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Straightforward Synthesis of Panaxytriol: An Active Component of Red Ginseng

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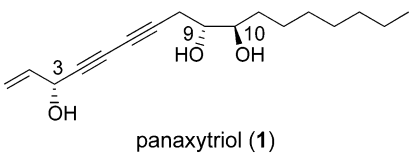
Abstract: A total synthesis of (3*R*,9*R*,10*R*)-panaxytriol (**1**) was accomplished enantioselectively (40% overall yield; 30% for the longest sequence). A key step was a Cadiot−Chodkiewicz cross-coupling reaction on two fragments containing, in the aggregate, three unprotected hydroxyl groups. One fragment was synthesized by a highly enantioselective reduction of an enynone. The other arose from a highly enantioselective dihydroxylation of an allylic alcohol.

Red Ginseng (the steamed and dried root of *Panax ginseng* C. A. Meyer), found in various Asian countries including China, Japan, and Korea, has been used in many folk medicines. Included among these are applications in what appear to be analeptic, erythropoietic, and cytotoxic contexts.[1] Panaxytriol (**1**, Figure 1), an apparently important contributor to the overall activity of Red Ginseng, was isolated in 1983.[2] After the structure of panaxytriol was established,[3] it was shown to have inhibitory activity against MK-1 cells ($IC_{50} \cong 8.5$ ng/mL) and to suppress the growth of B16 melanoma cells transplanted into mice.[4] Moreover, it was very effective at inhibiting cellular respiration and energy balance of a human breast carcinoma cell line.[5] In addition, it enhanced the cytotoxicity of mitomycin C against human gastric adenocarcinoma cell lines.[6]

Our goals in this project were several. The first was to accomplish an efficient total synthesis of panaxytriol, which would allow for a systematic and extensive evaluation of its promise. Moreover, it was hoped that mastery of the total synthesis issues would lead us to molecules that are more plausible looking drug candidates. Finally, we sought a total synthesis that would lay to rest all issues associated with relative and absolute stereochemistry of panaxytriol (**1**). Remarkably, the previous syntheses[7] did not serve to answer these questions *in a fully convincing way using chemically based criteria*.



panaxytriol (**1**)

FIGURE 1. Antitumor components of*Panax ginseng*, panaxytriol (**1**).

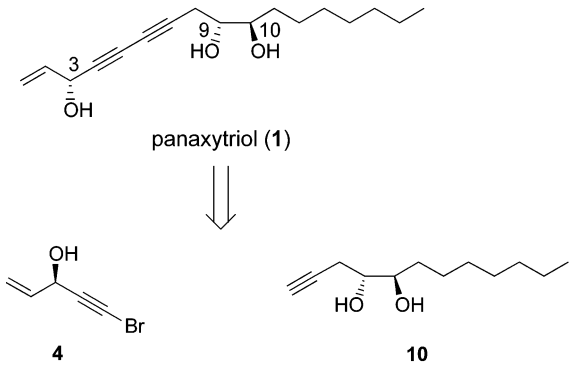
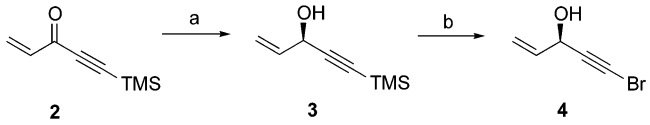


FIGURE 2. Retrosynthetic analysis.

SCHEME 1. Enantioselective Synthesis of Left-Hand Piece Using CBS Reduction[a]



[a] Reaction conditions: (a) (*R*)-Me-CBS, BMS, −30 °C, 10 min, 75%, >99% ee; (b) NBS, cat. $AgNO_3$, acetone, rt, 1 h, 100%.

Our synthetic building blocks would ultimately be **4** and **10**. These compounds would be linked using a key Cadiot−Chodkiewicz cross-coupling reaction. As will be seen, fragment **4** was to be synthesized by an oxazaborolidine-catalyzed enantioselective reduction of an enynone **2**. Correspondingly, asymmetric dihydroxylation of a TBS-protected allylic alcohol **6** would ultimately lead to **10**. The program started with the preparation of the known **2**.[8] Actually, enantiocontrolled reduction of this type of 1-trimethylsilyl-4-alken-1-yn-3-one with a long hydrocarbon chain at the β-position of the olefin had previously been reported, albeit with only moderate selectivity.[9] By contrast, reduction of **2** with the commercially available (*R*)-Me-CBS reducing agent afforded a 75% yield of **3** with a remarkably high enantiomeric excess (>99%) (Scheme 1), as determined by Mosher ester methodology. According to the Mosher precedents,[10]

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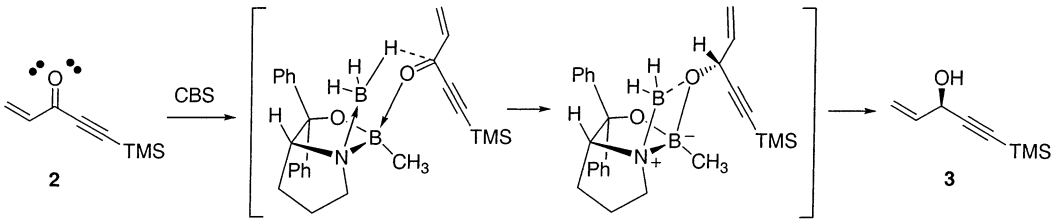
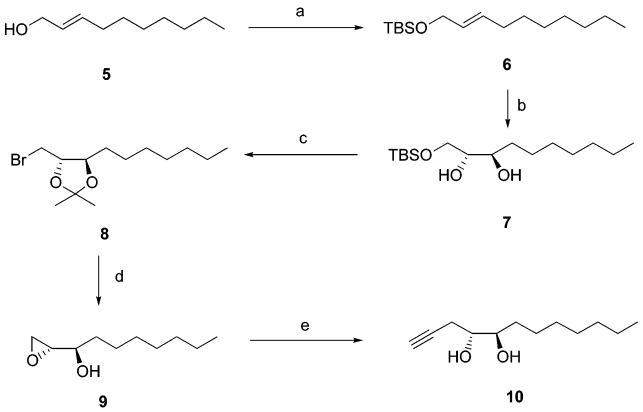


FIGURE 3. A proposed model for the CBS reduction of **2**.

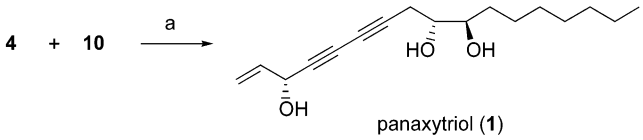
arising from the diamagnetic effect of the benzene ring, the ^{1}H NMR signals of (*R*)-MTPA ester should appear upfield relative to those of the (*S*)-MTPA ester. Indeed, the proton signals (δ 6.091, 5.868) of the corresponding Mosher ester of compound **3** appeared at higher fields than those (δ 6.119, 5.958) of the other Mosher ester. According to this analysis, compound **3** was assigned to have the (*R*) configuration. The sense of the reduction (vide infra) is also consistent with that proposed for alkynone substrates in the Corey model.[11] Applying this logic, the double bond of **2** is placed furthest from the B-methyl function to rationalize the result. To the best of our knowledge, this is the first example of attainment of such high enantioselectivity with an enynone system.[12] Following in situ deprotection of the C-silyl function and bromination of the terminal alkyne using NBS and $AgNO_3$, component **4** was in hand (100%). The route to the subunit containing the vicinal diol building block, commenced with the commercially available *trans*-2-decen-1-ol (**5**), which was protected as its *tert*-butyldimethylsilyl ether **6** (99%). Sharpless asymmetric dihydroxylation[13] of **6**, using AD-mix-β, afforded **7** in ca. 99% ee (100%). The assignment of the absolute configuration of compound **7** rests on several lines of evidence. First, governing precedents in Sharpless asymmetric dihydroxylation lead to the expectation that the principal product would have the (*R*,*R*) configuration.[13] Furthermore, the result of an application of the analytical Mosher ester methodology[10] to **7** is in accord with this assignment. The proton signals (δ 5.355, 5.282) of the corresponding bis-Mosher ester of compound **7** appeared at higher fields than those (δ 5.430, 5.291) of the other component. Accordingly, compound **7** was assigned to have the (*R*,*R*) configuration. Temporary protection of the diol as its isopropylidene derivative was followed by in situ deprotection of the primary alcohol and conversion of the primary hydroxyl function to a bromide (see compound **8**, 90% for 2 steps). Acid-induced cleavage of the acetonide linkage, followed by treatment of the diol bromide with potassium carbonate led to **9** (89% for 2 steps**)**. The epoxide linkage (possibly activated by the adjacent oxy function) of **9**,[14] served to alkylate lithium

SCHEME 2. Enantioselective Synthesis of Right-Hand Piece Using Sharpless Asymmetric Dihydroxylation[a]



[a] Reaction conditions: (a) TBSCl, imidazole, DMF, 0 °C to rt, 6 h, 99%; (b) AD-mix-β, $CH_3SO_2NH_2$, ^{t}BuOH/H_2O 1:1, 0 °C, 1 day, 100%, >99% ee; (c) (1) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, CH_2Cl_2, rt, 1 h, (2) PPh_3, Br_2, CH_2Cl_2, 30 min, 90% for 2 steps; (d) (1) 1 N HCl, rt, 3 days, (2) K_2CO_3, rt, overnight, 89% for 2 steps; (e) Li-acetylide EDA complex, HMPA, THF, 0 °C to rt, overnight, 80%

SCHEME 3. Cadiot−Chodkiewicz Cross-coupling Reaction[a]



[a] Reaction condition: (a) CuCl, $EtNH_2$, NH_2OH·HCl, MeOH, 0 °C, 1 h, 63%.

acetylide, under the conditions shown, to afford building block **10** (80%). The defining step of the synthesis was the last one. Thus, the nonprotected key subunits **4** and **10** were merged in a Cadiot−Chodkiewicz cross-coupling reaction[15] (Scheme 3) to produce a 63% yield of panaxytriol (**1**). The NMR spectrum of the fully synthetic product was identical with that obtained from an authentic sample of panaxytriol, kindly provided by Dr. Yun-Lian Lin.[16] This identity establishes that our fully synthetic

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(12) At the present writing, it is not clear to us why the reduction of **2** is significantly more selective than the model cases in ref 9, which bear substitution at the β-carbon of the olefin.

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(16) We thank Dr. Yun-Lian Lin, National Research institute of Chinese Medicine, Taipei 112, Taiwan, for sending us a specimen sample of panaxytriol.

product is in the same diastereomer family as is natural panaxytriol. The magnitude and sense of optical rotation[17] ($[\alpha]^{25}_D$ −21.8, c = 0.8, $CHCl_3$) of fully synthetic product confirms that our fully synthetic material is in the same enantiomeric class as panaxytriol.[18] The stereochemistry of panaxytriol (**1**) is thus rigorously established through chemical synthesis.

In summary, the synthesis of **1** was accomplished in 30% overall yield (40% for the largest linear sequence, comprising 8 steps). Parenthetically, the synthesis teaches the feasibility of achieving high enantioselectivity of an enynone such as **2** with appropriate CBS technology. Moreover, it establishes the relative and absolute stereochemistry of panaxytriol beyond reasonable doubt. Finally, it underscores the power of the Cadiot−Chodkiewicz cross-coupling reaction even in the setting of three nonprotected hydroxyl functions.[19]

Experimental Section

Compound 3. (*R*)-Me-CBS reagent (2.14 mL, 2.14 mmol, 1.0 M in toluene solution) was transferred into a freshly flame-dried flask, and toluene was completely removed in vacuo for 1 day. After the CBS reagent was diluted with THF, the resulting solution was transferred to a flask of compound **2**[8] (163 mg, 1.07 mmol) at room temperature, and the reaction temperature cooled to −30 °C. At −30 °C, BH_3·Me_2S (BMS) (0.589 mL, 1.18 mmol) was slowly added over 10 min. After addition of BMS, TLC analyses indicated complete reaction. Methanol was slowly added, and reaction mixture was slowly warmed to room temperature. The reaction mixture was diluted with diethyl ether, washed with 2:1 (v:v) NaOH/saturated $NaHCO_3$ solution until the aqueous phase was clear, and then washed with brine. After being dried over $MgSO_4$, solvent was removed. The resulting organic phase was diluted with diethyl ether, and to this was added 0.5 M HCl in methanol solution (4.5 mL, 2.14 mmol). Precipitates were removed by filtration, and solvent was removed. The crude product was purified by silica gel column chromatography (hexane/ether 5:1) to give compound **3** (0.123 g, 75%) as a colorless oil: R_f 0.4 (hexane/dichloromethane 2:1); $[\alpha]^{20.0}_D$ −24.1 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, 1H, J = 17.0, 10.1, 5.29), 5.46 (d, 1H, J = 17.0), 5.21 (d, 1H, J = 10.1), 4.86 (d, 1H, J = 3.87), 2.17 (br, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 116.8, 104.9, 91.3, 63.9, 0.2; IR (neat) ν 3368.7, 2961.3, 2927.0, 2855.3, 2174.4, 1250.9, 843.7 cm^{-1}; HRMS calcd 154.28, found 154.0817.

Following the appropriate protocols, the corresponding Mosher ester was prepared using (*R*)-MTPA-Cl.[10] The proton signals (δ 6.091, 5.868) of the corresponding Mosher ester of **3** appeared at higher fields than those (δ 6.119, 5.958) of the other (*S*)-isomer.

Compound 4. Compound **3** (204 mg, 1.32 mmol) was dissolved in acetone. NBS (353 mg, 1.98 mmol) and silver nitrate (45 mg, 0.26 mmol) were added to this solution. The reaction mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, mixed with cold water, and extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ether 4:1) to give compound **4** (212 mg, 100%) as a colorless oil: R_f 0.49 (hexane/ether 2:1); $[\alpha]^{20.4}_D$ −31.61 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.47 (d, 1H, J = 17.0), 5.24 (d, 1H, J = 10.1), 4.88 (d, 1H, J = 5.34), 2.44 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 117.4, 79.3, 64.3, 47.2; IR (neat) ν 3361.2, 2918.7, 2852.9, 2356.6 cm^{-1}; HRMS calcd 161.00, found 161.0334.

Compound 6. To a DMF solution of compound **5** (4.0 mL, 21.6 mmol) was added imidazole (2.0 g, 25.9 mmol) at room temperature, and the resulting reaction mixture was cooled to 0 °C. Then TBSCl (4.0 g, 25.9 mmol) was slowly added to the reaction mixture at 0 °C. Following warming room temperature, the resulting mixture was stirred at room temperature for 6 h. Water was added, and the organic phase was extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane only to hexane/ethyl acetate 10:1) to give compound **6** (5.78 g, 99%) as a colorless oil: R_f 0.35 (hexane only); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.6 (m, 1H), 5.5 (m, 1H), 4.12 (dd, 2H, J = 5.25, 1.19), 2.00 (dd, 2H, J = 13.5, 6.57), 1.38−1.27 (m, 10H), 0.91−0.86 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.7, 129.4, 64.6, 32.8, 32.4, 29.9, 29.8, 26.6, 23.3, 19.0, 14.7, −4.4; IR (neat) ν 2957.0, 2928.1, 2856.7, 1471.8, 1255.3, 1103.1, 836.7, 775.6 cm^{-1}; HRMS calcd 270.53, found 270.2403.

Compound 7. A flask, equipped with a magnetic stirrer, was charged with 1:1 *tert*-butyl alcohol/water solution, and AD-mix-β (42.8 g) and $MeSO_2NH_2$ (2.91 g, 30.6 mmol). The mixture was stirred at room temperature until both phases were clear and then cooled to 0 °C, and a 1:1 *tert*-butyl alcohol/water solution of compound **6** (8.24 g, 30.5 mmol) was added. The heterogeneous slurry was stirred vigorously at 0 °C for 1 day. The reaction was quenched at 0 °C by addition of sodium sulfite (45.7 g), warmed to room temperature, and stirred for 1 h. The reaction mixture was extracted with dichloromethane, washed with 2 N KOH, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 5:1) to give compound **7** (9.56 g, 100%) as a yellow oil: R_f 0.35 (hexane/ethyl acetate 5:1); $[\alpha]^{19.9}_D$ +9.72 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (m, 1H), 3.68 (m, 1H). 3.62 (m, 1H), 3.46 (m, 1H). 2.57 (br, 1H), 1.52−1.25 (m, 12H), 0.88 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.5, 72.8, 66.4, 34.1, 32.4, 30.2, 29.8, 29.2, 26.1, 23.2, 14.7, −4.7; IR (neat) ν 3394.3, 2954.4, 2930.7, 2859.3, 1468.4, 1260.3, 1111.7, 838.8 cm^{-1}; HRMS calcd 304.54, found 305.2540.

Following the Mosher's protocols, the corresponding bis-Mosher ester was prepared using (*R*)-MTPA-Cl.[10] The proton signals (δ 5.355, 5.282) of the corresponding bis-Mosher ester of **7** appeared at higher fields than those (δ 5.430, 5.291) of the other (*S*,*S*)-isomer.

Compound 8. Compound **7** (1.00 g, 3.28 mmol), 2,2-dimethoxypropane (0.6 mL, 4.93 mmol) and *p*-TsOH (catalytic) in dichloromethane were stirred at room temperature for 1 h. The reaction was neutralized with triethylamine and concentrated under reduced pressure. The crude product was used for a further step without additional purification. To a suspension of Ph_3PBr_2 in dichloromethane was added a solution of crude product in the previous reaction in dichloromethane at room temperature, and the resulting mixture was stirred at room temperature for 30 min. Subsequently, dichloromethane was added, and the solution washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 5:1) to give compound **8** (0.834 g, 90%) as a yellow oil. This material was used directly without further purification.

Compound 9. Compound **8** (0.834 g, 2.84 mmol) and 1 N HCl in ethanol was stirred at room temperature for 3 days and neutralized with potassium carbonate (0.4 g). More potassium carbonate (0.8 g) was then added to the reaction mixture, and the pH adjusted to around 8−9. The reaction mixture was vigorously stirred at room temperature overnight. Ethanol was

(17) Interestingly, the magnitude of optical rotation of synthetic panaxytriol seems to sharply depend on its concentration ($[\alpha]^{19.1}_D$ −13, c = 1.5, $CHCl_3$).

(18) The absolute configuration of panaxytriol shown in structure **1** is consistent with following well-precedented trends: (i) the sense of CBS reduction of **2**; (ii) the sense of asymmetric dihydroxylation of **6**; (iii) the chemical shift patterns[10] of the Mosher esters of **3** and **7**; and (iv) the sign of the optical rotation of **3**, assigned here as (*R*), with a recently reported, closely related (*S*) compound.[20] For the absolute configuration of panaxytriol to be opposite to that shown, *all* of these precedents would have to be inapplicable.

(19) A related Cadiot−Chodkiewicz cross-coupling reaction was reported in the process of total synthesis of panaxytriol (ref 7b). The novelty of our case lies in its application to a setting containing three nonprotected resident hydroxyl groups.

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removed under reduced pressure, and the residue was extracted with ether, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 10:1 to 7:1) to give compound **9** (0.354 g, 89% based on recovered starting material) as a yellow oil and starting material (0.158 g): R_f 0.6 (hexane/ethyl acetate 1:1); $[\alpha]^{19.1}_D$ −3.38 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (m, 1H), 2.94 (m, 1H), 2.77 (d, 1H, J = 4.84), 2.67 (d, 1H, J = 4.93), 2.45 (br, 1H), 1.62−1.26 (m, 12H), 0.84 (t, 3H, J = 6.72); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.1, 55.9, 45.5, 34.6, 32.1, 29.9, 29.5, 25.6, 22.9, 14.4; IR (neat) ν 3443.0, 2933.6, 2858.9, 2342.6, 1466.4, 1255.8, 923.0 cm^{-1}; HRMS calcd 172.26, found 171.1388.

Compound 10. To a solution of lithiumacetylide−ethylenediamine complex (0.330 g, 3.58 mmol) in THF and HMPA (0.2 mL) was added compound **9** (0.206 g, 1.19 mmol) at 0 °C. The reaction mixture was stirred at that temperature overnight, quenched with saturated ammonium chloride, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 4:1) to give compound **10** (0.189 g, 80%) as a yellow oil: R_f 0.24 (hexane/ethyl acetate 3:1); $[\alpha]^{19.7}_D$ +0.1131 (c = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (m, 2H), 2.47 (m, 2H), 2.31 (br, 2H), 2.06 (s, 1H), 1.50−1.24 (m, 12H), 0.87 (t, 3H, J = 6.75); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.0, 73.6, 72.5, 71.4, 34.1, 32.4, 30.1, 29.8, 26.2, 24.7, 23.3, 14.7; IR (neat) ν 3392.1, 2924.1, 2855.1, 2362.0, 1653.2, 1457.1 cm^{-1}; HRMS calcd 198.30, found 181.2777.

Panaxytriol (1). CuCl (1.5 mg), $NH_2OH{\cdot}HCl$ (10 mg) and ethylamine(0.23 mL) were added to a methanol solution of compound **10** (41 mg, 0.207 mmol) at room temperature. A dichloromethane solution of compound **4** (24.4 mg, 0.151 mmol) was added dropwise to reaction mixture at 0 °C over 1 h using a syringe pump. For an additional 1 h, reaction mixture was stirred at 0 °C. The reaction mixture was quenched by water, extracted with dichloromethane, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 2:1) to give panaxytriol (**1**) (26.6 mg, 63% isolated) and compound **10** (12.4 mg): R_f 0.13 (hexane/ethyl acetate 2:1); $[\alpha]^{25}_D$ −21.8 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, 1H, J = 17.0, 10.1, 5.35), 5.47 (ddd, 1H, J = 17.0, 1.31, 1.21), 5.25 (ddd, 1H, J = 10.4, 1.25, 1.15), 4.92 (d, 1H, J = 5.35), 3.62 (m, 2H), 2.58 (d, 2H, J = 5.78), 2.11 (br, 3H), 1.51−1.25 (m, 12H), 0.88 (t, 3H, J = 6.73); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 117.6, 78.5, 75.1, 73.5, 72.5, 71.3, 66.9, 63.9, 34.0, 32.2, 29.9, 29.6, 26.0, 25.4, 23.0, 14.5; IR (neat) ν 3524.8, 2930.7, 2854.8, 2360.0, 1457.1 cm^{-1}; HRMS calcd 278.39, found 261.1047.

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Supporting Information Available: Experimental procedures and full characterizations for all new compounds including panaxytriol (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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