Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2175–2184

RCM mediated synthesis of macrosphelides I and G☆

Gangavaram V. M. Sharma* and Kagita Veera Babu

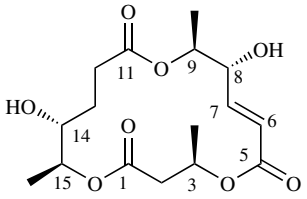
D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 2 July 2007; accepted 13 August 2007

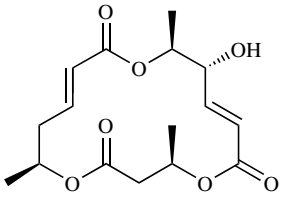
Abstract—The total synthesis of 16-membered macrolides, macraosphelides I and G, has been achieved starting from ethyl-(*S*)-lactate and (*S*)-malic acid. A combination of Jacobsen's hydrolytic kinetic resolution and Sharpless epoxidation is used for the creation of two stereogenic centres, while Yamaguchi esterification and ring-closing metathesis strategies were used for the construction of the lactone ring.

1. Introduction

Macrosphelides A–L were isolated as inhibitors of the adhesion of HL-60 cells to a monolayer of LPS-activated human-umbilical-vein endothelial cells. Macrosphelides I **1** and G **2** were isolated[1] along with A, C, E and H from a strain of *Periconia byssoides* separated from the gastrointestinal tract of the sea hare *Aplysia kurodai*. The absolute stereostructures of **1** and **2** were described by Numata et al.[1] based on spectroscopic analyses and some chemical transformations. Macrolide **1** is a 16-membered tris-lactone with five asymmetric centres; the absolute configuration was determined as (3*R*,8*R*,9*S*,14*R*,15*S*). The cytotoxic activity[1] of **1** was examined against P388 lymphocytic leukaemia cells and HL-60 cell in vitro. The ED_{50} value of **1** was found to be 20 μg cm^{-1} against P388 cells.[1] Due to their biological profiles and structural features, macrosphelides[2] have become highly attractive target molecules for the synthesis and use as the next generation of chemotherapeutical drugs against cancer. In continuation of our interest on the synthesis of macrolides,[3] we herein report the first synthesis of **1** and the total synthesis of **2**.



Macrosphelide **I 1**



Macrosphelide **G 2**

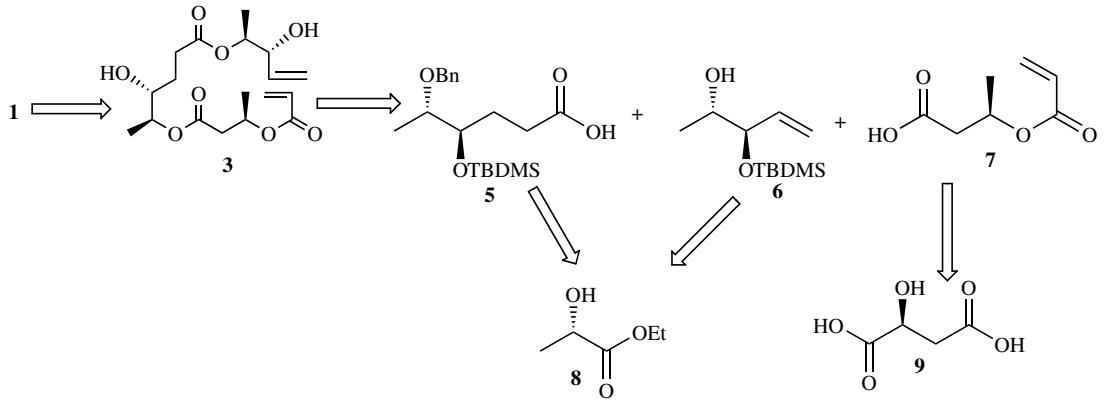
2. Results and discussion

Retrosynthetic analysis of **1** and **2** (Schemes 1 and 2) revealed that bis-olefins **3** and **4** could be late stage intermediates, which upon an RCM protocol would generate the macrolide ring structures. Ester **3** could in turn be realized by sequential esterification of **5** with **6** and **7**, while **6** and **7** could be envisaged from the easily accessible hydroxy acids viz. (*S*)-lactic acid **8** and (*S*)-malic acid **9**, respectively. Likewise, **4** could be realized by sequential esterification of **10** with **6** and **7**, while **10** could be envisaged from the easily accessible (*S*)-propylene oxide **11**. Thus, segments **6** and **7** are common intermediates for the synthesis of both **1** and **2**. The main strategy would be to condense the fragments through a Yamaguchi esterification reaction and C–C bond formation through an RCM protocol to result in the macrocyclic ring system.

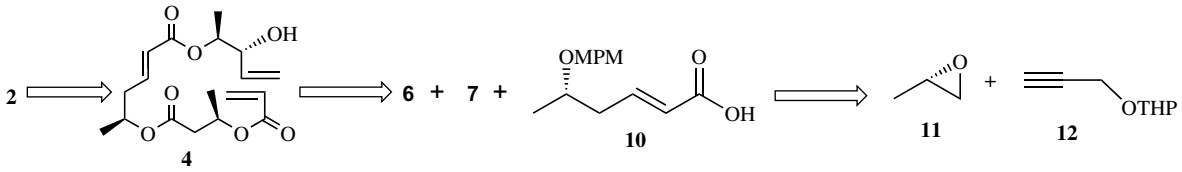
Segments **5** and **6** were synthesized from (*S*)-lactic acid **8**. Accordingly, allylic alcohol **13** prepared from the known alcohol[4] was subjected to Sharpless epoxidation with (+)-DIPT, $Ti(O^iPr)_4$ and cumene hydroperoxide in dry CH_2Cl_2 to afford **14** (88%). Treatment of alcohol **14** with Ph_3P and $NaHCO_3$ in CCl_4 gave chloride **15** in 88% yield, which on treatment with Na in dry ether afforded **16** (84%). Silylation of **16** with TBDMSCl and imidazole in CH_2Cl_2

☆ IICT Communication No. 070127.
* Corresponding author. E-mail: esmvee@iict.res.in

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.08.017



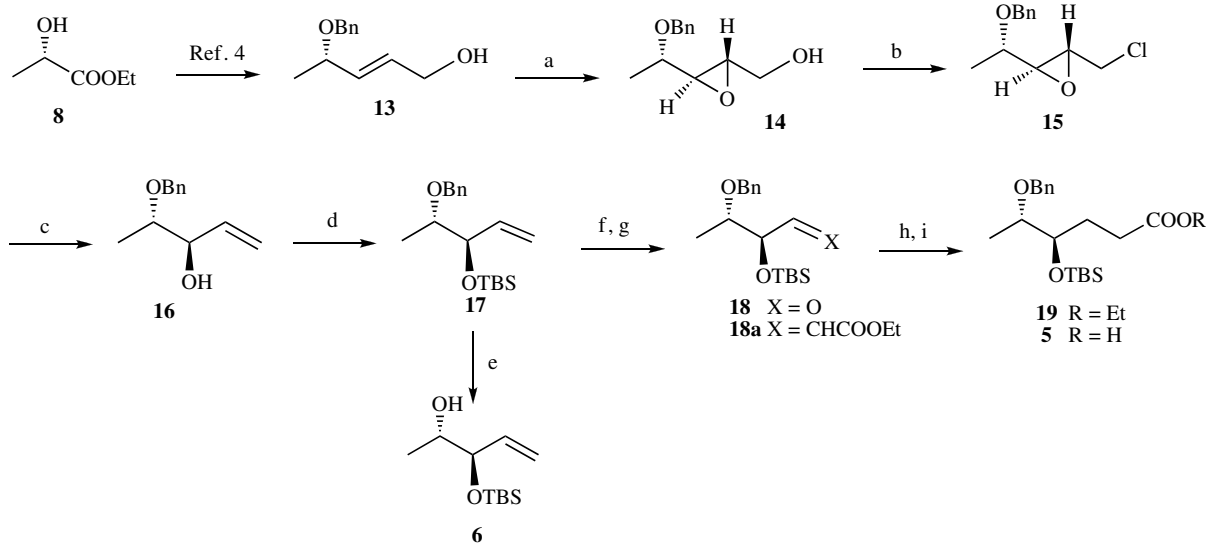
Scheme 1. Retrosynthesis of macrosphelide I (**1**).



Scheme 2. Retrosynthesis of macrosphelide G (**2**).

furnished ether **17** (84%), which on debenzylation with DDQ in aq CH_2Cl_2 afforded **6** in 86% yield. Olefin **17** was subjected to ozonolysis in CH_2Cl_2 to give the corresponding aldehyde **18**, which on immediate treatment with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene afforded **18a** in 77% yield. Catalytic hydrogenation of **18a** with PtO_2 in EtOAc under a hydrogen atmosphere gave ester **19** (92%), which on subsequent hydrolysis with LiOH in THF/MeOH/H_2O (3:1:1) afforded acid **5** in 82% yield, $[\alpha]_D = +22.0$ (*c* 0.2, $CHCl_3$). Thus, both segments **5** and **6**, encompassing four of the five stereocentres, were successfully prepared from (*S*)-lactic acid **8** (Scheme 3).

The known[5] alcohol **20** [prepared from (*S*)-malic acid] was treated with MPM–Br and NaH in THF to give ether **21** in 83% yield, which on acetonide deprotection using PTSA (cat.) in methanol afforded diol **22** (85%). Treatment of **22** with *p*-TsCl and Et_3N in CH_2Cl_2 gave monotosylate **22a** (65%), which on treatment with LAH in THF afforded **23** in 89% yield. Reaction of **23** with acryloyl chloride and DIPEA in CH_2Cl_2 afforded acrylate ester **24** (92%). Oxidative deprotection of **24** on treatment with DDQ in aq CH_2Cl_2 furnished alcohol **24a** in 89% yield. Oxidation of **24a** with Dess–Martin periodinane[6] in CH_2Cl_2 gave the corresponding aldehyde **25**, which on further oxidation



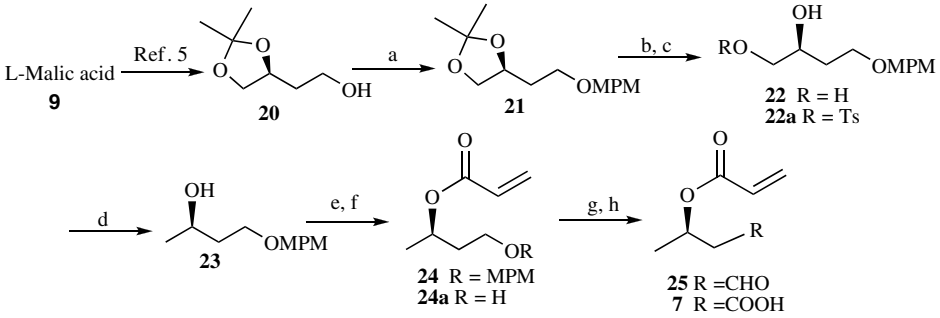
Scheme 3. Reagents and conditions: (a) (+)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, dry CH_2Cl_2, −20 °C, 5 h; (b) Ph_3P, CCl_4, cat. $NaHCO_3$, reflux, 3 h; (c) Na, dry ether, 0 °C–rt,12 h; (d) TBDMSCl, imidazole, CH_2Cl_2, rt, 3 h; (e) DDQ, aq CH_2Cl_2 (19:1), reflux, 3 h; (f) O_3, CH_2Cl_2, dimethylsulfide, −78 °C, 15 min; (g) $Ph_3P{=}CHCOOEt$, benzene, reflux, 2 h; (h) PtO_2, H_2, ethyl acetate, rt, 3 h; (i) LiOH, THF/MeOH/H_2O (3:1:1), rt, 4 h.

with $NaClO_2$ and NaH_2PO_4, 2-methyl-2-butene in aq *t*-butanol afforded **7** in 89% yield (Scheme 4).

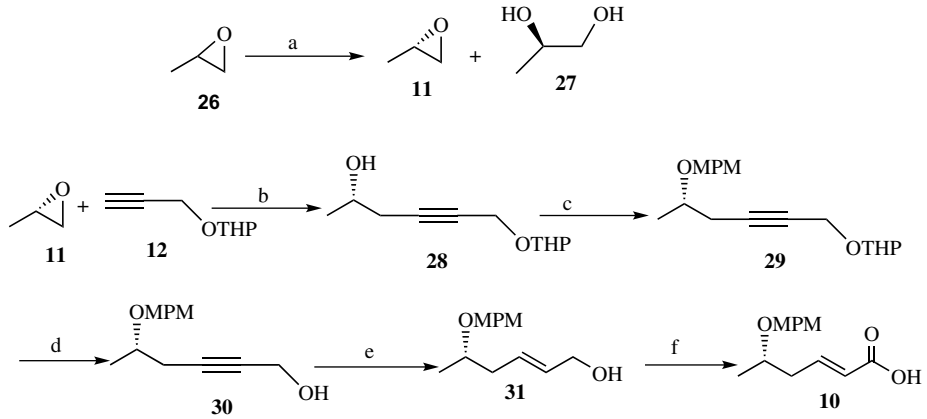
The synthesis of fragment **10** began with the kinetic resolution of **26** (Scheme 5) under Jacobsen reaction conditions[7] using (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) to give chiral epoxide **11** (43%) and diol **27**. (*S*)-Propylene oxide **11** was treated with 2-(2-propynyl)tetrahydro-2*H*-pyran **12** in the presence of *n*-BuLi and $BF_3{\cdot}Et_2O$ in THF to give **28** in 64% yield, which on treatment with MPM–Br and NaH in THF afforded **29** in 73% yield. Ether **29** was treated with cat. PTSA in THF to give **30** in 87% yield, which on reduction with LAH in THF afforded **31** in 91% yield. Swern oxidation of alcohol **31** gave the corresponding aldehyde, which on further oxidation with $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene in aq *t*-butanol afforded **10** in 76% yield.

Acid **5** under Yamaguchi[8] reaction conditions using 2,4,6-trichlorobenzoyl chloride and Et_3N in THF gave the mixed anhydride, which in turn was condensed with alcohol **6** in the presence of DMAP in toluene to afford ester **32** in 82% yield (Scheme 6). Oxidative deprotection of **32** on treatment with DDQ in aq CH_2Cl_2 gave hydroxy ester **33** in 71% yield. Esterification of **33** with the mixed anhydride prepared from acid **7** under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N in THF) in the presence of DMAP in toluene afforded **34** in 52% yield. Desilylation of tris-ester **34** with HF–pyridine complex in THF gave **3** in 84% yield. Finally, ester **3** on treatment with Grubbs'[9] second generation catalyst in CH_2Cl_2 at reflux for 24 h afforded macrosphelide I **1** in 84% yield, whose spectral and specific rotation data were comparable with the data reported in the literature.[1] This report constitutes the first total synthesis of **1**.

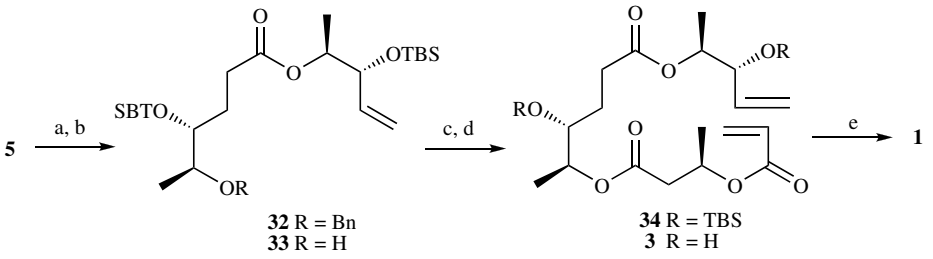
For the synthesis of macrosphelide G **2**, acid **10** was esterified with **6** via a mixed anhydride prepared by the reaction of **10** with 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) in the presence of DMAP in toluene to afford ester **35** in 68% yield (Scheme 7). Deprotection of the MPM group in ester **35** with DDQ in aq CH_2Cl_2 afforded alcohol **36** in 88% yield. Esterification of acid **7** under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP in toluene) with alcohol **36** afforded **37** in 55% yield. Tris-ester **37** on treatment with HF–pyridine complex in THF removed the TBS group and gave alcohol **4** in 93% yield. Finally, treatment of **37** with Grubbs' catalyst II[9] in CH_2Cl_2 afforded macrosphelide G **2** in 82% yield, $[\alpha]_D = +54.3$ (*c* 0.1, $CHCl_3$), whose spectral data was comparable with the reported data.



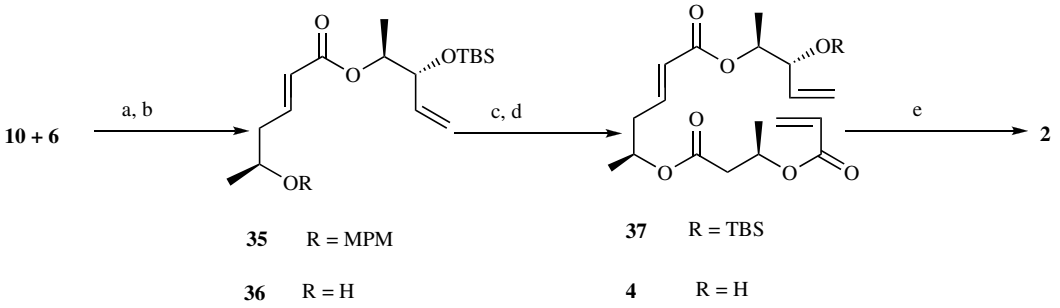
Scheme 4. Reagents and conditions: (a) MPM–Br, NaH, THF, 6 h; (b) cat. PTSA, MeOH, rt, 5 h; (c) TsCl, Et_3N, CH_2Cl_2, rt, 36 h, (d) LAH, THF, 0 °C–rt, 3 h; (e) acryloyl chloride, DIPEA, CH_2Cl_2, rt, 3 h; (f) DDQ, aq CH_2Cl_2, rt, 1 h; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuoH/water (2:1), 0 °C–rt, 3 h.



Scheme 5. Reagents and conditions: (a) (*S*,*S*)-Jacobsen catalyst, H_2O, AcOH, rt, 12 h; (b) *n*-BuLi, $BF_3{\cdot}Et_2O$, dry THF, −78 °C, 3 h; (c) MPM–Br, NaH, THF, rt, 6 h; (d) cat. PTSA, MeOH, rt, 1 h; (e) LAH, dry THF, 0 °C–rt, 2 h; (f) (i) $(COCl)_2$, DMSO, −78 °C, 2 h; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/water (2:1), 0 °C–rt, 3 h.



Scheme 6. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then alcohol **6**, DMAP, toluene, rt, 12 h; (b) DDQ, aq CH_2Cl_2 (19:1), reflux, 3 h; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, **7**, DMAP, toluene, rt, 24 h; (d) HF–pyridine complex, rt, 6 h; (e) Grubbs second generation catalyst, CH_2Cl_2, reflux, 24 h.



Scheme 7. Synthesis of macrosphelide G (**1**). Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 12 h; (b) DDQ, aq CH_2Cl_2 (19:1), rt, 1 h; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, **7**, DMAP, toluene, rt, 24 h; (d) HF–pyridine complex, rt, 6 h; (e) Grubbs catalyst II, CH_2Cl_2, reflux, 24 h.

3. Conclusion

Thus, in conclusion, the present report describes the first total synthesis of macrosphelide I **1** and the total synthesis of macrosphelide G by a combination of asymmetric synthesis and chiron approach. Of the five stereocentres, four are obtained from (*S*)-lactic acid and Sharpless epoxidation, while the remaining stereocentre is utilized from (*S*)-malic acid. The Yamaguchi protocol was efficiently utilized for the formation of the tris-ester, while Grubbs' second generation catalyst was used for the construction of the macrolide ring through an RCM protocol. In this series of compounds, the present synthesis utilized the RCM protocol for the construction of C-6 and C-7, with the specific purpose of establishing a general protocol, since the O4–O10 segment is found to be common in most of the macrosphelides. Thus, this flexible protocol developed in the present study paves the way for the construction of macrosphelides and macrosphelide like molecules for further biological studies.

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, Unity 400 MHz and Inova-500 MHz with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in Hz. IR spectra were recorded on at 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. (2*S*,3*R*)-3-[(1*S*)-1-(Benzyloxy)ethyl]oxiran-2-ylmethanol 14. To a stirred solution of (+)-DIPT (2.35 g, 10 mmol) in CH_2Cl_2 (15 mL) at −20 °C containing 4 Å MS (0.3 g), sequentially $Ti(O^iPr)_4$ (2.37 g, 8.3 mmol) and cumenehydroperoxide (5.14 g, 33.4 mmol) were added and stirred for 20 min. A solution of **13**[4] (3 g, 16.6 mmol) in CH_2Cl_2 (15 mL) was added and stirred for 5 h at −20 °C. The reaction mixture was quenched with 10% KOH solution (3 g in 30 mL brine), stirred for 3 h and filtered. The organic layers were dried over Na_2SO_4, evaporated and the residue obtained was purified by column chromatography (Silica gel, EtOAc/hexane, 2:3) to furnish **14** (2.87 g, 88%) as a yellow syrup. $[\alpha]_D = -50.9$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.58 (br s, 1H, –OH), 2.85–2.95 (m, 1H, –CH), 3.01–3.09 (m, 1H, –CH), 3.28–3.65 (m, 2H, $-CH_2$), 3.77–3.93 (m, 1H, –CH), 4.56 (s,

2H, $-CH_2C_6H_4$), 7.23–7.31 (m, 5H, C_6H_5); IR (neat): 3422, 3063, 2978, 2929, 2870, 1605, 1453 cm^{-1}; FABMS: 231 $(M+Na)^+$, 226 $(M+NH_4)^+$.

4.1.2. (2*R*,3*R*)-2-[(1*S*)-1-(Benzyloxy)ethyl]-3-(chloromethyl)-oxirane 15. To a stirred solution of **14** (2.2 g, 11.23 mmol) in CCl_4 (20 mL), Ph_3P (3.24 g, 12.34 mmol) and $NaHCO_3$ (cat.) were added and then heated at reflux for 3 h. The reaction mixture was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 5:95) to afford **15** (2.2 g, 88%) as a yellow syrup. $[\alpha]_D = -20.7$ (*c* 0.38, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 2.8 (dd, 1H, $J = 1.9$, 5.3 Hz, –CH), 3.13 (ddd, 1H, $J = 1.9$, 5.7, 11.33 Hz, –CH), 3.33–3.42 (m, 2H, $-CH_2$), 3.54–3.60 (m, 1H, –CH), 4.57 (d, 2H, $J = 7.6$ Hz, $-CH_2C_6H_4$), 7.26–7.31 (m, 5H, C_6H_5); IR (neat): 3063, 2926, 2864, 1606, 1451 cm^{-1}; ESIMS: 226 $(M)^+$.

4.1.3. (3*R*,4*S*)-4-(Benzyloxy)-1-penten-3-ol 16. To a suspension of Na (0.45 g, 19.6 mmol) in dry ether (10 mL), a solution of **15** (2.1 g, 9.8 mmol) in dry ether (10 mL) was added at 0 °C and stirred at room temperature for 12 h. The reaction mixture was quenched with methanol (5 mL), evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 15:85) to furnish **16** (1.49 g, 84%) as a yellow syrup. $[\alpha]_D = +14.9$ (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.12 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 2.07 (br s, 1H, –OH), 3.53–3.59 (m, 1H, –CH), 4.18–4.21 (m, 1H, –CH), 4.56 (q, 2H, $J = 11.7$ Hz, $-CH_2C_6H_4$), 5.16–5.33 (m, 2H, olefinic), 5.76–5.87 (m, 1H, olefinic), 7.28–7.31 (m, 5H, C_6H_5); IR (neat): 3444, 3065, 2927, 1661, 1452 cm^{-1}; ESIMS: 193 $(M+H)^+$.

4.1.4. ((1*R*)-1-[(1*S*)-1-(Benzyloxy)ethyl]-2-propenyloxy)-(*tert*-butyl)dimethylsilane 17. To a stirred solution of **16** (0.9 g, 4.7 mmol) in CH_2Cl_2 (10 mL), imidazole (0.8 g, 11.72 mmol) and TBDMS–Cl (0.78 g, 5.2 mmol) were added at 0 °C and stirred at room temperature for 3 h. Solvent was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 5:95) to give **17** (1.2 g, 84%) as a yellow syrup. $[\alpha]_D = +59.2$ (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.02 (s, 6H, $2\times-CH_3$), 0.90 (s, 9H, $3\times-CH_3$), 1.14 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 3.37–3.43 (m, 1H, –CH), 4.10–4.13 (m, 1H, –CH), 4.55 (s, 2H, $-CH_2C_6H_4$), 5.10–5.27 (m, 2H, olefinic), 5.80–5.91 (m, 1H, olefinic), 7.27–7.30 (m, 5H, C_6H_5); IR (neat): 3067, 2931, 2857, 1456 cm^{-1}; ESIMS: 329 $(M+Na)^+$, 307 $(M+H)^+$.

4.1.5. (2*S*,3*R*)-3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4-penten-2-ol 6. To a solution of **17** (2.0 g, 6.6 mmol) in aq CH_2Cl_2 (40 mL; 19:1), DDQ (5.94 g, 26.2 mmol) was added and stirred at reflux for 3 h after which it was quenched with saturated $NaHCO_3$ (10 mL) solution, filtered and washed with CH_2Cl_2 (20 mL). The filtrate was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 15:85) to furnish **6** (1.22 g, 86%) as a syrup. $[\alpha]_D = +51.7$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6H, $2\times-CH_3$), 0.90 (s, 9H, $3\times-CH_3$), 1.08 (*d*, 3H, $J = 5.9$ Hz, $-CH_3$), 1.99 (br s, 1H, –OH), 3.62–3.74 (m, 1H, –CH), 3.94–3.99 (m, 1H, –CH), 5.16 (s, 1H, olefinic), 5.21 (dd, 1H, $J = 0.85$, 5.9 Hz, olefinic), 5.74–5.88 (m, 1H, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.87, −4.26, 17.56, 25.94, 70.84, 78.26, 116.95, 137.11; IR (neat): 3446, 2923, 2853, 1643, 1102 cm^{-1}; HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{11}H_{24}O_2NaSi$, 239.1443; found, 239.1454.

4.1.6. Ethyl (4*R*,5*S*)-5-(benzyloxy)-4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2-hexenoate 18a. A solution of **17** (1.4 g, 4.5 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C and subjected to ozonolysis for 15 min and quenched with $(CH_3)_2S$ (2 mL). The solvent was evaporated, and the residue dissolved in benzene (30 mL) and treated with (ethoxycarbonylmethylene)triphenyl phosphorane (1.36 g, 5.4 mmol) at reflux. After 2 h, solvent was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 5:95) to furnish **18a** (*E*:*Z*/4:1) (1.32 g, 77%) as a yellow syrup. *E*-Isomer: $[\alpha]_D = -12.25$ (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6H, $2\times-CH_3$), 0.94 (s, 9H, $3\times-CH_3$), 1.15 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 1.32 (t, 3H, $J = 7.3$ Hz, $-CH_3$), 3.43–3.51 (m, 1H, –CH), 4.20 (q, 2H, $J = 6.6$ Hz, $-CH_2$), 4.34 (br s, 1H, –CH), 4.53 (q, 2H, $J = 12.1$ Hz, $-CH_2C_6H_5$), 6.01 (d, 1H, $J = 15.7$ Hz, olefinic), 6.93 (dd, 1H, $J = 4.4$, 15.7 Hz, olefinic), 7.26–7.32 (m, 5H, C_6H_5); IR (neat): 3031, 2955, 2858, 1721, 1658, 1465 cm^{-1}; ESIMS: 396 $(M+NH_4)^+$, 378 $(M)^+$. *Z*-Isomer: $[\alpha]_D = -8.7$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 6H, $2\times-CH_3$), 0.89 (s, 9H, $3\times-CH_3$), 1.10 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.29 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 3.48–3.54 (m, 1H, –CH), 4.16 (q, 2H, $J = 7.2$ Hz, $-CH_2$), 4.64 (q, 2H, $J = 12.5$ Hz, $-CH_2C_6H_5$), 5.51 (m, 1H, –CH), 5.74 (d, 1H, $J = 10.9$ Hz, olefinic), 6.16 (dd, 1H, $J = 8.3$, 11.7 Hz, olefinic), 7.20–7.33 (m, 5H, C_6H_5); IR (neat): 3033, 2932, 2889, 1725, 1664 cm^{-1}; ESIMS: 396 $(M+NH_4)^+$, 378 $(M)^+$.

4.1.7. Ethyl (4*R*,5*S*)-5-(Benzyloxy)-4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyhexanoate 19. To a solution of **18a** (1.3 g, 3.44 mmol) in ethyl acetate (5 mL), PtO_2 (10 mg) was added and stirred at room temperature for 3 h under a hydrogen atmosphere. The reaction mixture was filtered, evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 4:96) to afford **19** (1.2 g, 92%) as a yellow syrup. $[\alpha]_D = -21.1$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.10 (s, 6H, $2\times-CH_3$), 0.95 (s, 9H, $3\times-CH_3$), 1.19 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 1.31 (t, 3H, $J = 7.1$ Hz, $-CH_3$), 1.76–1.95 (m, 2H, $-CH_2$), 2.37 (t, 2H, $J = 7.8$ Hz, $-CH_2$), 3.37–3.53 (m, 1H, –CH), 3.72–3.81 (m, 1H, –CH), 4.17 (q, 2H, $J = 7.1$ Hz, $-CH_3$), 4.57 (d, 2H, $J = 4.7$ Hz, $-CH_2C_6H_5$), 7.31–7.35 (m, 5H, C_6H_5); IR (neat) 3031, 2955, 2931, 2858, 1735, 1463 cm^{-1}; HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{21}H_{36}O_4NaSi$, 403.2280; found, 403.2279.

4.1.8. (4*R*,5*S*)-5-(Benzyloxy)-4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyhexanoic acid 5. To a solution of **19** (1.2 g, 3.14 mmol) in THF/MeOH/water (3:1:1, 15 mL), LiOH (0.226 g, 9.4 mmol) was added and stirred at room

temperature for 4 h. The pH of reaction mixture was adjusted to acidic with 1 M HCl solution and extracted with ethyl acetate (20 mL). The organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 1:4) to give **5** (0.91 g, 82%) as a colourless oil, $[\alpha]_D = +22.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.11 (s, 6H, $2\times$–CH_3), 0.95 (s, 9H, $3\times$–CH_3), 1.20 (d, 3H, $J = 6.1$ Hz, –CH_3), 1.75–2.01 (m, 2H, –CH_2), 2.42 (t, 2H, $J = 6.8$ Hz, –CH_2), 3.41–3.48 (m, 1H, –CH), 3.74–3.79 (m, 1H, –CH), 4.55 (q, 2H, $J = 12.1$ Hz, –$CH_2C_6H_5$), 7.24–7.33 (m, 5H, –C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.68, −4.28, 18.15, 25.89, 27.86, 29.54, 70.97, 74.19, 77.44, 127.42, 127.7, 128.28, 138.64, 179.93; IR (neat): 3031, 2930, 2857, 1710, 1097 cm^{-1}; HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{19}H_{32}O_4NaSi$, 375.1967; found 375.1976.

4.1.9. (4*S*)-4-2-[(4-Methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolane 21. To a cooled (0 °C) solution of **20**[5] (8.0 g, 54.8 mmol) in dry THF (40 mL), NaH (2.63 g, 109.6 mmol) was added, stirred for 30 min and treated with a solution of MPM–Br (12.05 g, 60.28 mmol) in dry THF (40 mL). After 6 h stirring at room temperature, the reaction mixture was quenched with saturated NH_4Cl solution (8 mL) and extracted with EtOAc (2×40 mL). The organic layers were washed with water (2×10 mL), brine (10 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 15:85) to furnish **21** (12.1 g, 83%) as a yellow syrup. $[\alpha]_D = -8.3$ (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H, –CH_3), 1.36 (s, 3H, –CH_3), 1.77–1.87 (m, 2H, –CH_2), 3.50–3.65 (m, 2H, –CH_2), 3.79 (s, 3H, –CH_3), 3.97–4.02 (m, 1H, –CH), 4.15 (pentet, 1H, $J = 6.4$ Hz, –CH), 4.40 (s, 2H, –$CH_2C_6H_4$), 6.80 (d, 2H, $J = 8.7$ Hz, –C_6H_4), 7.17 (d, 2H, $J = 8.3$ Hz, –C_6H_4); IR (neat): 2985, 2936, 2863, 1613, 1513 cm^{-1}; ESIMS: 299 $(M+Na)^+$, 284 $(M+NH_4)^+$, 267 $(M+H)^+$.

4.1.10. (2*S*)-4-[(4-Methoxybenzyl)oxy]butane-1,2-diol 22. To a solution of **21** (4.0 g, 15 mmol) in methanol (40 mL), PTSA (cat.) was added and stirred at room temperature for 5 h after which it was quenched with Et_3N (2 mL), and the solvent evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 4:1) to give **22** (2.90 g, 85%). $[\alpha]_D = -5.2$ (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.68–1.82 (m, 2H, –CH_2), 3.52–3.58 (m, 1H, –CH), 3.61–3.72 (m, 3H, –CH), 3.80 (s, 3H, –CH_3), 3.91–3.99 (m, 1H, –CH), 4.45 (s, 2H, –$CH_2C_6H_4$), 6.88 (d, 2H, $J = 8.8$ Hz, –C_6H_4), 7.24 (d, 2H, $J = 8.8$ Hz, –C_6H_4); IR (neat): 3456, 2990, 2942, 2863, 1613, 1513 cm^{-1}; ESIMS: 249 $(M+Na)^+$, 227 $(M+H)^+$.

4.1.11. (2*S*)-2-Hydroxy-4-[(4-methoxybenzyl)oxy]butyl 4-methyl-1-benzenesulfonate 22a. To a solution of **22** (8.3 g, 36.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C, Et_3N (11.2 g, 110 mmol) and tosyl chloride (6.99 g, 36.7 mmol) were added and stirred at room temperature for 36 h. The reaction mixture was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, EtOAc/hexane, 1:1) to furnish **22a** (9.10 g, 65%) as a colourless oil, $[\alpha]_D = -1.35$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.69–1.78 (m, 2H, –CH_2), 2.45 (s, 3H, –CH_3), 3.52–3.65 (m, 2H, –CH), 3.79 (s, 3H, –CH_3), 3.89–4.02 (m, 3H, –CH), 4.39 (s, 2H, –$CH_2C_6H_4$), 6.83 (d, 2H, $J = 8.3$ Hz, –C_6H_4), 7.15 (d, 2H, $J = 8.7$ Hz, –C_6H_4), 7.33 (d, 2H, $J = 8.3$ Hz, –C_6H_4), 7.77 (d, 2H, $J = 8.3$ Hz, –C_6H_4); IR (neat): 3455, 2985, 2942, 2863, 1613, 1519 cm^{-1}; ESIMS: 403 $(M+Na)^+$, 381 $(M+H)^+$.

4.1.12. (2*R*)-4-[(4-Methoxybenzyl)oxy]butan-2-ol 23. To a suspension of LAH (0.6 g, 15.8 mmol) in THF (20 mL), a solution of **22a** (6.0 g, 15.8 mmol) in THF (40 mL) was added at 0 °C and stirred at room temperature for 3 h after which it was quenched with Na_2SO_4 solution (10 mL), filtered and washed with ethyl acetate (100 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 30:70) to furnish **23** (2.98 g, 89%) as a yellow syrup. $[\alpha]_D = -58.5$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (d, 3H, $J = 6.3$ Hz, –CH_3), 1.64–1.72 (m, 2H, –CH_2), 3.53–3.67 (m, 2H, –CH_2), 3.79 (s, 3H, –CH_3), 3.94 (sextet, 1H, $J = 6.3$ Hz, –CH), 4.43 (s, 2H, –$CH_2C_6H_4$), 6.80 (d, 2H, $J = 8.5$ Hz, –C_6H_4), 7.18 (d, 2H, $J = 8.5$ Hz, –C_6H_4); IR (neat): 3436, 2922, 2854, 1612, 1513 cm^{-1}; FABMS: 233 $(M+Na)^+$, 228 $(M+NH_4)^+$, 211 $(M+H)^+$.

4.1.13. (1*R*)-3-[(4-Methoxybenzyl)oxy]-1-methylpropyl acrylate 24. A solution of DIPEA (1.23 g, 9.52 mmol) and **23** (1.0 g, 4.76 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with acryloyl chloride (0.647 g, 7.15 mmol) and stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 1:9) to afford **24** (1.16 g, 92%) as a yellow syrup. $[\alpha]_D = -80.6$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (d, 3H, $J = 6.4$ Hz, –CH_3), 1.80–1.97 (m, 2H, –CH_2), 3.49 (t, 2H, $J = 5.7$ Hz, –CH_2), 3.80 (s, 3H, –CH_3), 4.41 (s, 2H, –$CH_2C_6H_4$), 5.14 (sextet, 1H, $J = 6.4$ Hz, –CH), 5.78 (dd, 1H, $J = 1.5$ Hz, $J = 10.2$ Hz, olefinic), 6.07 (dd, 1H, $J = 10.2$ Hz, $J = 17.4$ Hz, olefinic), 6.37 (dd, 1H, $J = 1.5$ Hz, $J = 17.4$ Hz, olefinic), 6.80 (d, 2H, $J = 8.7$ Hz, –C_6H_4), 7.18 (d, 2H, $J = 8.7$ Hz, –C_6H_4); IR (neat): 2926, 2856, 1720, 1613, 1512 cm^{-1}; ESIMS: 287 $(M+Na)^+$, 282 $(M+NH_4)^+$, 265 $(M+H)^+$.

4.1.14. (1*R*)-3-Hydroxy-1-methylpropyl acrylate 24a. To a solution of **24** (0.8 g, 3.03 mmol) in aq CH_2Cl_2 (20 mL, 19:1), DDQ (0.826 g, 3.64 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), filtered and washed with CH_2Cl_2 (40 mL). The filtrate was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, EtOAc/hexane, 1:4) to furnish **24a** (0.388 g, 89%) as a yellow syrup. $[\alpha]_D = -26.5$ (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (d, 3H, $J = 6.1$ Hz, –CH_3), 1.67–1.89 (m, 2H, –CH_2), 2.21 (br s, 1H, –OH), 3.49–3.65 (m, 2H, –CH_2), 5.12–5.24 (m, 1H, –CH), 5.82 (dd, 1H,

$J = 1.5$ Hz, $J = 10.6$ Hz, olefinic), 6.09 (dd, 1H, $J = 10.6$ Hz, $J = 17.4$ Hz, olefinic), 6.41 (dd, 1H, $J = 1.5$ Hz, $J = 17.4$ Hz, olefinic); IR (neat): 3442, 2922, 2853, 1716, 1630 cm^{-1}; ESIMS: 144 $(M)^+$.

4.1.15. (3*R*)-3-Acryloyloxybutanoic acid 7. To a solution of **24a** (0.2 g, 1.39 mmol) in CH_2Cl_2 (4 mL) at 0 °C, Dess–Martin periodinane[6] (0.707 g, 1.67 mmol) was added and allowed to stir at room temperature for 3 h after which it was quenched with $NaHCO_3$ solution (2 mL), $Na_2S_2O_3$ solution (2 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water (2 mL), brine (2 mL), dried over Na_2SO_4 and evaporated under reduced pressure to furnish the corresponding aldehyde (0.19 g, 96.5%).

To a cooled (0 °C) solution of the above aldehyde (0.19 g, 1.21 mmol) in *t*-butanol (4 mL), 2-methyl-2-butene (2 mL) was added, followed by a solution of $NaClO_2$ (0.131 g, 1.45 mmol) and NaH_2PO_4 (0.225 g, 1.45 mmol) in water (2 mL) and stirred at room temperature for 3 h after which it was worked up as described for **10** and purified by column chromatography (Silica gel, EtOAc/hexane, 1:4) to furnish **7** (0.188 g, 89%) as a colourless oil. $[\alpha]_D = +10.3$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 2.55 (dd, 1H, $J = 6.1$, 15.6 Hz, –CH), 2.74 (dd, 1H, $J = 6.9$, 15.6 Hz, –CH), 5.31 (sextet, 1H, $J = 6.1$ Hz, –CH), 5.82 (dd, 1H, $J = 1.7$, 10.4 Hz, olefinic), 6.06 (dd, 1H, $J = 10.4$, 17.4 Hz, olefinic), 6.38 (dd, 1H, $J = 1.7$, 17.4 Hz, olefinic); IR (neat): 2986, 1721, 1638, 1194, 1057 cm^{-1}; ESIMS: 181 $(M+Na)^+$, 159 $(M+H)^+$.

4.1.16. (1*S*,2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-3-butenyl (4*R*,5*S*)-5-(benzyloxy)-4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyhexanoate 32. To a solution of **5** (0.14 g, 0.4 mmol) and Et_3N (0.081 g, 0.8 mmol) in dry THF (3 mL) at 0 °C, 2,4,6-trichlorobenzoyl chloride (0.097 g, 0.4 mmol) was added dropwise and stirred at room temperature for 2 h. The reaction mixture was evaporated and the residue dissolved in toluene (2 mL). A solution of **6** (0.086 g, 0.4 mmol) and DMAP (0.098 g, 0.8 mmol) in dry toluene (2 mL) was added to the reaction mixture and stirred for 12 h at room temperature, after which it was filtered through Celite and washed with toluene (2×5 mL). The filtrate was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 6:94) to afford **32** (0.18 mg, 82%) as a yellow syrup. $[\alpha]_D = -23.0$ (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H, $2 \times -CH_3$), 0.09 (s, 6H, $2 \times -CH_3$), 0.94 (s, 9H, $3 \times -CH_3$), 0.95 (s, 9H, $3 \times -CH_3$), 1.18 (d, 3H, $J = 2.3$ Hz, $-CH_3$), 1.21 (d, 3H, $J = 2.3$ Hz, $-CH_3$), 1.70–1.98 (m, 2H, $-CH_2$), 2.31–2.40 (m, 2H, $-CH_2$), 3.39–3.49 (m, 1H, –CH), 3.73–3.81 (m, 1H, –CH), 4.16–4.26 (m, 1H, –CH), 4.55 (q, 2H, $J = 12.1$ Hz, $-CH_2C_6H_5$), 4.81–4.90 (m, 1H, –CH), 5.16–5.36 (m, 2H, olefinic), 5.72–5.86 (m, 1H, olefinic), 7.23–7.36 (m, 5H, $-C_6H_5$); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.90, −4.66, −4.57, −4.27, 13.89, 15.47, 25.76, 25.91, 28.16, 30.17, 70.99, 73.1, 74.28, 75.26, 77.63, 116.1, 127.36, 127.48, 127.59, 128.24, 137.63, 173.23; IR (neat): 3067, 2955, 2932, 2888, 2857, 1736, 1097 cm^{-1}; ESIMS: 569 $(M+NH_4)^+$, 552 $(M+H)^+$.

4.1.17. (1*S*,2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-3-butenyl (4*R*,5*S*)-4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-5-hydroxyhexanoate 33. To a solution of **32** (0.25 g, 0.46 mmol) in aq CH_2Cl_2 (5 mL; 19:1), DDQ (0.413 g, 1.82 mmol) was added and stirred at reflux for 3 h after which it was quenched with saturated $NaHCO_3$ solution (2 mL), filtered and washed with CH_2Cl_2 (20 mL). The filtrate was washed with water (2 mL), brine (2 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 1:9) to furnish **33** (0.148 g, 71%) as a syrup. $[\alpha]_D = -64.2$ (*c* 0.25, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 12H, $4 \times -CH_3$), 0.91 (s, 18H, $6 \times -CH_3$), 1.11–1.17 (m, 6H, $2 \times -CH_3$), 1.67–1.95 (m, 2H, $-CH_2$), 2.22–2.57 (m, 2H, $-CH_2$), 3.53–3.71 (m, 2H, –CH), 4.14–4.21 (m, 1H, –CH), 4.76–4.91 (m, 1H, –CH), 5.12–5.34 (m, 2H, olefinic), 5.68–5.88 (m, 1H, olefinic); IR (neat): 3461, 2955, 2930, 2857, 1734, 1465 cm^{-1}; HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{23}H_{48}O_5NaSi_2$; calculated 483.2938; found, 483.2953.

4.1.18. (1*R*)-3-((1*S*,2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy-5-[((1*S*,2*R*)-2-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-1-methyl-3-butenyl)oxy]-1-methyl-5-oxopentyloxy)-1-methyl-3-oxopropyl acrylate 34. To a solution of **7** (0.1 g, 0.64 mmol) and Et_3N (0.128 g, 1.27 mmol) in dry THF (2 mL), 2,4,6-trichlorobenzoyl chloride (0.155 g, 0.64 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was evaporated and the residue dissolved in toluene (2 mL). A solution of **33** (0.292 g, 0.64 mmol) and DMAP (0.155 g, 1.27 mmol) in dry toluene (2 mL) was added to the reaction mixture and stirred at room temperature for 24 h. The reaction mixture was filtered through Celite and washed with toluene (10 mL). The filtrate was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 3:97) to furnish **34** (0.197 g, 52%) as a yellow syrup. $[\alpha]_D = -27.6$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H, $2 \times -CH_3$), 0.05 (s, 6H, $2 \times -CH_3$), 0.89 (s, 9H, $3 \times -CH_3$), 0.91 (s, 9H, $3 \times -CH_3$), 1.15 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 1.16 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 1.33 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 1.68–1.8 (m, 2H, $-CH_2$), 2.22–2.73 (m, 4H, $2 \times -CH_2$), 3.62–3.80 (m, 1H, –CH), 4.12–4.23 (m, 1H, –CH), 4.74–4.92 (m, 2H, –CH), 5.10–5.30 (m, 3H, –CH, olefinic), 5.66–5.84 (m, 2H, olefinic), 5.97–6.14 (m, 1H, olefinic), 6.39 (dd, 1H, $J = 1.8$, 17.3 Hz, olefinic); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.92, −4.61, −4.55, −4.40, 13.93, 14.52, 19.82, 25.74, 25.80, 28.11, 30.34, 40.95, 67.56, 72.93, 73.29, 75.26, 116.18, 128.52, 130.74, 137.72, 165.20, 169.60, 172.77; IR (neat): 2930, 2857, 1735, 1061 cm^{-1}; ESIMS: 618 $(M+NH_4)^+$, 601 $(M+H)^+$.

4.1.19. (1*R*)-3-[((1*S*,2*R*)-2-Hydroxy-5-[(1*S*,2*R*)-2-hydroxy-1-methyl-3-butenyl]oxy-1-methyl-5-oxopentyl)oxy]-1-methyl-3-oxopropyl acrylate 3. To a cooled (0 °C) solution of **34** (0.026 g, 0.04 mmol) in THF (1 mL), HF–pyridine complex (0.016 g, 0.132 mmol) was added and stirred at room temperature for 6 h after which it was quenched with $CuSO_4$ solution (1 mL) and extracted with EtOAc (2×5 mL). The organic layers were washed with water (2 mL), brine (2 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column

chromatography (Silica gel, EtOAc/hexane, 35:65) to furnish **3** (0.0135 g, 84%) as a yellow syrup. $[\alpha]_D = +1.3$ (*c* 0.5, $CHCl_3$); IR (neat): 3465, 2960, 2857, 1736, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.20 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.34 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.56–1.83 (m, 2H, $-CH_2$), 2.02 (br s, 1H, –OH), 2.27 (br s, 1H, –OH), 2.38–2.66 (m, 4H, $2\times-CH_2$), 3.58–3.68 (m, 1H, –CH), 4.22–4.27 (m, 1H, –CH), 4.38–4.48 (m, 1H, –CH), 4.75–5.08 (m, 2H, –CH), 5.18–5.52 (m, 2H, olefinic), 5.76–5.89 (m, 2H, olefinic), 5.99–6.14 (m, 1H, olefinic), 6.35–6.47 (m, 1H, olefinic); IR (neat): 3465, 2960, 2857, 1736, 1465 cm^{-1}; ESIMS: 373 $(M+H)^+$.

4.1.20. Macrosphelide I 1. To a solution of **3** (0.01 g, 0.027 mmol) in CH_2Cl_2 (50 mL), 5 mol % Grubbs catalyst II (0.0012 g, 0.0014 mmol) was added and stirred at reflux for 24 h under N_2 atmosphere. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2 h under bubbling air in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (Silica gel, EtOAc/hexane, 2:3) to give **1** as a colourless syrup (7.8 mg, 84%). $[\alpha]_D = +9.6$ (*c* 0.15, $CHCl_3$); lit.[1] $[\alpha]_D = +10.3$ (*c* 0.31, EtOH); ^1H NMR (600 MHz, $CDCl_3$): δ 1.18 (d, 3H, $J = 6.6$ Hz, $-CH_3$), 1.32 (d, 3H, $J = 6.6$ Hz, $-CH_3$), 1.46–1.47 (m, 1H, –CH), 1.47 (d, 3H, $J = 6.6$ Hz, $-CH_3$), 1.68–1.74 (m, 1H, –CH), 2.36 (dt, 1H, $J = 5.1$, 14.7 Hz, –CH), 2.53 (br s, 1H, –OH), 2.62–2.68 (m, 2H, $-CH_2$), 2.70 (dd, 1H, $J = 2.9$, 16.1 Hz, –CH), 3.25 (d, 1H, $J = 11.4$ Hz, –CH), 3.83 (br s, 1H, –OH), 4.29 (br s, 1H, –CH), 4.83–4.87 (m, 2H, $2\times$–CH), 5.65 (dqd, 1H, $J = 3.7$, 6.6, 10.3 Hz, –CH), 6.24 (dd, 1H, $J = 2.2$, 15.4 Hz, olefinic), 7.21 (dd, 1H, $J = 2.9$, 15.4 Hz, olefinic); ^{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.

4.1.21. (*S*)-Propylene oxide 11 and (*R*)-propane 1,2-diol 27. A mixture of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)[7] (0.241 g, 0.40 mmol) in toluene (0.5 mL) and acetic acid (0.48 g, 0.80 mmol) was stirred while open to the air for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure and the brown residue was dried under vacuum. The racemic epoxide **26** (11.6 g, 200 mmol) was added in one portion at 0 °C, and water (2.0 mL, 110 mmol) was added dropwise over 5 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. (*S*)-Propylene oxide **11** (5.0 g, 43%) $[\alpha]_D = +10.8$ (*c* 1.0, $CHCl_3$) {lit.[7a] $[\alpha]_D = +11.6$ (neat)} was isolated by distillation from the reaction mixture at atmospheric pressure and diol **27** was removed by vacuum distillation (65 °C) to furnish 40% as a colourless liquid, $[\alpha]_D = -15.5$ (neat) {lit.[7b] $[\alpha]_D = -16.0$ (neat)}, ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (d, 3H, $J = 6.0$ Hz, –CH3), 2.05 (br s, 1H, –OH), 3.55 (t, 2H, $J = 6.0$ Hz, –CH2), 3.90 (q, 1H, $J = 6.0$ Hz, –CH); IR (neat): 3440, 3387, 1025, 820 cm^{-1}; EIMS (*m*/*z*): 76 (M^+).

4.1.22. (2*S*)-6-(Tetrahydro-2*H*-2-pyranyloxy)-4-hexyn-2-ol 28. *n*-BuLi (24.77 mL, 41.37 mmol, 1.6 M hexane solution) was added dropwise to a solution of 2-(2-propynyloxy)tetrahydro-2*H*-pyran **12** (5.31 g, 37.93 mmol) in dry THF (40 mL) under N_2 atmosphere at −78 °C and stirred for 30 min. The reaction mixture was sequentially treated with $BF_3{\cdot}Et_2O$ (4.77 mL, 41.37 mmolmol) and a solution of (*S*)-propylene oxide **11** (2.0 g, 34.48 mmol) in dry THF (10 mL) at 10 min interval and stirred for an additional 3 h at −78 °C. Saturated $NaHCO_3$ solution (20 mL) followed by saturated NH_4Cl solution (20 mL) were added to the reaction mixture at −78 °C and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×35 mL). The organic layers were washed with water (12 mL), dried over Na_2SO_4, evaporated and the residue obtained was purified by column chromatography (Silica gel, EtOAc/hexane, 15:85) to give **28** (4.5 g, 64%) as a yellow syrup. $[\alpha]_D = -22.3$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.52–1.89 (m, 6H, $3\times-CH_2$), 2.21–2.28 (br s, 1H, –OH), 2.33–2.38 (m, 2H, $-CH_2$), 3.49–3.57 (m, 1H, –CH), 3.75–3.87 (m, 1H, –CH), 3.92 (sextet, 1H, $J = 6.4$ Hz, –CH), 4.21 (dt, 2H, $J = 1.9$, 3.8 Hz, $-CH_2$), 4.79 (t, 1H, $J = 2.6$ Hz, –CH); IR (neat): 3442, 2931, 2865, 2234, 1022 cm^{-1}; FABMS: 198 $(M)^+$.

4.1.23. 2-((5*S*)-5-[(4-Methoxybenzyl)oxy]-2-hexynyloxy)tetrahydro-2*H*-pyran 29. To a cooled (0 °C) solution of **28** (6.2 g, 31.3 mmol) in dry THF (30 mL), NaH (1.5 g, 62.6 mmol) was added and stirred for 30 min. A solution of MPM–Br (6.96 g, 34.43 mmol) in dry THF (30 mL) was added and stirred at room temperature for 6 h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2×30 mL). The organic layers were washed with water (2×10 mL), brine (10 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 8:92) to afford **29** (7.27 g, 73%) as a yellow syrup. $[\alpha]_D = -12.1$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 1.48–1.89 (m, 6H, $3\times-CH_2$), 2.26–2.55 (m, 2H, $-CH_2$), 3.45–3.67 (m, 2H, $-CH_2$), 3.75–3.83 (m, 4H, –CH, $-CH_3$), 4.16–4.21 (m, 2H, $-CH_2$), 4.46 (s, 2H, $-CH_2C_6H_4$), 4.77 (t, 1H, $J = 3.0$ Hz), 6.80 (d, 2H, $J = 8.7$ Hz, $-C_6H_4$), 7.20 (d, 2H, $J = 8.7$ Hz, $-C_6H_4$); IR (neat): 2926, 2854, 2236, 1611, 1513 cm^{-1}; FABMS: 319 $(M+H)^+$.

4.1.24. (5*S*)-5-[(4-Methoxybenzyl)oxy]-2-hexyn-1-ol 30. To a solution of **29** (0.64 g, 2.02 mmol) in methanol (6 mL), PTSA (0.03 g, 0.202 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was quenched with Et_3N (0.1 mL), the solvent evaporated and the residue obtained purified by column chromatography (Silica gel, EtOAc/hexane 16:84) to furnish **30** (0.41 g, 87%) as a yellow syrup. $[\alpha]_D = -2.5$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 1.54–1.64 (br s, 1H, –OH), 2.30–2.51 (m, 2H, $-CH_2$), 3.60 (sextet, 1H, $J = 6.4$ Hz, –CH), 3.79 (s, 3H, $-CH_3$), 4.18 (s, 2H, $-CH_2$), 4.46 (s, 2H, $-CH_2C_6H_4$), 6.80 (d, 2H, $J = 8.6$ Hz, $-C_6H_4$), 7.20 (d, 2H, $J = 8.6$ Hz, $-C_6H_4$); IR (neat): 3415, 2970, 2927, 2230,1611, 1513 cm^{-1}; ESIMS: 257 $(M+Na)^+$.

4.1.25. (*E*,5*S*)-5-[(4-Methoxybenzyl)oxy]-2-hexen-1-ol 31. To a cooled suspension of LAH (58.5 mg, 1.54 mmol) in dry THF (2 mL), **30** (0.36 mg, 1.54 mmol) in dry THF (2 mL) was added and stirred at room temperature for 1 h. The reaction mixture was quenched with saturated Na_2SO_4 solution (2 mL) and stirred for 1 h. It was filtered, washed with EtOAc (2 × 15 mL) and the combined organic layers were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (Silica gel, EtOAc/hexane, 16:84) furnished **31** (0.331 g, 91%) as a yellow syrup. $[\alpha]_D = -2.1$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.35–1.44 (br s, 1H, –OH), 2.15–2.34 (m, 2H, $-CH_2$), 3.53 (sextet, 1H, $J = 6.1$ Hz, –CH), 3.79 (s, 3H, $-CH_3$), 4.05 (s, 2H, $-CH_2$), 4.44 (q, 2H, $J = 11.3$ Hz, $-CH_2C_6H_4$), 5.64–5.67 (m, 2H, olefinic), 6.80 (d, 2H, $J = 8.6$ Hz, C_6H_4), 7.18 (d, 2H, $J = 8.6$ Hz, C_6H_4); IR (neat): 3419, 2965, 2922, 1610, 1512 cm^{-1}; ESIMS: 254 $(M+NH_4)^+$.

4.1.26. (*E*,5*S*)-5-[(4-Methoxybenzyl)oxy]-2-hexenoic acid 10. To a solution of oxalyl chloride (0.131 g, 1.03 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C, dry DMSO (0.0872 g, 1.12 mmol) was added dropwise and stirred for 10 min. A solution of **31** (0.22 g, 0.94 mmol) in dry CH_2Cl_2 (2 mL) was added and stirred for 2 h at −78 °C after which it was quenched with Et_3N (0.283 g, 2.8 mmol) and diluted with CH_2Cl_2 (10 mL). The reaction mixture was washed with water (4 mL), brine (4 mL), dried over Na_2SO_4 and evaporated to furnish the corresponding aldehyde.

To a cooled (0 °C) solution of the above aldehyde (0.22 g, 0.92 mmol) in *t*-butanol (4 mL), 2-methyl-2-butene (2 mL) followed by a solution of $NaClO_2$ (0.0905 g, 1.13 mmol) and NaH_2PO_4 (0.176 g, 1.13 mmol) in water (2 mL) was added and stirred at room temperature for 3 h. The solvent was evaporated, and the residue dissolved in EtOAc (15 mL) and washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (Silica gel, EtOAc/hexane, 2:3) gave **10** (0.179 g, 76%) as a yellow syrup. $[\alpha]_D = +58.1$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 2.32–2.52 (m, 2H, $-CH_2$), 3.63 (sextet, 1H, $J = 6.1$ Hz, –CH), 3.78 (s, 3H, $-CH_3$), 4.45 (q, 2H, $J = 11.3$ Hz, $-CH_2C_6H_4$), 5.84 (d, 1H, $J = 15.5$ Hz, olefinic), 6.83 (d, 2H, $J = 8.7$ Hz, C_6H_4), 7.04 (dt, 1H, $J = 7.2$, 15.1 Hz, olefinic), 7.21 (d, 2H, $J = 8.3$ Hz, C_6H_4); IR (neat): 3410, 2925, 2853, 1695, 1653, 1608 cm^{-1}; FAB-MS: 268 $(M+NH_4)^+$.

4.1.27. (1*S*,2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-3-butenyl (*E*,5*S*)-5-[(4-methoxybenzyl)oxy]-2-hexenoate 35. To a solution of **10** (0.2 g, 0.8 mmol) and Et_3N (0.162 g, 1.6 mmol) in dry THF (3 mL) at 0 °C, 2,4,6-trichlorobenzoyl chloride (0.196 g, 0.8 mmol) was added dropwise and stirred at room temperature for 2 h. The reaction mixture was evaporated and the residue dissolved in toluene (2 mL). To a solution of **6** (0.173 g, 0.8 mmol), DMAP (0.196 g, 1.6 mmol) in dry toluene (2 mL) was added and stirred at room temperature for 12 h after which it was filtered through Celite and washed with toluene (10 mL). The filtrate was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 6:94) to furnish **35** (0.259 g, 68%) as a yellow syrup. $[\alpha]_D = +17.1$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.03 (s, 6H, 2 × $-CH_3$), 0.91 (s, 9H, 3 × $-CH_3$), 1.17–1.21 (m, 6H, 2 × $-CH_3$), 2.30–2.52 (m, 2H, $-CH_2$), 3.60 (sextet, 1H, $J = 6.1$ Hz, –CH), 3.80 (s, 3H, $-CH_3$), 4.24–4.27 (m, 1H, –CH), 4.44 (q, 2H, $J = 11.7$ Hz, $-CH_2C_6H_4$), 4.84–4.92 (m, 1H, –CH), 5.13 (d, 1H, $J = 10.2$ Hz, olefinic), 5.31 (d, 1H, $J = 16.9$ Hz, olefinic), 5.73–5.84 (m, 2H, olefinic), 6.80 (d, 2H, $J = 8.7$ Hz, $-C_6H_4$), 6.88–6.98 (m, 1H, olefinic), 7.19 (d, 2H, $J = 8.7$ Hz, $-C_6H_4$); IR (neat): 2955, 2932, 2857, 1719, 1654, 1612, 1513 cm^{-1}; ESIMS: 467 $(M+NH_4)^+$, 450 $(M+H)^+$.

4.1.28. (1*S*,2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-3-butenyl (*E*,5*S*)-5-hydroxy-2-hexenoate 36. To a solution of **35** (0.14 g, 0.32 mmol) in CH_2Cl_2/water (19:1, 5 mL), DDQ (0.086 g, 0.38 mmol) was added and stirred at room temperature for 1 h after which it was quenched with saturated $NaHCO_3$ (2 mL) solution, filtered and washed with CH_2Cl_2 (20 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried over Na_2SO_4, evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 15:85) to afford **36** (0.09 g, 88%) as a yellow syrup. $[\alpha]_D = +1.8$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.03 (s, 6H, 2 × $-CH_3$), 0.91 (s, 9H, 3 × $-CH_3$), 1.18 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.25 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 1.59 (br s, 1H, –OH) 2.37 (t, 2H, $J = 7.2$ Hz, $-CH_2$), 3.96 (sextet, 1H, $J = 6.4$ Hz, –CH), 4.24–4.27 (m, 1H, –CH), 4.87–4.95 (m, 1H, –CH), 5.14 (d, 1H, $J = 10.2$ Hz, olefinic), 5.29 (d, 1H, $J = 20.4$ Hz, olefinic), 5.73–5.84 (m, 1H, olefinic), 5.91 (d, 1H, $J = 16.9$ Hz, olefinic), 6.96 (dt, 1H, $J = 7.6$, 15.5 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.78, 13.67, 23.24, 25.97, 41.92, 66.87, 73.46, 75.28, 116.08, 124.27, 137.81, 144.96, 165.74; IR (neat): 3430, 2957, 2930, 2856, 1719, 1654, 1465 cm^{-1}; FABMS: 329 $(M+H)^+$.

4.1.29. (1*S*,2*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-3-butenyl (*E*,5*S*)-5-[(3*R*)-3-(acryloyloxy)butanoyl]-oxy-2-hexenoate 37. To a solution of **7** (0.04 g, 0.25 mmol) and Et_3N (0.052 g, 0.51 mmol) in dry THF (1 mL), 2,4,6-trichlorobenzoyl chloride (0.062 g, 0.25 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was evaporated and the residue dissolved in toluene (1 mL). A solution of **36** (0.083 g, 0.25 mmol) and DMAP (0.062 g, 0.51 mmol) in dry toluene (1 mL) was added to the reaction mixture and stirred at room temperature for 24 h. The reaction mixture was filtered through Celite and washed with toluene (5 mL). The filtrate was evaporated and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 1:9) to give **37** (0.065 g, 55%) as a yellow syrup. $[\alpha]_D = -0.75$ (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.03 (s, 6H, 2 × $-CH_3$), 0.91 (s, 9H, 3 × $-CH_3$), 1.16 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.23 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.32 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 2.39–2.72 (m, 4H, 2 × $-CH_2$), 4.22–4.29 (m, 1H, –CH), 4.80–5.35 (m, 5H, olefinic,

–CH), 5.70–5.86 (m, 3H, olefinic), 5.99–6.13 (m, 1H, olefinic), 6.38 (dd, 1H, $J = 1.9$, 17.2 Hz, olefinic), 6.83 (dt, 1H, $J = 7.5$, 15.3 Hz, olefinic); IR (neat): 2928, 1729, 1635 cm^{-1}; HRMS *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{40}O_7NaSi$, 491.2441; found, 491.2435.

4.1.30. (1*S*,2*R*)-2-Hydroxy-1-methyl-3-butenyl (*E*,5*S*)-5-[(3*R*)-3-(acryloyloxy)butanoyl]oxy-2-hexenoate 4. To a cooled (0 °C) solution of **38** (17.0 mg, 0.04 mmol) in THF (1 mL), HF–pyridine complex (7.0 mg, 0.06 mmol) was added and stirred at room temperature for 6 h after which it was quenched with $CuSO_4$ solution (1 mL), extracted with EtOAc (2×10 mL), washed with water (1 mL), brine (1 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, EtOAc/hexane, 1:3) to afford **4** (12.0 mg, 93%) as a yellow syrup. $[\alpha]_D = -23.7$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.18 (d, 3H, $J = 6.5$ Hz, $-CH_3$), 1.25 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 1.32 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 2.27–2.62 (m, 4H, $2 \times -CH_2$), 4.20–4.30 (m, 1H, –CH), 4.91–5.43 (m, 5H, olefinic, –CH), 5.74–6.14 (m, 4H, olefinic), 6.30–6.46 (m, 1H, olefinic), 6.71–6.96 (m, 1H, olefinic); IR (neat): 3447, 2927, 2854, 1725, 1654, 1455 cm^{-1}; HRMS *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{26}O_7Na$, 377.1576; found, 377.1587.

4.1.31. Macrosphelide G 2. To a solution of **4** (12.0 mg, 0.04 mmol) in CH_2Cl_2 (60 mL), 5 mol % Grubbs catalyst II (1.5 mg, 0.002 mmol) was added and stirred for 24 h at reflux under an N_2 atmosphere. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2 h under air bubbling in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (Silica gel, EtOAc/hexane, 3:7) to furnish **2** (9 mg, 82%) as a colourless syrup. $[\alpha]_D = +54.3$ (*c* 0.10, $CHCl_3$); lit.[1] $[\alpha]_D = +66.7$ (*c* 0.48, EtOH), lit.[2c] $[\alpha]_D = +51.7$ (*c* 0.35, EtOH); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.26 (d, 3H, $J = 6.8$ Hz, $-CH_3$), 1.40 (d, 3H, $J = 6.7$ Hz, $-CH_3$), 1.44 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 2.28–2.42 (m, 2H, $-CH_2$), 2.5 (dd, 1H, $J = 6.1$, 15.3 Hz, $-CH_2$), 2.76 (dd, 1H, $J = 3.7$, 15.3 Hz, $-CH_2$), 3.32 (br s, 1H, –OH), 4.35 (br s, 1H, –CH), 5.08 (m, 1H, –CH), 5.09 (m, 1H, –CH), 5.24 (quintd, 1H, $J = 4.3$, 6.7 Hz, –CH), 5.80 (dt, 1H, $J = 1.2$, 15.8 Hz, olefinic), 6.11 (dd, 1H, $J = 1.8$, 15.9 Hz, olefinic), 6.8 (ddd, 1H, $J = 6.1$, 8.5, 15.3 Hz, olefinic), 7.05 (dd, 1H, $J = 3.7$, 15.3 Hz, olefinic); ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.9, 19.3, 20.3, 38.3, 40.0, 67.2, 70, 75.3, 76.4, 122, 123, 145, 165, 167, 169; IR (KBr): 3458, 1725 cm^{-1}; HRMS *m/z*: $[M+Na]^+$ calcd for calcd $C_{16}H_{22}O_7Na$, 349.1263; found 349.1259.

Acknowledgement

One of the authors (K.V.B.) thanks the CSIR, New Delhi, India, for financial support in the form of a fellowship.

References

1. Yamada, T.; Iritani, M.; Doi, M.; Minoura, K.; Ito, T.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3046–3053.
2. (a) Matsuya, Y.; Nemoto, H. *Heterocycles* **2005**, *65*, 1741–1749; See, for the synthesis of macrosphelides using an RCM protocol: (b) Kawaguchi, T.; Funamori, N.; Matsuya, Y.; Nemoto, H. *J. Org. Chem.* **2004**, *69*, 505–509; Reported synthesis of macrosphelide G: (c) Nakumara, H.; Ono, M.; Shida, Y.; Akita, H. *Tetrahedron: Asymmetry* **2002**, *13*, 703–705; (d) Kobayashi, Y.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 4381–4384; (e) Akita, H.; Nakamura, H.; Ono, M. *Chirality* **2003**, *15*, 352–359.
3. (a) Sharma, G. V. M.; Chandra Mouli, Ch. *Tetrahedron Lett.* **2002**, *43*, 9159–9161; (b) Sharma, G. V. M.; Chandra Mouli, Ch. *Tetrahedron Lett.* **2003**, *44*, 8161–8163; (c) Sharma, G. V. M.; Reddy, Ch. G. *Tetrahedron Lett.* **2004**, *45*, 7483–7485; (d) Sharma, G. V. M.; Reddy, J. J.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 6531–6535; (e) Sharma, G. V. M.; Reddy, K. L.; Reddy, J. J. *Tetrahedron Lett.* **2006**, *47*, 6537–6540.
4. Radha Krishna, P.; Reddy, V. V. R.; Sharma, G. V. M. *Synthesis* **2004**, *13*, 2107–2114.
5. Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146–2147.
6. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
7. (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315; (b) Louis, J. T.; Nelson, W. L. *J. Org. Chem.* **1987**, *52*, 1309–1315.
8. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
9. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956; (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103–10109.