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Evidence for a Trianion Intermediate in the Metalation of 4-Hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic Acid. Methodology and Application to Racemic 5,5′-Didesisopropyl-5,5′-dialkylapogossypol Derivatives

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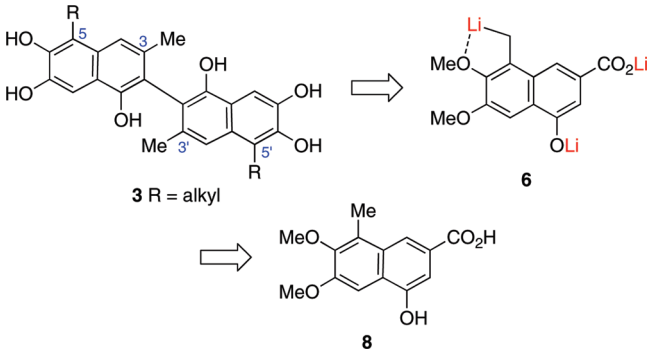

The metalation of 4-hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic acid (**8**) affording trianion **6** is presented and applied to the regioselective efficient construction of a series of 5,5′-didesisopropyl-5,5′-dialkylapogossypol derivatives **3** that are potent pan-active inhibitors of antiapoptotic Bcl-2 family proteins.

Introduction

Due to the ample ortho substitution present in the complex polyphenolic binaphthyl gossypol (**1**) (Figure 1), the yellow main pigment of cotton seed, restricted rotation about the symmetrically structural aryl−aryl bond shows relatively stable axially chiral enantiomers and indeed both have been isolated from natural sources.[1] Compound **1** displays multiple pharmacological applications: male oral contraceptive, treatment of bronchitis, total inhibitor of the replication of HIV 1, in vitro antiviral activity against herpes type 2 virus, influenza virus.[1]

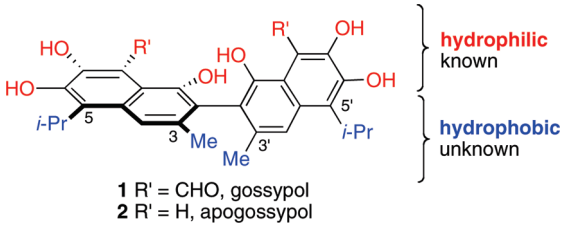

FIGURE 1. Gossypol (**1**) and apogossypol (**2**).

These are gossypol's anticancer properties that have most recently generated the most interest. Gossypol is a potent inhibitor of Bcl-2, Bcl-XL, and Mcl-1, functioning as a BH3

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(1) Reviews: (a) Kenar, J. A. *J. Am. Oil Chem. Soc.* **2006**, *83*, 269–302. (b) Dodou, K. *Expert Opin. Invest. Drugs* **2005**, *14*, 1419–1434.

(2) (a) Kitada, S.; Leone, M.; Sareth, S.; Zhai, D.; Reed, J. C.; Pellecchia, M. *J. Med. Chem.* **2003**, *46*, 4259–4264. (b) Zhang, M.; Liu, H.; Guo, R.; Ling, Y.; Wu, X.; Li, B.; Roller, P. P.; Wang, S.; Yang, D. *Biochem. Pharmacol.* **2003**, *66*, 93–103.

(3) Ascenta Therapeutics Web site. http://www.ascenta.com/development/index.php#at101 (accessed October 27, 2010). See also : Wang, S.; Yang, D. US2003008924A1, 2003.

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mimetic.[2] It is currently in phase II clinical trials, displaying single-agent antitumor activity in patients with advanced malignancies.[3]

In spite of its broad biological interest, very little attention has been paid to the total synthesis of **1**. A formal racemic synthesis was reported by Edwards and Cashaw in 1956.[4] In the course of their synthesis of desapogossypol hexamethyl ether, Shirley reported an organolithium−$CoBr_2$ oxidative coupling that proceeded in poor yield (25%).[5] The first asymmetric total synthesis of (*S*)-(+)-gossypol was described by Meyers using chiral oxazolines as the naphthyl substituent via an asymmetric Ullmann coupling.[6]

Whereas many efforts were focused on modifying the hydrophilicity of gossypol's structure by hemisynthesis to enhance its therapeutic effects while minimizing its toxicity,[1] almost nothing is known about the influence of the two hydrophobic 5,5′-diisopropyl and 3,3′-dimethyl moieties. Recent docking studies suggest that it might be possible to modulate the biological activity in terms of efficiency and specificity by modifying the substitution pattern at the 5,5′ positions.[7] In mice studies, compound **1** displays some toxicity and off target effects likely due to the two reactive aldehyde groups, which are important for targeting other cellular proteins such as dehydrogenases, for example. Apogossypol (**2**), a degradation derivative of **1** that lacks the aldehydes, retains activity against antiapoptotic Bcl-2 family proteins in vitro and in cells.[8]

A recent report by Pellecchia et al.[9] describing an hemisynthesis to 5,5′-substituted apogossypol derivatives **3** that replaces the isopropyl groups with alkyl groups prompts us to describe our own results in reaching these important substances. Retrosynthetic analysis pointed to a naphthoic acid such as **8** as a possible precursor to the apogossypol skeleton (Figure 2). Lateral lithiation of **8** followed by alkylation should afford in principle naphthoic acid **4** possessing the requisite alkyl substituent. Parent 1- and 2-naphthoic acids display a rather complex reactivity toward organolithium reagents.[10] Therefore, compound **8** can be metalated potentially by strong bases ortho to the carboxy[10] and methoxy[11] functions, i.e., in positions 1, 3, and 5. The CO_2H group is also

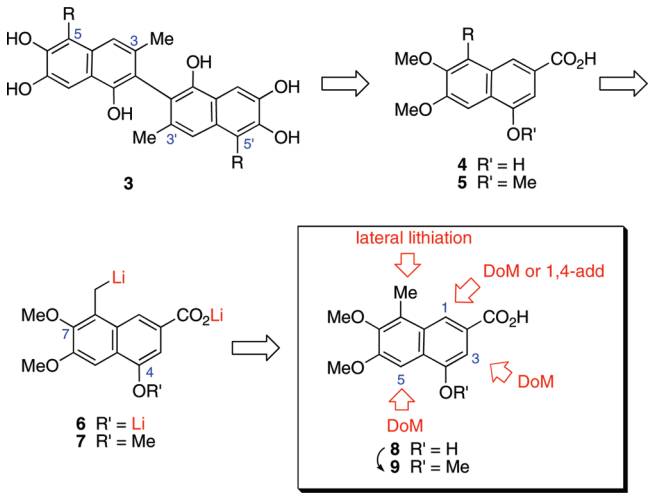
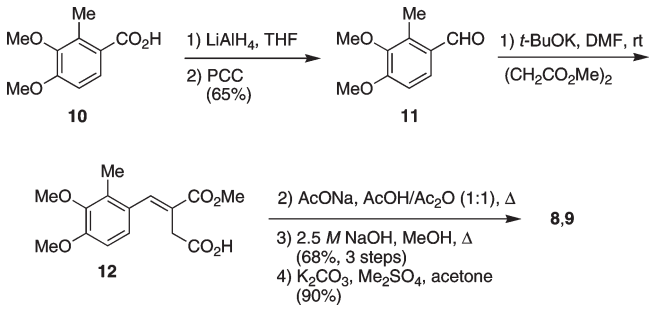


FIGURE 2. 5,5′-Didesisopropyl-5,5′-dialkylapogossypol derivatives **3** from naphthoic acid precursors **8** and **9**.

known to promote 1,4-addition of metallating agents to the naphthalene π-system.[12]

Since lateral lithiation of **8** involves the formation of a trianion **6** that is unprecedented in the naphthalene series, metalation of trimethoxylated naphthoic acid **9** via the intermediacy of dianion **7** was preliminarily tested. Last, reduction of the carboxylate of compound **4** followed by dimerization of the resulting α-naphthol should provide apogossypol derivatives **3**.

SCHEME 1. Preparation of 4-Hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic Acid (8) and 4,6,7-Trimethoxy-8-methyl-2-naphthoic Acid (9)



Results and Discussion

Naphthoic acids **8** and **9** were prepared according to Scheme 1. Reduction of 3,4-dimethoxy-2-methylbenzoic acid (**10**)[13] providing aldehyde **11** was achieved with $LiAlH_4$/PCC.[14] Aldehyde **11** was subjected to Stobbe condensation conditions[4c] by using *t*-BuOK/dimethyl succinate to give the half-ester acid **12**, which was not isolated but directly treated with sodium acetate in AcOH/Ac_2O (1:1). After saponification, naphthoic acid **8** was isolated in 68% yield (3 steps). Subsequent

(4) (a) Edward, J. D., Jr.; Cashaw, J. L. *J. Am. Chem. Soc.* **1956**, *78*, 3224–3225. See also: (b) Ognyanov, V. I.; Petrov, O. S.; Tiholov, E. P.; Mollov, N. M. *Helv. Chim. Acta* **1989**, *72*, 353–360. (c) Venuti, M. C. *J. Org. Chem.* **1981**, *46*, 3124–3127.

(5) Shirley, D. A.; Dean, W. L. *J. Am. Chem. Soc.* **1957**, *79*, 1205–1207.

(6) (a) Meyers, A. I.; Willemsen, J. J. *Chem. Commun* **1997**, 1573–1574. (b) Meyers, A. I.; Willemsen, J. J. *Tetrahedron* **1998**, *54*, 10493–10511.

(7) Brown, W. M.; Metzger, L. E.; Barlow, J. P.; Humsaker, L. A.; Deck, L. M.; Royer, R. E.; Vander Jagt, D. L. *Chem.-Biol. Interact* **2003**, *143−144*, 481–491.

(8) Becattini, B.; Kitada, S.; Leone, M.; Monosov, E.; Chandler, S.; Zhai, D.; Kipps, T. J.; Reed, J. C.; Pellecchia, M. *Chem. Biol.* **2004**, *11*, 389–395.

(9) Wei, J.; Kitada, S.; Rega, M. F.; Stebbins, J. L.; Zhai, D.; Cellitti, J.; Yuan, H.; Emdadi, A.; Dahl, R.; Zhang, Z.; Yang, L.; Reed, J. C.; Pellecchia, M. *J. Med. Chem.* **2009**, *52*, 4511–4523.

(10) Tilly, D.; Castanet, A.-S.; Mortier, J. *Chem. Lett.* **2005**, *34*, 446–447.

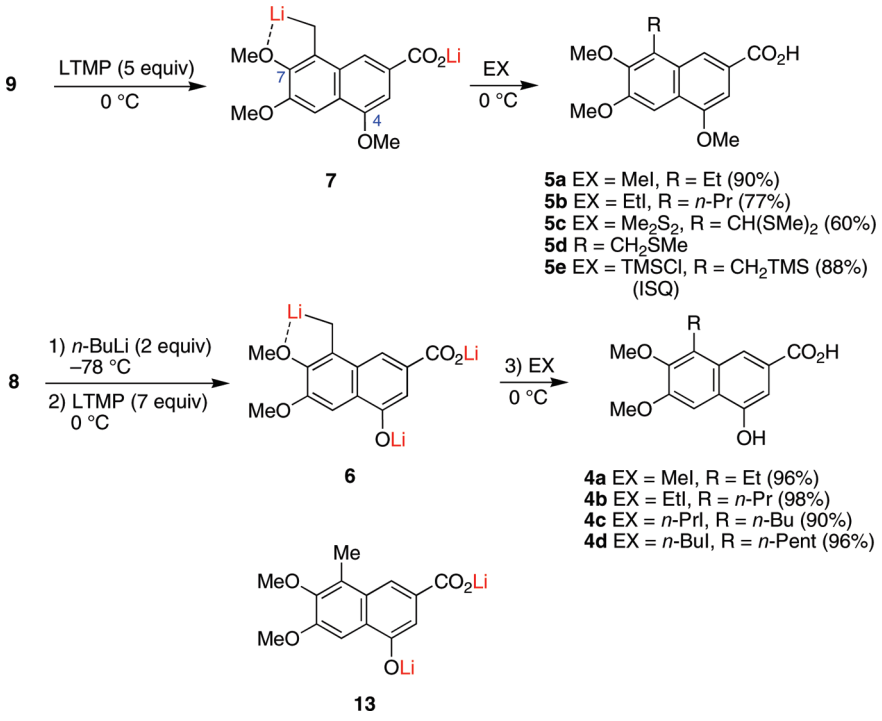
(11) (a) Nguyen, T. H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419–3429. (b) Nguyen, T. H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765–768. (c) Nguyen, T. H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445–2448. (d) Substitution of the methoxy group in unprotected 2-methoxy-1-naphthoic acid and 1-methoxy-2-naphthoic acid to afford the corresponding anthranilic acids occurs upon reaction with lithioamides: Belaud-Rotureau, M.; Le, T. T.; Phan, T. H. T.; Nguyen, T. H.; Aissaoui, R.; Gohier, F.; Derdour, A.; Nourry, A.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2010**, *12*, 2406–2409.

(12) Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206–5207.

(13) Prepared by metalation of veratric acid with LTMP (4 equiv) at 0 °C followed by quench with iodomethane. See: Chau, N. T. T.; Nguyen, T. H.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Tetrahedron* **2008**, *64*, 10552–10557.

(14) Borchardt, R. T.; Bhatia, P. *J. Med. Chem.* **1982**, *25*, 263–271.

SCHEME 2. Lateral Lithiation of 4,6,7-trimethoxy-8-methyl-2-naphthoic Acid (9) and 4-Hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic Acid (8)



methylation of **8** to give **9** was performed under standard conditions.

Lateral lithiation of benzenes requires an ortho-stabilizing group capable of either delocalizing a negative charge or stabilizing the organolithium by coordination.[15] Primary, allylic, and benzylic halides usually give good yields of laterally alkylated products. Secondary and acetylenic halides have been used in several instances. Successful reaction with these substrates is noteworthy since many aryllithiums arising from ortho-lithiation reactions do not alkylate or give poor yields with halides other than iodomethane.[16] Whereas lateral lithiation of *o*-toluic acids is readily accomplished by treatment with LDA, reaction of *o*-methylanisole with organolithium reagents suffers from competing ortho-lithiation.[15]

LTMP (5 equiv) deprotonated laterally the trimethoxylated naphthoic acid **9** to dianion **7** stabilized by coordination of the benzylic lithium with the etherial oxygen in position 7 (Scheme 2). Subsequent alkylation with MeI and EtI afforded **5a** (90%) and **5b** (77%). With dimethyl disulfide, the monosubstitution product **5d** was remetalated during the quench to provide **5c** exclusively.[17] Under in situ quench (ISQ) conditions, in which **9** was added to a mixture of LTMP/TMSCl at −78 °C,[18] **5e** was isolated in 88% yield.

To our delight, lateral lithiation/alkylation of naphthoic acid **8** with LTMP/MeI afforded **4a** in excellent yield (96%). Best results were obtained when the reaction was carried out with 7 equiv of LTMP in THF at 0 °C, after in situ formation of the dilithium salt **13** with 2 equiv of *n*-BuLi at −78 °C, followed by addition of MeI. The excess of LTMP produced a trilithium reagent presumed to be **6** as a reddish brown solution. No traces of ortho-substitution products were detected in the crude reaction mixture. An excess of LTMP was required presumably because the p-electrons of the methoxy and lithium alkoxide groups coordinate strongly with the base.[19] According to these optimized conditions, **6** also reacted with a variety of iodoalkanes to give the substitution products **4b**−**d** in excellent yields. The hydroxy substituent as the lithium alkoxide at position 4, which is expected to decrease the electrophilicity of the carbonyl group by an electronic effect, confers stability to **6**: self-condensation was not observed even at 0 °C. To the best of our knowledge, the formation of a trianion in the naphthalenic series is unprecedented.[20,21]

The pentasubstituted naphthalenes **8** and **4a**−**d** were converted to the alcohols **14** and **15a**−**d** by treatment with $LiAlH_4$ in refluxing THF (Scheme 3). Catalytic hydrogenation of **14**, **15a**−**d** to give 5-alkyl-6,7-dimethoxy-3-methylnaphthalen-1-ols

(15) (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1–314. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002; pp 73−85.

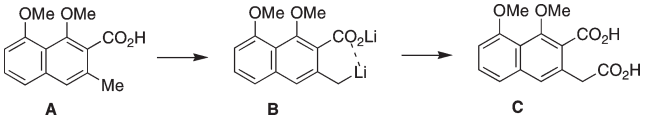
(16) (a) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265–1271. (b) Flippin, L. A. *Tetrahedron Lett.* **1991**, *32*, 6857–6860. (c) Buttery, C. D.; Knight, D. W.; Nott, A. P. *Tetrahedron Lett.* **1982**, *23*, 4127–4130. (d) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *39*, 3979–3982.

(17) Remetalation of **5d** presumably occurs faster than destruction of the excess of LTMP by the electrophile. See: Gohier, F.; Castanet, A.-S.; Mortier, J. *J. Org. Chem.* **2005**, *70*, 1501–1504.

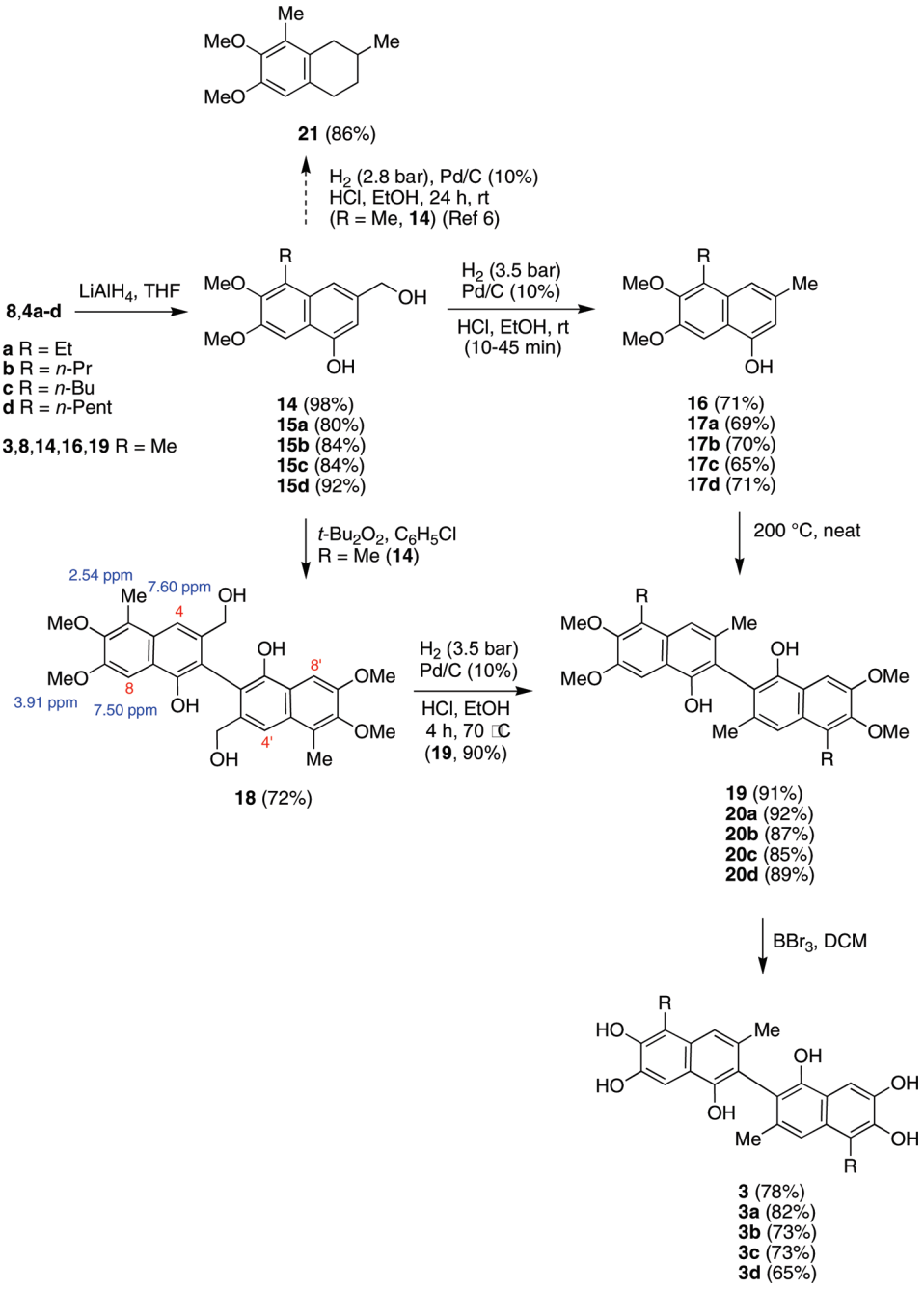
(18) Krizan, T.; Martin, J. *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157.

(19) Marsais, F.; Cronnier, A.; Trecourt, F.; Quéguiner, G. *J. Org. Chem.* **1987**, *52*, 1133–1136.

(20) Only one example of lateral lithiation of a naphthoic acid derivative was mentioned in the literature: Hauser, F. M.; Rhee, R. *J. Am. Chem. Soc.* **1977**, *99*, 4533–4534. Compound **A**, upon treatment with LDA, was converted to a dilithium anion **B** which was carboxylated and hydrolyzed to give naphthaleneacetic acid **C**. The benzylic anion is stabilized by coordination of the lithium with the carboxylate.



SCHEME 3. Synthesis of 5,5′-Didesisopropyl-5,5′-dialkylapogossypol (3)



16, **17a**−**d** was not straightforward.[22,23] The presence of three oxygen atoms makes the naphthalene ring easily reducible. Under the experimental conditions used by Meyers,[6] **14** was directly transformed into 1,2,3,4-tetrahydronaphthalene **21** (86%). At higher temperature (70 °C) a mixture of **16**, **21** was obtained (55:45). Best yields of **16**, **17a**−**d** were obtained when the reduction was carried out with 10% Pd/C under a pressure of 3.5 bar of H_2 and a catalytic amount of HCl for a shorter reaction time (10−45 min).[24]

The phenolic coupling of **14** leading to binaphthalenediol **18** was achieved with *t*-Bu_2O_2 in 72% yield.[25] Structure of **18** was determined by the NOESY technique.[26] Upon warming

(21) Lateral lithiations involving trianions are very scarce. See: (a) Tahara, N.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2004**, *45*, 5117–5120. (b) Katz, A. H.; Demerson, C. A.; Shaw, C. C.; Asselin, A. A.; Humber, L. G.; Conway, K. M.; Gavin, G.; Guinosso, C.; Jensen, N. P.; Mobilio, D.; Noureldin, R.; Schmid, J.; Shah, U.; Van Engen, D.; Chau, T. T.; Weichman, B. M. *J. Med. Chem.* **1988**, *31*, 1244–1250.

(22) Hudlicky, M. *Reductions in Organic Chemistry*; Wiley: New York, 1984; pp 76−81.

(23) (a) Bringmann, G.; Ochse, M.; Götz, R. *J. Org. Chem.* **2000**, *65*, 2069–2077. (b) Bringmann, G.; Hamm, A.; Schraut, M. *Org. Lett.* **2003**, *5*, 2805–2808.

(24) Frija, L. M. T.; Cristiano, M. L. S.; Guimarães, E. M. O.; Martins, N. C.; Loureiro, R. M. S.; Bickley, J. F. *J. Mol. Catal. A: Chem.* **2005**, *242* (1−2), 241–250.

(25) Armstrong, D. R.; Breckenbridge, R. J.; Cameron, C.; Nonhebel, D. C.; Pauson, P. L.; Perkins, P. G. *Tetrahedron Lett.* **1983**, *24*, 1071–1074.

(26) The protons H4,H4′ (7.60 ppm) show clear interactions with the methyl group at 2.54 ppm. There are also spatial interactions between H8, H8′ (7.50 ppm) and MeO (3.91 ppm).

at 200 °C, neat compounds **16**, **17a**−**d** dimerized to binaphthols **19**, **20a**−**d** in high yields. Binaphthol **19** was also obtained by catalytic hydrogenation of **18** (90%). Subsequent demethylation with boron tribromide[27] afforded the expected 5,5′-didesisopropyl-5,5′-dialkylapogossypols **3**, **3a**−**d**.

Conclusion

This straightforward de novo synthesis gives access to a variety of apogossypol derivatives which are not accessible by conventional hemisynthetic means.[9] The mesylates/tosylates derived from **14**, **15a**−**d** and **18** are particularly useful in that they may be used in substitution reactions with a wide variety of nucleophiles to give apogossypol analogues modified in the 3,3′ positions.[28] The 2,2′-binaphthalenes **3** were screened to determine their effect on the development of tumoral cells. These results will be reported elsewhere.

Experimental Section

A. Preparation of 4-Hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic Acid (8). To a solution of 3,4-dimethoxy-2-methylbenzaldehyde (**11**)[29] (6.50 g, 0.036 mol) and dimethyl succinate (4.8 mL, 0.036 mol) in dry DMF (150 mL) was added *t*-BuOK (4.83 g, 0.043 mol). The mixture was allowed to stir at rt overnight. Water (100 mL) was added and the mixture was washed with diethyl ether (3 × 100 mL). The aqueous layer was acidified to pH 3 by adding aq 3 M HCl and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated in vacuo to yield half ester acid **12** (10.26 g). The crude compound **12** was then dissolved in acetic acid/acetic anhydride (1:1, 200 mL), dry sodium acetate (6.50 g, 0.079 mol) was added, and the mixture was refluxed overnight. The resulting solution was cooled at 0 °C and neutralized to pH 6−7 with aq 2.5 M NaOH. Diethyl ether (100 mL) was added to dissolve the yellow precipitate. The aqueous layer was extracted with diethyl ether (5 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo to give a crude residue (21.71 g) that was dissolved in aq 2.5 M NaOH/methanol (1:1, 250 mL). The mixture was refluxed overnight. After evaporation of MeOH, the resulting solution was acidified at 0 °C to pH 2 by adding aq 3 M HCl, then the precipitate was filtered and washed with hot chloroform. The precipitate was dissolved in ethylacetate, then the organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield 4-hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic acid (**8**) as a pale yellow solid [6.37 g, 68% calculated from 3,4-dimethoxy-2-methylbenzaldehyde (**11**)]. Mp >250 °C dec. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.23 (s, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 4.02 (s, 3H), 3.86 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 167.8, 152.7, 152.4, 147.2, 128.5, 126.6, 126.2, 124.4, 117.3, 106.7, 99.7, 60.2, 55.4, 11.2. IR (ATR, cm^{-1}) 3418, 3002, 2942, 1678, 1601. HRMS calcd for $C_{14}H_{15}O_5$ ([M + H]$^+$) 263.0919, found 263.0912.

B. Preparation of 4,6,7-Trimethoxy-8-methyl-2-naphthoic Acid (9). To a solution of 4-hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic acid (**8**) (0.262 g, 1 mmol) in acetone (10 mL) were added successively potassium carbonate (0.553 g, 4 mmol) and dimethyl sulfate (0.21 mL, 2.2 mmol). The mixture was stirred at rt for 24 h, the insoluble was filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in DCM (20 mL), then the DCM solution was washed with water (3 × 10 mL), dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel (cyclohexane/ethylacetate 9:1) gave methyl 4,6,7-trimethoxy-8-methyl-2-naphthoate as a white solid (0.260 g, 90%). Mp 125−126 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H), 3.87 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 154.6, 153.7, 147.8, 128.8, 127.7, 125.7, 125.2, 119.9, 102.6, 99.6, 60.7, 55.7, 55.6, 52.1, 11.6. IR (ATR, cm^{-1}) 3002, 2947, 1709, 1599. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19, H, 6.25. Found: C, 65.95, H, 6.25. HRMS *m*/*z* calcd for $C_{16}H_{19}O_5$ ([M + H]$^+$) 291.1232, found 291.1241.

Methyl 4,6,7-trimethoxy-8-methyl-2-naphtoate (0.260 g, 0.896 mmol) was dissolved in aq 1 M KOH (12.5 mL). The resulting mixture was heated to reflux overnight, cooled to rt, and acidified to pH 2 (aq 2 M HCl). The white precipitate was filtered off, washed with water, and dissolved in ethylacetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to provide pure 4,6,7-trimethoxy-8-methyl-2-naphthoic acid (**9**) as a white solid (0.228 g, 92%). Mp 126−127 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.50 (s, 1H), 7.42 (s, 1H), 4.07 (s, 3H), 4.02 (s, 3H), 3.88 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 154.0, 153.2, 147.4, 128.0, 126.9, 126.1, 124.7, 118.9, 102.7, 99.3, 60.2, 55.6, 55.4, 11.2. IR (ATR, cm^{-1}) 2940, 1678, 1603. HRMS *m*/*z* calcd for $C_{15}H_{17}O_5$ ([M + H]$^+$) 277.1076, found 277.1073.

C. Lateral Lithiation of 4,6,7-Trimethoxy-8-methyl-2-naphthoic Acid (9) and 4-Hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic Acid (8). Lateral Lithiation of 4,6,7-Trimethoxy-8-methyl-2-naphthoic Acid (9). General Procedure. 4,6,7-Trimethoxy-8-methyl-2-naphthoic acid (**9**) in dry THF (20 mL/mmol of **9**) was added dropwise to a solution of LTMP in THF (1.5 M, 5 equiv) at 0 °C. The resulting mixture was allowed to warm to rt, stirred for 2 h, and treated with an electrophile (8−10 equiv). After 2 h of stirring, water (15 mL) was added. The aqueous layer was washed with diethyl ether (2 × 15 mL), acidified to pH 1−2 by adding aq 2 M HCl, and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was recrystallized to give naphthoic acids **5a**−**d**.

8-Ethyl-4,6,7-trimethoxy-2-naphthoic Acid (5a). 5a was prepared from 4,6,7-trimethoxy-8-methyl-2-naphthoic acid (**9**) (0.414 g, 1.5 mmol), LTMP (7.5 mmol), and iodomethane (0.93 mL, 15 mmol) according to the general procedure. Recrystallization (cyclohexane/ethylacetate) gave 8-ethyl-4,6,7-trimethoxy-2-naphthoic acid (**5a**) as a white solid (0.392 g, 90%). Mp 234 °C. ^{1}H NMR (200 MHz, acetone-d_6) δ 8.22 (s, 1H), 7.44 (s, 1H), 7.29 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.78 (s, 3H), 3.02 (q, J = 7.5 Hz, 2H), 1.16 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 154.2, 153.2, 146.9, 132.9, 127.0, 126.5, 125.0, 118.5, 102.6, 99.6, 60.6, 55.6, 55.4, 18.6, 15.4. IR (KBr, cm^{-1}) 2940, 2826, 2637, 1682, 1464. HRMS calcd for $C_{16}H_{19}O_5$ ([M + H]$^+$) 291.1232, found 291.1230.

4,6,7-Trimethoxy-8-propyl-2-naphthoic Acid (5b). 5b was prepared from 4,6,7-trimethoxy-8-methyl-2-naphthoic acid (**9**) (0.202 g, 0.73 mmol), LTMP (3.65 mmol), and iodoethane (0.47 mL, 5.84 mmol) according to the general procedure. Recrystallization (cyclohexane/ethylacetate) gave 4,6,7-trimethoxy-8-propyl-2-naphthoic acid (**5b**) as a white solid (0.170 g, 77%). Mp 223−224 °C. ^{1}H NMR (200 MHz, acetone-d_6) δ 8.44 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 3.91 (s, 3H), 3.11 (t, J = 8.0 Hz, 2H), 1.81−1.62 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 154.1, 153.0, 147.2, 131.3, 127.3, 126.5, 124.9, 118.6, 102.5, 99.6, 60.4, 55.5, 55.4, 27.3, 23.8, 14.2. IR (KBr, cm^{-1}) 3438, 2962, 2646, 1686, 1602, 1505, 1422, 1259, 1062, 838. HRMS calcd for $C_{17}H_{21}O_5$ ([M + H]$^+$) 305.1389, found 305.1391.

8-[Bis(methylthio)methyl]-4,6,7-trimethoxy-2-naphthoic Acid (5c). 5c was prepared from 4,6,7-trimethoxy-8-methyl-2-naphthoic

(27) Royer, R. E.; Deck, L. M.; Vander Jagt, T. J.; Martinez, F. J.; Mills, R. G.; Young, S. A.; Vander Jagt, D. L. *J. Med. Chem.* **1995**, *38*, 2427–2432.

(28) See: Mortier, J.; Castanet, A.-S.; Chau, N. T. T. WO2009080949A1, 2009.

(29) Prepared from 3,4-dimethoxy-2-methylbenzoic acid (**10**) according to ref 14. Compound **10** was prepared by metalation of veratric acid with LTMP (4 equiv) at 0 °C followed by quench with iodomethane: see ref 13.

acid (**9**) (0.120 g, 0.44 mmol), LTMP (2.2 mmol), and dimethyl disulfide (0.33 mL, 4.4 mmol) according to the general procedure. Recrystallization (cyclohexane/ethylacetate) gave 8-(bis(methylthio)methyl)-4,6,7-trimethoxy-2-naphthoic acid (**5c**) as a yellow solid (0.095 g, 60%). Mp >250 °C dec. ^{1}H NMR (200 MHz, acetone-d_6) δ 9.14 (s, 1H), 7.67 (s, 1H), 7.44 (s, 1H), 5.91 (s, 1H, C*H*(SCH$_3$)$_2$), 4.11 (s, 3H), 4.07 (s, 3 H), 3.96 (s, 3 H), 2.28 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 151.7, 149.8, 143.9, 126.4, 123.4, 123.2, 123.0, 119.2, 100.5, 99.1, 58.9, 53.4, 53.3, 46.8, 14.7. IR (KBr, cm^{-1}) 3423, 2940, 2635, 1682, 1601, 1501, 1429, 1260, 1040, 850, 697. HRMS calcd for $C_{16}H_{20}O_5S$ ([M − SCH$_3$]$^+$) 321.0797, found 321.0782.

4,6,7-Trimethoxy-8-[(trimethylsilyl)methyl]-2-naphthoic Acid (5e). To a solution of LTMP (4.2 mmol) in THF (10 mL) at −78 °C were added successively chlorotrimethylsilane (0.72 mL, 5.7 mmol) and 4,6,7-trimethoxy-8-methyl-2-naphthoic acid (**9**) (0.276 g, 1 mmol). Stirring was maintained at this temperature for 1 h. The reaction mixture was warmed gradually to rt over a period of 2 h. Water (10 mL) was added and the solution was basified to pH 10 by adding aq 2 M NaOH. The aqueous layer was washed with diethyl ether (2 × 15 mL), acidified to pH 1−2 (aq 2 M HCl), and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by recrystallization (cyclohexane/ethylacetate) to yield 4,6,7-trimethoxy-8-[(trimethylsilyl)methyl]-2-naphthoic acid (**5e**) as a white solid (0.307 g, 88%). Mp 236.5−237.5 °C. ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.37 (s, 1H), 7.44 (s, 1H), 7.40 (s, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 3.88 (s, 3H), 2.63 (s, 2H), 0.02 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 153.9, 153.2, 145.8, 130.4, 127.1, 125.3, 124.8, 120.0, 102.3, 98.0, 59.6, 55.5, 55.3, 16.0, −0.8. IR (KBr, cm^{-1}) 2942, 2646, 1686, 1599, 1468, 1420, 1263, 1121, 1031, 839. HRMS calcd for $C_{18}H_{25}O_5Si$ ([M + H]$^+$) 349.1471, found 349.1468.

Lateral Lithiation of 4-Hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic Acid (8). General Procedure. To a stirred solution of dilithium salt **13** [prepared by addition of 2 equiv of *n*-BuLi to 4-hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic acid (**8**) (0.524 g, 2 mmol) at −78 °C] in dry THF (8 mL) at 0 °C was added dropwise LTMP (14 mmol) in dry THF (16 mL). The mixture was stirred at 0 °C for 15 min and the electrophile (MeI, EtI, *n*-PrI, *n*-BuI, 10 equiv) was slowly added. The resulting solution was stirred for 1−3 h and quenched with water (5 mL). The aqueous phase was washed with ethylacetate (2 × 20 mL), acidified to pH 1−2 by adding aq 2 M HCl, and extracted with ethylacetate (3×40 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (ethylacetate) to give naphthoic acids **4a**−**d**.

8-Ethyl-4-hydroxy-6,7-dimethoxy-2-naphthoic Acid (4a). 4a was prepared according to the general procedure with iodomethane (1.3 mL, 20 mmol) as an electrophile. Stirring was maintained at 0 °C for 1 h. Purification by column chromatography on silica gel (ethylacetate) yielded 8-ethyl-4-hydroxy-6,7-dimethoxy-2-naphthoic acid (**4a**) as a beige solid (0.532 g, 96%). Mp 226−228 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.28 (s, 1H), 7.59 (s, 1H), 7.49 (s, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.15 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 171.1, 154.5, 153.5, 148.5, 134.2, 129.1, 127.2, 126.4, 119.2, 107.8, 101.2, 61.2, 56.0, 19.8, 15.9. IR (ATR, cm^{-1}) 3338, 2934, 1671, 1602, 1582, 1471, 1435, 1407, 1278, 1257, 1230, 1213, 1177. HRMS calcd for $C_{15}H_{17}O_5$ ([M + H]$^+$) 277.1076, found 277.1074.

4-Hydroxy-6,7-dimethoxy-8-propyl-2-naphthoic Acid (4b). 4b was prepared according to the general procedure with iodoethane (1.6 mL, 20 mmol) as an electrophile. Stirring was maintained at 0 °C for 2 h. Purification by column chromatography on silica gel (ethylacetate) afforded 4-hydroxy-6,7-dimethoxy-8-propyl-2-naphthoic acid (**4b**) as a beige solid (0.566 g, 98%). Mp 226−228 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.26 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 4.01 (s, 3H), 3.89 (s, 3H), 3.08 (m, 2H), 1.69 (m, 2H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3, 154.3, 153.3, 148.8, 132.5, 129.4, 126.9, 126.2, 119.3, 107.6, 101.1, 61.0, 55.9, 28.5, 24.9, 14.7. IR (ATR, cm^{-1}) 3390, 2963, 2929, 2873, 1675, 1617, 1468. HRMS calcd for $C_{16}H_{22}NO_5$ ([M + NH$_4$]$^+$) 308.1498, found 308.1495.

D. Preparation of 3-(Hydroxymethyl)-6,7-dimethoxy-5-alkylnaphthalen-1-ols 14 and 15a−d. 3-(Hydroxymethyl)-6,7-dimethoxy-5-methylnaphthalen-1-ol (14). To a suspension of LiAlH$_4$ (0.30 g, 7.92 mol) in dry THF (3 mL) was added dropwise a solution of 4-hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic acid (**8**) (1.04 g, 3.96 mmol) in dry THF (12 mL).[30] The reaction mixture was refluxed overnight, hydrolyzed (10 mL), and acidified to pH 1−2 by adding aq 2 M HCl. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to yield 3-(hydroxymethyl)-6,7-dimethoxy-5-methylnaphthalen-1-ol (**14**) as a beige solid (0.96 g, 98%). Mp 175−177 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.84 (s, 1H), 7.50 (s, 1H), 7.38 (s, 1H), 6.91 (s, 1H), 4.70 (d, J = 5.8 Hz, 1H), 4.17 (t, J = 5.8 Hz, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.8, 150.7, 146.8, 137.4, 129.4, 124.8, 120.9, 112.3, 106.4, 99.2, 64.3, 59.6, 54.5, 10.5. IR (ATR, cm^{-1}) 3419, 3169, 2935, 2872, 1607. HRMS calcd for $C_{14}H_{17}O_4$ ([M + H]$^+$) 249.1127, found 249.1136. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.83; H, 6.51.

General Procedure for the Preparation of 15a−d. To a suspension of LiAlH$_4$ (4 equiv) in dry THF (1 mL/mmol of **4a**−**d**) was added dropwise a solution of **4a**−**d** in dry THF (3 mL/mmol). The reaction mixture was heated at 30 °C overnight. After hydrolysis and acidification to pH 1−2 (aq 2 M HCl), the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over MgSO$_4$, and concentrated in vacuo to yield spectroscopically pure compounds **15a**−**d**.

5-Ethyl-3-(hydroxymethyl)-6,7-dimethoxynaphthalen-1-ol (15a). 15a was prepared according to the general procedure from 8-ethyl-4-hydroxy-6,7-dimethoxy-2-naphthoic acid (**4a**) (0.800 g, 2.90 mmol). Standard workup gave 5-ethyl-3-(hydroxymethyl)-6,7-dimethoxynaphthalen-1-ol (**15a**) as a beige solid (0.605 g, 80%). Mp 150−152 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.71 (s, 1H), 7.50 (s, 1H), 7.43 (s, 1H), 6.88 (s, 1H), 4.70 (d, J = 5.7 Hz, 2H), 4.10 (t, J = 5.7 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.12 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 153.4, 152.2, 147.9, 139.3, 132.4, 129.9, 122.7, 113.3, 107.6, 101.0, 65.5, 61.0, 55.7, 19.6, 15.7. IR (ATR, cm^{-1}) 3431, 3201, 2954, 2866, 1605, 1467, 1409, 1250, 1219. HRMS calcd for $C_{15}H_{18}O_4$ ([M]$^+$) 262.1205, found 262.1194.

3-(Hydroxymethyl)-6,7-dimethoxy-5-propylnaphthalen-1-ol (15b). 15b was prepared according to the general procedure from 4-hydroxy-6,7-dimethoxy-8-propyl-2-naphthoic acid (**4b**) (0.400 g, 1.38 mmol). Standard workup gave 3-(hydroxymethyl)-6,7-dimethoxy-5-propylnaphthalen-1-ol (**15b**) as a beige solid (0.320 g, 84%). Mp 169−170 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.69 (s, 1H), 7.50 (s, 1H), 7.42 (s, 1H), 6.87 (s, 1H), 4.68 (d, J = 5.6 Hz, 2H), 4.08 (t, J = 5.6 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.03−2.99 (m, 2H), 1.70−1.61 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 153.4, 152.1, 148.2, 139.3, 130.8, 130.2, 122.6, 113.4, 107.5, 101.0, 65.4, 60.9, 55.7, 28.6, 24.7, 14.8. IR (ATR, cm^{-1}) 3431, 3425, 3175, 2947, 2867, 1606, 1468, 1415. HRMS calcd for $C_{16}H_{21}O_4$ ([M + H]$^+$) 277.1440, found 277.1436.

E. Preparation of 6,7-Dimethoxy-3-methyl-5-alkylnaphthalen-1-ols 16, 17a−d and 6,7-Dimethoxy-2,8-dimethyl-1,2,3,4-tetrahydronaphthalene (21). General Procedure. To a solution of

(30) Tetsuya, T.; Hirohisa, D.; Tokutaro, O.; Tsuyoshi, O.; Iwao, O.; Eiichi, K. *Tetrahedron* **2004**, *60*, 6295–6310.

3-(hydroxymethyl)-6,7-dimethoxy-5-alkylnaphthalen-1-ols **14**, **15a−d** in ethanol (10 mL/mmol) was added 10% Pd/C (0.160 g/mmol) and aq 1 M HCl (1 mL/mmol). The reaction mixture was stirred for 45 min at 25 °C (10 min for **14**) under a hydrogen pressure of 3.5 bar. The catalyst was filtered off over Celite 545 and washed with acetone. The combined filtrates were concentrated in vacuo to give a residue that was dissolved in DCM (10 mL/mmol). The DCM layer was washed with sat. $NaHCO_3$ and water, and dried over $MgSO_4$. Concentration in vacuo gave a residue that was purified by chromatography on silica gel (cyclohexane/ethylacetate 8:2).

6,7-Dimethoxy-3,5-dimethylnaphthalen-1-ol (16). 16 was prepared according to the general procedure from 3-(hydroxymethyl)-6,7-dimethoxy-5-methylnaphthalen-1-ol (**14**) (1.656 g, 6.67 mmol). Standard workup followed by recrystallization (cyclohexane/ethylacetate) and chromatography on silica gel (cyclohexane/ethylacetate 9:1) provided pure 6,7-dimethoxy-3,5-dimethylnaphthalen-1-ol (**16**) as a beige solid (1.100 g, 71%). Mp 165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.35 (s, 1H), 7.09 (s, 1H), 6.66 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 2.43 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.2, 150.2, 146.7, 133.4, 129.6, 124.4, 119.8, 113.9, 109.5, 99.6, 60.1, 55.1, 21.7, 11.1. IR (ATR, cm^{-1}) 3342, 2932, 1605, 1583. HRMS m/z calcd for $C_{14}H_{17}O_3$ ([M + H]$^+$) 233.1178, found 233.1168.

5-Ethyl-6,7-dimethoxy-3-methylnaphthalen-1-ol (17a). 17a was prepared according to the general procedure from 5-ethyl-3-(hydroxymethyl)-6,7-dimethoxynaphthalen-1-ol (**15a**) (0.470 g, 1.80 mmol). Standard workup and purification afforded 5-ethyl-6,7-dimethoxy-3-methylnaphthalen-1-ol (**17a**) as a pale yellow solid (0.305 g, 69%). Mp 126−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.27 (s, 1H), 6.59 (s, 1H), 5.18 (s, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.06 (q, J = 7.5 Hz, 2H), 2.43 (s, 3H), 1.27 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 150.8, 147.0, 133.5, 131.8, 129.4, 120.3, 115.8, 110.1, 99.6, 61.1, 55.5, 22.0, 19.1, 15.2. IR (ATR, cm^{-1}) 3348, 2962, 2932, 1602, 1448, 1409, 1373, 1264, 1232, 1215, 1201, 1148. HRMS calcd for $C_{15}H_{19}O_3$ ([M + H]$^+$) 247.1334, found 247.1331.

6,7-Dimethoxy-3-methyl-5-propylnaphthalen-1-ol (17b). 17b was prepared according to the general procedure from 3-(hydroxymethyl)-6,7-dimethoxy-5-propylnaphthalen-1-ol (**15b**) (0.355 g, 1.28 mmol). Standard workup and purification provided 6,7-dimethoxy-3-methyl-5-propylnaphthalen-1-ol (**17b**) (0.234 g, 70%) as an orange solid. Mp 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.25 (s, 1H), 6.58 (s, 1H), 5.05 (br s, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.02−2.98 (m, 2H), 2.43 (s, 3H), 1.63−1.72 (m, 2H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 150.8, 147.3, 133.4, 130.3, 129.7, 120.2, 116.0, 110.1, 99.6, 61.0, 55.5, 28.0, 24.0, 22.0, 14.6. IR (ATR, cm^{-1}) 3401, 2956, 2924, 2868, 1601, 1582, 1464, 1411. HRMS calcd for $C_{16}H_{21}O_3$ ([M + H]$^+$) 261.1491, found 261.1503.

6,7-Dimethoxy-2,8-dimethyl-1,2,3,4-tetrahydronaphthalene (21). To a solution of 3-(hydroxymethyl)-6,7-dimethoxy-5-methylnaphthalen-1-ol (**14**) (77 mg, 0.31 mmol) in ethanol (4 mL) were added 10% Pd/C (0.15 g) and aq 3 M HCl (0.25 mL). The reaction mixture was stirred for 24 h at 25 °C under a hydrogen pressure of 2.7 bar. The catalyst was filtered off over Celite 545 and washed with ethanol (2 × 20 mL). The filtrate was concentrated in vacuo and the residue was dissolved in DCM (20 mL). The DCM layer was washed with sat. $NaHCO_3$ (10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated in vacuo to yield 6,7-dimethoxy-2,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**21**) as a yellow orange oil (59 mg, 86%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.56 (s, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 2.72−2.49 (m, 4H), 2.04 (s, 3H), 1.80−1.72 (m, 2H), 1.30−1.19 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 144.1, 131.0, 129.1, 127.1, 108.9, 59.4, 54.6, 34.4, 30.2, 29.1, 28.4, 21.3, 10.5. HRMS, m/z calcd for $C_{14}H_{24}NO_2$ ([M + NH_4]$^+$) 238.1807, found 238.1813.

F. Dimerization Reactions. Preparation of Binaphthalenes 19, 20a−d. General Procedure. The neat compounds **16**, **17a−d** were heated overnight at 200 °C[31] to give the products **19**, **20a−d** which were purified by sublimation.

2-(1-Hydroxy-6,7-dimethoxy-3,5-dimethylnaphthalen-2-yl)-6,7-dimethoxy-3,5-dimethylnaphthalen-1-ol (19). 19 was prepared according to the general procedure from 6,7-dimethoxy-3,5-dimethylnaphthalen-1-ol (**16**) (0.400 g, 1.72 mmol). 2-(1-Hydroxy-6,7-dimethoxy-3,5-dimethylnaphthalen-2-yl)-6,7-dimethoxy-3,5-dimethylnaphthalen-1-ol (**19**) was isolated as a brown solid (0.364 g, 91%). Mp > 290 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.48 (s, 2H), 7.33 (s, 2H), 3.90 (s, 6H), 3.76 (s, 6H), 2.51 (s, 6H), 1.98 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.3, 149.4, 146.6, 133.5, 128.9, 124.3, 120.7, 118.2, 115.3, 100.5, 60.2, 55.3, 20.5, 11.2. IR (ATR, cm^{-1}) 3342, 2954, 2901, 1604, 1573, 1486, 1473, 1457, 1412, 1400, 1368, 1334, 1244, 1189, 1138. HRMS calcd for $C_{28}H_{31}O_6$ ([M + H]$^+$) 463.2121, found 463.2138.

5-Ethyl-2-(5-ethyl-1-hydroxy-6,7-dimethoxy-3-methylnaphthalen-2-yl)-6,7-dimethoxy-3-methylnaphthalen-1-ol (20a). 20a was prepared according to the general procedure from 5-ethyl-6,7-dimethoxy-3-methylnaphthalen-1-ol (**17a**) (0.295 g, 1.20 mmol). 5-Ethyl-2-(5-ethyl-1-hydroxy-6,7-dimethoxy-3-methylnaphthalen-2-yl)-6,7-dimethoxy-3-methylnaphthalen-1-ol (**20a**) was isolated as a brown solid (0.270 g, 92%). Mp > 290 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 7.49 (s, 2H), 7.36 (s, 2H), 3.91 (s, 6H), 3.81 (s, 6H), 3.02 (q, J = 7.5 Hz, 4H), 1.97 (s, 6H), 1.24 (t, J = 7.5 Hz, 6H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 150.3, 149.6, 146.2, 133.6, 130.5, 127.9, 121.1, 118.0, 114.9, 100.8, 60.5, 55.3, 20.7, 18.5, 15.4. IR (ATR, cm^{-1}) 3383, 2958, 2925, 1600, 1573, 1456, 1401, 1367, 1236, 1191, 1140. HRMS calcd for $C_{30}H_{35}O_6$ ([M + H]$^+$) 491.2434, found 491.2441.

2-(1-Hydroxy-6,7-dimethoxy-3-methyl-5-propylnaphthalen-2-yl)-6,7-dimethoxy-3-methyl-5-propylnaphthalen-1-ol (20b). 20b was prepared according to the general procedure from 6,7-dimethoxy-3-methyl-5-propylnaphthalen-1-ol (**17b**) (0.300 g, 1.15 mmol). 2-(1-Hydroxy-6,7-dimethoxy-3-methyl-5-propylnaphthalen-2-yl)-6,7-dimethoxy-3-methyl-5-propylnaphthalen-1-ol (**20b**) was isolated as a brown solid (0.260 g, 87%). Mp 247−248 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 2H), 7.51 (s, 2H), 7.35 (s, 2H), 3.91 (s, 6H), 3.82 (s, 6H), 2.98 (t, J = 7.9 Hz, 4H), 1.99 (s, 6H), 1.64−1.70 (m, 4H), 1.04 (t, J = 7.5 Hz, 6H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 150.2, 149.5, 146.5, 133.5, 128.9, 128.2, 121.1, 118.0, 115.0, 100.8, 60.4, 55.3, 27.4, 23.7, 20.7, 14.5. IR (ATR, cm^{-1}) 3429, 3392, 2931, 2868, 1600, 1574, 1462, 1417, 1404, 1250, 1140, 1096. HRMS calcd for $C_{32}H_{39}O_6$ ([M + H]$^+$) 519.2747, found 519.2759.

3,3′-Bis(hydroxymethyl)-6,6′,7,7′-tetramethoxy-5,5′-dimethyl-2,2′-binaphthyl-1,1′-diol (18). To a solution of 3-(hydroxymethyl)-6,7-dimethoxy-5-methylnaphthalen-1-ol (**14**) (113 mg, 0.45 mmol) in chlorobenzene (6 mL) was added di-*tert*-butyl peroxide (82 μL, 0.45 mmol).[4b,25,32] The mixture was heated at 105 °C for 50 h, then cooled and concentrated in vacuo. The crude residue was recrystallized in benzene to yield 3,3′-bis-(hydroxymethyl)-6,6′,7,7′-tetramethoxy-5,5′-dimethyl-2,2′-binaphthyl-1,1′-diol (**18**) as a white solid (80 mg, 72%). Mp 289−291 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.60 (s, 2H), 7.50 (s, 2H), 5.00 (br s, 2H), 4.21 (d, J = 14.0 Hz, 2H), 4.05 (d, J = 14.0 Hz, 2H), 3.91 (s, 6H), 3.78 (s, 6H), 2.54 (s, 6H). In the NOESY spectrum, the protons H4,H4′ (7.60 ppm) show clear interactions with the methyl group at 2.54 ppm. There are also spatial interactions between H8,H8′ (7.50 ppm)

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and MeO (3.91 ppm). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 149.2, 146.7, 137.6, 128.9, 124.9, 121.4, 115.0, 112.5, 100.4, 61.6, 60.2, 55.4, 11.4. IR (KBr, cm^{-1}) 3465, 3348, 2942, 1741, 1686, 1604, 1577, 1470, 1253, 1083, 1004, 844. HRMS, *m*/*z* calcd for $C_{28}H_{31}O_8$ ([M + H]$^+$) 495.2019, found 495.2028.

G. Deprotection of the Methoxy Groups. Preparation of 5,5′-Didesisopropyl-5,5′-dialkylapogossypols 3, 3a−d. General Procedure. To a solution of binaphthalenes **19**, **20a−d** dissolved in dry DCM (40 mL/mmol) at −78 °C was added dropwise BBr_3 (1 M in DCM) (10 equiv).[9] The reaction mixture was stirred for 1 h at −78 °C and for 1 h at rt. Aq 6 M HCl (50 mL/mmol) (cooled beforehand at 0 °C) was added and the reaction mixture was stirred at 0 °C for 1 h. The aqueous layer was extracted with diethyl ether, then the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/ethylacetate 8:2 → 5:5) and C-18 column chromatography (H_2O/acetonitrile) to provide pure 5,5′-didesisopropyl-5,5′-dialkylapogossypols **3**, **3a−d**.

3,5-Dimethyl-2-(1,6,7-trihydroxy-3,5-dimethylnaphthalen-2-yl)-naphthalene-1,6,7-triol (3). 3 was prepared according to the general procedure from 2-(1-hydroxy-6,7-dimethoxy-3,5-dimethylnaphthalen-2-yl)-6,7-dimethoxy-3,5-dimethylnaphthalen-1-ol (**19**) (0.112 g, 0.24 mmol). 3,5-Dimethyl-2-(1,6,7-trihydroxy-3,5-dimethylnaphthalen-2-yl)naphthalene-1,6,7-triol (**3**) was isolated as a beige solid (0.077 g, 78%). Mp > 150 °C dec. ^{1}H NMR (200 MHz, acetone-d_6) δ 7.54 (s, 2H), 7.30 (s, 2H), 7.20 (br s, 2H), 2.52 (s, 6H), 2.08 (s, 6H). ^{13}C NMR (50 MHz, acetone-d_6) δ 150.8, 145.1, 144.6, 134.0, 131.1, 119.4, 116.0, 115.8, 114.7, 103.6, 21.0, 11.1. IR (KBr, cm^{-1}) 3442, 2921, 1691, 1639, 1619, 1508, 1458, 1349, 1310, 1232, 1165, 1041, 854. HRMS calcd for $C_{24}H_{23}O_6$ ([M + H]$^+$) 407.1495, found 407.1478.

5-Ethyl-2-(5-ethyl-1,6,7-trihydroxy-3-methylnaphthalen-2-yl)-3-methylnaphthalene-1,6,7-triol (3a). 3a was prepared according to the general procedure from 5-ethyl-2-(5-ethyl-1-hydroxy-6,7-dimethoxy-3-methylnaphthalen-2-yl)-6,7-dimethoxy-3-methylnaphthalen-1-ol (**20a**) (0.101 g, 0.21 mmol). 5-Ethyl-2-(5-ethyl-1,6,7-trihydroxy-3-methylnaphthalen-2-yl)-3-methylnaphthalene-1,6,7-triol (**3a**) was isolated as a beige solid (0.073 g, 82%). Mp > 150 °C dec. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.86 (br s, 2H), 7.56 (s, 2H), 7.38 (s, 2H), 7.14 (s, 2H), 3.12 (q, J = 7.5 Hz, 4H), 2.07 (s, 6H), 1.30 (t, J = 7.5 Hz, 6H). ^{13}C NMR (50 MHz, acetone-d_6) δ 151.0, 144.6 (2), 134.1, 130.2, 122.4, 119.7, 115.7, 114.6, 103.9, 21.1, 19.2, 14.7. IR (ATR, cm^{-1}) 3440, 2962, 2929, 2872, 1613, 1504, 1446, 1264, 1213, 1154. HRMS cacld for $C_{26}H_{27}O_6$ ([M + H]$^+$) 435.1808, found 435.1803.

3-Methyl-5-propyl-2-(1,6,7-trihydroxy-3-methyl-5-propylnaphthalen-2-yl)naphthalene-1,6,7-triol (3b). 3b was prepared according to the general procedure from 2-(1-hydroxy-6,7-dimethoxy-3-methyl-5-propylnaphthalen-2-yl)-6,7-dimethoxy-3-methyl-5-propylnaphthalen-1-ol (**20b**) (0.100 g, 0.19 mmol). 3-Methyl-5-propyl-2-(1,6,7-trihydroxy-3-methyl-5-propylnaphthalen-2-yl)-naphthalene-1,6,7-triol (**3b**) was isolated as a beige solid (0.065 g, 73%). Mp >150 °C dec. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.87 (br s, 2H), 7.56 (s, 2H), 7.40 (br s, 2H), 7.37 (s, 2H), 7.13 (s, 2H), 3.09−3.05 (m, 4H), 2.06 (s, 6H), 1.79−1.70 (m, 4H), 1.09 (t, J = 7.5 Hz, 6H). ^{13}C NMR (50 MHz, acetone-d_6) δ 150.9, 145.0, 144.5, 134.0, 130.5, 121.0, 119.6, 115.9, 114.6, 103.9, 28.1, 23.9, 21.1, 14.8. IR (ATR, cm^{-1}) 3445, 2956, 2929, 2864, 1698, 1614, 1504, 1447, 1376, 1349, 1243, 1210, 1148, 1089. HRMS calcd for $C_{28}H_{30}O_6$ ([M]$^+$) 462.2042, found 462.2052.

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Supporting Information Available: Complete experimental information and details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.