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Total synthesis of smenochromene B through ring contraction

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Abstract—A total synthesis of racemic smenochromene B has been achieved. The synthesis proceeds through an unusual rearrangement of smenochromene D with concomitant ring contraction and double bond isomerization.

1. Introduction

Natural products derived from farnesylated hydroquinones are relatively common (Fig. 1). Simple representatives of this class such as farnesyl hydroquinone (**1**)[1] and its more highly oxygenated congener **2**[2] have been found mostly in plants. By contrast, cyclofarnesylated compounds, such as the longithorols (**3** and **4**) and longithorones (**5**–**7**),[3] appear to have been isolated exclusively from marine organisms.

The smenochromenes and likonides form an interesting variant of this family (Fig. 2). The former, compounds **8**–**11**, were initially isolated by Faulkner and Clardy in 1991 from a Seychelles sponge of the genus *Smenospongia*.[4] In 2004, Kashman reported the isolation of likonides A (**12**) and B (**13**) from the Kenyan sponge *Hyatella* sp. and established their structure and absolute configuration.[5] Our subsequent synthetic studies led to the conclusion that likonide B (**13**) is identical to smenochromene D (**11**), with the exception of its absolute configuration.[6]

Structurally, the smenochromenes are marked by a highly electron-rich chromene system fused to a 16-membered macrocyclic ether or 14-membered carbocyclic ring system. Their individual members are further diversified through variations in their double bond geometries and catechol O-alkylation pattern. The macrocyclic ring is contracted in likonide A, which features a strained 12-membered ring including an (*E*) double bond.

Interestingly, smenochromene A was isolated as a racemate, whereas smenochromenes B, C, D, and the likonides were found to be optically active. Presumably, smenochromene A can undergo racemization through oxa-6π electrocyclic ring opening, followed by ring slip of the resultant macrocyclic ansa *ortho*-quinone methide and subsequent ring closure through electrocyclization.

Biosynthetically, the smenochromenes and likonides may arise through various cyclizations of the common farnesyl hydroquinone precursor **2** (Scheme 1). Dehydrogenation of

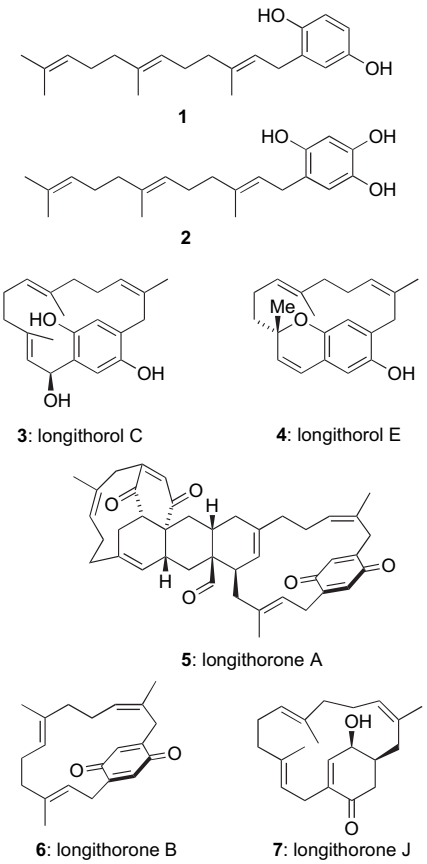

Figure 1. Natural products derived from farnesylated hydroquinones.

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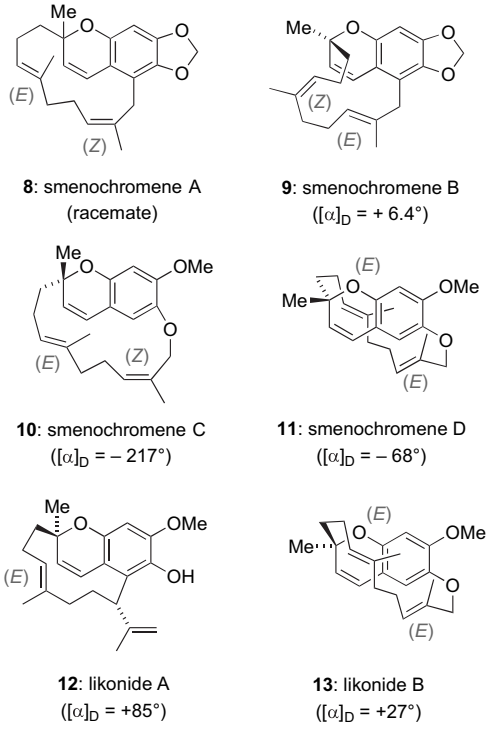
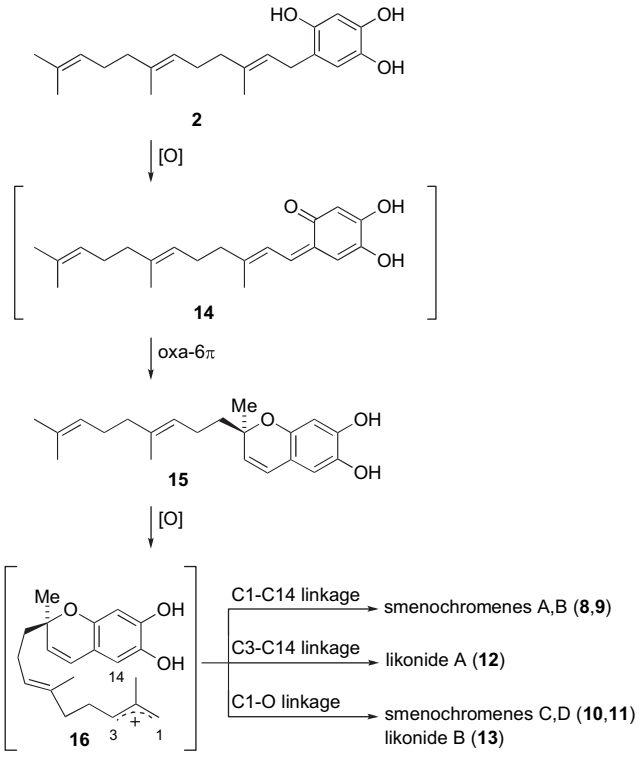


Figure 2. The smenochromenes and likonides.

this compound could afford vinyl *ortho*-quinone methide **14**, whose oxa-6π electrocyclization yields chromene **15** featuring the hydroxychromene core of the smenochromenes.[7] Further oxidation of the terminal allylic position then leads to an allylic cation **16**, which can undergo cyclization through various modes. Linkage between C1 and C14 affords the 14-membered carbocycle smenochromene A, and, after isomerization of the $\Delta^{6,7}$-double bond, smenochromene B. Conversely, bond formation between C1 and the phenolic oxygen leads to the 16-membered heterocyclic system of smenochromenes C and D. Finally, likonide A appears to arise from nucleophilic attack of C14 onto the C3 end of the allylic cation.

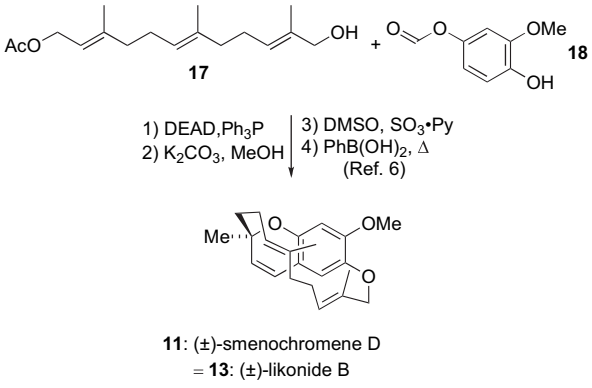


Scheme 1. Proposed biosyntheses of the smenochromenes and likonides.

2. Total synthesis of smenochromene D (likonide B)

We have recently described a short total synthesis of (±)-smenochromene D through an unprecedented macrocyclic chromene formation.[6] With sufficient quantities of the natural product in hand, we set out to explore its conversion to other members of the family. A straightforward synthesis of likonide A (**12**) would involve an intramolecular aromatic Claisen rearrangement of smenochromene D (**11**). So far, however, attempts to promote the [3,3]-sigmatropic rearrangement have been unsuccessful. Nevertheless, our studies have resulted in the discovery of an unusual ring contraction, which ultimately resulted in a total synthesis of smenochromene B (**9**).

The 16-membered macrocyclic ether smenochromene D (**11**) was prepared, as previously described,[6] in a four-step sequence starting from hydroxyfarnesyl acetate **17** and formate **18**, the product of Baeyer–Villiger oxidation of vanillin (Scheme 2, Supplementary data). While repeating this sequence, we obtained crystals that were suitable for X-ray analysis. The X-ray structure of synthetic (±)-smenochromene D is depicted in Figure 3. The compact, twisted architecture of this highly strained ansa-terpenoid is clearly visible from the projections shown. In view of this structure, the relatively low chemical shift of the C20 methyl group (δ 1.39 ppm) can be readily explained with the magnetic anisotropy exerted by the aromatic ring.



Scheme 2. Synthesis of smenochromene D.

3. Attempted conversion to likonide A and total synthesis of smenochromene B

With ample supplies of smenochromene D in hand, we sought to promote the envisioned [3,3]-sigmatropic rearrangement by heating the compound in diethyl aniline (Scheme 3). Under these conditions, which are typical for aromatic Claisen reactions, no traces of likonide A could

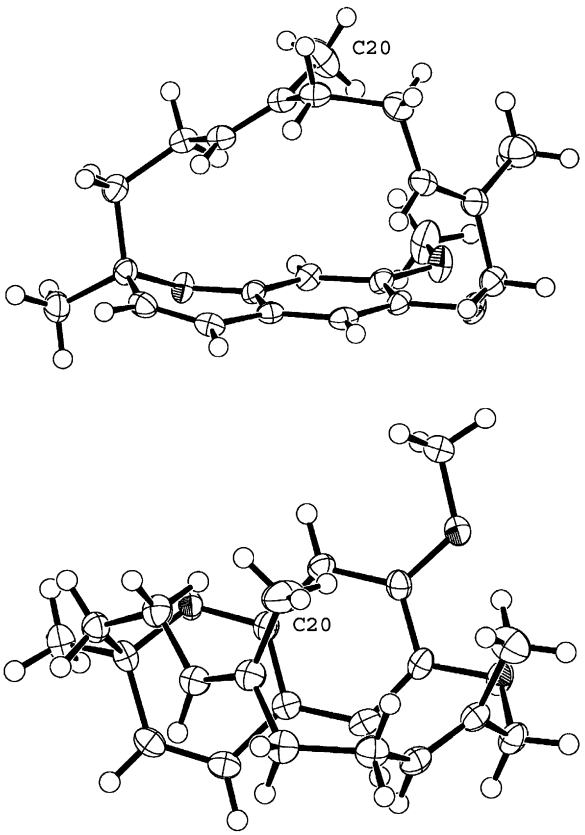


Figure 3. X-ray structure of racemic smenochromene D (likonide B).

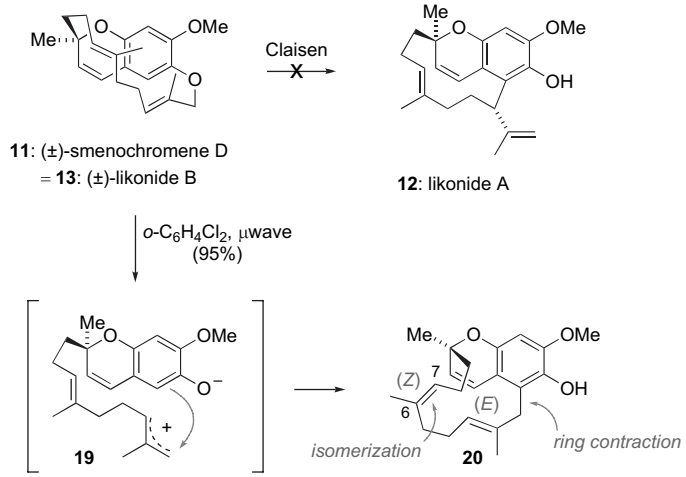
be detected. Instead, we isolated compound **20** in ca. 10% yield. Subsequently, we found that microwave irradiation of smenochromene D in *o*-dichlorobenzene gave **20** in excellent yield (95%).

Although a biradical mechanism cannot be ruled out, this ring contraction presumably involves ionization to afford zwitterion **19**, which then recombines with concomitant C,C-bond formation to afford macrocycle **20**. Note, however, that the formation of **20** not only involves a 1,3-migration of a single bond but also entails the isomerization of the $\Delta^{6,7}$-double bond. By contrast, the stereochemistry of the $\Delta^{2,3}$-double bond is retained. The precise order of the single bond migration and double bond isomerization remains unknown. We were never able to isolate a stereoisomer with a $\Delta^{6,7}$-(*E*) double bond as a possible intermediate en route to **20**.

Thermodynamically, the rearrangement appears to be driven by a decrease in ring strain as the 16-membered cyclic ether containing one (*Z*)- and two (*E*)-configured double bonds isomerizes to a 14-membered carbocycle with one (*E*)- and two (*Z*)-configured double bonds. Simple molecular mechanics calculations with Macromodel™ determined the relative energy between **11** and **20** to be $E_{rel}=-10.1$ kcal mol^{-1}.[8] In principle, it is possible that this rearrangement is biomimetic and that the smenochromenes C and D are biosynthetic precursors of smenochromenes A and B. It appears more likely, however, that **10** and **11** are formed directly through the intermediacy of an enzyme-bound carbocation **16** (cf. Scheme 1).

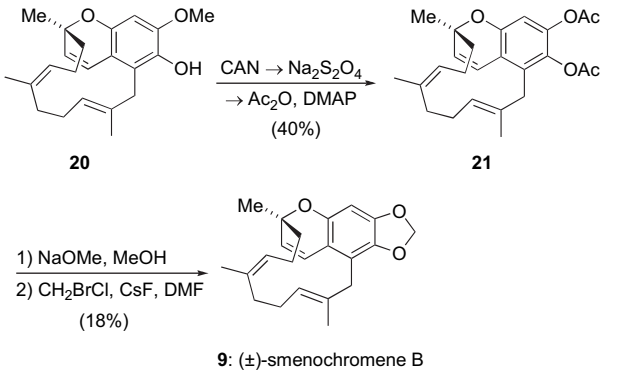
By contrast, molecular mechanics calculations using Macromodel™ suggest that the isomerization of smenochromene D to likonide A is thermodynamically less favorable ($E_{rel}=-4.3$ kcal mol^{-1}) at ambient pressure.

The unexpected inversion of the $\Delta^{6,7}$-double bond geometry was ultimately confirmed by the conversion of **20** into smenochromene B (**9**, Scheme 4). In principle, this transformation could be achieved by biomimetic oxidation of the phenolic methyl ether to the corresponding carboxonium ion, followed by interception of this species by the proximate phenolic hydroxy group. Unfortunately, we were unable to find conditions suitable to emulate this biosynthetic step. Despite extensive efforts, attempts to cleave the methyl ether in **20** to obtain the corresponding catechol directly were equally unsuccessful. Consequently, we resorted to demethylative CAN-oxidation to the corresponding *o*-benzoquinone,[9] followed by reduction to catechol and acetylation, which yielded the more tractable diacetate **21**. Zemplén saponification, followed by treatment of the resultant unstable catechol with bromochloromethane and a base finally gave smenochromene B (**9**) in low overall yield.[10] With the exception of its optical activity, the physical data



Scheme 3. Rearrangement of smenochromene D.

derived from synthetic smenochromene B matched those reported for the natural product.



Scheme 4. Total synthesis of smenochromene B.

4. Conclusion

In summary, we have achieved concise syntheses of smenochromenes D and B, which hinge on an unprecedented macrocyclization and ring contraction, respectively. Our work demonstrates the possibility of interconverting members of the smenochromene family and sheds light on synthetic strategies toward likonide A. Future investigations will be aimed at the asymmetric synthesis of these natural products.

5. Experimental

5.1. General methods

Unless otherwise noted, all reactions were monitored with Merck silica gel 60 F_{254} plates and visualized with 254 nm light, iodine on silica, or a charring solution of ceric ammonium molybdate. Flash chromatography was carried out using 32–63 D 60 Å silica gel. Toluene (PhMe) and methylene chloride (CH_2Cl_2) were purified according to the procedure described by Bergman.[11] Triethylamine (Et_3N) was distilled from CaH_2 and used immediately. Hexamethylphosphoramide (HMPA) was distilled from CaH_2 and stored over 4 Å molecular sieves. Unless otherwise noted, all other chemicals were used as obtained from commercial sources. Reactions were carried out under either argon or nitrogen atmosphere and magnetically stirred in an oven-dried glassware. All organic extracts were washed with brine, dried over magnesium sulfate, and filtered over Celite; solvents were then removed with a rotary evaporator at aspirator pressure. Unless otherwise noted, all NMR spectra were measured in deuterated chloroform ($CDCl_3$) with Bruker AM, DRX, or AVQ spectrometers at 400 MHz and 500 MHz for ^{1}H spectra and 100 MHz and 125 MHz for ^{13}C spectra. X-ray crystal structures were obtained from the CHEX-ray facility operated by the College of Chemistry, University of California at Berkeley. All infrared spectra were obtained by thin film on NaCl plates with a Nicolet Magna-IR 850 spectrometer. Low and high resolution mass spectra (LRMS and HRMS) were obtained using the Micro-Mass Facility operated by the College of Chemistry, University of California at Berkeley, using electron impact (EI+) at 70 eV or fast atom bombardment (FAB). Melting points were obtained using an electrothermal apparatus and are uncorrected. For compounds without elemental analysis data, ^{1}H NMR spectra are provided at the end of this document to substantiate purity.

5.2. Smenochromene D (11)

To a solution of farnesyl acetate alcohol **17** (140 mg, 0.500 mmol) in THF (5 mL) were added first formate **18** (114 mg, 0.750 mmol), then triphenylphosphine (1.58 g, 6.0 mmol), and finally DEAD (0.10 mL, 0.750 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight (14 h) at which time it was diluted with 5 mL of ether. This mixture was then washed with aqueous $NaHSO_4$ (20% wt:vol), aqueous NaOH (10% wt:vol), and brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by column chromatography (30% EtOAc in hexanes) to afford 154 mg (75%) of acetic acid (2*E*,6*E*,10*E*)-12-(4-formyloxy-2-methoxy-phenoxy)-3,7,11-trimethyl-dodeca-2,6,10-trienyl ester (**S1**, see Supplementary data) as a yellow oil. R_f 0.25 (30% EtOAc in hexanes, CAM); IR: 2930, 2849, 1738, 1507 cm^{-1}; ^{1}H NMR δ 8.27 (s, 1H), 6.55 (d, J=8.8 Hz, 1H), 6.22 (dt, J=8.8, 2.8 Hz, 2H), 5.49 (t, J=7.2 Hz, 1H), 5.33 (t, J=7.2 Hz, 1H) 5.08 (t, J=6.4 Hz, 1H), 4.57 (d, J=6.8 Hz, 2H), 4.43 (s, 2H), 3.38 (s, 3H), 2.11 (m, 11H), 1.7 (d, J=10 Hz, 6H), 1.58 (s, 3H); ^{13}C NMR δ 171.1, 159.7, 150.2, 146.6, 143.6, 142.2, 135.0, 130.7, 128.8, 123.9, 118.2, 113.8, 112.2, 105.4, 75.4, 61.3, 56.0, 39.4, 39.0, 26.3, 26.1, 21.0, 16.4, 16.0, 13.8; HRMS (EI+) *m/z* calcd for $C_{25}H_{34}O_6$: 430.2355; found: 430.2366.

To a solution of acetic acid (2*E*,6*E*,10*E*)-12-(4-formyloxy-2-methoxy-phenoxy)-3,7,11-trimethyl-dodeca-2,6,10-trienyl ester (**S1**, 4.64 g, 11.5 mmol) in MeOH (200 mL) was added potassium carbonate (2.23 g, 16.1 mmol). After 2 h the solution was concentrated in vacuo, the residue was taken up in ether and washed with water. The aqueous layer was acidified by addition of 2 M HCl until the pH of the solution was approximately 3, and then extracted with ether. The organic layers were combined, washed with brine, dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc in hexanes) to afford 3.88 g (94%) of 4-[(2*E*,6*E*,10*E*)-12-hydroxy-2,6,10-trimethyl-dodeca-2,6,10-trienyloxy]-3-methoxy-phenol (**S2**, see Supplementary data) as a yellow oil. R_f 0.18 (30% EtOAc in hexanes, CAM); IR: 3357, 2921, 1510, 1453 cm^{-1}; ^{1}H NMR δ 6.71 (d, J=8.4 Hz, 1H), 6.44 (d, J=2.8 Hz, 1H), 6.29 (dd, J=8.4, 2.8 Hz, 1H), 6.1–5.73 (s, 1H), 5.42 (q, J=7.2 Hz, 2H), 5.07 (t, J=5.6 Hz, 1H), 4.38 (s, 2H), 4.17 (d, J=6.8 Hz, 2H), 3.77 (s, 3H), 2.06 (m, 9H), 1.68 (d, J=18.8 Hz, 6H), 1.59 (s, 3H); ^{13}C NMR δ 150.8, 150.7, 141.9, 140.0, 134.8, 131.3, 128.3, 124.1, 122.9, 116.0, 105.9, 100.7, 76.2, 59.3, 55.7, 39.4, 39.0, 26.2, 26.0, 16.3, 15.8, 13.8; HRMS (EI+) *m/z* calcd for $C_{22}H_{32}0_4$: 360.2300; found: 360.2308; Anal. Calcd for $C_{22}H_{32}0_4$: C, 73.30; H, 8.95. Found C, 73.06; H, 8.85.

To a solution of 4-[(2*E*,6*E*,10*E*)-12-hydroxy-2,6,10-trimethyl-dodeca-2,6,10-trienyloxy]-3-methoxy-phenol (**S2**, 3.88 g, 10.7 mmol) in THF (30 mL) was added Et_3N (12 mL, 86.1 mmol) followed by DMSO (90 mL). Over the next 10 min, sulfur trioxide pyridine (5.14 g, 32.3 mmol) was

added in three portions. The reaction mixture was cooled to 0 °C after 3 h (white needle crystals formed), at which point 2 M HCl was added until the pH of the solution was approximately 3. The addition of aqueous HCl caused the solution to become cloudy. The reaction mixture was then extracted with three 50 mL portions of 1:1 EtOAc–Hex solution. The combined extracts were washed with three 100 mL portions of water and with 100 mL of brine. The organic layers were combined, washed with brine, dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford 3.34 g (87%) of (6*E*,10*E*)-11-((4-hydroxy-2-methoxyphenoxy)methyl)-3,7-dimethyldodeca-2,6,10-trienal (**S3**, see Supplementary data) as a 5:1 (*E*/*Z*) mixture with respect to the Δ^2-double bond (by NMR). All characterization data reported refer to this mixture. R_f 0.43 (50% EtOAc in hexanes); IR: 3384, 2918, 2886, 1671, 1509, 1198 cm^{-1}; ^1H NMR (400 MHz) δ 9.94 (d, J=8.3 Hz, 1H), 9.84 (d, J=8.3 Hz, 0.2H), 6.74–6.62 (m, 2.6H), 6.49–6.41 (m, 1.3H), 6.33–6.26 (m, 1.1H), 5.88 (d, J=8.2 Hz, 1.3H), 5.41 (t, J=6.8 Hz, 1.3H), 5.03 (t, J=6.4 Hz, 1.1H), 4.37 (s, 0.2H), 4.33 (s, 2.2H), 3.75 (s, 3.7H), 3.66 (s, 0.3H), 2.55 (t, J=7.4 Hz, 0.4H), 2.31 (s, 0.4H), 2.26–2.05 (m, 10.7H), 2.00–1.92 (m, 3.5H), 1.69 (s, 3.3H), 1.65 (s, 0.5H); ^{13}C NMR (125 MHz) δ 191.8, 191.7, 165.2, 165.1, 151, 150.6, 141.8, 136.8, 136.0, 131.4, 131.3, 128.4, 128.3, 128.1, 128.0, 127.2, 127.1, 122.6, 122.2, 116.2, 116.0, 105.9, 100.7, 76.3, 76.2, 55.8, 55.6, 40.5, 40.2, 38.9, 33.8, 32.5, 26.9, 26.0, 25.6, 25.5, 17.6, 17.4, 15.8, 14.2, 13.8, 13.7; HRMS (EI+) *m*/*z* calcd for $C_{25}H_{30}O_4$: 358.21441; found: 358.2138.

To a solution of (6*E*,10*E*)-11-((4-hydroxy-2-methoxyphenoxy)methyl)-3,7-dimethyldodeca-2,6,10-trienal (**S3**, 20.0 mg, 0.0558 mmol) in toluene (4 mL) were added phenylboronic acid (14.0 mg, 0.0837 mmol) and acetic acid (0.400 mL). The reaction mixture was then fitted with a Dean–Stark apparatus and heated under reflux for 3 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by column chromatography (10% EtOAc in hexanes, CAM) to afford 4.9 mg (26%) of smenochromene D (**11**) as a clear oil. R_f 0.26 (10% EtOAc in hexanes); IR: 3394, 2921, 2852, 1616, 1505 cm^{-1}; ^1H NMR δ 6.52 (s, 1H), 6.31 (d, J=12.8 Hz, 1H), 6.29 (s, 1H), 5.31 (d, J=12.8 Hz, 1H), 4.93 (t, J=7.2 Hz, 1H), 4.82 (t, J=8 Hz, 1H), 4.52 (d, J=15.2 Hz, 1H), 4.14 (d, J=15.2 Hz, 1H), 3.76 (s, 3H), 2.09 (m, 4H), 1.77 (m, 2H), 1.69 (s, 3H), 1.58 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 153.4, 150.3, 139.3, 132.0, 131.8, 129.8, 126.6, 125.8, 123.5, 119.1, 113.3, 99.9, 80.3, 79.0, 55.6, 41.4, 38.9, 30.2, 24.6, 23.1, 14.4, 14.1; HRMS (EI+) *m*/*z* calcd for $C_{22}H_{28}O_3$: 340.2038; found: 340.2033.

5.3. (7*E*,11*Z*)-3-Methoxy-7,11,15-trimethyl-19-oxa-tricyclo[13.3.1.0]nonadeca-1,3,5(18),7,11,16-hexaen-4-ol (20)

A solution of smenochromene D (**11**, 90.5 mg, 0.266 mmol) in *o*-dichlorobenzene (10 mL) was degassed by bubbling N_2 for 10 min. The vial was sealed and heated via microwave irradiation while stirring for 3.5 h. Heating to a maximum temperature of 163 °C required 1 h, although the temperature rose to 150 °C after less than 30 min. The solution color changed from colorless to light brown over the course of the heating. The solution was concentrated in vacuo and purified via column chromatography (10% EtOAc in hexanes) to afford 85.5 mg (95%) of **20** as a white solid, mp 115 °C. R_f 0.24 (10% EtOAc in hexanes); IR: 3522, 2923, 2852, 2484, 1613 cm^{-1}; ^1H NMR (400 MHz) δ 6.36 (s, 1H), 6.26 (d, J=9.6 Hz, 1H), 5.49 (d, J=9.6 Hz, 1H), 5.29 (s, 1H), 5.29 (t, J=7.2 Hz, 1H), 4.70 (t, J=8 Hz, 1H), 3.88 (s, 3H), 3.69 (d, J=16 Hz, 1H), 3.06 (d, J=16 Hz, 1H), 2.03 (m, 8H), 1.74 (s, 3H), 1.54 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz) δ 146.5, 146.2, 137.4, 132.7, 132.5, 127.5, 126.4, 123.8, 121.7, 121.0, 115.1, 98.3, 77.6, 55.9, 39.8, 37.9, 33.3, 27.0, 24.7, 22.5, 17.0, 14.4; HRMS (EI+) *m*/*z* calcd for $C_{22}H_{28}O_3$: 340.2041; found: 340.2038.

5.4. Acetic acid (7*E*,11*Z*)-4-acetoxy-7,11,15-trimethyl-19-oxa-tricyclo[13.3.1.0]nonadeca-1,3,5(18),7,11,16-hexaen-3-yl ester (21)

To a solution of **20** (38.8 mg, 0.114 mmol) in 3:1 acetonitrile–H_2O (9 mL) was added a solution of ammonium cerium(IV) nitrate (188.9 mg, 0.345 mmol) in H_2O (2.5 mL) over 1 min at 0 °C. The solution color changed from colorless to dark orange. After 15 min the reaction was warmed to rt and 0.25 M aqueous $Na_2S_2O_4$ (2.5 mL) was added. The solution immediately turned light yellow. The reaction mixture was then extracted with three 10 mL portions of EtOAc, to which DMAP (16.7 mg, 0.137 mmol) and Ac_2O (0.1 mL, 1.06 mmol) were added. After 1.5 h, the mixture was dried, filtered, and concentrated in vacuo. The product was purified via column chromatography (10% EtOAc in hexanes) to afford 18.5 mg (40%) of **21** as a colorless oil. R_f 0.58 (30% EtOAc in hexanes); IR: 2977, 2931, 2853, 1774, 1209 cm^{-1}; ^1H NMR (400 MHz) δ 6.57 (s, 1H), 6.20 (d, J=10 Hz, 1H), 5.54 (d, J=10 Hz, 1H), 5.18 (t, J=6.9 Hz, 1H), 4.67 (t, J=6.7 Hz, 1H), 3.20 (d, J=16 Hz, 1H), 3.07 (d, J=16 Hz, 1H), 2.26 (s, 3H), 2.23 (s, 3H), 2.21–2.09 (m, 3H), 2.09–1.82 (m, 4H), 1.80–1.69 (m, 1H), 1.63 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz) δ 168.68, 168.05, 151.42, 141.87, 134.29, 132.726, 131.50, 129.11, 128.87, 127.35, 125.42, 120.96, 119.85, 109.60, 78.34, 39.56, 39.22, 34.59, 27.54, 24.69, 22.57, 20.70, 20.30, 16.95, 14.44; HRMS (EI+) *m*/*z* calcd for $C_{25}H_{30}O_5$: 410.2093; found: 410.2090.

5.5. Smenochromene B (9)

To a solution of **21** (4.5 mg, 0.011 mmol) dissolved in MeOH (1 mL) was added 0.01 M NaOMe in MeOH (0.5 mL). The solution color changed from colorless to dark orange/red. After 1 h the solution was concentrated in vacuo, without exposing the reddish substrate to air. The residue was then dissolved in 1 mL of DMF, and 45 mg of CsF was added. The solution then darkened to black, at which point 0.1 M CH_2BrCl in DMF (0.1 mL) was added. The stirred solution was heated to 115 °C for 16 h under N_2. The mixture was quenched with 30 mL of H_2O, extracted with three 10 mL portions of Et_2O, dried, filtered, and concentrated in vacuo. The product was purified via column chromatography (5% EtOAc in hexanes) to afford 0.8 mg (18%) of smenochromene B as a colorless oil. R_f 0.34 (5% EtOAc in hexanes); IR: 2921, 1620, 1462, 942 cm^{-1}; see the table for comparison of carbon and hydrogen NMR

spectra in the Supplementary data. HRMS (EI+) *m*/*z* calcd for $C_{22}H_{26}O_3$: 338.1882; found: 338.1878.

Acknowledgements

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Supplementary data

Crystallographic data for smenochromene D (**9**) have been deposited at the Cambridge Crystallographic Data Centre (CCDC 621771). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.069.

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