18 (m, 1 H, 3-H_{ax}), 1.14 (s, 3 H, 15-H), 1.00 (dd, *J* = 11.5, 2.7 Hz, 1 H, 5-H), 0.86 (s, 3 H, 14-H), 0.85 (s, 3 H, 13-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 187.9 (C-5′), 182.3 (C-2′), 166.3 (C-9), 158.6 (C-3′), 142.3 (C-1′), 131.4 (C-6′), 110.9 (C-11), 107.1 (C-4′), 56.2 (3′-OCH_3), 53.9 (C-5), 42.0 (C-10), 41.6 (C-3), 38.2 (C-1), 34.0 (C-4), 33.7 (C-7), 33.2 (C-13), 31.6 (C-8), 22.8 (C-12), 22.2 (C-15), 21.8 (C-14), 18.7 (C-2), 17.5 (C-6) ppm. IR: $\tilde{\nu}$ = 2924 (s), 2856 (m), 1682 (m), 1642 (s), 1591 (m), 1498 (w), 1457 (m), 1314 (w), 1231 (s), 1060 (m), 904 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 342 (43) $[M]^+$, 327 (20), 260 (25), 245 (29), 231 (14), 218 (23), 205 (83), 191 (100), 175 (19), 153 (18), 133 (11), 119 (16), 109 (24), 95 (25), 69 (38), 55 (37). HRMS (ESI): calcd. for $C_{22}H_{31}O_3$ $[M + H]^+$ 343.2273; found 343.2258.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **7**, **14**, **5**, and **20**; ^{1}H, ^{13}C, COSY, HSQC, and HMBC NMR spectra for compounds **3** and **4**; and ^{1}H NMR spectra for the Mosher esters of (±)-drimanol (*rac*-**16**) and (+)-drimanol (**16**).

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