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Synthesis of the alkenyl-substituted tetracyclic core of the bisabosquals

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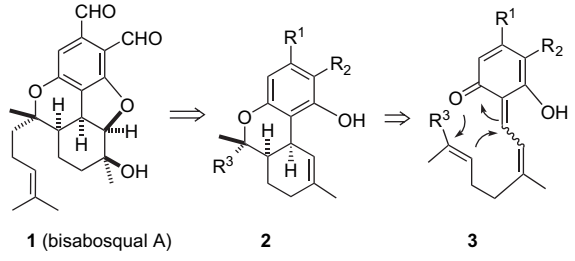
Abstract—HCl-catalyzed deprotection and cyclization of benzylic alcohol **15** cleanly provided tricycle **16** by a cis-selective intramolecular Diels–Alder reaction. Acetylation of the phenol, bis epoxidation, and base-catalyzed hydrolysis and cyclization afforded tetracycle **19** with the bisabosqual skeleton, but the opposite stereochemistry at the tertiary alcohol stereocenter. Selective dehydration of the tertiary alcohol to form the exocyclic alkene, ozonolysis, reductive deoxygenation of the side chain epoxide, and addition of MeMgBr to the ketone from the less hindered face gave tertiary alcohol **24** with the tetracyclic core of bisabosqual A (**1**).

1. Introduction

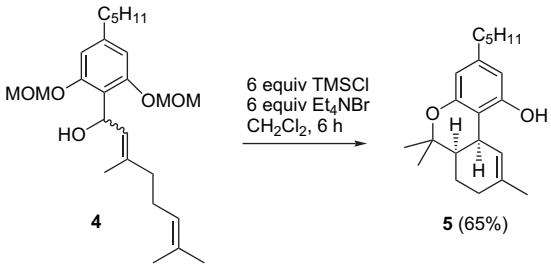
Bisabosqual A (**1**) was isolated in 2001 from the culture broth of *Stachybotrys* sp. RF-7260, obtained from decaying tree leaves.[1] Three related natural products, bisabosquals B–D, were isolated from *Stachybotrys ruwenzoriensis* RF-6853. Bisabosqual A (**1**) has broad spectrum antifungal activity in vitro and inhibits the microsomal squalene synthases from *Saccharomyces cerevisiae*, *Candida albicans*, HepG2 cell, and rat liver with IC_{50} values of 0.43, 0.25, 0.95, and 2.5 μg/mL, respectively, suggesting that bisabosqual A might be useful for the treatment of hypercholesterolemia.



Scheme 1. Retrosynthetic analysis of bisabosqual A.

The novel tetracyclic structure of bisabosqual A (**1**) was determined by 2D NMR experiments and confirmed by X-ray crystallography of bisabosqual B.[2] The three six-membered rings of **1** are analogous to those of tetrahydrocannabinoids (THCs), although the cyclohexane and pyran rings are trans-fused in the extensively investigated THCs[3] and cis-fused in **1**. The additional furan ring and tertiary alcohol of **1** pose additional synthetic challenges.

We envisaged that bisabosqual A (**1**) might be accessible by oxidative cyclization of *cis*-fused tricycle **2**, which should be available by an inverse electron demand Diels–Alder reaction of quinone methide **3** (see Scheme 1). Although hexahydrocannabinoids are invariably formed with a trans ring fusion, Rickards found that treatment of **4** with TMSCl and Et_4NBr cleaved the MOM ethers and generated a quinone methide that cyclized to give 65% of the *cis*-fused tetrahydrocannabinoid tricycle **5** (see Eq. 1).[4]



(1)

These observations are consistent with MMX calculations of transition state energies for the intramolecular Diels–Alder reaction.[5] The transition state leading to a *trans*-fused hexahydrocannabinoid is more stable than the lowest energy

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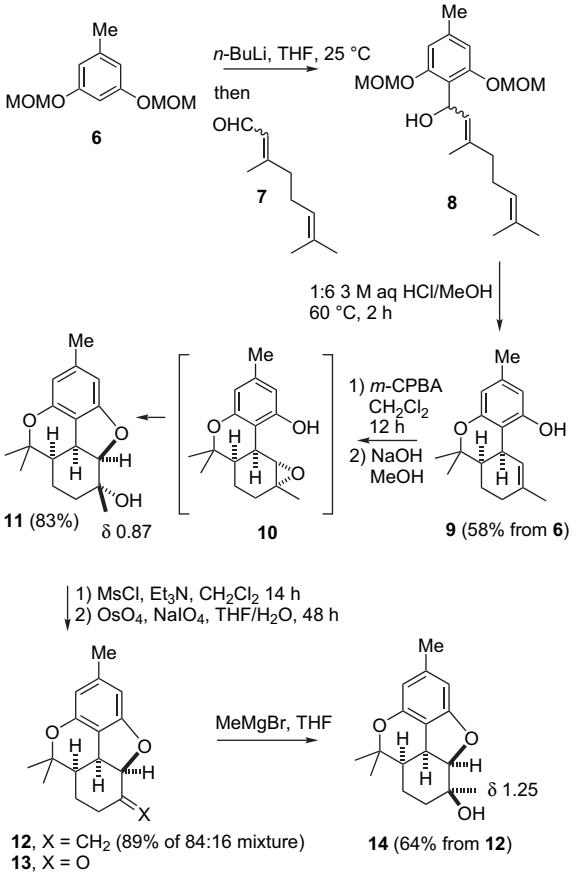
transition state leading to a *cis*-fused hexahydrocannabinoid by 1.2 kcal/mol. The presence of the double bond in the tether changes the transition state energies such that the one leading to the *cis*-fused tetrahydrocannabinoid **5** is more stable than the one leading to the *trans*-fused tetrahydrocannabinoid by 0.6 kcal/mol.

2. Results and discussion

Deprotonation of the bis MOM ether of orcinol (**6**)[6] at the 2-position with *n*-BuLi in THF followed by the addition of citral (**7**) afforded 90–100% of **8** as a ≈60:40 *E*/*Z* mixture that was used without purification (see Scheme 2).[7,8] In our hands, treatment of crude alcohol **8** with TMSBr,[9] TMSCl and Et_4NBr, or TMSCl and Bu_4NBr in CH_2Cl_2 at 25 °C did not give tricyclic phenol **9**. Use of TMSBr at −78 °C provided the MOM ether of **9** (not shown) in 60% yield, which can also be obtained in 70% yield with TMSCl and NaI at −20 °C.[10] Eventually, we found that complete cyclization of **8** and deprotection to give **9** can be effected in 58% overall yield from **6** by heating **8** in a 1:6 mixture of 3 M aqueous hydrochloric acid and MeOH at 60 °C for 2 h. Tricycle **9** is somewhat unstable and can only be purified on MeOH-deactivated silica gel.



Scheme 2. Synthesis of tetracyclic model **14**.

syn Oxidative cyclization[11,12] of **9** would yield the desired tertiary alcohol **14** in a single step. However, all previous oxidative cyclizations have started with unsaturated alcohols, rather than phenols. The electron rich resorcinol is more easily oxidized than the alkene of **9**. Treatment of **9** with bis(collidine)iodonium hexafluorophosphate[13] afforded the diiodo phenol. Reaction with $Hg(OAc)_2$ also occurred on the aromatic ring.[14] Not surprisingly, treatment of **9** with $(CF_3CO_2)ReO_3$, $(Cl_2HCCO_2)ReO_3$, or PCC led to complex mixtures of products.

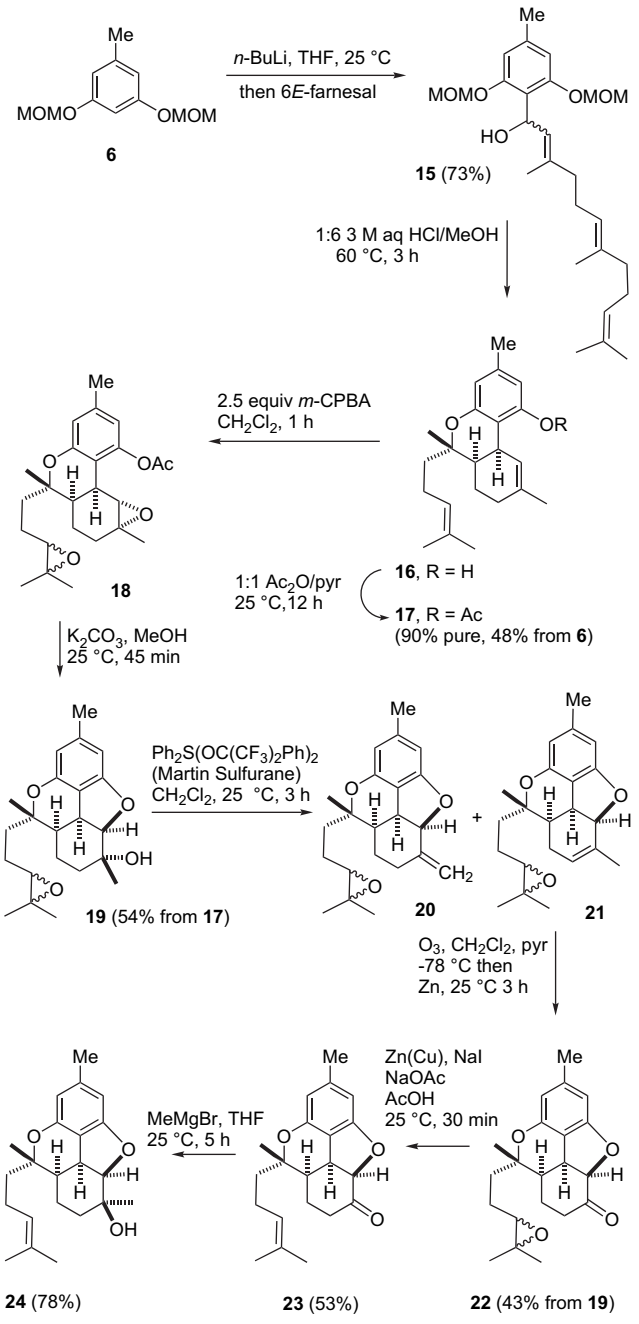
Epoxidation of **9** with *m*-CPBA in CH_2Cl_2 takes place at the alkene from the less hindered α-face as reported by Razdan in a similar system.[15] The initially formed epoxy phenol **10** partially cyclized to give tetracycle **11** with the desired ring system, but the opposite stereochemistry at the tertiary alcohol stereocenter. Treatment of this mixture with methanolic NaOH for 2 h provided 83% of **11**.

The rigidity of the ring system allowed us to develop an efficient procedure to convert **11** to the desired alcohol **14**. Treatment of **11** with MsCl and excess Et_3N in CH_2Cl_2 provided 89% of an 84:16 mixture of **12** and the endocyclic isomer. Formation of the less stable alkene **12** is favored because only the methyl protons can adopt the required antiperiplanar orientation to the equatorial leaving group. Oxidative cleavage of the alkene mixture with OsO_4 and $NaIO_4$ gave ketone **13**. Addition of MeMgBr to the ketone in THF occurred selectively from the less hindered α-face to afford the desired tertiary alcohol **14** in 64% yield from alkene **12**. The spectral data of the cyclohexanol protons and carbons of **14** correspond closely to those of bisabosqual A (**1**), while those of **11** are quite different. In particular, MeCOH absorbs at δ 1.25 in **14** and δ 1.31 in **1**, but at δ 0.87 in the epimeric alcohol **11**, in which the methyl group of the tertiary alcohol is in the shielding cone of the aromatic ring.

We then turned our attention to the preparation of **24**, containing the unsaturated side chain of the bisabosquals. Deprotonation of **6**[6] with *n*-BuLi in THF followed by addition of 6*E*-farnesal[16] afforded **15** as an *E*/*Z* mixture that partially decomposed on chromatography (see Scheme 3). Although benzylic alcohol **15** could be isolated in 73% yield, the overall yield of acetate **17** from **6** was higher when crude **15** was used for the intramolecular Diels–Alder reaction. Cyclization of **15** and deprotection to give phenol **16** were achieved by heating **15** in a 1:6 mixture of 3 M aqueous hydrochloric acid and MeOH in a 60 °C oil bath for 3 h. The yield of **16** decreased at higher temperatures. Chromatographic purification was best carried out after acetylation of crude phenol **16** in 1:1 Ac_2O/pyridine for 12 h at 25 °C to give acetate **17**. This three-step sequence afforded 90% pure **17** in 48% overall yield from **6**.

We were initially disappointed to find that epoxidation of either **16** or **17** with 1 equiv of *m*-CPBA occurred selectively on the side chain double bond rather than on the desired cyclohexene double bond. However, on further consideration, epoxidation of the side chain double bond would protect this double bond during the oxidative cleavage of the exocyclic double bond of **20** that generates cyclohexanone **22**.

We therefore epoxidized **17** with 2.5 equiv of *m*-CPBA in CH_2Cl_2 at 25 °C for 1 h to give bis epoxide **18** as a 1:1 mixture of diastereomers on the side chain epoxide. Hydrolysis of the acetate and cyclization with K_2CO_3 in MeOH at 25 °C for 45 min afforded tetracyclic alcohol **19** in 54% overall



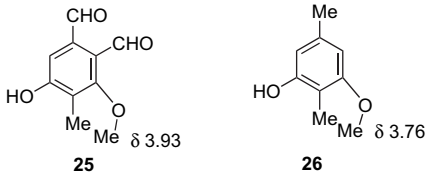
Scheme 3. Synthesis of alkenyl-substituted tetracyclic model **24**.

yield from dienyl acetate **17**. The spectra of the two diastereomers of **19** were surprisingly different, suggesting that they might differ in the stereochemistry at one or more of the ring positions, rather than simply at the epoxide on the side chain. Fortunately, Cornforth reductive deoxygenation[17] of the diastereomeric mixture with Zn, NaI, and NaOAc in HOAc afforded a single compound establishing that only a mixture of side chain epoxides was present in **19**.

Conversion of tertiary alcohol **19** to the exocyclic alkene **20** and then to ketone **22** proved much more challenging than for model **11** without the functionalized side chain. Treatment of **19** with MsCl and excess Et_3N in CH_2Cl_2 provided 4:1 to 8:1 mixtures of **20** and **21** in only 5–30% yield. Dehydration of **19** with Martin's sulfurane,[18] $Ph_2S(OC(CF_3)_2Ph)_2$, in CH_2Cl_2 proceeded cleanly, but with considerable loss of regioselectivity, to give an inseparable 2:1 mixture of **20** and **21**. Oxidative cleavage of the double bond of **20** with $OsO_4/NaIO_4$ with or without 2,6-lutidine[19] proceeded in low yield. Ozonolysis of the 2:1 mixture of **20** and **21** in CH_2Cl_2 containing pyridine at −78 °C followed by reduction with activated Zn[20] provided epoxy ketone **22** in 43% overall yield from epoxy alcohol **19**. Reductive deoxygenation of **22** by Cornforth's procedure[17] with Zn(Cu), NaI, and NaOAc in HOAc at 25 °C for 30 min afforded alkenyl ketone **23** in 53% yield. Slightly lower yields were obtained with activated Zn or Zn(Ag) and much lower yields were obtained with unactivated Zn dust. Epoxy ketone **23** was obtained in 0–20% yield with Cp_2TiCl_2/Zn,[21] WCl_6/BuLi,[22] or NaI/TMSCl in CH_3CN.[23]

Addition of MeMgBr to ketone **23** in THF occurred selectively from the less hindered α-face to afford the desired tertiary alcohol **24** in 78% yield. The spectral data of the cyclohexanol protons and carbons of **24** correspond closely to those of bisabosqual A (**1**), while those of **19** are quite different. In particular, MeCOH absorbs at δ 1.24 in **24** and at δ 1.31 in **1**, but at δ 0.86 and 0.87 in the two diastereomers of the epimeric epoxy alcohol **19**, in which the methyl group of the tertiary alcohol is in the shielding cone of the aromatic ring (see Fig. 1). The stereochemistry at C_7 of **24** was established by an NOE from H_5 at δ 3.61 to H_8 at δ 1.73–1.64 and δ 1.61–1.52, but not to H_{14} at δ 1.39.

The spectra of **1** and **24** are very similar except for H_4, C_4, and C_7 (see Table 1 and Fig. 1 for atom numbering scheme). The absorptions are further downfield in both the ^1H and ^{13}C NMR spectra of **1** as expected, because the two aldehydes of **1** are electron withdrawing whereas the aromatic methyl group of **24** is electron donating. The methoxy protons of **25**, which are analogous to H_4 of **1**, absorb at δ 3.93 in $CDCl_3$,[24] whereas the methoxy protons of **26**, which are analogous to H_4 of **24**, absorb at δ 3.76 in CCl_4.[25]



In conclusion, we have developed a short and efficient route to the tetracyclic core of the bisabosquals that effectively deals with the side chain unsaturation. We are currently

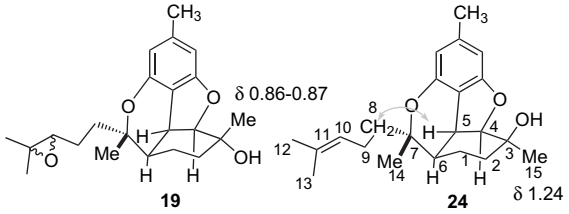


Figure 1. Three-dimensional structures of **19** and **24**.

Table 1. Comparison of the ^{1}H and ^{13}C NMR spectra of bisabosqual A (**1**) and tetracyclic model **24**

	^{1}H NMR		^{13}C NMR	
	1	**24**	**1**	**24**
1	1.55, 1.28	1.8–1.4, 1.3–1.1	16.3	16.4
2	1.79, 1.21	1.8–1.4, 1.3–1.1	34.9	35.1
3			69.1	69.5
4	4.97 (d, 8.8)	4.69 (d, 8.5)	93.8	90.5
5	3.66 (dd, 8.8, 6.6)	3.61 (dd, 8.5, 6.1)	33.3	33.7
6	2.05	1.96–1.88	35.9	36.5
7			83.5	81.0
8	1.67, 1.57	1.8–1.4	38.7	38.3
9	2.08	2.12–2.03	22.2	22.4
10	5.03	5.04	123.1	123.7
11			132.5	131.9
12	1.65	1.65	25.6	25.6
13	1.59	1.59	17.6	17.6
14	1.46	1.39	22.1	22.2
15	1.31	1.24	29.5	29.8

adapting this to more highly functionalized resorcinols needed for the synthesis of the bisabosquals.

3. Experimental section

3.1. General procedures

NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ, coupling constants in hertz, and IR spectra in cm^{-1}.

3.2. α-(2,6-Dimethyl-1,5-heptadienyl)-2,6-bis(methoxymethoxy)-4-methyl-benzenemethanol (8)

n-BuLi (6.6 mL of a 1.6 M solution in hexanes, 10.6 mmol) was added to a solution of **6**[6b] (2 g, 9.43 mmol) in THF (88 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was cooled to 0 °C and citral (**7**) (2.1 mL, 12.1 mmol) in THF (15 mL) was added dropwise. The reaction mixture was then stirred at 25 °C for 3 h, quenched with NH_4Cl, and extracted with Et_2O (3×40 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 3.78 g (110%) of **8** as a ≈6:4 *E*/*Z* mixture that was about 90% pure by ^{1}H NMR analysis: ^{1}H NMR 6.63 (s, 2), 5.900 (dd, 0.6×1, *J*=10.9, 9.1), 5.897 (dd, 0.4×1, *J*=12.2, 9.1), 5.70 (br d, 0.4×1, *J*=9.1), 5.68 (br d, 0.6×1, *J*=9.1), 5.24–5.18 (m, 4), 5.06 (t, 1, *J*=6.7), 3.59 (d, 0.6×1, *J*=10.9, OH), 3.53 (d, 0.4×1, *J*=12.2, OH), 3.50 (s, 0.6×6), 3.49 (s, 0.4×6), 2.30 (s, 3), 2.08–2.20 (m, 2), 2.08–1.95 (m, 2), 1.64 (s, 3), 1.55 (s, 3).

3.3. (6a*R*,10a*S*)-*rel*-6a,7,8,10a-Tetrahydro-3,6,6,9-tetramethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9)

A 3 M solution of HCl (22 mL, 65 mmol) was added to a solution of crude **8** (2.0 g, 5.49 mmol) in MeOH (130 mL). The reaction mixture was heated in a 60 °C oil bath for 2 h, cooled to 25 °C, quenched with saturated $NaHCO_3$, and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 1.48 g (104%) of crude **9**. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 825 mg (58%) of tricycle **9** that was 90–95% pure. Further chromatography on non-deactivated silica gel resulted in decomposition to give less pure **9**: ^{1}H NMR 6.24 (s, 1), 6.22 (br s, 1), 6.12 (s, 1), 4.92 (br s, OH), 3.58–3.53 (br, 1), 2.18 (s, 3), 2.00–1.89 (m, 3), 1.74–1.66 (m, 1), 1.68 (s, 3), 1.52–1.42 (m, 1), 1.39 (s, 3), 1.27 (s, 3); ^{13}C NMR 154.8, 153.8, 137.3, 135.0, 121.8, 110.7, 109.3, 108.7, 76.2, 40.0, 31.4, 29.7, 25.9, 25.2, 23.7, 20.9, 20.6; HRMS (DEI) calcd for $C_{17}H_{22}O_2$ (M^+) 258.1620, found 258.1612.

3.4. (3*R*,3a*R*,9a*R*,9b*S*)-*rel*-2,3,3a,9,9a,9b-Hexahydro-3,6,9,9-tetramethyl-1*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-ol (11)

A solution of *m*-CPBA (276 mg, 1.357 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **9** (254 mg, 0.984 mmol) in CH_2Cl_2 (54 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 12 h. The solvent was evaporated and the bright orange residue was dissolved in Et_2O. The solution was then washed with Na_2SO_3, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was taken up in MeOH (40 mL) and 4% NaOH (25.1 mL) was added to the solution. The reaction mixture was stirred at 25 °C for 2 h. The MeOH was evaporated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 224 mg (83%) of **11**: ^{1}H NMR 6.19 (s, 1), 6.16 (s, 1), 4.85 (br d, 1, *J*=8.6), 3.72 (dd, 1, *J*=8.6, 6.7), 2.26 (s, 3), 1.97 (ddd, 1, *J*=11.6, 6.7, 6.1), 1.74–1.65 (m, 2), 1.48–1.36 (m, 1), 1.41 (s, 3), 1.34 (s, 3), 0.96 (dddd, 1, *J*=14.3, 11.0, 11.0, 4.3), 0.87 (s, 3); ^{13}C NMR 161.2, 151.9, 140.4, 107.57, 107.51, 102.4, 93.6, 79.0, 73.2, 37.6, 35.2, 34.8, 26.7, 26.0, 24.6, 22.1, 19.3; HRMS (DEI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1558.

3.5. (3a*R*,9a*R*,9b*S*)-*rel*-2,3,3a,9,9a,9b-Hexahydro-6,9,9-trimethyl-3-methylene-1*H*-benzofuro[4,3,2-*cde*]-[1]benzopyran (12)

MsCl (0.8 mL, 10.2 mmol) was added dropwise to a solution of **11** (157 mg, 0.573 mmol) and Et_3N (2.7 mL, 18.8 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 14 h. The reaction was then quenched with 2 M HCl and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 130 mg (89%) of an 84:16 mixture of **12** and the endocyclic isomer: ^{1}H NMR (**12**) 6.25 (s, 1), 6.16 (s, 1), 5.33 (br d, 1, *J*=7.9), 5.14 (br s, 1), 4.81 (br s, 1), 3.68 (br dd, 1, *J*=7.9, 7), 2.27 (s, 3), 2.24 (ddd, 1, *J*=12, 3, 3), 2.00 (ddd, 1, *J*=12, 6, 6), 1.88–1.75 (m, 2), 1.40 (s, 3), 1.34 (s, 3), 0.92–0.82 (m, 1); ^{1}H NMR (partial data for endocyclic isomer) 5.50 (br d, 1, *J*=5.2), 5.20 (br d, 1, *J*=8), 3.77–3.72 (m, 1), 2.25 (s, 3); ^{13}C NMR 160.4, 151.9, 144.8, 140.0, 110.3, 107.7, 106.7, 103.3, 86.6, 78.7, 39.7, 36.5, 31.8, 26.4, 26.2, 23.7, 22.2; HRMS (DEI) calcd for $C_{17}H_{20}O_2$ (M^+) 256.1463, found 256.1471.

3.6. (3a*R*,9a*R*,9b*S*)-*rel*-1,2,3a,9,9a,9b-Hexahydro-6,9,9-trimethyl-3*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-one (13)

OsO_4 (42 μL of a 2.5% solution in *t*-BuOH, 0.004 mmol) and $NaIO_4$ (53 mg, 0.246 mmol) were added to a solution of **12** (21 mg, 0.082 mmol) in THF/H_2O (2:1, 1 mL). The reaction mixture was stirred at 25 °C for 48 h and concentrated under reduced pressure. The residue was taken up in H_2O and extracted with EtOAc. The combined extracts were washed with $Na_2S_2O_3$ and brine, and dried ($MgSO_4$). Flash chromatography of the residue on MeOH-deactivated silica gel (9:1 hexanes/EtOAc) gave 19 mg (92%) of 80% pure ketone **13**: ^{1}H NMR 6.36 (s, 1), 6.18 (s, 1), 5.04 (d, 1, *J*=7.3), 4.07 (dd, 1, *J*=7.3, 7.3), 2.40–2.28 (m, 3), 2.26 (s, 3), 2.10–2.05 (m, 1), 1.46 (s, 3), 1.40 (s, 3), 1.38–1.23 (m, 1); ^{13}C NMR 208.4, 160.5, 151.3, 141.1, 108.3, 104.6, 103.3, 87.4, 78.5, 39.1, 39.0, 38.7, 26.7, 26.4, 22.7, 22.1.

3.7. (3*S*,3a*R*,9a*R*,9b*S*)-*rel*-2,3,3a,9,9a,9b-Hexahydro-3,6,9,9-tetramethyl-1*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-ol (14)

MeMgBr (0.21 mL, 0.214 mmol) was added to a solution of partially purified ketone **13** (14 mg, 0.054 mmol) in THF (1 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 1 h, quenched with NH_4Cl, and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 10.4 mg (70%) of **14**: ^{1}H NMR 6.22 (s, 1), 6.17 (s, 1), 4.70 (br d, 1, *J*=8.5), 3.66 (br dd, 1, *J*=8.5, 6), 2.26 (s, 3), 1.84 (ddd, 1, *J*=11.6, 6, 6), 1.71 (br d, 1, *J*=11.6), 1.60–1.40 (m, 1), 1.42 (s, 3), 1.33 (s, 3), 1.25 (s, 3), 1.26–1.16 (m, 2); ^{13}C NMR 161.4, 151.6, 140.3, 108.1, 107.6, 101.4, 90.5, 78.8, 69.4, 38.6, 34.9, 34.1, 29.6, 26.7, 26.1, 22.2, 16.5; HRMS (DEI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1570.

3.8. α-(2,6,10-Trimethyl-1,5,9-undecatrienyl)-2,6-bis-(methoxymethoxy)-4-methyl-benzenemethanol (15)

n-BuLi (7.0 mL, 1.6 M in hexane, 11.2 mmol) was added at 0 °C to a solution of **6** (1.70 g, 8.0 mmol) in THF (50 mL). The resulting solution was warmed to 25 °C and stirred for 4 h. A THF solution (12 mL) of a 2:1 mixture of (2*E*,6*E*)- and (2*Z*,6*E*)-farnesal[16] (2.46 g, 11.2 mmol) was added dropwise to the reaction mixture and the reaction mixture was stirred at 25 °C for 4 h. The reaction was quenched with saturated NH_4Cl (40 mL) and extracted with Et_2O (3×50 mL). The combined Et_2O extracts were dried ($MgSO_4$) and concentrated to give crude **15** (3.40 g). A portion of the crude product (43 mg) was purified by flash chromatography on MeOH-deactivated silica gel (15:1 hexanes/EtOAc) to yield **15** (23 mg) as a mixture of cis and trans isomers: ^{1}H NMR 6.62 (s, 2), 5.91 (dd, 1, *J*=9.2, 9.2), 5.68 (d, 1, *J*=9.2), 5.21 (s, 2), 5.20 (s, 2), 5.11–5.04 (m, 2), 3.68–3.60 (m, 1, OH), 3.49 (s, 6), 2.29 (s, 3), 2.24–2.21 (m, 1), 2.11–1.89 (m, 7), 1.80 (s, 3), 1.67 (s, 3), 1.58 (br s, 3), 1.55 (br s, 3); ^{13}C NMR 154.8 (2C), 138.7, 137.3, 135.1, 131.2, 126.6, 124.3, 123.8, 118.6, 109.0 (2C), 94.4 (2C), 64.3, 56.2 (2C), 39.64, 39.60, 26.6, 26.3, 25.6, 21.8, 17.6, 16.4, 15.9; IR (neat) 3318, 2919, 2854, 1664, 1611; HRMS (EI$^+$) calcd for $C_{26}H_{40}O_5$ (M^+) 432.2876, found 432.2871.

3.9. (6*S*,6a*R*,10a*S*)-*rel*-6a,7,8,10a-Tetrahydro-3,6,9-trimethyl-6-(4-methyl-3-pentenyl)-6*H*-dibenzo[*b*,*d*]pyran-1-yl acetate (17)

Aqueous hydrochloric acid (30 mL, 3 M) was added dropwise to a solution of crude **15** (3.38 g) in MeOH (180 mL) at 60 °C. The resulting solution was heated in a 60 °C oil bath for 3 h and cooled to 25 °C. The reaction was quenched with saturated $NaHCO_3$ (40 mL) and extracted with Et_2O (3×50 mL). The combined Et_2O extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude **16**.

Acetic anhydride (6 mL) was added to a pyridine (6 mL) solution of crude **16**. The reaction mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted with Et_2O (60 mL) and washed with H_2O (2×30 mL), $NaHCO_3$ (3×30 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated to give crude **17**. Flash chromatography on MeOH-deactivated silica gel (40:1 hexanes/EtOAc) yielded 1.41 g (48% for three steps) of 90% pure **17** as a colorless oil: ^{1}H NMR 6.51 (s, 1), 6.40 (s, 1), 5.86–5.81 (br, 1), 5.07–5.00 (br, 1), 3.45–3.39 (br, 1), 2.33 (s, 3), 2.22 (s, 3), 2.06–1.86 (m, 3), 1.81–1.41 (m, 6), 1.67 (s, 3), 1.63 (s, 3), 1.53 (s, 3), 1.37 (s, 3); ^{13}C NMR 169.0, 153.4, 149.8, 137.2, 135.3, 131.7, 123.9, 121.1, 115.9, 115.3, 115.2, 78.2, 37.4, 37.0, 31.2, 29.6, 25.7, 23.7, 22.9, 22.3, 21.4, 20.9, 20.2, 17.4; IR (neat) 2966, 2927, 1766; HRMS (Q-TOF) calcd for $C_{24}H_{33}O_3$ (MH^+) 369.2430, found 369.2437.

3.10. (1a*R*,3a*R*,4*S*,9b*S*,9c*S*)-*rel*-4-[(*RS*)-2-(3,3-Dimethyloxiranyl)ethyl]-1a,2,3a,4,9b,9c-hexahydro-1a,4,7-trimethyl-3*H*-oxireno[3,4]benzo[1,2-*c*][1]benzopyran-9-yl acetate (18)

A solution of *m*-CPBA (1.05 g, 70%, 4.3 mmol) in CH_2Cl_2 (30 mL) was added to a solution of **17** (630 mg, 1.7 mmol) in CH_2Cl_2 (12 mL). The reaction mixture was stirred for 1 h at 25 °C and concentrated. The residue was redissolved in EtOAc (60 mL), washed with saturated Na_2SO_3 (2×30 mL), $NaHCO_3$ (2×30 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated to give 558 mg of crude **18** as an oil, which was used directly in the next step. A portion of the crude product (28 mg) was purified by flash chromatography on MeOH-deactivated silica gel (20:1 hexanes/EtOAc) to yield bis epoxide **18** (10 mg) as a 1:1 mixture of diastereomers: ^{1}H NMR 6.53 (s, 1), 6.51 (s, 1), [3.16–3.14 (br, 1), 3.13–3.11 (br, 1)], [3.11 (d, 1, *J*=6.1), 3.08 (d, 1, *J*=6.1)], [2.75 (t, 1, *J*=6.1), 2.74 (t, 1, *J*=6.1)], [2.37 (s, 3), 2.36 (s, 3)], 2.27 (s, 3), 2.03–1.03 (m, 9), 1.31 (s, 3), [1.28 (s, 3), 1.26 (s, 3)], 1.26 (s, 3), 1.24 (s, 3); ^{13}C NMR (169.48, 169.43), (154.21, 154.17), (149.57, 149.54), 138.37, (115.79, 115.76), (115.10, 115.05), (112.81, 112.80), (77.65, 77.49), (64.27, 64.17), (62.27, 62.24), (58.41, 58.37), (58.14, 58.09), (35.47, 35.14), 34.00, 32.34, (25.97, 25.88), 24.80, (23.10, 23.04), (22.75, 22.56), 21.93, (21.05, 21.03), 20.96, (19.38, 19.28), (18.63, 18.44); IR (neat) 2958, 2927, 1768; HRMS (Q-TOF) calcd for $C_{24}H_{33}O_5$ (MH^+) 401.2328, found 401.2327.

3.11. (*R*,3a*R*,9*S*,9a*R*,9b*S*)-*rel*-9-[(*RS*)-2-(3,3-Dimethyloxiranyl)ethyl]-2,3,3a,9,9a,9b-hexahydro-3,6,9-trimethyl-1*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-ol (19)

K_2CO_3 (1.0 g) was added to a solution of crude **18** (548 mg) in MeOH (15 mL). The reaction mixture was stirred at 25 °C for 45 min. The mixture was diluted with saturated NH_4Cl (15 mL) and extracted with EtOAc (3×30 mL). The combined EtOAc extracts were dried ($MgSO_4$) and concentrated to give crude **19**. Flash chromatography on MeOH-deactivated silica gel (3:2 hexanes/EtOAc) yielded 330 mg (54% from **17**) of **19** as a 1:1 mixture of diastereomers: ^{1}H NMR 6.19 (s, 1), [6.15 (s, 1), 6.14 (s, 1)], [4.87 (d, 1, *J*=8.0), 4.85 (d, 1, *J*=8.0)], [3.71 (dd, 1, *J*=8.0, 7.4), 3.66 (dd, 1, *J*=8.0, 7.4)], [2.69 (t, 1, *J*=6.1), 2.65 (t, 1, *J*=6.1)], 2.26 (s, 3), 2.08–2.00 (m, 2), 1.93–1.53 (m, 6), 1.52–1.29 (m, 1), [1.38 (s, 3), 1.35 (s, 3)], 1.27 (s, 3), 1.25 (s, 3), 1.05–0.93 (m, 1), [0.87 (s, 3), 0.86 (s, 3)]; ^{13}C NMR (161.23, 161.17), (151.64, 151.60), (140.48, 140.42), (107.57, 107.54), (107.44, 107.42), (102.58, 102.53), (93.74, 93.63), (80.71, 80.67), (73.15, 73.11), (64.23, 63.88), (58.49, 58.31), (35.98, 35.57), (34.97, 34.92), (34.88, 34.82), (34.79, 34.71), (24.77, 24.75), (24.48, 24.40), (23.63, 23.43), 22.37, (22.15, 22.11), (19.22, 19.16), (18.61, 18.57); IR (neat) 3432, 2946, 2870, 1623; HRMS (Q-TOF) calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2221.

3.12. (3a*R*,9*S*,9a*R*,9b*S*)-*rel*-9-[(*RS*)-2-(3,3-Dimethyloxiranyl)ethyl]-1,2,3a,9,9a,9b-hexahydro-6,9-dimethyl-3*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-one (22)

A solution of Martin's sulfurane (562 mg, 0.84 mmol) in dry CH_2Cl_2 (10 mL) was added to a solution of **19** (200 mg, 0.56 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 3 h. The reaction mixture was concentrated to give a 2:1 mixture of **20** and **21**.

The residue was dissolved in CH_2Cl_2 (25 mL) and pyridine (0.3 mL). The mixture was cooled to −78 °C. Ozone was bubbled through it for 12 min while the reaction was monitored by TLC (every 60 s). The ozone flow was replaced by an air flow and the reaction was quenched with the addition of Zn (300 mg, activated) at −78 °C. The mixture was slowly warmed to 25 °C over 1 h and stirred at 25 °C for an additional 2 h. The resulting mixture was filtered. The filtrate was concentrated to give crude **22**. Flash chromatography on MeOH-deactivated silica gel (1:1 hexanes/EtOAc) yielded 82 mg (43% from **4**) of **22** as a 1:1 mixture of diastereomers: ^{1}H NMR 6.36 (s, 1), [6.18 (s, 1), 6.17 (s, 1)], [5.06 (d, 1, *J*=7.8), 5.04 (d, 1, *J*=7.8)], [4.07 (dd, 1, *J*=7.8, 7.2), 4.02 (dd, 1, *J*=7.8, 7.2)], [2.71 (t, 1, *J*=6.0), 2.67 (t, 1, *J*=6.0)], 2.42–2.28 (m, 3), 2.25 (s, 3), 2.12–2.04 (m, 1), 1.97–1.57 (m, 5), [1.43 (s, 3), 1.40 (s, 3)], 1.29 (s, 3), 1.27 (s, 3); ^{13}C NMR (208.25, 208.17), (160.56, 160.50), 151.10, (141.24, 141.18), (108.42, 108.30), (104.63, 104.51), (103.54, 103.51), (87.47, 87.43), 80.29, (64.11, 63.71), (58.55, 58.35), (38.78, 38.76), 38.66, (37.34, 37.05), (35.03, 34.81), (24.79, 24.77), (23.65, 23.48), (22.77, 22.71), (22.66, 22.50), 22.15, (18.67, 18.64); IR (neat) 2966, 2928, 1732, 1624; HRMS (Q-TOF) calcd for $C_{21}H_{27}O_4$ (MH^+) 343.1909, found 343.1917.

3.13. (3a*R*,9*S*,9a*R*,9b*S*)-*rel*-9-(4-Methyl-3-pentenyl)-1,2,3a,9,9a,9b-hexahydro-6,9-dimethyl-3*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-one (23)

A mixture of sodium acetate (18 mg, 0.22 mmol), sodium iodide (62 mg, 0.41 mmol), and zinc–copper couple (54 mg, 0.83 mmol) was added to a solution of **22** (71 mg, 0.21 mmol) in acetic acid (0.6 mL). The resulting solution was stirred at 25 °C for 30 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3×15 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated to give crude **23**. Flash chromatography on MeOH-deactivated silica gel (5:1 hexanes/EtOAc) yielded 36 mg (53%) of pure **23** as a colorless oil: ^{1}H NMR 6.35 (s, 1), 6.18 (s, 1), 5.06 (t, 1, *J*=7.2), 5.04 (d, 1, *J*=7.6), 4.03 (dd, 1, *J*=7.6, 6.4), 2.42–2.31 (m, 3), 2.25 (s, 3), 2.18–2.02 (m, 3), 1.77–1.53 (m, 2), 1.67 (s, 3), 1.61 (s, 3), 1.43 (s, 3), 1.34–1.22 (m, 1); ^{13}C NMR 208.3, 160.5, 151.3, 141.1, 132.2, 123.4, 108.4, 104.7, 103.3, 87.5, 80.8, 38.9, 38.7, 38.4, 36.9, 25.6, 22.8, 22.7, 22.4, 22.1, 17.7; IR (neat) 2966, 2917, 1730, 1623; HRMS (Q-TOF) calcd for $C_{21}H_{27}O_3$ (MH^+) 327.1960, found 327.1965.

3.14. (3*S*,3a*R*,9*S*,9a*R*,9b*S*)-*rel*-9-(4-Methyl-3-pentenyl)-2,3,3a,9,9a,9b-hexahydro-3,6,9-trimethyl-1*H*-benzofuro[4,3,2-*cde*][1]benzopyran-3-ol (24)

MeMgBr (0.24 mL, 1.4 M in toluene/THF, 0.33 mmol) was added to a solution of **23** (27 mg, 0.083 mmol) in THF (10 mL) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 5 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3×15 mL). The combined EtOAc extracts were dried ($MgSO_4$) and concentrated to give crude **24**. Flash chromatography on MeOH-deactivated silica gel (15:1 hexanes/EtOAc) yielded 22 mg (78%) of pure **24** as a colorless oil: ^{1}H NMR 6.20 (s, 1), 6.17 (s, 1), 5.04 (t, 1, *J*=7.6, H_{10}), 4.69 (d, 1, *J*=8.5, H_4), 3.61 (dd, 1, *J*=8.5, 6.1, H_5), 2.25 (s, 3), 2.12–2.03 (m, 2, $2H_9$), 1.96–1.88 (m, 1, H_6), 1.75–1.45 (m, 4, H_1, H_2, and $2H_8$), 1.65 (s, 3), 1.59 (s, 3), 1.39 (s, 3, H_{14}), 1.33–1.13 (m, 2, H_1 and H_2), 1.24 (s, 3, H_{15}); ^{13}C NMR 161.4, 151.6, 140.3, 131.9, 123.7, 108.1, 107.7, 101.4, 90.5, 81.0, 69.5, 38.3, 36.5, 35.1, 33.7, 29.8, 25.6, 22.5, 22.4, 22.2, 17.6, 16.4; IR (neat) 3442, 2965, 1716, 1626; HRMS (EI^+) calcd for $C_{22}H_{30}O_3$ (M^+) 342.2195, found 342.2201. The relative stereochemistry of the side chain of **24** was established by a 1D NOESY experiment. Irradiation of H_5 at δ 3.61 showed an NOE to H_8 at δ 1.73–1.64 and δ 1.61–1.52, but not to H_{14} at δ 1.39.

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