Isolation, Identification, and Enantioselective Synthesis of Octane-1,3,7-triol: Determination of Its Absolute Configuration

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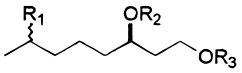
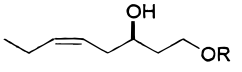
Extracts obtained by solid-phase extraction from apples were separated by multilayer countercurrent chromatography. In the most polar fractions, the novel octane-1,3,7-triol was identified by ^{1}H and ^{13}C NMR as well as LC−MS and by comparison with the synthesized racemic reference compound. Resolution of the enantiomers was achieved after acetylation of the triol followed by GC separation. The enantioselective synthesis of the stereoisomers of octane-1,3,7-triol was performed using the building blocks (*R*)- and (*R*,*S*)-butane-1,3-diol and (*S*)- and (*R*,*S*)-butane-1,2,4-triol. Comparison with the isolated products indicated that the natural compound consisted of a mixture of (3*R*,7*S*)- and (3*R*,7*R*)-octane-1,3,7-triol in a ratio of 2:3. Since the C3 chiral center is enantiomerically pure, the triol might be biogenetically related to the known antimicrobial (*R*)-(+)-octane-1,3-diol, the major volatile compound of some apple cultivars.

Octane-1,3-diol (**1**) has been patented for its antimicrobial effects as an additive to meats including fish, chicken, and beef and eggs and dairy products including butter and milk.[1]



1: R_1 = H, R_2 = H, R_3 = H
2: R_1 = H, R_2 = H, R_3 = ß-D-glucopyranoside
3: R_1 = OH, R_2 = H, R_3 = H
4: R_1 = OAc, R_2 = Ac, R_3 = Ac



5: R= H
6: R= ß-D-glucopyranoside

The diol is effective in controlling microorganisms associated with infections in humans and animals.[2] Raw grain, feed compositions, and intermediate moisture food compositions such as apple flakes show great resistance to the attack of molds, bacteria, and yeast when prepared with the 1,3-diol **1**.[3,4] Studies with membrane vesicles isolated from *Bacillus subtilis* indicated that inhibition of amino acid transport is the primary antimicrobial effect of the diol **1**.[5] The concentration of **1** to inhibit the growth of *B. subtilis* by 50% is 5 μmol/L. However, the LD_{50} in rats was found to be greater than 20 g/kg body weight. These data confirm that the diol is harmless to humans at concentrations exhibiting antimicrobial effects. In humans, the diol is completely resorbed and metabolized as previously observed for butane-1,3-diol.[6]

Independent of the studies referred to above, the β-glycol was isolated from apples in 1973.[7] Recently, additional C8 derivatives have been detected in apples and pears, e.g., 5(*Z*)-octene-1,3-diol (**5**),[8] 3-hydroxyoctyl β-D-glucopyranoside (**2**),[9] and 5(*Z*)-3-hydroxyoctenyl β-D-glucopyranoside (**6**).[10] Studies of the stereochemistry of **1** and **2** and **5** and **6** indicated the 3*R* configuration (>99% ee).[9−11] The compounds are formed by the apples postharvest,[12] and large amounts (>1 g/kg) have been found in French cider apples.[11] Radiolabeling studies indicated that linoleic acid and linolenic acid were the natural precursors of **1** and **5**, respectively.[13]

During our ongoing studies directed toward defining the biosynthesis of **1** and **5** in stored apple fruits we have isolated a novel trihydroxylated C8 derivative. In this paper, we report the identification of the naturally occurring octane-1,3,7-triol (**3**), the synthesis of racemic **3**, and the enantioselective synthesis of the stereoisomers of **3**.

Results and Discussion

A crude glycosidic extract was obtained from apples, cv. Peau de Chien, by solid-phase extraction on Amberlite XAD resin followed by methanol elution. The eluate was fractionated by two consecutive multilayer coil countercurrent chromatography (MLCCC) separations. MLCCC fractions were monitored by TLC and HPLC. Four pure compounds were isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy and atmospheric pressure chemical ionization−mass spectrometry (APCI−MS). The first three compounds were identified as (*R*)-3-hydroxy-octyl β-D-glucopyranoside (**2**), (*R*)-3-hydroxy-5(*Z*)-octenyl β-D-glucopyranoside (**6**), and vomifoliol β-D-glucopyranoside.[10] The ^{13}C NMR spectrum of the fourth substance showed eight carbon signals, and it strongly resembled that of the diol (**1**)[9] except for a signal at 68.6 ppm indicating the presence of a third hydroxyl group. The additional hydroxyl group was assigned to the C-7 position since a doublet (J = 5.9 Hz) at 1.34 ppm was observed for the proton at C-8. This observation agreed with a signal at 23.5 ppm in the ^{13}C NMR for the terminal methyl carbon (C-8) adjacent to a secondary alcohol. The APCI−MS spectrum displayed a pseudomolecular ion *m*/*z* 180 $[M + NH_4]^+$ as base peak when 0.05% NH_4Ac in H_2O was used as solvent. Subsequent MS/MS experiments generated the product ions *m*/*z* 163 $[M + H]^+$, *m*/*z* 145 $[M + H - H_2O]^+$, 127 $[M + H - 2H_2O]^+$, and 109 $[M + H - 3H_2O]^+$, confirming the presence of at least three hydroxy groups in the molecule. The novel compound was thus assigned the structure octane-1,3,7-triol (**3**).

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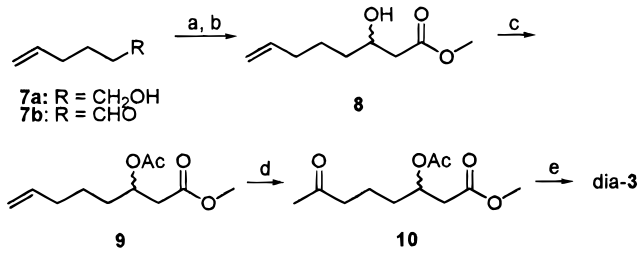
Scheme 1. Synthesis of Dia-**3**[a]



[a] Key: (a) DMSO, P_2O_5, NEt_3, CH_2Cl_2; (b) methyl acetate, LDA, THF, −78 °C; (c) Ac_2O, Py; (d) $PdCl_2$, CuCl, O_2, DMF−H_2O; (e) $LiAlH_4$, Et_2O.

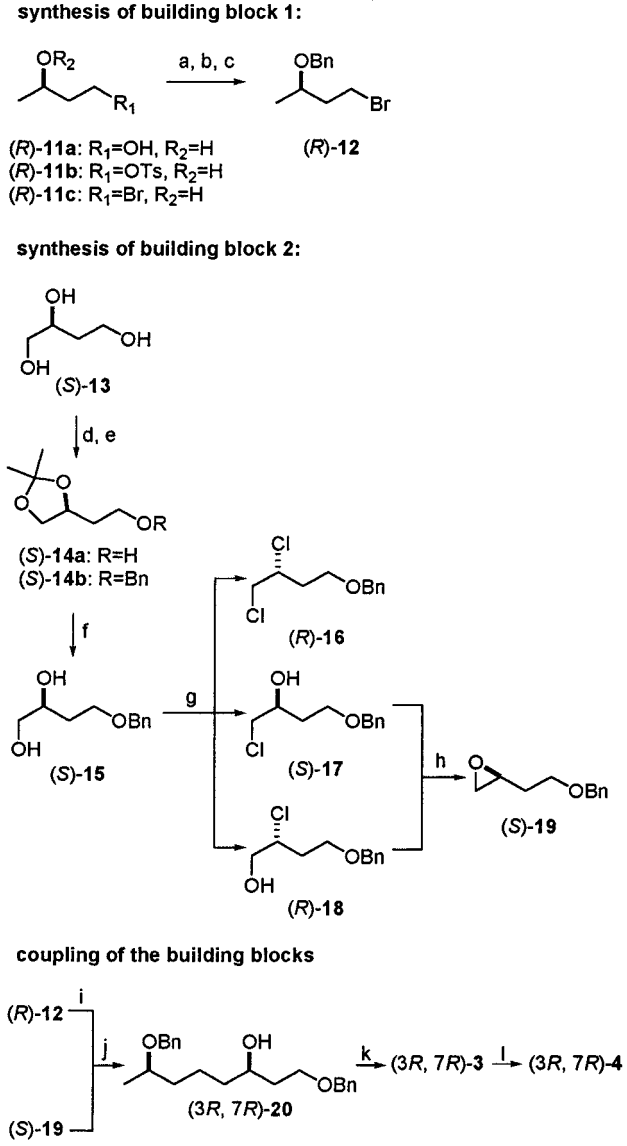
A mixture of all four stereoisomers of **3** (dia-**3**) was synthesized according to Scheme 1. The basis of our approach was the homologation of commercially available 5-hexen-1-ol (**7**)[14] and the $PdCl_2$-catalyzed oxidation of terminal olefins to methyl ketones.[15,16] Oxidation of 5-hexen-1-ol (**7a**) to 5-hexenal (**7b**) was effected by DMSO/P_2O_5. Elongation with LDA/methyl acetate yielded racemic methyl 3-hydroxy ester (*rac*-**8**). Several attempts to oxidize unprotected *rac*-**8** proved fruitless. However, the oxidation of acetylated derivative *rac*-**9** gave the methyl ketone *rac*-**10** in high yields (90%). Dia-**3** was readily obtained by reduction with $LiAlH_4$. The ^{13}C and ^1H NMR spectrum as well as the LC−MS spectrum corresponded well with those of the isolated natural product. The ^{13}C NMR spectrum of the natural product and dia-**3** showed two signals at 22.98/23.01 ppm for C-5 and two signals at 23.53/23.56 ppm for C-8. Therefore, we assumed that the natural product occurs as a diastereomeric mixture.

An enantioselective preparation of the stereoisomers of **3** was accomplished by the chiral building block strategy. The stereoisomers of the C8-triol **3** were obtained by fusion of the two C4 compounds **12** and **19** with defined absolute configuration. Scheme 2 shows the example of the coupling of (*R*)-**12** and (*S*)-**19** to yield (3*R*,7*R*)-**3**.[17] Modification of the coupling reaction, e.g., exchange of enantiomerically pure building blocks with the racemic compounds, led to the preparation of (3*R*,*S*,7*R*)-**3** and (3*R*,7*R*,*S*)-**3**.

The chiral building block (*R*)-**12** was synthesized from (*R*)-butane-1,3-diol ((*R*)-**11**) by a modification of literature procedures[18] in three steps as depicted in Scheme 2. In the same way, (*R*,*S*)-**12** was obtained from (*R*,*S*)-**11**. The reaction was conducted at −40 °C leading to the expected high regioselective tosylation of the primary hydroxyl group. Nucleophilic substitution of the tosyl group with LiBr funished (*R*)-**11c** or (*R*,*S*)-**11c**. Purification of (*R*)-**11c** and (*R*,*S*)-**11c** was monitored by GC as visualization of TLC spots by UV and vanillin/H_2SO_4 was too insensitive. Protection of the hydroxyl group prior to formation of the Grignard reagent was achieved by benzylation;[19] the benzyl group was chosen to allow simultaneous deprotection of the two benzyl groups in the product. Three benzylation procedures[19−21] were tested, but the method chosen furnished the highest yields for (*R*)-**12** and (*R*,*S*)-**12**.

The acetonides (*S*)-**14a** and (*R*,*S*)-**14a** were prepared by starting with either (*S*)-**13** or (*R*,*S*)-**13**. Although 10% of the six-membered acetonide was formed,[22] the mixture was used without purification for the following step. Benzylation of the remaining hydroxyl group represented a problem for a long time as the yield and purity of the crude product were unsatisfactory. Several procedures were applied, e.g., benzylation in DMF[21] or in THF with tetra-*N*-butylammonium iodide as catalyst.[20] Finally, the best yields for (*S*)-**14b** and (*R*,*S*)-**14b** were obtained with the first method, but only with reagents of the highest available purity. Hydrolysis of the acetonides (*S*)-**14b** and (*R*,*S*)-**14b** in 80% aqueous acetic acid resulted in the loss of products (*S*)-**15** and (*R*,*S*)-**15** during the workup procedure. The yields of the diols (*S*)-**15** and (*R*,*S*)-**15** were improved by the application of a strongly acidic cation exchanger in MeOH.[23] Reaction of (*S*)-**15** (or (*R*,*S*)-**15**) and PPh_3/CCl_4 resulted in formation of a mixture of the two desired monochloro alcohols, (*S*)-**17** (or (*R*,*S*)-**17**) and (*R*)-**18** (or (*R*,*S*)-**18**), and the dichloro derivative (*R*)-**16** (or (*R*,*S*)-**16**).[24] The reaction was monitored by GC. Inversion of configuration at the chiral carbon of (*S*)-**15** to give (*R*)-**18** is assumed on the basis of an understanding of the reaction mechanism (S_N2).[25] Chromatographic separation on silica gel provided a rapid method for removing (*R*)-**16** (or (*R*,*S*)-**16**). Cyclization of the mixture of (*S*)-**17** (or (*R*,*S*)-**17**) and (*R*)-**18** (or (*R*,*S*)-**18**) under basic conditions according to the S_N2 mechanism provided (*S*)-**19** (or (*R*,*S*)-**19**).[24] The stereoisomers of **20** were obtained by coupling the Grignard product of (*R*)-**12** or (*R*,*S*)-**12**, with the oxirane (*S*)-**19** or (*R*,*S*)-**19**.[26,27] Addition of catalytic amounts of Li_2CuCl_4 was necessary in order to increase the yield of the coupling product. Finally, hydrogenation[26] of the benzyl protected

Scheme 2. Enantioselective Synthesis of (3*R*,7*R*)-**3**



[a] Key: (a) *p*-TsCl, pyridine, −40 °C; (b) LiBr, Me_2CO; (c) benzyl trichloroacetimidate, CF_3SO_3H, C_6H_{12}−CH_2Cl_2; (d) *p*-TsOH, Me_2CO; (e) BnBr, NaH, DMF; (f) Dowex 50 (H^+), MeOH; (g) CCl_4, PPh_3, D; (h) KOH, H_2O−DMSO D; (i) Mg, $BrCH_2BrCH_2$, Et_2O; (j) Li_2CuCl_4, THF, −78 °C; (k) H_2, Pd/C, EtOH; (l) Ac_2O, Py.

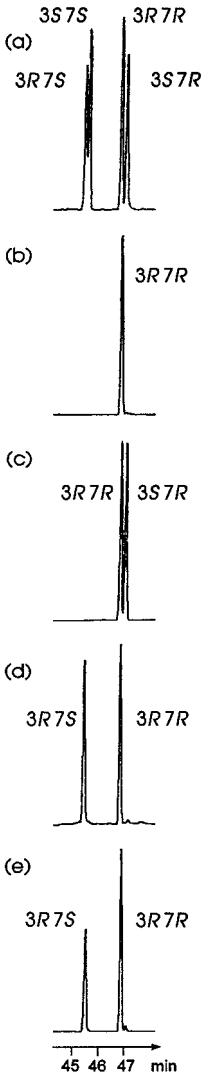


Figure 1. Gaschromatographic separation of the stereoisomers of **3**: (a) dia-3, (b) (3*R*,7*R*)-**3**, (c) (3*R*,7*R*)-**3** and (3*S*,7*R*)-**3**, (d) (3*R*,7*R*)-**3** and (3*R*,7*S*)-**3**, and (e) naturally occurring (3*R*,7*R*)-**3** and (3*R*,7*S*)-**3**.

stereoisomers **20** provided enantiomerically pure (>99%) (3*R*,7*R*)-**3**, (3*R*,*S*,7*R*)-**3**, and (3*R*,7*R*,*S*)-**3**. The data for (3*R*,7*S*)-octane-1,3,7-triol have been recently reported.[27]

GC resolution of dia-**3** was achieved on a capillary column coated with 2,3-*O*-diethyl-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrine/PS086 column after peracetylation to dia-**4** (Figure 1). The stereoisomers were identified on the basis of the retention times of the synthesized reference compounds (3*R*,7*R*)-**4**, (3*R*,*S*,7*R*)-**4**, (3*R*,7*R*,*S*)-**4**, and dia-**4**. Separation of the enantiomerically pure (3*R*,7*R*)-**4** (Figure 1b) showed a very high stereochemical purity (>99%), in agreement with previously published data.[24] By comparison with the synthesized reference compounds, the absolute configuration of the naturally occurring triol was unambiguously assigned as (3*R*,7*R*)-**3** and (3*R*,7*S*)-**3** in a ratio of 62:38. Since the chiral center of C-3 has the *R* configuration in both components of the natural product, it might be biogenetically related to the known antimicrobial (*R*)-(+)-octane-1,3-diol ((*R*)-**1**). It has been shown that (*R*)-**1** and (*R*)-**5** originate from linoleic acid and linolenic acid, respectively, in apples. Therefore, we propose two possible pathways for the bioformation of **3**: either hydroxylation of (*R*)-**1** by, e.g., a monooxygenase or transformation of 17-hydroxylinoleic acid according to the formation of (*R*)-**1** from linoleic acid.[13] Recently, a 17-hydroxylinolenic acid conjugate has been identified as the trigger compound starting the plant defense system.[28]

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a 250 MHz/63 or 400 MHz/100 MHz spectrometer. All NMR data are reported in ppm (δ) downfield from TMS, or residual signals ($CDCl_3$, $\delta_{H/C}$ 7.24/77.0 or CD_3OD, $\delta_{H/C}$ 3.35/49.0) were used as internal standards. Silica gel 60 (0.063−0.2 mm) was used for flash chromatography. HPLC separation was carried out using stainless steel columns (250 mm × 4 mm i.d.) filled with RP18 (5 μm). On-line UV and evaporative light scattering detection (ELSD) was applied. The purities of the compounds were shown to be ≥90% by ^{1}H NMR, TLC, HPLC, and/or GC/MS. Multilayer countercurrent chromatography (MLCCC) was performed with an ITO multilayer coil separator−extractor (P.C. Inc., Potomac, MD) equipped with a 160 m × 1.6 mm i.d. PTFE tube (analytical coil) or a 75 m × 2.6 mm i.d. PTFE tube (preparative coil). LC−MS experiments were conducted with a Finnigan TSQ 7000 triple-stage quadrupole mass spectrometer; solvent, MeOH/0.05% NH_4Ac in H_2O 1:1; flow rate, 200 μL/min; loop injection, 2 μL; capillary temperature, 220 °C; mass range, 100−400; scan duration, 1 s. MS/MS experiments: collision pressure, 2.11 mTorr argon; collision energies, −10 eV for product ion generation. An HP 5890-2 gas chromatograph with FID was used for the GC analyses. Split injection (1:20) was employed. The GC was either equipped with a J&W fused silica DB-Wax capillary column (30 m × 0.25 mm, d_f = 0.25 μm), with a DB-5 capillary column (30 m × 0.25 mm, d_f = 0.25 μm), or with a 30% 2,3-*O*-diethyl-6-*O*-(*tert*-butyldimethylsilyl)-β-CD/PS086 column (25 m × 0.25 mm, d_f = 0.15 μm) for the separation of the enantiomers of dia-**3**. The temperature program for the DB-Wax capillary column was 3 min isothermal at 50 °C and then increased from 50 to 240 °C at 4 °C/min. The temperature program for the DB-5 capillary column was from 60 to 300 °C at 5 °C/min and then held for 10 min. Helium was used as carrier gas (2.0 mL/min). Calculation of retention indices (R_i) was conducted on the basis of *n*-hydrocarbons with the aid of an additional BASIC program.[29] The temperature program for the 2,3-*O*-diethyl-6-*O*-(*tert*-butyldimethylsilyl)-β-CD/PS086 column was 1 min isothermal at 80 °C and then increased from 80 to 190 °C at 1.5 °C/min. Hydrogen was used as carrier gas (65 kPa). GC−MS was performed with a Fisons 8060 gas chromatograph with split injector (1:30) combined by direct coupling to the Fisons MD mass spectrometer with MassLab data system. The temperature program was 3 min isothermal at 50 °C and then increased from 50 to 240 °C at 4 °C/min. Conditions of the mass spectrometer: temperature of the ion source, 230 °C, and of all connection parts, 200 °C; electron energy, 70 eV; cathodic current, 4 mA; mass range 40−250 or 40−499 g.

Plant Material. Apple fruits cv. Peau de Chien were kindly provided by Pernod Ricard, France.

Extraction and Isolation. Apple juice (2.5 kg) was subjected to solid-phase extraction on Amberlite XAD-2 resin.[10] Separation of the MeOH eluate was achieved by MLCCC with the solvent system $CHCl_3$/MeOH/H_2O (7:13:8); flow rate, 1 mL/min; elution mode, tail to head; rotation speed, 800 rpm; solvent system for analytical MLCCC, EtOAc/*n*-BuOH/H_2O (3:2:5); flow rate, 1 mL/min; elution mode, head to tail; rotation speed, 800 rpm. Fractions were monitored by TLC on silica gel. Developing solvent: EtOAc/*n*-BuOH/H_2O (3:2:5) upper phase. Visualization by vanillin/H_2SO_4.

(3*R*,7*R*,*S*)-Octane-1,3,7-triol ((3*R*,7*R*,*S*)-3). The isolated compound (slightly yellow oil, 5 mg) showed the following data: R_f 0.63 (upper phase of EtOAc/*n*-BuOH/H_2O (3:2:5)); IR (KBr) ν_{max} 3300 (OH), 2900 (CH), 1440, 1100, 1040; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.70−3.80 (4H, m, C-1H_2, C-3H, C-7H), 1.65−1.75 (2H, m C-2H_2), 1.40−1.65 (6H, m, C-4H_2, C-5H_2, C-6H_2), 1.20 (3H, d, J = 5.88 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 70.0 (C-3), 68.5 (C-7), 60.4 (C-1), 40.7 (C-2), 40.2 (C-6), 38.7

(C-4), 23.53/23.56 (C-8), 22.98/23.01 (C-5); APCI-MS *m/z* 180 $[M + NH_4]^+$ (100); MS/MS of *m/z* 180, 163 $[M + H]^+$ (100), 145 $[M + H - H_2O]^+$ (95), 127 $[M + H - 2H_2O]^+$ (65), 109 $[M + H - 3H_2O]^+$ (75).

(*R*,*S*)-Methyl 3-Hydroxy-7-octenoate (*rac*-8). 5-Hexen-1-ol (**7a**) (7.1 g, 75 mmol, 0.2 M in CH_2Cl_2), was oxidized with dimethyl sulfoxide (11.7 g, 150 mmol), phosphorus pentoxide (19.2 g, 135 mmol), and freshly distilled triethylamine (26.6 g, 262.5 mmol) according to the published procedure.[15] Addition of lithium methyl acetate[15] (0.8 M in 140 mL of THF) to the crude aldehyde (**7b**) followed by purification on silica gel with pentane/Et_2O/MeOH (50:6:3) gave *rac*-**8** as a clear oil (62% based on **7a**): R_f 0.34 (pentane/Et_2O/MeOH (50:6:3)); t_R 1918; IR (KBr) ν_{max} 3420 (OH), 2920 (CH), 1720 (C═O), 1630 (C═C), 1510, 1420, 1250, 900; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78 (1H, m, C-7*H*), 5.00 (1H, dd, J_1 = 17 Hz, J_2 = 3.3 Hz, *trans*-C-8*H*), 4.95 (1H, d, J = 10.3 Hz, *cis*-C-8*H*), 4.00 (1H, m, C-3*H*), 3.70 (3H, s, OCH_3), 2.50 (1H, dd, J_1 = 16.6 Hz, J_2 = 3.3 Hz, C-2H_a), 2.41 (1H, dd, J_1 = 16.6 Hz, J_2 = 8.8, Hz, C-2H_b), 2.06 (2H, m, C-6H_2), 1.61−1.37 (4H, m, C-4H_2, C-5H_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9 (C-1), 138.1 (C-7), 114.3 (C-8), 67.6 (C-3), 51.3 (OCH_3), 40.9 (C-2), 35.6 (C-6), 33.1 (C-4), 24.4 (C-5); EIMS *m/z* 71 (100), 43 (95), 103 (91), 81 (83), 80 (82), 54 (78), 94 (72), 74 (72), 55 (49), 79 (46), 61 (37), 95 (30), 99 (28), 97 (25), 129 (25), 116 (18), 122 (12), 154 $[M - H_2O]^+$ (4).

(*R*,*S*)-Methyl 3-Acetoxy-7-octenoate (*rac*-9). For acetylation, a solution of *rac*-**8** (0.215 g, 1.25 mmol), pyridine (1.275 g, 16.12 mmol), and acetic anhydride (2.55 g, 25 mmol) was kept at room temperature overnight. After addition of H_2O (20 mL), the mixture was extracted 3× with 10 mL of CH_2Cl_2. The combined organic layer was washed with 2 × 10 mL of 2 N HCl and saturated $NaHCO_3$ solution (10 mL). Purification on silica gel with pentane/Et_2O (1:1) yielded *rac*-**9** as a clear oil (95%). It was important to remove the pyridine completely as it poisons the catalyst of the following reaction: R_f 0.76 (pentane/Et_2O (1:1)); t_R 1924; IR (KBr) ν_{max} 3080 (C═CH), 2920 (CH), 1725 (C═O), 1630, 1420, 1360 (OCOCH_3), 1225, 1160, 1010, 900; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 (1H, m, C-7*H*), 5.21 (1H, m, C-3*H*), 5.02 (1H, m, *trans*-C-8*H*), 4.97 (1H, m, *cis*-C-8*H*), 3.67 (3H, s, OCH_3), 2.59 (1H, dd, J_1 = 15.0 Hz, J_2 = 7.7 Hz, C-2H_a), 2.52 (1H, dd, J_1 = 15.0 Hz, J_2 = 5.5, Hz, C-2H_b), 2.05 (2H, m, C-6H_2), 2.03 (3H, s, COCH_3), 1.62 (2H, m, C-4H_2), 1.42 (2H, m, C-5H_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (C-1), 170.3 (*C*O−CH_3), 138.1 (C-7), 114.9 (C-8), 70.4 (C-3), 51.7 (OCH_3), 39.1 (C-2), 33.4 (C-4), 33.3 (C-6), 24.4 (C-5), 21.0 (CO-*C*H_3); EIMS *m/z* 54 (100), 80 (47), 81 (28), 55 (26), 94 (25), 71 (22), 79 (21), 59 (16), 74 (15), 67 (14), 95 (14), 69 (7), 68 (7), 123 (7), 122 (6), 154 $[M - CH_3COOH]^+$ (4).

(*R*,*S*)-Methyl 3-Acetoxy-7-oxo-octanoate (*rac*-10). The methyl ketone *rac*-**10** was synthesized by palladium-catalyzed oxidation of the terminal olefin *rac*-**9** according to published procedures.[16,17] A flask containing *rac*-**9** (0.172 g, 1 mmol), $PdCl_2$ (0.018 g, 0.1 mmol), CuCl (0.099 g, 1 mmol), and 2 mL of a mixture of DMF/H_2O (7:1) was evacuated and closed with a balloon filled with O_2. The suspension was stirred overnight. The catalyst was removed by filtration, and after addition of 20 mL of H_2O the solution was extracted 3 × 20 mL of with Et_2O. The combined organic phase was washed with brine and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel with Et_2O (90% based on *rac*-**9**): R_f 0.50 (Et_2O); t_R 1962; IR (KBr) ν_{max} 2940 (CH), 1725 (C═O), 1700 (C═O), 1425, 1360 (OCOCH_3), 1220, 1010; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.22 (1H, m, C-3*H*), 3.70 (3H, s, OCH_3), 2.64 (1H, dd, J_1 = 15.4 Hz, J_2 = 7.4 Hz C-2H_a), 2.57 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.5 Hz, C-2H_b), 2.50 (2H, m, C-6H_2), 2.15 (3H, s, C-8H_3), 2.06 (3H, s, CO−CH_3), 1.55−1.70 (4H, m, C-4H_2, C-5H_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.6 (C-7), 170.2 (C-1), 169.9 (*C*O−CH_3), 69.5 (C-3), 51.3 (O*C*H3), 42.4 (C-6), 38.4 (C-2), 32.8 (C-4), 29.4 (C-9), 20.5 (CO-*C*H_3), 18.7 (C-5); EIMS *m/z* 68 (100), 71 (99), 96 (93), 58 (89), 59 (78), 81 (68), 85 (68), 55 (68), 113 (57), 97 (63), 74 (63), 95 (54), 100 (50), 67 (54), 138 (32), 53 (35), 69 (38), 110 (31), 128 (24), 170 $[M - CH_3COOH]^+$ (12), 157 (11).

(3*R*,*S*,7*R*,*S*)-Octane-1,3,7-triol (Dia-3). *rac*-**10** (48 mg, 0.21 mmol) dissolved in 2 mL of Et_2O was added dropwise to absolute EtO_2 (2.5 mL) containing $LiAlH_4$ (13 mg, 0.327 mmol). The mixture was stirred under reflux for 1 h. Water (2 mL) and 10% H_2SO_4 were added until the precipitate was dissolved. After extraction with Et_2O (3 × 2 mL), the aqueous phase was evaporated to dryness in vacuo, and the residue was extracted with EtOAc/MeOH (8:2) (3 × 1 mL) (75%). The spectral data (IR, ^{1}H NMR, ^{13}C NMR, APCI−MS) were in accordance with those obtained for the natural product. The ^{13}C NMR spectrum of dia-**3** and the spectrum of the natural product showed two signals at 22.98/23.01 ppm for C-5 and 23.53/23.56 ppm for C-8; *anal.* C 58.83%, H 11.44%, calcd for $C_8H_{18}O_3$, C 59.23%, H 11.18%.

(*R*,*S*)- and (*R*)-1-*O*-Tosylbutane-1,3-diol (*rac*-11b and (*R*)-11b). The synthesis was conducted according to literature procedures.[18,30−34] The residue was purified by flash chromatography on silica gel with Et_2O (59%). The IR and ^{1}H and ^{13}C NMR data were identical to those reported in the literature:[22,31−32] R_f 0.5 (Et_2O); t_R 1962; EIMS *m/z* 172 (100), 91 (100), 72 (69), 173 (57), 155 (52), 107 (45), 108 (43), 200 (5), 216 (4), 229 $[M - CH_3]^+$ (1), 245 $[M]^+$ (<1).

(*R*,*S*)- and (*R*)-1-Bromobutane-3-ol (*rac*-11c and (*R*)-11c). The preparation was performed in the same manner as reported.[18,32,35] The crude product was purified by flash chromatography on silica gel with Et_2O−pentane (2:1) (52%): R_f 0.4 (Et_2O/pentane (2:1)); t_R 1616; $[\alpha]^{25}_D$ −32.8° (*c* 3.21, $CHCl_3$);[19] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.01 (1H, m, C-3*H*), 3.51 (2H, m, C-1H_2) 1.97 (2H, m, C-2H_2), 1.91 (1H, s, O*H*), 1.24 (3H, d, J = 6 Hz, C-4H_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 66.0 (C-3), 41.5 (C-2), 30.3 (C-1), 23.5 (C-4); EIMS *m/z* 45 (100), 73 $[M - Br]^+$ (35), 57 (19), 55 (19), 126/124 (10), 139/137 $[M - CH_3]^+$ (8), 109/107 $[BrC_2H_5]^+$ (5), 95/93 $[BrCH_2]^+$ (4), 153/151 $[M]^+$ (1), 136/134 $[M - H_2O]^+$ (1).

(*R*,*S*)- and (*R*)-1-Bromo-3-*O*-benzylbutane-3-ol (*rac*-12 and (*R*)-12). Benzylation of (*R*,*S*)- and (*R*)-1-bromobutan-3-ol was performed according to the literature.[19] The residue was purified by flash chromatography on silica gel with pentane−Et_2O (15:1) (52%): R_f 0.72 (pentane−Et_2O (15:1)); t_R 2100; $[\alpha]^{25}_D$ −80,1° (*c* 4.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3−7.5 (5H, m, C6H_5), 4.45−4.61 (2H, dd, J_1 = 11 Hz, J_2 = 2 Hz, CH_2−C_6H_5), 3.77 (1H, m, C-3*H*), 3.52 (2H, m, C-1H_2), 1.96−2.15 (2H, m, C-2H_2), 1.24 (3H, d, J = 6 Hz, C-4H_3); ^{13}C NMR ($CDCl_3$, 100 MHz) d 128.4, 127.7, 127.6 (C_6-H_5), 72.9 (*C*H_2−C_6H_5), 70.8 (C-3), 40.1 (C-2), 30.2 (C-1), 19.3 (C-4); EIMS *m/z* 91 (100), 92 (50), 135 (13), 107 (8), 172/170 (2), 153/151 $[M - CH_2 - C_6H_5]^+$ (1), 244/242 $[M]^+$ (<1).

(*R*,*S*)- and (*S*)-1,2-*O*-Isopropylidenebutane-1,2,4-triol (*rac*-14a and (*S*)-14a). (*R*,*S*)- and (*S*)-1,2-acetonide were prepared starting with racemic (*rac*-**13**) and (*S*)-butane-1,2,4-triol ((*S*)-**13**), respectively.[36,37] The crude product (90% 1,2-acetonide and 10% 2,4-acetonide according to GC and ^{1}H and ^{13}C NMR analysis) was used for the next step without purification. IR and ^{1}H NMR data were identical to those in the literature:[36,37] R_f 0.45 (Et_2O); t_R 1750; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.0 (O*C*O), 74.9 (C-2), 69.4 (C-1), 60.3 (C-4), 35.6 (C-3), 26.8, 25.6 (2 CH_3); EIMS *m/z* 71 (100), 131 $[M - CH_3]^+$ (61), 59 (60), 61 (32), 101 (29), 85 (28), 57 (28), 146 $[M]^+$ (<1).

(*R*,*S*)- and (*S*)-1,2-*O*-Isopropylidene-4-*O*-benzylbutane-1,2,4-triol (*rac*-14b and (*S*)-14b). The benzylation of the (*R*,*S*)- and (*S*)-1,2-acetonide was performed in an analogous manner as described.[21] The workup was modified as follows: water (300 mL) was added to the reaction mixture, and the solution consisting of DMF and H_2O was extracted with Et_2O (3 × 250 mL). The combined organic layer was washed with saturated NH_4Cl solution (2 × 200 mL) and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash chromatography with pentane−Et_2O (2:1) on silica gel (74%): R_f 0.64 (pentane−Et_2O (2:1)); t_R = 2265; ^{1}H NMR and MS data were in accordance with the published data;[21] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4 ($CH_2C(C_5H_5)$), 128.4, 127.6 ($CH_2C(C_5H_5)$), 108.5 (O*C*O), 73.9 (C-2), 73.1 (*C*$H_2C_6H_5$), 69.6 (C-1), 67.1 (C-4), 33.9 (C-3), 26.9, 25.8 (2 *C*H3).

(*R*,*S*)- and (*S*)-4-*O*-Benzylbutane-1,2,4-triol (*rac*-15 and (*S*)-15). Hydrolysis of acetonides was performed either by the

published method[21] using 80% aqueous acetic acid or by the following procedure:[23] (*S*)-1,2-*O*-Isopropylidene-4-*O*-benzylbutane-1,2,4-triol (31.4 g, 133 mmol) and freshly prepared strong acidic cation exchanger Dowex 50 (H^+ form) suspended in MeOH (300 mL) were stirred at room temperature. Dowex 50 was replaced daily by fresh material. After 3 d, Dowex 50 was filtered off and the solvent was removed in vacuo. Flash chromatography with Et_2O−MeOH (15:1) yielded 48% of (*R*,*S*)- and (*S*)-4-*O*-benzylbutane-1,2,4-triol: R_f 0.3 (Et_2O); t_R = 2975; $[\alpha]^{25}_D$ +4.3° (*c* 2.50, $CHCl_3$);[37] ^{1}H NMR data were identical to those in the literature;[21] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9 ($CH_2C(C_5H_5)$), 128.4, 127.8, 127.7 ($CH_2C(C_5H_5)$), 73.3 ($CH_2C_6H_5$), 71.2 (C-2), 68.1 (C-1), 66.6 (C-4), 32.9 (C-3); EIMS *m*/*z* 91 (100), 107 (38), 65 (20), 79 (19), 92 (15), 178 $[M - H_2O]^+$ (1), 177 (1), 196 $[M]^+$ (<1).

(*R*,*S*)- and (*R*)-1,2-Dichloro-4-*O*-benzylbutan-4-ol (*rac*-16 and (*R*)-16), (*R*,*S*)- and (*S*)-1-Chloro-4-*O*-benzylbutane-2,4-diol (*rac*-17 and (*S*)-17), and (*R*,*S*)- and (*R*)-2-Chloro-4-*O*-benzylbutane-1,4-diol (*rac*-18 and (*R*)-18). Compounds **16**−**18** were prepared according to the published procedure.[24] Separation of undesired **16** was achieved by flash chromatography with pentane−Et_2O (1:1) to give 43% of **17** and **18**. IR and ^{1}H and ^{13}C NMR data of **16**−**18** were identical to those previously published.[24] **16**: R_f 0.77 (pentane−Et_2O (1:1)); t_R 2404; EIMS *m*/*z* 91 (100), 65 (36), 79 (31), 92 (25), 89 (20), 77 (14), 127/125 (12), 107 (12), 234/232 $[M]^+$ (1). **17**: R_f 0.41 (pentane−Et_2O (1:1)); t_R 2648; EIMS *m*/*z* 91 (100), 107 (88), 65 (28), 92 (15), 77 (13), 55 (11), 214/216 $[M]^+$ (1). **18**: R_f 0.30 (pentane−Et_2O (1:1)); t_R 2744; EIMS *m*/*z* 91 (100), 107 (85), 92 (28), 65 (25), 79 (24), 77 (12), 55 (11), 214/216 $[M]^+$ (1).

(*R*,*S*)- and (*S*)-1,2-Epoxy-4-*O*-benzylbutan-4-ol (*rac*-19 and (*S*)-19). The mixture of monochloro alcohols was converted to the oxirane as described.[24] The residue was purified by flash chromatography with pentane−Et_2O (1:1) (99%): R_f 0.42 (pentane−Et_2O (1:1)); t_R 2138; $[\alpha]^{25}_D$ −13.9° (*c* 2.75, $CHCl_3$);[24,38] spectral data (IR, ^{1}H NMR, ^{13}C NMR) were as previously reported;[24] EIMS *m*/*z* 91 (100), 107 (28), 105 (21), 79 (20), 65 (12), 177 $[M]^+$ (6), 159 $[M - H_2O]^+$ (5), 150 (4), 132 (4), 147 (3).

(3*R*,7*R*,*S*)-, (3*R*,*S*,7*R*)-, and (3*R*,7*R*)-1,7-Di-*O*-benzyloctane-1,3,7-triol ((3*R*,7*R*,*S*)-20, (3*R*,*S*,7*R*)-20, and (3*R*,7*R*)-20). (3*R*,7*R*,*S*)-**20** was prepared from (*R*,*S*)-**12** and (*S*)-**19**, (3*R*,*S*,7*R*)-**20** was synthesized from (*R*)-**12** and (*R*,*S*)-**19**, and (3*R*,7*R*)-**20** was prepared from (*R*)-**12** and (*S*)-**19** by the following modified procedure:[26,28] Magnesium (0.35 g, 14.4 mmol) and (*R*,*S*)-**12** or (*R*)-**12** (2.76 g, 11.4 mmol) were dissolved in 10 mL of absolute Et_2O, and the solution was gently warmed until reaction commenced. The reaction mixture was refluxed for 1 h and then cooled to −78 °C. A solution of Li_2CuCl_4 (2.53 mL of 0.1 M) in THF was introduced into the reaction mixture. After a further 1 h of stirring, (*R*,*S*)-**19** or (*S*)-**19** (1.35 g, 7.58 mmol) in 15 mL of absolute Et_2O was added dropwise. The mixture was stirred at −78 °C for an additional 3 h and was then allowed to warm to room temperature overnight. The reaction mixture was quenched with cold (0 °C) saturated aqueous NH_4Cl (50 mL). The organic layer was separated, and the aqueous layer was extracted 3× with 25 mL of Et_2O. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography with pentane−Et_2O (6:4) on silica gel (62%): R_f 0.45 (pentane−Et_2O (6:4)); t_R 2672 (DB-5); (3*R*,7*R*,*S*)-**20**, $[\alpha]^{25}_D$ +5.6° (*c* 2.85, $CHCl_3$); (3*R*,*S*,7*R*)-**20**, $[\alpha]^{25}_D$ −13.0° (*c* 3.52, $CHCl_3$); (3*R*,7*R*)-**20**, $[\alpha]^{25}_D$ −5.5° (*c* 3.92, $CHCl_3$); IR (KBr) ν_{max} 3425 (OH), 3040 (C=CH), 3010 (C=CH), 2910 (CH), 2840 (CH), 1440, 1360, 1190, 1080 (C−O), 720, 690; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26−7.35 (10H, m, C_6H_5), 4.44−4.59 (4H, m, CH_2−C_6H_5), 3.81 (1H, m, C-7*H*), 3.62−3.75 (2H, m, C-1H_2), 3.52 (1H, m, C-3*H*), 1.74 (2H, m, C-2H_2), 1.30−1.65 (6H, m, C-4*H*, C-5*H*, C-6*H*), 1.20 (3H, d, *J* = 6.3 Hz, C-8*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2 and 138.0 ($OCH_2C(C_5H_5)$), 127.0−128.4 ($OCH_2C(C_5H_5)$) 74.8 and 73.3 ($OCH_2C_6H_5$), 71.2 (C-7), 70.3 (C-3), 69.2 (C-1), 37.5 (C-2), 36.6 (C-4), 36.5 (C-6), 21.5 (C-8), 19.8 (C-5); EIMS *m*/*z* 91 (100), 92 (13), 65 (13), 107 (9), 109 (7), 79 (7), 77 (6), 55 (5), 110 (4), 105 (4), 99 (4), 67 (4); ESI-MS *m*/*z* 343 $[M + H]^+$ (100), 360 $[M + NH_4]^+$ (20); MS/MS of *m*/*z* 343, 235 $[M - C_7H_7OH]^+$ (100), 181 (60), 143 (40), 128 (38), 91 (35), 217 (20), 99 (12), 325 $[M + H - H_2O]^+$ (5), 199 (5), 157 (5); *anal.* C 77.49%, H 8.92%, calcd for $C_{22}H_{30}O_3$, C 77.16%, H 8.83%.

(3*R*,7*R*,*S*)-, (3*R*,*S*,7*R*)-, and (7*R*,3*R*)-Octane-1,3,7-triol ((3*R*,7*R*,*S*)-3, (3*R*,*S*,7*R*)-3, and (7*R*,3*R*)-3). A mixture of **20** (1.17 g, 3.42 mmol) and 120 mg of 10% Pd/C in 22 mL of EtOH was hydrogenated[26] at room temperature and 73 psi for 24 h. The reaction mixture was filtered over Celite and concentrated in vacuo (colorless, viscous liquid) (95%): (3*R*,7*R*,*S*)-**3**, $[\alpha]^{25}_D$= −3.6° (*c* 1.49, $CHCl_3$); (3*R*,*S*,7*R*)-**3**, $[\alpha]^{25}_D$ = −7.6° (*c* 2.79, $CHCl_3$); (7*R*,3*R*)-**3**, $[\alpha]^{25}_D$ = −14.44° (*c* 5.76, $CHCl_3$). All spectral data (IR, ^{1}H NMR, ^{13}C NMR, LC−MS) corresponded well with the data obtained for the natural product.

(3*R*,7*R*,*S*)-, (3*R*,*S*,7*R*)-, and (7*R*,3*R*)-Tri-*O*-acetyloctane-1,3,7-triol ((3*R*,7*R*,*S*)-4, (3*R*,*S*,7*R*)-4, and (7*R*,3*R*)-4). Acetylation of the triol was performed according to the literature.[9] Dia-**3** (17 mg, 0.1 mmol) and acetic anhydride (300 mg, 2.9 mmol) were dissolved in pyridine (200 mg, 2.5 mmol) and kept overnight. The product was purified by preparative TLC with Et_2O (95%): R_f 0.73 (Et_2O); t_R 2496; IR (KBr) ν_{max} 2920 (CH), 1720 (C=O), 1360, ($OCOCH_3$), 1230, 1010; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.97 (1H, m, C-7*H*), 4.87 (1H, m, C-3*H*), 4.08 (2H, t, *J* = 6.5 Hz, C-1H_2), 2.04 (6H, s, $COCH_3$), 2.02 (3H, s, $COCH_3$), 1.86 (2H, m, C-2H_2), 1.25−1.72 (6H, m, C-4H_2, C-5H_2, C-6H_2), 1.20 (3H, d, *J* = 6 Hz, C-8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.6, 170.5 (3 CH_3CO), 70.9 (C-3), 70.6 (C-7), 60.8 (C-1), 35.6 (C-2), 34.0 (C-6), 33.1 (C-4), 19.8 (C-8), 21.1 (C-5), 21.3, 21.1, 20.8 (3 CH_3CO); EIMS *m*/*z* 43 (100), 99 (74), 93 (60), 81 (56), 108 $[M - 3AcOH]^+$ (55), 79 (48), 54 (41), 67 (39), 117 (34), 126 (17), 159 (15), 171 (6), 168 $[M - 2AcOH]^+$ (6), 185 (5), 213 (2), $[M]^+$ (<1); *anal.* C 57.93%, H 8.51%, calcd for $C_{14}H_{24}O_6$, C 58.32%, H 8.39%.

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