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Studies directed toward the first total synthesis of acremodiol and acremonol

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ABSTRACT

Studies directed toward the synthesis of acremodiol and acremonol resulted in the synthesis of two macrodiolides **1**, **1a,** and **2** besides **3**. The attempted synthesis of **1** and **2** confirmed that the absolute stereochemistry defined in the earlier report is incorrect. Compound **1** was synthesized by RCM-mediated macrocyclization. Attempted synthesis of **2** failed to give good yields in the cyclization, and **1a** and **2** were synthesized by the Yamaguchi macrolactonization method.

1. Introduction

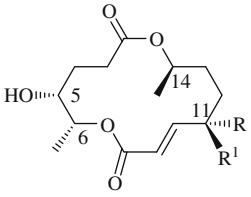
Acremodiol **1** and acremonol **2**, two 14-membered bis-macrolides, were isolated by Berge et al.[1] from a soil sample of the Bermuda Islands, *Acremonium*-like anamorphic fungus. The structure of these two macrolides was assigned based on the NMR, ESI-MS, and FAB-MS spectroscopy.[1] Compound **1** has four stereocenters (5*R*, 6*R*, 11*R*, and 14*R*) with a 5,6-*vic* diol and an α,β-unsaturated ester moiety. Similarly, **2** has three asymmetric centers (6*R*, 11*R*, and 14*R*) with a carbonyl group at C-5 and two α,β-unsaturated esters. Structurally, these compounds are closely related to clonostachydiol,[2,3] while the relative stereochemistry was reported[1] to be the same for colletodiol.[4,5] Macrolides **1** and **2**, unlike colletodiol have shown activity against a series of Gram positive bacteria and fungi. In continuation of our studies on the synthesis of macrodiolides,[6] macrotriolides[6] herein, we report our attempts on the first synthesis of **1** and **2**, to determine their absolute stereochemistry. The synthesis of **1** was achieved by RCM-mediated macrocyclization, while **1a** and **2** were synthesized by macrolactonization method.

2. Results and discussion

Retrosynthetic analysis of **1** (Scheme 1) revealed bis-olefin **4** as a late stage intermediate which could be made by the acryloylation of **5**. Ester **5** could in turn be prepared by the esterification of acid **6** and alcohol **7**, while **6** and **7** were envisioned to derive from **8** and **9**.

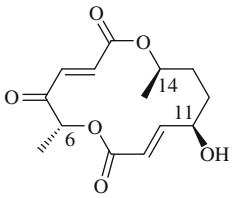
2.1. Synthesis of the C-2 to O-7 segment

Accordingly, ester **8** (Scheme 2) upon asymmetric dihydroxylation[7a] with AD-mix-β and methane sulfonamide afforded the known diol **10**[7b] (61%), which on reaction with TBSCl, Et_3N, and cat. DMAP in CH_2Cl_2[8] gave **11a** (major, 50%) and **11b** (minor, 12%). Alcohol **11a** on treatment with MEMCl and DIPEA in CH_2Cl_2 furnished **12** in 84% yield. Catalytic hydrogenation of ester **12** with PtO_2 in EtOAc under an H_2-atmosphere gave ester **13** in 94%, which on subsequent hydrolysis with 0.5 N NaOH in MeOH/H_2O (1:1) afforded acid **6** in 87% yield.

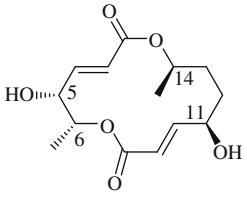


acremodiol **1** R^1=OH, R=H
(5*R*,6*R*,11*R*,14*R*)

acremodiol **1a** R^1=H, R=OH
(5*R*,6*R*,11*S*,14*R*)



acremonol **2**
(6*R*,11*R*,14*R*)



epi clonostachydiol **3**
(5*R*,6*R*,11*R*,14*R*)

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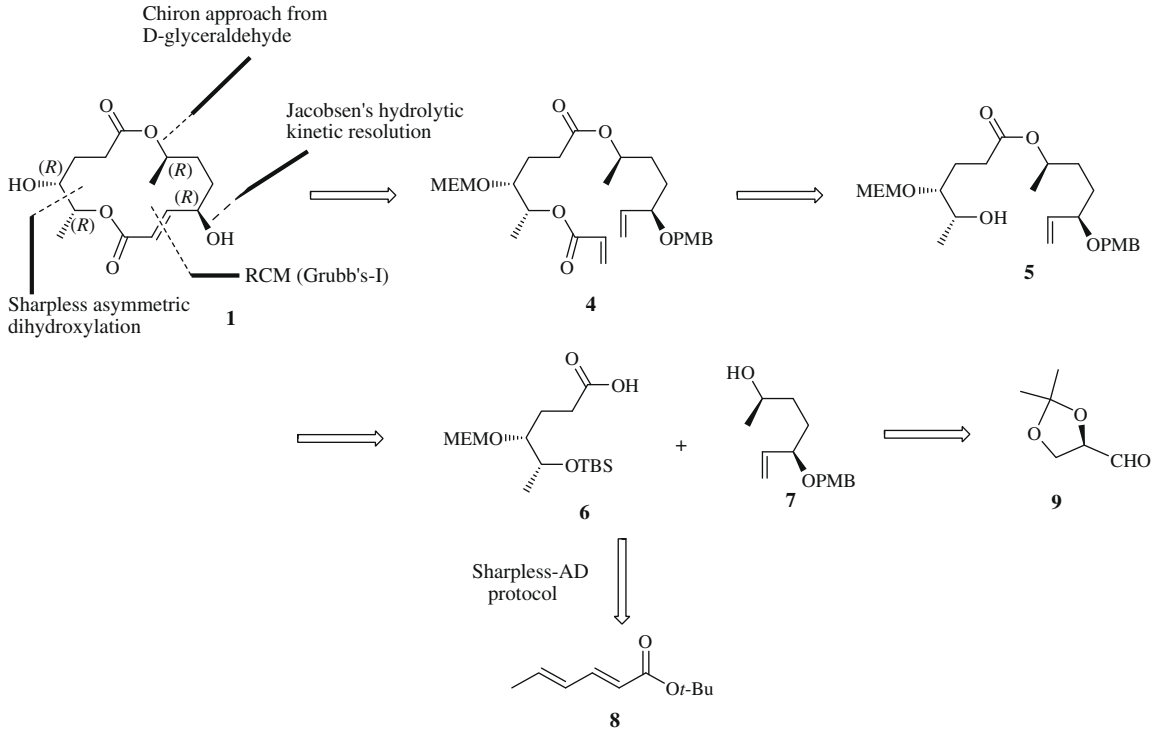
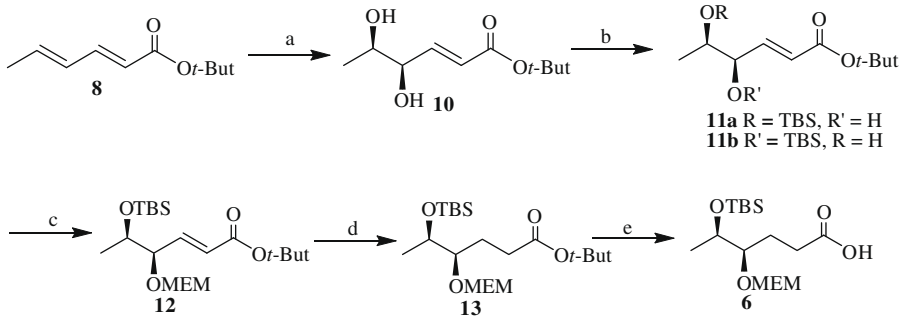


Scheme 1. Retrosynthesis of acremodiol **1**.



Scheme 2. Reagents and conditions: (a) AD-mix-β, methane sulfonamide, *t*-BuOH/H_2O (1:1), 0 °C to rt, 27 h; (b) TBSCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C to rt, 12 h; (c) MEMCl, DIPEA, CH_2Cl_2, rt, 24 h; (d) H_2, PtO_2, EtOAc, 40 psi, rt, 4 h; (e) NaOH, 0.5 N, MeOH, rt, 18 h.

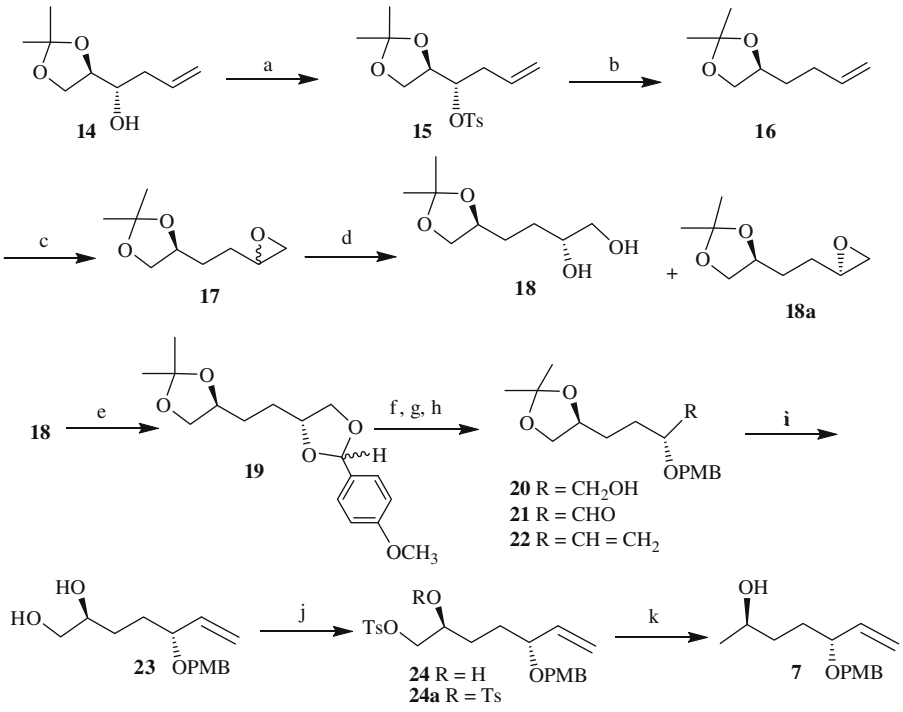
2.2. Synthesis of the C-9 to O-1 segment

Reaction of the alcohol **14** (Scheme 3) prepared from **9** with *p*-TsCl and Et_3N in CH_2Cl_2, followed by deoxygenation of tosylate **15** with LAH in dry THF afforded **16** in 87% yield. The terminal olefin **16** upon treatment with *m*-CPBA was converted into racemic epoxide **17** in 75% yield.

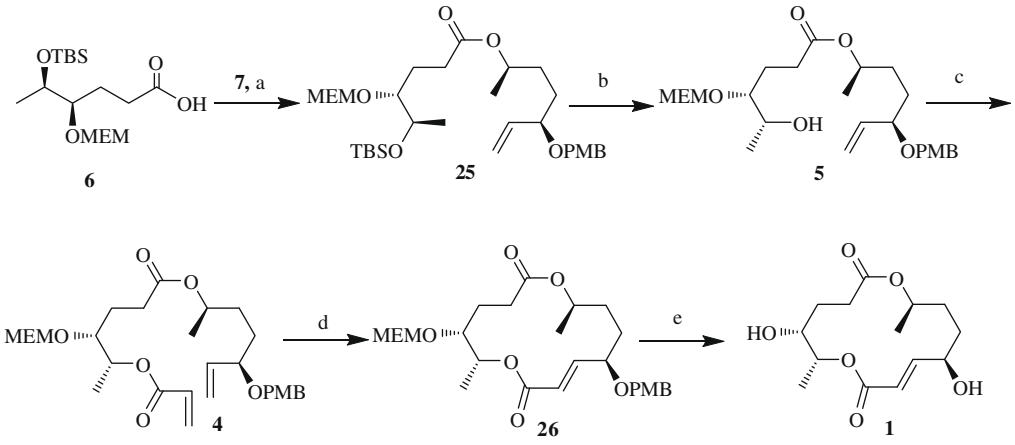
The kinetic resolution of **17** with (*S*,*S*)-Jacobsen catalyst,[9] gave the diol **18** (39%) and epoxide **18a** (43%). The reaction of diol **18** with anisaldehyde dimethyl acetal gave cyclic derivative **19** (73%, dr 5:4), which on reductive opening with DIBAL-H in CH_2Cl_2 furnished the alcohol **20** in 76% yield. Oxidation of **20** under Swern conditions followed by Wittig olefination of **21** in THF at 0 °C to room temperature afforded olefin **22** in 50% yield. Acid (60% aq AcOH)-catalyzed hydrolysis of acetonide **22** furnished the diol **23** (88%), which on tosylation (*p*-TsCl, Et_3N, DMAP) in CH_2Cl_2 afforded **24** in 73% yield. Further, treatment of tosylate **24** with LAH gave deoxy compound **7** in 95% yield, constituting the synthesis of the C-9 to O-1 segment.

Having successfully synthesized both the fragments **6** and **7**, acid **6** was subjected to esterification with alcohol **7** under Yamaguchi[10] conditions to furnish ester **25** (Scheme 4) in 82% yield. Desilylation of **25** using $ZrCl_4$ in CH_3CN[11] gave alcohol **5** (68%), which on further treatment with acryloyl chloride and DIPEA in CH_2Cl_2 afforded **4** in 88% yield. The bis-olefin **4** was subjected to RCM with Grubbs first generation catalyst[12] in CH_2Cl_2 at reflux to furnish the bis-lactone **26** in 60% yield. Finally, removal of PMB and MEM groups in **26**, on treatment with $TiCl_4$ in CH_2Cl_2[13] afforded **1** in 69% yield. The synthetic compound **1** was fully characterized by ^1H, ^{13}C, ESI-MS, and IR spectra. The spectral analysis data of compound **1** was found to be not matching with those reported for **1**. Similarly the specific rotation value of synthetic **1** $[\alpha]_D = -35.3$ (*c* 0.15, $CHCl_3$)] was not corresponding with that reported[1] for **1** {[α]$_D$ = +98 (*c* 0.3, MeOH)}. Thus, the synthesis of **1** has amply indicated that the structure originally assigned to the natural product acremodiol[1] is incorrect.

Having been unsuccessful in achieving the synthesis of acremodiol **1**, next we aimed at the synthesis of acremonol **2**



Scheme 3. Reagents and conditions: (a) *p*-TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 24 h; (b) LAH, dry THF, 0 °C-reflux,12 h; (c) *m*-CPBA, $CHCl_3$, rt, 24 h; (d) *S*,*S*(+)-*N*,*N*-bis(3,5-di*tert*-butyl salicylidine)-1,2-cyclo hexane diamino cobalt(II), AcOH, toluene, rt, 1 h; H_2O, 15 °C to rt, 12 h; (e) anisaldehyde dimethylacetal, PPTS, CH_2Cl_2, rt, 2 h; (f) DIBAL-H, CH_2Cl_2, 0 °C to rt, 12 h; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h; (h) $Ph_3P^+CH_3\ I^-$, *n*-BuLi, THF, 0 °C to rt, 12 h; (i) 60% aq AcOH, rt, 12 h; (j) *p*-TsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C to rt, 14 h; (k) $LiAlH_4$, dry THF, 0 °C to rt, 12 h.



Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, **7**, DMAP, toluene, rt, 14 h; (b) $ZrCl_4$, dry CH_3CN, 0 °C, 20 min; (c) acryloyl chloride, DIPEA, CH_2Cl_2, 0 °C to rt, 2 h; (d) Grubbs' catalyst—**I**, CH_2Cl_2, reflux, 48 h; (e) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 6 h.

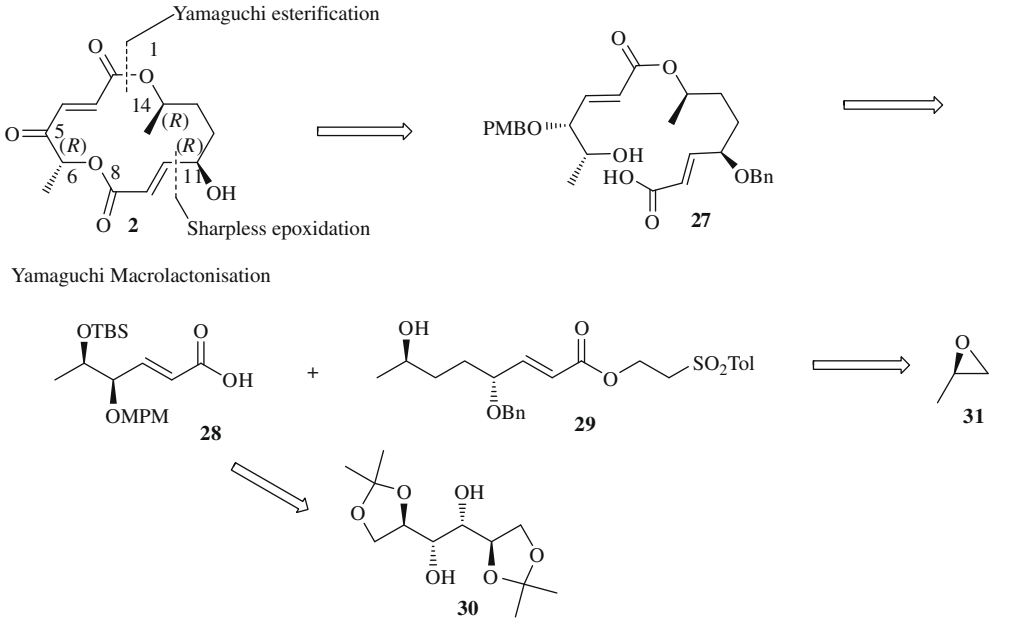
since the C5–OH group of **1** was in keto form in **2**. Thus, **2** is devoid of a stereocenter at C-5. Hence, it was presumed that the synthesis of **2** would well define the stereochemistry at C-6, C-11, and C-14, so that C-5 stereochemistry could be redefined later.

2.3. Synthesis of acremonol 2

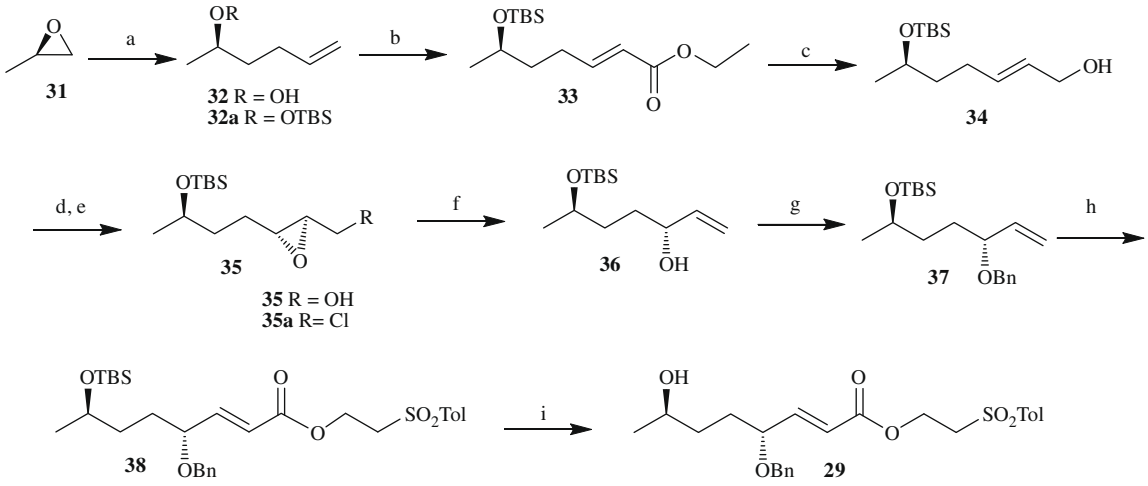
The retrosynthetic analysis of acremonol **2** is shown in Scheme 5. Compound **2** could be realized by macrolactonization from the seco-acid **27**, which in turn could be made from acid **28** and alcohol **29**. The acid was envisioned to come from D-mannitol derivative **30**, while **29** was planned from chiral propylene oxide **31**.

2.4. Synthesis of the C-8 to O-1 segment

Opening of the known epoxide **31**[9] (Scheme 6) with allyl magnesium chloride in ether and subsequent silylation of the secondary alcohol **32** with TBSCl and imidazole in CH_2Cl_2 gave **32a** in 70% yield. Ozonolysis of **32a** and olefination of the resulting aldehyde with (ethoxycarbonylmethylene)triphenyl phosphorane gave **33** in 72% yield. Reduction of ester **33** with DIBAL-H furnished allylic alcohol **34** in 77% yield. Sharpless epoxidation[14] of **34** with (−)-DIPT in CH_2Cl_2 afforded epoxide **35** in 75% yield. Treatment of epoxy alcohol **35** with Ph_3P and $NaHCO_3$ in CCl_4 gave chloride **35a** (71%), which on further treatment with Na in dry ether afforded **36** in 73% yield. Benzylation of **36** with BnBr and Ag_2O in CH_2Cl_2 gave **37** (78%). Ozonolysis of olefin **37** in CH_2Cl_2 followed by the olefination with (*p*-tol-



Scheme 5.



Scheme 6. Reagents and conditions: (a) (i) allyl chloride, Mg, dry ether, −78 °C, 2 h; (ii) TBSCl, imidazole, CH_2Cl_2, rt, 4 h; (b) (i) O_3, CH_2Cl_2, −78 °C, 30 min; (ii) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, rt, 4 h; (c) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (d) (−)-DIPT, 4 Å, cumene hydroperoxide, $Ti(O^iPr)_4$, CH_2Cl_2, −20 °C, 3 h; (e) Ph_3P, $NaHCO_3$, CCl_4, reflux, 30 min; (f) Na, ether, rt, 12 h; (g) Ag_2O, BnBr, CH_2Cl_2, reflux, 12 h; (h) (i) O_3, CH_2Cl_2, −78 °C, 30 min; (ii) $Ph_3P{=}CHCOOC_2H_4SO_2Tol$, CH_2Cl_2, rt, 4 h; (i) TMSCl, H_2O, CH_3CN, rt, 1 h.

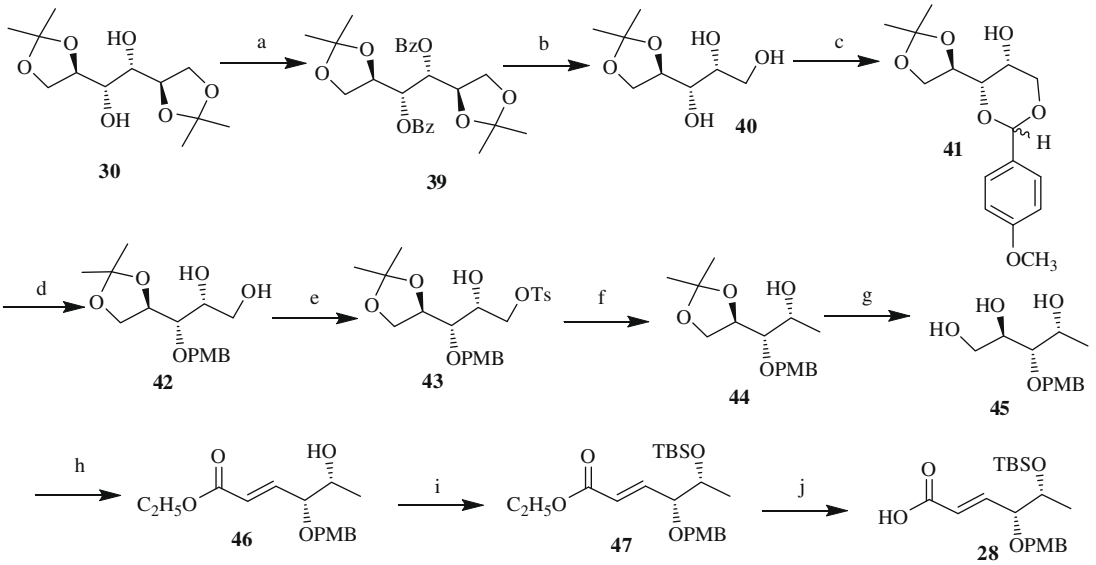
uenesulfonylethoxycarbonylmethylene)triphenyl phosphorane[15] afforded **38** in 71% yield. Finally, desilylation of **38** with TMSCl (cat.) and H_2O in CH_3CN gave **29** in 88% yield.

2.5. Synthesis of the C-2 to O-7 segment

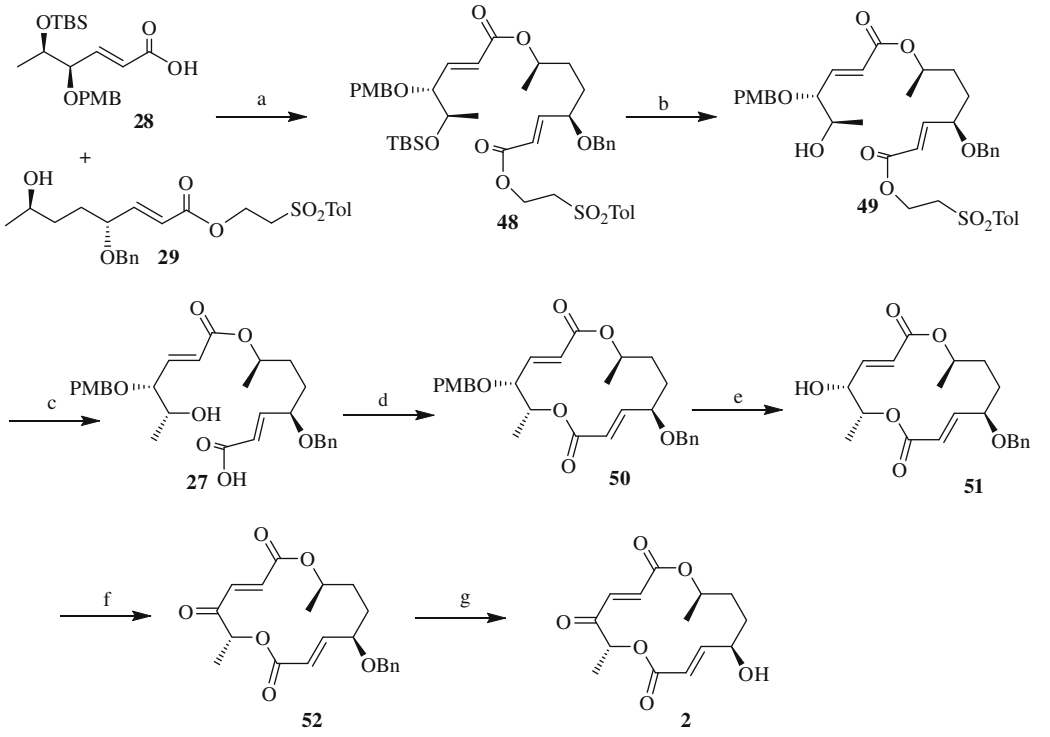
Diol **30** was benzoylated with BzCl and Et_3N in CH_2Cl_2 to give **39** in 78% yield. Selective acetonide deprotection and oxidative cleavage with H_5IO_6 in ether[16] and subsequent reduction with LAH afforded **40** in 42% yield in three steps (see Scheme 7).

Reaction of triol **40** with anisaldehyde dimethyl acetal and PPTS in CH_2Cl_2 gave acetal **41** in 71% yield (dr 3:2). Reductive opening of the PMB acetal from the less hindered side with DIBAL-H in CH_2Cl_2 gave the diol **42** (75%), which on selective tosylation gave **43** (71%). Reduction of tosylate **43** with $NaBH_4$ in DMSO[17] at 160 °C furnished **44** (92%), which on acetonide deprotection with 60% aq AcOH afforded triol **45** in 88% yield. Oxidative cleavage of **45** and subsequent olefination with (ethoxycarbonylmethylene)triphenyl phosphorane gave the unsaturated ester **46** in 72% yield. Treatment of **46** with TBSCl gave **47** (90%), which finally on hydrolysis with 0.5 M NaOH in MeOH gave acid **28** in 94% yield.

Acid **28** was subjected to esterification with alcohol **29** under Yamaguchi reaction conditions[10] to give **48** in 77% yield (Scheme 8). Desilylation of **48** with TMSCl (cat.) and H_2O in CH_3CN furnished **49** (87%), which on selective hydrolysis of the sulfonyl ester with DBN in dry benzene[15] afforded **27** in 78% yield. Macrolactonization of the resulting seco-acid **27** was then realized under the Yamaguchi protocol[6,10] with 2,4,6-tirchlorobenzoyl chloride, under high dilution conditions in toluene to afford **50** in 52% yield. The oxidative deprotection of **50** with DDQ in aq CH_2Cl_2 gave **51** in 68% yield. Oxidation of secondary alcohol **51** with Dess–Martin periodinane[18] in CH_2Cl_2 afforded **52** in 80% yield. Finally, **52** on debenzylation with $TiCl_4$ in CH_2Cl_2 at room temperature for 2 h gave **2** in 79% yield. $[\alpha]_D = -55.3$ (*c* 0.22, MeOH); lit.[1] $[\alpha]_D = +40$ (*c* 0.3, MeOH).



Scheme 7. Reagent and conditions: (a) BzCl, CH_2Cl_2, Et_3N, 0 °C to rt, 12 h; (b) (i) H_5IO_6, ether, rt, 6 h; (ii) LAH, THF, 0 °C to rt, 12 h; (c) anisaldehyde dimethylacetal, PPTS, CH_2Cl_2, rt, 2 h; (d) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h; (e) TsCl, Et_3N, CH_2Cl_2, rt, 14 h; (f) DMSO, $NaBH_4$, 160 °C, 10 min; (g) 60% aq AcOH, rt, 12 h; (h) (i) $NaIO_4$, MeOH/H_2O (5:1), 0 °C to rt, 3 h; (ii) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 0 °C to rt, 4 h; (i) TBSCl, imidazole, CH_2Cl_2, rt, 4 h; (j) 0.5 N NaOH, MeOH, rt, 24 h.



Scheme 8. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h, **29**, DMAP, toluene, rt, 1 h; (b) cat. TMSCl, H_2O, CH_3CN, rt, 1 h; (c) DBN, dry benzene, rt, 12 h; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h, DMAP, toluene, 90 °C, 10 h; (e) DDQ, CH_2Cl_2/H_2O (19:1), rt, 3 h; (f) Dess–Martin periodinane, dry CH_2Cl_2, rt, 12 h; (g) $TiCl_4$, dry CH_2Cl_2, rt, 2 h.

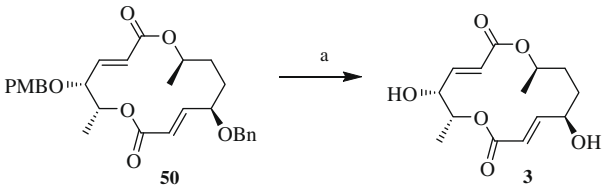
However, the spectral data[7] and specific rotation value[7] obtained for synthetic **2** and the data reported in the literature[1] did not correspond to each other. Thus, it is indeed evident from the synthesis of **2** that the structure proposed in the literature for natural **2** is also incorrect.

2.6. Synthesis of *epi*-clonostachydiol

Bis-lactone **50** (Scheme 9) was treated with $TiCl_4$ in CH_2Cl_2 at room temperature for 2 h to afford *epi*-clonostachydiol **3** in 78% yield as white solid, mp 165–168 °C; $[\alpha]_D = -15.7$ (*c* 0.23, $CHCl_3$); lit.[7b] $[\alpha]_D = -31$ (*c* 1.0, MeOH).

2.7. Synthesis of macrolide 1a

From the literature data on the macrodiolide class of natural products **1** and **2**, it was assumed that the stereochemistry at C-6 and C-14 of **1** and **2** is the same. From the synthetic studies on acremonol **2**, it was proposed to synthesize the (5*R*, 6*R*, 11*S*, 14*R*) diastereomer of the originally proposed structure of acremodiol.



Scheme 9. Reagents and conditions: (a) $TiCl_4$, dry CH_2Cl_2, rt, 2 h.

Accordingly, allylic alcohol **34** on reaction with (+)-DIPT and $Ti(O^iPr)_4$ in CH_2Cl_2 gave the epoxy alcohol **53** in 72% yield (Scheme 10). The epoxy alcohol **53** on reaction with Ph_3P and $NaHCO_3$ (cat.) in refluxing CCl_4 was converted into epoxy chloride **53a** in 66% yield. Treatment of **53** with Na in dry ether afforded olefin **54** (75%), which on reaction with BnBr and Ag_2O in CH_2Cl_2 at reflux furnished ether **55** (70%). Ozonolysis of **55** in CH_2Cl_2 to give an aldehyde and subsequent olefination with (*p*-toluenesulfonylethoxycarbonylmethylene) triphenyl phosphorane[15] gave **56** in 70% yield. Finally, desilylation of **56** with TMSCl (cat.) and H_2O in CH_3CN afforded **57** in 85% yield.

Catalytic hydrogenation of the ester **48** (Scheme 11) with PtO_2 in EtOAc afforded **58** (94%), which on hydrolysis with 0.5 M NaOH in MeOH gave acid **59** (90%).

Condensation of acid **59** with alcohol **57** through its mixed anhydride gave the ester **60** in 72% yield (Scheme 12). Desilylation of **60** with HF–pyridine complex in THF afforded **61** (73%), which on hydrolysis of **61** with DBN gave the seco-acid **62** (68%). Macrolactonization of **62** under Yamaguchi high dilution conditions afforded **63** in 58% yield. Finally, bis-lactone **63** was treated with $TiCl_4$ in CH_2Cl_2 to give **1a** in 80% yield, $[\alpha]_D = -52.7$ (*c* 0.23, MeOH); lit.[1] $[\alpha]_D = +98$ (*c* 0.33, MeOH).

The spectroscopic data of **1a** did not match with those of acremodiol[1] and hence the structure of the natural product is still unresolved.

3. Conclusion

Thus, in conclusion, we have synthesized three bis-macrolides **1**, **2,** and **1a** and *epi*-clonostachydiol **3**, while attempting the first synthesis of acremonol and acremodiol. The spectral (^1H, ^{13}C, ESI-MS, and IR) analysis data of synthetic **1**, **1a,** and **2**, besides the specific rotation values were found not to match with the data reported for the natural products. Thus, all efforts in the direction of the first synthesis[19] of acremodiol and acremonol met with failure in the synthesis of these natural products.

4. Experimental

4.1. General methods

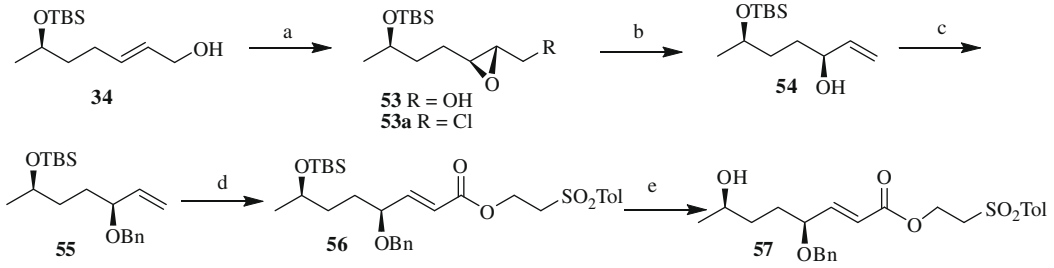
Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^1H NMR (200 MHz, 300 MHz, and 400 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer, Bruker Avance 300 MHz, Varian Inova 400 MHz, and Varian Unity Inova-500 MHz with tetramethylsilane as an internal standard for solutions in deuteriochloroform. *J* values are given in hertz. IR spectra were recorded on Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21–11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. (4*R*,5*R*,E)-*tert*-Butyl 4,5-dihydroxyhex-2-enoate 10

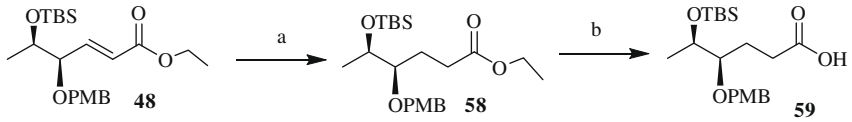
A well-stirred solution of AD-mix-β (4.63 g, 5.95 mmol) in *t*-BuOH/H_2O (1:1, 20 mL) was treated with methane sulfonamide (0.28 g, 2.97 mmol) at room temperature. After 30 min, the clear yellow solution was cooled to 0 °C and ester **8** (0.50 g, 2.97 mmol) was added. The reaction mixture was stirred vigorously at 0 °C for 27 h, and then the reaction was quenched with solid Na_2SO_4 (5 g), and the reaction mixture was warmed to room temperature, and stirred for another 50 min. The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (60–120 silica gel, 3:7 EtOAc/*n*-hexane) to afford **10** (0.37 g, 61%) as a yellow syrup. $[\alpha]_D = +10.5$ (*c* 0.92, $CHCl_3$), lit.[7b] $[\alpha]_D = +11.0$ (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 6.74 (dd, 1H, *J* = 5.2, 15.6 Hz, olefinic), 6.03 (dd, 1H, *J* = 1.50, 15.6 Hz, olefinic), 3.97 (m, 1H, –CH), 3.66 (m, 1H, –CH), 3.12 (br s, 2H, 2 × –OH), 1.47 (s, 9H, $3CH_3$ *t*-Bu), 1.22 (d, 3H, *J* = 5.90 Hz, $–CH_3$); IR (neat): 3433, 1715, 1370, 1160 cm^{-1}; EIMS (*m*/*z*%): 203 (M^++1) (4), 188 (3), 156 (10), 103 (95), 85(30), 58 (100).

4.1.2. (4*R*,5*R*,E)-*tert*-Butyl 5-(*tert*-butyldimethylsilyloxy)-4-hydroxyhex-2-enoate 11a

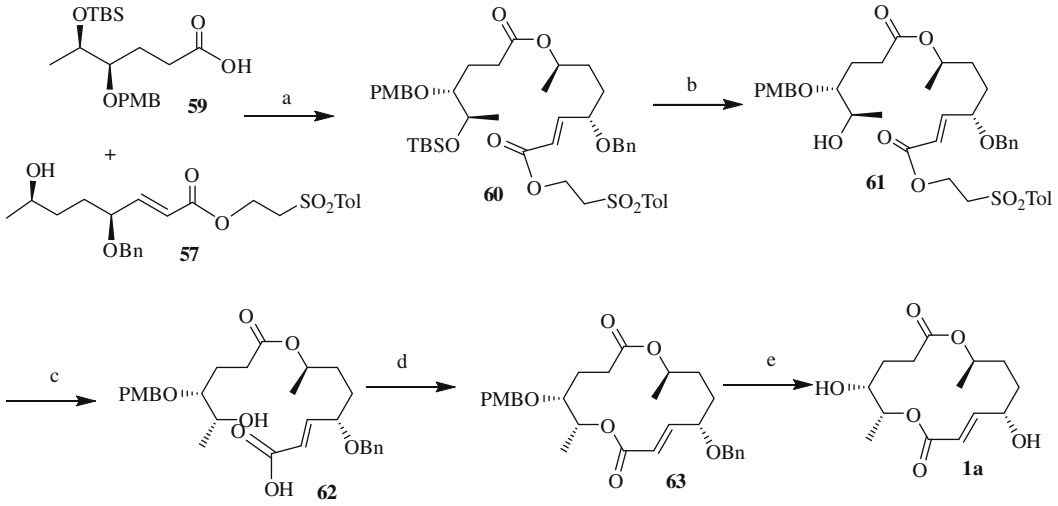
A solution of diol **10** (0.36 g, 1.78 mmol), DMAP (0.01 g, 0.09 mmol), and TBSCl (0.58 g, 3.92 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and Et_3N (0.43 g, 4.27 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, and quenched with H_2O (5 mL). The mixture was then extracted with $CHCl_3$ (3 × 10 mL) and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give the residue, which was purified by column chromatography (60–120 silica gel, 1:19 EtOAc/*n*-hexane). First eluted was **11a** (0.28 g, 50%) (70% yield based on recovered **10**) as a yellow syrup. $[\alpha]_D = -5.7$ (*c* 0.69, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 6.76 (dd, 1H, *J* = 4.4, 15.6 Hz, olefinic), 6.0 (dd, 1H, *J* = 2.2, 15.6 Hz, olefinic), 3.96 (m, 1H, –CH), 3.73 (m, 1H, –CH), 2.42 (d, 1H, *J* = 5.2 Hz, –OH), 1.47 (s, 9H, $3CH_3$ *t*-Bu), 1.21 (d, 3H, *J* = 5.9 Hz, $–CH_3$), 0.89 (s, 9H, 3 × $–CH_3$), 0.08 (s, 3H, CH_3–Si), 0.06 (s, 3H, CH_3–Si); IR (neat): 3434,



Scheme 10. Reagents and conditions: (a) (+)-DIPT, 4 Å, cumene hydroperoxide, $Ti(O^iPr)_4$, CH_2Cl_2, −20 °C, 3 h; (b) (i) Ph_3P, $NaHCO_3$, CCl_4, reflux, 30 min; (ii) Na, ether, rt, 12 h; (c) BnBr, Ag_2O, CH_2Cl_2, rt, 12 h; (d) (i) O_3, CH_2Cl_2, −78 °C, 2 h; (ii) $Ph_3P{=}CHCOOC_2H_4SO_2Tol$, CH_2Cl_2, 0 °C to rt, 4 h; (e) cat. TMSCl, H_2O, CH_3CN, rt, 1 h.



Scheme 11. Reagents and conditions: (a) PtO_2, H_2, EtOAc, rt, 4 h; (b) 0.5 N NaOH, MeOH, rt, 24 h.



Scheme 12. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h, **57**, DMAP, toluene, rt, 1 h; (b) HF–pyridine complex, dry THF, rt, 6 h; (c) DBN, dry benzene, rt, 12 h; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h, DMAP, toluene, 90 °C 10 h; (e) $TiCl_4$, dry CH_2Cl_2, rt, 2 h.

2980, 2856, 1716, 1371, 1159, 1096 cm^{-1}; FABMS (*m*/*z*%): 317 (M^++1) (30), 299 (39), 261 (35), 185 (16), 159 (67), 137 (14), 73 (100).

The second eluted was **11b** (0.07 g, 12%) as a yellow syrup. ^1H NMR (200 MHz, $CDCl_3$): δ 6.73 (dd, 1H, *J* = 6.0 Hz, 15.7 Hz, olefinic), 5.86 (d, 1H, *J* = 15.7 Hz, olefinic), 3.97 (m, 1H, –CH), 3.60 (m, 1H, –CH), 2.30 (m, 1H, –OH), 1.48 (s, 9H, $3CH_3$, *t*-Bu), 1.14 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.90 (s, 9H, 3 × $-CH_3$), 0.08 (s, 3H, CH_3–Si), 0.06 (s, 3H, CH_3–Si).

4.1.3. (4*R*,5*R*,E)-*tert*-Butyl 5-(*tert*-butyldimethylsilyloxy)-4-((2-methoxyethoxy) methoxy)hex-2-enoate 12

A solution of alcohol **11a** (0.27 g, 0.85 mmol) and DIPEA (0.44 g, 3.42 mmol) in CH_2Cl_2 (5 mL) was treated with MEMCl (0.21 g, 1.71 mmol) and stirred at room temperature for 24 h. The reaction was quenched with water (2 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (60–120 silica gel, 1:19 EtOAc/*n*-hexane) to afford **12** (0.29 g, 84%) as a yellow syrup. $[\alpha]_D$ = +5.8 (*c* 1.39, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 6.75 (dd, 1H, *J* = 5.20, 15.6 Hz, olefinic), 5.91 (d, 1H, *J* = 15.6 Hz, olefinic), 4.69 (m, 2H, $-OCH_2O$– MEM), 4.09 (m, 1H, –CH), 3.89 (m, 1H, –CH), 3.73–3.60 (2 m, 2H, $-OCH_2$ MEM), 3.50 (m, 2H, $-OCH_2$ MEM), 3.36 (s, 3H, $-OCH_3$ MEM), 1.49 (s, 9H, $3CH_3$, *t*-Bu), 1.09 (d, 3H, *J* = 5.9 Hz, $-CH_3$), 0.89 (s, 9H, 3 × $-CH_3$), 0.06 (s, 6H, 2 × $-CH_3$); IR (neat): 3436, 2958, 2933, 2856, 1716, 1368, 1253, 1155, 1104 cm^{-1}; FABMS (*m*/*z*,%): 405 (M^++1) (4), 329 (6), 299 (14), 273 (20), 159 (44), 111 (22), 89 (100), 59 (66).

4.1.4. (4*R*,5*R*)-*tert*-Butyl 5-(*tert*-butyldimethylsilyloxy)-4-((2-methoxyethoxy) methoxy) hexanoate 13

To a suspension of PtO_2 (0.02 g, 0.09 mmol) in EtOAc (2 mL), unsaturated ester **12** (0.18 g, 0.44 mmol) was added and subjected to hydrogenation at 40 psi for 4 h. The catalyst was filtered off through Celite and the filtrate was evaporated to afford **13** (0.17 g, 94%) as a liquid. $[\alpha]_D$ = +21.7 (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.70 (dd, 2H, *J* = 6.9, 21.1 Hz, $-OCH_2O$– MEM), 3.89 (m, 1H, –CH), 3.66 (m, 2H, $-OCH_2$ MEM), 3.51 (m, 2H, $-OCH_2$ MEM), 3.36 (m, 4H, –CH, $-OCH_3$ MEM), 2.29 (m, 2H, $-CH_2$), 1.88–1.60 (2 m, 2H, $-CH_2$), 1.43 (s, 9H, $3CH_3$ *t*-Bu), 1.10 (d, 3H, *J* = 6.4 Hz, $-CH_3$), 0.87 (s, 9H, 3 × $-CH_3$), 0.05 (s, 6H, 2 × $-CH_3$); IR (neat): 2924, 2854, 1731, 1463, 1514, 1368, 1254, 1152, 1043 cm^{-1}; FABMS (*m*/*z*%): 407 (M^++1) (7), 331 (12), 293 (5), 275 (44), 187 (12), 154 (30), 89 (100), 59 (64).

4.1.5. (4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-((2-methoxyethoxy) methoxy)hexanoic acid 6

A mixture of **13** (0.16 g, 0.39 mmol) and 0.5 M NaOH (2 mL) in MeOH (5 mL) was stirred at room temperature for 18 h and then neutralized with HCl (0.5 M, 2 mL). The reaction mixture was extracted with $CHCl_3$ (3 × 15 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (60–120 silica gel, 1:1 EtOAc/*n*-hexane) to give **6** (0.12 g, 87%) as a colorless oil. $[\alpha]_D$ = +93.5 (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.68 (2d, 2H, *J* = 6.7, Hz, $-OCH_2O$– MEM), 3.90 (m, 1H, –CH), 3.68 (m, 2H, $-OCH_2$ MEM), 3.52 (m, 2H, $-OCH_2$ MEM), 3.39 (m, 4H, –CH, $-OCH_3$ MEM), 2.45 (m, 2H, $-CH_2$), 1.96–1.65 (2 m, 2H, $-CH_2$), 1.10 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.87 (s, 9H, 3 × $-CH_3$), 0.05 (s, 6H, 2 × $-CH_3$); IR (neat): 3435, 2958, 2855, 1727, 1614, 1520, 1369, 1299, 1174, 1012 cm^{-1}; FABMS (*m*/*z*%): 373 (M^++23) (10), 349 (5), 307 (5), 275 (40), 245 (32), 154 (28), 89 (60), 73 (100), 59 (74).

4.1.6. (*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl 4-methylbenzenesulfo-nate 15

To a cooled (0 °C) solution of alcohol **14** (5.8 g, 33.72 mmol), DMAP (0.41 g, 3.37 mmol), and Et_3N (6.8 g, 67.44 mmol) in CH_2Cl_2 (25 mL), *p*-TsCl (7.06 g, 37.1 mmol) was added portionwise and stirred at room temperature for 24 h. The solvent was evaporated

and the residue was purified by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) to afford **15** (9.0 g, 82%) as a syrup. $[\alpha]_D$ = +12.5 (*c* 1.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.80, 7.30 (2d, 4H, *J* = 8.0 Hz, Ar), 5.64 (m, 1H, olefinic), 5.03 (m, 2H, olefinic), 4.55 (m, 1H, –CH), 4.00 (m, 2H, –CH), 3.75 (m, 1H, –CH), 2.40 (m, 5H, $-CH_2$, CH_3 Ar), 1.30, 1.28 (2s, 6H, 2 × $-CH_3$); IR (neat): 2850, 1550, 1360, 1145 cm^{-1}; FABMS (*m*/*z*,%): 349 (M^++23) (20), 311 (30), 245 (15), 101 (40), 89 (100), 73, (80), 59 (74).

4.1.7. (*S*)-4-(But-3-enyl)-2,2-dimethyl-1,3-dioxolane 16

To a stirred suspension of LAH (1.39 g, 36.8 mmol) in dry THF (30 mL) a solution of **15** (6.0 g, 18.4 mmol) in dry THF (30 mL) was added dropwise at 0 °C under nitrogen atmosphere and the mixture was stirred at reflux for 12 h. The reaction mixture was cooled to 0 °C, treated with saturated aq Na_2SO_4 solution (25 mL), filtered, and the filtrate was dried (Na_2SO_4) and evaporated (below 30 °C). The crude residue was distilled under vacuum at 100 °C/12 mm to give **16** (2.5 g, 87%) as a colorless liquid. $[\alpha]_D$ = +15.9 (*c* 2.85, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 5.80 (m, 1H, olefinic), 5.00 (m, 2H, olefinic), 4.02 (m, 2H, $-CH_2$), 3.47 (m, 1H, –CH), 2.15 (m, 2H, $-CH_2$), 1.79–1.51 (m, 2H, $-CH_2$), 1.37, 1.34 (2s, 6H, 2 × $-CH_3$); IR (neat): 2948, 1620, 1540, 1454, 1248, 1036 cm^{-1}; EIMS (*m*/*z*%): 157 (M^++1) (32), 89 (65), 73, (50), 59 (80), 43 (100).

4.1.8. (*S*)-2,2-Dimethyl-4-(2-(oxiran-2-yl)ethyl)-1,3-dioxolane 17

To a stirred solution of olefin **16** (2.4 g, 15.38 mmol) in $CHCl_3$ (25 mL), *m*-CPBA (3.98 g, 23.07 mmol) was added and stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was washed with saturated $NaHCO_3$ solution (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) to furnish **17** (1.98 g, 75%) as a colorless liquid. ^1H NMR (200 MHz, $CDCl_3$): δ 4.02 (m, 2H, $-CH_2$), 3.48 (m, 1H, –CH), 2.90 (m, 1H, –CH), 2.70 (m, 1H, –CH), 2.44 (m, 1H, –CH), 1.66 (m, 4H, 2 × $-CH_2$), 1.39, 1.28 (2s, 6H, 2 × CH_3); IR (neat): 3050, 2932, 1620, 1452, 1034, 950, 860 cm^{-1}; EIMS (*m*/*z*%): 173 (M^++1) (22), 154, (30), 89 (72), 73 (50), 59 (100), 43 (60).

4.1.9. (*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butane-1,2-diol 18

A mixture of (*S*,*S*)-Jacobsen's catalyst (0.01 g, 0.02 mmol) and AcOH (0.02 g, 0.04 mmol) in toluene (1 mL) was stirred in open air at room temperature for 1 h. The solvent was removed by rotary evaporator, and the brown residue was dried under vacuum. To this catalyst, epoxide **17** (1.95 g, 11.33 mmol) was added in one portion and the stirred mixture was cooled in an ice-water bath. H_2O (0.11 g, 6.23 mmol) was slowly added keeping the bath temperature at 15 °C. After 1 h, ice-water bath was removed and the reaction mixture was stirred at room temperature for 12 h. The crude reaction mixture was purified by column chromatography (60–120 silica gel, 1:1 EtOAc/*n*-hexane). First eluted was **18a** (0.850 g, 43% yield) as a yellow liquid. ^1H NMR (200 M Hz, $CDCl_3$): δ 4.12 (m, 1H, –CH), 4.01 (m, 1H, –CH), 3.49 (m, 1H, –CH), 2.91 (m, 1H, –CH), 2.72 (m, 1H, –CH), 2.44 (m, 1H, –CH), 1.66 (m, 4H, 2 × $-CH_2$), 1.38, 1.32 (2s, 6H, 2 × CH_3).

Second eluted was **18** (0.84 g, 39%) as a yellow syrup. $[\alpha]_D$ = +17.4 (*c* 0.63, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 4.03 (m, 2H, $-CH_2$), 3.75–3.30 (m, 6H, 2 × –CH, $-CH_2$, 2 × OH), 1.80–1.40 (m, 4H, 2 × $-CH_2$), 1.39, 1.32 (2s, 6H, 2 × $-CH_3$); IR (neat): 3450, 3310, 2935, 1642, 1375, 1125, 1075 cm^{-1}; FABMS (*m*/*z*%): 191 (M^++1) (18), 175 (8), 154 (100), 137 (78), 89 (28), 69, (29), 55 (36).

4.1.10. (*S*)-4-(2-((*4R*)-2-(4-Methoxyphenyl)-1,3-dioxolan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxolane 19

To a stirred solution of **18** (0.83 g, 4.36 mmol) and PPTS (0.02 g, 0.09 mmol) in dry CH_2Cl_2 (10 mL), anisaldehyde dimethylacetal (1.20 g, 6.55 mmol) was added at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with Et_3N, the solvent was evaporated, and the residue was purified by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) to give **19** (0.98 g, 73%) as an oil, $[\alpha]_D$ = +1.3 (*c* 0.31, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.36, 6.84 (2d, 4H, *J* = 6.0 Hz, Ar), 5.83, 5.71 (2s, 1H, –CH Ar), 4.25–3.95 (m, 4H, 2 × $-CH_2$), 3.80 (s, 3H, $-OCH_3$ Ar), 3.69–3.44 (m, 2H, 2 × –CH), 1.70 (m, 4H, 2 × $-CH_2$), 1.38, 1.32 (2s, 6H, 2 × $-CH_3$); IR (neat); 3050, 2950, 1600, 1580, 1126, 1073, 750 cm^{-1}; FABMS (*m*/*z*%): 309 (M^++1) (10), 265 (15), 150 (30), 122 (45), 89 (25), 57, (26), 55 (100).

4.1.11. (*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxybenzyloxy)butan-1-ol 20

To a stirred solution of **19** (0.97 g, 3.15 mmol) in dry CH_2Cl_2 (10 mL), DIBAL-H (2.36 mL, 4.72 mmol, 2 M solution in toluene) was added at 0 °C and stirred at the same temperature for 12 h. Methanol (2 mL) was added to the reaction mixture at 0 °C and stirred for 10 min. Saturated aq solution of sodium potassium tartrate (5 mL) was added and after 10 min, the methanol was evaporated. It was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 1:3 EtOAc/*n*-hexane) to afford **20** (0.74 g, 76%) as a gummy syrup. $[\alpha]_D$ = +42.0 (*c* 0.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.21, 6.83 (2d, 4H, *J* = 7.3 Hz, Ar), 4.50 (m, 2H, $-OCH_2$ Ar), 4.01 (m, 2H, $-CH_2$), 3.80 (s, 3H, $-OCH_3$, Ar), 3.65 (m, 1H, –CH), 3.49 (m, 3H, $-CH_2$, –CH), 1.84 (br s, 1H, –OH), 1.44–1.70 (m, 4H, 2 × $-CH_2$), 1.39, 1.33 (2s, 6H, 2 × $-CH_3$); IR (neat); 3448, 2985, 2933, 1613, 1514, 1373, 1176, 1060 cm^{-1}; FABMS (*m*/*z*%): 311 (M^++1) (7), 252 (40), 196 (45), 121 (70), 90 (30), 57, (100).

4.1.12. (*S*)-4-((*R*)-3-(4-Methoxybenzyloxy)pent-4-enyl)-2,2-dimethyl-1,3-dioxolane 22

To a stirred solution of oxalyl chloride (0.62 g, 3.53 mmol) in dry CH_2Cl_2 (5 mL), DMSO (0.55 g, 7.06 mmol) was added at −78 °C and stirred at the same temperature for 0.5 h. A solution of alcohol **20** (0.73 g, 2.35 mmol) in CH_2Cl_2 (2 mL) was added at −78 °C and stirred for another 2.5 h at the same temperature. Then Et_3N (1.42 g, 14.12 mmol) was added at 0 °C and stirred for further 45 min. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give **21** in quantitative yield as a pale yellow syrup, which was used as such for the next reaction.

To a solution of (methylenetriphenyl)phosphonium iodide (1.88 g, 4.67 mmol) in dry THF (10 mL), *n*-BuLi (2.92 mL, 4.675 mmol, 1.6 N) was added at 0 °C and the mixture was stirred for 1 h. Aldehyde **21** (0.72 g, 2.33 mmol) in dry THF (2 mL) was added at 0 °C and the mixture was stirred for an additional 12 h. The reaction was quenched with saturated NH_4Cl (5 mL) solution and the reaction mixture was extracted with ether (2 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), concentrated, and the crude residue was purified by column chromatography (60–120 silica gel, 1:19 EtOAc/*n*-hexane) to afford **22** (0.35 g, 50%) as a yellow syrup. $[\alpha]_D$ = +33.0 (*c* 0.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.20, 6.84 (2d, 4H, *J* = 8.2 Hz, Ar), 5.70–5.61 (m, 1H, olefinic), 5.24–5.10 (m, 2H, olefinic), 4.45, 4.25 (2d, 2H, *J* = 11.7 Hz, $-OCH_2$ Ar), 4.10–3.65 (m, 3H, –CH, $-CH_2$) 3.71 (s, 3H, $-OCH_3$ Ar), 3.49 (m, 1H, –CH), 1.78–1.48 (m, 4H, 2 × –CH), 1.38–1.33 (2s, 6H, 2 × $-CH_3$); IR (neat);

3049, 2932, 1614, 1512, 1454, 1375, 1090, 824 cm^{-1}; FABMS (*m*/*z*%): 307 (M^++1) (8), 252 (20), 193 (5), 121 (100), 91 (30), 77 (25), 57 (70).

4.1.13. (2*S*,5*R*)-5-(4-Methoxybenzyloxy)hept-6-ene-1,2-diol 23

A mixture of **22** (0.35 g, 1.14 mmol) in 60% aq AcOH (5 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralized with $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by filtration through a small pad of silica gel with 1:1 EtOAc/*n*-hexane to afford **23** (0.27 g, 88%) as a colorless syrup. $[\alpha]_D$ = +41.3 (*c* 0.65, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.20, 6.84 (2d, 4H, *J* = 8.0 Hz, Ar), 5.75 (m, 1H, olefinic), 5.22 (m, 2H, olefinic), 4.52, 4.25 (2d, 2H, *J* = 12.0 Hz, $-OCH_2$ Ar), 3.84–3.71 (m, 4H, –CH, $-OCH_3$ Ar), 3.70–3.50 (m, 2H, $-CH_2$), 3.40 (m, 1H, –CH), 1.70, 1.53 (2 m, 4H, 2 × $-CH_2$); IR (neat): 3448, 3310, 3049, 2932, 1612, 1512, 1451, 1398, 1075 cm^{-1}; EIMS (*m*/*z*%): 267 (M^++1) (7), 229 (15), 155 (30), 121 (20), 91 (100), 57 (70).

4.1.14. (2*S*,5*R*)-2-Hydroxy-5-(4-methoxybenzyloxy)hept-6-enyl 4-methylbenzene sulfonate 24

To a cooled (0 °C) solution of diol **23** (0.26 g, 0.97 mmol), DMAP (cat.), and Et_3N (0.19 g, 1.95 mmol) in CH_2Cl_2 (15 mL), *p*-TsCl (0.18 g, 0.97 mmol) was added portionwise at 0 °C and the mixture was stirred at room temperature for 14 h. Worked up as described for **15** and purified by column chromatography (60–120 silica gel, 1:4 EtOAc/*n*-hexane). First eluted was **24a** (0.05 g, 8%) as a yellow syrup. ^1H NMR (200 MHz, $CDCl_3$): δ 7.78, 7.32 (2 m, 8H, SO_2Ph), 7.18, 6.84 (2d, 4H, *J* = 7.7 Hz, Ar), 5.70 (m, 1H, olefinic), 5.21 (m, 2H, olefinic), 4.58 (m, 1H, –CH), 4.51–4.23 (2d, 2H, *J* = 11.5 Hz, $-OCH_2$ Ar), 3.88–3.65 (m, 6H, $-CH_2$, –CH, $-OCH_3$ Ar), 2.45, 2.44 (2s, 6H, 2 × $-CH_3$ Ar), 1.71–1.39 (m, 4H, 2 × $-CH_2$).

Second eluted was **24** (0.3 g, 73%) as a yellow syrup. $[\alpha]_D$ = +39.7 (*c* 0.79, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.76, 7.31 (2d, 4H, *J* = 7.7 Hz, SO_2Ph); 7.17, 6.83 (2d, 4H, *J* = 7.7 Hz, Ar), 5.70 (m, 1H, olefinic), 5.21 (m, 2H, olefinic), 4.50, 4.22 (2d, 2H, *J* = 11.5 Hz, $-OCH_2$ Ar), 3.88 (m, 7H, 2 × –CH, $-CH_2$ $-OCH_3$ Ar), 2.45 (s, 3H, $-CH_3$ Ar), 1.70–1.40 (m, 4H, 2 × $-CH_2$); IR (neat): 3444, 2924, 2855, 1610, 1512, 1457, 1351, 1247, 1149 cm^{-1}; FABMS (*m*/*z*%): 421 (M^++1) (5), 391 (10), 229 (13), 154 (32), 137 (46), 121 (100), 77 (24), 69 (50), 57 (76).

4.1.15. (2*R*,5*R*)-5-(4-Methoxybenzyloxy)hept-6-en-2-ol 7

To a stirred suspension of LAH (0.05 g, 1.38 mmol) in dry THF (3 mL), a solution of **24** (0.29 g, 0.69 mmol) in dry THF (2 mL) was added dropwise at 0 °C under a nitrogen atmosphere and the mixture was stirred at room temperature for 12 h. The reaction mixture was worked-up as described for **16** and the residue was purified by column chromatography (60–120 silica gel, 1:3 EtOAc/*n*-hexane) to give **7** (0.16 g, 95%) as a colorless syrup. $[\alpha]_D$ = +28.1 (*c* 0.49, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.19, 6.82 (2d, 4H, *J* = 10.7 Hz, Ar), 5.72 (m, 1H, olefinic), 5.20 (m, 2H, olefinic), 4.51, 4.24 (2d, 2H, *J* = 13.6 Hz, $-OCH_2$ Ar), 3.82–3.65 (m, 5H, 2 × –CH, $-OCH_3$ Ar), 1.70, 1.40 (m, 4H, 2 × $-CH_2$), 1.14 (d, 3H, *J* = 8.7 Hz, –CH), ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.8, 129.2, 116.9, 113.7, 80.2, 69.8, 67.7, 55.2, 35.0, 31.7, 23.3; IR (neat): 3448, 2932, 1611, 1513, 1455, 1374, 1093, 928 cm^{-1}; EIMS (*m*/*z*%): 251 (M^++1) (28), 154 (10), 137 (32), 121 (100), 95 (12), 69 (14), 57 (20).

4.1.16. (4*R*,5*R*)-((2*R*,5*R*)-5-(4-Methoxybenzyloxy)hept-6-en-2-yl) 5-(*tert*-butyl dimethylsilyloxy)-4-((2-methoxyethoxy)-methoxy)hexanoate 25

To a solution of acid **6** (0.11 g, 0.31 mmol) and Et_3N (0.063 g, 0.628 mmol) in dry THF (5 mL), 2,4,6-trichlorobenzoyl chloride (0.07 g, 0.314 mmol) was added and the reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was filtered and the filtrate was evaporated. The resulting anhydride was dissolved in toluene (2 mL) and treated with alcohol **7** (0.07 g, 0.31 mmol) and DMAP (0.07 g, 0.62 mmol) in toluene (3 mL). It was stirred at room temperature for 12 h, filtered through Celite, and evaporated. The residue was purified by column chromatography (60–120 silica gel, 1:4 EtOAc/*n*-hexane) to afford **25** (0.15 g, 82%) as an oil. $[\alpha]_D$ = +35.5 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.17, 6.79 (2d, 4H, *J* = 8.3 Hz, Ar), 5.69 (m, 1H, olefinic), 5.19 (m, 2H, olefinic), 4.86 (m, 1H, –CH), 4.69 (m, 2H, $-OCH_2O-$ MEM), 4.46, 4.21 (2d, 2H, *J* = 11.3 Hz, $-OCH_2$ Ar), 3.89 (m, 1H, –CH), 3.79 (s, 3H, $-OCH_3$ Ar), 3.65 (m, 3H, –CH, $-OCH_2$ MEM), 3.50 (m, 2H, $-OCH_2$ MEM), 3.35 (m, 4H, –CH, $-OCH_3$ MEM), 2.33 (m, 2H, $-CH_2$), 1.91 (m, 1H, –CH), 1.57 (m, 5H, 2 × $-CH_2$, –CH), 1.20 (d, 3H, *J* = 6.8 Hz, $-CH_3'$), 1.10 (d, 3H, *J* = 6.8 Hz, $-CH_3$), 0.87 (s, 9H, 3 × $-CH_3$), 0.04 (s, 6H, 2 × CH_3); IR (neat): 2948, 2860, 1726, 1614, 1511, 1456, 1370, 1248, 822 cm^{-1}; FABMS (*m*/*z*%): 583 (M^++1, 10), 393 (5), 307, (7), 275 (5), 229 (8), 154 (30), 137 (27), 121 (100), 89 (18), 77 (15), 59 (50).

4.1.17. (4*R*,5*R*)-((2*R*,5*R*)-5-(4-Methoxybenzyloxy)hept-6-en-2-yl) 5-hydroxy-4-((2-methoxyethoxy)methoxy)hexanoate 5

To a solution of **25** (0.10 g, 0.17 mmol) in dry CH_3CN (1 mL), $ZrCl_4$ (0.008 g, 0.03 mmol) in dry CH_3CN (0.5 mL) was added at 0 °C. The reaction mixture was stirred for 20 min at the same temperature, the reaction was quenched with saturated $NaHCO_3$ solution (1 mL), and the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 3:7 EtOAc/*n*-hexane) to afford **5** (0.05 g, 68%) as a yellow syrup. $[\alpha]_D$ = +19.7 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.17, 6.82 (2d, 4H, *J* = 8.5 Hz, Ar), 5.69 (m, 1H, olefinic), 5.20 (m, 2H, olefinic), 4.86 (m, 1H, –CH), 4.74 (dd, 2H, *J* = 6.9, 26.2 Hz, $-OCH_2O-$ MEM), 4.46, 4.24 (2d, 2H, *J* = 11.5 Hz, $-OCH_2$ Ar), 3.79 (m, 4H, –CH, $-OCH_3$ Ar), 3.65 (m, 3H, –CH, $-OCH_2$ MEM), 3.52 (m, 2H, $-OCH_2$ MEM), 3.36 (s, 3H, $-OCH_3$ MEM), 3.27 (m, 1H, –CH), 2.33 (m, 2H, $-CH_2$), 1.89 (m, 1H, –CH), 1.60 (m, 5H, 2 × $-CH_2$, –CH), 1.19 (d, 3H, *J* = 6.2 Hz, $-CH_3'$), 1.12 (d, 3H, *J* = 6.4 Hz, $-CH_3$); IR (neat): 3449, 2931, 1727, 1612, 1513, 1454, 1375, 1299, 1176, 1036, 929, 823 cm^{-1}; FABMS (*m*/*z*%): 469 (M^++1) (5), 393 (3), 307, (5), 256 (3), 229 (4), 154 (29), 137 (27), 121 (100), 107 (10), 89 (18), 77 (15), 59 (12).

4.1.18. (4*R*,5*R*)-((2*R*,5*R*)-5-(4-Methoxybenzyloxy)hept-6-en-2-yl) 5-(acryloyloxy)-4-((2-methoxyethoxy)methoxy)hexanoate 4

To a stirred solution of alcohol **5** (0.05 g, 0.11 mmol) and DIPEA (0.07 g, 0.53 mmol) in dry CH_2Cl_2 (1 mL), acryloyl chloride (0.04 g, 0.43 mmol) was added at 0 °C under nitrogen atmosphere. After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed sequentially with H_2O (5 mL), 10% HCl (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL). The combined extracts were dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 1:4 EtOAc/*n*-hexane) to afford **4** (0.05 g, 88%) as a colorless syrup. $[\alpha]_D$ = +25.5 (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.19, 6.79 (2d, 4H, *J* = 8.3 Hz, Ar), 6.38 (d, 1H, *J* = 17.3 Hz, olefinic), 6.07 (dd, 1H, *J* = 10.5, 17.3 Hz, olefinic), 5.81–5.63 (m, 2H, olefinic), 5.19 (m, 2H, olefinic), 5.05 (m, 1H, –CH), 4.84 (m, 1H, –CH), 4.71 (m, 2H, $-OCH_2O-$ MEM), 4.50, 4.24 (2d, 2H, *J* = 12.0 Hz, $-OCH_2$ Ar), 3.78 (s, 3H, $-OCH_3$ Ar), 3.64 (m, 4H, 2 × –CH, $-OCH_2$ MEM), 3.50 (m, 2H, $-OCH_2$ MEM), 3.35 (s, 3H, $-OCH_3$ MEM), 2.35 (m, 2H, $-CH_2$), 1.89, 1.74 (2 m, 2H, $-CH_2$), 1.55 (m, 4H, 2 × CH_2), 1.23 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 1.18 (d, 3H, *J* = 6.0 Hz, $-CH_3$); IR (neat): 2950, 1728, 1613, 1550, 1453, 1390, 1292, 1175, 1038, 925, 825 cm^{-1}; FABMS (*m*/*z*%): 523 (M^++1) (5), 391 (7), 307, (4), 289 (3), 185 (5), 154 (30), 137 (30), 121 (100), 107 (12), 89 (26), 77 (12), 69 (26), 57 (40).

4.1.19. (5*R*,6*R*,11*R*,14*R*,*E*)-11-(4-Methoxybenzyloxy)-5-(2-methoxyethoxy) methoxy)-6,14-dimethyl-1,7-dioxacyclotetradec-9-ene-2,8-dione 26

Ester **4** (0.04 g, 0.07 mmol) was dissolved in freshly distilled and degassed anhydrous CH_2Cl_2 (160 mL) and Grubbs' I catalyst (0.013 g, 0.02 mmol) was added. The mixture was heated at reflux for 48 h under a nitrogen atmosphere. Most of the solvent was then distilled off and the concentrated solution was left to stir at room temperature for 2 h under air bubbling in order to decompose the catalyst. Evaporation to dryness gave a brown residue which on purification by column chromatography (60–120 silica gel, 1:3 EtOAc/*n*-hexane) afforded **26** (0.02 g, 60%) as a brown syrup. $[\alpha]_D = -10.9$ (*c* 0.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18, 6.79 (2d, 4H, *J* = 8.3 Hz, Ar), 6.67 (dd, 1H, *J* = 3.0, 15.8 Hz, olefinic), 5.98 (d, 1H, *J* = 15.8 Hz, olefinic), 5.05 (m, 1H, –CH), 4.76 (m, 3H, –CH, $-OCH_2O-$ MEM), 4.47 (m, 2H, $-OCH_2$ Ar), 4.17 (m, 1H, –CH), 3.93 (m, 1H, –CH), 3.79 (s, 3H, $-OCH_3$ Ar), 3.70 (m, 2H, $-OCH_2$ MEM), 3.54 (m, 2H, $-OCH_2$ MEM), 3.37 (s, 3H, $-OCH_3$ MEM), 2.70, 2.29 (2 m, 2H, CH_2–CO), 1.83 (m, 5H, 2 × $-CH_2$, –CH), 1.49 (m, 1H, –CH), 1.26 (d, 3H, *J* = 6.8 Hz, $-CH_3$), 1.14 (d, 3H, *J* = 6.8 Hz, $-CH_3$); IR (neat): 2935, 1722, 1612, 1548, 1451, 1399, 1296, 105, 925 cm^{-1}; FABMS (*m*/*z*%): 495 (M^++1) (23), 440 (18), 353, (5), 281 (16), 154 (68), 137 (60), 121 (82), 81 (43), 69 (68), 55 (100).

4.1.20. (5*R*,6*R*,11*R*,14*R*,*E*)-5,11-Dihydroxy-6,14-dimethyl-1,7-dioxacyclotetradec-9-ene-2,8-dione 1

To a stirred solution of **26** (0.02 g, 0.04 mmol) in CH_2Cl_2 (1 mL), $TiCl_4$ (0.02 g, 0.08 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C and stirred at room temperature for 6 h. Saturated $NaHCO_3$ solution (10 mL) was added and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (60–120 silica gel, 1:1 EtOAc/*n*-hexane) to afford **1** (8 mg, 69%) as a colorless syrup. $[\alpha]_D = -35.3$ (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6): δ 6.83 (dd, 1H, *J* = 3.0, 15.8 Hz, H-10), 5.78 (dd, 1H, *J* = 2.2, 15.8 Hz, H-9), 5.15 (d, 1H, *J* = 3.7 Hz, OH-5), 4.95 (d, 1H, *J* = 6.0 Hz, OH-11), 4.83 (dq, 1H, *J* = 3.0, 6.7 Hz, H-6), 4.65 (m, 1H, H-14), 4.47 (m, 1H, H-11), 3.80 (m, 1H, H-5), 2.72, 2.66 (2dd, 1H, *J* = 3.0, 11.3 Hz, H′-3), 2.34, 2.28 (2dd, 1H, *J* = 3.6, 6.7 Hz, H-3), 1.78 (m, 1H, H-4), 1.72 (m, 2H, H-12), 1.64, 1.43 (2 m, 3H, H-13, H-4), 1.17 (d, 3H, *J* = 6.0 Hz, CH_3-15), 1.07 (d, 3H, *J* = 6.0 Hz, CH_3-16); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.2, 164.2, 152.8, 118.4, 72.7, 68.6, 67.3, 67.0, 28.2, 28.1, 27.7, 26.5, 19.5, 13.7; IR (neat): 3424, 2931, 1722, 1653, 1648, 1535, 1399 1027, 1002 cm^{-1}; FABMS (*m*/*z*%): 287 (M^++1) (26), 269 (20), 154 (46), 81 (43), 69 (66), 55 (100).

4.1.21. (*R*)-*tert*-Butyl(hex-5-en-2-yloxy)dimethylsilane 32

A suspension of Mg (3.97 g, 165.5 mmol) and dry ether (30 mL) was treated with allyl chloride (6.8 mL, 82.55 mmol) at room temperature and stirred for 30 min. It was cooled to −78 °C and a solution of **31** (4 mL, 55.17 mmol) in dry ether (10 mL) was added dropwise and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with aq NH_4Cl solution (10 mL), and the reaction mixture was extracted with ether (2 × 50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated to afford the crude alcohol **32** (5.0 g, 90%) as a colorless liquid. It is used as such for next reaction.

A mixture of the above-mentioned alcohol **32** (5 g, 50 mmol) and imidazole (10.2 g, 150 mmol) in dry CH_2Cl_2 (50 mL) was treated with TBSCl (8.29 g, 55 mmol) at 0 °C under nitrogen atmosphere and stirred at room temperature for 4 h. The reaction was quenched with aq NH_4Cl solution (10 mL) and the reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (60–120 silica gel, *n*-Hexane) to furnish **32a** (7.5 g, 70%) as a colorless liquid, $[\alpha]_D = -57.4$ (*c* 0.76, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$)**:** δ 5.72 (m, 1H, olefinic), 4.89 (q, 2H, *J* = 17.3, 3.7 Hz, olefinic), 3.76 (q, 1H, *J* = 6.0 Hz, –CH), 2.02 (m, 2H, allylic $-CH_2$), 1.44 (m, 2H, $-CH_2$), 1.07 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.84 (s, 9H, 3 × $-CH_3$), 0.00 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 114.2, 77.1, 32.0, 29.5, 26.2, 22.9, 14.2, −3.2; IR (neat): 2956, 2858, 1467, 1370, 1254, 1135, 1053, 997 cm^{-1}; ESIMS: 237 $(M+Na)^+$.

4.1.22. (*R*,*E*)-Ethyl 6-(*tert*-Butyldimethylsilyloxy)hept-2-enoate 33

Ozone was bubbled through a cooled (−78 °C) solution of **32a** (7.4 g, 34.57 mmol) in CH_2Cl_2 (70 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (2 mL) and stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde, which was used for a further reaction.

To a solution of the above-mentioned aldehyde in dry CH_2Cl_2 (50 mL) (ethoxycarbonylmethylene)triphenyl phosphorane (7.82 g, 0.79 mmol) dissolved in dry CH_2Cl_2 (20 mL) was added at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with water (10 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated. Purification of the residue by column chromatography (60–120 silica gel, 0.4:9.6 EtOAc/*n*-hexane) afforded **33** (6.8 g, 72%) as a colorless liquid. $[\alpha]_D = -21.5$ (*c* 1.66, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (m, 1H, olefinic), 5.70 (d, 1H, *J* = 6.7 Hz, olefinic), 4.10 (q, 2H, *J* = 6.7 Hz, $-OCH_2$), 3.76 (q, 1H, *J*= 6.0 Hz, –CH), 2.20 (m, 2H, allylic $-CH_2$), 1.50 (m, 2H, $-CH_2$), 1.24 (m, 3H, $-CH_3$), 1.08 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.84 (s, 9H, 3 × $-CH_3$), 0.01 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 120.9, 67.7, 51.5, 37.8, 28.4, 25.3, 25.2, 23.9, −4.4, −4.3; IR (neat): 3457, 2949, 1722, 1656, 1440, 1277, 1196, 1045, 844 cm^{-1}; HRMS *m*/*z* $[M+Na]^+$: calculated for $C_{14}H_{28}O_3SiNa$, 309.1705; found: 309.1703.

4.1.23. (*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)hept-2-en-1-ol 34

To a stirred solution of ester **33** (6.7 g, 24.63 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C, DIBAL-H (35 mL, 49.26 mmol, 20 mol % in toluene) was added and stirred at the same temperature for 2 h. The reaction was quenched with few drops of MeOH and aq sodium potassium tartrate (5 mL) and the reaction mixture was filtered through Celite. It was dried (Na_2SO_4), evaporated, and the residue was purified by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) to give **34** (4.7 g, 77%) as a colorless liquid. $[\alpha]_D = -30.6$ (*c* 1.07, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (m, 1H, olefinic), 5.03 (q, 1H, *J* = 17.3, 42.3 Hz, olefinic), 4.0 (m, 1H, –CH), 3.82 (m, 2H, $-CH_2$), 2.2 (d, 1H, *J* = 6.7 Hz, $-CH_2$), 1.46 (m, 2H, $-CH_2$), 1.07 (d, 3H, *J* = 6.0 Hz, $-CH_2$), 0.83 (s, 9H, 3 × $-CH_3$), 0.01 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.4, 128.9, 68.3, 63.8, 38.8, 28.5, 25.7, 23.1, 17.9, −4.9, −4.2; IR: 3363, 2926, 2856, 1496, 1443 cm^{-1}; HRMS *m*/*z* $[M+Na]^+$: calculated for $C_{13}H_{28}O_2SiNa$, 267.1756; found: 267.1765.

4.1.24. ((2*R*,3*R*)-3-((*R*)-3-(*tert*-Butyldimethylsilyloxy)butyl)oxiran-2-yl)methanol 35

To a cooled (−20 °C) suspension of activated powdered 4 Å MS (1.5 g) in CH_2Cl_2 (20 mL), (−)-DIPT (0.57 g, 2.45 mmol) in dry CH_2Cl_2 (2 mL),) $Ti(O^iPr)_4$ (0.36 mL, 1.22 mmol), and cumene hydroperoxide (4.4 M, 3.8 mL, 24.59 mmol) were added sequentially and stirred for 20 min. A solution of alcohol **34** (3.0 g, 12.29 mmol) in CH_2Cl_2 (10 mL) was added at −20 °C. The resulting mixture was stirred at the same temperature for 3 h. The reaction was quenched with 10% NaOH-saturated NaCl solution (30 mL) and the reaction mixture was stirred at room temperature for 4 h. It was filtered through Celite, dried (Na_2SO_4), and evaporated. The residue was

purified by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) to give **35** (2.4 g, 75%) as a colorless liquid. $[\alpha]_D$ = +20.5 (*c* 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (m, 2H, $-CH_2$), 3.56 (m, 1H, –CH), 2.85 (d, 2H, *J* = 14.3 Hz, 2 × –CH), 1.84 (t, 1H, *J* = 6.7 Hz, –OH), 1.64–1.41 (m, 4H, 2 × $-CH_2$), 1.07 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.83 (s, 9H, 3 × $-CH_3$), 0.01 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.1, 61.6, 58. 56.0, 36.0, 28.0, 25.9, 23.7, −4.3, −4.8; IR (KBr): 3423, 2955, 2931, 2858, 1465, 1253, 1045, 835 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{13}H_{28}O_3SiNa$, 283.1705; found: 283.1718.

4.1.25. (3*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)hept-1-en-3-ol 36

To a stirred solution of **35** (2.3 g, 8.84 mmol) in CCl_4, Ph_3P (4.63 g, 17.69 mmol) and $NaHCO_3$ (0.2 g/g) were added and stirred at reflux for 30 min. The reaction mixture was evaporated and the residue was purified by column chromatography (60–120 silica gel, 0.2:9.8 EtOAc/*n*-hexane) to afford **35a** (1.77 g, 71%) as a colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (q, 1H, *J* = 6.0, 11.3 Hz, –CH), 3.61 (q, 1H, *J* = 5.2 Hz, –CH), 3.39 (q, 1H, *J* = 6.0, 11.3 Hz, –CH), 2.94 (m, 1H, –CH), 2.83 (t, 1H, *J* = 4.5 Hz, –CH), 1.69–1.45 (m, 4H, 2 × $-CH_2$), 1.13 (d, 3H, *J* = 6.0 Hz, $-CH_3$) 0.89 (s, 9H, 3 × $-CH_3$), 0.05 (s, 6H, 2 × $-CH_3$).

To a solution of **35a** (1.7 g, 6.10 mmol) in dry ether, sodium metal pieces (0.56 g, 24.40 mmol) were added and stirred at room temperature for 12 h. The reaction was quenched with a few drops of MeOH, evaporated, and the reaction mixture was extracted with EtOAc (2 × 50 mL). It was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), and evaporated. Purification of the residue by column chromatography (60–120 silica gel, 0.6:9.4 EtOAc/*n*-hexane) afforded **36** (1.1 g, 73%) as a colorless oil. $[\alpha]_D$ = −37.4 (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (m, 1H, olefinic), 5.11 (q, 2H, *J* = 14.8 Hz, olefinic), 4.02 (m, 1H, –CH), 3.83 (m, 1H, –CH), 1.60–1.37 (m, 4H, 2 × $-CH_2$), 1.06 (d, 3H, *J* = 5.4 Hz, $-CH_3$), 0.84 (s, 9H, 3 × $-CH_3$), 0.01 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 114.3, 73.1, 68.6, 35.1, 32.9, 26.0, 23.3, 18.0, −4.4, −4.8; IR (KBr): 3386, 2929, 2857, 1465, 1373, 1253, 1134, 1048, 833 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{13}H_{28}O_2SiNa$, 267.1756; found: 267.1759.

4.1.26. ((2*R*,5*R*)-5-(Benzyloxy)hept-6-en-2-yloxy)(*tert*-butyl)-dimethylsilane 37

To a stirred solution of **36** (1.05 g, 4.30 mmol) in dry CH_2Cl_2, Ag_2O (1.99 g, 8.60 mmol) was added and stirred at room temperature for 30 min. It was treated with BnBr (0.6 mL, 4.73 mmol) and stirred at reflux for 12 h. The reaction mixture was filtered through a pad of Celite, evaporated, and the residue was purified by column chromatography (60–120 silica gel, 0.4:9.6 EtOAc/*n*-hexane) to afford **37** (1.12 g, 78%) as a colorless liquid. $[\alpha]_D$ = −23.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.12 (m, 5H, $-C_6H_5$), 5.77–5.61 (heptet, 1H, *J* = 7.5, 10.3 Hz, olefinic), 5.19 (q, 2H, *J* = 4.1, 10.3 Hz, olefinic), 4.54, 4.30 (2d, 2H, *J* = 11.8 Hz, $-OCH_2$ Ar), 3.76–3.62 (m, 2H, 2 × –CH), 1.61–1.32 (m, 4H, 2 × $-CH_2$), 1.20 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.85 (s, 9H, 3 × $-CH_3$) 0.00 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 131.5, 128.5, 128.2, 127.6, 121.0, 72.7, 57.80, 55.60, 35.3, 30.2, 25.8, 23.8, 22.4, −4.4; IR (KBr): 3427, 2926, 2858, 1722, 1456, 1268, 1106 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{20}H_{34}O_2SiNa$, 357.2225; found: 357.2232.

4.1.27. (4*R*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)oct-2-enoate 38

Ozone was bubbled through a cooled (−78 °C) solution of **37** (1.1 g, 3.29 mmol) in CH_2Cl_2 (10 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (0.5 mL) and stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give the aldehyde.

The above-mentioned aldehyde in dry CH_2Cl_2 (5 mL) was treated with (*p*-toluenesulfonyl-ethoxycarbonylmethylene)triphenyl phosphorane (2.44 g, 6.58 mmol) dissolved in dry CH_2Cl_2 (5 mL) at 0 °C and stirred at room temperature for 4 h. Worked up as described for **33** and purification by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) afforded **38** (1.32 g, 71% for two steps) as a colorless liquid, $[\alpha]_D$ = +22.8 (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 7.27 (m, 7H, $-C_6H_5$, $-C_6H_4$), 6.63 (dd, 1H, *J* = 6.0, 15.8 Hz, olefinic) 5.72 (d, 1H, *J* = 15.8 Hz, olefinic), 4.46 (d, 1H, *J* = 12.0, benzylic $-CH_2$) 4.42 (t, 2H, *J* = 6.0 Hz, $-OCH_2$), 4.30 (d, 1H, *J* = 11.3 Hz, benzylic $-CH_2$), 3.82 (q, 1H, *J* = 5.2, 11.3 Hz, –CH) 3.69 (m, 1H, –CH), 3.39 (t, 2H, *J* = 6.7 Hz, $-CH_2SO_2$), 2.38 (s, 3H, $-CH_3$) 1.70–1.40 (m, 4H, 2 × $-CH_2$), 1.09 (d, 3H, *J* = 6.7 Hz, $-CH_3$), 0.84 (s, 9H, 3 × $-CH_3$) 0.00 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9, 129.95, 128.4, 128.1, 127.6, 120.4, 71.1, 68.3, 67.8, 57.4, 55.1, 35.0, 30.8, 25.8, 23.8, 21.6, –4.4; IR (Neat): 2924, 2855, 1723, 1655, 1459, 1266, 1179, 1045, 980 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{30}H_{44}O_6SSiNa$, 583.2525; found 583.2536.

4.1.28. (4*R*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-hydroxyoct-2-enoate 29

To a solution of **38** (1.25 g, 2.23 mmol) in CH_3CN (10 mL), TMSCl (0.04 g, 0.44 mmol) in CH_3CN (2 mL) was added followed by H_2O (0.04 g, 2.23 mmol) at 0 °C and stirred at room temperature for 1 h. The reaction was quenched with $NaHCO_3$ (0.2 g), and the reaction mixture was diluted with water (5 mL), and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), evaporated, and the residue was purified by column chromatography (60–120 silica gel 2.5.:7.5 EtOAc/*n*-hexane) to furnish **29** (0.88 g, 88%) as a syrup. $[\alpha]_D$ = −19.6 (*c* 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 7.36–7.23 (m, 7H, $-C_6H_5$, $-C_6H_4$), 6.65 (dd, 1H, *J* = 6.0, 15.8 Hz, olefinic), 5.76 (dd, 1H, *J* = 1.1, 15.8 Hz, olefinic), 4.49 (d, 1H, *J* = 11.7 Hz, benzylic –CH), 4.43 (t, 1H, *J* = 6.2, 12.2 Hz, $-OCH_2$), 4.34 (d, 1H, *J* = 11.8 Hz, benzylic –CH), 3.90 (q, 1H, *J* = 5.2, 1.7 Hz, –CH), 3.77–3.67 (m, 1H, –CH), 3.42 (t, 2H, *J* = 6.0, 12.2 Hz, $-OCH_2$), 2.40 (s, 3H, $-CH_3$), 1.76–1.32 (m, 4H, 2 × $-CH_2$), 1.14 (d, 3H, *J* = 6.2 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 149.5, 145.0, 137.6, 136.3, 129.9, 128.4, 128.0, 127.7, 127.6, 120.7, 77.5, 71.0, 67.5, 57.7, 55.0, 34.4, 30.8, 23.5, 21.5; IR (neat): 3375, 3059, 2925, 1722, 1656, 1596, 1491, 1318, 1143, 1086, 817 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{24}H_{30}O_6SNa$, 469.1660; found: 469.1681.

4.1.29. (1*R*,2*R*)-1,2-Bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diyl-dibenzoate 39

To a stirred solution of diol **30** (10 g, 37.87 mmol) and Et_3N (27 mL, 189.39 mmol) in dry CH_2Cl_2 (100 mL), benzoyl chloride (11.7 g, 83.33 mmol) was added at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 12 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed sequentially with H_2O (50 mL), 10% HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The combined extracts were dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 1:9 EtOAc/*n*-hexane) to afford **39** (13.85 g, 78%) as a white solid, mp: 82–85 °C; $[\alpha]_D$ = −112.7 (*c* 3.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.0 (t, 4H, *J* = 6.7 Hz, 13.5 Hz, $-C_6H_5$), 7.53 (t, 2H, *J* = 6.7, 14.3 Hz, $-C_6H_5$), 7.41 (t, 4H, *J* = 7.5, 15.1 Hz, $-C_6H_5$), 5.48 (d, 1H, *J* = 5.2 Hz, –CH), 4.88 (p, 1H, *J* = 6.0, 10.5 Hz, –CH), 4.37 (q, 2H, *J* = 6.0, 12.8 Hz, benzylic $-CH_2$), 4.11 (dd, 1H, *J* = 5.2, 11.3 Hz, –CH), 3.96 (p, 2H, *J* = 9.0, 15.8 Hz, benzylic $-CH_2$), 3.70 (q,1H, *J* = 6.7, 11.3 Hz, –CH), 1.52 (s, 3H, $-CH_3$), 1.44 (s, 3H, $-CH_3$), 1.34 (s, 3H, $-CH_3$), 1.31 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 165.4, 133.1, 129.8, 129.6, 129. 128.3, 128.3, 108.9, 99.8, 74.5, 70.5, 69.8, 66.2, 66.1, 62.1, 26.9,

26.5, 25.4, 20.4; IR (neat): 3433, 3062, 2991, 2896, 1727, 1600, 1453, 1378, 1206, 1112, 1067 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{26}H_{30}O_8Na$, 493.1838; found, 493.1835.

4.1.30. (1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)propane-1,2,3-triol 40

To a solution of diester **39** (13.8 g, 30.94 mmol) in dry ether (140 mL), H_5IO_6 (9.17 g, 40.22 mmol) was added at 0 °C and the reaction mixture was stirred for 6 h at room temperature for 6 h. Then, it was neutralized with $NaHCO_3$ (10 g), stirred for 30 min, filtered through a pad of Celite, and evaporated to give the crude aldehyde, which was used as such for the next reaction.

To a stirred suspension of LAH (2.35 g, 61.88 mmol) in dry THF (100 mL) a solution of the above-mentioned aldehyde in dry THF (30 mL) was added dropwise at 0 °C under a nitrogen atmosphere and the mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 0 °C, treated with saturated aq Na_2SO_4 (10 mL) solution, filtered, and the filtrate was dried (Na_2SO_4). It was evaporated and the residue was purified by column chromatography (60–120 silica gel, 7:3 EtOAc/*n*-hexane) to give **40** (2.4 g, 42%) as a white solid, mp: 65–67 °C, $[\alpha]_D$ = +11.1 (*c* 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.54–4.19 (br s, 3H, 3 × –OH), 4.11 (m, 2H, $–CH_2$), 3.98 (m, 1H, –CH), 3.80 (s, 1H, –CH), 3.70 (s, 2H, $–CH_2$), 3.56 (s, 1H, –CH), 1.38 (d, 6H, *J* = 15.4 Hz, 2 × $–CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.5, 75.5, 72.4, 71.0, 66.7, 64.2, 26.8, 25.2; IR (neat): 3433, 3063, 2996, 2896, 1727, 1603, 1453, 1318, 1204, 1170, 1067 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_8H_{16}O_5Na$, 215.0895; found: 215.0900.

4.1.31. (4*S*,5*R*)-4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxyphenyl)-1,3-dioxan-5-ol 41

To a stirred solution of **40** (4.75 g, 24.73 mmol) and PPTS (0.02 g, 0.08 mmol) in dry CH_2Cl_2 (50 mL), anisaldehyde dimethylacetal (9 g, 49.47 mmol) was added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was neutralized with Et_3N, the solvent was evaporated, and the residue was purified by column chromatography (60–120 silica gel, 2:8 EtOAc/*n*-hexane) to give **41** (5.5 g, 71%) as a yellowish red syrup, $[\alpha]_D$ = +16.6 (*c* 0.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, 2H, *J* = 8.3 Hz, $–C_6H_4$), 6.85 (t, 2H, *J* = 8.3, 12.8 Hz, $–C_6H_4$), 5.83 (s, 1H, benzylic –CH) 4.21 (p, 2H, *J* = 7.5, 12.8 Hz, $–CH_2$), 4.07 (m, 3H, 3 × –CH), 3.98 (q, 2H, *J* = 5.2, 11.3 Hz, $–CH_2$), 3.78 (s, 3H, $–OCH_3$), 3.46 (br s, –OH), 1.37 (s, 3H, $–CH_3$), 1.31 (s, 3H, $–CH_3$); IR (neat): 3050, 2950, 1600, 1580, 1126, 1073, 750 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{16}H_{22}O_6Na$, 333.1314; found: 333.1317.

4.1.32. (2*R*,3*S*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(4-methoxy-benzyloxy)-propane-1,2-diol 42

To a stirred solution of **41** (5.4 g, 17.41 mmol) in dry CH_2Cl_2 (30 mL), DIBAL-H (25 mL, 34.83 mmol, 20% solution in toluene) was added dropwise at 0 °C and stirred at the same temperature for 2 h. The reaction mixture was worked up as described for **34** and purified by column chromatography (60–120 silica gel, 4:6 EtOAc/*n*-hexane) to afford **42** (4.07 g, 75%) as a syrup. $[\alpha]_D$ = +55.4 (*c* 0. 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, 2H, *J* = 7.5 Hz, $–C_6H_4$), 6.84 (d, 2H, *J* = 8.3 Hz, $–C_6H_4$), 4.58 (q, 1H, *J* = 6.0, 14.3 Hz, –CH), 4.47 (s, 1H, –CH), 4.07–3.87 (m, 2H, benzylic $–CH_2$), 3.78 (s, 3H, $–OCH_3$), 3.69 (m, 4H, 2 × $–CH_2$), 3.45 (q, 1H, *J* = 6.0, 9.0 Hz, –CH), 2.97 (br s, –OH), 2.7 (br s, –OH), 1.34 (q, 6H, *J* = 5.2, 7.5 Hz, 2 × $–CH_3$), ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 130.2, 129.9, 114.2, 80.7, 78.2, 73.1, 71.7, 71.2, 55.0, 27.3, 27.0; IR (neat): 3412, 2924, 2855, 1610, 1512, 1487, 1376, 1275, 1170, 1114, 1067 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{16}H_{24}O_6Na$, 335.1470; found: 335.1454.

4.1.33. (2*S*,3*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-hydroxy3-(4-methoxybenzyloxy)-propyl benzenesulfonate 43

To a cooled (0 °C) solution of diol **42** (4.0 g, 12.82 mmol) and Et_3N (3.88 g, 38.46 mmol) in CH_2Cl_2 (60 mL), *p*-TsCl (2.77 g, 14.10 mmol) was added in a single portion at 0 °C and the mixture was stirred at room temperature for 14 h. The reaction was worked up as described for **15** and purified by column chromatography (60–120 silica gel, 1:4 EtOAc/*n*-hexane). First eluted was ditosylate **43a** (0.05 g, 8%) as a yellow syrup. ^1H NMR (200 MHz, $CDCl_3$): δ 7.80, 7.75 (2d, 4H, *J* = 8.0 Hz, 2 × $–C_6H_4$), 7.30 (m, 4H,, 2 × $–C_6H_4$) 7.22 (t, 2H, *J* = 12.4 Hz, $–C_6H_4$), 6.75 (d, 2H, *J* = 8.8 Hz, $–C_6H_4$), 4.42 (s, 2H, benzylic $–CH_2$), 4.28 (d, 1H, *J* = 8.0 Hz, –CH), 4.11 (p, 2H, *J* = 6.6, 12.4 Hz, $–CH_2$), 3.66 (s, 3H, $–OCH_3$), 3.54 (d, 2H, *J* = 6.6 Hz, $–CH_2$), 3.48 (dd, 1H, *J* = 2.2, 10.2 Hz, –CH), 3.42 (dd, 1H, *J* = 5.2, 9.5 Hz, –CH), 2.44, 2.40 (s, 6H, 2 × Ar–CH_3), 1.58 (s, 3H, $–CH_3$), 1.33 (d, 3H, *J* = 2.2 Hz, $–CH_3$).

Second eluted was **43** (4.3 g, 71%) as a yellow syrup, $[\alpha]_D$ = −24.5 (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (d, 2H, *J* = 8.0 Hz, $–C_6H_4$), 7.26 (t, 4H, *J* = 12.4, 19.1 Hz, $–C_6H_4$), 6.92 (d, 2H, *J* = 8.8 Hz, $–C_6H_4$), 4.48 (s, 2H, benzylic $–CH_2$), 4.29 (d, 1H, *J* = 8.0 Hz, –CH), 4.14 (p, 2H, *J* = 6.6, 12.4 Hz, $–CH_2$), 3.81 (s, 3H, $–OCH_3$), 3.74 (d, 2H, *J* = 6.6 Hz, $–CH_2$), 3.61 (dd, 1H, *J* = 2.2, 10.2 Hz, –CH), 3.47 (dd, 1H, *J* = 5.1, 9.5 Hz, –CH), 2.43 (s, 3H, Ar–CH_3), 1.58 (s, 3H, $–CH_3$), 1.33 (d, 3H, *J* = 2.2 Hz, $–CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 144.7, 132.8, 129.7, 129.4, 128.0, 113.8, 110.0, 76.6, 76.0, 73.1, 71.6, 70.7, 69.8, 55.2, 26.9, 26.7, 21.6; IR (neat): 3444, 2924, 2855, 1610, 1512, 1457, 1351, 1247, 1149 cm^{-1}; ESIMS: 489 $(M+Na)^+$.

4.1.34. 1(1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxybenzyloxy) propan-2-ol 44

To a stirred solution of **43** (4.2 g, 8.89 mmol) in dry dimethyl sulfoxide (20 mL), $NaBH_4$ (0.67 g, 17.79 mmol) was added at 0 °C and the reaction mixture was stirred for 10 min at 160 °C. It was neutralized with H_2O (10 mL) and stirred for another 10 min at room temperature. The reaction mixture was diluted with EtOAc (100 mL), washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated. The crude residue was purified by column chromatography (60–120 silica gel, 8.5:1.5 EtOAc/*n*-hexane) to afford **44** (2.42 g, 92%) as a colorless syrup. $[\alpha]_D$ = +21.8 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, 2H, *J* = 9.0 Hz, $–C_6H_4$), 6.81 (d, 2H, *J* = 8.3 Hz, $–C_6H_4$), 4.47 (s, 2H, benzylic $–CH_2$), 4.02 (p, 1H, *J* = 6.0, 12.0 Hz, –CH), 3.79 (s, 3H, $–OCH_3$), 3.75–3.64 (m, 1H, –CH), 3.59 (dd, 1H, *J* = 3.0, 9.0 Hz, –CH), 3.43 (p, 2H, *J* = 6.0, 9.8 Hz, $–CH_2$), 2.29 (d, 1H, *J* = 6.0, –OH),1.35 (s, 3H, $–CH_3$), 1.31 (s, 3H, $–CH_3$), 1.21 (d, 3H, *J* = 6.0, $–CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 129.6, 114.1, 75.4, 73.2, 71.1, 71.0, 66.8, 55.2, 29.6, 19.3; IR (neat): 3470, 2983, 2927, 1612, 1513, 1458, 1374, 1248, 1173, 1090, 1042 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{16}H_{24}O_5Na$, 319.1521; found: 319.1527.

4.1.35. (2*R*,3*S*,4*R*)-3-(4-Methoxybenzyloxy)pentane-1,2,4-triol 45

A mixture of **44** (2.35 g, 7.93 mmol) in 60% aq AcOH (20 mL) was stirred at room temperature for 12 h. It was neutralized with anhydrous $NaHCO_3$, extracted with EtOAc (2 × 50 mL), dried (Na_2SO_4), evaporated, and the residue was purified by column chromatography (60–120 silica gel, 8:2 EtOAc/*n*-hexane) to afford **45** (1.8 g, 88%) as a colorless syrup. $[\alpha]_D$ = +8.75 (*c* 0.57, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J* = 8.0 Hz, $–C_6H_4$), 6.86 (d, 2H, *J* = 8.0 Hz, $–C_6H_4$), 4.47 (s, 2H, benzylic $–CH_2$), 3.95 (m, 1H, –CH), 3.83 (m, 2H, $–CH_2$), 3.82 (s, 3H, $–OCH_3$), 3.64–3.55 (m, 2H, $–CH_2$), 3.14 (s, 1H, –OH), 2.92 (br d, 2H, 2-OH), 1.20 (d, 3H, *J* = 6.5 Hz, $–CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 137.5, 128.8, 128.1, 127.8, 127.1, 87.3, 83.2, 80.1, 77.0, 73.9, 71.3, 35.9; HRMS

m/z [M+Na]$^+$: calculated for $C_{13}H_{20}O_5Na$, 279.1208; found: 279.1200.

4.1.36. (4*R*,5*R*,*E*)-Ethyl 5-hydroxy-4-(4-methoxybenzyloxy)hex-2-enoate 46

To a solution of triol **45** (1.75 g, 6.83 mmol) in MeOH/H_2O (5:1, 20 mL), $NaIO_4$ (2.92 g, 13.67 mmol) was added and stirred at room temperature for 3 h. MeOH was removed and the residue was extracted with CH_2Cl_2 (2 × 50 mL). It was dried (Na_2SO_4) and concentrated to give aldehyde (1.53 g) in quantitative yield as a yellow liquid, which was used as such for the next reaction

To a solution of the above-mentioned aldehyde (1.53 g, 5.12 mmol) in dry CH_2Cl_2 (10 mL) (ethoxycarbonylmethylene)triphenyl phosphorane (3.36 g, 10.24 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added at 0 °C and stirred at room temperature for 4 h. Then the organic layer was evaporated and the residue was purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to afford ester **46** (1.45 g, 72%) as a colorless liquid. $[\alpha]_D = -197.5$ (*c* 1.2, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, 2H, *J* = 8.0 Hz, $-C_6H_4$), 6.82 (d, 1H, *J* = 8.8 Hz, $-C_6H_4$), 6.76 (dd, 1H, *J* = 5.1 Hz, olefinic), 6.07 (d, 1H, *J* = 15.4 Hz, olefinic), 4.53 (d, 1H, *J* = 11.0 Hz, benzylic –CH), 4.22 (sextet, 3H, *J* = 6.6, 13.9 Hz, benzylic –CH, $-CH_2$), 3.79 (s, 3H, $-OCH_3$), 3.68 (q, 2H, *J* = 5.1, 11.0 Hz, 2 × –CH), 2.66 (s, 1H, –OH), 1.32 (t, 3H, *J* = 7.3, 14.6 Hz, $-CH_3$), 1.10 (d, 3H, *J* = 5.8 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 159.4, 144.3, 129.6, 124.6, 114.2, 83.1, 71.2, 69.4, 60.6, 55.2, 18.3, 14.1; IR (neat): 3479, 2978, 2935, 1717, 1655, 1513, 1461, 1249, 1176, 1035, 987 cm^{-1}; HRMS *m/z* [M+Na]$^+$: calculated for $C_{16}H_{22}O_5Na$, 317.1388; found: 317.1395.

4.1.37. (4*R*,5*R*,*E*)-Ethyl 5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy) hex-2-enoate 47

To a mixture of alcohol **46** (1.4 g, 4.76 mmol) and imidazole (0.97 g, 14.28 mmol) in dry CH_2Cl_2 (15 mL), TBSCl (0.78 g, 5.23 mmol) was added at 0 °C under a nitrogen atmosphere and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (60–120 silica gel, 5:95 EtOAc/*n*-hexane) to furnish **47** (1.75 g, 90%) as a yellow syrup. $[\alpha]_D = -6.8$ (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 6.85 (dd, 1H, *J* = 4.5, 15.8 Hz, olefinic), 6.81 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 6.05 (d, 1H, *J* = 15.8 Hz, olefinic), 4.55–4.31 (q, 2H, *J* = 11.3, 59.6 Hz, benzylic $-CH_2$), 4.22 (sextet, 2H, *J* = 6.6, 13.9 Hz, $-CH_2$)3.85 (p, 2H, *J* = 6.0, 11.3 Hz, 2 × –CH), 3.79 (s, 3H, $-OCH_3$), 1.30 (t, 3H, *J* = 7.3, 14.6 Hz, $-CH_3$), 1.07 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.86 (s, 9H, 3 × $-CH_3$), 0.01 (d, 6H, *J* = 5.2 Hz, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 159.1, 145.7, 130.0, 129.2, 122.5, 113.7, 81.6, 71.2, 69.6, 55.3, 51.6, 25.9, 18.7, 17.9, −4.8, −4.8; IR (neat): 2952, 2890, 1726, 1658, 1513, 1464, 1378, 1170, 1105, 1035 cm^{-1}; HRMS *m/z* [M+Na]$^+$: calculated for $C_{22}H_{36}O_5SiNa$ 431.2073; found: 431.2085.

4.1.38. (4*R*,5*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)hex-2-enoic acid 28

A mixture of **47** (0.9 g, 2.20 mmol) and 0.5 N NaOH (10 mL) in MeOH (10 mL) was stirred at room temperature for 24 h and then neutralized with HCl (0.5 M, 10 mL). The reaction mixture was extracted with EtOAc (3 × 30 mL), the combined extracts were dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 2:8 EtOAc/*n*-hexane) to give **28** (0.79 g, 94%) as a colorless oil. $[\alpha]_D = -84.8$ (*c* 4.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 6.99 (dd, 1H, *J* = 4.5, 15.8 Hz, olefinic), 6.84 (d, 2H, *J* = 9.0 Hz, $-C_6H_4$), 6.03 (d, 1H, *J* = 15.8 Hz, olefinic), 4.53, 4.34 (2d, 2H, *J* = 11.3 Hz, benzylic $-CH_2$), 3.87 (q, 2H, *J* = 4.5, 9.0 Hz, 2 × –CH), 3.8 (s, 3H, $-OCH_3$), 1.05 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.86 (s, 9H, 3 × $-CH_3$), 0.00 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6,129.9, 128.4, 128.1, 127.7, 120.7, 77.8, 71.1, 67.7, 57.7, 55.0, 34.5, 30.9, 23.5, 21.6; IR (neat): 3435, 2930, 2856, 1714, 1607, 1512, 1462, 1170, 1105, 1033 cm^{-1}; HRMS *m/z* [M+Na]$^+$: calculated for $C_{20}H_{32}O_5SiNa$, 403.1916; found: 403.1929.

4.1.39. (4*R*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-((4*R*,5*R*,*E*)-5-(*tert*-butyldimethyl silyloxy)-4-(4-methoxybenzyloxy)hex-2-enoyloxy)oct-2-enoate 48

To a solution of acid **28** (0.75 g, 1.99 mmol) and Et_3N (0.50 g, 4.97 mmol) in dry THF (6 mL), 2,4,6-trichlorobenzoyl chloride (0.60 g, 2.48 mmol) in dry THF (2 mL) was added and the reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. It was filtered and the filtrate was evaporated. The resulting anhydride was dissolved in toluene (3 mL), treated with alcohol **29** (0.75 g, 1.65 mmol) in toluene (3 mL) and DMAP (0.40 g, 3.31 mmol) in toluene (2 mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to afford a residue, which was purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to give **48** (1.05 g, 77%) as an oil, $[\alpha]_D = -50.6$ (*c* 0.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J* = 8.1 Hz, $-C_6H_4$), 7.31 (q, 7H, *J* = 7.9, 14.7 Hz, $-C_6H_5$, $-C_6H_4$), 7.19 (d, 2H, *J* = 8.4 Hz, $-C_6H_4$), 6.87 (dd, 1H, *J* = 4.1, 15.8 Hz, olefinic), 6.82 (d, 2H, *J* = 8.6 Hz, $-C_6H_4$), 6.65 (dd, 1H, *J* = 6.0, 16.9 Hz, olefinic), 6.01 (d, 1H, *J* = 15.8 Hz, olefinic), 5.77 (d, 1H, *J* = 15.8 Hz, olefinic), 4.93 (sext., 1H, *J* = 6.2, 11.8 Hz, –CH), 4.45 (t, 2H, *J* = 6.0, 12.0 Hz, benzylic $-CH_2$), 4.37–4.30 (m, 4H, benzylic $-CH_2$, 2 × –CH), 3.99–3.82 (m, 3H, $-OCH_2$, –CH), 3.79 (s, 3H, $-OCH_3$), 3.43 (t, 2H, *J* = 6.2, 12.4 Hz, $-CH_2SO_2$), 2.41 (s, 3H, $-CH_3$), 1.70–1.52 (m, 4H, 2 × $-CH_2$), 1.25 (d, 1H, *J* = 6.4 Hz, $-CH_3$), 1.06 (d, 1H, *J* = 5.6 Hz, $-CH_3$), 0.87 (s, 9H, 3 × $-CH_3$), 0.00 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 166.0, 149.1, 145.53, 129.9, 129.2, 128.4, 128.1, 127.7, 127.6, 123.0, 120.8, 113.7, 96.1, 81.5, 77.4, 71.3, 71.0, 70.6, 69.7, 57.7, 55.1, 31.5, 30.6, 25.8, 21.6, 20.0, 18.8, –4.7; IR (neat): 3423, 2924, 2854, 1726, 1604, 1510, 1458, 1382, 1250, 1216, 1143, 1084, 1032, 812, 757 cm^{-1}; HRMS *m/z* [M+Na]$^+$: calculated for $C_{44}H_{60}O_{10}SSiNa$, 831.3574; found: 831.3587.

4.1.40. (4*R*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-((4*R*,5*R*,*E*)-5-hydroxy-4-(4-methoxy benzyloxy)hex-2-enoyloxy)oct-2-enoate 49

To a solution of **48** (1.0 g, 1.23 mmol) in CH_3CN (8 mL) TMSCl (0.26 g, 2.47 mmol) in CH_3CN (2 mL) followed by H_2O (0.02 g, 1.23 mmol) was added at 0 °C and stirred at room temperature for 1 h. Worked up as described for **29** and purified by column chromatography (60–120 silica gel, 3:7 EtOAc/*n*-hexane) to furnish **49** (0.75 g, 87%) as a syrup, $[\alpha]_D = -36.5$ (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 7.29 (q, 7H, *J* = 8.12, 15.67 Hz, $-C_6H_5$, $-C_6H_4$), 7.18 (d, 2H, *J* = 7.5 Hz, $-C_6H_4$), 6.81 (d, 2H, *J* = 8.6 Hz, $-C_6H_4$), 6.75 (dd, 1H, *J* = 6.6, 15.8 Hz, olefinic), 6.67 (dq, 1H, *J* = 2.0, 5.8 Hz, olefinic), 5.99 (d, 1H, *J* = 15.6 Hz, olefinic), 5.78 (d, 1H, *J* = 16.0 Hz, olefinic), 4.92 (m, 1H, –CH), 4.54 (t, 2H, *J* = 11.5, 21.7 Hz, benzylic $-CH_2$), 4.43 (t, 2H, *J* = 6.0, 12.2 Hz, $-OCH_2$), 4.31 (t, 2H, *J* = 3.0, 11.8 Hz, benzylic $-CH_2$), 3.90 (sext, 1H, *J* = 3.9, 9.4 Hz, –CH), 3.78 (s, 3H, $-OCH_3$), 3.66 (p, 2H, *J* = 7.1, 10.1 Hz, 2 × –CH), 3.40 (t, 1H, *J* = 6.2, 12.4 Hz, $-CH_2SO_2$), 2.14 (s, 3H, $-CH_3$), 1.73–1.53 (m, 4H, 2 × $-CH_2$), 1.25 (t, 3H, *J* = 6.2, 12.2 Hz, $-CH_3$), 1.11 (d, 3H, *J* = 5.4 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 159.8, 149.4, 144.7, 137.9, 137.1, 129.8, 129.4, 128.4, 128.2, 127.8, 127.6, 124.6, 121.0, 113.9, 96.2, 83.1, 77.1, 71.3, 71.0, 70.9, 69.4, 57.7, 55.1, 55.0, 31.4, 30.7, 21.6, 20.1, 18.5; IR (neat): 3505, 2925, 2856, 1717, 1654, 1513, 1456, 1380, 1249, 1173, 986 cm^{-1}; HRMS *m/z* [M+Na]$^+$: calculated for $C_{38}H_{46}O_{10}SNa$, 717.2709; found: 717.2711.

4.1.41. (4*R*,7*R*,*E*)-4-(Benzyloxy)-7-((4*R*,5*R*,*E*)-5-hydroxy-4-(4-methoxybenzyloxy) hex-2-enoyloxy)oct-2-enoic acid 27

To a solution of **49** (0.7 g, 1.0 mmol) in dry benzene (5 mL), a solution of DBN (0.12 g, 1.0 mmol) in dry benzene (2 mL) was added and the mixture was stirred at room temperature for 12 h under nitrogen atmosphere. The reaction mixture was poured into ether and water (1:1, 20 mL) and the aqueous layer separated was acidified with 1 M HCl and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (60–120 silica gel, 4.5:5.5 EtOAc/*n*-hexane) to afford **27** (0.39 g, 78%) as a yellow syrup. $[\alpha]_D = -46.8$ (*c* 0.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 5H, $-C_6H_5$), 7.25 (d, 2H, *J* = 8.0 Hz, $-C_6H_4$), 6.90 (dd, 1H, *J* = 5.8, 15.4 Hz, olefinic), 6.80 (d, 2H, *J* = 8.8 Hz, $-C_6H_4$), 6.74 (dd, 1H, *J* = 5.1, 15.4 Hz, olefinic), 5.97 (dd, 2H, *J* = 2.9, 15.4 Hz, olefinic), 4.92 (q, 1H, *J* = 9.5, 15.4 Hz, –CH), 4.60 (dd, 2H, *J* = 2.9, 11.7 Hz, benzylic $-CH_2$), 4.30 (q, 2H, *J* = 11.7, 18.3 Hz, benzylic $-CH_2$), 3.97 (m, 1H, –CH), 3.78 (s, 3H, $-OCH_3$), 3.66 (d, 2H, *J* = 4.4 Hz, 2 × –CH), 1.72–1.55 (m, 4H, 2 × $-CH_2$), 1.25 (t, 3H, *J* = 5.8 Hz, $-CH_3$), 1.11 (d, 3H, *J* = 4.4 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 165.2, 159.2, 149.9, 144.2, 137.6, 129.5, 129.3, 128.2, 127.5, 124.5, 121.6, 113.7, 82.8, 77.4, 71.1, 69.3, 55.0, 31.2, 30.4, 19.8, 18.1; IR (neat): 3540, 3020, 2978, 1713, 1655, 1514, 1452, 1176, 1069, 1034 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{29}H_{36}O_8Na$, 535.2307; found: 535.2305.

4.1.42. (3*E*,5*R*,6*R*,9*E*,11*R*,14*R*)-11-(Benzyloxy)-5-(4-methoxybenzyloxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione 50

To a stirred solution of **27** (0.35 g, 0.70 mmol) and Et_3N (0.21 g, 2.11 mmol) in dry THF (3 mL), a solution of 2, 4, 6-trichlorobenzoyl chloride (0.25 g, 1.05 mmol) in dry THF (1 mL) was added. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere and evaporated to afford the mixed anhydride. It was diluted with toluene (10 mL) and filtered quickly through Celite. The filtrate was added dropwise to a stirred solution of DMAP (0.07 g, 0.63 mmol) in toluene (490 mL) (total volume used for this operation was 500 mL) at 90 °C over a period of 8 h. After the complete addition, the reaction mixture was stirred at 100 °C for 2 h. It was cooled, washed with 7% aq $NaHCO_3$ (40 mL), 2 M aq HCl (40 mL), and brine (40 mL), and dried (Na_2SO_4). The organic layer was evaporated and the obtained residue was purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to give **50** (0.17 g, 52%) as a syrup. $[\alpha]_D = -52.6$ (*c* 0.16, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (m, 5H, $-C_6H_5$), 7.23 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 6.90 (dd, 1H, *J* = 5.8, 15.4 Hz, olefinic), 6.85 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 6.72 (dq, 2H, *J* = 3.3, 15.7 Hz, olefinic), 5.98 (q, 1H, *J* = 15.7, 39.8 Hz, olefinic), 5.32–5.00 (m, 2H, 2 × –CH), 4.61 (d, 1H, *J* =11.6 Hz, –CH), 4.39 (q, 2H, *J* =12.4, 31.5 Hz, benzylic $-CH_2$), 4.20 (d, 2H, *J* = 11.6 Hz, benzylic $-CH_2$), 4.01 (s, 1H, –CH), 3.79 (s, 3H, $-OCH_3$), 2.15–1.49 (m, 4H, 2 × $-CH_2$), 1.34 (d, 3H, *J* = 6.6 Hz, $-CH_3$), 1.18 (d, 3H, *J* = 6.6 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 159.4, 150.2, 144.0, 137.9, 129.7, 129.2, 128.2, 127.5, 127.2, 123.5, 121.9, 113.7, 78.3, 76.9, 76.4, 71.3, 70.5, 70.2, 69.4, 55.1, 27.2, 26.2, 17.5, 16.1; IR (neat): 3429, 2924, 2854, 1719, 1611, 1513, 1458, 1170, 1063 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{29}H_{34}O_7Na$, 517.2202; found: 517.2213.

4.1.43. (3*E*,5*R*,6*R*,9*E*,11*R*,14*R*)-11-(Benzyloxy)-5-hydroxy-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione 51

To a solution of **50** (0.12 g, 0.24 mmol) in a mixture of CH_2Cl_2 (1.9 mL) and H_2O (0.1 mL), DDQ (0.08 g, 0.32 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was filtered through Celite, dried (Na_2SO_4), and evaporated to give the residue, which was purified by column chromatography (60–120 silica gel, 1:3 EtOAc/*n*-hexane) to afford **51** (0.06 g, 68%) as a white solid, mp: 139–141 °C; $[\alpha]_D = +31.0$ (*c* 0.12, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.34–7.19 (m, 5H, $-C_6H_5$), 6.85 (d, 1H, *J* = 5.8 Hz, olefinic), 6.70 (dt, 2H, *J* = 5.8, 4.1 Hz, olefinic), 6.01 (dq, 1H, *J* = 1.6 Hz, olefinic), 5.29 (dq, 2H, *J* = 1.6, 6.6 Hz, –CH), 5.15 (hept, 1H, *J* = 2.4, 5.8 Hz, –CH), 4.45 (q, 2H, *J* = 11.6, 30.7 Hz, benzylic $-CH_2$), 4.37 (s, 1H, –CH), 4.22 (t, 1H, *J* = 4.9 Hz, –CH), 2.18–1.71 (m, 2H, $-CH_2$), 1.64–1.48 (m, 2H, $-CH_2$), 1.42 (d, 3H, *J* = 6.6 Hz, $-CH_3$), 1.17 (d, 3H, *J* = 6.6 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 150.6, 146.7, 137.9, 128.3, 127.6, 127.3, 122.2, 121.8, 96.1, 73.2, 71.0, 70.6, 69.4, 27.2, 26.0, 17.4,15.9; IR (KBr): 3404, 2923, 2853, 1717, 1459, 1257, 1172, 1052 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{21}H_{26}O_6Na$, 397.1621; found: 397.1627.

4.1.44. (3*E*,6*R*,9*E*,11*R*,14*R*)-11-(Benzyloxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,5,8-trione 52

To a stirred solution of **51** (0.05 g, 0.13 mmol) in dry CH_2Cl_2 (2 mL) Dess–Martin periodinane (0.08 g, 0.20 mmol) was added at 0 °C and stirred at room temperature for 12 h. The reaction mixture was neutralized with saturated aq $NaHCO_3$ solution (5–6 drops), stirred for another 10 min, and diluted with CH_2Cl_2 (50 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to give **52** (0.04 g, 80%) as a white semi solid. $[\alpha]_D = -31.2$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.38 (s, 5H, $-C_6H_5$) 7.32 (d, 1H, *J* = 16.1 Hz, olefinic), 7.00 (dd, 1H, *J* = 4.4, 16.1 Hz, olefinic), 6.47 (d, 1H, *J* = 16.1 Hz, olefinic), 6.14 (d, 1H, *J* = 15.4 Hz, olefinic), 5.30 (q, 1H, *J* = 7.3, 14.6, –CH), 5.05 (t, 1H, *J* = 6.6, 13.2, –CH), 4.51 (q, 2H, *J* = 11.7, 19.1 Hz., benzylic $-CH_2$), 4.51 (d, 1H, *J* = 7.4 Hz., –CH), 4.22 (d, 1H, *J* = 3.6 Hz, –CH), 1.96–1.78 (m, 4H, 2 × $-CH_2$), 1.52 (d, 3H, *J* = 7.3 Hz, $-CH_3$), 1.25 (d, 3H, *J* = 5.8 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 166.7, 164.0, 150.4, 137.7, 135.2, 131.1, 128.4, 127.7, 120.7, 77.4, 76.5, 75.5, 71.9, 70.7, 28.0, 27.9, 18.4, 16.3; IR (neat): 3446, 2923, 2853, 1719, 1633, 1454, 1260, 1078, 982 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{21}H_{24}O_6Na$, 395.1460; found: 395.1470.

4.1.45. (3*E*,6*R*,9*E*,11*R*,14*R*)-11-Hydroxy-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,5,8-trione 2

To a stirred solution of **52** (0.02 g, 0.06 mmol) in CH_2Cl_2 (1 mL), $TiCl_4$ (0.01 g, 0.06 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (60–120 silica gel, 1:3 EtOAc/*n*-hexane) to afford **2** (0.02 g, 79%) as a colorless syrup, $[\alpha]_D = -55.3$ (*c* 0.25, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, 1H, *J* = 16.6 Hz, H-3), 7.06 (dd, 1H, *J* = 3.7, 15.8 Hz, H-4), 6.40 (d, 1H, *J* = 15.8 Hz, H-10), 6.10 (dd, 1H, *J* = 15.8 Hz, H-9), 5.29 (q, 1H, *J* = 7.5, 14.3 Hz, H-6), 5.00 (p, 1H, *J* = 4.5, 10.5 Hz, H-14), 4.49 (d, 1H, *J* = 6.0 Hz, H-11), 2.02–1.69 (m, 2H, H-13) 1.67–1.36 (m, 2H, H-12), 1.53 (d, 3H, *J* = 7.5 Hz, H-15), 1.27 (d, 3H, *J* = 6.7 Hz, H-16); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 165.5, 163.2, 151.3, 135.7, 130.8, 119.6, 75.5, 72.2, 70.3, 31.0, 29.6, 28.2, 18.9; IR (neat): 3448, 2853, 1722, 1642, 1456, 1338, 1220, 1165, 1066 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{14}H_{18}O_6Na$, 305.1001; found: 305.1001.

4.1.46. (3*E*,5*R*,6*R*,9*E*,11*R*,14*R*)-5,11-Dihydroxy-6,14-dimethyl-1,7-dioxacyclotetra deca-3,9-diene-2,8-dione 3

To a stirred solution of **50** (0.04 g, 0.08 mmol) in CH_2Cl_2 (1 mL), $TiCl_4$ (0.02 g, 0.08 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C and

stirred at room temperature for 2 h. It was worked up as described for **2** and the residue was purified by column chromatography (60–120 silica gel, 2:3 EtOAc/*n*-hexane) to afford **3** (0.02 g, 78%) as a white solid, m. p: 165–168 °C; $[\alpha]_D = -15.7$ (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 6.81 (t, 1H, *J* = 4.3, 7.3 Hz, H-10), 6.77 (t, 1H, *J* = 4.3, 7.3 Hz, H-4), 6.16 (dd, 1H, *J* = 1.4, 16.1 Hz, H-3), 5.90 (dd, 1H, *J* = 2.1, 16.1 Hz, H-9), 5.26 (dq, 1H, *J* = 2.1, 6.5 Hz, H-6), 5.24–5.17 (m, 1H, H-14), 4.63 (s, 1H, H-5), 4.45 (s, 1H, H-11), 3.70 (br s, 2-OH), 2.06–1.96 (m, 2H, H-13), 1.75–1.48 (m, 2H, H-12), 1.44 (d, 3H, *J* = 6.5 Hz, H-15), 1.20 (d, 3H, *J* = 6.5 Hz, H-16); ^{13}C NMR (100 MHz, MeOH-d_4): δ 167.8, 167.6, 153.4, 149.4, 122.9, 121.5, 73.8, 72.8, 70.9, 70.5, 29.2, 26.8, 17.6, 16.3; IR (neat): 3423, 2933, 1725, 1691, 1655, 1453, 1393, 1206, 1143, 1055 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{14}H_{20}O_6Na$, 307.1152; found: 307.1154.

4.1.47. ((2*S*,3*S*)-3-((*R*)-3-(*tert*-Butyldimethylsilyloxy)butyl)oxiran-2-yl)methanol 53

To a cooled (−20 °C) suspension of activated, powdered 4 Å MS (0.75 g) in CH_2Cl_2 (10 m), (+) DIPT (0.30 g, 1.31 mmol), $Ti(O^iPr)_4$ (0.18 g, 0.65 mmol), and cumene hydroperoxide (2.01 g, 13.11 mmol) were added sequentially and stirred for 20 min. A solution of alcohol **34** (1.6 g, 6.55 mmol) in CH_2Cl_2 (5 mL) was added at −20 °C and the resulting mixture was stirred at the same temperature for 3 h. The reaction was worked up as described for **35** and purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to give **53** (1.23 g, 72%) as a colorless liquid. $[\alpha]_D = -84.1$ (*c* 0.62, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (m, 2H, $-CH_2$), 3.54 (m, 1H, –CH), 2.85 (d, 2H, *J* = 14.3 Hz, 2 × –CH), 1.84 (t, 1H, *J* = 6.7 Hz, –OH), 1.64–1.41 (m, 4H, 2 × $-CH_2$), 1.07 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.83 (s, 9H, 3 × $-CH_3$), 0.01 (s, 6H, 2 × $-CH_3$); IR (neat): 3430, 2939, 2861, 1462, 1373, 1252, 1134, 1045, 834 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{13}H_{28}O_3SiNa$, 283.1729; found: 283.1717.

4.1.48. (3*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)hept-1-en-3-ol 54

To a solution of **53** (1.2 g, 4.61 mmol) in CCl_4 (6 mL), Ph_3P (1.81 g, 6.92 mmol) and $NaHCO_3$ (0.2 g/g.) were added and stirred at reflux for 30 min. The reaction was worked up as described for **35a** and purified by column chromatography (60–120 silica gel, 0.2:9.8 EtOAc/*n*-hexane) to afford **53a** (0.85 g, 66%) as a colorless syrup. ^1H NMR (200 MHz, $CDCl_3$): δ 3.85 (q, 1H, *J* = 6.0, 11.3 Hz, –CH), 3.61 (q, 1H, *J* = 5.2, 11.3 Hz, –CH), 3.39 (q, 1H, *J* = 6.0, 11.3 Hz, –CH), 2.94 (t, 1H, *J* = 5.2 Hz, –CH), 2.83 (t, 1H, *J* = 4.5 Hz, –CH), 1.67–1.43 (m, 4H, 2 × $-CH_2$), 1.13 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.89 (s, 9H, 3 × $-CH_3$), 0.05 (s, 6H, 2 × $-CH_3$).

To a solution of epoxy chloride **53a** (0.8 g, 2.87 mmol) in dry ether (10 mL), sodium metal pieces (0.25 g, 11.48 mmol) were added at room temperature and stirred for 12 h. It was worked up as described for **36** and purified by column chromatography (60–120 silica gel, 0.6:9.4 EtOAc/*n*-hexane) to afford **54** (0.52 g, 75%) as a colorless oil. $[\alpha]_D = -22.5$ (*c* 0.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (m, 1H, olefinic), 5.11 (q, 2H, *J* = 14.8, 10.6 Hz, olefinic), 4.08 (br s, 1H, –CH), 3.82 (m, 1H, –CH), 1.85 (br s, –OH), 1.62–1.45 (m, 4H, 2 × $-CH_2$), 1.12 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.88 (s, 9H, 3 × $-CH_3$), 0.04 (s, 6H, 2 × $-CH_3$); IR (neat): 3386, 2929, 2857, 1465, 1253, 1048, 833 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{13}H_{28}O_2SiNa$, 267.1756; found: 267.1768.

4.1.49. ((2*R*,5*S*)-5-(Benzyloxy)hept-6-en-2-yloxy)(*tert*-butyl)dimethylsilane 55

To a solution of **54** (0.5 g, 2.04 mmol) in dry CH_2Cl_2, Ag_2O (1.99 g, 4.09 mmol) was added and stirred for 30 min at room temperature, then BnBr (0.38 g, 2.25 mmol) was introduced. The reaction mixture was stirred at reflux for 12 h. The reaction was worked up as described for **37** and purified by column chromatography (60–120 silica gel, 0.4:9.6 EtOAc/*n*-hexane) to afford **55** (0.48 g, 70%) as a colorless oil. $[\alpha]_D = -69.9$ (*c* 0.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.59–7.12 (s, 5H), 5.77–5.61 (m, 1H, olefinic), 5.19 (d, 2H, *J* = 4.1 Hz, olefinic), 4.54, 4.30 (d, 1H, *J* = 12.0 Hz, benzylic $-CH_2$), 3.76–3.62 (m, 2H, 2 × –CH), 1.61–1.32 (m, 4H, 2 × $-CH_2$), 1.2 (d, 3H, *J* = 6.0 Hz, $-CH_3$), 0.85 (s, 9H, 3 × $-CH_3$), 0.04 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, CDCl3): δ 149.03, 137.49, 130.56, 128.27, 127.69, 127.35, 120.11, 72.32, 57.82, 55.17, 35.31, 31.81, 25.86, 23.80, 22.74, −4.44; IR (KBr): 3428, 2932, 2861, 1720, 1454, 1375, 1266, 1069,836 cm^{-1} HRMS *m/z* $[M+Na]^+$: calculated for $C_{20}H_{34}O_2SiNa$, 357.2225; found: 357.2213.

4.1.50. (4*S*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)oct-2-enoate 56

Ozone was bubbled through a cooled (−78 °C) solution of **55** (0.45 g, 1.34 mmol) in CH_2Cl_2 (5 mL) until the pale blue color persisted, excess ozone was quenched with Me_2S (0.5 mL), and stirred for 2 h. at 0 °C. The reaction mixture was concentrated under reduced pressure and used as such without further purification.

To the above-mentioned aldehyde (0.45 g, 1.34 mmol) in dry CH_2Cl_2 (4 mL) (*p*-toluenesulfonylethoxycarbonylmethylene)triphenyl phosphorane (1.0 g, 2.0 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise at 0 °C and worked up as described for **38** and purified by column chromatography (60–120 silica gel, 1.2:8.8 EtOAc/*n*-hexane) to afford **56** (0.52 g, 70%) as a colorless liquid. $[\alpha]_D = -61.2$ (*c* 3.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 7.31–7.25 (m, 7H, $-C_6H_4$, $-C_6H_5$), 6.64 (dd, 1H, *J* = 6.0, 15.8 Hz, olefinic), 5.74 (d, 1H, *J* = 15.8 Hz, olefinic), 4.49, 4.30 (2d, 2H, *J* = 12.0 Hz, benzylic $-CH_2$), 4.44 (t, 2H, *J* = 6.0, 12.0 Hz, $-OCH_2$), 3.84 (q, 1H, *J* = 5.2, 11.3 Hz, –CH), 3.70 (sext, 1H, *J* = 6.0, 12.8 Hz, –CH), 3.42 (t, 2H, *J* = 6.7, 12.8 Hz, $-CH_2-SO_2$), 2.4 (s, 3H, Ar–CH_3), 1.72–1.31 (m, 4H, 2 × $-CH_2$), 1.07 (d, 3H, *J* = 6.0, $-CH_3$), 0.86 (s, 9H, 3 × $-CH_3$), 0.04 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 149.9, 129.9, 128.4, 128.1, 127.6, 120.5, 77.6, 70.9, 68.0, 57.8, 55.1, 34.6, 30.5, 25.8, 23.7, 21.6, –4.3, –4.6; IR (KBr): 2954, 2928, 1725, 1461, 1322, 1256, 1144, 1086 cm^{-1}; ESIMS: 583 $[M+Na]^+$.

4.1.51. (4*S*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-hydroxyoct-2-enoate 57

To a solution of **56** (0.5 g, 0.89 mmol) in CH_3CN (4 mL) TMSCl (0.02 g, 0.17 mmol) in CH_3CN (1 mL) followed by H_2O (0.02 g, 0.89 mmol) was added at 0 °C and stirred at room temperature for 1 h. The reaction was worked up as described for **29** and purified by column chromatography (60–120 silica gel, 1:3 EtOAc/*n*-hexane) to furnish **57** (0.34 g, 85%) as a syrup. $[\alpha]_D = -35.9$ (*c* 3.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 7.5 Hz, $-C_6H_4$), 7.27 (q, 7H, *J* = 5.2, 12.0 Hz, $-C_6H_5$, $-C_6H_4$), 6.65 (dd, 1H, *J* = 6.0, 15.8 Hz, olefinic), 5.79 (d, 1H, *J* = 15.8, olefinic), 4.51, 4.29 (2d, 2H, *J* = 12.0 Hz, benzylic $-CH_2$), 4.44 (t, 2H, *J* = 6.2, 12.2 Hz, $-OCH_2$), 3.90 (q, 1H, *J* = 6.7, 14.3 Hz, –CH), 3.77–3.67 (m, 1H, –CH), 3.42 (t, 2H, *J* = 6.0, 12.2 Hz, $-CH_2SO_2$), 2.40 (s, 3H, Ar–CH_3), 1.76–1.32 (m, 4H, 2 × $-CH_2$), 1.14 (d, 3H, *J* = 6.2 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 149.5, 145.0, 137.6, 136.3, 129.9, 128.4, 128.0, 127.8, 127.7, 120.6, 77.7, 71.1, 67.6, 57.7, 55.0, 34.5, 30.9, 23.5, 21.5; IR (neat): 3754, 3448, 2924, 2854, 1721, 1654, 1597, 1457, 1380, 1318, 1289, 1141, 1082 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{24}H_{30}O_6SNa$, 469.1660; found: 469.1652.

4.1.52. (4*R*,5*R*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)hexanoate 58

To a suspension of PtO_2 (0.02 g, 0.09 mmol) in EtOAc (1 mL), ester **47** (0.8 g, 1.96 mmol) in EtOAc (1 mL) was added and then subjected to hydrogenation at 40 psi for 4 h. The catalyst was filtered off through Celite and the solvent was evaporated to afford **58** (0.75 g, 94%) as a liquid. $[\alpha]_D = +61.9$ (*c* 1.53, $CHCl_3$); ^1H NMR

(200 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.5 Hz, $-C_6H_4$), 6.76 (d, 2H, J = 7.8 Hz, $-C_6H_4$), 4.50 (q, 2H, J = 10.9, 26.5 Hz, benzylic $-CH_2$), 4.38 (q, 2H, J = 10.9 Hz, $-OCH_2$), 3.87 (p, 1H, J = 6.2, 11.7 Hz, –CH), 3.75 (s, 3H, $-OCH_3$),, 3.21 (p, 1H, J = 3.9, 8.5 Hz, –CH), 2.28 (sext, 1H, J = 7.8, 14.8 Hz), 1.94–1.74,1.71–1.49 (2 m, 3H, –CH, $-CH_2$), 1.12 (t, 3H, J = 10.9 Hz, $-CH_3$) 1.05 (d, 3H, J = 6.2 Hz, $-CH_3$), 0.84 (s, 9H, $3 \times -CH_3$) 0.02 (s, 6H, $3 \times -CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 159.3, 130.6, 129.6, 113.7, 81.2, 72.0, 68.7, 55.2, 51.4, 30.6, 25.7, 23.8, 17.1, –4.6; IR (neat): 2924, 2854, 1731, 1514, 1463, 1368, 1254, 1152, 1043 cm^{-1}; HRMS m/z $[M+Na]^+$: calculated for $C_{22}H_{38}O_5SiNa$, 433.2386; found: 433.2376.

4.1.53. (4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)hexanoic acid 59

A mixture of **58** (0.70 g, 1.71 mmol) and 0.5 M NaOH (10 mL) in MeOH (10 mL) was stirred at room temperature for 24 h. The reaction was worked up as described for **28** and the residue was purified by column chromatography (60–120 silica gel, 2:8 EtOAc/*n*-hexane) to give **59** (0.59 g, 90%) as a colorless oil. $[\alpha]_D$ = +15.2 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (br s, 1H, –COOH), 7.19, 6.83 (2d, 4H, J = 8.3 Hz, $-C_6H_4$), 4.41 (q, 2H, J = 11.3, 36.2 Hz, benzylic $-CH_2$), 3.9 (p, 1H, J = 6.0, 12.0 Hz, –CH), 3.76 (s, 3H, $-OCH_3$), 3.27–3.22 (m, 1H, –CH), 2.39–2.25 (m, 2H, $-CH_2$), 2.01–1.82 (m, 1H, –CH), 1.69–1.57 (m, 1H, –CH), 1.07 (d, 3H, J = 6.0 Hz, $-CH_3$), 0.85 (s, 9H, $3 \times -CH_3$), 0.00 (s, 6H, $3 \times -CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 159.3, 129.5, 128.4, 127.8, 113.8, 70.9, 70.5, 67.9, 55.4, 34.7, 30.8, 25.4, 19.9, –4.3; IR (neat): 3435, 2958, 2855, 1727, 1614, 1520, 1369, 1299, 1174, 1012 cm^{-1}; HRMS m/z $[M+Na]^+$: calculated for $C_{20}H_{34}O_5SiNa$, 405.2073; found: 405.2060.

4.1.54. (4*S*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-((4*R*,5*R*)-5-(*tert*-butyldimethyl silyl-oxy)-4-(4-methoxybenzyloxy)hexanoyloxy)-oct-2-enoate 60

To a solution of acid **59** (0.3 g, 0.8 mmol) and Et_3N (0.20 g, 2.01 mmol) in dry THF (3 mL) 2, 4, 6-trichlorobenzoyl chloride (0.24 g, 1.0 mmol) was added and the reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated. The resulting anhydride was dissolved in toluene (2 mL), treated with alcohol **57** (0.3 g, 0.67 mmol) in toluene (2 mL) and DMAP (0.16 g, 1.34 mmol) in toluene (1 mL), and stirred at room temperature for 1 h. The reaction was worked up as described for **48** and purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to give **60** (0.39 g, 72%) as an oil. $[\alpha]_D$ = −7.9 (*c* 0.24, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 7.28 (q, 7H, J = 8.3, 17.3 Hz, $-C_6H_5$, $-C_6H_4$), 7.16 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 6.77 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 6.60 (dd, 1H, J = 6.0, 15.8 Hz, olefinic), 5.77 (d, 1H, J = 15.8 Hz, olefinic), 4.79 (q, 1H, J = 4.5, 10.5 Hz, –CH), 4.45 (q, 2H, J = 11.3, 27.9 Hz, benzylic $-CH_2$), 4.44 (d, 2H, J = 8.3 Hz, benzylic $-CH_2$), 4.32 (t, 2H, J = 12.0, 27.2 Hz, $2 \times$ –CH), 3.83 (d, 2H, J = 5.2 Hz, $-OCH_2$), 3.76 (s, 3H, $-OCH_3$), 3.40 (t, 2H, J = 6.0, 12.0 Hz, $-CH_2-SO_2$), 3.21 (p, 1H, J = 3.7, 9.0 Hz, –CH), 2.39 (s, 3H, $-CH_3$), 2.39–2.18 (m, 2H, $-CH_2$-CO), 1.86 (m, 1H, –CH), 1.67–1.43 (m, 3H, $-CH_2$, –CH), 1.25 (t, 2H, J = 6.7, 14.3 Hz, $-CH_2$), 1.12 (d, 3H, J = 6.0 Hz, $-CH_3$), 1.07 (d, 3H, J = 6.0 Hz, $-CH_3$), 0.86 (s, 9H, $3 \times -CH_3$), 0.018 (s, 6H, $2 \times -CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 165.1, 159.0, 149.2, 144.8, 137.7, 136.4, 129.8, 129.2, 128.3, 128.0, 127.7, 127.5, 120.7, 113.6, 81.5, 77.1, 72.1, 71.0, 69.9, 68.67, 57.7, 55.1, 55.0, 31.1, 30.3, 28.1, 25.7, 24.3, 21.5, 19.9, 17.9, –4.7; IR (neat): 3415, 2923, 2853, 1717, 1630, 1460, 1384, 1251, 1080, 758 cm^{-1}; HRMS m/z $[M+Na]^+$: calculated for $C_{44}H_{62}O_{10}SSiNa$, 833.3730; found: 833.3726.

4.1.55. (4*S*,7*R*,*E*)-2-Tosylethyl 4-(benzyloxy)-7-((4*R*,5*R*,*E*)-5-hydroxy-4-(4-meth-oxy-benzyloxy)hex-2-enoyloxy)oct-2-enoate 61

To a cooled (0 °C) solution of **60** (0.35 g, 0.43 mmol) in dry THF (2 mL), HF–pyridine complex (0.04 g, 0.43 mmol) was added and then stirred at room temperature for 6 h. The reaction was quenched with $CuSO_4$ solution (1 mL) and the reaction mixture was extracted with EtOAc (2×25 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (60–120 silica gel, 3:7 EtOAc/*n*-hexane) to furnish **61** (0.22 g, 73%) as a yellow syrup. $[\alpha]_D$ = −71.7 (*c* 1.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 7.26 (q, 7H, J = 9.0, 5.2 Hz, $-C_6H_5$, $-C_6H_4$), 7.19 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 6.8 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 6.65 (dd, 1H, J = 6.0, 15.8 Hz, olefinic), 5.76 (d, 1H, J = 15.8 Hz, olefinic), 4.82 (m, 1H, –CH), 4.55 (dd, 2H, J = 3.7, 10.5 Hz, benzylic $-CH_2$), 4.43 (t, 2H, J = 6.0,12.8 Hz, $-OCH_2$), 4.30 (q, 2H, J = 12.0 Hz, benzylic $-CH_2$), 3.88 (q, 1H, J = 5.2, 10.5 Hz, –CH), 3.78 (s, 3H, $-OCH_3$), 3.65 (p, 1H, J = 6.0, 12.8 Hz, –CH), 3.41 (t, 2H, J = 6.0, 12.8 Hz, $-CH_2-SO_2$), 3.20 (q, 1H, J = 6.0, 10.5 Hz, –CH), 2.41 (s, 3H, $-CH_3$), 2.33 (t, 2H, J = 7.5, 12.8 Hz, $-CH_2CO$), 2.20 (br s, –OH), 2.05–1.87 (m, 3H, $-CH_2$, –CH), 1.80–1.68 (m, 1H, –CH), 1.15 (d, 3H, J = 6.7 Hz, $-CH_3$), 1.11 (d, 3H, J = 6.0, 12.8 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 165.2, 159.8, 149.0, 144.9, 137.8, 129.9, 129.3, 128.4, 127.8, 128.1, 127..6, 121.8, 113.7, 81.6, 72.2, 71.6, 70.2, 69.4, 69.1, 57.8, 55.1, 31.8, 31.2, 30.4, 25.8, 24.4, 21.6, 20.0 18.0; IR (KBr): 3521, 2927, 2859, 1724, 1690, 1520, 1470, 1143 cm^{-1}; HRMS m/z $[M+Na]^+$: calculated for $C_{38}H_{48}O_{10}SNa$, 719.2865; found: 719.2896.

4.1.56. (4*S*,7*R*,*E*)-4-(Benzyloxy)-7-((4*R*,5*R*)-5-hydroxy-4-(4-methoxybenzyloxy) hexanoyloxy)oct-2-enoic acid 62

To a solution of **61** (0.2 g, 0.28 mmol) in dry benzene (2 mL) a solution of DBN (0.03 g, 0.28 mmol) in dry benzene (2 mL) was added and stirred at room temperature for 12 h under nitrogen atmosphere. Worked up as described for **27** and purified by column chromatography (60–120 silica gel, 5:5 EtOAc/*n*-hexane) to afford **62** (0.1 g, 68%) as a yellow syrup. $[\alpha]_D$ = −57.58 (*c* 0.96, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (s, 5H, $-C_6H_5$), 7.22 (d, 2H, J = 8.3 Hz, $-C_6H_4$), 6.87 (dd, 1H, J = 6.0, 15.8 Hz, olefinic), 6.83 (d, 1H, J = 8.3 Hz, $-C_6H_4$), 5.96 (d, 1H, J = 15.8 Hz, olefinic), 4.83 (d, 1H, J = 5.2 Hz, –CH), 4.56 (t, 2H, J = 12.0, 24.1 Hz, benzylic $-CH_2$), 4.37 (q, 2H, J = 10.5, 25.6 Hz, benzylic $-CH_2$), 3.95 (d, 1H, J = 5.2 Hz, –CH), 3.80 (s, 3H, $-OCH_3$), 3.68 (t, 1H, J = 6.0, 12.0 Hz, –CH), 3.22 (q, 1H, J = 6.0, 10.5 Hz, –CH), 2.23 (t, 2H, J = 6.0, 13.5 Hz, $-CH_2CO$), 2.07 (s, 1H, –OH), 2.0–1.89 (m, 1H, –CH), 1.79–1.51 (m, 5H, $2 \times -CH_2$, –CH), 1.14 (t, 6H, J = 5.2, 9.8 Hz, $2 \times -CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 164.0, 150.1, 129.5, 129.2, 128.4, 127.8, 121.4,113.8, 82.2, 78.7, 71.8, 70.7, 70.4, 68.7, 55.2, 34.4, 30.8. 25.1, 23.4, 19.9, 17.2; IR (neat): 2924, 2854, 1720, 1655, 1611, 1513, 1458, 1376, 1249, 1176, 1075 cm^{-1}; HRMS m/z $[M+Na]^+$: calculated for $C_{29}H_{38}O_8Na$, 537.2464; found: 537.2451.

4.1.57. (3*E*,5*R*,6*R*,9*E*,11*S*,14*R*)-11-(Benzyloxy)-5-(4-methoxybenzyloxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione 63

To a solution of **62** (0.08 g, 0.15 mmol) and Et_3N (0.04 g, 0.46 mmol) in dry THF (2 mL), 2, 4, 6-trichlorobenzoyl chloride (0.05 g, 0.23 mmol) in dry THF (1 mL) was added. The resulting mixture was stirred at room temperature for 2 h under nitrogen atmosphere. It was evaporated to afford the mixed anhydride, which was diluted with toluene (10 mL) and filtered quickly through Celite. The filtrate was added dropwise to a stirred solution of DMAP (0.15 g, 1.24 mmol) in toluene (90 mL) (total volume used for this operation was 100 mL) at 90 °C for 10 h. The reaction was worked up as described for **50** and purified by column chromatography (60–120 silica gel, 1.5:8.5 EtOAc/*n*-hexane) to give

63 (0.04 g, 58%) as an oil. $[\alpha]_D = -10.4$ (*c* 0.21, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.25 (m, 7H, $-C_6H_5$, $-C_6H_4$), 6.83 (d, 2H, *J* = 8.3 Hz, $-C_6H_4$), 6.55 (q, 1H, *J* = 9.0, 15.8 Hz, olefinic), 5.82 (d, 1H, *J* = 15.8 Hz, olefinic), 5.19 (dd, 1H, *J* = 2.2, 6.7 Hz, –CH), 4.77 (q, 1H, *J* = 6.0, 10.5 Hz, –CH), 4.55, 4.31 (2d, 2H, *J* = 12.0 Hz, benzylic $-CH_2$), 4.55 (s, 2H, benzylic $-CH_2$), 3.81 (s, 3H, $-OCH_3$), 3.74 (m, 2H, 2 × –CH), 2.72 (dq, 1H, *J* = 2.2, 10.5 Hz, –CHCO), 2.33 (dq, 1H, *J* = 3.0, 6.7 Hz,, –CHCO), 2.11–1.93 (m, 1H, –CH), 1.88–1.45 (m, 5H, 2 × $-CH_2$, –CH), 1.33 (d, 3H, *J* = 6.7 Hz, $-CH_3$), 1.16 (d, 3H, *J* = 6.0 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 164.2, 159.2, 147.6, 137.7, 130.4, 129.3, 128.4, 127.65, 124.7, 113.7, 78., 77.0, 75.6, 71.5, 70.4, 68.9, 55.2, 29.2, 28.8, 28.3, 23.9, 19.4, 14.0; IR (neat): 3435, 2925, 2854, 1728, 1645, 1611, 1512, 1459, 1374, 1251, 1176, 1068 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{29}H_{36}O_7Na$, 519.2358; found: 519.2353.

4.1.58. (5*R*,6*R*,11*S*,14*R*,*E*)-5,11-Dihydroxy-6,14-dimethyl-1,7-dioxacyclotetradec-9-ene-2,8-dione 1a

To a stirred solution of **63** (0.03 g, 0.07 mmol) in CH_2Cl_2 (1 mL), $TiCl_4$ (0.01 g, 0.07 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C and then stirred at room temperature for 2 h. The reaction was worked up as described for **3** and purified by column chromatography (60–120 silica gel, 4:6 EtOAc/*n*-hexane) to afford **1a** (0.02 g, 80%) as a white solid, mp: 118–120 °C; $[\alpha]_D = -52.7$ (*c* 0.23, MeOH); ^1H NMR (400 MHz, DMSO): δ 6.53 (q, 1H, *J* = 7.8, 15.7 Hz, H-10), 5.74 (d, 1H, *J* = 15.7 Hz, H-9), 5.10 (d, 1H, *J* = 3.9 Hz, H-6), 4.97 (d, 1H, *J* = 4.9 Hz, H-14), 4.80 (q, 1H, *J* = 3.9, Hz, H-11), 4.60 (q, 1H, *J* = 5.8, 9.8 Hz, H-5), 3.98 (s, 1H, OH-5), 3.79 (d, 1H, *J* = 3.9 Hz, OH-11), 2.64 (q, 1H, *J* = 1.9, 10.7 Hz, H-3), 2.30 (dd, 1H, *J* = 2.9, 7.8 Hz, H-3), 1.77 (t, 1H, *J* = 13.7 Hz, H-4), 1.64–1.57 (m, 4H, H-4, H-13, H-12), 1.41–1.47 (m, 1H. H-12), 1.16 (d, 3H, *J* = 5.8 Hz, –H-15), 1.05 (d, 3H, *J* = 6.8 Hz, H-16); ^{13}C NMR (75 MHz, DMSO): δ 172.4, 164.5, 151.1, 120.9, 73.2, 69.9, 68.7, 67.0, 30.6, 29.2, 28.4, 26.6, 19.7, 13.7; IR (KBr): 3435, 2925, 2854, 1715, 1642, 1358, 1263, 770 cm^{-1}; HRMS *m/z* $[M+Na]^+$: calculated for $C_{14}H_{22}O_6Na$, 309.1308; found: 309.1312.

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