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Enantioselective total synthesis of macrosphelides A and E

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ABSTRACT

Enantioselective synthesis of 16-membered trilactone macrolides, macrosphelide A and E from (*S*)-lactic acid is described. Key features of the synthesis include the utility of a hitherto unexplored β-keto-phosphonate derived from lactic acid and Yamaguchi lactonization leading to the title compounds.

1. Introduction

Macrosphelides A–M are a class of 16-membered trilactones isolated from a culture broth of *Microsphaeropsis* sp. FO-5050 and from the strain *Periconia byssoides*.[1] Macrosphelide A **1a**, is reported to inhibit the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells. The adhesion of tumor cells apparently is the crucial step in tumor metastasis and **1a** is found to be orally active against lung metastasis of B16/BL6 melanoma in mice (50 mg/kg) without being toxic to normal mammalian cells.[1a] Macrosphelide E **1b** is structurally similar to macrosphelide A **1a** and is epimeric at the third position (Fig. 1). Recently, hybrid structures based on macrosphelides have also been shown to exhibit potent apoptosis-inducing activity toward human lymphoma cells.[2] Owing to the diverse bio-activity of the macrosphelides, they are considered as good lead compounds for anti-cancer drug development.

Several approaches for the synthesis of **1a** and **1b** have been reported, which mainly rely on either asymmetric dihydroxylation or modification of lactic acid or carbohydrates for the source of chirality.[3] Herein, we report a concise and facile synthesis of macrosphelides A and E from (*S*)-lactic acid. Our approach (Scheme 1) is based on the elaboration of β-ketophosphonate **4**, which is easily derived from (*S*)-lactic acid. Synthesis of the key orthogonally protected diol acid fragment **2** is expected from Wittig–Horner homologation of **4** with allylglyoxalate and subsequent transformations.

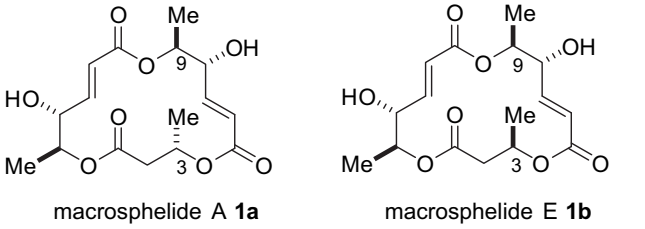
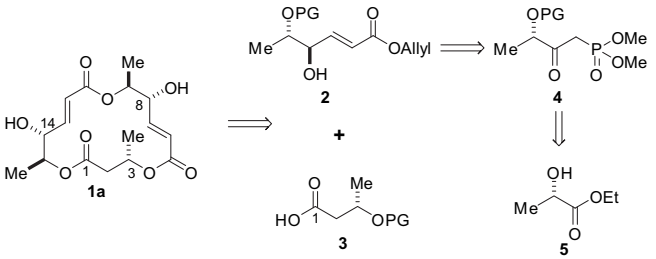


Fig. 1. Macrosphelides A and E.



Scheme 1. Retrosynthesis for macrosphelide A.

2. Results and discussion

Our synthetic sequence commenced with addition of the lithium anion generated from dimethyl methylphosphonate to ethyl-(*S*)-trityloxy lactate **6**[4] to afford the β-ketophosphonate **7** in 89% yield. Treatment of the phosphonate **7** with allylglyoxalate[5] under mild basic conditions afforded the α,β-unsaturated esters (*E*)-**8** and

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(*Z*)-**8** in 75% and 19% yields, respectively, which were separated on silica gel column chromatography. Reduction of **8** with $NaBH_4$ in MeOH produced a separable mixture of diastereomeric alcohols **9** and **10** in 60:40 ratio, while reduction with $NaBH_4/CeCl_3$ increased the ratio to 67:33. Employing either $LiBH_4$ or $Zn(BH_4)_2$ as the reducing agent furnished the alcohols in 55:45 ratio.[6] All these results are summarized in Table 1. Mitsunobu inversion[7] of **9** furnished the *p*-nitrobenzoate of **10**, which was treated with K_2CO_3 in presence of allyl alcohol to give **10** in 88% yield for two steps, thus enabling an efficient sequence for the synthesis of **10** (Scheme 2).

Table 1
Reduction of **8** with various reducing agents

S. No	Reducing agent	Solvent	Temp	Time	dr **9**:**10**[a]
1	$NaBH_4$	MeOH	−50 °C	1 h	60:40
2	$NaBH_4/CeCl_3$	MeOH	−40 °C	2 h	67:33
3	$LiBH_4$	THF	−78 °C	1 h	55:45
4	$Zn(BH_4)_2$	THF	−78 °C	3 h	55:45

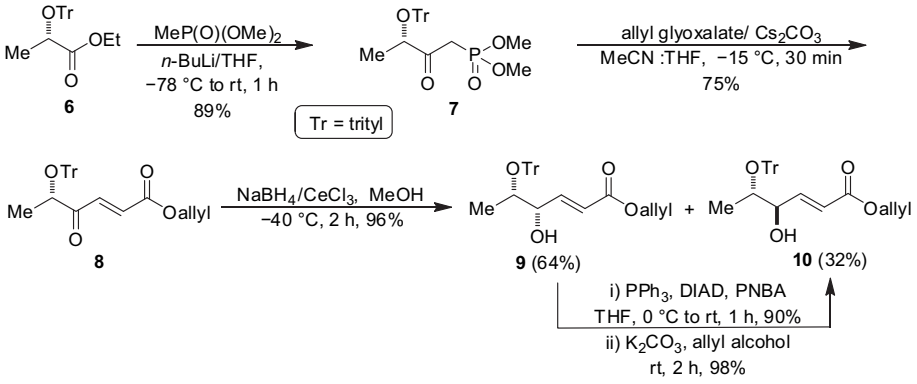
[a] Diastereomeric ratio was estimated by ^1H NMR.

by Paek et al.[3k] allyl ester **18a** was transformed into the free acid **19a**[8] by reaction with $Pd(PPh_3)_4$, which on Yamaguchi lactonization furnished the macro trilactone **20a** in 70% yield (for two steps). Final deprotection of the MOM ethers to the corresponding hydroxy groups was accomplished by treating **20a** with TFA resulting in macrosphelide A **1a** in 88% yield. The spectral data of **1a** is identical to that reported for the natural product in literature (Scheme 4).[1a]

Following the same sequence, synthesis of macrosphelide E was accomplished from **15** employing (*R*)-silyloxybutanoic acid (Scheme 5). The spectral data of **1b** is identical to that reported in literature for the natural product.[1e]

3. Conclusions

In conclusion, a facile strategy for the synthesis of macrosphelides A and E is presented from (*S*)-ethyl lactate in almost 19% overall yield via the corresponding β-ketophosphonate. The procedure is operationally simple, high yielding and is amenable for the synthesis of a number of analogues.



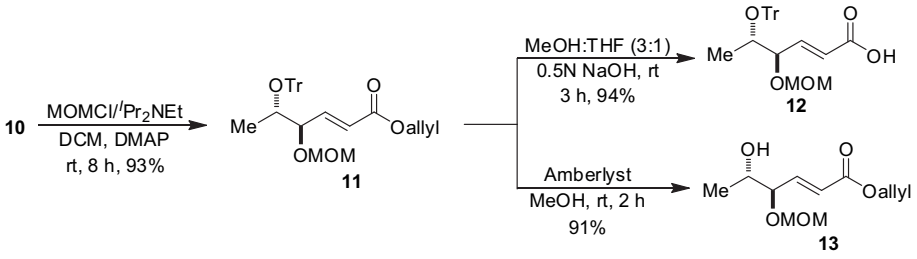
Scheme 2. Synthesis of **10**.

Allyl ester **10** served as the key unit for the synthesis of the required acid **12** and alcohol **13** fragments. The free hydroxy group in **10** was protected as the MOM ether **11**, which on saponification with NaOH resulted in the free acid **12** in 94% yield, while reaction with amberlyst resin produced the alcohol **13** in 91% yield (Scheme 3).

4. Experimental section

4.1. General procedures

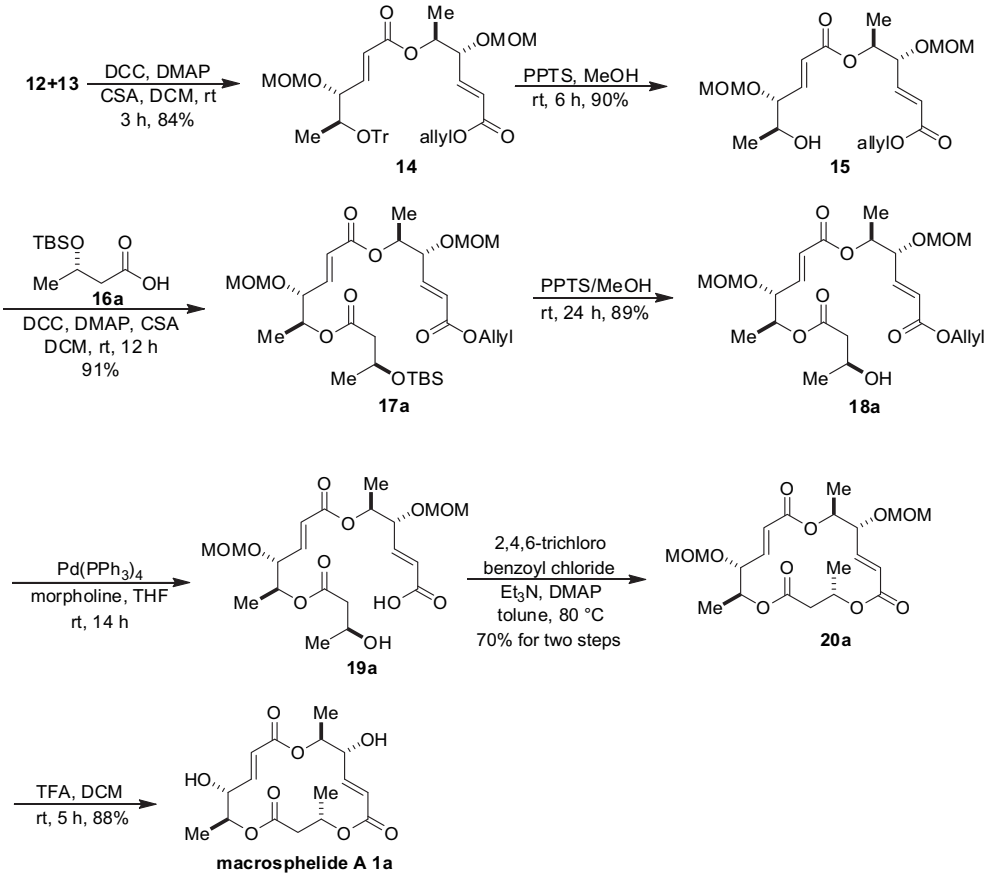
Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an



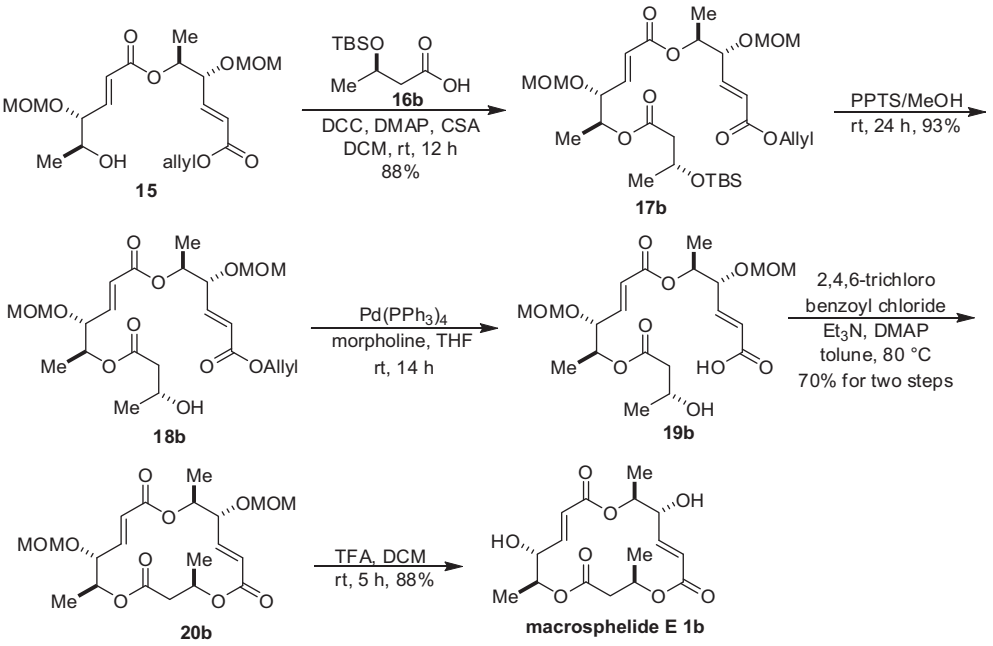
Scheme 3. Synthesis of acid and alcohol fragments **12** and **13**.

After successfully obtaining the required acid and alcohol units, DCC coupling of **12** and **13** under standard conditions afforded the ester **14** in 84% yield. Deprotection of the trityl group is accomplished by treating **14** with PPTS in methanol to furnish the diester **15** in 90% yield. Esterification of the free alcohol in **15** with (*S*)-silyloxybutanoic acid **16a**[3a] produced the ester **17a** in 91% yield. Deprotection of the silyl group in **17a** with PPTS in methanol resulted in the allyl ester **18a** in 89% yield. Following a similar sequence described

iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenoneketyl. Melting points were uncorrected. Unless stated otherwise, ^1H NMR and ^{13}C NMR spectra were recorded either on a bruker AC400 in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, all the reactions were performed under inert atmosphere.



Scheme 4. Synthesis of macrosphelide A.



Scheme 5. Total synthesis of macrosphelide E.

*4.1.1. (S)-Ethyl 2-(trityloxy)propionate (**6**).* To a stirred solution of chlorotriphenylmethane (1.17 g, 4.25 mmol) and DBU (0.9 mL, 5.92 mmol) in dichloromethane (5 mL), a solution of (*S*)-ethyl lactate **5** (0.5 g, 4.25 mmol) in dichloromethane (3 mL) was added and the reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the reaction mixture was poured into ice cold water (10 mL) and extracted with diethyl ether (3×20 mL). The combined ether layers were washed with

brine (2×10 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by silica gel column chromatography using petroleum ether/Et_2O (10:1) to give triphenylmethylether (1.25 g, 82%) as a colorless sticky mass. $[\alpha]_D^{24}$ −38.7 (*c* 2.1, CH_2Cl_2); lit.[4] $[\alpha]_D^{24}$ −37.0 (*c* 1.0, CH_2Cl_2); IR (Neat) 2983, 1752, 1732, 1491, 1448, 1131, 705 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 6H), 7.35–7.23 (m, 9H), 4.21 (q, 1H, *J*=6.7 Hz), 3.69 (q, 2H, *J*=7.2 Hz), 1.38 (d, 3H, *J*=6.7 Hz), 1.06 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C_q), 143.9 (C_q), 129.0 (CH), 127.7 (CH), 127.2 (CH), 87.9 (C_q), 69.7 (CH), 60.2 (CH_2), 20.1 (CH_3), 13.9 (CH_3); HRMS (M+Na) found 383.1650. $C_{24}H_{24}O_3$+Na requires 383.1623.

*4.1.2. Dimethyl (S)-2-oxo-3-(trityloxy)butylphosphonate (**7**).* To a THF (5 mL) solution of dimethyl methylphosphonate (0.75 mL, 6.9 mmol) placed in a 50 mL round bottom flask, cooled to −78 °C, was added *n*-BuLi (2.4 mL of a 2.2 M solution in hexanes, 5.28 mmol) drop wise. The reaction mixture was stirred at −78 °C for 30 min and a solution of **6** (1.24 g, 3.44 mmol) in THF (10 mL) was added drop wise and stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was cautiously quenched by the addition of saturated NH_4Cl (10 mL). It was then poured into water (20 mL) and extracted with EtOAc (3×20 mL). Combined organic layers were washed with brine (2×10 mL) and dried over Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the resultant residue with diethyl ether as eluent furnished **7** (1.34 g, 89%) as a colorless sticky mass. $[\alpha]_D^{24}$ −25.3 (*c* 4.0, $CHCl_3$); IR (Neat) 3468, 2955, 1721, 1449, 1056, 706 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.24 (m, 15H), 4.2 (q, 1H, *J*=6.9 Hz), 3.69 (d, 3H, *J*=11.2 Hz), 3.66 (d, 3H, *J*=11.2 Hz), 3.30 (dd, 1H, *J*=18.0, 15.6 Hz), 1.74 (dd, 1H, *J*=24.0, 15.5 Hz), 1.38 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2 (C_q), 143.5 (C_q), 128.9 (CH), 128.1 (CH), 127.6 (CH), 88.2 (C_q), 53.0 (CH_3), 52.9 (CH_3), 52.7 (CH_3), 52.6 (CH_3), 34.3 (CH_2), 33.0 (CH_2), 19.0 (CH_3); HRMS (M+Na) found 461.1493. $C_{25}H_{27}O_5P$+Na requires 461.1494.

*4.1.3. (S,E)-Allyl 4-oxo-5-(trityloxy)hex-2-enoate (**8**).* In a 50 mL two-neck round bottom flask equipped with Argon balloon was placed a solution of **7** (1.33 g, 3.04 mmol) in MeCN (5 mL). Solid Cs_2CO_3 (1.98 g, 6.08 mmol) was then introduced into the flask and stirred for 45 min at room temperature. The reaction mixture was cooled to −15 °C, and a solution of allylglyoxalate (0.69 g, 6.08 mmol) in MeCN (5 mL) was added drop wise and stirred for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was cautiously quenched by the addition of saturated citric acid (10 mL), poured into water (20 mL) and extracted with diethyl ether (3×20 mL). Combined organic layers were washed with brine (2×10 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified on silica gel column chromatography using petroleum ether/Et_2O (10:1) as eluent to furnish **8** (*E*-isomer) (0.97 g, 75%) as a colorless sticky mass and *Z*-**8** (*Z*-isomer) (0.25 g, 19%) as a colorless sticky mass. *E*-**8**: $[\alpha]_D^{24}$ −93.6 (*c* 2.6, $CHCl_3$); IR (Neat) 3058, 3024, 2978, 2930, 1726, 1700, 1623, 1364, 977 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.40 (m, 6H), 7.27–7.21 (m, 9H), 7.11 (d, 1H, *J*=15.8 Hz), 6.22 (d, 1H, *J*=15.8 Hz), 5.91 (ddt, 1H, *J*=16.1, 10.9, 5.6 Hz), 5.32 (d, 1H, *J*=17.2 Hz), 5.26 (d, 1H, *J*=10.4 Hz), 4.63 (d, 2H, *J*=5.5 Hz), 4.32–4.27 (m, 1H), 1.38 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1 (C_q), 165.0 (C_q), 143.6 (C_q), 133.6 (CH), 131.6 (CH), 129.0 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 118.5 (CH_2), 88.1 (C_q), 75.7 (CH), 65.5 (CH_2), 19.5 (CH_3); HRMS (M+Na) found 449.1716. $C_{28}H_{26}O_4$+Na requires 449.1729.

*4.1.4. (E,5S)-Allyl 4-hydroxy-5-(trityloxy)hex-2-enoate (**9** and **10**).* To a stirred solution of *E*-**8** (0.9 g, 2.1 mmol) in MeOH (5 mL), was added $CeCl_3 \cdot 7H_2O$ (1.18 g, 3.17 mmol) and allowed to stir for 45 min at room temperature. The reaction mixture was cooled to −40 °C, and $NaBH_4$ (0.12 g, 3.17 mmol) was added portionwise for over 10 min and stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by the addition of water (1 mL) at −40 °C, slowly allowed to warm up to room temperature, and stirred for further 30 min. It was then poured into water (10 mL) and extracted with diethyl ether (3×20 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether/Et_2O (4:1) as eluent furnished **10** (minor isomer, less polar compound) (0.29 g, 32%) as a colorless sticky mass and **9** (major isomer, more polar compound) (0.58 g, 64%) as a colorless sticky mass.

Compound **9**: $[\alpha]_D^{24}$ −42.0 (*c* 0.9, $CHCl_3$); IR (Neat) 3460, 3058, 2855, 1716, 1704, 1652, 1268, 1070, 707 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.47 (m, 6H), 7.31–7.22 (m, 9H), 6.99 (dd, 1H, *J*=15.8, 4.1 Hz), 6.05 (dd, 1H, *J*=15.7, 1.5 Hz), 5.93 (ddt, 1H, *J*=16.3, 11.0, 5.6 Hz), 5.32 (dd, 1H, *J*=17.2, 1.1 Hz), 5.23 (d, 1H, *J*=10.4 Hz), 4.63 (d, 2H, *J*=5.6 Hz), 3.77 (d, 1H, *J*=3.8 Hz), 3.57 (quintet, 1H, *J*=6.0 Hz), 2.04 (br s, 1H), 0.94 (d, 3H, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C_q), 147.5 (CH), 144.6 (C_q), 132.2 (CH), 128.8 (CH), 127.8 (CH), 127.2 (CH), 121.4 (CH), 118.0 (CH_2), 87.2 (C_q), 73.4 (CH), 72.6 (CH), 65.0 (CH_2), 16.8 (CH_3); HRMS (M+Na) found 451.1889. $C_{28}H_{28}O_4$+Na requires 451.1885.

Compound **10**: $[\alpha]_D^{24}$ +25.7 (*c* 2.3, $CHCl_3$); IR (Neat) 3469, 3086, 2934, 1719, 1656, 1490, 931 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 6H), 7.33–7.24 (m, 9H), 6.60 (dd, 1H, *J*=15.7, 4.1 Hz), 5.96–5.86 (m, 2H), 5.30 (d, 1H, *J*=17.2 Hz), 5.22 (d, 1H, *J*=10.5 Hz) 4.60 (d, 2H, *J*=5.5 Hz), 3.81 (dq, 1H, *J*=12.6, 2.6 Hz), 3.35 (br s, 1H), 2.31 (br s, 1H),1.04 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C_q), 146.2 (CH), 144.4 (C_q), 132.1 (CH), 128.7 (CH), 128.0 (CH), 127.4 (CH), 120.6 (CH), 118.1 (CH_2), 87.5 (C_q), 72.7 (CH), 72.0 (CH), 65.0 (CH_2), 15.3 (CH_3).

*4.1.5. Synthesis of **10** from **9**.* To a pre-cooled (0 °C) solution of triphenylphosphine (0.7 g, 2.7 mmol), DIAD (0.38 mL, 2 mmol) in THF, a solution of **9** (0.58 g, 1.35 mmol) in THF was added and stirred for 10 min at the same temperature. Solid *p*-nitrobenzoic acid (0.34 g, 2.7 mmol) was added at once to the reaction mixture and slowly allowed to warm up to room temperature and stirred for 1 h. After completion of the reaction (monitored by TLC) most of the solvent was evaporated under vacuum and the residue obtained was purified by silica gel column chromatography using petroleum ether/diethyl ether (5:1) as eluent to give *p*-nitrobenzoate as a colorless sticky mass (0.7 g, 90%). $[\alpha]_D^{24}$ +3.1 (*c* 1.9, $CHCl_3$); IR (Neat) 3058, 2360, 1727, 1529, 1269, 1015, 707 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (ABq, 4H, *J*=8.8 Hz), 7.49–7.46 (m, 6H), 7.30–7.25 (m, 9H), 6.79 (dd, 1H, *J*=15.8, 5.1 Hz), 5.92 (ddt, 1H, *J*=16.3, 11.0, 5.8 Hz), 5.85 (dd, 1H, *J*=15.7, 1.3 Hz), 5.32 (dd, 1H, *J*=17.3, 1.3 Hz), 5.25 (d, 1H, *J*=10.3 Hz), 5.18–5.17(m, 1H), 4.62 (d, 1H, *J*=5.7 Hz), 3.92 (qd, 1H, *J*=6.3, 2.3 Hz), 1.10 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (C_q), 163.4 (C_q), 150.7 (C_q), 144.3 (C_q), 142.3 (CH), 135.3 (C_q), 131.8 (CH), 130.8 (CH), 128.9 (CH), 127.8 (CH), 127.3 (CH), 123.7 (CH), 122.5 (CH), 118.6 (CH_2), 87.5 (C_q), 77.1 (CH), 70.7 (CH), 65.4 (CH_2), 16.5 (CH_3); HRMS (M+Na) found 600.1998. $C_{35}H_{31}NO_7$+Na requires 600.1998.

To a solution of the *p*-nitrobenzoate (0.7 g, 1.21 mmol) (obtained above) in allyl alcohol (5 mL) was added K_2CO_3 (0.32 g, 2.42 mmol) and stirred for 2 h at room temperature. After completion of reaction (monitored by TLC) the reaction mixture was poured into water (10 mL) and extracted with diethyl ether (3×20 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by silica gel column chromatography using petroleum ether/Et_2O (4:1) as eluent to furnish **10** (0.51 g, 98%) as a colorless sticky mass. $[\alpha]_D^{24}$ +25.7 (*c* 2.3, $CHCl_3$); IR (Neat) 3469, 3086, 2934,

1719, 1656, 1490, 931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 6H), 7.33–7.24 (m, 9H), 6.60 (dd, 1H, *J*=15.7, 4.1 Hz), 5.96–5.86 (m, 2H), 5.30 (d, 1H, *J*=17.2 Hz), 5.22 (d, 1H, *J*=10.5 Hz), 4.60 (d, 2H, *J*=5.5 Hz), 3.81 (dq, 1H, *J*=12.6, 2.6 Hz), 3.35 (br s, 1H), 2.31 (br s, 1H), 1.04 (d, 3H, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C_q), 146.2 (CH), 144.4 (C_q), 132.1 (CH), 128.7 (CH), 128.0 (CH), 127.4 (CH), 120.6 (CH), 118.1 (CH_2), 87.5 (C_q), 72.7 (CH), 72.0 (CH), 65.0 (CH_2), 15.3 (CH_3); HRMS (M+Na) found 451.1675. $C_{28}H_{28}O_4$+Na requires 451.1885.

*4.1.6. Allyl (E,4R,5S)-4-(methoxymethoxy)-5-(trityloxy)hex-2-enoate (**11**).* To a pre-cooled (0 °C) solution of **10** (0.8 g, 1.87 mmol) and DMAP (0.03 g, 0.187 mmol) in DCM (5 mL), was added *N,N* diisopropylethylamine (1.5 mL, 9.35 mmol) drop wise and stirred for 15 min. MOMCl (0.45 mL, 5.61 mmol) was introduced into the reaction mixture and slowly allowed to warm up to room temperature and stirred for 8 h. After completion of the reaction (indicated by TLC) the reaction mixture was then poured into water (10 mL) and extracted with diethyl ether (3×20 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by silica gel column chromatography using petroleum ether/diethyl ether (5:1) as eluent to furnish **11** (0.82 g, 93%) as a colorless oil (sticky mass). $[\alpha]_D^{24}$ +8.2 (*c* 3.5, $CHCl_3$); IR (Neat) 3058, 2936, 1722, 1656, 1448, 1033, 921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.53 (m, 6H), 7.33–7.23 (m, 9H), 6.56 (dd, 1H, *J*=15.7, 5.3 Hz), 5.92 (ddt, 1H, *J*=16.2, 10.7, 5.6 Hz), 5.82 (dd, 1H, *J*=15.7, 1.5 Hz), 5.31 (dd, 1H, *J*=17.2, 12.0 Hz), 5.23 (d, 1H, *J*=10.4 Hz), 4.61 (ABq, 2H, *J*=6.5 Hz), 4.61 (d, 2H, *J*=5.6 Hz), 3.74 (dq, 1H, *J*=12.6, 2.0 Hz), 3.51–3.50 (m, 1H), 3.32 (s, 3H), 1.05 (d, 3H, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C_q), 146.3 (CH), 144.7 (C_q), 132.1 (CH), 129.0 (CH), 127.8 (CH), 127.2 (CH), 121.6 (CH), 118.2 (CH_2), 95.5 (CH_2), 87.3 (C_q), 78.1 (CH), 72.1 (CH), 65.1 (CH_2), 55.6 (CH_3), 15.7 (CH_3); HRMS (M+Na) found 495.2144. $C_{30}H_{32}O_5$+Na requires 495.2147.

*4.1.7. (E,4R,5S)-4-(Methoxymethoxy)-5-(trityloxy)hex-2-enoic acid (**12**).* A solution of **11** (0.5 g, 1.06 mmol) in MeOH/THF (3:1, 5 mL) was added 0.5 N NaOH (2 mL) and stirred for 3 h. After completion of the reaction (indicated by TLC), the reaction mixture was neutralized with 0.2 N HCl (5 mL) at 0 °C. The reaction mixture was then poured into water (10 mL) and extracted with $CHCl_3$ (3×15 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by silica gel column chromatography using petroleum ether/diethyl ether (2:3) as eluent to furnish **12** (0.43 g, 94%) as a colorless oil (sticky mass). $[\alpha]_D^{24}$ +11.5 (*c* 2.2, $CHCl_3$); IR (Neat) 3059, 3034, 2935, 2825, 1698, 1449, 1282, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 6H), 7.32–7.23 (m, 9H), 6.61 (dd, 1H, *J*=15.7, 5.1 Hz), 5.77 (dd, 1H, *J*=15.7, 1.3 Hz), 4.60 (ABq, 2H, *J*=6.6 Hz), 3.75–3.73 (m, 1H), 3.48–3.46 (m, 1H), 3.31 (s, 3H), 1.04 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C_q), 147.0 (CH), 144.6 (C_q), 128.9 (CH), 127.8 (CH), 127.2 (CH), 122.4 (CH), 95.4 (CH_2), 87.3 (C_q), 78.1 (CH), 72.0 (CH), 55.6 (CH_3), 15.6 (CH_3); HRMS (M+Na) found 455.1832. $C_{27}H_{28}O_5$+Na requires 455.1834.

*4.1.8. (E,4R,5S)-Allyl 5-(hydroxy)-4-(methoxymethoxy)hex-2-enoate (**13**).* To a stirred solution of **11** (0.3 g, 0.63 mmol) in MeOH (5 mL) was added Amberlyst-15 (0.3 g) at room temperature and stirred for 2 h. After completion of the reaction (indicated by TLC), the reaction mixture was diluted with diethyl ether (10 mL) and was then filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether/EtOAc (1:1) as eluent yielded **13** (0.133 g, 91%) as a colorless oil. $[\alpha]_D^{24}$ −74.9 (*c* 3.8, $CHCl_3$); IR (Neat) 3471, 2977, 2893, 1722, 1715, 1682, 1454, 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 6.88 (dd, 1H, *J*=15.8, 6.3 Hz), 6.07 (dd, 1H, *J*=15.8, 1.2 Hz), 5.93 (ddt, 1H, *J*=16.2, 10.6, 5.8 Hz), 5.32 (dd, 1H, *J*=17.2, 1.4 Hz), 5.23 (dd, 1H, *J*=10.4, 1.1 Hz), 4.65–4.62 (m, 4H), 4.15 (dq, 1H, *J*=6.0, 1.1 Hz), 3.92–3.91 (m, 1H), 3.38 (s, 3H), 2.59 (br s, 1H), 1.14 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C_q), 144.1 (CH), 132.0 (CH), 123.7 (CH), 118.3 (CH_2), 95.4 (CH_2), 80.2 (CH), 69.1 (CH), 65.2 (CH_2), 55.8 (CH_3), 17.8 (CH_3); HRMS (M+Na) found 253.1047. $C_{11}H_{18}O_5$+Na requires 253.1052.

*4.1.9. Preparation of diester (**14**).* In a 25 mL single neck round bottom flask was placed a solution of the acid **12** (0.32 g, 0.74 mmol) in DCM (2 mL) under argon atmosphere. A solution of the alcohol **13** (0.13 g, 0.56 mmol) in DCM (2 mL) was introduced via syringe into the flask. Solid DMAP (0.014 g, 0.112 mmol), DCC (0.23 g, 1.12 mmol), and camphorsulfonic acid (0.007 g, 0.03 mmol) were added to the reaction mixture at once, and stirred for 3 h at room temperature. After completion of the reaction (indicated by TLC), the reaction mixture was diluted with diethyl ether (10 mL) and was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether/Et_2O (5:1) as eluent yielded **14** (0.3 g, 84%) as a colorless oil. $[\alpha]_D^{24}$ −19.0 (*c* 2.3, $CHCl_3$); IR (Neat) 3059, 2986, 1723, 1659, 1449, 1154, 709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 6H), 7.32–7.22 (m, 9H), 6.85 (dd, 1H, *J*=15.7, 6.0 Hz), 6.52 (dd, 1H, *J*=15.7, 5.3 Hz), 6.10 (dd, 1H, *J*=15.8, 1.2 Hz), 5.94 (ddt, 1H, *J*=17.0, 10.6, 4.9 Hz), 5.75 (dd, 1H, *J*=15.7, 1.5 Hz), 5.34 (dd, 1H, *J*=17.2, 1.4 Hz), 5.25 (dd, 1H, *J*=10.4, 1.0 Hz) 5.06–5.03 (m, 1H), 4.67–4.54 (m, 6H), 4.35–4.32 (m, 1H), 3.73–3.71 (m, 1H), 3.48–3.46 (m, 1H), 3.34 (s, 3H), 3.31 (s, 3H), 1.23 (d, 3H, *J*=6.5 Hz) 1.04 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C_q), 146.4 (CH), 144.6 (C_q), 143.8 (CH), 132.0 (CH), 128.9 (CH), 127.8 (CH), 127.2 (CH), 123.7 (CH), 121.7 (CH), 118.4 (CH_2), 95.5 (CH_2), 94.8 (CH_2), 87.3 (C_q), 78.2 (CH), 76.5 (CH), 72.0 (CH), 71.3(CH), 65.2 (CH_2), 55.7 (CH_3), 55.6 (CH_3), 15.6 (CH_3), 14.9 (CH_3); HRMS (M+Na) found 667.2885. $C_{38}H_{44}O_9$+Na requires 667.2883.

*4.1.10. Preparation of hydroxydiester (**15**).* To a stirred solution of **14** (0.29 g, 0.45 mmol) in MeOH (5 mL) was added PPTS (0.15 g, 0.9 mmol) and stirred at room temperature for 6 h. After completion of the reaction (indicated by TLC), MeOH was evaporated under vacuum and the reaction mixture was diluted with DCM (5 mL). Solid $NaHCO_3$ (0.08 g, 0.9 mmol) was added and stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether/EtOAc (1:1) as eluent yielded **15** (0.162 g, 90%) as a colorless oil. $[\alpha]_D^{24}$ −71.0 (*c* 1.0, $CHCl_3$); IR (Neat) 3474, 2940, 1722, 1659, 1451, 1271, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, 1H, *J*=6.1, 2.0 Hz), 6.84 (dd, 1H, *J*=6.0, 2.0 Hz), 6.08 (dd, 2H, *J*=21.3, 15.7 Hz), 5.93 (ddt, 1H, *J*=16.5, 10.9, 5.8 Hz), 5.32 (d, 1H, *J*=17.2 Hz), 5.24 (d, 1H, *J*=10.4 Hz), 5.09 (dq, 1H, *J*=12.7, 6.4 Hz), 4.67–4.60 (m, 6H), 4.36–4.34 (m, 1H), 4.17–4.14 (m, 1H), 3.93–3.90 (m, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.51 (br s, 1H), 1.25 (d, 3H, 6.5 Hz) 1.14 (d, 3H, 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C_q), 165.0 (C_q), 144.3 (CH), 143.8 (CH), 132.0 (CH), 123.8 (2 CH), 118.4 (CH_2), 95.5 (CH_2), 95.0 (CH_2), 80.4 (CH), 76.6 (CH), 71.5 (CH), 69.2 (CH), 65.3 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 17.9 (CH_3), 15.0 (CH_3); HRMS (M+Na) found 425.1787. $C_{19}H_{30}O_9$+Na requires 425.1788.

*4.1.11. Preparation of triester **17a** and **17b**.* The following procedure for **17a** is representative. To a solution of **15** (0.08 g, 0.20 mmol) in DCM (2 mL) in a 25 mL round bottom flask, was added a solution of the acid *S*-**16** (0.069 g, 0.30 mmol) in DCM (2 mL). Solid DMAP

(0.005 g, 0.04 mmol), DCC (0.083 g, 0.40 mmol), and camphorsulfonic acid (0.004 g, 0.02 mmol) were introduced at once in to the flask and stirred for 12 h at room temperature. After completion of the reaction (indicated by TLC), the reaction mixture was diluted with diethyl ether (10 mL) and was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether/EtOAc (5:1) as eluent yielded **17a** (0.11 g, 91%) as a colorless oil. $[\alpha]_D^{24}$ −41.9 (*c* 2.7, $CHCl_3$); IR (Neat) 3085, 2857, 1727, 1661, 1463, 1281, 1034 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (dd, 1H, *J*=12.7, 6.0 Hz), 6.83 (dd, 1H, *J*=9.8, 3.1 Hz), 6.09 (td, 2H, *J*=17.0, 1.0 Hz), 5.92–5.82 (m, 1H), 5.33 (dd, 1H, *J*=17.2, 1.1 Hz), 5.25 (dd, 1H, *J*=10.5, 1.0 Hz), 5.11–5.08 (m, 1H), 5.03–5.01 (m, 1H), 4.66–4.60 (m, 6H), 4.38–4.36 (m, 1H), 4.32–4.30 (m, 1H), 4.26–4.21 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.49 (dd, 1H, *J*=14.7, 6.7 Hz), 2.36 (dd, 1H, *J*=14.7, 6.1 Hz), 1.26 (d, 3H, *J*=6.6 Hz), 1.21 (d, 3H, *J*=6.6 Hz), 1.18 (d, 3H, *J*=6.2 Hz), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C_q), 165.3 (C_q), 164.9 (C_q), 144.0 (CH), 143.7 (CH), 132.0 (CH), 123.8 (CH), 123.7 (CH), 118.7 (CH_2), 94.9 ($2CH_2$), 76.5 (CH), 71.6 (CH), 71.2 (CH), 65.6 (CH), 65.3 (CH_2), 55.7 ($2CH_3$), 44.9 (CH_2), 25.7 ($3CH_3$), 23.7 (CH_3), 17.9 (C_q), 14.8 (CH_3), −4.6 (CH_3), −4.9 (CH_3); HRMS (M+Na) found 625.3019. $C_{29}H_{50}O_{11}Si$+Na requires 625.3020.

Compound **17b**: yield: 88% $[\alpha]_D^{24}$ −60.5 (*c* 1.8, $CHCl_3$); IR (Neat) 3086, 2955, 1728, 1661, 1473, 1281, 1035 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (td, 2H, *J*=15.6, 6.0 Hz), 6.1 (dd, 1H, *J*=15.8, 1.2 Hz), 6.06 (dd, 1H, *J*=15.9, 1.4 Hz), 5.94 (ddt, 1H, *J*=16.1, 11.3, 5.7 Hz), 5.33 (dd, 1H, *J*=17.2, 1.3 Hz), 5.24 (dd, 1H, *J*=10.4, 1.2 Hz), 5.09 (dq, 1H, *J*=12.8, 6.3 Hz), 5.01 (dq, 1H, *J*=12.8, 6.3 Hz), 4.65–4.59 (m, 6H), 4.37–4.35 (m, 1H), 4.31–4.22 (m, 2H), 3.36 (s, 3H), 3.36 (s, 3H), 2.48 (dd, 1H, *J*=14.8, 7.2 Hz), 2.35 (dd, 1H, *J*=14.8, 5.6 Hz) 1.26 (d, 3H, *J*=6.5 Hz), 1.21 (d, 3H, *J*=6.5 Hz), 1.17 (d, 3H, *J*=6.1 Hz), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C_q), 165.3 (C_q), 164.9 (C_q), 144.0 (CH), 143.7 (CH), 132.0 (CH), 123.8 (CH), 123.7 (CH), 118.4 (CH_2), 94.9 ($2CH_2$), 76.5 (CH), 71.5 (CH), 71.0 (CH), 65.6 (CH), 65.2 (CH_2), 55.6 ($2CH_3$), 44.8 (CH_2), 25.7 ($3CH_3$), 23.8 (CH_3), 17.9 (C_q), 14.9 (CH_3), 14.8 (CH_3), −4.6 (CH_3), −5.0 (CH_3); HRMS (M+Na) found 625.3018. $C_{29}H_{50}O_{11}Si$+Na requires 625.3020.

*4.1.12. Preparation of hydroxytriester (**18a** and **18b**).* The following procedure for **18a** is representative. To a stirred solution of **17a** (0.10 g, 0.166 mmol) in MeOH (4 mL) was added PPTS (0.055 g, 0.33 mmol) at room temperature and stirred for 24 h. After completion of the reaction (indicated by TLC), MeOH was evaporated under vacuum and the reaction mixture was diluted with DCM (5 mL). Solid $NaHCO_3$ (0.028 g, 0.33 mmol) was added and stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether/EtOAc (1:1) as eluent yielded **18a** (0.072 g, 89%) as a colorless oil. $[\alpha]_D^{24}$ −57.4 (*c* 2.4, $CHCl_3$); IR (Neat) 3514, 2983, 1725, 1660, 1409, 1252, 1033 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (td, 2H, *J*=15.8, 6.0 Hz), 6.09 (td, 2H, *J*=17.1, 1.2 Hz), 5.94 (ddt, 1H, *J*=16.2, 11.2, 5.7 Hz), 5.33 (dd, 1H, *J*=17.2, 1.4 Hz), 5.25 (dd, 1H, *J*=10.4, 1.0 Hz), 5.09(m, 2H), 4.66–4.60 (m, 6H), 4.37–4.35 (m, 1H), 4.31–4.28 (m, 1H), 4.18–4.16 (m, 1H), 3.37 (s, 3H), 3.37 (s, 3H), 3.03 (br d, 1H, *J*=3.0 Hz), 2.48 (dd, 1H, *J*=12.1, 4.2 Hz), 2.42 (dd, 1H, *J*=16.0, 8.3 Hz) 1.27–1.21 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C_q), 165.3 (C_q), 164.9 (C_q), 143.7 (CH), 131.9 (CH), 124.0 (CH), 123.8 (CH), 118.4 (CH_2), 94.9 (CH_2), 94.9 (CH_2), 76.6 (CH), 76.5 (CH), 71.6 (CH), 71.4 (CH), 65.3 (CH_2), 64.3 (CH), 55.7 (CH_3), 43.1 (CH_2), 22.5 (CH_3), 15.1 (CH_3), 14.8 (CH_3); HRMS (M+Na) found 511.2152. $C_{23}H_{36}O_{11}$+Na requires 511.2155.

Compound **18b**: yield: 93%; $[\alpha]_D$ −75.7 (*c* 4.3, $CHCl_3$); IR (Neat) 3501, 2939, 1724, 1660, 1454, 1173, 1033 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, 1H, *J*=12.4, 6.0 Hz), 6.81 (dd, 1H, *J*=12.5, 6.1 Hz), 6.07 (td, 2H, *J*=15.7, 1.2 Hz), 5.92 (ddt, 1H, *J*=16.3, 10.6, 5.8 Hz), 5.31 (dd, 1H, *J*=17.2, 1.4 Hz), 5.22 (dd, 1H, *J*=10.4, 1.0 Hz), 5.07(dq, 2H, *J*=12.9, 2.7 Hz), 4.63–4.57 (m, 6H), 4.35–4.32 (m, 1H), 4.29–4.26 (m, 1H), 4.17 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.08 (br s, 1H), 2.47 (dd, 1H, *J*=16.1, 3.7 Hz), 2.39 (dd, 1H, *J*=16.1, 8.7 Hz) 1.24 (d, 3H, *J*=6.5 Hz), 1.21 (d, 3H, *J*=7.0 Hz), 1.19 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C_q), 165.3 (C_q), 164.8 (C_q), 143.6 (2CH), 131.9 (CH), 124.0 (CH), 123.8 (CH), 118.4 (CH_2), 94.9 (CH_2), 94.8 (CH_2), 76.6 (CH), 76.5 (CH), 71.6 (CH), 71.3 (CH), 65.3 (CH_2), 64.1 (CH), 55.7 (CH_3), 55.6 (CH_3), 43.3 (CH_2), 22.3 (CH_3), 15.1 (CH_3), 14.9 (CH_3); HRMS (M+Na) found 511.2191. $C_{23}H_{36}O_{11}$+Na requires 511.2155.

*4.1.13. Macrolactone **20a** and **20b**.* The following procedure for **20a** is representative. $Pd(PPh_3)_4$ (0.165 g, 0.143 mmol) and morpholine (0.012 mL, 0.143 mmol) were added to a stirred solution of **18a** (0.07 g, 0.143 mmol) in THF (5 mL) and stirred for 12 h at room temperature. The reaction mixture was quenched with 1 N HCl (2 mL), and poured into water (10 mL). The reaction mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent gave crude residue of the hydroxy acid **19a**. It was cumbersome to purify the seco-acid from an unidentifiable impurity on column chromatography. Hence the seco acid (0.064 g, 0.143 mmol) was used as such in the next step without further purification.

Triethylamine (0.12 mL, 0.86 mmol) and 2,4,6-trichlorobenzoyl chloride (0.12 mL, 0.86 mmol) were added to a stirred solution of **19a** (0.064 g, 0.143 mmol) in dry toluene (5 mL) and stirred for 1 h at room temperature. It was diluted with toluene (30 mL) and was added to a pre-heated solution of 4-dimethylaminopyridine (0.435 g, 3.6 mmol) in toluene at 80 °C for over 3 h. The reaction mixture was stirred for 4 h at 80 °C, and after completion of the reaction (monitored by TLC) it was poured into saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (3×20 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to furnish **20a** (0.043 g, 70% over two steps) as a colorless oil. $[\alpha]_D$ −102.2 (*c* 2.3, $CHCl_3$); IR (Neat) 2982, 2826, 1734, 1724, 1656, 1458, 1251, 1032 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74–6.67(m, 2H), 5.96 (d, 1H, *J*=15.8 Hz), 5.9 (d, 1H, *J*=15.8 Hz), 5.31–5.28 (m, 1H), 5.03–4.90 (m, 2H), 4.65–4.53 (m, 4H), 4.10–4.00(m, 2H), 3.36 (s, 3H), 3.35 (s, 3H), 2.57 (dd, 1H, *J*=15.0, 2.5 Hz), 2.48 (dd, 1H, *J*=15.0, 8.7 Hz) 1.40 (d, 3H, *J*=6.2 Hz), 1.30 (d, 3H, *J*=6.3 Hz), 1.28 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C_q), 164.2 (C_q), 145.1 (CH), 144.0 (CH), 124.3 (CH), 124.2 (CH), 94.9 (CH_2), 94.3 (CH_2), 78.4 (CH), 76.3 (CH), 71.7 (CH), 70.6 (CH), 67.5 (CH), 55.9 (CH_3), 55.8 (CH_3), 40.8 (CH_2), 19.5 (CH_3), 17.8 (CH_3), 17.6 (CH_3); HRMS (M+Na) found 453.1735. $C_{20}H_{30}O_{10}$+Na requires 453.1737.

Compound **20b**: $[\alpha]_D$ −65.2 (*c* 2.0, $CHCl_3$); IR (Neat) 2983, 2827, 1722, 1655, 1453, 1273, 1030 cm−1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dd, 1H, *J*=15.7, 6.1 Hz), 6.78 (dd, 1H, *J*=15.8, 6.6 Hz), 6.13 (d, 1H, *J*=15.8 Hz), 5.96 (d, 1H, 15.8 Hz), 5.24 (td, 1H, *J*=6.6, 3.1 Hz), 5.11 (dq, 2H, *J*=12.9, 4.6 Hz), 4.62 (d, 4H, *J*=2.0 Hz), 4.25–4.22 (m, 1H), 4.10–4.07 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.76 (dd, 1H, *J*=14.8, 3.0 Hz), 2.55 (dd, 1H, *J*=14.9, 6.5 Hz) 1.41 (d, 3H, *J*=6.5 Hz), 1.38 (d, 3H, *J*=6.5 Hz), 1.22 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C_q), 165.0 (C_q), 164.4 (C_q), 143.2 (CH), 143.1 (CH), 124.9 (CH), 124.5 (CH), 94.6 (CH_2), 94.5 (CH_2), 77.6 (CH), 76.5 (CH), 72.0 (CH), 71.3 (CH), 67.3 (CH), 55.9 (CH_3), 55.8 (CH_3), 40.6 (CH_2), 19.3 (CH_3), 17.5 (CH_3), 17.2 (CH_3); HRMS (M+Na) found 453.1737. $C_{20}H_{30}O_{10}$+Na requires 453.1737.

*4.1.14. Macrosphelides A and E (**1a** and **1b**).* A stirred solution of **20a** (0.040 g, 0.093 mmol) in DCM (5 mL) was treated with TFA (2.5 mL)

for 5 h at room temperature. After completion of the reaction (indicated by TLC), TFA was removed under reduced pressure. Silica gel column chromatography of the resulting residue using petroleum ether/EtOAc (1:1) as eluent yielded macrosphelide A **1a** (0.028 g, 88%) as white needles. $[\alpha]_D$ +74.3 (*c* 0.75, MeOH); lit.[1a] $[\alpha]_D$ +84.1 (*c* 0.59, MeOH); mp 142–143 °C; lit.[1a] mp 141–142 °C; IR (KBr) 3434, 2936, 1732, 1704, 1648, 1458, 1290, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (dt, 2H, *J*=15.7, 3.7 Hz), 6.06 (d, 1H, *J*=15.7 Hz), 6.04 (dd, 1H, *J*=15.7, 1.1 Hz), 5.43–5.35 (m, 1H), 5.00–4.94 (m, 1H), 4.90–4.83 (m, 1H), 4.24–4.23 (m, 1H), 4.15–4.13 (m, 1H), 2.63 (dd, 1H, *J*=15.5, 8.7 Hz), 2.58 (dd, 1H, *J*=15.6, 3.6 Hz) 1.46 (d, 3H, *J*=6.5 Hz), 1.37 (d, 3H, *J*=6.3 Hz), 1.33 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C_q), 165.7 (C_q), 164.8 (C_q), 146.3 (CH), 145.4 (CH), 122.6 (CH), 122.1 (CH), 74.6 (CH), 73.7 (CH), 72.9 (CH), 67.6 (CH), 40.9 (CH_2), 19.6 (CH_3), 17.8 (CH_3), 17.7 (CH_3); HRMS (M+Na) found 365.1212. $C_{16}H_{22}O_8$+Na requires 365.1212. Anal. Calcd for $C_{16}H_{22}O_8$ (365.1212): Found: C, 55.99; H, 6.36. $C_{16}H_{22}O_8$ requires C, 56.13; H, 6.48.

Similarly reaction with **20b** produced macrosphelide E **1b** in 88% yield: $[\alpha]_D$ +58.1 (*c* 0.75, EtOH); lit.[1e] $[\alpha]_D$ +56.8 (*c* 0.46, EtOH); IR (Neat) 3449, 2984, 1718, 1663, 1277, 1053, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, 1H, *J*=15.6, 4.2 Hz), 6.81 (dd, 1H, *J*=15.6, 5.3 Hz), 6.13 (dd, 1H, *J*=15.6, 1.1 Hz), 6.06 (dd, 1H, *J*=15.6, 1.2 Hz), 5.34–5.26 (m, 1H), 5.11 (dq, 1H, *J*=11.6, 4.9 Hz), 4.97 (dq, 1H, *J*=12.8, 6.4 Hz), 4.36–4.35 (m, 1H), 4.18–4.15 (m, 1H), 2.73 (dd, 1H, *J*=15.9, 3.1 Hz), 2.59 (dd, 1H, *J*=15.9, 7.0 Hz) 1.41 (d, 3H, *J*=7.2 Hz), 1.38 (d, 3H, *J*=7.4 Hz), 1.3 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C_q), 166.6 (C_q), 165.3 (C_q), 145.4 (CH), 145.1 (CH), 123.0 (CH), 122.3 (CH), 75.8 (CH), 75.1 (CH), 75.0 (CH), 73.6 (CH), 66.7 (CH), 40.4 (CH_2), 19.5 (CH_3), 17.6 (CH_3), 17.3 (CH_3); HRMS (M+Na) found 365.1213.$C_{16}H_{22}O_8$+Na requires 365.1212.

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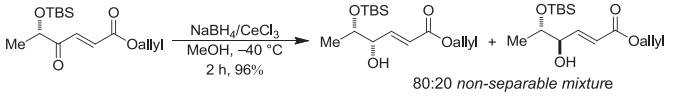
6. Diastereomeric ratio of the alcohols was estimated by ^1H NMR. Reduction of the corresponding TBS analogue gave the diastereomeric alcohols in 80:20 ratio, which are non separable.



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8. It was cumbersome to purify the acid from an unidentifiable impurity. Silica gel column chromatography of the acid always furnished the required acid **19** admixed with the impurity; hence the crude acid obtained was used as such in the next step without further purification.