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Synthesis of the Putative Structure of 15-Oxopuupehenoic Acid

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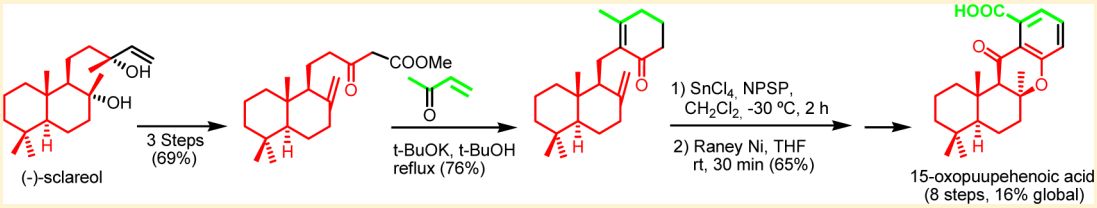
Supporting Information



ABSTRACT: Synthesis of the putative structure of the marine natural 15-oxopuupehenoic acid has been achieved starting from commercial (−)-sclareol. Key steps of the synthetic sequence are the Robinson annulation of a *β*-ketoester and methyl vinyl ketone and an unprecedented cyclization of the resulting *α*,*β*-enone, which is mediated by tin(IV) chloride in the presence of *N*-phenylselenophthalimide. The physical properties of the synthetic compound are somewhat different from those reported for the natural product.

The interesting biological activity of certain merosesquiterpenes, particularly those having a bicyclic sesquiterpene fragment joined to a phenol or quinone moiety such as the 15-human lipoxygenase inhibitor jaspic acid **1**[1] and related benzopyran derivatives, antibacterial hongoquercin A **2** and B **3**,[2] and oxopuupehenoic acid **4**,[3] has driven research to generate procedures for carrying out their synthesis.

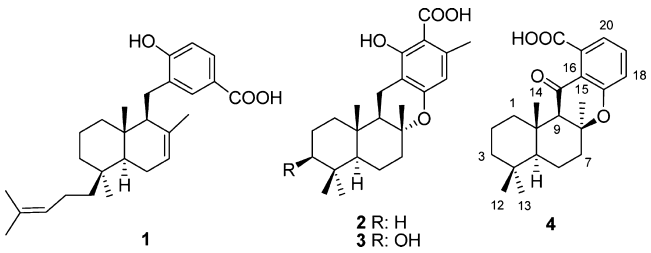
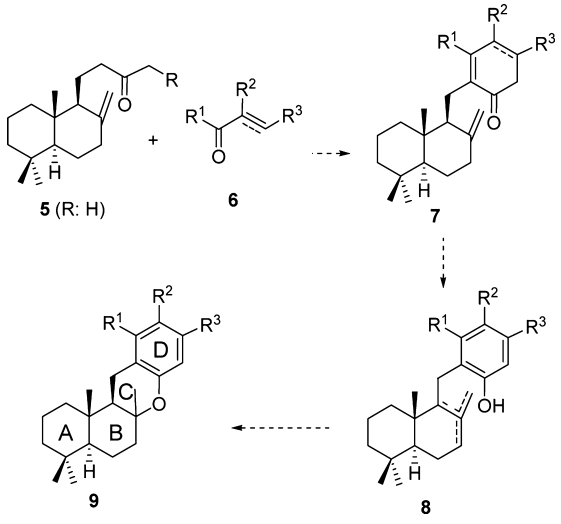


Figure 1. Representative bioactive merosesquiterpenes.

In most cases, these processes involve the condensation of a sesquiterpene derivative, usually with electrophilic character, with an aromatic derivative of a nucleophilic nature.[4] In certain cases, preparation of the latter can be difficult because of either its substitution pattern or the presence of electrophilic groups (e.g., CN, COR, COOR, etc.) in the aromatic ring, resulting in consequent lengthening of the synthetic sequence. It is therefore of interest to investigate new processes that allow for the elaboration of the aromatic fragment of these target compounds in an alternative way.

Considering the argument detailed above, a new synthetic strategy to generate these types of merosesquiterpenes has been developed (Scheme 1). The aromatic ring of target compounds **8** and **9** will be elaborated after the Michael addition of the kinetic enolate of methyl ketone **5**[5] to a suitable electron-deficient alkene or alkyne **6** and subsequent intramolecular aldol condensation. This procedure could allow for the preparation of compounds similar to **8** and **9** that have functional A and/or B rings; importantly, A- or B-ring-functionalized methyl ketones similar to **5** have been obtained in good yields from different types of diterpenes, such as communic acids,[6] larixol,[7] and abietic acid.[8] Regiocontrol in the formation of suitable enol derivatives from compound **5** can be achieved by utilizing a corresponding *β*-ketoester (R:

Scheme 1. A Robinson Annulation Based Strategy toward Merosesquiterpenes



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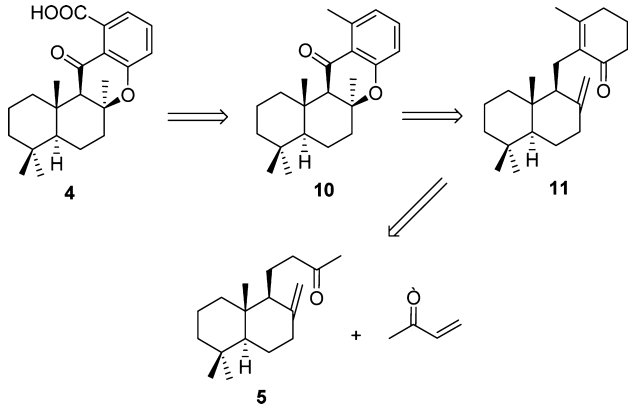
COOMe), which, under the proper reaction conditions, undergoes decarboalkoxylation.[9]

We investigated the preparation of 15-oxopuupehenoic acid **4**, a marine sponge metabolite that has not yet been synthesized, utilizing this strategy. Scheme 2 shows the

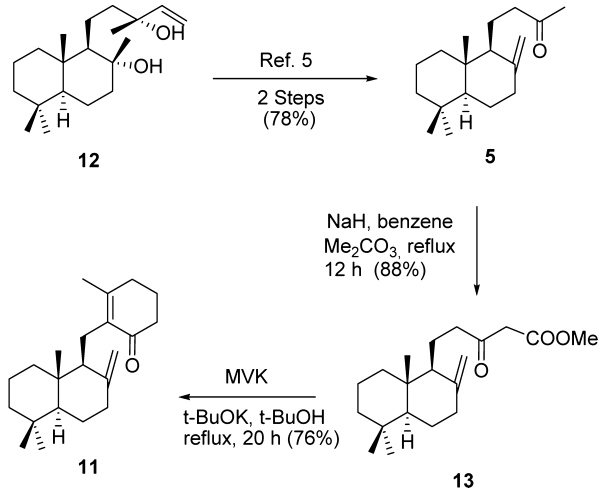
Scheme 2. Retrosynthesis of 15-Oxopuupehenoic Acid 4



retrosynthesis of acid **4** from methyl ketone **5**, which is easily otained from commercial (−)-sclareol **12**. Compound **4** will be obtained after successive benzylic oxidation of benzopyran resulting from the cyclization of phenol prepared after aromatization of *α,β*-enone **11**. This ketone will be obtained after Robinson annulation of methyl ketone **5** with methyl vinyl ketone.

Scheme 3 shows the construction of the merosesquiterpene skeleton starting from commercial (−)-sclareol **12**. This was

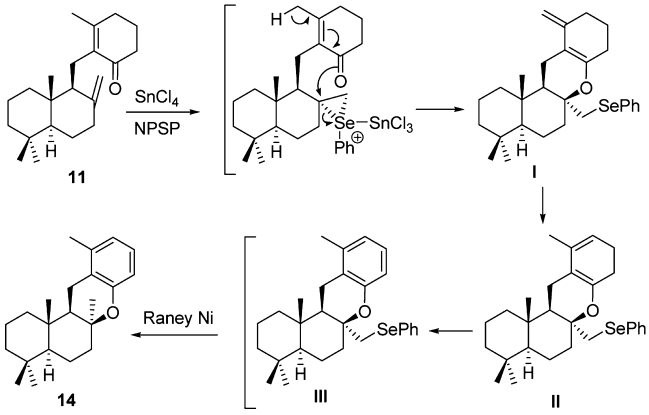
Scheme 3. Construction of the Merosesquiterpene Skeleton: Synthesis of *α,β*-Enone 11



converted into methyl ketone **5** in a two-step sequence resulting in 78% global yield utilizing a procedure previously developed in our laboratory.[5] The treatment of *β*-ketoester **13** with methyl vinyl ketone and *t*-BuOK in *t*-BuOH under reflux resulted in the synthesis of *α,β*-enone **11** directly with 76% yield.

The next step was to address the transformation of enone **11** into the tetracyclic benzopyran framework of the target compound. The most common method for achieving this type of tetracyclic skeleton involves the diastereoselective cyclization of a drimenyl phenol;[10] however, all attempts at converting compound **11** into the corresponding drimenyl phenol, after dehydrogenation of the enone moiety, were unsuccessful. Interestingly, it was observed that this enone undergoes direct cyclization without previous aromatization. Thus, benzopyran **14** was obtained at 65% yield when ketone **11** was treated first with $SnCl_4$ and *N*-phenylselenophthalimide (NPSP) in dichloromethane and then with Raney nickel in THF (Scheme 4).[11] Compound **14** is most likely formed after the cyclization of a dienol derived from enone **11** and further aromatization of the tetracyclic diene. A possible mechanism for this transformation is depicted in Scheme 5. Under acidic

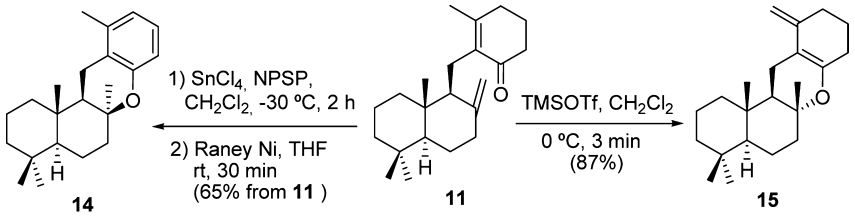
Scheme 5. A Possible Mechanism for the Direct Transformation of *α,β*-Enone 11 into Benzopyran 14



conditions, diene **I** isomerizes to give **II**, which then undergoes in situ air oxidation leading to selenide **III**. A result that supports this mechanism is the formation of unstable diene **15** after treatment of enone **11** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at 0 °C. The *R* configuration on C-8 of compound **15** was confirmed by the NOE effect observed between Me-15 (singlet at 1.12 ppm) and Me-14 (singlet at 0.85 ppm).[12]

Finally, benzylic oxidation of compound **14** to achieve acid **4** was undertaken (Scheme 6). The treatment of benzopyran **14** with sodium chromate in the presence of sodium acetate, acetic acid, and acetic anhydride gave ketone **10**.[13] This was

Scheme 4. Cyclization of Enone 11: Synthesis of Benzopyrans 14 and 15



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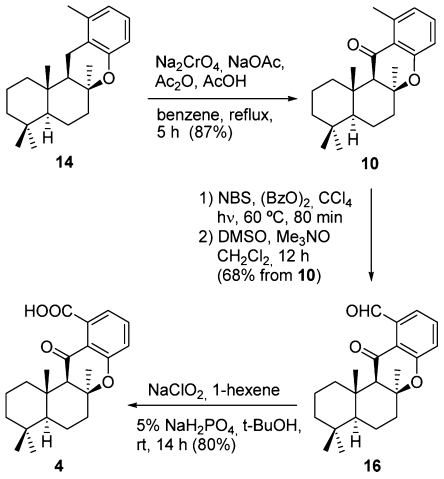
Scheme 6. Synthesis of 15-Oxopuupehenoic Acid 4



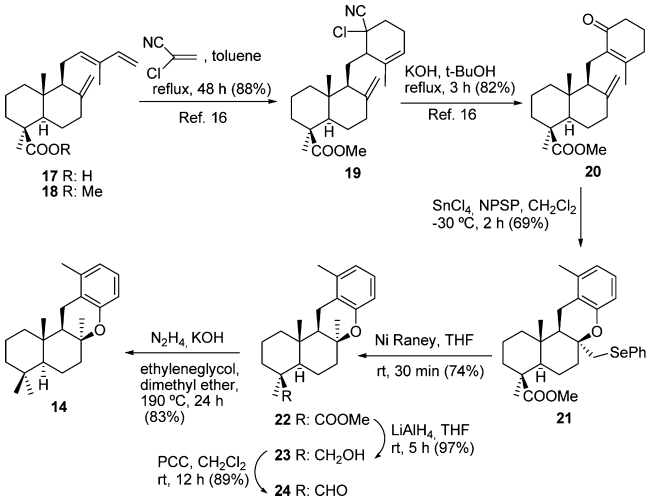
transformed into aldehyde **16** by reacting **10** with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide under light irradiation and subsequently treating the crude product with DMSO and trimethylamine *N*-oxide in CH_2Cl_2. Finally, aldehyde **16** was converted into acid **4** after oxidation with $NaClO_2$. The *S* configuration on C-8 was confirmed by the NOE correlation between Me-15 (singlet at 1.21 ppm) and H-9 (singlet at 1.96 ppm).

The ^1H and ^{13}C NMR data of synthetic 15-oxopuupehenoic acid (**4**) were similar to those reported for the natural compound, but significant differences were observed for the aromatic protons in the ^1H NMR. In the synthetic acid, these protons appear at δ 7.38 (dd, J = 8.4, 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), and 6.88 (d, J = 8.4 Hz, 1H), whereas the data reported by Crews et al. for the natural acid were δ 7.48 (dd, J = 8.0, 7.5 Hz, 1H), 7.27 (dd, J = 7.5, 1.5 Hz, 1H), and 7.01 (dd, J = 8.0, 1.5 Hz, 1H). The optical rotation was also different: $[\alpha]_D^{25}$ − 21.2 (*c* 0.3, $CHCl_3$) for the synthetic acid and $[\alpha]_D^{25}$ + 27 (*c* 0.1, $CHCl_3$) for the natural product.[3]

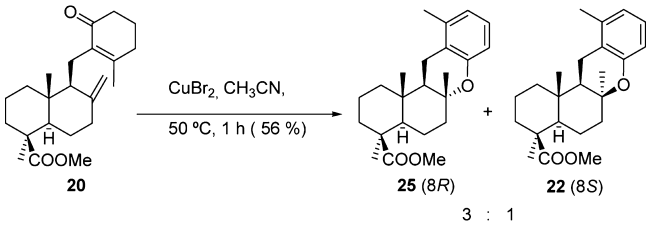
Even though the structure of synthetic 15-oxopuupehenoic acid (**4**) appears to be confirmed based on the well-known diastereoselectivity of cyclization and on the NOE effects observed in the ^1H NMR spectra, we have developed an alternative route to generating this compound starting from labdane diterpene (+)-*trans*-communic acid **17**,[14] which has also been utilized in the synthesis of a variety of terpenoids.[15] Scheme 7 shows the synthesis of intermediate **14** from acid **17**. The key intermediate was *α,β*-enone **20**, which was obtained after the Diels−Alder cycloaddition of ester **18** with 2-chloroacrylonitrile and subsequent alkalyne treatment of adduct **19**.[16] When compound **20** was treated with $SnCl_4$ in the presence of NPSP at −30 °C for 2 h, selenoderivative **21** was obtained. The ^1H NMR spectrum of this compound shows a characteristic AB system (doublets at 3.03 and 3.08 ppm, J = 12.2 Hz) based on the CH_2−Se group.[17] Further treatment of this compound with Raney nickel afforded ester **22**. These results are in agreement with the mechanism depicted in Scheme 5. After succesive reductions, the expected compound **14** was obtained.

As expected, compound **25**, the 8*R* epimer of benzopyran **22**, was obtained after acid cyclization of *α,β*-enone **20**. Thus, the treatment of **20** with $CuBr_2$ in acetonitrile at 50 °C for 1 h gave a mixture of epimers **25** and **22** in a 3:1 ratio (Scheme 8). The ^1H NMR spectrum of compound **25** shows an NOE correlation

Scheme 7. Alternative Synthesis of Benzopyran 14 from *trans*-Communic Acid 17



Scheme 8. Acid Cyclization of *α,β*-Enone 20



of Me-14 (singlet at 0.75) and Me-15 (singlet at 1.18). The results depicted in Schemes 7 and 8 are consistent with those previously reported for the cyclization of drimenyl phenols and confirm the diastereoselectivity of these processes.[10−12]

The results presented here allowed us to establish unequivocally the structure of synthetic 15-oxopuupehenoic acid **4**. At this point, it should be noted that the last stage of the structural determination of natural oxopuupehenoic acid by Crews' group involves establishing the substitution pattern on the aromatic ring. These authors proposed four alternative structures for the natural compound, including two acid regioisomers and two seven-membered lactones; they ultimately decided in favor of structure **4** on the basis of J_{HC} gHMBC correlations. The results reported here suggest that revising the structure of the natural compound is advisable.

In summary, enantiospecific synthesis of the putative structure of 15-oxopuupehenoic acid **4**, starting from commercial (−)-sclareol **12**, has been achieved utilizing a new synthetic strategy. Key steps of this process include the Robinson annulation of a *β*-ketoester and methyl vinyl ketone followed by unprecedented cyclization of the resulting *α,β*-enone mediated by tin(IV) chloride in the presence of NPSP. Unstable tetracyclic dienol ether **15** was isolated when the cyclization of enone **11** was carried out with TMSOTf. An alternative route starting with (+)-*trans*-communic acid (**17**) has also been developed. The generated synthetic acid **4** showed physical properties that differed from those reported for the natural compound.

EXPERIMENTAL SECTION

General Methods. Reactions were performed under an argon atmosphere using dry solvents. Dichloromethane was dried over

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calcium hydride; benzene and tetrahydrofuran were dried over sodium benzophenone. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV-fluorescent quenching and phosphomolybdic acid solution staining. Chromatography separations were carried out by conventional columns on silica gel 60 (230−400 mesh) using MeO-*t*-Bu/hexanes (ether/hexanes) mixtures of increasing polarity. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. $CDCl_3$ was treated with K_2CO_3. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, br d, t, q, and m denoting singlet, broad singlet, doublet, broad doublet, triplet, quartet, and multiplet, respectively. J is the coupling constant in hertz. ^{13}C NMR signals were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations. Infrared spectra (IR) were recorded as thin films on an FTIR spectrophotometer with samples between sodium chloride plates and are reported in frequency of absorption (cm^{-1}). Only selected absorbances (ν_{max}) are reported. $[\alpha]_D$ measurements were carried out in a polarimeter, utilizing a 1 dm length cell and $CHCl_3$ as a solvent. Concentration is expressed in milligrams per milliliter. HRMS mass spectra were recorded on a spectrometer utilizing a quadrupole MS/MS analyzer and using FAB with thioglycerol or a glycerol matrix doped in 1% NaI.

Methyl-3-oxo-5-((1′*S*,4′a*S*,8′a*S*)-5′,5′,8′a-trimethyl-2′-methylene-decahydronaphthalen-1′-yl)pentanoate (13). Dimethyl carbonate (855 g, 9.5 mmol) and 60% NaH (190 mg, 4.75 mmol) were added to a solution of ketone **5** (250 mg, 0.95 mmol) in anhydrous benzene (25 mL), and the mixture was kept stirring at reflux under an argon atmosphere for 12 h. Then, the reaction was carefully quenched with water (0.3 mL), and ether (30 mL) was added. The organic solution was washed with water (4 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (20% ether/hexanes) to yield **13** (267 mg, 88%) as a colorless syrup. $[\alpha]_D^{25}$ + 18.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.81 (d, J = 0.86 Hz, 1H), 4.41 (s, 1H), 3.71 (s, 3H), 3.40 (s, 2H), 2.67 (m, 1H), 2.46−2.33 (m, 2H), 1.99−1.00 (m, 13H), 0.85 (s, 3H), 0.79 (s, 3H), 0.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.1 (C), 167.7 (C), 148.3 (C), 106.3 (CH_2), 56.1 (CH), 55.5 (CH), 52.3 (CH_3), 49.2 (CH_2), 42.2 (CH_2), 42.1 (CH_2), 39.8 (C), 39.0 (CH_2), 38.3 (CH_2), 33.67 (CH_3), 33.63 (C), 24.5 (CH_2), 21.7 (CH_3), 19.4 (CH_2), 17.3 (CH_2), 14.3 (CH_3). IR (film): 1749, 1717, 1646, 1457, 1437, 1318, 1236, 889, 667 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{20}H_{32}O_3Na$, 343.2249; found, 343.2253.

3-Methyl-2-(((4′a*S*,8′a*S*)-5′,5′,8′a-trimethyl-2′-methylene-decahydronaphthalen-1-yl)methyl)cyclohex-2-enone (11). *t*-BuOK (16 mg, 0.14 mmol) was added to a solution of ketoester **13** (900 mg, 2.81 mmol) and methyl vinyl ketone (200 mg, 2.85 mmol) in *t*-BuOH (10 mL), and the mixture was stirred at room temperature for 30 min. Then, additional *t*-BuOK (64 mg, 0.56 mmol) was added, and the mixture was refluxed with stirring for 20 h. Then, 1 N HCl (10 mL) was added, and the mixture was extracted with ether (60 mL). The organic phase was washed with water (5 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude residue, which, after column chromatography on silica gel (5% ether/hexanes), afforded enone **11** (670 mg, 76%). $[\alpha]_D^{25}$ − 21.6 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.68 (s, 1H), 4.53 (s, 1H), 2.51 (dd, J = 14.3, 9.1 Hz, 1H), 2.43 (m, 1H), 2.39−2.24 (m, 4H), 2.11 (dd, J = 8.8, 4.2 Hz, 1H), 1.95 (s, 3H), 1.93−1.10 (m, 13H), 0.85 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.2 (C), 155.0 (C), 149.6 (C), 136.7 (C), 106.9 (CH_2), 55.7 (CH), 55.7 (CH), 42.3 (CH_2), 40.6 (C), 38.9 (CH_2), 38.7 (CH_2), 38.2 (CH_2), 33.8 (CH_3), 33.7 (C), 33.4 (CH_2), 24.7 (CH_2), 22.2 (CH_3), 22.0 (CH_2), 21.9 (CH_3), 20.7 (CH_2), 19.6 (CH_2), 14.3 (CH_3). IR (film): 1718, 1663, 1618, 1543, 1509, 1458, 1378, 882, 756 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{34}ONa$, 337.2507; found, 337.2509.

(4a*S*,6a*S*,12b*S*)-4,4,6a,11,12b-Pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene (14). To a solution of NPSP (318 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $SnCl_4$ (0.3 mL) at −30 °C, and the mixture was stirred for 5 min. Then, a solution of enone **11** (300 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was kept stirring at this temperature for 2 h, at which time TLC showed no starting material. Then, ether (30 mL) was added, and the organic phase was washed with water (3 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to afford a crude residue. A 60−70% aqueous dispersion of Raney nickel (2 mL) was then added to a solution of the above residue in THF (10 mL), and the mixture was stirred at room temperature for 30 min. After this, the mixture was filtered through a silica gel/anhydrous Na_2SO_4 pad and evaporated to afford a crude product, which was then purified using a flash cromatography column on silica gel (2% ether/hexanes) to afford pure **14** (125 mg, 65% from **11**). $[\alpha]_D^{25}$ − 13.9 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.96 (dd, J = 8.1, 7.3 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 2.68 (d, J = 18.3 Hz, 1H), 2.64 (dd, J = 18.3, 6.7 Hz, 1H), 2.21 (s, 3H), 2.15 (m, 1H), 1.85 (br d, J = 8.7 Hz, 1H), 1.67−1.52 (m, 5H), 1.50−1.37 (m, 3H), 1.17 (m, 1H), 1.15 (s, 3H), 0.94 (dd, J = 11.9, 2.7 Hz, 1H), 0.90 (s, 3H), 0.81 (s, 3H), 0.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.6 (C), 136.3 (C), 126.0 (CH), 121.4 (C), 121.1 (CH), 114.8 (CH), 74.8 (C), 55.3 (CH), 49.8 (CH), 41.9 (CH_2), 40.7 (CH_2), 40.2 (CH_2), 38.4 (C), 33.7 (CH_3), 33.3 (C), 27.1 (CH_3), 21.9 (CH_3), 20.7 (CH_2), 19.2 (CH_3), 18.5 (CH_2), 18.3 (CH_2), 14.2 (CH_3). IR (film): 2924, 1586, 1467, 1260, 774, 665 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{32}ONa$, 335.2351; found, 335.2346.

(4a*S*,6a*R*,12b*S*)-4,4,6a,12b-Tetramethyl-11-methylene-1,3,4,4a,5,6,6a,8,9,10,11,12,12a,12b-tetradecahydro-1*H*-benzo[a]xanthene (15). TMSOTf (0.5 mL, 2.76 mmol) was added to a solution of enone **11** (264 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 3 min, after which time TLC showed no **11** remaining. Then, ether (20 mL) was added, and the organic phase was washed with water (3 × 20 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give unstable diene **15** (228 mg, 87%). ^{1}H NMR (500 MHz, CD_3COCD_3): δ 4.57 (s, 1H), 4.44 (s, 1H), 2.50−0.90 (m, 20H), 1.12 (s, 3H), 0.90 (s, 6H), 0.85 (s, 3H). ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 150.6 (C), 144.4 (C), 105.5 (C), 100.4 (CH_2), 76.2 (C), 56.1 (CH), 52.6 (C), 41.7 (CH_2), 40.8 (CH_2), 39.0 (CH_2), 36.6 (C), 32.9 (C), 32.9 (CH_3), 28.8 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 21.0 (CH_3), 19.8 (CH_3), 19.5 (CH_2), 18.4 (CH_2), 18.1 (CH_2), 14.4 (CH_3).

(4a*S*,6a*S*,12b*S*)-4,4,6a,11,12b-Pentamethyl-1,2,3,4,4a,5,6,6a-octahydro-12a*H*-benzo[a]xanthen-12(12b*H*)-one (10). Na_2CrO_4 (71 mg, 0.44 mmol) was added to a solution of compound **14** (55 mg, 0.176 mmol), sodium acetate (30 mg, 0.36 mmol), acetic acid (0.3 mL), and acetic anhydride (0.3 mL) in benzene (5 mL), and the mixture was kept stirring at reflux for 5 h, at which time TLC showed no **14** remaining. Then, water (10 mL) and ether (25 mL) were added successively, and the phases were shaken. The organic phase was washed with water (4 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give a crude product, which was purified using a flash chromatography column on silica gel (15% hexanes/ether) to afford pure ketone **10** (50 mg, 87%). $[\alpha]_D^{25}$ − 23.4 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (dd, J = 8.3, 7.4 Hz, 1H), 6.74 (dd, J = 8.3, 0.7 Hz, 1H), 6.72 (dd, J = 7.4, 0.7 Hz, 1H), 2.61 (s, 3H), 2.22 (dt, J = 6.1, 3.3 Hz, 1H), 1.93 (s, 1H), 1.76−1.67 (m, 2H), 1.66−1.46 (m, 3H), 1.45−1.37 (m, 2H), 1.32−1.25 (m, 1H), 1.24 (s, 3H), 1.21−1.14 (m, 1H), 0.91 (s, 3H), 0.89 (dd, J = 5.5, 2.6 Hz, 1H), 0.83 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.6 (C), 161.3 (C), 141.0 (C), 134.1 (CH), 123.8 (CH), 120.8 (C), 116.0 (CH), 79.1 (C), 66.1 (CH), 54.2 (CH), 41.7 (CH_2), 40.3 (CH_2), 39.8 (CH_2), 38.1 (C), 33.8 (CH_3), 33.4 (C), 26.5 (CH_3), 23.1 (CH_2), 22.0 (CH_3), 18.4 (CH_2), 18.1 (CH_2), 15.5 (CH_3). IR (film): 2927, 1674, 1599, 1315, 1270, 777, 665 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{30}O_2Na$, 349.2143; found, 349.2150.

(4a*S*,6a*S*,12b*S*)-4,4,6a,12b-Tetramethyl-12-oxo-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene-11-carbaldehyde (16). NBS (40 mg, 0.225 mmol) and benzoyl peroxide (3 mg) were added to a solution of ketone **10** (60 mg, 0.184 mmol) in carbon tetrachloride (8 mL), and the mixture was stirred

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under light irradiation at 60 °C in argon atmosphere for 80 min. After evaporation under a vacuum, the resulting crude product was purified by column chromatography on silica gel (20% hexanes/ether) affording a solid residue (55 mg). This was dissolved in dichloromethane−dimethyl sulfoxide (3:3 mL), and trimethylamine *N*-oxide dihydrate (45 mg, 0.40 mmol) was added at 0 °C. After the mixture had been stirred at room temperature for 12 h, ether was added (20 mL), and the organic phase was washed with water (3 × 30 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give a crude product, which was purified by column chromatography on a silica gel (30% hexanes/ether) to afford pure aldehyde **16** (42 mg, 68%). $[\alpha]_D^{25}$ + 1.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.68 (s, 1H), 7.51 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.13 (dd, *J* = 8.3, 1.1 Hz, 1H), 2.29 (dt, *J* = 14.4, 3.0 Hz, 1H), 2.05 (s, 1H), 1.75−1.66 (m, 2H), 1.56−1.54 (m, 3H), 1.52−1.41 (m, 2H), 1.27 (s, 3H), 1.26−1.21 (m, 2H), 0.93 (s, 3H), 0.92 (dd, *J* = 11.8, 2.5 Hz, 1H), 0.89 (s, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.4 (C), 193.8 (CH), 160.7 (C), 138.2 (C), 135.0 (CH), 123.1 (CH), 121.1 (C), 120.3 (CH), 80.6 (C), 65.5 (CH), 54.1 (CH), 41.5 (CH_2), 40.2 (CH_2), 39.6 (CH_2), 38.5 (C), 33.8 (CH_3), 33.4 (C), 26.5 (CH_3), 22.0 (CH_3), 18.3 (CH_2), 18.1 (CH_2), 15.5 (CH_3). IR (film): 2924, 1673, 1589, 1466, 1283, 773, 665 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{28}O_3Na$, 363.1936; found, 363.1941.

15-Oxopuupehenoic Acid (4). A solution of sodium chlorite (13 mg, 0.14 mmol) in aqueous 5% NaH_2PO_4 (3 mL) was added to a solution of aldehyde **16** (20 mg, 0.059 mmol) and 1-hexene (0.4 mL) in *t*-BuOH (6 mL), and the mixture was stirred at room temperature under an argon atmosphere for 14 h. After the solvent had evaporated under vacuum, ether−water (20:5 mL) was added to the residue, and the phases were shaken. The organic phase was extracted with saturated $NaHCO_3$ (3 × 10 mL). Combined aqueous phases were acidified by the addition of 2 N HCl and extracted with ether (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give pure acid **4** (17 mg, 80%). $[\alpha]_D^{25}$ − 21.2 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 2.23 (dt, *J* = 14.7, 3.3 Hz, 1H), 1.96 (s, 1H), 1.74−1.59 (m, 2H), 1.56−1.32 (m, 3H), 1.31−1.22 (m, 2H), 1.21 (s, 3H), 1.20−1.08 (m, 2H), 0.90 (s, 3H), 0.87 (dd, *J* = 9.0, 1.9 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.8 (C), 174.0 (C), 160.5 (C), 135.4 (C), 135.4 (CH), 120.1 (CH), 118.9 (CH), 118.3 (C), 80.1 (C), 65.0 (CH), 54.2 (CH), 41.6 (CH_2), 39.8 (CH_2), 39.7 (CH_2), 38.6 (C), 33.8 (CH_3), 33.4 (C), 26.4 (CH_3), 22.0 (CH_3), 18.3 (CH_2), 18.2 (CH_2), 15.4 (CH_3). IR (film): 3417, 2923, 1685, 1579, 1474, 772, 666 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{28}O_4Na$, 379.1885; found, 379.1882.

(4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-Methyl-4,11,12b-trimethyl-6a-(phenylselanylmethyl)-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene-4-carboxylate (21). To a solution of NPSP (350 mg, 1.16 mmol) in anhydrous CH_2Cl_2 (7 mL) was added $SnCl_4$ (0.3 mL) at −30 °C, and the mixture was stirred for 5 min. Then, a solution of ester **20** (300 mg, 0.837 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was kept stirring at this temperature for 2 h, at which time TLC showed no starting material. Then, ether (30 mL) was added, and the organic phase was washed with water (3 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give a crude product, which was purified by a flash cromatography column (5% ether/hexanes) to afford selenide **21** (295 mg, 69%). $[\alpha]_D^{25}$ + 29.4 (*c* 9.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47−7.43 (m, 2H), 7.22−7.18 (m, 3H), 6.95 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 3.57 (s, 3H), 3.08 (d, *J* = 12.2 Hz, 1H), 3.03 (d, *J* = 12.2 Hz, 1H), 2.52 (d, *J* = 18.2 Hz, 1H), 2.39 (dd, *J* = 18.2, 7.5 Hz, 1H), 2.23−2.13 (m, 2H), 2.12 (s, 3H), 2.05 (m, 1H), 1.92−1.72 (m, 3H), 1.50−0.75 (m, 6H), 1.21 (s, 3H), 1.20−0.83 (m, 3H), 0.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.8 (C), 153.7 (C), 136.3 (C), 133.0 (2CH), 130.9 (C), 129.1 (2CH), 127.0 (CH), 126.4 (CH), 121.7 (CH), 120.9 (C), 115.1 (CH), 76.6 (C), 55.8 (CH), 51.2 (CH_3), 45.9 (CH), 43.8 (C), 40.5 (CH_2), 38.7 (C), 38.0 (CH_2), 38.0 (CH_2), 37.7 (CH_2), 28.7 (CH_3), 20.5 (CH_2), 19.4 (CH_2), 19.1 (CH_3), 19.1 (CH_2), 13.0 (CH_3). IR (film): 2922, 1720, 1585, 1466, 1002, 773, 665 cm^{-1}.

(4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-Methyl-4,6a,11,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene-4-carboxylate (22). Aqueous Raney nickel (60−70%, 1.5 mL) was added to a solution of selenide **21** (160 mg, 0.31 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 30 min. Then, it was filtered through a silica gel/anhydrous Na_2SO_4 pad and evaporated under vacuum to give ester **22** (83 mg, 74%). $[\alpha]_D^{25}$ + 7.39 (*c* 24.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.96 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 3.57 (s, 3H), 2.70 (dd, *J* = 18.1, 7.4 Hz, 1H), 2.64 (d, *J* = 18.1 Hz, 1H), 2.21 (s, 3H), 2.17 (dt, *J* = 13.6, 2.9 Hz, 1H), 2.08 (m, 1H), 1.92 (m, 1H), 1.86−1.76 (m, 2H), 1.63 (m, 1H), 1.56−1.41 (m, 2H), 1.40 (dd, *J* = 12.9, 1.5 Hz, 1H), 1.21 (s, 3H), 1.34−0.87 (m, 3H), 1.16 (s, 3H), 0.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.8 (C), 154.4 (C), 136.3 (C), 126.1 (CH), 121.2 (CH), 120.8 (C), 114.9 (CH), 74.3 (C), 56.0 (CH), 51.2 (CH), 48.9 (CH_3), 43.8 (C), 40.7 (CH_2), 40.5 (CH_2), 38.5 (C), 38.1 (CH_2), 28.7 (CH_3), 27.0 (CH_3), 20.9 (CH_2), 19.6 (CH_2), 19.2 (CH_3), 19.0 (CH_2), 12.8 (CH_3). IR (film): 2934, 1720, 1459, 1466, 1108, 773, 662 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{23}H_{32}O_3Na$, 379.2249; found, 379.2257.

((4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-4,6a,11,12b-Tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthen-4-yl)methanol (23). To a solution of ester **22** (200 mg, 0.56 mmol) in THF (15 mL) was added $LiAlH_4$ (85 mg, 2.23 mmol) at 0 °C, and the mixture was stirred at room temperature under an argon atmosphere for 5 h, at which time TLC showed no **22** remaining. Then, 2 N HCl (1 mL) was added slowly at 0 °C, and the mixture was diluted with ether (25 mL). The organic phase was washed with water (3 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give pure alcohol **23** (180 mg, 97%). $[\alpha]_D^{25}$ − 15.5 (*c* 15.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.96 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.42 (dd, *J* = 11.0, 1.0 Hz, 1H), 2.66 (dd, *J* = 18.2, 7.2 Hz, 1H), 2.60 (d, *J* = 18.2 Hz, 1H), 2.21 (s, 3H), 2.15 (dt, *J* = 13.7, 3.0 Hz, 1H), 1.96−1.61 (m, 4H), 1.60−1.47 (m, 2H), 1.48−1.32 (m, 2H), 1.15 (s, 3H), 1.10 (m, 1H), 1.01 (s, 3H), 1.00−0.91 (m, 2H), 0.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.6 (C), 136.3 (C), 126.1 (CH), 121.3 (CH), 121.2 (C), 114.8 (CH), 74.6 (C), 65.2 (CH_2), 55.9 (CH), 50.0 (CH), 41.0 (CH_2), 40.1 (CH_2), 38.6 (C), 38.3 (C), 35.3 (CH_2), 27.1 (CH_3), 27.0 (CH_3), 20.8 (CH_2), 19.2 (CH_3), 18.3 (CH_2), 18.2 (CH_2), 15.0 (CH_3). IR (film): 3372, 2926, 1585, 1468, 1261, 1002, 755, 665 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{32}O_2Na$, 351.2300; found, 351.2294.

(4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-4,6a,11,12b-Tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene-4-carbaldehyde (24). PDC (345 mg, 0.98 mmol) was added to a solution of alcohol **23** (130 mg, 0.396 mmol) in dichloromethane (6 mL) under an argon atmosphere, and the mixture was stirred at room temperature for 12 h, at which time TLC showed no **23** remaining. Then, the mixture was diluted with ether (20 mL), filtered on a silica gel, and washed again with ether (5 mL). The filtrate was washed with 2 N HCl (2 × 5 mL), water, and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to afford aldehyde **24** (115 mg, 89%). $[\alpha]_D^{25}$ − 14.72 (*c* 23.76, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.73 (s, 1H), 6.97 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 2.70 (dd, *J* = 18.1, 7.5 Hz, 1H), 2.63 (d, *J* = 7.5 Hz, 1H), 2.20 (m, 1H), 2.21 (s, 3H), 2.06 (m, 1H), 1.93−1.82 (m, 2H), 1.63−1.38 (m, 3H), 1.32 (dd, *J* = 12.9, 1.8 Hz, 1H), 1.18 (s, 3H), 1.16 (m, 1H), 1.04 (s, 3H), 1.03−0.92 (m, 2H), 0.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.3 (C), 154.2 (C), 136.3 (C), 126.2 (CH), 121.4 (CH), 120.8 (C), 114.9 (CH), 74.3 (C), 55.6 (CH), 48.3 (C), 48.3 (CH), 40.7(CH_2), 39.6 (CH_2), 38.4 (C), 33.9 (CH_2), 26.8 (CH_3), 24.3 (CH_3), 20.8 (CH_2), 19.2 (CH_3), 18.3 (CH_2), 17.6 (CH_2), 13.5 (CH_3). IR (film): 2931, 1716, 1467, 1261, 1168, 755, 665 cm^{-1}. HRMS−FAB (*m*/*z*): [M + Na^+] calcd for $C_{22}H_{30}O_2Na$, 349.2143; found, 349.2150.

(4a*S*,6a*S*,12b*S*)-4,4,6a,11,12b-Pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene (14). Solid KOH (30 mg) and hydrazine hydrate (0.6 mL) were added

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to a solution of aldehyde **24** (117 mg, 0.359 mmol) in ethylene glycol dimethyl ether (5 mL), and the mixture was heated at 190 °C with stirring for 24 h, at which time TLC showed no **24** remaining. Then, ether (25 mL) was added, and the organic phase was washed with water (10 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give a crude product, which was purified by column chromatography on silica gel (2% ether/hexanes) to afford benzopyran **14** (93 mg, 83%).

Treatment of Ester 20 with $CuBr_2$. $CuBr_2$ (800 mg, 3.62 mmol) was added to a solution of ester **20** (650 mg, 1.81 mmol) in acetonitrile (10 mL), and the mixture was stirred at 50 °C for 1 h. After evaporation under vacuum, ether (40 mL) was added, and the organic solution was washed with 2 N HCl (3 × 10 mL), water (3 × 10 mL) and brine, dried over anhydrous Na_2SO_4, and evaporated to give a crude product. This crude product was then purified by column chromatography on silica gel (5% ether/hexanes) to give a mixture of benzopyrans **25** and **22** (361 mg, 56%) in a 3:1 ratio. Running this mixture through column chromatography on silica gel with 1% ether/hexanes gives pure **25**.

(4*S*,4a*R*,6a*R*,12a*R*,12b*S*)-Methyl-4,6a,11,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1*H*-benzo[a]xanthene-4-carboxylate (25). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.99 (dd, J = 8.1, 7.3 Hz, 1H), 6.70 (d, J = 7.3 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 3.67 (s, 3H), 2.56 (dd, J = 16.7, 5.1 Hz, 1H), 2.33 (dd, J = 16.7, 13.4 Hz, 1H), 2.22 (s, 3H), 2.21 (m, 1H), 2.10 (dt, J = 12.7, 3.3 Hz, 1H), 2.04 (m, 1H), 1.97−1.67 (m, 3H), 1.66−1.48 (m, 4H), 1.23 (s, 3H), 1.18 (s, 3H), 1.19−0.97 (m, 2H), 0.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.48 (C), 152.71 (C), 137.17 (C), 126.33 (CH), 120.94 (CH), 120.76 (C), 114.53 (CH), 75.61 (C), 56.39 (CH_3), 51.28 (CH), 51.05 (CH), 43.57 (C), 40.89 (CH_2), 39.30 (CH_2), 37.60 (CH_2), 37.09 (C), 28.45 (CH_3), 21.04 (CH_2), 20.13 (CH_2), 19.97 (CH_3), 18.91 (CH_3), 18.85 (CH_2), 12.42 (CH_3). HRMS−FAB (m/z): [M + Na^+] calcd for $C_{23}H_{32}O_3Na$, 379.2249; found, 379.2242.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Obtention of the 8*S* configuration, which exhibits compound **14**, has been previously achieved through selenium- or palladium-induced cyclization. Cyclization of a drimenyl phenol utilizing $SnCl_4$ and NPSP was first reported by our group in the first synthesis of (+)-puupehenone (ref 4c). This method has since been utilized by other groups, see: (a) Hua, D. H.; Huang, X.; Chen, Y.; Battina, S. K.; Tamura, M.; Noh, S. K.; Koo, S. I.; Namatame, I.; Tomoda, H.; Perchellet, E. M.; Perchellet, J.-P. *J. Org. Chem.* **2004**, *69*, 6065−6078. (b) Gansäuer, A.; Rosales, A.; Justicia, J. *Synlett* **2006**, 927−929. Here, it must be noted that rearrangement has never been observed during this cyclization process.

(12) Previous investigations have revealed that acid cyclization of drimenyl phenols takes place with high diastereoselectivity, affording as the major, or even as the only, isomer the epimer benzopyran with the 8*R* configuration, which exhibits as compound **15**. For a study on this subject, see ref 4d.

(13) A similar benzylic oxidation has been utilized in the synthesis of 15-oxopuupehenol, which has the same absolute stereochemistry as compounds **10**, **16**, and **4**. This process takes places without isomerization. See ref 4h.

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