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Enantiodivergent total synthesis of trioxilins B_3 using Sharpless asymmetric olefin dihydroxylation†

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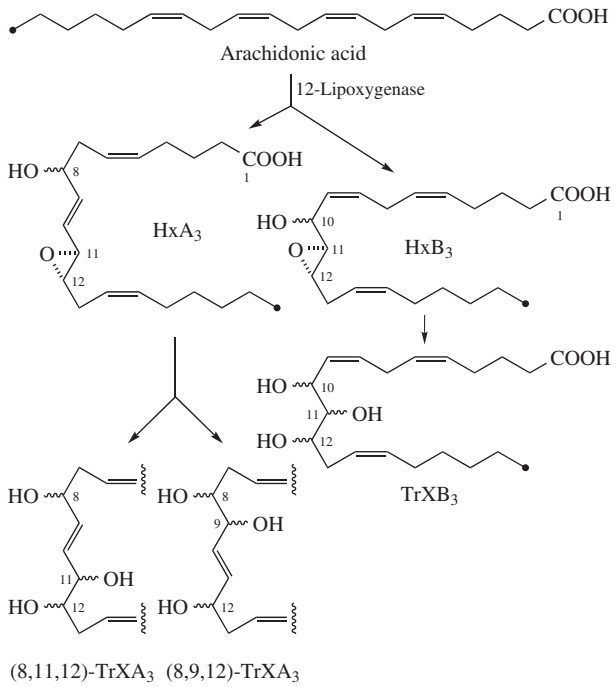
The unknown 11,12-*threo*-stereoisomers of B-type trioxilins, (10*R*,11*R*,12*S*)-TrXB_3, its (10*S*)-epimer and their enantiomers were synthesized (as methyl esters) from a common racemic precursor, *viz.*, methyl *rac*-10-hydroxyeicos-11(*E*)-ene-5,8,14-triynoate, by Sharpless enantiodirected dihydroxylation of the double bond as the key step.

Trioxilins (TrX)‡ are regio- and stereoisomeric triply hydroxylated metabolites of arachidonic acid and related C_{20} acids formed by the 12-lipoxygenase metabolic pathway *via* the corresponding hepoxilins as a result of hydrolytic cleavage of the epoxy ring in the compounds.[2] Series 3 trioxilins (from arachidonic acid) and series 4 trioxilins (from eicosapentaenoic acid[3]) have been identified. Depending on the locations of the hydroxyl groups in the 20-carbon chain, A-type trioxilins with hydroxyl groups at the 8,9,12- or 8,11,12-positions, as well as B-type trioxilins with hydroxyl groups at the 10,11,12-positions, are distinguished (see Scheme 1). Although trioxilins were the first identified 12-lipoxygenase metabolites of arachidonic acid,[4] much less is known about them as compared with their precursors. We are not familiar with any publications about the bioactivity

† Communication 11 from the series 'Synthetic study of hepoxilins'. For communication 10, see ref. 1.



Scheme 1

of trioxilins; the isomeric composition of endogenous mixtures of trioxilins has certainly been studied insufficiently,[5] and even the enzymatic nature of biosynthesis of B-type trioxilin precursors, *i.e.*, B-type hepoxilins, is sometimes challenged.[6] To clarify these issues, a number of total syntheses of various trioxilins have recently been described, all of which started from natural chiral precursors (carbohydrates,[7] quinic acid[8]), as well as one partial synthesis from hepoxilins.[9]

The recently discovered reaction of enantiodirected dihydroxylation of olefins (REDO)[10] opens up new prospects for the total synthesis of trioxilins because all compounds have an α-glycol moiety. The REDO provides not only the possibility of chiral synthesis from nonchiral or racemic starting materials but also makes it possible to obtain both enantiomers by a single synthetic scheme (enantiodivergent synthesis). We have performed just this type of total synthesis.

The synthesis was based on previously described hydroxyenetriyne *rac*-**3**[11,12] as the starting compound. In this work, we obtained this compound in a shorter way from hydroxyenyne **1**[13] *via* unstable aldehyde **2** by an elongation of the carbon chain by two standard methods (Scheme 2).[11,14] Hydroxyenetriyne *rac*-**3**, which is even less stable, was partially stabilised by conversion into *tert*-butyldimethylsilyl (BMS) ether *rac*-**4**. The applicability of enetriyne *rac*-**4** as a substrate for selective oxidation only of a single double bond is based on the known inertness of triple bonds under REDO conditions.[15]

Dihydroxylation of enetriyne *rac*-**4** by commercial reagent mixtures for REDO (AD-mix-α and AD-mix-β) proceeded very slowly and resulted in the tarring of the major part of this labile substrate. These reagents in quantities recommended for the oxidation of 1 mol of an olefin[§] contain 0.2 mol% $K_2OsO_4·2H_2O$. To accelerate the reactions, the commercial reagents were modified by addition of $K_2OsO_4·2H_2O$ up to a concentration of 0.8 mol% and of $MeSO_2NH_2$ (a catalyst of intermediate osmate ester hydrolysis[17]). Henceforth, these modified mixtures are referred to as mod-AD-mix-α and mod-AD-mix-β, respectively.[¶] According to literature data, this modification of AD-mixtures does not decrease the enantioselectivity of REDO.[10]

Oxidation of enetriyne *rac*-**4** with an equimolar amount[§,¶] of mod-AD-mix-β in a thoroughly degassed solution and in an argon atmosphere was carried out until the reaction slowed down considerably (48 h at 0 °C). Chromatographic separation of the resulting mixture gave 36% of enantiomerically enriched (*R*)-**4** and 29% (45% from unrecovered **4**) of a mixture of epimers (3:1) of partially protected triols (10*R*/*S*,11*S*,12*R*)-**5**.[††,‡‡] The balance consisted of more polar products resulting from additional oxidation by the reagent or atmospheric oxygen during the reaction and isolation. Similar oxidation of hydroxyenetriyne *rac*-**3**, which is even more labile, mainly gave overoxidation products.[§§]

The absolute configuration of 11,12-hydroxyl groups in triols **5** is clear *a priori* from the reliably established enantiodirection of REDO carried out with chiral controllers, $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$.[10] This configuration and the ee ≥ 95% of the products were later confirmed experimentally for products obtained from triols **5** (see ref. 19). A proof of the configurations of the products at C^{10} is given below.

It follows from the identical absolute configuration at C^{12} of the mixture (10*R*/*S*,11*S*,12*R*)-**5** components that the major epimer, (10*R*,11*S*,12*R*)-**5**, is formed from the (10*S*)-enantiomer of substrate *rac*-**4**,[¶¶] whereas the minor epimer, (10*S*,11*S*,12*R*)-**5**, is formed from the (10*R*)-enantiomer. Thus, in our case, both enantiomers of the racemic substrate undergo the REDO but with different rates. The enantiomer (*R*)-**4** reacting more slowly

‡ Trivial names and abbreviations: arachidonic acid is (all-*Z*)-5,8,11,14-eicosatetraenoic acid; eicosapentaenoic acid is (all-*Z*)-5,8,11,14,17-eicosapentaenoic acid; eicosanoids of series 3 or 4 are eicosanoids with 3 or 4 double bonds in a molecule, respectively; hepoxilins (of types A_3/B_3) are stereoisomers of 8/10-hydroxy-11,12-epoxyeicosa-5(*Z*),9(*E*)/8(*Z*),14(*Z*)-trienoic acids; $TrXA_3$ are stereoisomers of 8,9(or 11),12-trihydroxyeicosa-5(*Z*),10(or 9)(*E*),14(*Z*)-trienoic acid; $TrXB_3$ are stereoisomers of 10,11,12-trihydroxyeicosa-5(*Z*),8(*Z*),14(*Z*)-trienoic acid (each eicosanoid can occur as a free acid or its methyl ester); $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ are dihydroquinine and dihydroquinidine diethers of 1,4-dihydroxyphthalazine, respectively.

§ The repeated statements in the literature regarding the necessity of using AD-mix amounts containing *three* mol of $K_3Fe(CN)_6$ per mole of an olefin in REDO[10] should probably be considered as a *practical* requirement. *Theoretically*, according to the reaction equation, *two* mol of $K_3Fe(CN)_6$ (in the appropriate amount of an AD-mix) per mole of an olefin are required. Several instances were reported where this stoichiometry was used for a better control of the degree of olefin conversion.[16]

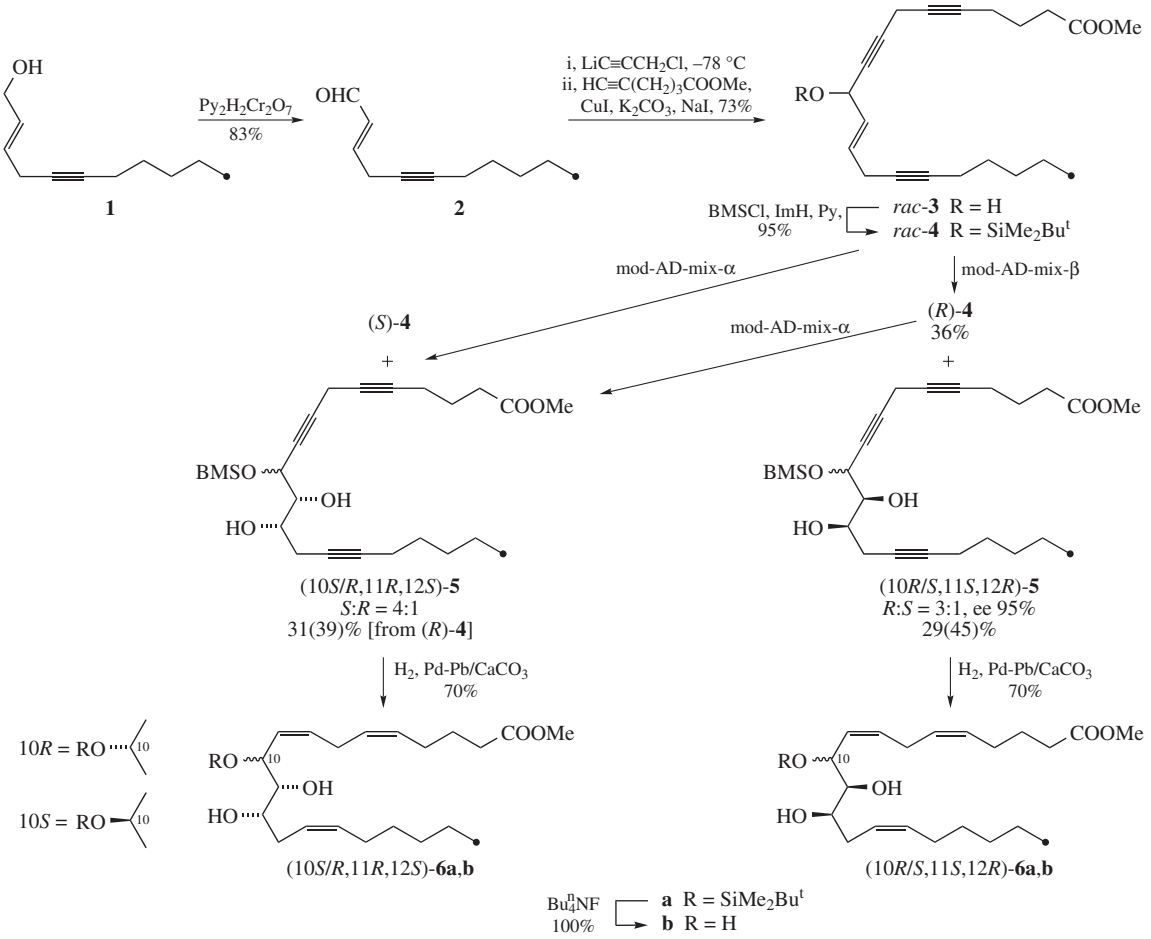
¶ These mod-AD-mixs contain (per 1.036 g of the reagent) 658 mg (2.0 mmol) of $K_3Fe(CN)_6$, 276 mg (2.0 mmol) of K_2CO_3, 95 mg (1 mmol) of $MeSO_2NH_2$, 1.91 mg (5.2 μmol, 0.52 mol% with respect to an olefin) of $K_2OsO_4·2H_2O$ and 5.2 mg (6.7 μmol, 0.67 mol%) of a chiral controller, *viz*., $(DHQ)_2PHAL$ (mod-AD-mix-α) or $(DHQD)_2PHAL$ (mod-AD-mix-β). The specified amount of these mixtures is theoretically sufficient for dihydroxylation of 1 mmol of an olefin and is referred to as 1 mmol of the reagent.

†† Henceforth, the major epimer is indicated first in designations of the mixtures.

‡‡ The solution of enetriyne *rac*-**4** (4.1 g, 9.3 mmol) and mod-AD-mix-β (9.63 g, 9.3 mmol) in Bu^tOH (30 ml) and water (30 ml) was degassed by evacuation, covered with argon and stirred for 48 h at 0 °C until conversion of the original compound slowed down considerably (TLC monitoring). Crystalline Na_2SO_3 (10 g) was added; the mixture was stirred for 1 h and extracted with EtOAc. The organic extracts were washed with a 2 N KOH solution (20 ml) and then with water to pH 7, dried and concentrated. Rapid chromatography of the residue on 100 g of SiO_2 (EtOAc–hexane, 1:9 + 0.1% Et_3N) afforded 1.49 g (36%) of (*R*)-**4**, light yellow oil, R_f 0.50 (system A: Silufol UV_{254} silica gel plates; hexane–EtOAc, 8:2), $[\alpha]_D^{25}$ +3.5° (*c* 1.038, $CHCl_3$), and 1.25 g (29%, 45% on unrecovered **4**) of a mixture (10*R*/*S*,11*S*,12*R*)-**5** with the 3:1 ratio (according to NMR). For characterization, an aliquot portion of the mixture was separated into individual epimers by preparative TLC (system A + 0.1% Et_3N, two developments).

Major epimer (10*R*,11*S*,12*R*)-**5**: light yellow oil, R_f 0.19 (system A), $[\alpha]_D^{25}$ –17.6° (*c* 1.325, $CHCl_3$). ^1H NMR (80 MHz, $CDCl_3$) δ: 0.16 and 0.19 (2s, 6H, $SiMe_2$), 0.91 (m, 12H, $SiBu^t$ + $C^{20}H_3$), 1.25–1.37 (m, 6H, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.81 (quintet, 2H, C^3H_2, *J* 7.5 Hz), 2.05–2.36 (m, 4H, C^4H_2, $C^{16}H_2$), 2.42 (t, 2H, C^2H_2, *J* 7.5 Hz), 2.51 (m, 2H, $C^{13}H_2$), 2.74 (br. d, 1H, 11-OH, *J* 8.0 Hz), 3.0 (br. d, 1H, 12-OH, *J* 3.0 Hz), 3.16 (q, 2H, C^7H_2, *J* 2.5 Hz), 3.50–3.74 (m, 1H, H^{11}), 3.68 (s, 3H, OMe), 4.24 (td, 1H, H^{12}, *J* 13.5 and 1.5 Hz), 4.61 (dt, 1H, H^{10}, *J* 4.25 and 2.0 Hz). IR (ν/cm^{-1}): 3456 (OH), 1742 (C=O), 1245 ($SiMe_2Bu^t$), 839, 779.

Minor epimer (10*S*,11*S*,12*R*)-**5**: light yellow oil, R_f 0.24 (system A), $[\alpha]_D^{25}$ +12.5° (*c* 0.51, $CHCl_3$). The IR and NMR spectra are identical to those of the (10*R*)-epimer with the following exceptions: 3.93 (td, 1H, $C^{12}H$, *J* 13.7 and 2.0 Hz), 4.53 (dt, 1H, H^{10}, *J* 4.25 and 2.0 Hz).



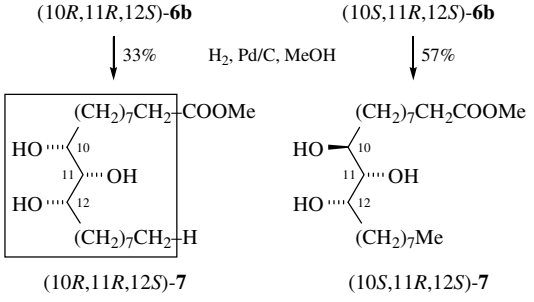
Scheme 2

is gradually accumulated in the unreacted fraction of the substrate; as a result, the reaction slows down.

Enetriyne *rac*-**4** can equally be used to synthesize enantiomers of the above products since, as expected, its reaction with mod-AD-mix-α gave (*S*)-**4** and (10*S*/*R*,11*R*,12*S*)-**5** with results similar to those reported above for the quasi-enantiomeric mod-AD-mix-β. However, the efficiency of such an enantiodivergent synthesis is inferior to another possibility, *viz.*, to the use (as the substrate for mod-AD-mix-α) of scalemic enetriyne (*R*)-**4** obtained in the reaction with the β-reagent and enriched with the enantiomer that reacts more rapidly with the quasi-enantiomeric α-reagent. In fact, this reaction resulted in (10S/*R*,11*R*,12*S*)-**5** with an epimer ratio of 4:1, which reflects the larger proportion of the corresponding enantiomer in the substrate. Unreacted enetriyne **4** (21%) was, in this case, virtually a racemate, $[\alpha]_D^{25}$ ±0° (*c* 1.17, $CHCl_3$). This scheme of enantiodivergent synthesis with two subsequent REDOs of *rac*-**4** makes it possible to obtain, in two stages, four practically homochiral stereoisomers of **5** in an overall yield of 40% (or 43% on the unrecovered starting compound). The fact that the scheme involves few stages is particularly important when one works with highly labile triacetylenic compounds, which are mostly lost due to degradation during manipulations.

Products **5** constitute triacetylenic analogues of 10-protected trioxilins B_3, hence the completion of the synthesis is trivial. Simultaneous partial hydrogenation of all the three triple bonds in triacetylenes **5** under the conditions developed previously for similar polyacetylenes[13,14] results in 10-silyl esters of $TrXB_3$ **6a**, desilylation of which gives four stereoisomers of trioxilins B_3 **6b**. It is convenient to perform the steps **5** → **6a** → **6b** with mixtures of C^{10} epimers; in this case, it is necessary to separate only epimers of $TrXB_3$ **6b** by high-performance flash chromatography.[20,†††]

To determine the configurations at C^{10} for all the compounds obtained, 10-epimeric compounds (10*R*,11*R*,12*S*)-**6b** and (10*S*,11*R*,12*S*)-**6b** were subjected to exhaustive hydrogenation to the corresponding saturated 10-epimeric triols (10*R*,11*R*,12*S*)-**7** and (10*S*,11*R*,12*S*)-**7** ($TrXB_0$) (Scheme 3). In molecules of each of these compounds, two substituents at the ends of the triol moieties are nearly identical; differences in substituents appear only behind eight methylene groups. Therefore, the isomer with the *syn*,*syn*-configuration of hydroxyl groups, and this isomer



Scheme 3

§§ Two additional attempts to improve the process were undertaken. The use of a mild stoichiometric REDO version[18] (osmylation at –78 °C) with *rac*-**4** resulted mainly in tar formation at the osmate ester decomposition at 20 °C. An oxidation of the *E*,*Z*,*Z*,*Z*-tetraene corresponding to enetriyne *rac*-**4** (obtained by hydrogenation of the enetriyne with the Lindlar catalyst) by treatment with mod-AD-mix-β proceeded with total lack of selectivity for the *E*-double bond.[10]

¶¶ In compounds (*S*)-**4** and (10*R*,11*S*,12*R*)-**5** (and in other similar pairs), the 10-hydroxy groups have the same 'real' absolute configurations. The differences in the designations of these configurations by the *R*,*S*-nomenclature are due to different orders of precedence of the substituents at the asymmetric C^{10} centres in such pairs of compounds.

only, can be considered as having a quasi-symmetric triol moiety. Indeed, the ^{1}H NMR spectra in the region of carbinol protons (δ 3.2–3.9) contain three one-proton signals for triol (10*S*,11*R*,12*S*)-**7** but only two signals (one- and two-proton) for triol (10*R*,11*R*,12*S*)-**7** (obtained from the minor REDO epimer) because the chemical shifts of the H^{10} and H^{12} protons in this *syn*,*syn*-isomer are virtually identical. The relative C^{10} configurations of triols and all their precursors were deduced from this fact.‡‡‡

The procedure developed allows one to perform an enantiodirected and enantiodivergent synthesis of chiral trioxilins B_3 in no more than ten chemical steps from commercially available starting compounds. Intermediate partially protected derivatives **6a** can also be used to synthesise type-A_3 trioxilins.

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† † † A solution of freshly purified triyne (10*S*/*R*,11*R*,12*S*)-**5** (460 mg) and quinoline (854 µl) in a suspension of the Lindlar catalyst (593 mg) in benzene (10 ml) was hydrogenated at 7–10 °C and 1 atm until the starting and intermediate products disappeared (TLC monitoring) (1 h, 82 ml of H_2). The catalyst was filtered off, and the filtrate was directly and quickly chromatographed on 40 g of neutral Al_2O_3 (Brockman activity grade II). Elution with benzene removed quinoline; elution with an EtOAc–hexane mixture (1:1) resulted in the isolation of 327 mg (70%) of a triene mixture (10*S*/*R*,11*R*,12*S*)-**6a**, light yellow oil, $[\alpha]_D^{25}$ ±0° (*c* 0.74, $CHCl_3$), R_f 0.32 (system A), HPLC (200×4 mm column with Silasorb SPH 300, 6 µm, system: 4% THF in hexane, 2.0 ml/min, UV detector at 210 nm): RT 9.4 (minor *R*-epimer) and 10.0 min, 10*R*:10*S* epimer ratio = 1:4. A solution of this mixture (120 mg, 0.25 mmol) and Bu^n_4NF (261 mg, 1 mmol) in THF (3 ml) was kept for 1 h at 20 °C, diluted with water (3 ml) and extracted with EtOAc. A mixture of triols (10*S*/*R*,11*R*,12*S*)-**6b** (92 mg, 100%) was isolated from the extract and separated by HPLC (benzene, then EtOAc–hexane, 5:95 → 40:60) into individual epimers.

Major epimer (10*S*,11*R*,12*R*)-**6b** ($TrXB_3$): colourless oil, R_f 0.12 (system B: Silufol UV_{254} silica gel plates; hexane–EtOAc, 6:4), $[\alpha]_D^{25}$ +17.3° (*c* 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: 0.86 (t, 3H, $C^{20}H_3$, *J* 6.5 Hz), 1.22–1.37 (m, 6H, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.67 (quintet, 2H, C^3H_2, *J* 7.4 Hz), 2.04 (q, 2H, $C^{16}H_2$, *J* 7.4 Hz), 2.01–2.14 (m, 2H, C^4H_2), 2.28 (dt, 1H, H^{13A}, *J* 14.8 and 7.4 Hz), 2.33 (t, 2H, C^2H_2, *J* 7.4 Hz), 2.39 (dtd, 1H, H^{13B}, *J* 14.8, 7.4 and 1.5 Hz), 2.60 (d, 1H, 12-OH, *J* 3.9 Hz), 2.67 (d, 1H, 11-OH, *J* 7.0 Hz), 2.74 (dt, 1H, H^{7A}, *J* 16.2 and 6.0 Hz), 2.78 (d, 1H, 10-OH, *J* 4.7 Hz), 2.91 (dt, 1H, H^{7B}, *J* 16.2 and 6.8 Hz), 3.38 (ddd, 1H, H^{11}, *J* 2.3, 4.7 and 7.0 Hz), 3.65 (s, 3H, OMe), 3.89 (m, 1H, $C^{12}H$), 4.64 (dt, 1H, H^{10}, *J* 9.4 and 4.7 Hz), 5.32–5.41 (m, 3H, H^5, H^6, H^{14}), 5.46–5.61 (m, 3H, H^8, H^9, H^{15}).

Minor epimer (10*R*,11*R*,12*S*)-**6b** ($TrXB_3$): colourless oil, R_f 0.15 (system B), $[\alpha]_D^{25}$ –29.5° (*c* 0.95, $CHCl_3$). The ^{1}H NMR (400 MHz, COSY, $CDCl_3$) is similar to the spectrum of the major epimer, with the following differences: 1.60 (1H, br. s, 10-OH), 2.43 (d, 1H, 12-OH, *J* 6.5 Hz), 2.74 (d, 1H, 11-OH, *J* 6.5 Hz), 2.78 (dt, 1H, H^{7A}, *J* 16.2 and 6.0 Hz), 2.95 (dt, 1H, H^{7B}, *J* 16.2 and 7.2 Hz), 3.31 (t, 1H, H^{11}, *J* 6.5 Hz), 3.61 (m, 1H, $C^{12}H$), 3.65 (s, 3H, OMe), 4.54 (dd, 1H, H^{10}, *J* 6.5 and 8.9 Hz).

‡‡‡ (10*R*,11*R*,12*S*)-**7** ($TrXB_0$): white crystals, mp 59–60 °C (EtOAc), R_f 0.17 (system B), $[\alpha]_D^{25}$ –11.9° (*c* 0.17, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $C^{20}H_3$, *J* 6.6 Hz), 1.31 (m, 18H, C^4H_2, C^5H_2, C^6H_2, C^7H_2, $C^{15}H_2$, $C^{16}H_2$, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.53 (m, 10H, C^3H_2, C^8H_2, C^9H_2, $C^{13}H_2$, $C^{14}H_2$), 2.30 (t, 2H, C^2H_2, *J* 6.6 Hz), 3.27 (m, 1H, H^{11}), 3.65 (m, 2H, H^{10}, H^{12}), 3.66 (s, 3H, OMe).

(10*S*,11*R*,12*S*)-**7** ($TrXB_0$): white crystals, mp 103–104 °C (EtOAc), R_f 0.14 (system B), $[\alpha]_D^{25}$ +9.2° (*c* 0.29, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $C^{20}H_3$, *J* 6.6 Hz), 1.31 (m, 18H, C^4H_2, C^5H_2, C^6H_2, C^7H_2, $C^{15}H_2$, $C^{16}H_2$, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.60 (m, 10H, C^3H_2, C^8H_2, C^9H_2, $C^{13}H_2$, $C^{14}H_2$), 2.30 (t, 2H, C^2H_2, *J* 6.6 Hz), 3.32 (m, 1H, H^{11}), 3.66 (s, 3H, OMe), 3.77 (m, 1H, H^{12}), 3.88 (t, 1H, H^{10}, *J* 6.1 Hz).

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