Stereoselective Synthesis of Macrosphelide I

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Received: 02.05.2014; Accepted after revision: 31.05.2014

Abstract: An efficient total synthesis of macrosphelide I, has been achieved starting from commercially available chiral materials, ethyl (*S*)-lactate and methyl (*R*)-3-hydroxybutyrate. Titanium(IV) promoted the regioselective nucleophilic opening reaction of epoxy alcohol with benzoic acid, Sharpless epoxidation, ring-closing metathesis and Yamaguchi esterification as key steps for the construction of the 16-membered macrotriolide.

Key words: macrosphelide I, regioselective opening, Yamaguchi esterification, ring-closing metathesis

The interesting biological properties and complex molecular architecture of the macrosphelides have attracted the attention of organic chemists.[1] Macrosphelides A–L are unique 16-membered macrocyclic trislactones that were isolated from various natural sources.[2] Macrosphelides A–L showed activity as inhibitors of the adhesion of HL-60 cells to a monolayer of LPS-activated human-umbilical-vein endothelial cells and this class of macrotriolides has attracted attention as lead compounds for the development of novel anticancer drugs.[1,2]

Macrosphelide I (**1**; Figure 1) is a 16-membered trislactone, isolated from a strain of *Periconia byssoides* by the Numata group.[3] It was found to be cytotoxic against P388 lymphocytic leukaemia cells and HL-60 cell in vitro while its ED_{50} was found to be 20 μg cm^{-1} against P388 cells. The stereochemistry of **1** was confirmed by spectroscopic analysis.[3] Prior to this work there has been only one approach to the synthesis of macrosphelide I (**1**) reported in the literature.[4] In continuation of our interest in the synthesis of macrolides,[5] we herein describe the synthesis of **1** by using regioselective opening of an epoxy alcohol and ring-closing metathesis as the key steps.

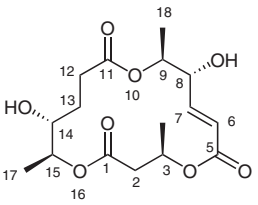
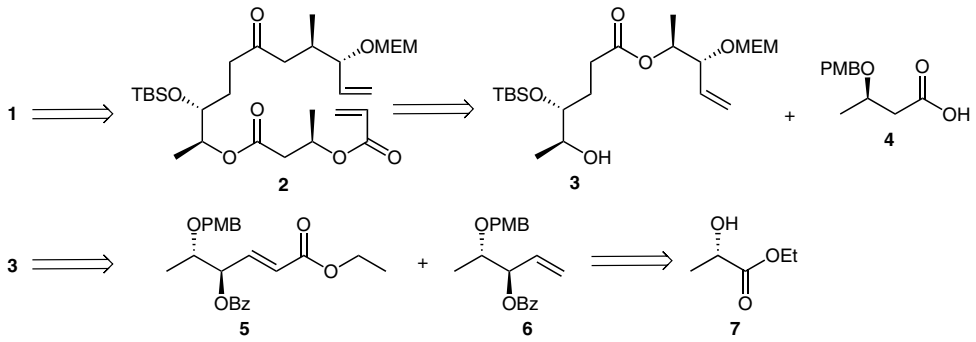


Figure 1 Macrosphelide I (**1**)

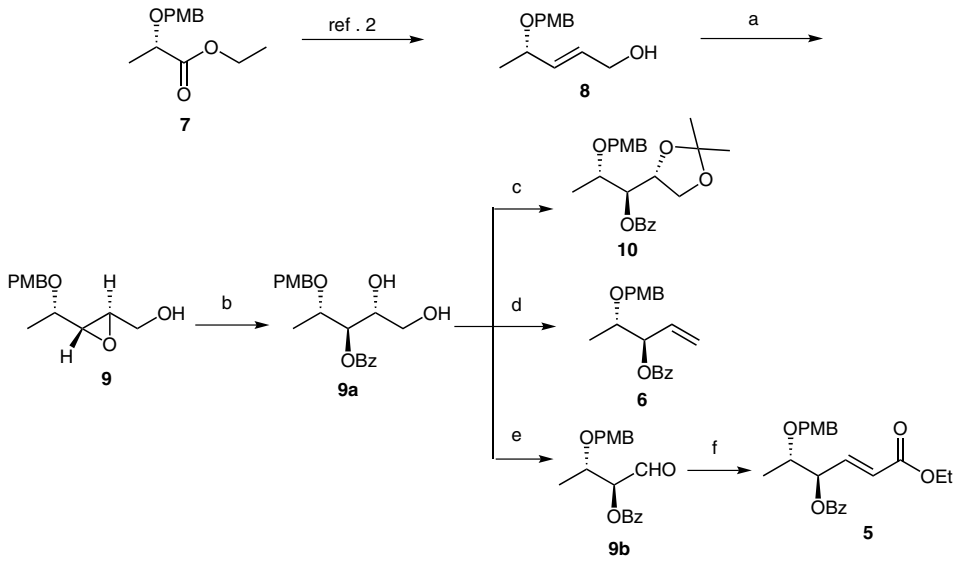
The retrosynthetic analysis of **1** is presented in Scheme 1. Macrocyclization of **2** was envisaged to give **1**, while the bisolefin **2** was proposed to be available from alcohol **3** and acid **4**. Alcohol **3** was in turn envisaged to be derived from **5** and **6**, with both fragments being formed from **7** as a common starting material. Thus, the main synthetic strategy involves regioselective nucleophilic opening of an epoxy alcohol, RCM-mediated macrocyclization and Yamaguchi esterification.

The macrosphelide I, fragment **5**, with two contiguous stereogenic centers and an ester group correlating to C(11)–O(16), and **6**, with two stereogenic centers correlating to the C(6)–O(10) unit of macrosphelide I (**1**) were obtained from ethyl L-(+)-lactate, which provided one stereogenic center. The other stereocenter was created by a regioselective nucleophilic opening reaction of an epoxy alcohol with benzoic acid.[6] Fragment **4**, which constitutes the



Scheme 1 Retrosynthesis of macrosphelide I (**1**)

SYNLETT 2014, 25, 2039–2043
Advanced online publication: 16.07.2014
DOI: 10.1055/s-0033-1338657; Art ID: st-2014-d0371-l



Scheme 2 *Reagents and conditions*: (a) (–)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, 4 Å MS, CH_2Cl_2, –20 °C, 12 h, 88%; (b) Ti(O*i*-Pr)$_4$, benzoic acid, CH_2Cl_2, 0 °C to r.t., 2 h; (c) 2,2-DMP, cat. PTSA, 0 °C to r.t., 2 h (83% in two steps); (d) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C to r.t., 4 h, (68% in two steps); (e) $NaIO_4$, acetone–H_2O, 0 °C to r.t., 1 h; (f) Ph_3P=CHCOOEt, benzene, reflux, 2 h, (77% in three steps).

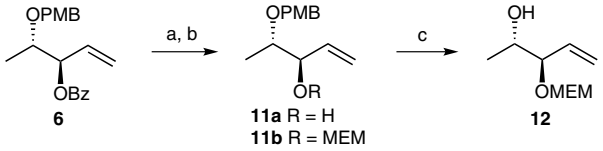
C(1)–O(4) unit of macrosphelide I (**1**), was prepared from (*R*)-3-hydroxybutyrate **16**.

According to the synthetic strategy, the known allylic alcohol **8**[7] was subjected to Sharpless epoxidation on treatment with (–)-DIPT, Ti(O*i*-Pr)$_4$ and TBHP in anhydrous CH_2Cl_2 at –20 °C for 12 hours to furnish epoxide **9** in 88% yield (Scheme 2).

Regioselective ring opening of the epoxide **9** with benzoic acid and Ti(O*i*-Pr)$_4$ in anhydrous CH_2Cl_2 at room temperature for 24 hours afforded the 1,2-diol as the exclusive product. In order to overcome difficulties in separation of the diol from the reaction mixture (as the epoxide and diol have the same R_f value) and to verify whether the ring opening of the epoxy alcohol had favored the formation of the 1,2-diol or 1,3-diol, the crude diol was converted into **10**.

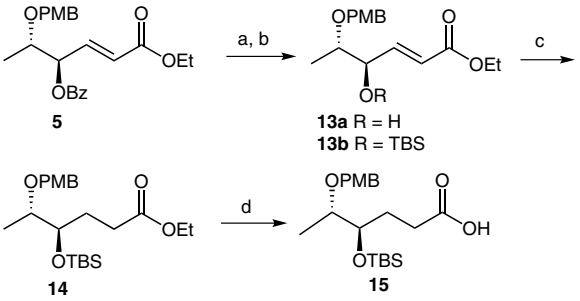
Thus, treatment of **9a** with 2,2-dimethoxypropane and PTSA in CH_2Cl_2 at 0 °C to room temperature for two hours gave **10** in 83% of overall yield. Diol **9a** was used as common intermediate for the synthesis of **5** and **6**. Accordingly, diol **9a**, on treatment with Ph_3P, imidazole and I_2[8] at room temperature for four hours gave olefin **6** in 68% yield (Scheme 2). Equally, diol **9a**, on oxidative cleavage with $NaIO_4$ in acetone/water at room temperature for one hour, gave the corresponding aldehyde **9b**, which on subsequent treatment with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux for two hours afforded **5** in 77% yield.

Base hydrolysis of benzoate **6** with K_2CO_3 in MeOH at room temperature for one hour afforded the allyl alcohol **11a**[5f] in 89% yield. Further, treatment of **11a** with MEMCl and DIPEA in CH_2Cl_2 at room temperature for 12 hours gave **11b** in 76% yield (Scheme 3). Finally, oxidative deprotection of **11** with DDQ in CH_2Cl_2 and H_2O at room temperature for 30 minutes furnished alcohol **12**[9] in 84% yield.



Scheme 3 *Reagents and conditions*: (a) K_2CO_3, MeOH, r.t., 1 h, 89%; (b) MEMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 12 h, 76%; (c) DDQ, CH_2Cl_2, 0 °C to r.t., 84%.

Benzoate **5** on mild base hydrolysis with K_2CO_3 in MeOH at room temperature for one hour gave alcohol **13a** in 78% yield (Scheme 4). Treatment of **13a** with TBSCl and imidazole in CH_2Cl_2 at room temperature for two hours gave **13b** in 86% yield.

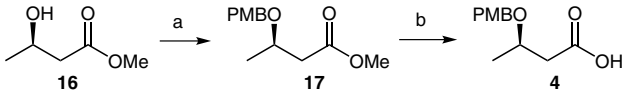


Scheme 4 *Reagents and conditions*: (a) K_2CO_3, MeOH, r.t., 1 h, 78%; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 2 h, 86%; (c) PtO_2, H_2, EtOAc, r.t., 3 h, 88%; (d) LiOH, THF–MeOH–H_2O (3:1:1), r.t., 3 h, 89%.

Subsequently, catalytic hydrogenation of **13** with PtO_2 in EtOAc under hydrogen atmosphere at room temperature

for three hours gave **14** in 88% yield. Ester **14**, on hydrolysis with LiOH in THF–MeOH–H_2O (3:1:1) at room temperature for three hours, afforded acid **15** in 89% yield.

Having synthesized **12** and **15**, the next goal was the synthesis of **4**. Accordingly, commercially available methyl (*R*)-3-hydroxybutyrate (**16**), on reaction with *p*-methoxybenzyl trichloroacetimidate and PTSA (cat.) in CH_2Cl_2, gave **17** in 72% yield (Scheme 5). Hydrolysis of ester **17** with LiOH in THF–MeOH–H_2O (3:1:1) at room temperature for three hours afforded acid **4**[10] in 82% yield (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) PMBOC(=NH)Cl_3, PTSA, CH_2Cl_2, 0 °C to r.t., 72%; (b) LiOH, THF–MeOH–H_2O (3:1:1), r.t., 3 h, 82%.

Having synthesized all the three fragments **12**, **15** and **4**, our next aim was their further conversion into the macrosphelide I (**1**) core structure. Accordingly, coupling of acid **15** with alcohol **12** was achieved using Yamaguchi esterification[11] conditions in the presence of 2,4,6-trichlorobenzoyl chloride and Et_3N in THF through the anhydride prepared from **15** in the presence of DMAP in toluene to afford ester **18** in 73% yield (Scheme 6). Ester **18** on oxidative deprotection with DDQ in aqueous CH_2Cl_2 gave alcohol **3** in 82% yield.

Yamaguchi esterification of acid **4** with alcohol **3** by the use of 2,4,6-trichlorobenzoyl chloride and Et_3N in THF in the presence of DMAP in toluene afforded ester **19** in 62% yield. Reaction of **19** with DDQ in aqueous CH_2Cl_2 at room temperature for one hour furnished alcohol **20** in 88% yield and esterification of alcohol **20** with acryloyl chloride and DIPEA in CH_2Cl_2 at room temperature for 40 minutes furnished the bisolefin **2** in 80% yield. Bisolefin **2** on macrocyclization by RCM reaction in the presence of Grubbs II catalyst[12] (5 mol%) in CH_2Cl_2 at reflux for 18 hours gave **21** in 74% yield (Scheme 6).

Reaction of **21** with CF_3COOH in CH_2Cl_2 at room temperature for 24 hours afforded **1** in 67% yield (Scheme 6). The specific rotation value of the synthetic **1** {$[\alpha]^{22}_D$ +12.4 (c = 0.09, $CHCl_3$)}, was in good accordance with that of the natural product {$[\alpha]^{22}_D$ +10.3 (c = 0.31, EtOH)}.[3] The IR, mass, ^{1}H NMR and ^{13}C NMR data of the synthetic macrosphelide I (**1**)[13] were also in good accordance with those of the natural product.[3]

In conclusion, the synthesis of macrosphelide I (**1**)[3] has been achieved from ethyl L-(+)-lactate (**7**) and methyl (*R*)-3-hydroxybutyrate (**16**), wherein the required stereochemical configurations at C-8 and C-14 were successfully secured by using regioselective nucleophilic opening reaction of an epoxy alcohol with benzoic acid. The Yamaguchi protocol was quite efficient for the triester formation, while, the triester bisolefin was very effectively transformed into the target natural product **1** using a RCM method under Grubbs' reaction conditions.

Acknowledgment

B.V. thanks the CSIR, New Delhi, for financial support in the form of a fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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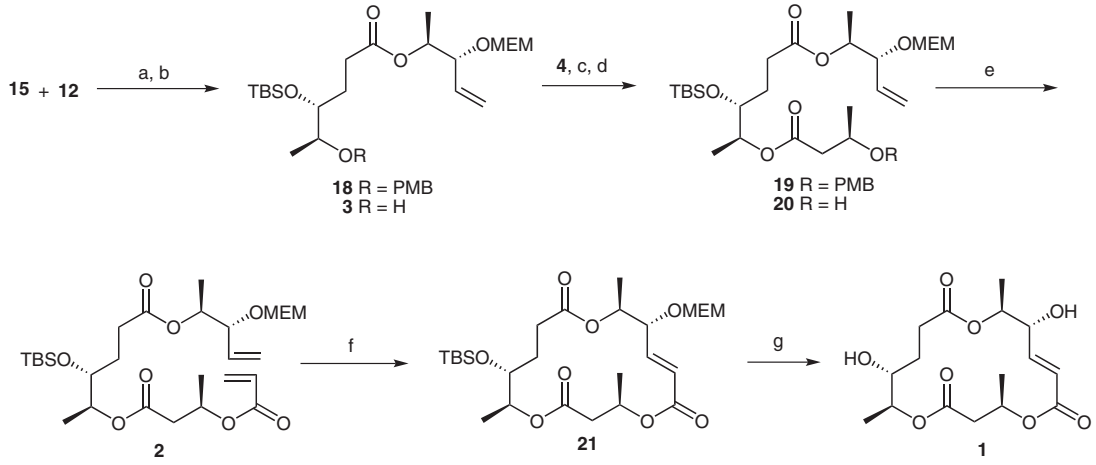

Scheme 6 *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 2 h, DMAP, toluene, 0 °C to r.t., 5 h, 73%; (b) DDQ, CH_2Cl_2–H_2O (19:1), 0 °C to r.t., 1 h, 82%; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 2 h, then alcohol **3**, DMAP, toluene, 0 °C to r.t., 5 h, 62%; (d) DDQ, CH_2Cl_2–H_2O (19:1), 0 °C to r.t., 1 h, 88%; (e) acryloyl chloride, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 40 min, 80%; (f) Grubbs II, CH_2Cl_2, reflux, 18 h, 74%; (g) TFA, CH_2Cl_2, 0 °C, 24 h, 67%.

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(13) **Spectroscopic Data for Selected Compounds**: **(2*S*,3*R*,*E*)-6-Ethoxy-2-(4-methoxybenzyloxy)-6-oxohex-4-en-3-ylbenzoate (5)**: yellow syrup; $[\alpha]_D^{25}$ +91.7 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.7 Hz, 2 H, ArH), 7.58 (t, *J* = 7.7 Hz, 1 H, ArH), 7.46 (t, *J* = 7.7 Hz, 2 H, ArH), 7.23–7.25 (m, 3 H, ArH), 7.04 (dd, *J* = 5.0, 15.5 Hz, 1 H, ArH), 6.82 (d, *J* = 8.6 Hz, 2 H, =CH), 6.04 (d, *J* = 16.0 Hz, 1 H, =CH), 5.77–5.78 (m, 1 H, OCHBz), 4.55 (dd, *J* = 11.4 Hz, 2 H, CH_2Ar), 4.19 (q, *J* = 6.8 Hz, 2 H, OCH), 3.76–3.84 (m, 4 H, OCH_2, OCH_2), 1.21–1.33 (m, 6 H, 2 × Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 165.3, 159.2, 142.2, 133.2, 130.0, 129.7, 129.3, 128.4, 123.0, 113.7, 75.0, 74.6, 70.9, 60.5, 55.1, 15.9, 14.1. IR (neat): 3396, 3032, 2941, 1721, 1453, 1112 cm^{-1}. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{26}O_6Na$: 421.1652; found: 421.4387. **(3*R*,4*S*)-4-(4-Methoxybenzyloxy)pent-1-en-3-ylbenzoate (6)**: colorless syrup; $[\alpha]_D^{25}$ +43.7 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 6.9 Hz, 2 H, ArH), 7.57 (t, *J* = 7.1 Hz, 1 H, ArH), 7.42–7.47 (m, 2 H, ArH), 7.25–7.27 (m, 2 H, ArH), 6.81 (d, *J* = 8.4 Hz, 2 H, ArH), 5.93–6.05 (m, 1 H, =CH), 5.59–5.62 (m, 1 H, CHOBz), 5.29–5.41 (m, 2 H, $=CH_2$), 4.60 (dd, *J* = 11.3 Hz, 2 H, CH_2Ar), 3.74–3.85 (m, 4 H, OCH, OMe), 1.25 (d, *J* = 6.4 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 159.1, 132.9, 130.4, 129.6, 129.2, 128.3, 118.3, 113.7, 76.5, 75.4, 70.8, 55.1, 15.8. IR (neat): 3396, 3067, 2967, 2969, 1721, 1597, 1453, 1279, 1113 cm^{-1}. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}O_4Na$: 349.1416; found: 349.3761. **(4*R*,5S)-4-*(tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)hexanoic Acid (15)**: colorless oil; $[\alpha]_D^{25}$ +44.6 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.9 Hz, 2 H, ArH), 6.85 (d, 2 H, *J* = 8.4 Hz, ArH), 4.48 (dd, *J* = 11.3 Hz, 2 H, CH_2Ar), 3.79 (s, 3 H, OMe), 3.67–3.71 (m, 1 H, OCH), 3.38–3.44 (m, 1 H, OCH), 2.36–2.44 (m, 2 H, CH_2CO), 1.88–1.96 (m, 1 H, CH), 1.75–1.82 (m, 1 H, CH), 1.16 (d, *J* = 6.4 Hz, 3 H, Me), 0.89 (br s, 9 H, 3 × Me), 0.05 (s, 6 H, 2 × Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 130.7, 129.2, 113.7, 76.9, 74.1, 70.6, 60.2, 55.2, 29.4, 27.8, 25.9 (3 × C), 18.1, 15.6, –4.2, –4.6. IR (neat): 3031, 2930, 2857, 1710, 1097 cm^{-1}. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{34}O_5NaSi$: 405.2091; found: 405.2073. **(4*R*,5*S*)-{(2*S*,3*R*)-3-[(2-Methoxyethoxy)methoxy]pent-4-en-2-yl}-4-(*tert*-butyldimethylsilyloxy)-5-hydroxyhexanoate (3)**: colorless liquid; $[\alpha]_D^{25}$ –145.0 (*c* = 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.68–5.74 (m, 1 H, $=CH=CH_2$), 5.30 (d, *J* = 12.5 Hz, 2 H, $=CH_2$), 5.00–5.05 (m, 1 H, CHCO), 4.69–4.76 (m, 2 H, OCH_2), 4.07–4.11 (m, 1 H, OCH), 3.76–3.83 (m, 1 H, OCH), 3.71–3.72 (m, 1 H, OCH), 3.60–3.68 (m, 2 H, OCH_2), 3.54–3.56 (m, 2 H, OCH_2), 3.39 (s, 3 H, OMe), 2.42–2.50 (m, 1 H, CHC=O), 2.28–2.35 (m, 1 H, CHCO), 1.84–1.91 (m, 1 H, CH), 1.71–1.78 (m, 1 H, CH), 1.23 (d, *J* = 6.5 Hz, 3 H, Me), 1.13 (d, *J* = 6.5 Hz, 3 H, Me), 0.91 (s, 9 H, 3 × Me), 0.09 (s, 6 H, 2 × Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 133.9, 119.7, 92.8, 78.7, 74.9, 71.6 (2 × C), 69.8, 66.9, 58.9, 29.8, 25.8 (3 × C), 25.6, 18.0, 17.7, 15.3, –4.5 (2 × C). IR (neat): 3430, 2957, 2930, 2856, 1719, 1654, 1465 cm^{-1}. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{42}O_7NaSi$: 457.2592; found: 457.2590. **(4*R*,5*S*)-{(2*S*,3*R*)-3-[(2-Methoxyethoxy)methoxy]pent-4-en-2-yl}-4-(*tert*-butyldimethylsilyloxy)-5-[(*R*)-3-hydroxybutanoyloxy]hexanoate (20)**: colorless liquid; $[\alpha]_D^{25}$ –127.8(*c* = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.63–5.77 (m, 1 H, $CH=CH_2$), 5.25–5.33 (m, 2 H, $=CH_2$), 4.98–5.05 (m, 1 H, CHCO), 4.85–4.93 (m, 1 H, CHCO), 4.77 (d, *J* = 6.7 Hz, 1 H, OCH), 4.67 (d, *J* = 6.7 Hz, 2 H, OCH_2), 4.14–4.26 (m, 2 H, OCH_2), 4.04–4.15 (m, 2 H, OCH_2), 3.70–3.98 (m, 2 H, OCH_2), 3.58–3.67 (m, 1 H, OCH), 3.51–3.58 (m, 1 H, OCH), 3.39 (s, 3 H, OMe), 3.07–3.13 (m, 1 H, OCH), 2.29–2.48 (m, 4 H, CH_2CO, CH_2CO), 1.73–1.83 (m, 2 H, CH_2), 1.17–1.26 (m, 9 H, 3 × Me), 0.89 (s, 9 H, 3 × Me), 0.05 (s, 6 H, 2 × Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 172.1, 133.9, 129.1, 119.8, 92.8, 78.7, 73.2, 72.9, 71.6 (2 × C), 66.9, 64.1, 59.0, 43.1, 30.1, 28.0, 25.8 (3 × C), 22.3, 18.1, 15.4, 14.6, –4.4, –4.6. IR (neat): 3352, 2983, 2842, 1719, 1654, 1553, 1402 cm^{-1}. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{48}O_9NaSi$: 543.2959; found: 543.2963. **(4*R*,9*R*,10*S*,15*R*,16*S*,*E*)-15-*(tert*-Butyldimethylsilyloxy)-9-[(2-methoxyethoxy)methoxy]-4,10,16-trimethyl-1,5,11-trioxacyclohexadec-7-ene-2,6,12-trione (21)**: yellow liquid; $[\alpha]_D^{25}$ –84.0(*c* = 0.45, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 6.9, 15.4 Hz, 1 H, CH=CH), 6.02 (dd, *J* = 15.4 Hz, 1 H, CH=CH), 5.23–5.29 (m, 1 H, CHCO), 5.07–5.12 (m, 1 H, CHCO), 4.80–4.86 (m, 1 H, CHCO), 4.69 (dd, *J* = 16.9 Hz, 2 H, OCH_2), 4.19–4.21 (m, 1 H, OCH), 3.74–3.78 (m, 1 H, OCH), 3.61–3.67 (m, 2 H,

OCH_2), 3.53–3.54 (m, 2 H, OCH_2), 3.38 (s, 3 H, OMe), 2.74 (dd, *J* = 3.9, 14.4 Hz, 1 H, =CHCH), 2.53 (dd, *J* = 6.4, 14.9 Hz, 1 H, =CHCH), 2.29–2.44 (m, 2 H, $=CHCH_2$), 1.55–1.79 (m, 2 H, CH_2), 1.43 (d, *J* = 6.4 Hz, 3 H, Me), 1.30 (d, *J* = 6.4 Hz, 3 H, Me), 1.17 (d, *J* = 6.4 Hz, 3 H, Me), 0.88 (s, 9 H, 3 × Me), 0.07 (d, *J* = 15.4 Hz, 6 H, 2 × Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 169.3, 164.6, 143.0, 125.0, 93.3, 77.5, 73.7, 73.1, 71.5, 71.1, 67.5, 67.2, 59.0, 40.5, 30.7, 29.6, 28.3, 25.7 (3 × C), 19.5, 17.3, 15.5, –4.4, –4.6. IR (neat): 2856, 1734, 1657, 1615, 1517, 1466, 1093 cm^{-1}. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{46}O_{10}NaSi$: 569.2752; found: 569.2763.

Macrosphelide I (1): colorless syrup; $[\alpha]_D^{25}$ +12.4 (*c* = 0.09, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.6 Hz, 3 H, Me), 1.32 (d, *J* = 6.6 Hz, 3 H, Me), 1.46–1.47 (m, 1 H, CH), 1.47 (d, *J* = 6.6 Hz, 3 H, Me), 1.68–1.74 (m, 1 H, CH), 2.36 (dt, *J* = 5.1, 14.7 Hz, 1 H, CH), 2.53 (br s, 1 H, OH), 2.62–2.68 (m, 2 H, CH_2), 2.70 (dd, *J* = 2.9, 16.1 Hz, 1 H, CH), 3.25 (d, *J* = 11.4 Hz, 1 H, CH), 3.83 (br s, 1 H, OH), 4.29 (br s, 1 H, CH), 4.83–4.87 (m, 2 H, 2 × CH), 5.65 (m, 1 H, CH), 6.24 (dd, *J* = 2.2, 15.4 Hz, 1 H, HC=CH), 7.21 (dd, *J* = 2.9, 15.4 Hz, 1 H, CH=CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 12.70, 18.60, 20.10, 27.50, 30.40, 41.80, 67.00, 71.10, 74.40, 74.80, 78.30, 121.90, 147.80, 166.90, 168.60, 175.30. IR (neat): 3447, 2925, 1628 cm^{-1}. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{24}O_8Na$: 367.1368; found: 367.1383.