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Synthesis and absolute configuration of hylodiglyceride isolated from *Hylodendron gabunensis*

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ABSTRACT

A recently isolated bismonoglyceride of heptadecanedioic acid, which represents a novel type of natural monoglycerides (i.e., with two instead of only one glycerol unit in the molecular architecture), was synthesized in enantiopure forms using a chiral-pool based approach with the 17-carbon chain constructed from undec-10-enoic acid and oct-7-en-1-ol via a cross metathesis and the stereogenic centers derived from (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol. An analogue with a longer alkyl chain was also synthesized. The synthetic samples not only allowed for establishment of the absolute configuration but also helped to reveal some minor yet unignorable errors in the ^{1}H NMR data for the natural product. Optical rotation and NMR data acquired in DMSO and DMSO-d_6, respectively, are also presented.

1. Introduction

Natural 1 (or 3)-acyl-*sn*-glycerols comprise an important family of lipids.[1,2] They are also essential precursors to the related di- and triglycerides. The glycerol residue in 1 (or 3)-acyl-*sn*-glycerols is structurally asymmetric and thus may be of either (*R*) or (*S*) configuration. Although such species are unpretentious compared with most other natural products, the tough (though hidden to most investigators who are not familiar with this area) problems unavoidable in their synthesis and handling as well as analysis caused by the unbelievably facile acyl group migrations,[2a,3] along with their biological significance, make these seemingly rather simple molecules worthy/challenging targets of study.

Recently, in their investigations of medical plants from Africa, Nyongha et al.[4] isolated and characterized two previously unknown glycerides (**1** and **2**, Fig. 1), one of which (**1**) represents the longest alkyl chain in the natural monoglycerides so far known, while the other (**2**) illustrates a novel (or at least rare)[5] subtype of natural monoglycerides that contain two (rather than only one) glycerol residue.[6] Herein we wish to report on the synthesis and configuration of **2**.

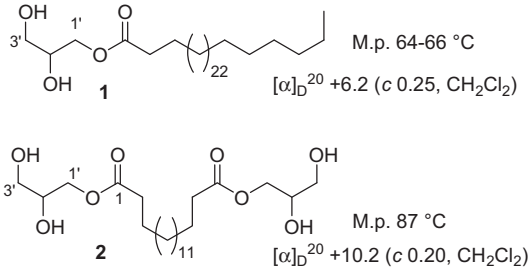

Fig. 1. The planar structures given in the literature for the natural hyloglyceride (**1**) and hylodiglyceride (**2**).

2. Results and discussion

We reasoned that because compound **2** is optically active, it must have a C_2 axis rather than a σ plane (a plane of symmetry). Consequently, the two stereogenic centers must have the same absolute configuration. Considering that the **1** and **2** have the same biogenic origin, we presumed that the glycerol residues in **1** and **2** share the same absolute configuration, which has been proven[3] to be (*S*) for **1**. On the basis of these assumptions, we decided to target our synthesis at (*S*,*S*)-**2**.

The required bifunctional 17-carbon linear chain was assembled (Scheme 1) from oct-7-en-1-ol (**3**) and methyl undec-10-enoicate

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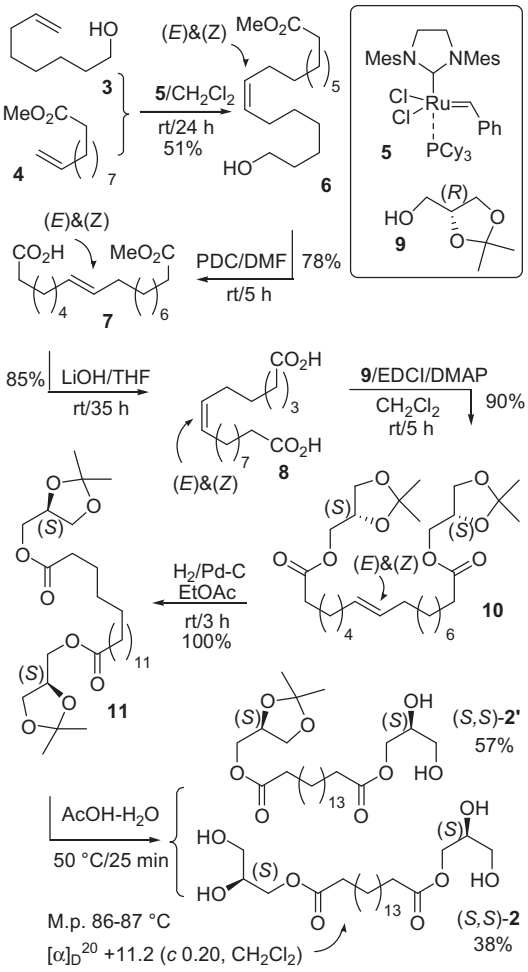


Scheme 1.

(**4**) using a cross metathesis catalyzed by Grubbs II catalyst (**5**). The cross coupling product could be readily separated from the two self-coupling products because of the (carefully chosen) distinct differences in the functional groups.[7] It is noteworthy that treatment[8] of the reaction mixture with 30% H_2O_2 made it easier to remove the last traces of colored (Ru containing) impurities from the product **6**, but the oxidative workup also generated new components; chromatography became more tedious than otherwise.

The newly-formed C–C double bond was a mixture of (*E*) and (*Z*) isomers as expected. Although it was somewhat annoying to see the 'extra' signals ^{13}C NMR caused by the co-existence of two isomers, we decided to keep the double bond for a few more steps to avoid any possible sluggish reactions (caused by a long alkyl chain), which might occur according to our experience on similar lipid related compounds.

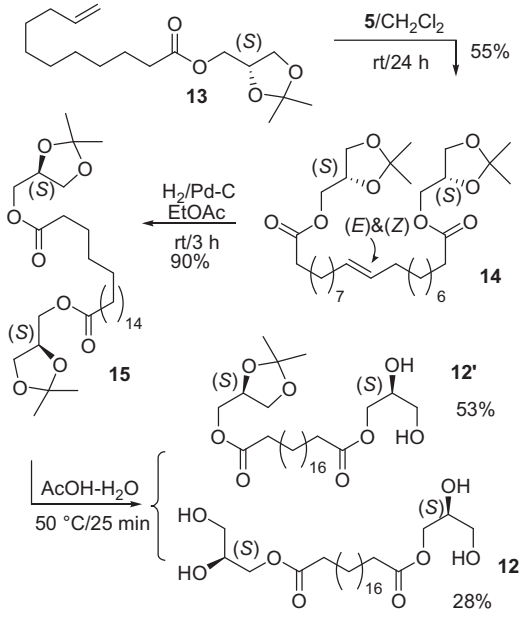
The alcohol **6** was then oxidized with PDC (pyridium dichromate), giving the corresponding acid **7** in 78% yield. The methyl ester at the other terminal of the long chain was hydrolyzed to deliver diacid **8**, which was condensed with the commercially available **9** to afford bis-ester **10** with the aid of EDCI (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide) and DMAP (4-(dimethylamino)-pyridine).

The C–C double bond in **10** was then saturated by atmospheric hydrogenation over 10% Pd–C, affording **11** as a single species in essentially quantitative yield.

As the main purpose of this work was to establish the absolute configuration of the natural **2**, we opted to stop the reaction at an early stage to secure the optical purity of the hydrolysis product (by minimizing any possible acyl group migrations). Thus, the bis-acetonide **11** was treated with AcOH–H_2O (4:1) at 50 °C for 25 min, when TLC showed disappearance of **11** with substantial amounts of the intermediate monoacetonide **2′** still present, the mixture was quenched and worked up. After column chromatography, rather pure (*S*,*S*)-**2** was obtained, which showed an optical rotation in good consistence with that for the natural **2**, confirming that the latter must be of (*S*,*S*) configuration. The ^1H and ^{13}C NMR for the synthetic **2** were also in excellent consistence with those reported for the natural **2**, except that the exocyclic alkoxy CH_2 in the glycerol residues appears at δ 4.15 and 4.20 ppm in ^1H NMR instead of 4.37 and 4.40 ppm as reported[4] for the natural **2**.

Then we recalled that very similar discrepancies were also observed between the natural and synthetic **1** in our previous work,[3] where the confusion was eventually cleared by the data for a closely related natural analogue as well as its synthetic counterpart. Therefore, we decided to synthesize **12**, a readily accessible analogue of **2** (with three additional CH_2 units in the long chain) to see if the exocyclic alkoxy CH_2 show similar chemical shifts in ^1H NMR.

Following the route shown in Scheme 2, the known **13**[3] was treated with Grubbs II catalyst (**5**) to afford the self-coupling product **14** as a mixture of (*E*) and (*Z*) isomers. The C–C double bond was then saturated by hydrogenation. The resulting **15**, a close analogue of **11**, was then subjected to the mild hydrolysis conditions (AcOH–H_2O/50 °C/25 min) to give **12** along with the intermediate monoacetonide **12′**.



Scheme 2.

As expected from our previous experience with **1**, the ^1H NMR for **12** indeed looked almost the same as that for the synthetic **2**, except the six additional protons for the extra non-functionalized CH_2's in the 1.38–1.16 ppm region; the exocyclic alkoxy CH_2 under concern appeared at δ 4.15 and 4.21 ppm, unambiguously confirming that the data for the synthetic **2** indeed objectively reflected the depicted structure, whereas those in the literature did not (some errors must have occurred therein).

It is also worth of mentioning that the solubility for **2** is rather poor in CH_2Cl_2 and somewhat better in DMSO (dimethyl-sulfoxide), so that it is impossible to acquire a solution of **2** in either solvent with the concentration higher than *c*=0.2 (g/100 mL). The solubility for **12** is even worse.[9] However, DMSO remained to be a much more suitable solvent for measuring the optical rotations than CH_2Cl_2 or

$CHCl_3$ as previously observed[3] with other monoglycerides, because of the smaller data errors (more stable readings) and substantially larger absolute values for the optical rotations.

3. Conclusion

The recently isolated hylodiglyceride (**2**), a unique natural monoglyceride that contains two (instead of only one as in all previously known cases) glycerol subunits in the molecular structure, was synthesized in an enantiopure form through a chiral-pool based route. The presence of an extra glycerol subunit made the acyl migrations (a serious, though hidden, problem common to monoglycerides) even more facile than observed with simple monoacylglycerols. By careful control of the reaction time (before acyl migrations occurred to any discernible extents) for the hydrolysis of the acetonide protecting groups under the previously established optimal conditions, the desired bis-monoglycerides was eventually obtained. The data acquired on the synthetic samples not only allowed for reliable assignment of the absolute configuration, but also helped to reveal some minor yet unignorable errors in the ^{1}H NMR data previously reported for the natural product. Optical rotation and NMR data for **2** in DMSO and DMSO-d_6, respectively, were also recorded, which may serve as more convenient/reliable references compared with their counterparts measured in CH_2Cl_2 (for optical rotation) or $CDCl_3$ (for NMR).

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on an Agilent 500/54 NMR spectrometer (operating at 500 MHz for ^{1}H) or a Bruker Avance^{III} 400 (operating at 400 MHz for ^{1}H) as specified in each individual case below. For spectra recorded in $CDCl_3$, the solvent residue was set to 7.26 ppm in ^{1}H NMR, while the middle line of $CDCl_3$ was set to 77.00 ppm in ^{13}C NMR, respectively, as the internal reference unless otherwise stated. The IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. HRMS data were obtained with a Bruker APEX^{III} 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. Melting points were uncorrected (measured on a hot stage melting point apparatus equipped with a microscope). CH_2Cl_2 was dried with activated 4 Å MS (molecular sieves). All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (300–400 mesh) under slightly positive pressure. PE=petroleum ether (chromatography solvent, bp 60–90 °C).

4.2. Cross metathesis reaction of 3 and 4 leading to 6

A suspension of **3** (200 mg, 1.56 mmol), **4** (890 mg, 4.49 mmol), and Grubbs II catalyst **5** (89 mg, 0.11 mmol) in dry CH_2Cl_2 (4 mL) was stirred at ambient temperature under argon for 24 h (initially purple and gradually turned to dark brown with time). When TLC showed complete disappearance of **3**, aq H_2O_2 (30%, 3 mL) was added slowly to the mixture (gas bubbles evolved) with cooling in an ice-water bath. After stirring at ambient temperature for 2 h, the almost black mixture was partition between H_2O (10 mL) and EtOAc (50 mL). The aq layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10:1 PE/EtOAc) on silica gel gave **6** as a colorless oil (235 mg, 0.79 mmol, 51% from **3**). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.42–5.29 (m, 2H), 3.65 (s, 3H), 3.61 (t, J=6.9 Hz, 2H), 2.28 (t, J=7.5 Hz, 2H), 2.06–1.84 (m, 5H), 1.66–1.48 (m, 4H), 1.42–1.18 (m, 16H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.4, 130.5–130.0 (several not so well resolved lines), 62.8, 51.4, 34.0, 32.6, 32.51, 32.47, 32.4, 32.2, 32.1, 29.6–28.6 (several not so well resolved lines), 27.1, 25.63, 25.58, 25.5, 25.2, 24.8 ppm. FT-IR (film): ν=3466 (br), 2926, 2854, 1741, 1460, 1437, 1199, 1172, 968 cm^{-1}. ESI-MS m/z 299.4 ([M+H]$^+$). ESI-HRMS calcd for $C_{18}H_{34}O_3Na$ ([M+Na]$^+$): 321.2400, found 321.2395.

4.3. Oxidation of alcohol 6 to afford acid 7

PDC (472 mg, 1.25 mmol) was added slowly to a solution of alcohol **6** (249 mg, 0.84 mmol) in dry DMF (1.0 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at the same temperature for 10 min. The cooling bath was removed. Stirring was continued at ambient temperature for 5 h. When TLC showed disappearance of **6**, Et_2O was added, followed by H_2O. The phases were separated. The aq layer was extracted with Et_2O (50 mL×4). The combined organic layers were washed with H_2O (several times, to remove DMF as much as possible) and brine before concentrated on a rotary evaporator. The residue was passed through a short pad of silica gel eluting with Et_2O. The effluent was concentrated to left a residue, which was chromatographed (5:1 PE/EtOAc) on silica gel to give acid **7** as a yellowish oil (204 mg, 0.65 mmol, 78% from **6**). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.44–5.28 (m, 2H), 3.65 (s, 3H), 2.33 (t, J=7.5 Hz, 2H), 2.29 (t, J=7.5 Hz, 2H), 2.10–1.84 (m, 4H), 1.70–1.50 (m, 4H), 1.42–1.18 (m, 14H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8, 174.4, 130.9–129.5 (several not so well resolved lines), 51.4, 34.1, 33.9, 33.8, 33.2, 32.5, 32.4, 32.3, 32.1, 31.7, 29.6–28.5 (several not so well resoled lines), 24.9, 24.53, 24.49, 24.4, 24.1 ppm. FT-IR (film): ν=3650–2400 (a huge lump), 2925, 2854, 1741, 1711, 1459, 1437, 1172 cm^{-1}. ESI-MS m/z 311.8 (M$^-$). ESI-HRMS calcd for $C_{18}H_{31}O_4$ (M$^-$): 311.2228, found 311.2233.

4.4. Hydrolysis of 7 to give diacid 8

A solution of **7** (204 mg, 0.65 mmol) and LiOH (monohydrate, 58 mg, 1.38 mmol) in THF (4 mL) and H_2O (0.5 mL) was stirred at ambient temperature for 36 h, when TLC showed completion of the reaction. The reaction mixture was acidified with 1 N HCl to ca. pH 5 before being extracted with EtOAc, washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE/EtOAc) on silica gel afforded diacid **8** as a white solid (160 mg, 0.54 mmol, 85%). Mp 83–84 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.42–5.32 (m, 2H), 2.34 (t, J=7.5 Hz, 4H), 2.06–1.88 (m, 4H), 1.63 (br quint, J=6.8 Hz, 4H), 1.44–1.14 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=180.5, 131.0–129.5 (several not so well resolved lines), 34.10, 34.06, 33.96, 32.53, 32.51, 32.46, 32.28, 32.25, 32.1, 29.6–28.4 (several not so well resolved lines), 27.2, 26.9, 24.6, 24.5, 24.1 ppm. FT-IR (film of a solution in CH_2Cl_2): ν=3630–2200 (a huge lump), 2926, 2853, 1708, 1410, 1287, 1234, 967, 929 cm^{-1}. ESI-MS m/z 297.4 (M$^-$). ESI-HRMS calcd for $C_{17}H_{29}O_4$ (M$^-$): 297.2071, found 297.2070.

4.5. Condensation of diacid 8 with alcohol 9 to give bis-ester 10

To a solution of diacid **8** (35 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) stirred in an ice-water bath were added in turn alcohol **9** (31 mg, 0.24 mmol), DMAP (2 mg, 0.016 mmol), and EDCI (60 mg, 0.31 mmol). After completion of the addition, the mixture was stirred at the same temperature for 30 min. The cooling bath was removed. Stirring was continued at ambient temperature for 5 h. When TLC showed completion of the reaction, the mixture was concentrated on a rotary evaporator. The residue was chromatographed (10:1 PE/EtOAc) on silica gel to give bis-ester **10** as a colorless oil (55 mg, 0.10 mmol, 90%). $[\alpha]_D^{30}$ +1.3 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.43–5.27 (m, 2H), 4.29 (br quint,

J=5.8 Hz, 2H), 4.14 (dd, J=11.7, 4.8 Hz, 2H), 4.07 (dd, J=17.1, 5.6 Hz, 2H), 4.06 (dd, J=7.5, 2.8 Hz, 2H), 3.72 (dd, J=8.3, 6.4 Hz, 2H), 2.32 (t, J=7.3 Hz, 4H), 2.10–1.86 (m, 4H), 1.75–1.50 (m, 4H), 1.41 (s, 6H), 1.35 (s, 6H), 1.34–1.20 (m, 14H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.5, 131.6–129.5 (several not so well resolved lines), 109.7, 73.6, 66.3, 64.5, 34.04, 34.01, 33.90, 33.3, 32.50, 32.47, 32.4, 32.3, 32.1, 29.6–28.5 (several not so well resolved lines), 26.6, 25.3, 24.8, 24.7, 24.3 ppm. FT-IR (film): ν=2986, 2926, 2855, 1748, 1456, 1380, 1371, 1215, 1161, 1057, 972, 842 cm^{-1}. ESI-MS m/z 549.6 ([M+Na]$^+$). ESI-HRMS calcd for $C_{29}H_{50}O_8Na$ ([M+Na]$^+$): 549.3398, found 549.3411.

4.6. Hydrogenation of 10 to give 11

A mixture of **10** (126 mg, 0.24 mmol) and 10% Pd–C (60 mg, washed with water, EtOH and EtOAc before use) in EtOAc (2.5 mL) was stirred under H_2 (1 atm) at ambient temperature for 3 h, when TLC showed completion of the reaction (no yellow spot could be seen on the TLC plate when visualizing with $KMnO_4$). The solids were filtered off. The filtrate was concentrated by rotary evaporation to afford **11** as a white waxy solid (130 mg, 0.25 mmol, 100%). Mp 51–52 °C. $[\alpha]_D^{30}$ +1.1 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.28 (br quint, J=5.8 Hz, 2H), 4.13 (dd, J=11.5, 4.7 Hz, 2H), 4.06 (dd, J=15.1, 6.6 Hz, 2H), 4.05 (dd, J=5.8, 4.3 Hz, 2H), 3.71 (dd, J=8.7, 6.4 Hz, 2H), 2.31 (t, J=7.5 Hz, 4H), 1.59 (br, quint, J=7.1 Hz, 4H), 1.40 (s, 6H), 1.34 (s, 6H), 1.31–1.15 (m, 22H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.6, 109.7, 73.6, 66.3, 64.4, 34.0, 29.6, 29.54, 29.52, 29.49, 29.4, 29.1, 29.0, 26.6, 25.3, 24.8 ppm. FT-IR (film of a solution in CH_2Cl_2): ν=2926, 2854, 1741, 1458, 1371, 1260, 1160, 1089, 800 cm^{-1}. ESI-MS m/z 551.8 ([M+Na]$^+$). ESI-HRMS calcd for $C_{29}H_{52}O_8Na$ ([M+Na]$^+$): 551.35544, found 551.3566.

4.7. Hydrolysis of the acetonide in 11 to afford (*S*,*S*)-2 and (*S*,*S*)-2′

A solution of **11** (130 mg, 0.25 mmol) in HOAc–H_2O (4:1, v/v, 2.5 mL) was stirred at 50 °C for 25 min (when TLC showed disappearance of **11**). The heating bath was removed. H_2O (10 mL) was added to the reaction mixture. Powdered solid $NaHCO_3$ (ca. 3.0 g) was added very slowly to neutralize the HOAc. The mixture was extracted with EtOAc (30 mL×3), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left a residue, which was chromatographed on silica to give (*S*,*S*)-**2′** (the less polar component, a white solid, eluting with 1:2 PE/EtOAc, 70 mg, 0.14 mmol, 57% from **11**) and (*S*,*S*)-**2** (the more polar component, a white solid, eluting with 8:1 CH_2Cl_2/MeOH, 42 mg, 0.09 mmol, 38% from **11**). Data for (*S*,*S*)-**2′**: Mp 47–48 °C. $[\alpha]_D^{26}$ +0.4 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.30 (br quint, J=5.8 Hz, 1H), 4.20–4.10 (m, 3H), 4.10–4.03 (m, 2H), 3.91 (br quint, J=5.2 Hz, 1H), 3.72 (dd, J=8.5, 6.1 Hz, 1H), 3.68 (dd, J=10.9, 3.4 Hz, 1H), 3.58 (dd, J=12.1, 5.9 Hz, 1H), 2.32 (br t, J=7.7 Hz, 4H), 1.60 (br quint, J=7.1 Hz, 4H), 1.42 (s, 3H), 1.35 (s, 3H), 1.33–1.16 (m, 22H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.3, 173.7, 109.8, 73.6, 70.2, 66.3, 65.1, 64.5, 63.3, 34.09, 34.05, 29.5–29.0 (several not so well resolved lines), 26.6, 25.3, 24.8 ppm. FT-IR (film of a solution in CH_2Cl_2): ν=3391 (br), 2918, 2850, 1738, 1467, 1386, 1373, 1246, 1198, 1172, 1082, 1052, 847, 772 cm^{-1}. ESI-MS m/z 511.8 ([M+Na]$^+$). ESI-HRMS calcd for $C_{26}H_{48}O_8Na$ ([M+Na]$^+$): 511.32414, found 511.3238. Data for (*S*,*S*)-**2**: Mp 86–87 °C. $[\alpha]_D^{28}$ +11.3 (c 0.20, CH_2Cl_2) (lit.[4] $[\alpha]_D^{20}$ +10.2 (c 0.20, CH_2Cl_2)), $[\alpha]_D^{28}$ +17.6 (c 0.20, DMSO). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.20 (dd, J=12.0, 4.5 Hz, 2H), 4.15 (dd, J=11.5, 6.3 Hz, 2H), 3.93 (br quint, J=5.1 Hz, 2H), 3.70 (dd, J=12.1, 4.0 Hz, 2H), 3.60 (dd, J=10.8, 5.9 Hz, 2H), 2.35 (t, J=7.6 Hz, 4H), 2.25–1.90 (a lump, 4H), 1.63 (br quint, J=7.3 Hz, 4H), 1.38–1.16 (m, 22H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=174.4, 70.3, 65.2, 63.3, 34.1, 29.7–29.0 (several not so well resolved lines), 24.9 ppm. FT-IR (film of a solution in CH_2Cl_2): ν=3253 (br), 2916, 2849, 1733, 1178, 1108, 1052 cm^{-1}. ESI-MS m/z 471.6 ([M+Na]$^+$). ESI-HRMS calcd for $C_{23}H_{44}O_8Na$ ([M+Na]$^+$): 471.29284, found 471.2927.

4.8. Self-coupling of 13 to afford 14

A (purple) suspension of **13** (315 mg, 1.06 mmol) and catalyst **5** (45 mg, 0.05 mmol) in dry CH_2Cl_2 (4 mL) was stirred at ambient temperature under argon for 24 h. Aq H_2O_2 (30%, 2 mL) was added slowly to the dark brown mixture (gas bubbles evolved). After stirring at ambient temperature for 2 h, the further darked mixture was partition between H_2O (10 mL) and EtOAc (50 mL). The aq layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE/EtOAc) on silica gel gave a mixture of (*E*)- and (*Z*) isomers of **14** as a colorless oil (in a fridge it became an off-white wax, which melt at round 28 °C, 165 mg, 0.29 mmol, 55%). $[\alpha]_D^{28}$ +1.0 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.40–5.28 (m, 2H), 4.28 (br quint, J=5.8 Hz, 2H), 4.13 (dd, J=11.7, 4.9 Hz, 2H), 4.09–4.01 (m, 4H), 3.71 (dd, J=8.3, 6.1 Hz, 2H), 2.31 (t, J=7.6 Hz, 4H), 2.04–1.82 (m, 4H), 1.59 (br quint, J=6.9 Hz, 4H), 1.40 (s, 6H), 1.34 (s, 6H), 1.32–1.18 (m, 20H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.5, 130.3, 130.24, 130.17, 129.8, 109.7, 73.6, 66.3, 64.4, 34.0, 32.5, 29.63, 29.58, 29.50, 29.4, 29.25, 29.20, 29.1, 29.0, 28.97, 28.90, 28.8, 27.1, 26.6, 25.3, 24.8 ppm. FT-IR (film of a concd. solution in CH_2Cl_2): ν=2986, 2928, 2854, 1743, 1381, 1372, 1219, 1159, 1087, 1056, 841, 772 cm^{-1}. ESI-MS m/z 591.9 ([M+Na]$^+$). ESI-HRMS calcd for $C_{32}H_{56}O_8Na$ ([M+Na]$^+$): 551.38674, found 591.38773.

4.9. Hydrogenation of 14 to give 15

A mixture of **14** (140 mg, 0.25 mmol) and 10% Pd–C (60 mg, washed with water, EtOH and EtOAc before use) in EtOAc (2.5 mL) was stirred under H_2 (1 atm) at ambient temperature for 3 h, when TLC showed completion of the reaction (no more yellow spot could be seen on the TLC plate when visualizing with $KMnO_4$). The solids were filtered off. The filtrate was concentrated by rotary evaporation to afford **15** as a white wax (128 mg, 0.22 mmol, 90%). Mp 54–55 °C. $[\alpha]_D^{28}$ +1.0 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.30 (br quint, J=6.1 Hz, 2H), 4.15 (dd, J=11.3, 4.6 Hz, 2H), 4.08 (dd, J=17.1, 6.3 Hz, 2H), 4.07 (dd, J=7.2, 3.1 Hz, 2H), 3.73 (dd, J=8.4, 6.2 Hz, 2H), 2.33 (t, J=7.0 Hz, 4H), 1.61 (br quint, J=7.2 Hz, 4H), 1.43 (s, 6H), 1.36 (s, 6H), 1.34–1.18 (m, 28H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=173.6, 109.8, 73.6, 66.3, 64.5, 34.1, 29.66, 29.65, 29,62, 29.57, 29.4, 29.2, 29.1, 26.7, 25.4, 24.9 ppm. FT-IR (film of a concd. solution in CH_2Cl_2): ν=2985, 2961, 2919, 2850, 1735, 1261, 1160, 1091, 1051, 1028, 801 cm^{-1}. ESI-MS m/z 593.9 ([M+Na]]$^+$). ESI-HRMS calcd for $C_{32}H_{58}O_8Na$ ([M+Na]$^+$): 593.40239, found 593.4023.

4.10. Hydrolysis of the acetonides in 15 to afford 12 and 12′

A solution of **15** (104 mg, 0.18 mmol) in HOAc–H_2O (4:1, v/v, 2.5 mL, with the stock solution pre-warmed at 50 °C before use) was stirred at 50 °C for 25 min (when TLC showed disappearance of **15**). The heating bath was removed. H_2O (10 mL) was added to the reaction mixture. Powdered $NaHCO_3$ (ca. 3.0 g) was added very slowly to neutralize the HOAc. The mixture was extracted with EtOAc (30 mL×3), washed with brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left a residue, which was chromatographed on silica to give **12′** (the less polar component, a white waxy solid, eluting with 1:2 PE/EtOAc, 50 mg, 0.09 mmol, 53% from **15**) and **12** (the more polar component, a white powder, eluting with 8:1 CH_2Cl_2/MeOH, 25 mg, 0.05 mmol, 28% from **11**).

Data for **12′**: Mp 55–56 °C. $[\alpha]_D^{27}$ +0.3 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ=4.29 (br quint, *J*=5.9 Hz, 1H), 4.19–4.09 (m, 3H), 4.09–4.01 (m, 2H), 3.90 (br quint, *J*=5.2 Hz, 1H), 3.72 (dd, *J*=8.3, 6.3 Hz, 1H), 3.67 (dd, *J*=10.8, 3.3 Hz, 1H), 3.57 (dd, *J*=11.6, 5.8 Hz, 1H), 2.32 (t, *J*=7.1 Hz, 4H), 1.60 (br quint, *J*=7.3 Hz, 4H), 1.41 (s, 3H), 1.35 (s, 3H), 1.32–1.16 (m, 28H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=174.3, 173.6, 109.8, 73.6, 70.2, 66.3, 65.1, 64.4, 63.3, 34.09, 34.05, 29.60, 29.58, 29.56, 29.51, 29.34, 29.2, 29.0, 26.6, 25.3, 24.83, 24.82 ppm. FT-IR (film of a solution in CH_2Cl_2): ν=3412 (br), 2986, 2918, 2849, 1733, 1473, 1386, 1374, 1263, 1228, 1191, 1095, 1051, 847, 802 cm^{-1}. ESI-MS *m*/*z* 553.9 ($[M+Na]^+$). ESI-HRMS calcd for $C_{29}H_{54}O_8Na$ ($[M+Na]^+$): 553.37109, found 553.3701.

Data for **12**: Mp 91–92 °C. $[\alpha]_D^{26}$ +15.8 (*c* 0.20, DMSO). ^1H NMR (500 MHz, $CDCl_3$): δ=4.21 (dd, *J*=11.6, 5.1 Hz, 1.8H), 4.15 (dd, *J*=11.5, 6.4 Hz, 1.8H), 3.96–3.90 (m, 1.8H), 3.72–3.58 (m, 4.6H), 2.35 (t, *J*=7.4 Hz, 4H), 1.63 (br quint, *J*=7.3 Hz, 4H), 1.40–1.20 (m, 28H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6, with the central line for the solvent signal set to 39.52 ppm as the internal reference) δ=173.0, 69.3, 65.5, 62.6, 33.5, 29.04 (ca. twice as intense as other lines in the 29–28 ppm region), 28.99, 28.89, 28.7, 28.5, 24.5 ppm. FT-IR (film of a solution in CH_2Cl_2): ν=3257 (br), 2916, 2848, 1733, 1462, 1194, 1176, 1051 cm^{-1}. ESI-MS *m*/*z* 513.7 ($[M+Na]^+$). ESI-HRMS calcd for $C_{26}H_{50}O_8Na$ ($[M+Na]^+$): 513.33979, found 513.3399.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.021. These data include MOL files and InChiKeys of the most important compounds described in this article.

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