A Stereoselective Total Synthesis of Xyolide, a Natural Bioactive Nonenolide[1])

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A stereoselective total synthesis of xyolide, a naturally occurring bioactive nonenolide, has been accomplished. The acid fragment of the molecule has been prepared from D-mannitol and the alcohol fragment from (2*Z*)-but-2-ene-1,4-diol. The synthesis involves the coupling of these two fragments using the *Yamaguchi* esterification protocol, followed by intramolecular ring-closing methathesis. The diastereoisomeric alcohol fragment has also been utilized in this synthesis by employing the *Mitsunobu* esterification.

Introduction. – Naturally occurring nonanolides and nonenolides (ten-membered lactones) possess interesting structural patterns and impressive biological properties [1]. They contain various functionalities with different configurations. They also bear alkyl side chains of various lengths. Some of the natural nonenolides, such as herbarumins I, II, and III [2], stagonolides A and B [3], and seimatopolides A and B [4] (*Fig.*), have been found to exhibit diverse bioactivities including phytotoxic, herbicidal, and anticancer properties.

Xyolide (**1**; *Fig.*), a ten-membered lactone, has recently been isolated from an Amazonian endophyte *Xylaria ferieensis* [5]. The structure of the compound was established by 1D- and 2D-NMR spectral analysis, and its absolute configuration (4*S*,7*S*,8*S*,9*R*) by exciton-coupled circular dichroism spectroscopy. The molecule contains a long-chain alkyl group at C(9), along with *cis*-vicinal OH groups at C(7) and C(8) with α-configuration. The third OH group at C(4) (also with α-configuration) of **1** is esterified with succinic acid. The compound was found to inhibit the plant pathogen, *Pythium utimum* with a *MIC* value of 425 μM. The structure and bioactivity of xyolide (**1**) have attracted the attention of organic chemists to perform its synthesis [6]. Here, we report our approach for a stereoselective total synthesis of **1**.

Results and Discussion. – In continuation of our work [7] on the stereoselective construction of natural bioactive molecules, we have realized that xyolide (**1**) might be synthesized from the diene **2**, which can be prepared from the alcohol fragment **3** and acid fragment **4** (*Scheme 1*). A similar strategy has been applied in a previous synthesis of xyolide [6c]. However, the stereoselective preparation of the two fragments, **3** and **4**, are different here, and they were obtained from (2*Z*)-but-2-ene-1,4-diol (**5**) and D-mannitol (**6**), respectively.

[1]) Part 82 in the series 'Synthetic Studies on Natural Products'.

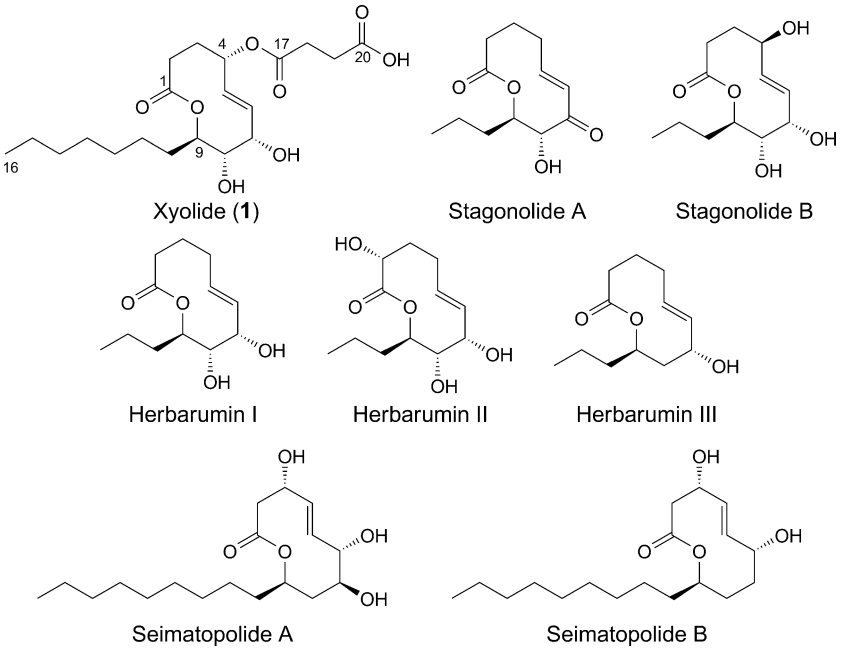
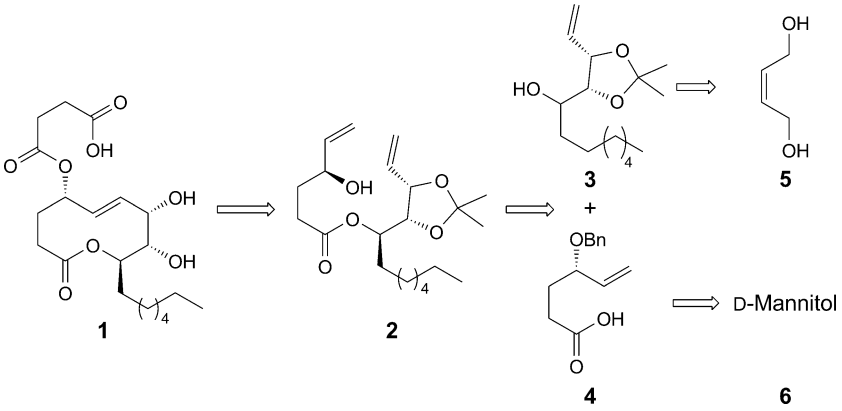


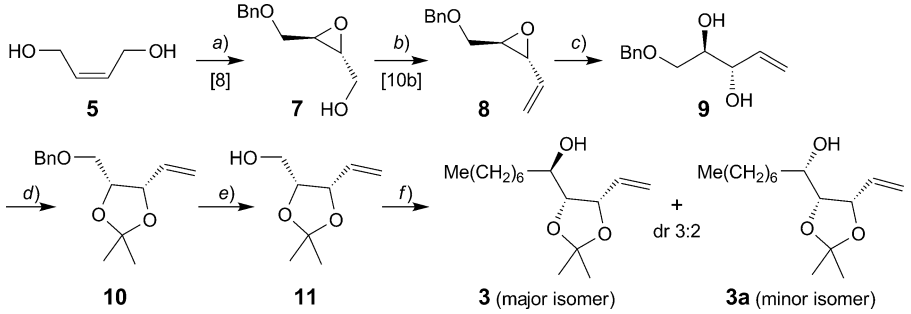
Figure. *Structures of some nonenolides*

Scheme 1. *Retrosynthetic Analysis of* **1** (see also [6c])



Synthesis of the Alcohol Fragment **3**. For the synthesis of **3**, (2*Z*)-but-2-ene-1,4-diol (**5**) was converted to the known chiral epoxy alcohol **7** [8], which was oxidized with $SO_3 \cdot Py$ [9] in CH_2Cl_2, and the corresponding aldehyde was subjected to C_1-*Wittig* olefination [10a] with Ph_3PCH_3Br using NaHMDS in THF to form the epoxy alkene **8** (*Scheme 2*). The analogous transformation of **7** into **8** has been already described in [10b]. The epoxy ring of **8** was opened with $Sc(OTf)_3$ in THF/H_2O 10 : 1 to furnish the diol **9** [11]. The two OH groups of **9** were protected as acetonide (→**10**) by treatment

Scheme 2. *Synthesis of the Alcohol Fragment* **3**



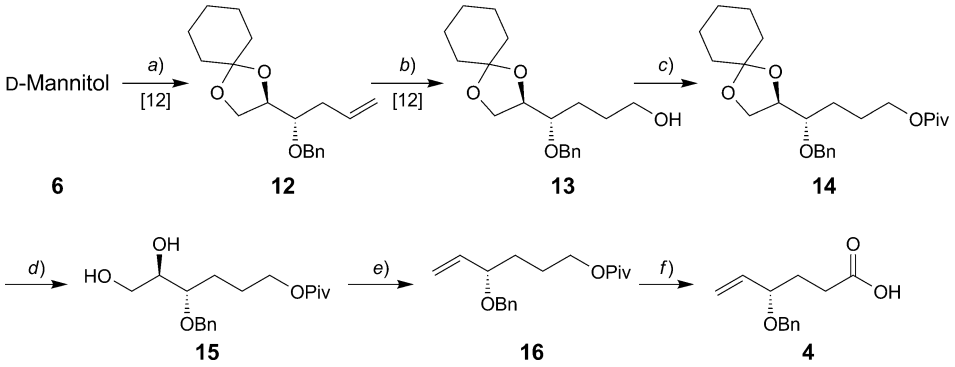
a) See [8]. *b*) *i*) $SO_3 \cdot Py$, CH_2Cl_2/DMSO 3:1, Et_3N, 0°, 2 h; *ii*) Ph_3PCH_3Br, sodium bis(trimethylsilyl)-amide (NaHMDS), THF, 0° – r.t., 8 h; 84% (for two steps). *c*) Scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$), THF/H_2O (10:1), 3 h; 94%. *d*) 2,2-Dimethoxypropane(2,2-DMP), CH_2Cl_2, pyrodonium *p*-toluenesulfonate (PPTS), 0° – r.t., 4 h; 98%. *e*) Li Metal, naphthalene, dry THF, – 25°, 2 h; 96%. *f*) *i*) $SO_3 \cdot Py$, CH_2Cl_2/DMSO 3:1, Et_3N, 0°, 1 h; *ii*) $Me(CH_2)_6MgBr$ (1.2M in THF), THF, 0° – r.t., 6 h; 96% (for two steps).

with 2,2-dimethoxypropane (2,2-DMP) and PPTS. The Bn group of **10** was removed with Li and naphthalene to afford the alcohol **11** in high yield. The latter was oxidized with $SO_3 \cdot Py$ in CH_2Cl_2, and the aldehyde obtained was treated with the *Grignard* reagent $Me(CH_2)_6MgBr$ to afford the diastereoisomeric alcohols **3** (major) and **3a** (minor) in a ratio of 3:2. The alcohols **3** and **3a** were separated and used for the next steps. Comparison of the data of the newly introduced stereogenic center C(9) of the target molecule, or C(5) of the diastereoisomers **3** and **3a** with those reported previously confirmed the presence of **3** [6c] as (9*R*) and **3a** as (9*S*)-isomer. Both diastereoisomers were utilized for the synthesis of the target molecule and reconfirmed the absolute configuration of the diastereoisomers at C(5) of the alcohol fragment.

Synthesis of the Acid Fragment **4**. For the synthesis of the acid fragment **4**, D-mannitol (**6**) was initially converted to the known alcohol **13** *via* the alkene **12**, as described in [12] (*Scheme 3*). The free OH group of **13** was protected by treatment with Piv–Cl and Et_3N to afford ester **14**, which was treated with 90% CF_3COOH in H_2O to afford the diol **15**. The latter was reacted with I_2, Ph_3P, and 1*H*-imidazole under reflux to furnish the alkene ester **16** [13]. The ester group in **16** was deprotected by using methanolic K_2CO_3 under reflux, and the alcohol obtained was oxidized with [bis(acetoxy)iodo]benzene (BIAB) and TEMPO in MeCN and H_2O to give the desired acid fragment **4**.

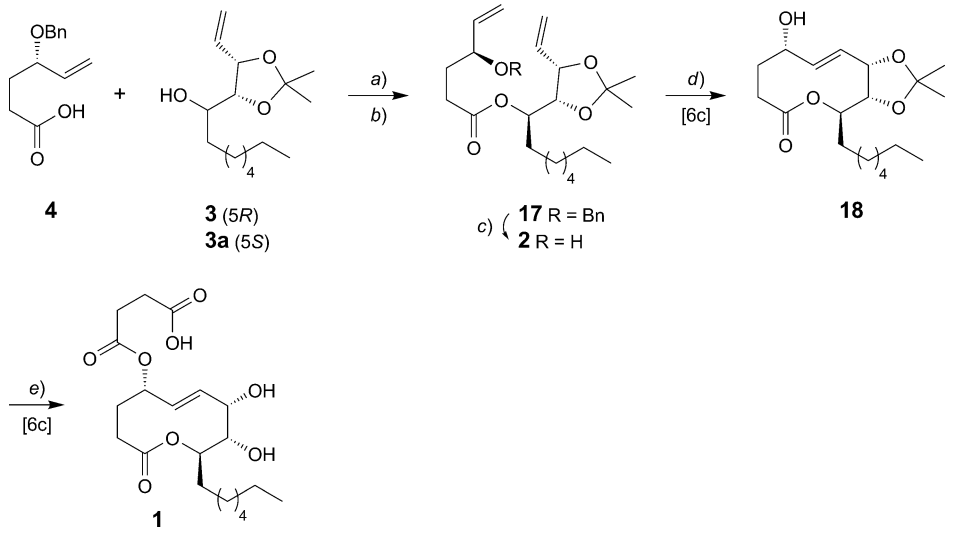
Synthesis of Xyolide (**1**). The alcohol fragment **3** was coupled with the acid **4** under *Yamaguchi* esterification conditions [14] using 2,4,6-trichlorobenzoyl chloride in Et_3N and DMAP to furnish the ester **17** (*Scheme 4*). The same ester **17** was also produced when the alcohol **3a** was esterified with the acid **4** under *Mitsunobu* esterification conditions [15] using Ph_3P and DIAD. Thus, both the major and minor diastereoisomeric alcohols **3** and **3a** (in *Scheme 3*) were employed to obtain the required ester **17**. The Bn-ether group of **17** was cleaved with Li and naphthalene to generate the diene ester **2**, which underwent intramolecular ring-closing methathesis (RCM) [16] in the

Scheme 3. *Synthesis of the Acid Fragment* **4**



a) See [12]. *b*) See [12]. *c*) Pivaloyl chloride (2,2-dimethylpropanoyl chloride; Piv–Cl), Et_3N, CH_2Cl_2, 0° – r.t., 2 h; 98%. *d*) 90% CF_3CO_2H in H_2O, 0°, 2 h; 86%. *e*) Ph_3P, I_2, 1*H*-imidazole, toluene, reflux, 4 h, 92%. *f*) *i*) K_2CO_3, MeOH, reflux, 3 h; *ii*) (Diacetoxyiodo)benzene, (2,2,6,6,-tetramethylpiperidin-1-yl)oxyl (TEMPO), MeCN/H_2O 10 : 1, 0°, 3 h; 90% (for two steps).

Scheme 4. *Synthesis of Xyolide* (**1**)



a) For **3**: 2,4,6-Trichlorobenzoyl chloride, Et_3N, 4-(dimethylamino)pyridine (DMAP), toluene, 0° to r.t., 6 h; 98%. *b*) for **3a**: Ph_3P, diisopropyl azodicarboxylate (DIAD), THF, 0° – r.t., 10 h, 80%. *c*) Li Metal, naphthalene, dry THF, –25°, 4 h, 96%. *d*) *Grubbs*' *II* (cat.), CH_2Cl_2, reflux, 12 h; 82%. *g*) *i*) Succinic anhydride, DMAP, CH_2Cl_2, 0° to r.t., 1 h; *ii*) MeCN, 4N HCl, 0° to r.t., 4 h; 90% (for two steps).

presence of *Grubbs*' second-generation catalyst to yield the nonanolide **18**. The esterification of the free OH group of **18** with succinic anhydride and DMAP, followed by treatment of the product with 4N HCl afforded the xyolide (**1**). The physical (optical

rotation) and spectral (^{1}H-NMR, ^{13}C-NMR, and MS) properties of the synthetic compound **1** were in agreement with those reported for the natural product [5]. It should be mentioned that the reaction steps shown in *Scheme 4* were also used in the earlier synthesis of xyolide, however, the protecting group was different [6c]. The new input is that, in the present synthesis, both diastereoisomers **3** and **3a** have been utilized for the preparation of **17** and **2**.

In conclusion, we have described a simple and straightforward stereoselective synthesis of xyolide, a naturally occurring bioactive nonenolide. The synthesis involves D-mannitol and (2*Z*)-but-2-ene-1,4-diol as the starting materials. The key steps of the synthesis are *Yamaguchi* and *Mitsunobu* esterification and intramolecular ring-closing metathesis. The present synthesis is an access to various analogs of xyolide, required for advanced biological screening.

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Experimental Part

General. All reactions were monitored by TLC (silica gel F_{254} pre-coated plates; visualization with UV light or I_2 stain). Column chromatography (CC): silica gel 60–120 mesh (*Qingdao Marine Chemical*, P. R. China); solvents (AcOEt and hexane) were of technical grade. Optical rotations: *JASCO DIP 360* digital polarimeter. IR: *Perkin-Elmer RX* FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR: *Bruker* (*Avance*) 300 (^{1}H) and 75 MHz (^{13}C), and *Varian Unity* (*Innova*) 500 (^{1}H) and 125 MHz (^{13}C) spectrometers at r.t. ESI-MS: *VG-Autospec* micromass spectrometer; in *m*/*z*.

*(2*R*,3*R*)-2-((Benzyloxy)methyl)-3-vinyloxirane* (= *3,4-Anhydro-5*-O-*benzyl-1,2-dideoxy*-D-threo-*pent-1-enitol*; **8**). To a stirred soln. of *{(2*R*,3*R*)-3-[(benzyloxy)methyl]oxiran-2-yl}methanol* (**7** [8]; 1.5 g, 7.73 mmol) in a mixture of CH_2Cl_2/DMSO 3:1 (15 ml) at 0°, Et_3N (5.43 ml, 38.65 mmol) and SO_3·Py (6.2 g, 38.65 mmol) were added subsequently under N_2. The resulting mixture was stirred at the same temp. for 1 h. After completion of the reaction (TLC), the mixture was diluted with cold H_2O (5 ml), and the org. layer was extracted with Et_2O (3 × 15 ml). The combined org. layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude aldehyde (1.4 g, 96%) was used directly after flash chromatography (FC) for the next reaction.

Methyl(triphenyl)phosphonium bromide (5.12 g, 14.34 mmol) was thoroughly flame-dried, and anh. THF (25 ml) was added, and the resulting suspension was cooled to 0° prior to the dropwise addition of NaHMDS in THF (14.34 ml, 14.34 mmol). The resulting cold suspension was warmed to 25° for 30 min and recooled to −10° prior to the addition of the above aldehyde (1.40 g, 7.29 mmol) soln. in anh. THF (5 ml). The mixture was stirred at r.t. for 10 h, and the reaction was quenched by the addition of sat. aq. NH_4Cl (20 ml). The mixture was then extracted with Et_2O (4 × 10 ml), washed sequentially with H_2O (15 ml) and sat. NaCl (3 × 10 ml), and dried (Na_2SO_4). Removal of solvents under reduced pressure, followed by FC (SiO_2; AcOEt/hexane, 3:7) gave compound **8** (1.2 g, 84%). Colorless oil. $[\alpha]_D^{25} = +10.00$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2988, 2859, 1643, 1454, 1360, 1103, 927, 877, 739, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.38–7.27 (*m*, 5 H); 5.61–5.53 (*m*, 1 H); 5.49 (*d*, *J* = 16.0, 1 H); 5.29 (*d*, *J* = 9.0, 1 H); 4.60 (*d*, *J* = 12.0, 1 H); 4.53 (*d*, *J* = 12.0, 1 H); 3.75 (*dd*, *J* = 12.0, 4.0, 1 H); 3.51 (*dd*, *J* = 12.0, 6.0, 1 H); 3.28 (*dd*, *J* = 7.0, 2.0, 1 H); 3.11–3.08 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 137.7; 134.9; 128.3; 127.6 (2C); 119.6; 73.2; 69.7; 58.5; 55.8. ESI-MS: 191 ($[M+H]^+$). Anal. calc. for $C_{12}H_{14}O_2$ (190.24): C 75.76, H 7.42; found: C 75.61, H 7.38.

(*2*R*,3*S*)-*1-(Benzyloxy)pent-4-ene-2,3-diol* (= *5*-O-*Benzyl-1,2-dideoxy*-D-erythro-*pent-1-enitol*; **9**). To a stirred soln. of **8** ([10]; 1.0 g, 5.26 mmol) in THF/H_2O 10:1 (10 ml) was added $Sc(OTf)_3$ (0.52 g, 0.45 mmol), and the mixture was stirred at r.t. for 3 h. The resulting diol was extracted with AcOEt (4 × 10 ml) and washed sequentially with sat. aq. NH_4Cl and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by CC (SiO_2; AcOEt/hexane 4:6) to provide **9** (1.02 g, 94%). Colorless oil. $[\alpha]_D^{25} = -4.64$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3420, 2921, 2867, 1454, 1098, 994, 928, 698.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.39–7.30 (*m*, 5 H); 5.93–5.84 (*m*, 1 H); 5.35 (*d*, *J* = 16.0, 1 H); 5.22 (*d*, *J* = 9.0, 1 H); 4.56 (*d*, *J* = 12.0, 1 H); 4.52 (*d*, *J* = 12.0, 1 H); 4.29–4.23 (*m*, 1 H); 3.81 (*q*, *J* = 7.0, 1 H); 3.64–3.59 (*m*, 2 H); 2.74 (br. *s*, 1 H); 2.61 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 137.5; 136.4; 128.5; 127.8; 127.9; 116.8; 74.2; 73.6; 72.3; 71.0. ESI-MS: 209 ($[M+H]^+$). Anal. calc. for $C_{12}H_{16}O_3$ (208.25): C 69.21, H 7.74; found: C 69.32, H 7.69.

*(4*R*,5*S*)-4-((Benzyloxy)methyl)-5-ethenyl-2,2-dimethyl-1,3-dioxolane* (*=5-*O*-Benzyl-1,2-dideoxy-3,4-*O*-(1-methylethylidene)-*D*-*erythro*-pent-1-enitol*; **10**). To a stirred soln. of **9** (1.0 g, 4.80 mmol) in 15 ml of dry CH_2Cl_2 was added a cat. amount of PPTS and 2,2-DMP (1.18 ml, 9.61 mmol) at 0°. The mixture was stirred at 0° to r.t. for 6 h. After completion (TLC), the reaction was quenched with cold H_2O (5 ml), and then the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by CC (SiO_2; AcOEt/hexane 2:98) to afford **10** (1.168 g, 98%). Colorless liquid. $[\alpha]_D^{25} = -5.41$ (*c* = 1.0, $CHCl_3$). IR (KBr): 2867, 1453, 1218, 1094, 928, 771, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.38–7.27 (*m*, 5 H); 5.84–5.76 (*m*, 1 H); 5.35 (*d*, *J* = 16.0, 1 H); 5.21 (*d*, *J* = 9.0, 1 H); 4.62–4.56 (*m*, 2 H); 4.51 (*d*, *J* = 12.0, 1 H); 4.39 (*q*, *J* = 7.0, 1 H); 3.48–3.42 (*m*, 2 H); 1.50 (*s*, 3 H); 1.39 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.1; 133.6; 128.5; 127.8; 127.7; 118.1; 109.0; 78.6; 77.0; 73.6; 69.5; 27.9; 25.3. ESI-MS: 249 ($[M+H]^+$). Anal. calc. for $C_{15}H_{20}O_3$ (248.32): C 72.55, H 8.12; found: C 72.68, H 8.06.

*[(4*R*,5*S*)-5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]methanol* (*=1,2-Dideoxy-3,4-*O*-(1-methylethylidene)-*D*-erythro-pent-1-enitol*; **11**). To soln. of naphthalene (2.0 g, 16.13 mmol) in dry THF (15 ml) was added Li metal (112 mg, 16.13 mmol). After 30 min, a dark-green color developed which turned darker after 1.5 h. This soln. was cooled to −25°, and a soln. of **10** (1.0 g, 4.0 mmol) in dry THF (3 ml) was added by cannula. The resulting mixture was stirred at −25° for 3 h. After completion of reaction (TLC), sat. aq. NH_4Cl (5 ml) and H_2O (15 ml) were added. The resulting mixture was extracted with Et_2O (3 × 10 ml), the org. phase was washed with brine and dried (anh. Na_2SO_4). The solvent was removed under reduced pressure to a yield a crude compound, which was purified by CC (AcOEt/hexane 15:85) to afford **11** (0.6 g, 96%). $[\alpha]_D^{25} = -2.22$ (*c* = 1.0, $CHCl_3$). IR (KBr): 3420, 2927, 1646, 1039, 770. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.91–5.82 (*m*, 1 H); 5.41 (*d*, *J* = 16.0, 1 H); 5.29 (*d*, *J* = 9.0, 1 H); 4.64 (*t*, *J* = 7.0, 1 H); 4.28 (*d*, *J* = 7.0, 1 H); 3.59 (*d*, *J* = 7.0, 2 H); 2.21 (br. *s*, 1 H); 1.51 (*s*, 3 H); 1.40 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 133.1; 118.8; 108.8; 78.2; 78.1; 61.8; 27.8; 25.1. ESI-MS: 181 ($[M+Na]^+$). Anal. calc. for $C_8H_{14}O_3$ (158.19): C 60.74, H 8.92; found: C 60.63, H 8.88.

*(1*R*)-1-[(4*R*,5*S*)-5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]octan-1-ol* (**3**). To a stirred soln. of **11** (0.5 g, 3.164 mmol) in CH_2Cl_2/DMSO 3:1 (15 ml) at 0°, Et_3N (2.22 ml, 15.82 mmol) and $SO_3 \cdot Py$ (2.53 g, 15.82 mmol) were added subsequently under N_2. The resulting soln. was stirred at same temp. for 1 h. After completion of the reaction (TLC), the mixture was diluted with cold H_2O (5 ml), and the org. layer was extracted with Et_2O (3 × 15 ml). The combined org. layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude aldehyde was used directly after FC for the next reaction.

To a stirred soln. of the aldehyde (0.45 g, 2.88 mmol) in dry THF (10 ml) was added heptylmagnesium bromide (1.2M soln. in THF) at 0°, and the mixture was stirred for 4 h at the same temp. After completion of the reaction (TLC), sat. aq. NH_4Cl (10 ml) was added at 0°. The mixture was extracted with AcOEt (3 × 10 ml), the org. phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (hexane/AcOEt 97:3) to obtain pure **3** (0.42 g, 1.64 mmol) and **3a** (0.28 g, 1.093 mmol) as colorless liquid (0.70 g, 2.73 mmol, dr 3:2, 96% (for two steps)).

Data of **3**. $[\alpha]_D^{25} = +11.2$ (*c* = 1.0, $CHCl_3$). IR (KBr): 3444, 2926, 2856, 1664, 1379, 1217, 1055, 925, 874, 770, 723. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.08–6.01 (*m*, 1 H); 5.43 (*d*, *J* = 16.0, 1 H); 5.31 (*d*, *J* = 9.0, 1 H); 4.65 (*t*, *J* = 7.0, 1 H); 3.98 (*t*, *J* = 7.0, 1 H); 3.69–3.62 (*m*, 1 H); 1.75–1.68 (*m*, 2 H); 1.49 (*s*, 3 H); 1.38 (*s*, 3 H); 1.34–1.22 (*m*, 10 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 134.9; 118.5; 108.9; 80.9; 79.0; 70.1; 33.9; 31.8; 29.8; 29.2; 28.0; 25.2; 25.1; 22.5; 14.0. ESI-MS: 257 ($[M+H]^+$). Anal. calc. for $C_{15}H_{28}O_3$ (256.38): C 70.27, H 11.01; found: C 70.40, H 11.05.

*Data of (1*S*)-1-[(4*R*,5*S*)-5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]octan-1-ol* (**3a**). $[\alpha]_D^{25} = +7.66$ (*c* = 1.0, $CHCl_3$). IR (KBr): 3445, 2928, 2857, 1717, 1446, 1216, 1067, 765. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.02–5.93 (*m*, 1 H); 5.35 (*d*, *J* = 16.0, 1 H); 5.29 (*d*, *J* = 9.0, 1 H); 4.58 (*t*, *J* = 7.0, 1 H); 4.02 (*t*, *J* = 7.0, 1 H); 3.60–3.53 (*m*, 1 H); 1.52 (*s*, 3 H); 1.48–1.41 (*m*, 4 H); 1.39 (*s*, 3 H); 1.35–1.24 (*m*, 8 H); 0.89

(*t*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 134.1; 119.2; 108.7; 81.0; 79.1; 71.1; 33.8; 31.9; 30.2; 27.5; 25.6; 25.1; 24.4; 22.6; 14.0. ESI-MS: 257 ($[M+H]^+$). Anal. calc. for $C_{15}H_{28}O_3$ (256.38): C 70.27, H 11.01; found: C 70.16, H 10.94.

*4-*O*-Benzyl-5,6-*O*-cyclohexane-1,1-diyl-2,3-dideoxy-1-*O*-(2,2-dimethylpropanoyl)-*D*-*erythro*-hexitol* (**14**). To a stirred soln. of **13** ([12]; 3.0 g, 9.375 mmol) in dry CH_2Cl_2 (15 ml) were added Et_3N (3.16 ml, 22.5 mmol) and Piv–Cl (1.38 ml, 11.25 mmol) subsequently at 0° under N_2. The mixture was stirred for 4 h at r.t. After completion of the reaction (TLC), the mixture was diluted with cold H_2O (10 ml), extracted with CH_2Cl_2 (3 × 10 ml), and the org. layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (hexane/AcOEt 95 : 5) to furnish **14** (3.70 g, 9.16 mmol, 98%). $[\alpha]_D^{25} = +5.4$ (*c* = 1.0, $CHCl_3$). IR (KBr): 2935, 1726, 1282, 1161, 935, 712. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.37–7.28 (*m*, 5 H); 4.61 (*q*, *J* = 11.4, 2 H); 4.10–4.02 (*m*, 4 H); 3.91–3.86 (*m*, 1 H); 3.56–3.52 (*m*, 1 H); 1.65–1.51 (*m*, 12 H); 1.44–1.34 (*m*, 2 H); 1.20 (*s*, 6 H); 1.18 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.5; 138.3; 128.3 (2C); 127.8; 127.7; 109.6; 78.7; 72.5; 66.2; 64.2; 36.3; 34.8; 27.3; 25.1; 24.1; 24.0; 23.8. ESI-MS: 427 ($[M+H]^+$). Anal. calc. for $C_{24}H_{36}O_5$ (404.54): C 71.27, H 8.97; found: C 71.14, H 8.89.

*(4*S*,5*R*)-4-(Benzyloxy)-5,6-dihydroxyhexyl Pivalate* (= *4-*O*-Benzyl-2,3-dideoxy-1-*O*-(2,2-dimethylpropanoyl)-*D*-erythro-hexitol*; **15**). Compound **14** (3.5 g, 9.5 mmol) was dissolved in 90% aq. CF_3CO_2H (10 ml) at 0°, and the mixture was stirred at the same temp. for 2 h. The mixture was then extracted with CH_2Cl_2 (3 × 30 ml). The collected org. layers were combined, washed with 10% $NaHCO_3$ (3 × 50 ml), H_2O, and brine, and dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC (AcOEt/hexane 3 : 7) to afford **15** (2.63 g, 86%). Syrup. $[\alpha]_D^{25} = -6.2$ (*c* = 1.0, $CHCl_3$). IR (KBr): 3442, 2960, 1723, 1283, 1163, 714. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.31 (*m*, 5 H); 4.62 (*d*, *J* = 12.0, 1 H); 4.58 (*d*, *J* = 12.0, 1 H); 4.17–4.03 (*m*, 2 H); 3.80–3.70 (*m*, 3 H); 3.66–3.54 (*m*, 1 H); 1.85–1.80 (*m*, 4 H); 1.20 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.7; 137.9; 129.7; 128.4; 127.8; 79.6; 72.1; 72.0; 63.9; 63.0; 38.5; 27.0; 26.3; 24.2. ESI-MS: 325 ($[M+H]^+$). Anal. calc. for $C_{18}H_{28}O_5$ (324.41): C 66.64, H 8.70; found: C 66.78, H 8.74.

*(*S*)-4-(Benzyloxy)hex-5-en-1-yl Pivalate* (= *(4*S*)-4-(Benzyloxy)hex-5-en-1-yl 2,2-Dimethylpropanoate*; **16**). To a soln. of **15** (2.5 g, 7.71 mmol) in dry toluene (20 ml) was added Ph_3P (8.0 g, 30.54 mmol), followed by 1*H*-imidazole (2.1 g, 30.88 mmol), and stirred vigorously. To the resulting soln. was added I_2 (5.87 g, 23.14 mmol), and the mixture was heated under reflux at 110° for 3 h. The mixture was cooled to r.t., and decanted into excess sat. aq. $Na_2S_2O_3$ (20 ml) and sat. aq. $NaHCO_3$ (30 ml) in a separating funnel. The residue in the reaction flask was extracted with AcOEt (3 × 10 ml). This org. layers were combined with the material in the separating funnel and shaken until the I_2 was consumed. The org. phase was washed with H_2O (2 × 10 ml), and dried and concentrated. The crude residue was purified by CC (hexanes/AcOEt 95 : 5) to give **16** (2.0 g, 6.89 mmol, 92%). Viscous liquid. $[\alpha]_D^{25} = +5.2$ (*c* = 1.0, $CHCl_3$). IR (KBr): 2935, 1736, 1282, 1161, 935, 712. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.24 (*m*, 5 H); 5.81–5.66 (*m*, 1 H); 5.29–5.19 (*m*, 2 H); 4.60 (*d*, *J* = 12.0, 1 H); 4.35 (*d*, *J* = 12.0, 1 H); 4.03 (*t*, *J* = 7.0, 2 H); 3.75 (*q*, *J* = 7.0, 1 H); 1.78–1.58 (*m*, 4 H); 1.19 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.6; 138.6; 138.5; 128.2; 127.6; 127.4; 117.5; 79.9; 70.0; 64.2. 38.6; 31.7; 27.1; 24.5. ESI-MS: 291 ($[M+H]^+$). Anal. calc. for $C_{18}H_{26}O_3$ (290.40): C 74.45, H 9.02; found: C 74.34, H 8.96.

*(*S*)-4-(Benzyloxy)hex-5-enoic Acid* (**4**). To a stirred soln. of **16** (1.8 g, 6.20 mmol) in MeOH (15 ml) was added K_2CO_3 (4.28 g, 31.0 mmol) at r.t., and the mixture was heated at reflux for 2 h. After completion of the reaction (TLC), MeOH was removed under vacuum. Then, the residue was diluted with AcOEt (20 ml), and the mixture was filtered through *Celite* pad. The org. layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield the corresponding alcohol. The crude alcohol was used directly after FC for the next reaction.

To a soln. of the alcohol (1.2 g, 5.82 mmol) in MeCN/H_2O 2 : 1 (20 ml) were added [bis(acetoxy)-iodo]benzene (BAIB; 4.126 g, 12.81 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO; 182 mg, 1.164 mmol) at 0°. The mixture was stirred at r.t. for 3 h. After completion of the reaction (TLC), the mixture was filtered and extracted with AcOEt (3 × 10 ml). The combined org. phases were dried and concentrated under reduced pressure. The crude residue was purified by CC (hexanes/AcOEt 95 : 5) to give the acid fragment **4** (1.15 g, 90% yield). Pale-yellow liquid. $[\alpha]_D^{25} = -25.49$ (*c* = 1.0, $CHCl_3$). IR (neat): 3421, 2925, 1708, 1423, 1070, 929, 698. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.25 (*m*, 5 H); 5.79–5.69 (*m*, 1 H); 5.30–5.22 (*m*, 2 H); 4.60 (*d*, *J* = 12.0, 1 H); 4.33 (*d*, *J* = 12.0, 1 H); 3.81 (*q*, *J* = 7.0, 1 H);

2.50–2.43 (*m*, 2 H); 1.99–1.82 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.5; 138.2; 138.0; 128.2; 127.7; 127.4; 117.8; 79.1; 70.1; 30.1; 29.6. ESI-MS: 221 ($[M+H]^+$). Anal. calc. for $C_{13}H_{16}O_3$ (220.26): C 70.89; H 7.32; found: C 70.74; H 7.25.

*(1*R*)-1-[(4*R*,5*S*)-5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]octyl (4*S*)-4-(Benzyloxy)hex-5-enoate* (**17**). *a*) To a stirred soln. of **4** (0.2 g, 0.90 mmol) in toluene (5 ml) were added Et_3N (0.16 ml, 1.163 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.18 ml, 1.172 mmol) at 0°. The mixture was stirred for 1 h at 0°, and a soln. of **3** (0.2 g, 0.78 mmol) and DMAP (190 mg, 1.56 mmol) in toluene (5.0 ml) were then added at 0°. The resulting mixture was stirred at r.t. for 6 h. After completion of the reaction (TLC), the reaction was quenched with sat. $NaHCO_3$ at 0°, and the mixture was extracted with AcOEt (3 × 10 ml), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by FC (AcOEt/hexane 1:9) to give **17** (0.35 g, 0.76 mmol, 98%). Colorless oil. $[\alpha]_D^{25} = +3.88$ (c = 1.0, $CHCl_3$). IR (neat): 2927, 2856, 1738, 1380, 1248, 1168, 1069, 927, 874, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.38–7.27 (*m*, 5 H); 5.82–5.69 (*m*, 2 H); 5.32–5.18 (*m*, 4 H); 4.90 (*t*, *J* = 7.0, 1 H); 4.60–4.56 (*m*, 2 H); 4.32 (*d*, *J* = 12.0, 1 H); 4.16 (*t*, *J* = 7.0, 1 H); 3.79 (*q*, *J* = 7.0, 1 H); 2.44–2.37 (*m*, 1 H); 2.34–2.27 (*m*, 1 H); 1.97–1.88 (*m*, 1 H); 1.86–1.79 (*m*, 1 H); 1.72–1.64 (*m*, 1 H); 1.63–1.56 (*m*, 2 H); 1.48 (*s*, 3 H); 1.47–1.44 (*m*, 1 H); 1.33 (*s*, 3 H); 1.32–1.22 (*m*, 8 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 172.7; 138.5; 138.2; 133.3; 128.3; 127.7; 127.4; 118.2; 118.0; 108.9; 79.6; 79.1; 78.7; 72.0; 70.1; 32.0; 31.1; 30.2; 30.1; 29.8; 29.2; 27.2; 25.1; 24.8; 22.8; 14.0. ESI-MS: 459 ($[M+H]^+$). Anal. calc. for $C_{28}H_{42}O_5$ (458.63): C 73.33, H 9.23; found: C 73.19, H 9.18.

b) To a soln. of **3a** (0.2 g, 0.78 mmol), **4** (0.2 g, 0.94 mmol), and PPh_3 (0.29 g, 1.1 mmol) in THF (15 ml) at 0° was added DIAD (0.21 ml, 1.1 mmol). Stirring was continued at 0° for 1 h and then at r.t. for 10 h, then the soln. was concentrated and the crude residue was purified by CC (AcOEt/hexane 5:95) to afford **17** (0.29 g, 0.62 mmol, 80%). Colorless oil.

*(1*R*)-1-[(4*R*,5*S*)-5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]octyl (4*S*)-4-Hydroxyhex-5-enoate* (**2**). To soln. of naphthalene (0.67 g, 5.24 mmol) in dry THF (15 ml) was added Li metal (0.037 g, 5.24 mmol). After 30 min, a dark-green color developed which turned darker after 1 h. This soln. was cooled to −25°, and to this a soln. of **17** (0.6 g, 1.31 mmol) in dry THF (3 ml) was added by cannula. The resulting mixture was stirred at −25° for 3 h. After completion of reaction (TLC), the reaction was quenched with sat. aq. NH_4Cl (5 ml) and H_2O (15 ml). The resulting soln. was extracted into Et_2O (4 × 10 ml) and washed with brine, dried (Na_2SO_4). The solvent was removed under reduced pressure to yield crude compound, which was purified by CC (AcOEt/hexane 1:9) to afford **2** (0.46 g, 96%). $[\alpha]_D^{25} = +28.6$ (c = 1.0, $CHCl_3$). IR (neat): 3446, 2928, 1734, 1646, 1217, 771. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.89–5.76 (*m*, 2 H); 5.32 (*d*, *J* = 16.0, 1 H); 5.27 (*d*, *J* = 16.0, 1 H); 5.22 (*d*, *J* = 9.0, 1 H); 5.15 (*d*, *J* = 9.0, 1 H); 4.92 (*t*, *J* = 7.0, 1 H); 4.80 (*t*, *J* = 7.0, 1 H); 4.20–4.14 (*m*, 2 H); 2.41–2.35 (*m*, 2 H); 1.90–1.81 (*m*, 2 H); 1.75–1.66 (*m*, 1 H); 1.64–1.58 (*m*, 3 H); 1.48 (*s*, 3 H); 1.36 (*s*, 3 H); 1.32–1.22 (*m*, 8 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 173.0; 140.3; 133.2; 118.6; 115.1; 109.0; 79.0; 78.4; 72.1; 72.0; 31.9; 31.6; 31.1; 30.3; 29.5; 29.1; 27.8; 25.1; 24.7; 22.3; 14.0. ESI-MS: 391 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{36}O_5$ (368.51): C 68.48, H 9.85; found: C 68.36, H 9.78.

*(3a*R*,4*R*,9*S*,10*E*,11a*S*)-4-Heptyl-3a,4,7,8,9,11a-hexahydro-9-hydroxy-2,2-dimethyl-6*H*-[1,3]dioxolo[4,5-*c*]oxecin-6-one* (**18**). *Grubbs*' second-generation catalyst (45 mg, 0.05 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (120 ml). After heating the soln. to reflux, **2** (0.05 g, 0.14 mmol) dissolved in deoxygenated dry CH_2Cl_2 (80 ml) was added dropwise over 30 min. The mixture was heated at reflux for 12 h at 50°. After completion of the reaction (TLC), the mixture was concentrated *in vacuo*, and the residue was purified by CC (AcOEt/hexane 3:7) to afford **18** (0.037 g, 0.11 mmol, 82%). Light-yellow oil. $[\alpha]_D^{25} = +47.5$ (c = 1.0, $CHCl_3$). IR (neat): 3444, 2928, 2858, 1731, 1379, 1217, 1073, 770. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.82 (*dd*, *J* = 16.0, 3.0, 1 H); 5.68 (*ddd*, *J* = 16.0, 10.0, 2.0, 1 H); 4.92 (*td*, *J* = 7.0, 3.0, 1 H); 4.71–4.66 (*m*, 1 H); 4.21–4.13 (*m*, 1 H); 3.97 (*dd*, *J* = 10.0, 5.0, 1 H); 2.37–2.31 (*m*, 1 H); 2.09–2.00 (*m*, 2 H); 1.83–1.74 (*m*, 1 H); 1.71–1.54 (*m*, 1 H); 1.54 (*s*, 3 H); 1.52–1.41 (*m*, 1 H); 1.38 (*s*, 3 H); 1.32–1.22 (*m*, 10 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 175.1; 128.4; 126.2; 109.4; 78.8; 75.9; 75.8; 71.1; 33.8; 32.0; 31.9; 31.1; 29.1; 29.0; 28.5; 26.2; 24.4; 22.6; 14.0. ESI-MS: 341 ($[M+H]^+$). Anal. calc. for $C_{19}H_{32}O_5$ (340.45): C 67.03, H 9.47; found: C 67.14, H 9.41.

Xyolide (= *4-{[(5*S*,6*E*,8*S*,9*S*,10*R*)-10-Heptyl-3,4,5,8,9,10-hexahydro-8,9-dihydroxy-2-oxo-2*H*-oxecin-5-yl]oxy}-4-oxobutanoic Acid*; **1**). To a stirred soln. of **2** (0.02 g, 0.058 mmol) and DMAP (0.010 g,

0.09 mmol) in CH_2Cl_2 under N_2 at 0°, succinic anhydride (0.009 g, 0.09 mmol) in CH_2Cl_2 was added dropwise, and the mixture was stirred at r.t. for 1 h. After completion of the reaction (TLC), the mixture was concentrated. The crude mixture was dissolved in MeCN (10 ml), then 4N HCl was added until the mixture became acidic. The mixture was stirred at r.t. for 4 h. After completion of the reaction, the mixture was carefully extracted with AcOEt (3×5 ml). The org. extract was dried (Na_2SO_4) and concentrated. The crude mixture was purified by CC (AcOEt/hexane 9:1 to AcOEt) to provide **1** (0.021 g, 0.052 mmol, 90%). Yellow solid. $[\alpha]_D^{25} = +2.8$ ($c = 1.0$, $CHCl_3$). IR (neat): 3615, 3494, 3044, 1742, 1698, 1375, 1059, 968, 770. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.87 (*dd*, $J = 15.5, 2.0$, 1 H); 5.49 (*ddd*, $J = 15.5, 10.0, 1.5$, 1 H); 5.19–5.11 (*m*, 1 H); 5.00 (*td*, $J = 10.0, 2.0$, 1 H); 4.51 (br. *s*, 1 H); 3.59 (*dd*, $J = 10.0, 2.0$, 1 H); 2.65 (*t*, $J = 6.0$, 1 H); 2.60 (*t*, $J = 5.5$, 1 H); 2.39–2.28 (*m*, 1 H); 2.08–1.98 (*m*, 3 H); 1.91–1.82 (*m*, 1 H), 1.66–1.48 (*m*, 1 H); 1.35–1.20 (*m*, 3 H); 0.88 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.2; 174.9; 171.9; 132.9; 123.7; 76.8; 73.5; 72.8; 71.0; 31.8; 31.6; 31.3; 29.6; 29.4; 29.3; 29.2; 28.9; 24.5; 22.7; 14.1. ESI-MS: 423 ($[M + Na]^+$). Anal. calc. for $C_{20}H_{32}O_8$ (400.46): C 59.98, H 8.05; found: C 59.86, H 8.03.

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