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General Stereodivergent Enantioselective Total Synthetic Approach toward Macrosphelides A–G and M

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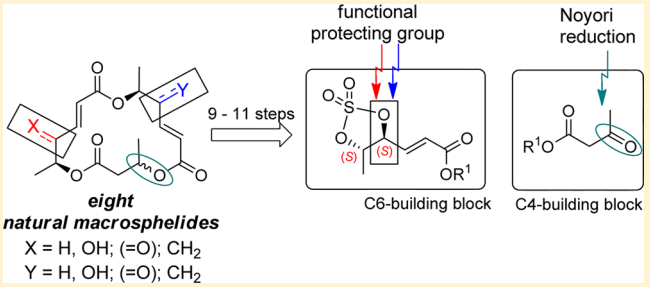
Supporting Information

ABSTRACT: A straightforward enantioselective total synthesis algorithm for the preparation of 8 out of 13 macrosphelides within 9–11 steps starting from *tert*-butyl sorbate is presented. The use of a cyclic sulfate as both protecting and reactivity directing group is the key element within this algorithm. A high-pressure transesterification allows for the selective ring-enlargement of the 15-membered macrosphelides into the 16-membered counterparts. The absolute configurations of the natural products were unambiguously assigned both by the chemical synthesis and by X-ray structure analysis.



INTRODUCTION

The macrosphelide-type natural product family consists currently of 13 members that are 15- or 16-membererd macrotriolides (Figure 1).[1,2] Since the first isolation of macrosphelide A in 1995[3] from *Microsphaeropsis sp.* FO-5050, strong research efforts devoted to the isolation of further macrosphelide members, the exploration of their bioactivity, and the total synthesis of these natural products were undertaken.[4] The main driving force for these investigations certainly lies in the fact that selected members were shown to inhibit the cell–cell adhesion of HL-60 cells to human umbilical vein endothelial cells (HUVECs).[1,3−5] This process might be regarded as a key step within the metastasis process,[6] and hence there is significant interest in the elaboration of a versatile and short total synthetic approach.

Among the various total syntheses published to date the cleavage of the ester groups represents the most common disconnection leading to one C4- and two C6-building blocks.[4] The C6-building blocks differ in their oxidation state. Although allylic γ-hydroxyl-, -carbonyl- or even -methylene groups are found within the C6-building block, all macrosphelides that were isolated to date possess an (*S*)-configured hydroxyl group at the δ-carbon. However, the stereocenter in the β-hydroxy butyric acid motif can be either (*R*)- or (*S*)-configured. In summary, the structural diversity of the macrosphelide family is the consequence of a combination of ring size, oxidation state of the C6-building blocks, and absolute configuration of the C4-building block. This structural similarity represents one of the key synthetic challenges, that is, the development of chemo-, regio-, and stereoselective functional group transformations within a molecular scaffold possessing various almost identical functional groups.

Traditionally, well-elaborated protecting group manipulations were used in order to establish the correct relative configuration within the vic-diol motif in the C6-building block and to set the stage for a regioselective esterification of only one out of the two adjacent OH-groups.[4] With regard to the interesting biological activity, we became interested in developing chemistry, in which the central diol-motif in the C6-building block is manipulated in a way that the diol is protected if necessary but that the protecting group also serves as a synthon that allows an inverting hydrolytic deprotection, an inverting esterificative deprotection, or a deoxygentative deprotection.

In the present manuscript, we report the successful synthesis of 8 out of 13 macrosphelide members within 9–11 steps starting from commercial *t*-butyl sorbate (Figure 1). Hence, to the best of our knowledge this represents the shortest total synthesis approach published to date. The straightforwardness and modularity is based on the following basic ideas:

- The cyclic sulfate as a functional protecting group: Elaboration of efficient stereoselective synthetic methods to convert (*S*,*S*)-*syn*-dihydroxysorbate derived cyclic sulfate into the various oxygenated C6-building blocks.
- Elaboration of an efficient ring-enlarging transesterifcation method using high pressure chemistry.

RESULTS AND DISCUSSION

We started our investigations with the development of a straightforward synthetic strategy for the preparation of both the C4- and the C6-building blocks. The former were obtained using the enantioselective reduction of *t*-butyl acetoacetate following a protocol reported by Noyori.[7] The corresponding (*R*)- or (*S*)-configured alcohols **7** were obtained in exclusive enantioselectivities of >98% ee. The *t*-butyl esters were used

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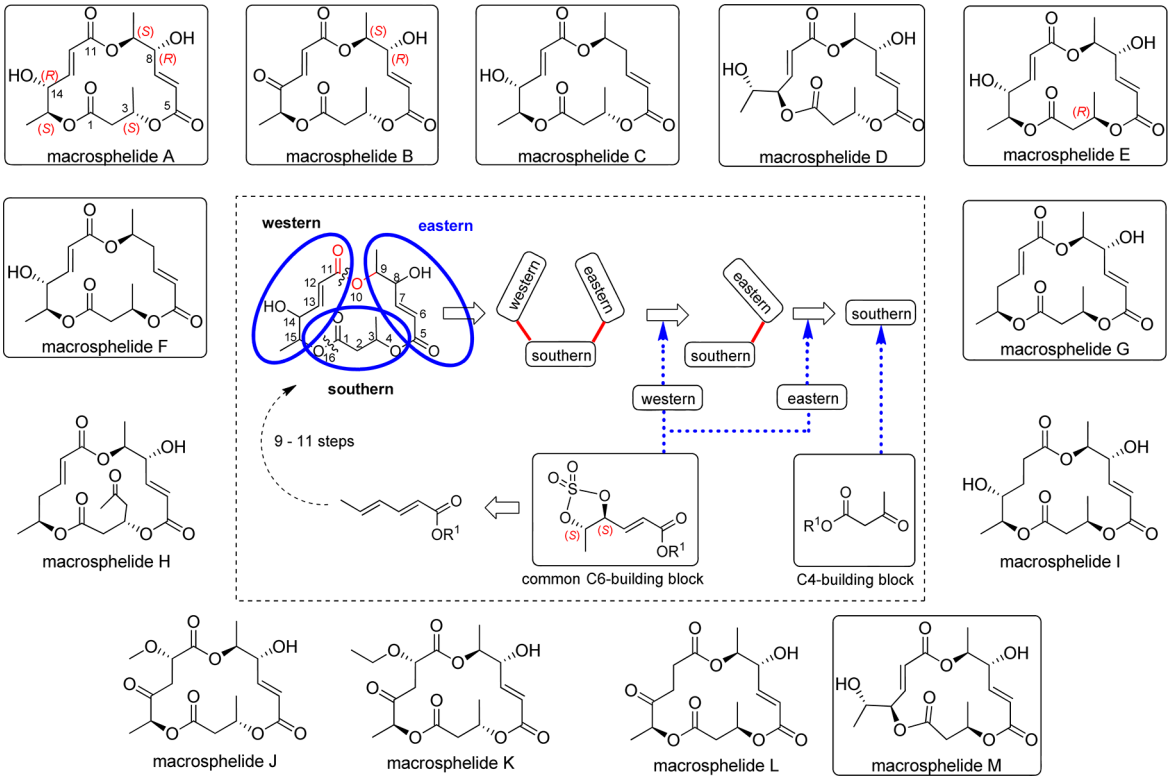


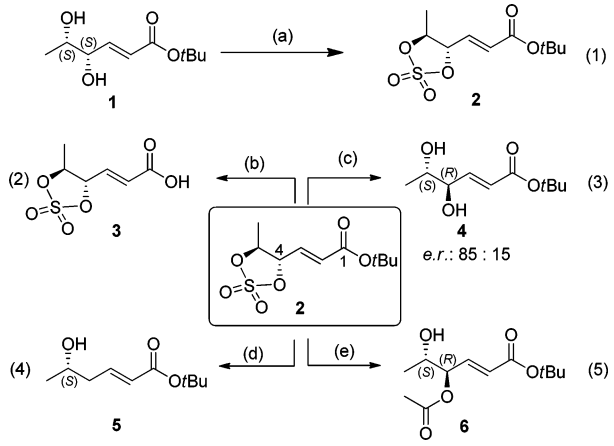
Figure 1. Macrosphelide natural product family[1,2] and retrosynthetic approach.

throughout the entire synthesis and were chosen for their ability to be cleaved under slightly acidic conditions using a silane and trifluoroacetic acid thus avoiding the undesired and literature known β-elimination of the β-acylbutyrates to the corresponding crotonates.[8]

For the C6-building blocks, we applied slightly modified conditions for a Sharpless asymmetric dihydroxylation of *t*-butyl sorbate.[9] After careful optimization, the desired (*S*,*S*)-configured vic-diol **1** was obtained in good yields and significantly improved enantiomeric excess of >94% ee. Depending on the specific macrosphelide diol, (*S*,*S*)-**1** needed to be converted into the various oxygenated C6-building blocks (Scheme 1). Different from the literature reports, we were seeking for a method to protect the diol motif albeit with the option of using the protecting group to generate an electronic bias between the two C−O-bonds in a way that the deprotection goes hand in hand with the selective activation of the C-4−O-bonds, like the inversion of the C-4 stereocenter, C-4 deoxygenation, or an inverting esterification.

After detailed analysis of suitable protecting groups (cyclic carbonates, sulfites, etc.), **1**-derived cyclic sulfate **2**[10] turned out to be the optimum choice (eq 1, Scheme 1). This protecting group proved to be stable in the *t*-butyl ester cleavage using TFA to give the corresponding carboxylic acid **3** (eq 2, Scheme 1), but it sets the stage for a deprotection with inversion of the C-4 stereochemistry upon treatment with ammonium formate and subsequent saponification of the resulting sulfate monoester with methanolic HCl solution to give the (*R*,*S*)-diol **4** (eq 3, Scheme 1). The change of the ammonium carboxylate allows the introduction of an ester motif at C-4 with inversion of the stereochemistry to give the corresponding acyloxyalcohol **6** in good enantiomeric ratio (eq 5, Scheme 1). The change of the nucleophile to $NaBH_4$ results in an exclusive deoxygenation at C-4 to the homoallylic alcohol **5** with full

Scheme 1. Cyclic Sulfates: Protecting and Reactivity Directing Group[a]



[a]Reagents and conditions: (a) SO_2Cl_2 (1 equiv), DMAP (40 mol %), Et_3N (4 equiv), CH_2Cl_2, −80 °C, 15 h, 60%; (b) Et_3SiH (1.1 equiv), TFA (40 equiv), CH_2Cl_2, 0 °C to rt, 3 h, quant.; (c) NH_3*HCOOH (1 equiv), DMF, rt, 15 h, then $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 15 h, 80%; (d) $NaBH_4$ (1.5 equiv), DMA, rt, 15 min, then $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 3 h, 63%; (e) CH_3COOH (1 equiv), NEt_3 (1.5 equiv), DMF, rt, 15 h, then $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 4.5 h, 72% (regioselectivity 74:26).

conservation of the enantiopurity (eq 4, Scheme 1). Importantly, the *t*-butyl ester remained unaffected under these conditions. Having in hand the desired chemical toolbox, we turned our attention to the application of these methods in total synthesis.

The Total Synthesis of Macrosphelides A, C, D, E, F, and M. A closer structural analysis of macrosphelides A, C, D,

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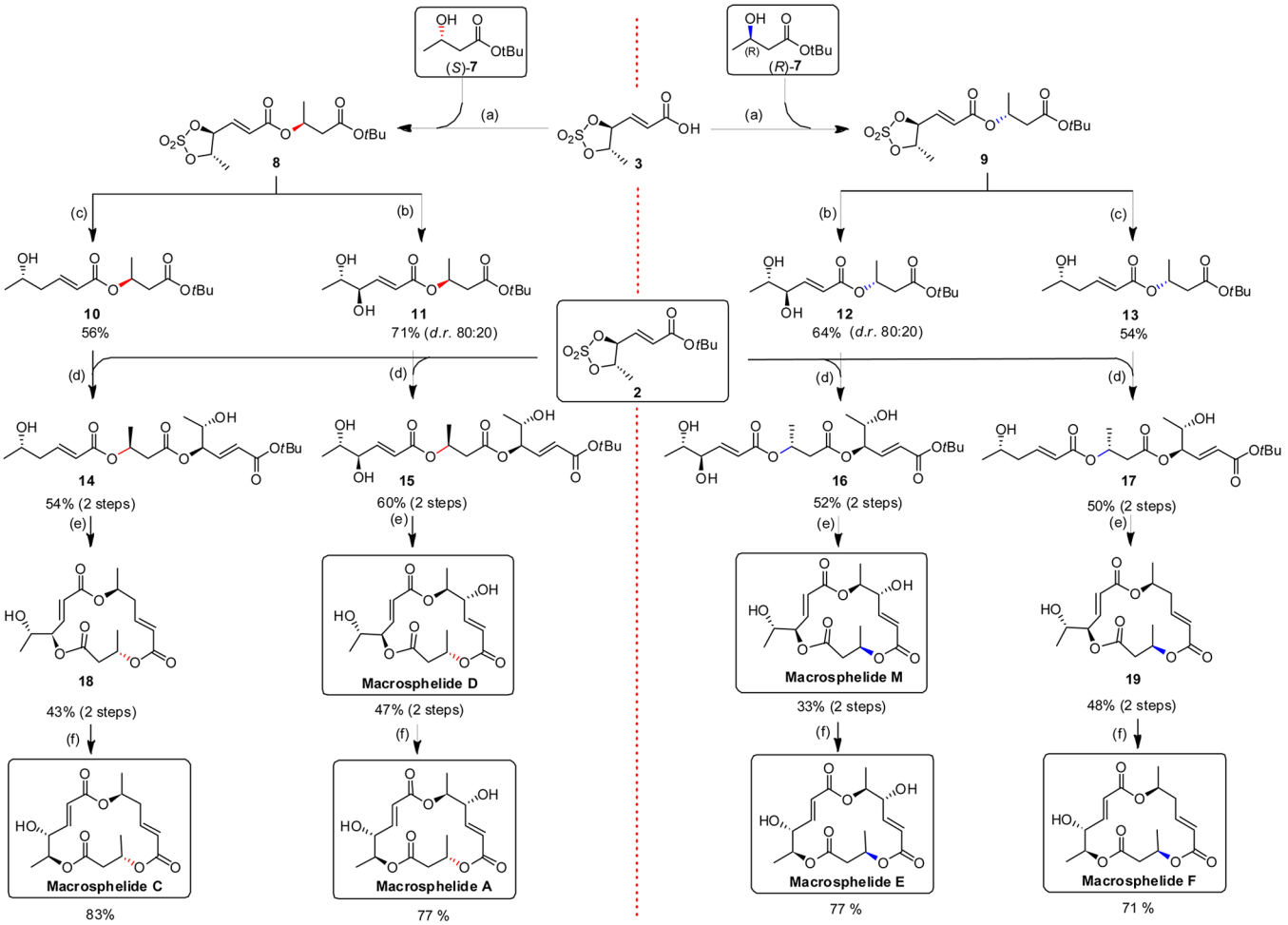
Scheme 2. Total Syntheses of Macrosphelides A, D, E, and M[a]



[a]Reagents and conditions: (a) DCC (1.5 equiv), DMAP (5 mol %), CH_2Cl_2, 0 °C to rt, 15 h, 53%; (b) NH_3*HCOOH (1 equiv), DMF, rt, 3.5 h, then $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 3.5 h; (c) $NaBH_4$ (1.0 equiv), DMA, rt, 30 min, then $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 3 h; (d) (i) TFA (40 equiv), Et_3SiH (1.1 equiv), CH_2Cl_2, 0 °C to rt, 2 h; (ii) **2** (1 equiv), NEt_3 (1.5 equiv), DMF, rt, 9 h, then $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 4 h; (e) (i) TFA (100 equiv), Et_3SiH (1.1 equiv), CH_2Cl_2, 0 °C to rt, 1.5 h; (ii) 2-methyl-6-nitrobenzoic anhydride (1.2 equiv), NEt_3 (2.2 equiv), DMAP (0.25 equiv), CH_2Cl_2/THF, rt, 8 h; (f) Ti(*i*OPr)$_4$ (50 equiv), CH_2Cl_2, rt, 15 h, 7 kbar.

E, F, and M reveals that they differ (a) in the ring size (D and M are 15-membered macrotriolides; A, C, E, and F are 16-membered macrotriolides), (b) in the oxygenation degree (A, D, E, and M possess a hydroxy group at C-8; C and F are deoxygenated at C-8), and (c) in the configuration at C-3 ((*S*)-configuration for A, C, and D; (*R*)-configuration for E, F, and M).

The total synthesis of this set of natural products started with the esterification of the respective (*S*)- or (*R*)-configured *β*-hydroxybutyric acid **7** with building block **3** under slightly modified Steglich conditions (Scheme 2). The corresponding diastereomeric sulfates **8** and **9** were obtained in good yields.

For the synthesis of macrosphelides A, D, E, and M, an *inverting cleavage of the sulfate group* using ammonium formate and HCl was performed that led to the formation of the corresponding *trans*-configured diols **11** and **12** in good diastereoselectivities. For macrosphelides C and F, the *deoxygenative cleavage of the sulfate group* and subsequent saponification of the sulfate monoester using HCl led to the formation of the corresponding homoallyl alcohols **10** and **13**. All subsequent transformations toward macrosphelides A, C, D, E, F, and M were performed using identical reaction conditions.

The chemoselective saponification of the *t*-butyl ester in **10**–**13** allowed the liberation of the corresponding carboxylic acids, which were directly employed in an *inverting esterification*–*sulfate cleavage* using sulfate building block **2** to give the respective triesters **14**–**17** in good yields and excellent diastereoselectivities. After the subsequent selective saponification of the *t*-butyl ester moiety, the respective carboxylic acids underwent a clean Shiina macrolactonization reaction[11] to the 15-membered ring products **18**, **19**, and macrosphelides D and M. Importantly, no acyl group migration with formation of the 16-membered macrosphelides were observed under these conditions.

The correct relative and absolute configurations of macrosphelide D and M were confirmed by comparison of the spectral data with literature reports.[2a] Furthermore, we were able to obtain a crystal structure of macrosphelide D confirming the correct relative and absolute configuration of all stereocenters (Supporting Information, Supplementary Figure 65).

With the 15-membered macrotriolides in hand, we finally set out to develop the ring-enlarging transesterification. A plethora of conditions were tested, but only mixtures of 15- and 16-membered rings were observed. At this point, we revisited the

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X-ray structures of macrosphelide D and A[1a] (Figure 2). Based on these solid phase structures, we assumed that, in order to

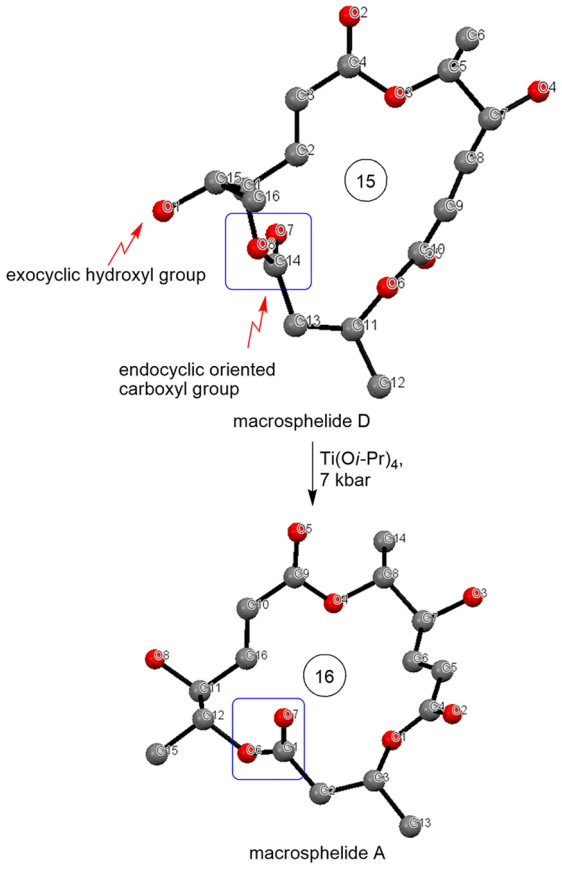


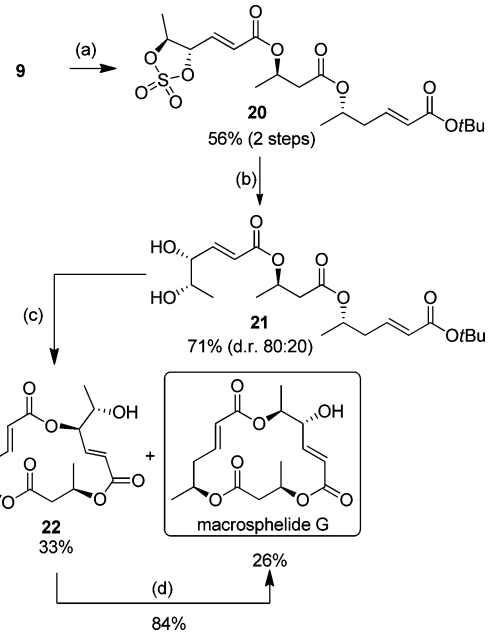
Figure 2. Conformation driven selective ring-enlarging transesterification under high pressure.

allow the transesterification to proceed, the 15-membered macrocycle needs to undergo a conformational change in such a way that the migrating ester carbonyl group is not oriented into the ring but needs to flip out of the ring in order to approach the free exocyclic secondary alcohol (Figure 2).

One way to provide the energy that allows the 15-membered macrocycle to adopt this desired reactive conformation and to favor the more ordered (and sterically disfavored) transition state is the application of high pressure conditions.[12] We found that after intense screening of various transesterification methods, the corresponding 16-membered macrocyclic macrosphelides A, C, E, and F were obtained in high yields with exclusive selectivity using an excess of $Ti(O\textit{i}\text{-}Pr)_4$ at 7 kbar (Scheme 2). We disclose a total synthesis algorithm that allows six natural and two non-natural macrosphelides to be prepared from *t*-butyl sorbate in 9−10 steps.

The Total Synthesis of Macrosphelide G. With these total syntheses in hands, we turned our attention to the synthesis of macrosphelide G. This natural product is an isomer of macrosphelide F and possesses a C-8-hydroxyl group but is deoxygenated at C-14. In order to generate this substitution pattern, sulfate **2**-derived deoxygenated C6-building block **5** (Scheme 1) was subjected to an esterification using **9**-derived carboxylic acid (Scheme 3) to give triester **20** in good overall yield. The inverting sulfate hydrolysis to diol **21** proceeded in good yields using the established conditions (*vide supra*). Very much to our surprise, the missing hydroxyl group in **21** had a

Scheme 3. Total Synthesis of Macrosphelide G[a]



[a]Reagents and conditions: (a) (i) TFA (40 equiv), Et_3SiH (1.1 equiv), CH_2Cl_2, 0 °C to rt, 2 h; (ii) **5** (0.5 equiv), DCC (1.7 equiv), DMAP (0.1 equiv), camphorsulfonic acid (4 mol %), $ClCH_2CH_2Cl$, −20 °C, 15 h; (b) NH_3*HCOOH (1 equiv), DMF, rt, 5 h, then: $HCl_{(MeOH)}$ (2 equiv), THF, 0 °C, 2.5 h; (c) (i) TFA (100 equiv), Et_3SiH (1.1 equiv), CH_2Cl_2, 0 °C to rt, 1.5 h; (ii) 2-methyl-6-nitrobenzoic anhydride (1.3 equiv), NEt_3 (2.3 equiv), DMAP (0.25 equiv), CH_2Cl_2/THF, rt, 8 h; (d) $Sc(OTf)_3$ (0.7 equiv), DMAP (3.3 equiv), CH_2Cl_2, rt, 5 min.

significant influence on the ring-size selectivity of the subsequent Shiina macrolactonization. Different from the macrosphelide C and F synthesis, a 1:1-mixture of 15- and 16-membered macrotriolides was obtained. Separation of the isomers and subsequent treatment of the 15-membered ring **22** with $Sc(OTf)_3$/DMAP[13] however led to a transesterificative ring-enlargement to the desired 16-membered natural product macrosphelide G in 84% yield. The application of the high-pressure Ti-mediated transesterification that proved successful for the other macrosphelide synthesis turned out to be less suitable for this substrate and gave comparable lower yields of the 16-membered ring product (40%). Hence, starting from the acylic precursor **21**, the natural product was obtained in 54% combined isolated yield over two (respectively, three) steps.

Also in this case, we were able to obtain a crystal structure of macrosphelide G confirming the correct relative and absolute configuration of all stereocenters (Supporting Information, Supplementary Figure 66).

Site Selectivity in Macrosphelide Oxidations: Total Synthesis of Macrosphelide B. At the end of our study, we were wondering whether a site selective oxidations of bis-hydroxyl macrosphelides like macrosphelide A would allow access to macrosphelides with differently oxidized C6-building blocks (e.g., macrosphelide B). However, we envisioned the site selecitvity to be particularly challenging since the respective two hydroxyl groups at C-8 and C-14 (Figure 1) differ only in the substitution of the adjacent ester moiety at C-9 and C-15, respectively (Figure 1).[9] Despite these structural similarities, we were surprised to find that treatment of macrosphelide A with Dess−Martin periodinane at low temperatures gave the desired macrosphelide B in 36% isolated yield and good chemo-

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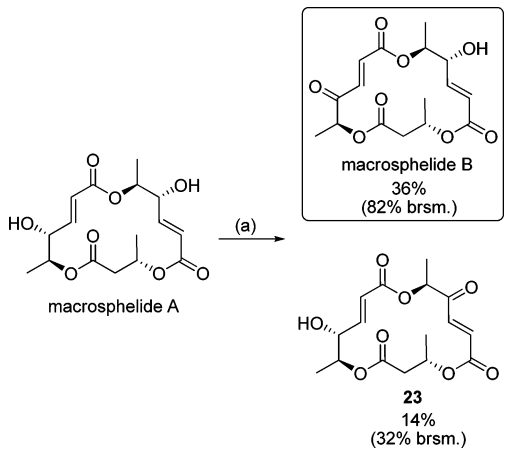
selectivity (Scheme 4). The corresponding regioisomer of macrosphelide B was formed in about 14% isolated yield.

Scheme 4. Total Synthesis of Macrosphelide B[a]



[a]Reagents and conditions: (a) Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, −20 °C, 6 h.

Importantly, the starting material was recovered to about 44%. Only minor amounts of the corresponding overoxidation product, that is, the diketone, were formed.

CONCLUSION

Herein we report a straightforward enantioselective total synthesis algorithm for the preparation of 8 out of 13 macrosphelides within 9–11 steps starting from *tert*-butyl sorbate. The use of a cyclic sulfate as both protecting and reactivity directing group set the stage for a flexible mild introduction and derivatization of a common C6-building blocka either within the synthesis or at a separate stage. X-ray structure-derived molecular consideration led to the development of a highly selective ring-enlarging transesterification that is to date without precedence in the literature. Future work is dedicated to the application of this algorithm to the synthesis of defined libraries of macrosphelide analogues in order to investigate cell–cell adhesion effects.

EXPERIMENTAL SECTION

General Remarks. All reactions and manipulations of reagents sensitive to air or moisture were performed under nitrogen atmosphere using standard Schlenk techniques. Chemical shifts are expressed in ppm with residual chloroform (δ = 7.26 ppm (^{1}H), δ = 77.0 ppm (^{13}C)) as reference or with TMS as internal standard. For HRMS (ESI) measurments Q-TOF was used as mass analyzer. *tert*-Butyl-3-hydroxybutanoate (**7**)[7] and *tert*-butylsorbate[14] were prepared according to known methods.

(4*S*,5*S*,*E*)-*tert*-Butyl-4,5-dihydroxyhex-2-enoate, 1. K_2CO_3 (3.4 g, 24.8 mmol, 3.2 equiv), $K_3[Fe(CN)_6]$ (8.2 g, 24.8 mmol, 3.2 equiv), $K_2OsO_4{\cdot}2H_2O$ (11.9 mg, 0.03 mmol, 0.4 mol %), hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQ)_2PYR$, 69.3 mg, 0.08 mmol, 1 mol %], and methane sulfonamide (727.2 mg, 7.6 mmol, 1 equiv) were dissolved in 76 mL of a 1:1 mixture of *tert*-butanol and water. After 1 h of vigorous stirring, the mixture was cooled to 0 °C and *tert*-butyl sorbate (1.3 g, 7.7 mmol) was added. After stirring overnight at 0 °C, saturated Na_2SO_3 solution was added, and the reaction mixture was allowed to warm to room temperature (1 h). Water was added to the mixture, which was then extracted with dichloromethane (5×). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 1:1) to yield **1** (1.1 g, 71%, 94 % ee). The enantiomeric excess was detected by chiral HPLC (Chiralcel OD, heptane/2-propanol (95:5), 1.0 mL/min, 220 nm), $t_R(R)$ = 12.25, $t_R(S)$ = 13.49), R_f = 0.35 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −40.3 (c = 9.7 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.81 (dd, J = 15.7, 5.3 Hz, 1H), 6.07 (dd, J = 15.7, 1.6 Hz, 1H), 4.02–4.07 (m, 1H), 3.69–3.79 (m, 1H), 1.49 (s, 9H), 1.25 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.7, 145.1, 124.4, 80.8, 75.7, 70.3, 28.1 (3C), 19.0; IR (film) ν (cm^{-1}) = 3398 (m), 1712 (s), 1694 (s), 1657 (w), 1368 (w), 1151 (s), 982 (m); MS (EI) m/z (%) = 203 (1), 187 (1), 129 (8), 102 (100), 84 (23), 73 (12), 57 (37), 45 (12); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{10}H_{18}O_4Na$ 225.1097, found 225.1104.

(*E*)-*tert*-Butyl 3-((4*S*,5*S*)-5-Methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl)acrylate, 2. (4*S*,5*S*,*E*)-*tert*-Butyl-4,5-dihydroxyhex-2-enoate, **1** (202 mg, 1 mmol), was dissolved in 22 mL of dichloromethane. 4-Dimethylaminopyridine (DMAP; 50 mg, 0.4 mmol, 0.4 equiv) was added, and the mixture was cooled to −78 °C. After triethylamine (553.3 μL, 4 mmol, 4 equiv) was added, the mixture was stirred for 10 min. Sulfuryl chloride (freshly distilled, 80.8 μL, 1 mmol, 1 equiv) was dissolved in 22 mL of dichloromethane and added to the reaction mixture over 14 h via syringe pump. Meanwhile, the solution was allowed to warm to −60 °C. Afterward, the mixture was stirred for additional 30 min at −60 °C. The mixture was poured into a separation funnel containing pentane and sat. sodium bicarbonate solution. The organic layer was washed with brine. The aqueous layers were extracted 3× with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to yield **2** (159.8 mg, 60%) as a white solid (amorphous). R_f = 0.31 (5:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −24.5 (c = 8.5 mg cm^{-3} in EtOH); mp 66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.71 (dd, J = 15.7, 6.5 Hz, 1H), 6.19 (dd, J = 15.6, 1.2 Hz, 1H), 5.02 (ddd, J = 8.9, 6.5, 1.2 Hz, 1H), 4.78 (dq, J = 8.9, 6.2 Hz, 1H), 1.61 (d, J = 6.2 Hz, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 163.5, 134.1, 129.7, 86.0, 82.7, 82.1, 28.0 (3C), 16.4; IR (film) ν (cm^{-1}) = 1718 (s), 1666 (w), 1371 (s), 1208 (s), 1155 (s), 980 (m), 953 (m), 831 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{10}H_{16}O_6SNa$ 287.0560, found 287.0561.

(*E*)-3-((4*S*,5*S*)-5-Methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl)-acrylic Acid, 3. To a solution of sulfate **2** (26.4 mg, 0.1 mmol) in 0.5 mL of dichloromethane, triethylsilane (17 μL, 0.11 mmol, 1.1 equiv) and TFA (309 μL, 4.0 mmol, 40 equiv) were added subsequently at 0 °C. The reaction mixture was allowed to warm to room temperature. After the conversion was completed (3 h), the solvent was removed under reduced pressure. The TFA was coevaporated with toluene 10 times. The crude product (20.8 mg, quant.) was used in the next step without any further purification. R_f = 0.17 (2:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −30.2 (c = 5.8 mg cm^{-3} in EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 9.04 (bs, 1H, COOH), 6.94 (dd, J = 15.6, 5.9 Hz, 1H), 6.30 (dd, J = 15.6, 1.1 Hz, 1H), 5.09 (ddd, J = 8.6, 6.0, 1.0 Hz, 1H), 4.80 (dq, J = 8.6, 6.2 Hz, 1H), 1.64 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.2, 138.1, 126.2, 85.3, 82.5, 16.5; IR (film) ν (cm^{-1}) = 2939 (m), 1696 (s), 1667 (m), 1650 (m), 1374 (s), 1202 (s), 1138 (w), 982 (m), 940 (m), 817 (s); HRMS (ESI-TOF) (m/z) [M − H]$^+$ calculated for $C_6H_7O_6S$ 206.9958, found 206.9972.

(4*R*,5*S*,*E*)-*tert*-Butyl-4,5-dihydroxyhex-2-enoate, 4. To a solution of sulfate **2** (27.8 mg, 0.1 mmol) in 0.8 mL of DMF, ammonium formate (6.3 mg, 0.1 mmol, 1 equiv) was added. The mixture was stirred overnight at room temperature. The solvent was coevaporated with ethyl acetate. The residue was dissolved in 0.8 mL of THF, and methanolic HCl (1.25 M, 160 μL, 0.2 mmol, 2 equiv) was added at 0 °C. The reaction mixture was stirred overnight at 0 °C. Then sodium bicarbonate (20 mg, 0.24 mmol, 2.4 equiv) was added. The mixture was stirred for additional 20 min. After addition of water and ethyl acetate, the organic layer was washed with brine. The aqueous layers were extracted with ethyl acetate (3×). The combined organic layers

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were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 1:1). Compound **4** (16.2 mg, 80%, 70% ee) was obtained as a colorless oil. The enantiomeric excess was detected by chiral HPLC (Chiralcel OD-H, heptane/2-propanol (95:5), 0.5 mL/min, 220 nm), t_R(5*R*) = 24.45, t_R(5*S*) = 26.06), R_f = 0.28 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 27.7 (c = 13.3 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.84 (dd, J = 15.7, 5.2 Hz, 1H), 6.04 (dd, J = 15.7, 1.7 Hz, 1H), 4.29 (ddd, J = 5.2, 3.6, 1.6 Hz, 1H), 3.96 (dq, J = 6.5, 3.6 Hz, 1H), 1.49 (s, 9H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) = 165.5, 143.9, 124.6, 80.7, 74.6, 70.0, 28.1 (3C), 17.5; IR (film) ν (cm^{-1}) = 3428 (m), 1714 (s), 1690 (s), 1657 (w), 1368 (w), 1148 (s), 981 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{10}H_{18}O_4Na$ 225.1097, found 225.1094.

(*S*,*E*)-*tert*-Butyl 5-Hydroxyhex-2-enoate, 5. To a solution of sulfate **2** (100 mg, 0.38 mmol) in 4.2 mL of DMA, 21.5 mg of $NaBH_4$ (0.57 mmol, 1.5 equiv) was added. After 15 min stirring at room temperature, the solvent was coevaporated with ethyl acetate. The residue was dissolved in 4.2 mL of THF and cooled to 0 °C before addition of a 1.25 M solution of HCl in methanol (606 μL, 0.76 mmol, 2 equiv). The reaction mixture was stirred for 3 h at 0 °C. Then $NaHCO_3$ (75.8 mg, 0.90 mmol, 2.4 equiv) was added, and the mixture was stirred for an additional 20 min. After addition of water and ethyl acetate, the organic layer was washed with brine. The aqueous layers were extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 3:1). Compound **5** (44.1 mg, 63%) was obtained as a colorless oil, R_f = 0.48 (2:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 9.4 (c = 3.1 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.85 (dt, J = 15.3, 7.6 Hz, 1H), 5.83 (dt, J = 15.5, 1.5 Hz, 1H), 3.91−4.01 (m, 1H), 2.31−2.36 (m, 2H), 1.48 (s, 9H), 1.24 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.7, 143.6, 125.7, 80.3, 66.7, 41.7, 28.1 (3C), 23.2; IR (film) ν (cm^{-1}) = 3416 (w), 1713 (s), 1654 (w), 1368 (w), 1156 (s), 981 (w); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1145.

(4*R*,5*S*,*E*)-*tert*-Butyl 4-acetoxy-5-hydroxyhex-2-enoate, 6. To a solution of sulfate **2** (27.2 mg, 0.1 mmol) in 0.8 mL of DMF, acetic acid (5.7 μL, 0.1 mmol, 1 equiv) and triethylamine (20.8 μL, 0.15 mmol, 1.5 equiv) were added subsequently at room temperature. The reaction mixture was stirred overnight. The solvent was coevaporated with ethyl acetate. The residue was dissolved in 0.8 mL of THF, and methanolic HCl (1.25 M, 160 μL, 0.2 mmol, 2 equiv) was added at 0 °C. After the mixture was stirred for 4 h 20 min at 0 °C, $NaHCO_3$ (20 mg, 0.24 mmol, 2.4 equiv) was added. The mixture was stirred for additional 20 min. After addition of water and ethyl acetate, the organic layer was washed with brine. The aqueous layers were extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 1:1) and semipreparative HPLC (petroleum ether/ethyl acetate, 2:1). Compound **6** (13.3 mg, 53%) was obtained as a colorless oil, R_f = 0.18 (3:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −21.8 (c = 6.8 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.79 (dd, J = 15.8, 5.8 Hz, 1H), 5.95 (dd, J = 15.8, 1.4 Hz, 1H), 5.35 (ddd, J = 5.5, 4.0, 1.4 Hz, 1H), 4.01 (dq, J = 6.5, 3.8 Hz, 1H), 2.15 (s, 3H), 1.49 (s, 9H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 170.1, 164.9, 139.7, 126.0, 80.9, 76.4, 68.9, 28.1 (3C), 21.0, 18.1; IR (film) ν (cm^{-1}) = 3466 (m), 1741 (m), 1713 (s), 1660 (w), 1368 (m), 1150 (s), 981 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{12}H_{20}O_5Na$ 267.1203, found 267.1183.

As a side product, regioisomer (4*S*,5*R*,*E*)-*tert*-butyl 5-acetoxy-4-hydroxyhex-2-enoate, **S6**, was isolated in 19% yield (4.6 mg), R_f = 0.69 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 4.2 (c = 1.7 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.79 (dd, J = 15.7, 4.9 Hz, 1H), 6.06 (dd, J = 15.8, 1.8 Hz, 1H), 5.01 (dq, J = 6.5, 3.2 Hz, 1H), 4.40−4.42 (m, 1H), 2.37 (bs, 1H, OH), 2.08 (s, 3H), 1.49 (s, 9H), 1.23 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 170.8, 165.4, 143.1, 124.7, 80.7, 73.1 (2C), 28.1 (3C), 21.2, 14.4; IR (film) ν (cm^{-1}) = 3462 (m), 1737 (m), 1713 (s), 1659 (m), 1369 (m), 1149 (s), 982 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{12}H_{20}O_5Na$ 267.1203, found 267.1198.

(*S*)-*tert*-Butyl 3-(((*E*)-3-((4*S*,5*S*)-5-Methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl)acryloyl)oxy)butanoate, 8. Sulfate **2** (515 mg, 2.0 mmol) was dissolved in 10 mL of dichloromethane, and the solution was cooled to 0 °C. Triethylsilane (330 μL, 2.1 mmol, 1.1 equiv) and TFA (5.9 mL, 77 mmol, 40 equiv) were added subsequently, and the mixture was allowed to warm slowly to room temperature. After complete conversion (2−3 h), the solvent was removed under reduced pressure. TFA was coevaporated with toluene 10 times. The residue was dissolved in 10 mL of THF, the solution was cooled to 0 °C, and (*S*)-alcohol (*S*)-**7** (1.5 g, 9.6 mmol, 5 equiv), DCC (602.4 mg, 2.9 mmol, 1.5 equiv), and DMAP (11.9 mg, 0.1 mmol, 5 mol %) were added subsequently. The mixture was stirred overnight at room temperature, diluted with ethyl acetate, and washed with a diluted $CuSO_4$-solution and brine. The aqueous solutions were extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 7:1 then 5:1) to yield **8** as a colorless oil (362.1 mg, 53%); 68% of (*S*)-alcohol (*S*)-**7** (1.05 g) could be reisolated, R_f = 0.19 (5:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −12.1 (c = 5.7 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.80 (dd, J = 15.6, 6.3 Hz, 1H), 6.25 (dd, J = 15.7, 1.2 Hz, 1H), 5.30−5.41 (m, 1H), 5.01−5.06 (m, 1H), 4.73−4.82 (m, 1H), 2.60 (dd, J = 15.5, 7.7 Hz, 1H), 2.47 (dd, J = 15.5, 5.5 Hz, 1H), 1.61 (d, J = 6.2 Hz, 3H), 1.43 (s, 9H), 1.34 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.2, 163.5, 135.4, 127.7, 85.7, 82.6, 81.1, 68.9, 42.0, 28.0 (3C), 19.7, 16.4; IR (film) ν (cm^{-1}) = 1719 (s), 1668 (w), 1384 (m), 1367 (w), 1209 (s), 1159 (s), 963 (m), 818 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{14}H_{22}O_8SNa$ 373.0928, found 373.0946.

(*R*)-*tert*-Butyl 3-(((*E*)-3-((4*S*,5*S*)-5-Methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl)acryloyl)oxy)butanoate, 9. Compound **9** was prepared according to the procedure described for **8**, starting from sulfate **2** (600 mg, 2.3 mmol) and (*R*)-**7** (1.79 g, 11.2 mmol, 5 equiv). Compound **9** was obtained as a colorless oil (445.4 mg, 56%), R_f = 0.32 (3:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −18.1 (c = 1.3 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.81 (dd, J = 15.6, 6.2 Hz, 1H), 6.25 (dd, J = 15.6, 1.2 Hz, 1H), 5.29−5.41 (m, 1H), 5.01−5.07 (m, 1H), 4.78 (dq, J = 8.8, 6.2 Hz, 1H), 2.60 (dd, J = 15.5, 7.8 Hz, 1H), 2.47 (dd, J = 15.5, 5.5 Hz, 1H), 1.61 (d, J = 6.2 Hz, 3H), 1.43 (s, 9H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.2, 163.5, 135.4, 127.6, 85.7, 82.6, 81.1, 68.9, 42.0, 28.0 (3C), 19.8, 16.4; IR (film) ν (cm^{-1}) = 1719 (s), 1668 (w), 1385 (m), 1367 (m), 1210 (s), 1160 (m), 964 (m), 819 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{14}H_{22}O_8SNa$ 373.0928, found 373.0934.

(*S*,*E*)-(*S*)-4-(*tert*-Butoxy)-4-oxobutan-2-yl 5-Hydroxyhex-2-enoate, 10. To a solution of sulfate **8** (17.5 mg, 0.05 mmol) in 0.55 mL of DMA, $NaBH_4$ (1.9 mg, 0.05 mmol, 1 equiv) was added. After 30 min of stirring at room temperature, the solvent was coevaporated with ethyl acetate. The residue was dissolved in 0.55 mL of THF and cooled to 0 °C before addition of a 1.25 M solution of methanolic HCl (80.2 μL, 0.1 mmol, 2 equiv). The reaction mixture was stirred for 2 h 40 min at 0 °C; then $NaHCO_3$ (10 mg, 0.12 mmol, 2.4 equiv) was added, and the mixture was stirred for additional 20 min. After addition of water and ethyl acetate, the organic layer was washed with brine. The aqueous layers were extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1). Compound **10** (7.6 mg, 56%) was obtained as a colorless oil, R_f = 0.45 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 17.6 (c = 6.4 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.95 (dt, J = 15.2, 7.6 Hz, 1H), 5.87 (dt, J = 15.6, 1.5 Hz, 1H), 5.27−5.34 (m, 1H), 3.93−3.99 (m, 1H), 2.58 (dd, J = 15.2, 7.6 Hz, 1H), 2.45 (dd, J = 15.2, 5.8 Hz, 1H), 2.35−2.37 (m, 2H), 1.74 (bs, 1H, OH), 1.43 (s, 9H), 1.31 (d, J = 6.3 Hz, 3H), 1.24

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(d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.5, 165.4, 145.1, 123.9, 80.8, 67.6, 66.7, 42.3, 41.8, 28.0 (3C), 23.2, 19.8; IR (film) ν (cm^{-1}) = 3436 (m), 1718 (s), 1655 (m), 1368 (m), 1159 (s), 982 (m); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{14}H_{24}O_5Na$ 295.1516, found 295.1501.

(4*R*,5*S*,*E*)-(*S*)-4-(*tert*-Butoxy)-4-oxobutan-2-yl 4,5-Dihydroxyhex-2-enoate, 11. To a solution of **8** (95.8 mg, 0.27 mmol) in 2.2 mL of DMF, ammonium formiate (17.2 mg, 0.27 mmol, 1 equiv) was added. The mixture was stirred for 3 h 30 min at room temperature. The solvent was coevaporated with ethyl acetate. The residue was dissolved in 2.2 mL of THF and cooled to 0 °C, and then 1.25 M methanolic HCl (436 μL, 0.55 mmol, 2 equiv) was added. After stirring for 3 h 20 min at 0 °C, sodium bicarbonate (59.4 mg, 0.71 mmol, 2.6 equiv) was added, and the mixture was stirred for additional 20 min. Water and ethyl acetate were added, the organic layer was washed with brine, and the aqueous layers were extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified via column chromatography (petroleum ether/ethyl acetate, 1:1) to yield **11** (55.7 mg, 71%) as a diastereomeric mixture (dr 80:20). Because the diastereomeres could not be separated by standard methods, **11** was used within the next step without further purification. R_f = 0.33 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 27.4 (c = 5.0 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.94 (dd, J = 15.7, 4.9 Hz, 1H), 6.09 (*app*. d, J = 15.7 Hz, 1H), 5.28−5.35 (m, 1H), 4.29−4.33 (m, 1H), 3.93−3.98 (m, 1H), 2.58 (dd, J = 15.3, 8.0 Hz, 1H), 2.46 (dd, J = 15.2, 5.6 Hz, 1H), 1.43 (s, 9H), 1.32 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.6, 165.4, 145.7, 122.5, 81.0, 74.5, 69.9, 67.9, 42.2, 28.0 (3C), 19.8, 17.5; IR (film) ν (cm^{-1}) = 3432 (m), 1722 (s), 1658 (w), 1368 (w), 1163 (m), 986 (w); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{14}H_{24}O_6Na$ 311.1465, found 311.1465.

(4*R*,5*S*,*E*)-(*R*)-4-(*tert*-Butoxy)-4-oxobutan-2-yl 4,5-Dihydroxyhex-2-enoate, 12. Compound **12** was prepared according to the procedure described for **11**, starting from **9** (180 mg, 0.51 mmol). Compound **12** was isolated as colorless oil (94.6 mg, 64%). R_f = 0.27 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 8.4 (c = 2.3 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.93 (dd, J = 15.7, 4.9 Hz, 1H), 6.10 (dd, J = 15.7, 1.4 Hz, 1H), 5.28−5.35 (m, 1H), 4.30−4.32 (m, 1H), 3.96 (dq, J = 6.4, 3.7 Hz, 1H), 2.59 (dd, J = 15.2, 7.7 Hz, 1H), 2.46 (dd, J = 15.2, 5.7 Hz, 1H), 2.42 (bs, 2H, OH), 1.43 (s, 9H), 1.32 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.6, 165.3, 145.5, 122.6, 81.0, 74.5, 69.9, 67.9, 42.2, 28.0 (3C), 19.8, 17.4; IR (film) ν (cm^{-1}) = 3431 (s), 1718 (s), 1657 (w), 1368 (w), 1160 (s), 983 (m); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{14}H_{24}O_6Na$ 311.1465, found 311.1480.

(*S*,*E*)-(*R*)-4-(*tert*-Butoxy)-4-oxobutan-2-yl 5-Hydroxyhex-2-enoate, 13. Compound **13** was prepared according to the procedure for **10** starting from **9** (17.5 mg, 0.05 mmol). Compound **13** was yielded as colorless oil (7.4 mg, 54%). R_f = 0.59 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 3.4 (c = 3.6 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.94 (dt, J = 15.3, 7.6 Hz, 1H), 5.86 (dt, J = 15.8, 1.3 Hz, 1H), 5.26−5.32 (m, 1H), 3.92−3.98 (m, 1H), 2.57 (dd, J = 15.2, 7.7 Hz, 1H), 2.43 (dd, J = 15.2, 5.7 Hz, 1H), 2.33−2.36 (m, 2H), 1.71 (bs, 1H, OH), 1.41 (s, 9H), 1.30 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.5, 165.4, 145.2, 123.9, 80.8, 67.6, 66.7, 42.3, 41.8, 28.0 (3C), 23.2, 19.8; IR (film) ν (cm^{-1}) = 3440 (m), 1722 (s), 1655 (w), 1368 (m), 1164 (s), 984 (w); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{14}H_{24}O_5Na$ 295.1516, found 295.1517.

(4*R*,5*S*,*E*)-*tert*-Butyl 5-Hydroxy-4-(((*S*)-3-(((*S*,*E*)-5-hydroxyhex-2-enoyl)oxy)butanoyl)oxy)hex-2-enoate, 14. To a solution of **10** (13.6 mg, 0.051 mmol) in 205 μL of dichloromethane, triethylsilane (9.0 μL, 0.057 mmol, 1.1 equiv) and TFA (157.2 μL, 2.0 mmol, 40 equiv) were added subsequently at 0 °C. The mixture was allowed to warm slowly to room temperature. After the conversion was completed (2 h), the solvent was removed under reduced pressure. The TFA was coevaporated with toluene 10 times. The residue was dissolved in 0.4 mL of DMF. Sulfate **2** (13.2 mg, 0.05 mmol, 1 equiv) and triethylamine (10.4 μL, 0.075 mmol, 1.5 equiv) were added. The mixture was stirred at room temperature for 9 h. The solvent was coevaporated with ethyl acetate. The residue was dissolved in 0.4 mL of THF and cooled with an ice-bath; then 1.25 M methanolic HCl (80.6 μL, 0.1 mmol, 2 equiv) was added. After the mixture was stirred for 4 h at 0 °C, sodium bicarbonate (10.1 mg, 0.12 mmol, 2.4 equiv) was added, and the mixture was stirred for additional 20 min. Water and ethyl acetate were added, the organic layer was washed with brine, and the aqueous layers were extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified via column chromatography (ethyl acetate) and preparative HPLC (petroleum ether/ethyl acetate, 1:2) to yield **14** (10.7 mg, 54%). R_f = 0.27 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −0.7 (c = 1.5 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.99 (dt, J = 15.3, 7.6 Hz, 1H), 6.75 (dd, J = 15.7, 6.0 Hz, 1H), 5.90 (*app*. t, J = 15.6 Hz, 2H), 5.45−5.51 (m, 1H), 5.36−5.38 (m, 1H), 3.93−3.99 (m, 2H), 2.64−2.69 (m, 2H), 2.30−2.40 (m, 2H), 2.09 (bs, 2H, OH), 1.48 (s, 9H), 1.36 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.1, 165.8, 164.9, 146.4, 139.5, 125.9, 123.5, 81.0, 76.8, 68.5, 67.2, 66.6, 41.9, 41.5, 28.1 (3C), 23.3, 20.2, 17.8; IR (film) ν (cm^{-1}) = 3436 (m), 1712 (s), 1656 (m), 1368 (m), 1152 (s), 981 (m); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{20}H_{32}O_8Na$ 423.1989, found 423.1990.

(4*R*,5*S*,*E*)-(*S*)-4-(((2*S*,3*R*,*E*)-6-(*tert*-Butoxy)-2-hydroxy-6-oxohex-4-en-3-yl)oxy)-4-oxobutan-2-yl 4,5-Dihydroxyhex-2-enoate, 15. Compound **15** was prepared according to the procedure described for **14**, starting from **11** (19.3 mg, 0.067 mmol) and sulfate **2** (17.7 mg, 0.067 mmol, 1 equiv). The crude material was purified using column chromatography (ethyl acetate) and semipreparative HPLC (ethyl acetate). Compound **15** was obtained as colorless oil (16.6 mg, 60%). R_f = 0.15 (1:2 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 6.1 (c = 7.4 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.98 (dd, J = 15.8, 5.0 Hz, 1H), 6.74 (dd, J = 15.8, 5.8 Hz, 1H), 6.09 (dd, J = 15.6, 1.3 Hz, 1H), 5.89 (dd, J = 15.8, 1.6 Hz, 1H), 5.42−5.49 (m, 1H), 5.34−5.36 (m, 1H), 4.24−4.27 (m, 1H), 3.93−4.00 (m, 2H), 2.71 (dd, J = 15.0, 8.9 Hz, 1H), 2.66 (dd, J = 15.0, 4.2 Hz, 1H), 2.52 (bs, 3H, OH), 1.48 (s, 9H), 1.37 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ (ppm) = 169.9, 166.1, 165.5, 149.7, 142.6, 125.2, 121.5, 80.9, 77.3, 75.6, 70.6, 68.7, 68.0, 41.3, 28.2 (3C), 20.1, 19.1 (2C); IR (film) ν (cm^{-1}) = 3435 (s), 1699 (s), 1658 (m), 1368 (m), 1151 (s), 981 (s); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{20}H_{32}O_9Na$ 439.1939, found 439.1943.

(4*R*,5*S*,*E*)-(*R*)-4-(((2*S*,3*R*,*E*)-6-(*tert*-Butoxy)-2-hydroxy-6-oxohex-4-en-3-yl)oxy)-4-oxobutan-2-yl 4,5-Dihydroxyhex-2-enoate, 16. Compound **16** was prepared according to the procedure described for **14**, starting from **12** (8.5 mg, 0.029 mmol) and sulfate **2** (7.8 mg, 0.03 mmol, 1 equiv). The crude material was purified using column chromatography (ethyl acetate) and semipreparative HPLC (ethyl acetate). Compound **16** was obtained as colorless oil (6.4 mg, 52%). R_f = 0.53 (ethyl acetate); $[\alpha]_D^{22}$ = 4.4 (c = 0.9 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.05 (dd, J = 15.7, 5.3 Hz, 1H), 6.68 (dd, J = 15.8, 6.3 Hz, 1H), 6.11 (dd, J = 15.8, 1.3 Hz, 1H), 5.90 (dd, J = 15.8, 1.2 Hz, 1H), 5.45−5.52 (m, 1H), 5.27−5.31 (m, 1H), 4.21−4.23 (m, 1H), 3.90−4.04 (m, 2H), 2.80 (bs, 3H, OH), 2.74 (dd, J = 15.7, 8.2 Hz, 1H), 2.67 (dd, J = 15.5, 4.5 Hz, 1H), 1.48 (s, 9H), 1.35 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 169.2, 165.8, 165.3, 147.3, 139.7, 126.2, 122.4, 81.4, 76.9, 74.8, 70.0, 68.6, 67.1, 41.1, 28.0 (3C), 20.1, 18.0, 17.9; IR (film) ν (cm^{-1}) = 3435 (s), 1715 (s), 1659 (w), 1369 (m), 1155 (s), 984 (m); HRMS (ESI-TOF) (m/z) $[M + Na]^+$ calculated for $C_{20}H_{32}O_9Na$ 439.1939, found 439.1940.

(4*R*,5*S*,*E*)-*tert*-Butyl 5-Hydroxy-4-(((*R*)-3-(((*S*,*E*)-5-hydroxyhex-2-enoyl)oxy)butanoyl)oxy)hex-2-enoate, 17. Compound **17** was prepared according to the procedure described for **14**, starting from **13** (17.4 mg, 0.064 mmol) and sulfate **2** (16.9 mg, 0.064 mmol, 1 equiv). Compound **17** was obtained as colorless oil (12.7 mg, 50%). R_f = 0.13 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 9.4 (c = 1.2 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.99 (dt, J = 15.3,

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7.6 Hz, 1H), 6.73 (dd, J = 15.8, 6.0 Hz, 1H), 5.91 (dd, J = 15.7, 1.2 Hz, 1H), 5.89 (dt, J = 15.6, 1.4 Hz, 1H), 5.38−5.44 (m, 1H), 5.34 (ddd, J = 5.8, 3.4, 1.4 Hz, 1H), 3.94−4.03 (m, 2H), 2.75 (dd, J = 15.6, 8.4 Hz, 1H), 2.63 (dd, J = 15.5, 4.4 Hz, 1H), 2.29−2.42 (m, 2H), 1.48 (s, 9H), 1.35 (d, J = 6.4 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.4, 165.7, 164.9, 146.2, 139.4, 126.2, 123.6, 81.0, 76.9, 68.6, 67.1, 66.6, 41.8, 41.1, 28.1 (3C), 23.3, 20.2, 18.0; IR (film) ν (cm^{-1}) = 3434 (m), 1716 (s), 1656 (m), 1369 (m), 1156 (s), 982 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{20}H_{32}O_8Na$ 423.1989, found 423.1984.

(2*S*,6*R*,7*E*,11*S*,13*E*)-6-((*S*)-1-Hydroxyethyl)-2,11-dimethyl-1,5,10-trioxacyclopentadeca-7,13-diene-4,9,15-trione, 18. To a solution of ester **14** (7.4 mg, 0.019 mmol) in 150 μL of dichloromethane, triethylsilane (3.2 μL, 0.02 mmol, 1.1 equiv) and TFA (144.0 μL, 1.9 mmol, 100 equiv) were added at 0 °C. The mixture was stirred for 20 min at 0 °C and then for 1 h at room temperature. The solvent was removed under reduced pressure, and the TFA was coevaporated with toluene 10 times. The residue was dissolved in a THF/dichloromethane-mixture (1:1, 3.8 mL). The solution was added to a solution of 2-methyl-6-nitrobenzoic anhydride (7.7 mg, 0.022 mmol, 1.2 equiv), DMAP (0.6 mg, 4.9 μmol, 0.25 equiv), and triethylamine (5.7 μL, 0.041 mmol, 2.2 equiv) in 5.6 mL of dichloromethane over 7 h. Afterward, the reaction mixture was stirred for an additional hour. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1). Compound **18** (2.6 mg, 43%) was isolated as a colorless oil. R_f = 0.40 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 36.0 (c = 0.7 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.71 (ddd, J = 15.6, 10.6, 5.1 Hz, 1H), 6.59 (dd, J = 16.1, 8.5 Hz, 1H), 5.93 (*app*. d, J = 16.1 Hz, 1H), 5.85 (*app*. d, J = 15.5 Hz, 1H), 5.29−5.36 (m, 1H), 5.04 (*app*. dd, J = 8.4, 3.9 Hz, 1H), 4.94−5.01 (m, 1H), 4.03−4.08 (*m*, 1H), 2.63 (dd, J = 13.4, 11.8 Hz, 1H), 2.46−2.52 (m, 2H), 2.34−2.41 (m, 1H), 1.38 (d, J = 6.2 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.8, 164.8, 164.3, 143.1, 140.4, 127.0, 126.1, 77.9, 69.0, 68.9, 68.3, 41.7, 39.7, 20.8, 20.3, 18.3; IR (film) ν (cm^{-1}) = 3485 (m), 1717 (s), 1658 (w), 1364 (w), 1176 (s), 981 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_7Na$ 349.1258, found 349.1266.

Macrosphelide D. Macrosphelide D was prepared according to the procedure described for **18**, starting from **15** (15.3 mg, 0.037 mmol). The crude material was purified using column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:2). Macrosphelide D was obtained as a colorless oil (5.9 mg, 47%). Macrosphelide D was crystallized from $CDCl_3$ (white crystals). R_f = 0.16 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 55.0 (c = 0.9 mg cm^{-3} in CH_3OH); mp 171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.65 (dd, J = 15.8, 7.9 Hz, 1H), 6.58 (dd, J = 16.0, 8.4 Hz, 1H), 5.95 (*app*. d, J = 15.9 Hz, 2H), 5.31−5.38 (m, 1H), 5.05 (*app*. dd, J = 8.5, 3.9 Hz, 1H), 4.76 (dq, J = 8.2, 6.4 Hz, 1H), 4.16 (*app*. t, J = 8.2 Hz, 1H), 4.06 (dq, J = 6.1, 5.1 Hz, 1H), 2.64 (dd, J = 13.7, 11.7 Hz, 1H), 2.52 (dd, J = 13.8, 3.0 Hz, 1H), 1.47 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.7, 164.3, 164.1, 145.6, 140.8, 126.9, 124.4, 77.7, 76.0, 72.5, 69.2, 68.2, 41.5, 20.2, 18.4, 17.8; IR (film) ν (cm^{-1}) = 3456 (m), 1719 (s), 1660 (w), 1367 (w), 1183 (w), 982 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_8Na$ 365.1207, found 365.1219.

Macrosphelide M. Macrosphelide M was prepared according to the procedure described for **18**, starting from **16** (13.1 mg, 0.031 mmol). The crude material was purified using column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:2). Macrosphelide M was obtained as a colorless oil (3.6 mg, 33%). R_f = 0.30 (1:2 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 34.0 (c = 2.5 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.06 (dd, J = 15.8, 3.2 Hz, 1H), 6.47 (dd, J = 15.8, 9.5 Hz, 1H), 6.08 (dd, J = 15.8, 1.9 Hz, 1H), 6.02 (*app*. d, J = 15.8 Hz, 1H), 5.32−5.38 (m, 1H), 5.28 (*app*. q, J = 6.9 Hz, 1H), 5.19 (*app*. dd, J = 9.5, 4.4 Hz, 1H), 4.42−4.44 (m, 1H), 3.98−4.02 (m, 1H), 3.11−3.12 (m, 1H, OH), 2.76 (dd, J = 14.8, 4.1 Hz, 1H), 2.59 (dd, J = 14.8, 11.1 Hz, 1H), 2.04 (bs, 1H, OH), 1.45 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ (ppm) = 169.1, 166.2, 164.7, 147.3, 144.4, 126.2, 122.9, 78.2, 75.2, 75.1, 69.0, 68.5, 42.1, 20.1, 19.1, 17.9; IR (film) ν (cm^{-1}) = 3460 (m), 1716 (s), 1657 (w), 1381 (w), 1171 (m), 984 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_8Na$ 365.1207, found 365.1201.

(2*R*,6*R*,7*E*,11*S*,13*E*)-6-((*S*)-1-Hydroxyethyl)-2,11-dimethyl-1,5,10-trioxacyclopentadeca-7,13-diene-4,9,15-trione, 19. Compound **19** was prepared according to the procedure described for **18**, starting from **17** (9.8 mg, 0.025 mmol). Compound **19** was obtained as a colorless oil (3.8 mg, 48%). R_f = 0.49 (1:2 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 25.3 (c = 0.8 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.94 (ddd, J = 15.6, 10.0, 5.6 Hz, 1H), 6.49 (dd, J = 15.8, 9.5 Hz, 1H), 5.98 (*app*. d, J = 15.8 Hz, 1H), 5.69 (*app*. d, J = 15.6 Hz, 1H), 5.24−5.31 (m, 1H), 5.18 (*app*. dd, J = 9.5, 4.2 Hz, 1H), 5.10−5.16 (m, 1H), 3.99 (dq, J = 6.4, 4.3 Hz, 1H), 2.76−2.82 (m, 1H), 2.79 (dd, J = 14.8, 4.2 Hz, 1H), 2.55 (dd, J = 14.9, 9.9 Hz, 1H), 2.29−2.33 (m, 1H), 1.86 (bs, 1H, OH), 1.42 (d, J = 6.7 Hz, 3H), 1.37 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ (ppm) = 169.0, 165.6, 165.1, 144.3, 143.3, 127.4, 126.1, 78.1, 69.9, 68.9, 68.2, 42.0, 37.2, 20.1, 19.6, 19.3; IR (film) ν (cm^{-1}) = 3480 (m), 1717 (s), 1655 (w), 1381 (w), 1179 (m), 983 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_7Na$ 349.1258, found 349.1243.

Macrosphelide A. Macrosphelide D (4 mg, 0.012 mmol) was dissolved in 0.69 mL of dichloromethane and transferred into a 1.5 mL vial. A 0.77 M Ti(^{i}OPr)$_4$ solution (in dichloromethane, 760 μL, 0.59 mmol, 50 equiv) was added, and the vial was shaken before being put into the high-pressure chamber. A pressure of 7 kbar was adjusted, and the reaction mixture was left in the chamber overnight. The mixture was washed subsequently with 1 M hydrochloric acid and saturated sodium bicarbonate solution. The combined aqueous layers were filtered and extracted with ethyl acetate (3×x). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the crude material was purified via column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:2). Macrosphelide A (3.1 mg, 77%) was obtained as colorless oil. R_f = 0.34 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 81.0 (c = 1.0 mg cm^{-3} in CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.87 (dd, J = 15.7, 4.6 Hz, 1H), 6.87 (dd, J = 15.7, 4.8 Hz, 1H), 6.05 (dd, J = 15.8, 1.1 Hz, 1H), 6.04 (dd, J = 15.7, 1.4 Hz, 1H), 5.36−5.42 (m, 1H), 4.96 (dq, J = 6.4, 4.8 Hz, 1H), 4.86 (dq, J = 6.5, 6.5 Hz, 1H), 4.22−4.24 (m, 1H), 4.13−4.15 (m, 1H), 2.92 (bs, 1H, OH), 2.62 (dd, J = 15.6, 9.1 Hz, 1H), 2.57 (dd, J = 15.5, 3.3 Hz, 1H), 1.64 (bs, 1H, OH), 1.45 (d, J = 6.6 Hz, 3H), 1.37 (d, J = 6.4 Hz, 3H), 1.33 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 170.2, 165.8, 164.6, 146.0, 145.0, 122.7, 122.3, 75.0, 74.8, 74.1, 73.1, 67.7, 41.0, 19.7, 18.0, 17.8; IR (film) ν (cm^{-1}) = 3435 (m), 1716 (s), 1646 (w), 1379 (w), 1186 (m), 982 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_8Na$ 365.1207, found 365.1219.

Macrosphelide C. Macrosphelide C was prepared according to the procedure described for macrosphelide A, starting from **18** (1.8 mg, 5.5 μmol). The crude material was purified using column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1). Macrosphelide C was obtained as a colorless oil (1.5 mg, 83%). R_f = 0.45 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 42.9 (c = 0.6 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.89 (dd, J = 15.7, 4.9 Hz, 1H), 6.86 (ddd, J = 15.6, 9.2, 6.3 Hz, 1H), 6.06 (dd, J = 15.7, 1.6 Hz, 1H), 5.80 (app. d, J = 15.7 Hz, 1H), 5.27−5.33 (m, 1H), 5.07−5.13 (m, 1H), 4.92 (dq, J = 6.4, 6.4 Hz, 1H), 4.16 (*app*. dd, J = 5.1, 5.1 Hz, 1H), 2.63 (dd, J = 14.7, 2.9 Hz, 1H), 2.52−2.57 (m, 1H), 2.51 (dd, J = 14.7, 8.4 Hz, 1H), 2.33−2.40 (m, 1H), 2.06 (bs, 1H, OH) 1.37 (d, J = 6.7 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 170.0, 165.0, 164.8, 144.9, 143.8, 124.7, 123.0, 73.7, 72.9, 69.0, 67.4, 40.9, 38.8, 20.5, 19.5, 17.5; IR (film) ν (cm^{-1}) = 3468 (m), 1718 (s), 1659 (w), 1381 (w), 1177 (m), 979 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_7Na$ 349.1258, found 349.1282.

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Macrosphelide E. Macrosphelide E was prepared according to the procedure described for macrosphelide A, starting from macrosphelide M (2.6 mg, 7.6 μmol). Macrosphelide E was obtained as a colorless oil (2.0 mg, 77%). R_f = 0.23 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 64.4 (c = 0.9 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.02 (dd, J = 15.6, 4.2 Hz, 1H), 6.80 (dd, J = 15.7, 5.1 Hz, 1H), 6.11 (dd, J = 15.7, 1.3 Hz, 1H), 6.07 (dd, J = 15.7, 1.2 Hz, 1H), 5.29−5.35 (m, 1H), 5.12 (dq, J = 6.8, 1.7 Hz, 1H), 4.98 (dq, J = 6.5, 4.4 Hz, 1H), 4.36−4.38 (m, 1H), 4.18−4.19 (m, 1H), 3.37 (d, J = 6.7 Hz, 1H, OH), 3.09 (d, J = 5.4 Hz, 1H, OH), 2.72 (dd, J = 16.0, 3.0 Hz, 1H), 2.60 (dd, J = 16.0, 7.5 Hz, 1H), 1.43 (d, J = 6.8 Hz, 3H), 1.39 (d, J = 6.5 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 170.9, 166.8, 165.3, 145.4, 145.0, 123.0, 122.3, 76.1, 75.4, 75.2, 73.8, 66.6, 40.5, 19.6, 17.8, 17.3; IR (film) ν (cm^{-1}) = 3456 (m), 1716 (s), 1662 (w), 1358 (m), 1191 (m), 984 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_8Na$ 365.1207, found 365.1210.

Macrosphelide F. Macrosphelide F was prepared according to the procedure described for macrosphelide A, starting from **19** (1.7 mg, 5.2 μmol). The crude material was purified using column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1). Macrosphelide F was obtained as a colorless oil (1.2 mg, 71%). R_f = 0.52 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 24.0 (c = 0.7 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.88 (dt, J = 14.9, 7.4 Hz, 1H), 6.84 (dd, J = 15.6, 4.3 Hz, 1H), 6.09 (dd, J = 15.5, 1.7 Hz, 1H), 5.80 (*app.* d, J = 15.8 Hz, 1H), 5.27−5.33 (m, 1H), 5.12−5.18 (m, 1H), 4.94 (dq, J = 6.5, 3.9 Hz, 1H), 4.19−4.23 (m, 1H), 2.98 (d, J = 7.6 Hz, 1H, OH), 2.69−2.74 (m, 1H), 2.67 (dd, J = 15.9, 2.9 Hz, 1H), 2.59 (dd, J = 15.8, 7.8 Hz, 1H), 2.39 (ddd, J = 14.5, 7.2, 7.2 Hz, 1H), 1.39 (d, J = 6.4 Hz, 3H), 1.36 (d, J = 6.5 Hz, 3H), 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 171.0, 165.1, 165.0, 144.2, 143.6, 124.7, 123.1, 76.0, 73.6, 68.9, 66.5, 40.7, 37.7, 19.8, 19.7, 17.4; IR (film) ν (cm^{-1}) = 3471 (m), 1714 (s), 1656 (w), 1361 (w), 1181 (s), 979 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_7Na$ 349.1258, found 349.1256.

(*S*,*E*)-*tert*-Butyl 5-(((*R*)-3-(((*E*)-3-((4*S*,5*S*)-5-Methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl)acryloyl)oxy)butanoyl)oxy)hex-2-enoate, 20. To a solution of sulfate **9** (37.6 mg, 0.11 mmol, 2 equiv) in 0.48 mL of dichloromethane, triethylsilane (18 μL, 0.11 mmol, 2.2 equiv) and TFA (320.8 μL, 4.2 mmol, 80 equiv) were added at 0 °C. The mixture was allowed to warm slowly to room temperature. After complete conversion (2−3 h), the solvent was removed under reduced pressure. The TFA was coevaporated with toluene 10 times. The residue was dissolved in 0.6 mL of 1,2-dichloroethane and cooled to −20 °C. Alcohol **5** (10 mg, 0.05 mmol, 1 equiv), DCC (36.5 mg, 0.18 mmol, 3.3 equiv), DMAP (1.3 mg, 0.01 mmol, 0.2 equiv), and β-camphorsulfonic acid (1 mg, 4.3 μmol, 8 mol %) were added subsequently. The mixture was stirred overnight at −20 °C, then diluted with ethyl acetate and washed with a diluted $CuSO_4$ solution and brine. The aqueous solutions were extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1) to yield **20** as colorless oil (14.0 mg, 56%). R_f = 0.63 (3:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −23.1 (c = 5.8 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.81 (dd, J = 15.6, 6.3 Hz, 1H), 6.74 (dt, J = 15.1, 7.6 Hz, 1H), 6.26 (*app.* d, J = 15.6 Hz, 1H), 5.79 (*app.* d, J = 15.8 Hz, 1H), 5.33−5.40 (m, 1H), 5.00−5.09 (m, 2H), 4.80 (dq, J = 8.6, 6.2 Hz, 1H), 2.67 (dd, J = 15.7, 7.6 Hz, 1H), 2.54 (dd, J = 15.7, 5.5 Hz, 1H), 2.37−2.47 (m, 2H), 1.61 (d, J = 6.2 Hz, 3H), 1.48 (s, 9H), 1.35 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.4, 165.5, 163.5, 141.8, 135.7, 127.5, 126.0, 85.7, 82.6, 80.4, 69.8, 68.5, 40.8, 38.1, 28.1 (3C), 19.7, 19.6, 16.5; IR (film) ν (cm^{-1}) = 1728 (s), 1656 (w), 1390 (m), 1369 (w), 1211 (s), 1159 (s), 976 (m), 823 (w); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{20}H_{30}O_{10}SNa$ 485.1471, found 485.1452.

(4*R*,5*S*,*E*)-(*R*)-4-(((*S*,*E*)-6-(*tert*-Butoxy)-6-oxohex-4-en-2-yl)oxy)-4-oxobutan-2-yl 4,5-Dihydroxyhex-2-enoate, 21. A solution of sulfate **20** (18.6 mg, 0.04 mmol) and ammonium formate (2.5 mg, 0.04 mmol, 1 equiv) in 320 μL of DMF was stirred at room temperature for 5 h. The solvent was coevaporated with ethyl acetate. The residue was dissolved in 320 μL of THF and cooled to 0 °C, and then 1.25 M methanolic HCl (64 μL, 0.08 mmol, 2 equiv) was added. The mixture was stirred for 2.5 h at 0 °C. $NaHCO_3$ (8 mg, 0.10 mmol, 2.4 equiv) was added, and the mixture was stirred for additional 20 min at 0 °C. Then ethyl acetate and water were added. The organic layer was washed with brine. The aqueous layers were extracted 3× with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 1:1) to yield **21** (11.5 mg, 71%) as a diastereomeric mixture (dr 80:20). Because the diastereomeres could not be separated using standard methods, **21** was used as mixture within the next step. R_f = 0.40 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 0.8 (c = 1.3 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 6.98 (dd, J = 15.7, 5.0 Hz, 1H), 6.73 (dt, J = 15.1, 7.5 Hz, 1H), 6.09 (dd, J = 15.7, 1.4 Hz, 1H), 5.78 (dt, J = 15.5, 1.4 Hz, 1H), 5.31−5.37 (m, 1H), 5.00−5.06 (m, 1H), 4.27−4.29 (m, 1H), 3.96 (dq, J = 6.3, 4.1 Hz, 1H), 2.65 (dd, J = 15.4, 7.8 Hz, 1H), 2.55 (dd, J = 15.5, 5.2 Hz, 1H), 2.40−2.43 (m, 2H), 1.48 (s, 9H), 1.33 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.6, 165.8, 165.2, 146.1, 142.5, 125.8, 122.4, 80.7, 74.6, 69.9, 69.7, 67.3, 41.1, 38.1, 28.1 (3C), 19.8, 19.7, 17.7; IR (film) ν (cm^{-1}) = 3466 (m), 1715 (s), 1656 (m), 1368 (m), 1160 (s), 982 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{20}H_{32}O_8Na$ 423.1989, found 423.1997.

Macrosphelide G. To a solution of ester **21** (6.6 mg, 0.017 mmol) in 140 μL of dichloromethane, triethylsilane (3.0 μL, 0.018 mmol, 1.1 equiv) and TFA (133.3 μL, 1.7 mmol, 100 equiv) were added at 0 °C. The mixture was stirred for 20 min at 0 °C and then for 1 h at room temperature. The solvent was removed under reduced pressure, and TFA was coevaporated with toluene 10 times. The residue was dissolved in a THF/dichloromethane-mixture (1:1, 3.6 mL). The solution was added to a solution of 2-methyl-6-nitrobenzoic anhydride (7.2 mg, 0.02 mmol, 1.3 equiv), DMAP (0.5 mg, 4.1 μmol, 0.25 equiv), and triethylamine (5.3 μL, 0.038 mmol, 2.3 equiv) in 5.2 mL of dichloromethane over 7 h. Afterward, the reaction mixture was stirred for an additional hour. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1). Macrosphelide G (1.4 mg) and 1.8 mg of **22** were isolated as colorless oils (59%, 1:1.3). Afterward, **22** could be transesterified into macrosphelide G. Macrosphelide G was crystallized from $CDCl_3$ (white needles). R_f = 0.47 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 36.0 (c = 4.7 mg cm^{-3} in EtOH); mp 86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.05 (dd, J = 15.6, 3.7 Hz, 1H), 6.80 (ddd, J = 15.3, 8.7, 6.3 Hz, 1H), 6.11 (dd, J = 15.5, 1.6 Hz, 1H), 5.80 (dt, J = 15.6, 1.3 Hz, 1H), 5.21−5.27 (m, 1H), 5.05−5.11 (m, 2H), 4.34−4.37 (m, 1H), 3.37 (d, J = 8.2 Hz, 1H, OH), 2.76 (dd, J = 15.7, 3.9 Hz, 1H), 2.35−2.53 (m, 3H), 1.45 (d, J = 6.5 Hz, 3H), 1.41 (d, J = 6.9 Hz, 3H), 1.26 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.4, 167.1, 165.5, 145.5, 145.5, 123.4, 121.9, 76.4, 75.3, 70.0, 67.2, 39.9, 38.3, 20.2, 19.2, 17.8; IR (film) ν (cm^{-1}) = 3469 (m), 1718 (s), 1660 (w), 1374 (w), 1194 (m), 981 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_7Na$ 349.1258, found 349.1258.

(4R,7E,9R,12E,15S)-9-((S)-1-Hydroxyethyl)-4,15-dimethyl-1,5,10-trioxacyclopentadeca-7,12-diene-2,6,11-trione, ***22****.* R_f = 0.47 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 27.5 (c = 1.5 mg cm^{-3} in EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 6.95 (dd, J = 16.2, 5.7 Hz, 1H), 6.84 (dt, J = 15.5, 7.7 Hz, 1H), 5.96−6.09 (m, 2H), 5.34−5.39 (m, 1H), 5.12−5.23 (m, 1H), 4.90−5.03 (m, 1H), 4.08−4.17 (m, 1H), 2.71 (dd, J = 14.0, 5.4 Hz, 1H), 2.44−2.50 (m, 2H), 2.34 (dd, J = 14.0, 2.4 Hz, 1H), 1.97 (bs, 1H, OH), 1.49 (d, J = 6.6 Hz, 3H), 1.31 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 169.6, 166.8, 164.6, 146.6, 140.3, 126.6, 124.6, 77.3, 71.7, 67.9, 67.6, 39.7, 38.2, 20.6, 18.5 (2C); IR (film) ν (cm^{-1}) = 3489 (m), 1723 (s), 1655 (w), 1369 (m), 1193 (s), 980 (m);

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HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{22}O_7Na$ 349.1258, found 349.1251.

Macrosphelide G. Compound **22** (4.4 mg, 0.013 mmol) was dissolved in 0.56 mL of dichloromethane, and scandium triflate (4.7 mg, 0.01 mmol, 0.7 equiv) was added. After the mixture was stirred for 2 min at room temperature, DMAP (5.5 mg, 0.045 mmol, 3.3 equiv) was added. The reaction mixture was stirred for 5 min. The mixture was filtered through a silica plug, which was rinsed with ethyl acetate. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate 1:1). Macrosphelide G (3.7 mg) was isolated in 84% yield.

Macrosphelide B. To a solution of macrosphelide A (3.6 mg, 0.01 mmol) in 2.3 mL of dichloromethane, DMP (4.1 mg, 0.01 mmol, 0.92 equiv) was added at −20 °C. More DMP (after 2.5 h, 1 mg, 2.4 μmol, 0.23 equiv; after 3 h 20 min, 0.8 mg, 1.9 μmol, 0.18 equiv) was added to the reaction mixture. The reaction was stopped after 6 h by filtering through a silica plug, which was then rinsed with ethyl acetate. The crude product was purified by column chromatography (ethyl acetate) and semipreparative HPLC (petroleum ether/ethyl acetate, 1:1). Macrosphelide B (1.3 mg, 36%) was obtained as the main product. As side products, **23** (0.5 mg, 14%) and diketone **24** (0.2 mg, 6%) could be isolated. Macrosphelide A (1.6 mg, 44%) could be reisolated. R_f = 0.55 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 9.2 (c = 1.1 mg cm^{-3} in CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.03 (d, J = 15.8 Hz, 1H), 6.92 (dd, J = 15.7, 3.5 Hz, 1H), 6.74 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.7, 2.0 Hz, 1H), 5.44−5.50 (m, 1H), 5.05−5.10 (m, 1H), 5.06 (q, J = 7.1 Hz, 1H), 4.31−4.34 (m, 1H), 2.86 (d, J = 8.3 Hz, 1H, OH), 2.83 (dd, J = 16.2, 11.1 Hz, 1H), 2.62 (dd, J = 16.2, 2.1 Hz, 1H), 1.50 (d, J = 6.8 Hz, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 196.2, 170.3, 165.4, 164.1, 144.2, 132.5, 132.1, 122.6, 76.9, 75.8, 74.9, 67.7, 40.6, 19.8, 17.9, 16.1; IR (film) ν (cm^{-1}) = 3497(m), 1719 (s), 1647 (w), 1388 (m), 1181 (m), 985 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{20}O_8Na$ 363.1050, found 363.1046.

(4S,7E,10S,13E,15R,16S)-15-Hydroxy-4,10,16-trimethyl-1,5,11-trioxacyclohexadeca-7,13-diene-2,6,9,12-tetraone, ***23****.* R_f = 0.53 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = 57.6 (c = 0.8 mg cm^{-3} in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.25 (d, J = 16.0 Hz, 1H), 7.01 (dd, J = 15.8, 5.3 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 6.19 (dd, J = 15.8, 1.3 Hz, 1H), 5.32−5.38 (m, 1H), 5.21 (q, J = 7.2 Hz, 1H), 4.89 (dq, J = 8.4, 6.3 Hz, 1H), 4.17−4.22 (m, 1H), 2.70 (dd, J = 16.3, 10.8 Hz, 1H), 2.57 (dd, J = 16.3, 2.1 Hz, 1H), 1.51 (d, J = 7.4 Hz, 3H), 1.40 (d, J = 6.3 Hz, 3H), 1.36 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 198.0, 169.4, 164.6, 163.4, 147.1, 133.2, 132.3, 121.8, 75.5, 73.1, 73.0, 68.9, 40.9, 19.5, 17.9, 17.0; IR (film) ν (cm^{-1}) = 3508 (m), 1723 (s), 1625 (w), 1388 (m), 1187 (m), 984 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{20}O_8Na$ 363.1050, found 363.1055.

(4S,7E,10S,13E,16S)-4,10,16-Trimethyl-1,5,11-trioxacyclohexadeca-7,13-dien-2,6,9,12,15-pentaone, ***24****.* R_f = 0.63 (1:1 petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ = −13.5 (c = 4.6 mg cm^{-3} in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.36 (d, J = 16.1 Hz, 1H), 7.16 (d, J = 15.8 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.63 (d, J = 16.0 Hz, 1H), 5.33−5.44 (m, 1H), 5.26 (q, J = 7.1 Hz, 1H), 5.20 (q, J = 7.0 Hz, 1H), 2.90 (dd, J = 16.6, 11.2 Hz, 1H), 2.67 (dd, J = 16.6, 2.2 Hz, 1H), 1.58 (d, J = 7.1 Hz, 3H), 1.46 (d, J = 6.9 Hz, 3H), 1.41 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 197.4, 195.6, 170.1, 163.5, 163.1, 134.3, 132.3, 132.3, 132.0, 76.3, 75.5, 69.2, 40.6, 19.5, 17.1, 15.9; IR (film) ν (cm^{-1}) = 1728 (s), 1711 (s), 1626 (w), 1388 (w), 1180 (m), 980 (m); HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calculated for $C_{16}H_{18}O_8Na$ 361.0894 found 361.0902.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR for all reported compounds and cif-files for the reported X-ray structures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01171.

NMR data for all reported compounds and crystal structures of macrosphelide D and G (PDF)

X-ray structure for macrosphelide G (CIF)

X-ray structure for macrosphelide D (CIF)

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Notes

The authors declare no competing financial interest.

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