Tetrahedron Letters 51 (2010) 5757–5760

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of hemigossypol and its derivatives

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ARTICLE INFO

Article history:
Received 11 August 2010
Revised 27 August 2010
Accepted 30 August 2010
Available online 6 September 2010

Keywords:
Hemigossypol
Gossypol
Hemigossylic lactone

ABSTRACT

Hemigossypol (**3**), a sesquiterpene natural product, was previously isolated from *Gossypium barbadense* and was shown to display improved anti-fungal activity compared to gossypol (**1**), the disesquiterpene dimer of hemigossypol (**3**). Gossypol exhibits multiple biological activities. In order to study whether hemigossypol and its derivatives retain the various bioactivities of gossypol, we developed a short and convenient synthetic scheme to synthesize hemigossypol. This is the first de novo synthesis of this natural product. In addition derivatives of hemigossypol with various 2,5-alkyl substituents were synthesized. Modification of the synthetic scheme also afforded the natural product hemigossylic lactone (**4**) and its 2,5-substituted derivatives.

Gossypol (**1**), a natural product from cottonseed, is a disesquiterpene exhibiting atropisomerism owing to restricted rotation around the binaphthyl bond (Fig. 1). Gossypol exhibits multiple biological properties, including spermicidal,[1] antiparasitic,[2] anticancer,[3] and antiviral activities.[4] Gossypol displays potent inhibition against anti-apoptotic Bcl-2 family proteins where it functions as a BH3 mimic.[5] (−)-Gossypol is currently in phase II clinical trails, displaying single-agent antitumor activity in patients with advanced malignancies.[6,7] Multiple bioactivities of gossypol have stimulated wide interest in the development of gossypol derivatives to explore structure–activity relationships.[8–13] We have previously reported that gossylic lactone (**2**)[9] (Fig. 1), in which the aldehyde groups of gossypol that contribute to toxicity have been modified, retains antimalarial activity and exhibits enhanced inhibitory activity compared to gossypol against aldose reductase, an enzyme implicated in the etiology of diabetic complications.[9,14]

The question of interest is whether hemigossypol (**3**) and hemigossylic lactone (**4**) (Fig. 1), the monomers of gossypol and gossylic lactone, respectively, still retain the various bioactivities of gossypol. Hemigossypol, a natural product isolated from the *verticillium*-infected stele tissue of *Gossypium barbadense*,[15] is at least threefold more toxic to the cotton seedling disease pathogen, *Rhizoctonia solani*, than gossypol.[16] Furthermore, it was reported that methylated hemigossypol displayed comparable spermicidal activity as gossypol.[17] Hemigossylic lactone with a methoxy group on position six is a natural product isolated from the root bark of *Bombax malabarium*;[18] however, bioactivity has not been reported. In order to explore SAR of hemigossypol and hemigossylic lactone, we developed a short and convenient synthetic scheme to synthesize hemigossypol and its 2,5-alkyl-substituted derivatives. Modification of the synthetic scheme also afforded hemigossylic lactone and its 2,5-alkyl-substituted derivatives.

Synthetic Scheme 1 features the incorporation of the carbon atoms for the second ring of the naphthalene system in one step by the reaction of the Grignard reagent formed from 1-bromo-2-isopropyl-3,4-dimethoxybenzene (**5a**) and 1-bromo-3,4-dimethoxy-2-propylbenzene (**5c**) with ethyl 3-methyl-4-oxobutanoate (**6a**) and ethyl 2,3-dimethyl-4-oxobutanoate (**6b**) to form lactones **7a**, **7b**, and **7c** in 63–70% yield.[19] The precursor bromides are readily prepared from commercially available starting materials using procedures described in the literature.[20–22] In some preparations of the bromides using the Edward's procedure[22] small amounts

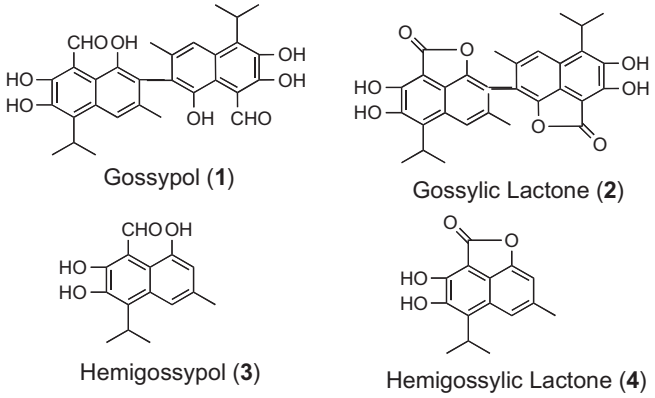

Figure 1.

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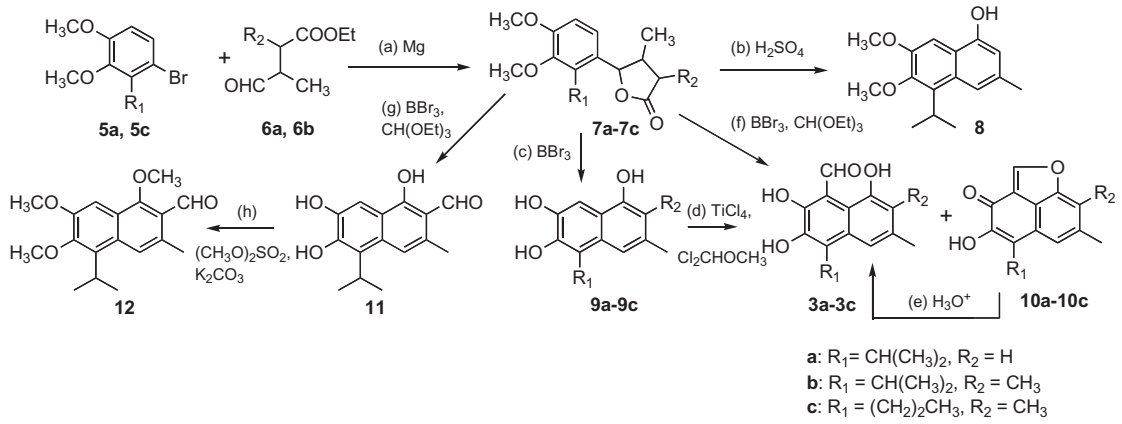
doi:10.1016/j.tetlet.2010.08.089



Scheme 1. Synthesis of hemigossypol. Reagents and conditions: (a) Mg (3 equiv), $BrCH_2CH_2Br$ (0.1 equiv), THF, reflux, 1.0 h then **6** (1.2 equiv), 0 °C to rt, 12 h, H_2O/HCl, rt, 5 h, 70% of **7a**, 66% of **7b**, 63% of **7c**; (b) concentrated sulfuric acid, rt, 60 °C, 2.0 h, 5%; (c) BBr_3 (5 equiv), CH_2Cl_2, 2.0 h, −78 °C, 24 h, rt, 90% of **9a**, 70% of **9b**, 81% **9c**; (d) $TiCl_4$ (5 equiv), Et_2O/CH_2Cl_2, 0 °C, 15 min, then Cl_2CHOCH_3 (2 equiv), 0 °C, 3 h, rt, 18 h, 16% of **3a**, 10% of **3b**, 20% of **3c**, and 4% of **10a**, 34% of **10b**, 25% of **10c**; or **9b**, hexamethylenetetramine (0.5 equiv), HAc, 100 °C, 1.0 h, then H_2SO_4/H_2O, 60 °C, 2 h, 25% **10b**; (e) CH_3CN/H_2O, 6 M HCl, rt, 18 h, 90% of **3b**, 100% of **3c**; (f) BBr_3 (7 equiv), CH_2Cl_2, 0 °C, then reflux 3 h, 0 °C, $CH(OC_2H_5)_3$ (6 equiv), reflux, 1.0 h, rt, 24 h, 10% of **10b** from **7b**, 10% of **10c** from **7c**; (g) BBr_3 (5 equiv), CH_2Cl_2, 0 °C, reflux, 3 h, then $CH(OC_2H_5)_3$ (6 equiv), 0 °C, reflux, 1 h, rt, 24 h, 25%; (h) $(CH_3O)_2SO_2$ (6.5 equiv), K_2CO_3 (6.5 equiv), $(CH_3)_2C{=}O$, reflux, 24 h, 90%.

(5–10%) of the isomeric bromides 5-bromo-3-alkyl-1,2-dimethoxybenzene were formed.[23] An alternate highly regioselective silica gel catalyzed bromination, using *N*-bromosuccinimide proved more effective.[24] The precursors ethyl 3-methyl-4-oxobutanoate (**6a**) and ethyl 2,3-dimethyl-4-oxobutanoate (**6b**) were prepared by a Horner–Emmons–Wadsworth reaction followed by hydrogenation of the alkene bond and hydrolysis of the resulting acetal as previously described.[25,26] In our hands hydrogenation using palladium on charcoal resulted in loss of a methoxy group of the acetal but use of palladium on calcium carbonate gave the desired acetal, which was then hydrolyzed.

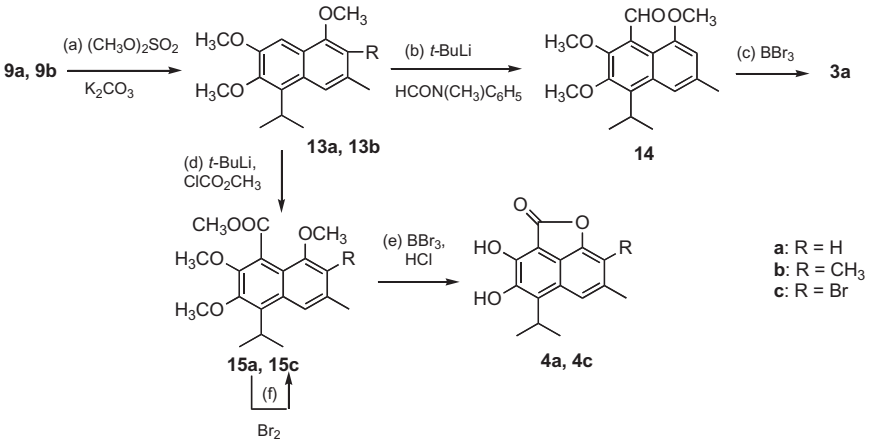
In the synthesis of gossypol performed by Venuti[27] compound **5a** was transformed to naphthalenol compound **8** in six steps. In one of the steps Venuti proposed compound **7a** as an intermediate, but it was never isolated. We envisioned that lactone **7a** could be converted to naphthalenol **8** in one step using a strong Lewis acid which would cause the opening of the lactone ring followed by Friedel–Crafts cyclization of the resulting acid, dehydration, and aromatization.[28] Attempts using dilute hydrochloric acid, phosphorous trichloride, or titanium tetrachloride failed and concentrated sulfuric acid afforded only 5% of the product. However lactones **7a–7c** were successfully converted to naphthalenols **9a**–**9c** using boron tribromide in 70–90% yield.[29] Compound **9a** is slightly unstable and degrades during chromatography. The aldehyde group was introduced by formylation of naphthalenols **9a**–**9c** with titanium tetrachloride and dichloromethyl methyl ether[30,31] followed by hydrolysis, to successfully afford the natural product hemigossypol **3a** and its derivatives **3b** and **3c** in moderate yield.[32] The proton NMR spectrum of compound **3a** generally agreed with the literature.[15] Anhydrohemigossypol **10a** has been observed in the mass spectrum of hemigossypol[15] and anhydrogossypol, the dimer of compound **10a**, is well documented in the literature.[33,34] The proton NMR spectrum of anhydrohemigossypol **10a** and its derivatives **10b** and **10c** is similar to that of anhydrogossypol.[35] The anhydro compounds **10a–10c** could be converted back to aldehydes **3a–3c** using dilute hydrochloric acid in acetonitrile.

Alternate synthetic methods for the formation of compounds **3** from naphthalenols **9a** and **9b** were investigated in hopes of increasing the yield of product. Vilsmeier and *N*,*N*-diphenylformamidine methods did not afford product.[36–38] The Duff reaction, which involves the use of hexamethylenetetramine in the presence of acetic acid, on compound **9b** gave the dehydrated compound **10b** in a 25% yield.[39] These disappointing results led to the one pot reaction of compound **7a** with boron tribromide followed by triethylorthoformate to give compound **11** in 25% yield.[40] Unfortunately, compound **11**[41] is the 2-formyl regioisomer of compound **3** and its structure was verified by methylation to give the known compound **12**.[17] Using the same conditions on compound **7b**, which has a methyl group in position two, 10% of compound **10b** was obtained.

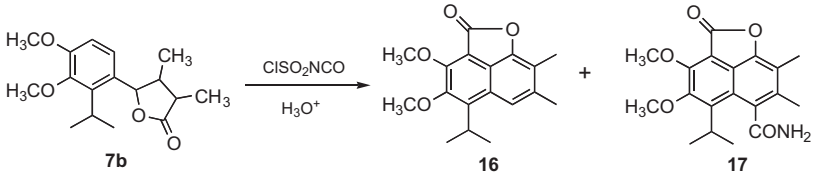
Since formylation of naphthalenols **9** resulted in poor yields of product, compounds **9a** and **9b** were methylated using dimethylsulfate to give compounds **13a** and **13b**.[42] (Scheme 2). Formylation reactions on the dimeric (5,5′-diisopropyl-1,1′,6,6′,7,7′-hexamethoxy-3,3′-dimethyl-2,2′-binaphthalene) and the monomeric form of compound **13a** have been published by Meltzer.[37] Meltzer found that bisformylation and concomitant loss of both isopropyl groups occurred on reaction of the dimeric form of compound **13a** using titanium tetrachloride and dichloromethyl methyl ether. Identical treatment of the monomeric compound, **13a**, resulted in formylation in the 8 position, peri to the isopropyl group. Using these same conditions we reacted compound **13b** and obtained a mixture of products with the major product lacking an isopropyl group. Fortunately, formylation of compound **13a** using *t*-butyllithium followed by the electrophile *N*-methylformanilide and hydrolysis gave a 49% yield of compound **14** (Scheme 2) whereas reaction of **13b** using these conditions failed to give the desired product.[17,43] Demethylation of compound **14** with boron tribromide[10] afforded an 80% yield of compound **3a**.

Synthesis of hemigossylic lactone **4a** and its derivative, **4c**, is similar to the synthesis of compound **14** except for the electrophile. The reaction of compound **13a** with *t*-butyllithium followed by methylchloroformate resulted in ester **15a**.[44] Bromination of compound **15a** gave bromide **15c**.[43,45] The methyl ether groups in compounds **15** were readily removed using boron tribromide and the resulting mixtures were gently refluxed in dilute hydrochloric acid to undergo intramolecular lactonization and afford lactones **4a** and **4c** in 71–80% yield.[46]

A one step transformation from the readily available intermediate **7b** to naphtholactone **16** is an attractive route to explore. Since lactones **7a–7c** have been successfully converted to naphthalenols **8** and **9a–9c** in one step using Lewis acids (Scheme 1), we further envisioned that chlorosulfonyl isocyanate (CSI),[47] a strong Lewis acid containing a reactive electrophilic isocyanate group, could convert lactone **7b** into naphtholactone **16** in one step. Treatment of compound **7b** with excess CSI followed by an acidic hydrolysis (Scheme 3) successfully afforded naphtholactone **16** in a 10% yield along with the unexpected amide compound **17** in 30% yield.[48] We



Scheme 2. Synthesis of hemigossylic lactone and derivatives. Reagents and conditions: (a) $(CH_3O)_2SO_2$ (13 equiv), K_2CO_3 (13 equiv), $(CH_3)_2C{=}O$, reflux, 85% of **13a** and **13b**; (b) *t*-BuLi (8 equiv), C_6H_{12}, 0 °C, 18 h then $HCON(CH_3)C_6H_5$ (2.5 equiv), 8 h, 49%; (c) BBr_3 (3 equiv), CH_2Cl_2, −78 °C, 1.0 h, 0 °C, 1.0 h, rt, 1.0 h, 80%; (d) *t*-BuLi (7 equiv), C_6H_{12}, 0 °C, then 18 h, rt, then $ClCOOCH_3$ (19 equiv), −10 °C, 8 h, 60% of **15a**; (e) BBr_3 (4 equiv), CH_2Cl_2, −78 °C, 1.0 h, 0 °C, 1.0 h, rt, 3 h, 6 M HCl, reflux, 3 h, 80% of **4a** and 71% **4c**; (f) Br_2 (1 equiv), $CHCl_3$, 0 °C, 2 h, 88% of **15c**.



Scheme 3. Synthesis of dimethylhemigossylic lactones. Reagents and conditions: (a) $ClSO_2NCO$ (9 equiv), CH_2Cl_2, rt, 24 h, then HCl/H_2O, EtOH, reflux, 1.0 h, 10% of **16** and 30% of **17**.

propose that initially the CSI acts as a Lewis acid and readily converts the lactone **7b** to the 2-methyl-substituted naphthalenol adduct of compound **8**. This naphthalenol adduct further reacts with the electrophilic carbonyl carbon in the CSI and hydrolysis using dilute acid causes intramolecular attack of the carbonyl by the peri hydroxyl group on position one resulting in the formation of lactone **16**. Amide **17** was formed by the reaction of CSI with the substituted naphthalenol at position four followed by acidic hydrolysis. Because of the brevity of this synthetic sequence and the promising results, reaction conditions are being investigated to improve the yield.

In conclusion, a short and convenient synthetic scheme was developed to afford the bioactive natural product hemigossypol **3a** and its 2,5-substituted derivatives **3b** and **3c**. The modification of the synthetic scheme afforded hemigossylic lactones **4a** and **4c** as derivatives of the natural product 3-methylhemigossylic lactone. Bioactivities of hemigossypol, hemigossylic lactones, and their derivatives are currently being investigated.

Acknowledgments

This research was supported in part by grant HL68598 from the National Institutes of Health. High resolution mass spectra (HRMS) were obtained at UNM Mass Spec Facility, Albuquerque, New Mexico.

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19. *Data for lactones* **7**: *dihydro-5-(2-isopropyl-3,4-dimethoxyphenyl)-4-methyl-2-furanone* **7a**: yellow oil; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.09 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 5.80 (d, J = 5.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.89 (m, 2H), 2.34 (d, 1H), 1.34 (d, J = 6.4 Hz, 3H), 1.33 (s, 3H), 0.66 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 176.1, 152.4, 148.2, 137.2, 125.6, 120.4, 109.7, 82.0, 60.3, 55.3, 37.8, 34.4, 28.4, 21.6, 21.2, 15.4. HRMS (EI) calcd for $C_{16}H_{22}O_4$ [M+H]+: 279.1596; found, 279.1592. *Dihydro-5-(2-isopropyl-3,4-dimethoxyphenyl)-3,4-dimethyl-2-furanone* **7b**: yellow oil; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.11 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 5.66 (d, J = 5.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.02 (m, 1H), 2.92 (m, 1H), 2.76 (m, 1H), 1.34 (t, J = 7.2 Hz, 6H), 1.21 (d, J = 7.2 Hz, 3H), 0.51 (d, J = 7.2 Hz, 3H); ^{13}C NMR: δ 178.4, 152.4, 148.3, 137.2, 125.6, 120.7, 109.7, 80.6, 60.5, 55.4, 41.0, 39.5, 28.5, 21.6, 21.3, 10.0, 9.8. HRMS (EI) calcd for $C_{17}H_{24}O_4$ [M+H]$^+$: 293.1753; found, 293.1744.

Dihydro-5-(3,4-dimethoxy-2-propylphenyl)-3,4-dimethyl-2-furanone **7c**: yellow oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.00 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 5.78 (d, J = 5.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.75 (m, 1H), 2.55 (m, 1H), 2.31 (m, 1H), 1.34 (m, 6H), 1.23 (m, 3H), 0.65 (m, 3H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 179.2, 151.2, 146.6, 134.0, 120.6, 109.8, 103.2, 77.3, 68.3, 60.4, 55.4, 34.3, 28.3, 26.1, 24.2, 14.5, 12.9. HRMS (EI) calcd for $C_{17}H_{24}O_4$ $[M+H]^+$: 293.1753; found, 293.1751.

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29. *Data for naphthalenols* **9**: *5-isopropyl-3-methyl-1,6,7-naphthalenetriol* **9a**: red oil; ^{1}H NMR ($CDCl_3$, 250 MHz) ^{1}H NMR: δ 7.41 (s, 1H), 7.37 (s, 1H), 6.48 (s, 1H), 5.92 (br s, 2H), 5.40 (br s, 1H), 3.84 (m, 1H), 2.33 (s, 3H), 1.44 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 143.1, 136.7, 135.4, 126.2, 122.7, 118.7, 110.9, 108.5, 102.0, 95.0, 19.8, 13.7, 7.9. HRMS (EI) calcd for $C_{14}H_{16}O_3$ $[M+H]^+$: 233.1177; found, 233.1122. *5-Isopropyl-3,4-dimethyl-1,6,7-naphthalenetriol* **9b**: light grey solid; mp 194–195 °C; ^{1}H NMR: (acetone-d_6, 250 MHz) δ 8.87 (br s, 1H), 7.48 (s, 1H), 7.41 (s, 1H), 7.37 (br s, 1H), 7.15 (br s, 1H), 3.84 (m, 1H), 2.36 (s, 3H), 2.26 (s, 3H), 1.46 (d, J = 7.2 Hz, 6H); ^{13}C NMR: (methanol-d_4, 250 MHz) δ 149.2, 145.2, 144.7, 133.3, 128.2, 125.7, 121.5, 116.8, 116.5, 102.8, 27.8, 21.5, 21.3, 12.2. HRMS (EI) calcd for $C_{15}H_{18}O_3$ $[M+H]^+$: 247.1334; found, 247.1332. *3,4-Dimethyl-5-propyl-1,6,7-naphthalenetriol* **9c**: light grey solid; mp 168–170 °C; ^{1}H NMR: (acetone-d_6, 250 MHz) δ 9.29 (s, 1H), 7.79 (s, 1H), 7.45 (s, 1H), 7.44 (s, 1H), 7.19 (s, 1H), 2.96 (m, 2H), 2.34 (s, 3H), 2.24 (s, 3H), 1.63 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR: (acetone-d_6, 250 MHz) δ 148.9, 144.0, 143.3, 132.7, 127.8, 120.1, 120.0, 115.4, 115.2, 102.5, 27.4, 23.2, 20.9, 14.1, 11.8. HRMS (EI) calcd for $C_{15}H_{18}O_3$ $[M+H]^+$: 247.1334; found, 247.1334.
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32. *Data for hemigossypols* **3**: *2,3,8-trihydroxy-4-isopropyl-6-methyl-1-naphthaldehyde* **3a**: yellow solid; mp 158–160 °C (lit.[15] 159–163 °C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 15.10 (s, 1H), 11.20 (s, 1H), 7.53 (s, 1H), 6.69 (s, 1H), 6.33 (s, 1H), 5.71 (s, 1H), 3.85 (m, 1H), 2.43 (s, 3H), 1.50 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 250 MHz): δ 199.3, 155.6, 151.6, 142.8, 134.2, 133.9, 129.5, 116.9, 114.4, 113.2, 111.6, 28.0, 21.6, 20.3. HRMS (EI) calcd for $C_{15}H_{16}O_4$ $[M+H]^+$: 261.1127; found, 261.1172. *2,3,8-Trihydroxy-4-isopropyl-6,7-dimethyl-1-naphthaldehyde* **3b**: yellow solid; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 15.21 (s, 1H), 11.23 (s, 1H), 7.57 (s, 1H), 6.29 (s, 1H), 5.42 (s, 1H), 3.85 (m, 1H), 2.45 (s, 3H), 2.33 (s, 3H), 1.50 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 199.2, 155.9, 149.5, 142.1, 134.1, 133.3, 126.9, 117.8, 117.4, 115.1, 113.4, 27.7, 20.0, 20.3, 11.8. HRMS (EI) calcd for $C_{16}H_{18}O_4$ $[M+H]^+$: 275.1283; found, 275.1328. *2,3,8-Trihydroxy-6,7-dimethyl-4-propyl-1-naphthaldehyde* **3c**: yellow solid; mp 194–195 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.47 (s, 1H), 7.29 (s, 1H), 7.05 (br s, 1H), 2.79 (t, J = 7.4 Hz, 2H), 2.47 (s, 3H), 2.44 (s, 3H), 1.70 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 175.0, 152.4, 149.3, 149.0, 135.5, 126.5, 123.6, 122.6, 120.7, 118.6, 117.0, 27.7, 22.5, 19.9, 14.4, 12.0. HRMS (EI) calcd for $C_{16}H_{18}O_4$ $[M+H]^+$: 275.1283; found, 275.1288.
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35. *Data for anhydrohemigossypols* **10**: *4-hydroxy-5-isopropyl-7-methyl-3-naphtho[1,8-bc]furan-3-one* **10a**: yellow oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.48 (s, 1H), 7.50 (s, 1H), 7.31 (s, 1H), 7.27 (s, 1H), 3.52 (m, 1H), 2.56 (s, 3H), 1.50 (d, J = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 175.3, 152.3, 149.1, 148.8, 135.2, 130.7, 123.2, 123.0, 120.4, 118.6, 116.7, 27.1, 19.8, 12.0. HRMS (EI) calcd for $C_{15}H_{14}O_3$ $[M+H]^+$: 243.1021; found, 243.0976. *4-Hydroxy-5-isopropyl-7,8-dimethyl-3-naphtho[1,8-bc]furan-3-one* **10b**: brown solid; mp 192–193 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.50 (s, 1H), 7.49 (s, 1H), 7.22 (s, 1H), 3.46 (m, 1H), 2.49 (s, 3H), 2.49 (s, 3H), 1.50 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 175.2, 152.5, 149.2, 148.8, 135.3, 130.8, 123.3, 123.1, 120.6, 118.6, 116.7, 27.1, 20.5, 19.9, 12.0. HRMS (EI) calcd for $C_{16}H_{16}O_3$ $[M+H]^+$: 257.1177; found, 257.1176. *4-Hydroxy-7,8-dimethyl-5-propyl-3-naphtho[1,8-bc]furan-3-one* **10c**: yellow solid; mp 163–165 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 15.17 (s, 1H), 11.24 (s, 1H), 7.35 (s, 1H), 6.12 (s, 1H), 5.38 (s, 1H), 3.02 (t, J = 7.6 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 3H), 1.66 (m, 2H), 1.04 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 200.1, 157.0, 151.1, 142.8, 134.8, 130.8, 128.1, 121.0, 117.8, 117.2, 112.8, 28.5, 23.3, 21.1, 14.6, 12.6. HRMS (EI) calcd for $C_{16}H_{18}O_4$ $[M+H]^+$: 257.1177; found, 257.1284.
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41. *Data for aldehyde* **11**: *1,6,7-trihydroxy-5-isopropyl-3-methyl-2-naphthaldehyde*: yellow solid; mp 160–161 °C; ^{1}H NMR (acetone-d_6, 500 Hz) δ 13.69 (s, 1H), 10.24 (s, 1H), 7.64 (s, 1H), 7.33 (s, 1H), 3.83 (m, 1H), 2.67 (s, 3H), 1.45 (d, J = 7.3 Hz, 6H); ^{13}C NMR (acetone-d_6, 500 Hz) δ 195.2, 162.7, 149.0, 144.6, 133.2, 132.1, 126.0, 118.3, 115.3, 112.1, 104.3, 26.8, 20.3, 18.5. HRMS (EI) calcd for $C_{15}H_{16}O_4$ $[M+H]^+$: 261.1127; found, 261.1127.
42. *Data for compound* **13b**: *1-isopropyl-2,3,5-trimethoxy-6,7-dimethyl-1-naphthalene*: oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 7.69 (s, 1H), 7.31 (s, 1H), 3.98 (s, 3H), 3.88 (s, 3H), 3.87 (m, 1H), 3.86 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H), 1.50 (d, J = 7.2 Hz, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 Hz) δ 152.9, 151.8, 147.0, 135.0, 133.4, 127.1, 124.8, 124.4, 120.0, 99.8, 61.0, 60.7, 55.4, 26.8, 22.2, 21.1, 12.4. HRMS (EI) calcd for $C_{18}H_{24}O_3$ $[M+H]^+$: 289.1803; found, 289.1730.
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44. *Data for ester* **15a**: *methyl 4-isopropyl-2,3,8-trimethoxy-6-methyl-1-naphthalenecarboxylate*: colorless oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 7.53 (s, 1H), 6.65 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.92 (m, 1H), 3.91 (s, 3H), 2.50 (s, 3H), 1.49 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 500 Hz) δ 169.2, 154.4, 150.1, 148.3, 136.6, 134.8, 131.1, 121.3, 117.6, 116.1, 107.0, 61.4, 60.6, 56.3, 52.0, 27.0, 22.4, 22.0. HRMS (EI) calcd for $C_{19}H_{24}O_5$ $[M+Na]^+$: 355.1624; found, 355.1615.
45. *Data for bromide* **15c**: *methyl 7-bromo-2,3,8-trimethoxy-6-methyl-4-isopropyl-1-naphthalenecarboxylate*: white solid; mp 98–100 °C; ^{1}H NMR: δ 7.77 (s, 1H), 3.96 (s, 3H), 3.90 (s, 6H), 3.82 (s, 3H), 3.81 (m, 1H), 2.54 (s, 3H), 1.45 (d, J = 7.2 Hz, 6H); ^{13}C NMR: δ 168.4, 152.4, 150.4, 149.6, 137.1, 135.4, 129.8, 122.2, 121.2, 120.9, 116.4, 61.9, 61.5, 60.8, 52.3, 27.1, 24.2, 22.0. HRMS (EI) calcd for $C_{19}H_{23}BrO_5$ $[M+H]^+$: 411.0807; found, 411.0740.
46. *Data for lactones* **4**: *3,4-dihydroxy-4-isopropyl-6-methyl-1,8-naphtholactone* **4a**: white solid; mp 220–222 °C; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 8.70 (br s, 1H), 7.51 (s, 1H), 6.92 (s, 1H), 6.08 (s, 1H), 3.93 (m, 1H), 2.55 (s, 3H), 1.49 (d, J = 7.2 Hz, 6H); ^{13}C NMR: (acetone-d_6, 500 Hz) δ 166.1, 149.3, 148.0, 147.8, 136.3, 135.7, 124.4, 122.3, 117.7, 106.1, 100.9, 28.1, 22.9, 21.0. HRMS (EI) calcd for $C_{15}H_{14}O_4$ $[M+H]^+$: 259.0970; found, 259.0970. *7-Bromo-2,3-dihydroxy-4-isopropyl-6-methyl-1,8-naphtho-lactone* **4c**: white solid; mp 254–255 °C; ^{1}H NMR (acetone-d_6, 500 Hz) δ 7.78 (d, J = 1.0 Hz, 1H), 3.89 (m, 1H), 2.57 (d, J = 1.0 Hz, 3H), 1.49 (d, J = 7.2 Hz, 6H); ^{13}C NMR (acetone-d_6, 500 Hz) δ 164.7, 148.3, 147.6, 147.5, 136.6, 135.5, 123.4, 123.2, 119.8, 101.2, 100.0, 28.4, 23.4, 21.0. HRMS (EI) calcd for $C_{15}H_{13}BrO_4$ $[M+H]^+$: 337.0075; found, 337.0088.
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48. *Data for compounds* **16** and **17**: *4-isopropyl-2,3-dimethoxy-6,7-dimethyl-1,8-naphtholactone* **16**: oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 7.59 (s, 1H), 4.56 (s, 3H), 3.86 (s, 3H), 3.85 (m, 1H), 2.47 (s, 3H), 2.39 (s, 3H), 1.51 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 500 Hz) δ 165.6, 155.0, 149.8, 146.7, 144.9, 136.3, 124.6, 122.1, 118.5, 116.1, 103.3, 62.5, 61.6, 27.7, 22.2, 20.9, 11.9. HRMS (EI) calcd for $C_{18}H_{20}O_4$ $[M+H]^+$: 301.1440; found, 301.1435. *5-Carboxamido-4-isopropyl-2,3-dimethoxy-6,7-dimethyl-1,8-naphtholactone* **17**: solid; mp 259–260 °C; ^{1}H NMR: (acetone-d_6, 500 Hz) δ 4.50 (s, 3H), 4.22 (m, 1H), 3.94 (s, 3H), 2.44 (s, 3H), 2.37 (s, 3H), 1.43 (d, J = 6.5 Hz, 3H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR (dimethylformamide-d_7, 500 MHz) δ 173.4, 164.9, 155.5, 153.4, 146.4, 146.3, 134.2, 130.2, 124.2, 120.2, 116.3, 104.7, 62.6, 61.7, 28.8, 21.4, 21.3, 16.9, 12.2. HRMS (EI) calcd for $C_{19}H_{21}NO_5$ $[M+H]^+$: 344.1498; found, 344.1498.