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Total synthesis of patulolide C and 11-epipatulolide C

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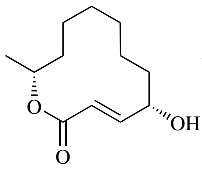
Abstract—The total synthesis of 12-membered macrolides, patulolide C, 11-epipatulolide C and formal synthesis of patulolide A and epipatulolide A, starting from 1,8-octane diol is reported. A combination of Jacobsen's hydrolytic kinetic resolution and Sharpless epoxidation is used for the creation of two stereogenic centres, while ring-closing metathesis strategy was used for the construction of the lactone ring.

1. Introduction

Patulolides C **1** and **2** and A **3** and **4**, isolated from *Penicillium urticae* S11R59, have shown antifungal, antimicrobial, anti-inflammatory activity and were characterized by Yamada and co-workers.[1] Due to their biological profiles and structural features, patulolides[2] have become highly attractive target molecules for the synthesis. In continuation of our interest on the synthesis of macrolides,[3] herein, we report the synthesis of patulolide C **1** and 11-epipatulolide C **2**.



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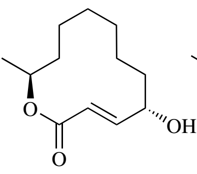

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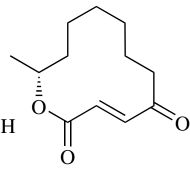

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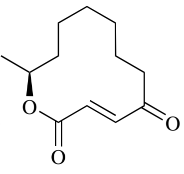

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2. Results and discussion

The retrosynthetic analysis of patulolides **1** and **2** indicates bis-olefins **5** and **6**, respectively, and are last stage intermediates, which upon RCM would give the targets. Olefins **5** and **6** could be envisaged as deriving from epoxides **7** and **8**, respectively, which in turn could be realized from the common intermediate, racemic epoxide **9**. Compound **9** could be made from **10**, which in turn would be obtained from the inexpensive 1,8-octane diol **12**. Thus, in the present strategy, the (4*S*)-hydroxy group could be installed through Sharpless epoxidation, while the 11-hydroxy group would be introduced by Jacobsen's hydrolytic kinetic resolution (Scheme 1).

The synthesis of patulolides **1** and **2** was initiated from commercially available 1,8-octane diol **12** as illustrated in Scheme 2. Thus, selective monoprotection of **12** with 2,3-dihyropyran in the presence of PTSA (cat.) in CH_2Cl_2 gave THP–ether **13** in 82% yield, which on oxidation under Swern conditions[4] gave the corresponding aldehyde **13a**. Wittig olefination of **13a** with (methoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux for 2 h furnished the α,β-unsaturated ester **14** in 91% yield. Ester **14** was reduced with DIBAL-H in CH_2Cl_2 at room temperature to allylic alcohol **15** in 81% yield. Sharpless epoxidation of allylic alcohol **15** with (+)-DIPT, $Ti(O^iPr)_4$ and cumene hydroperoxide in dry CH_2Cl_2 for 5 h afforded **11** (90%). The treatment of alcohol **11** with Ph_3P and $NaHCO_3$ in CCl_4 at reflux for 4 h gave chloride **16** in 93% yield,

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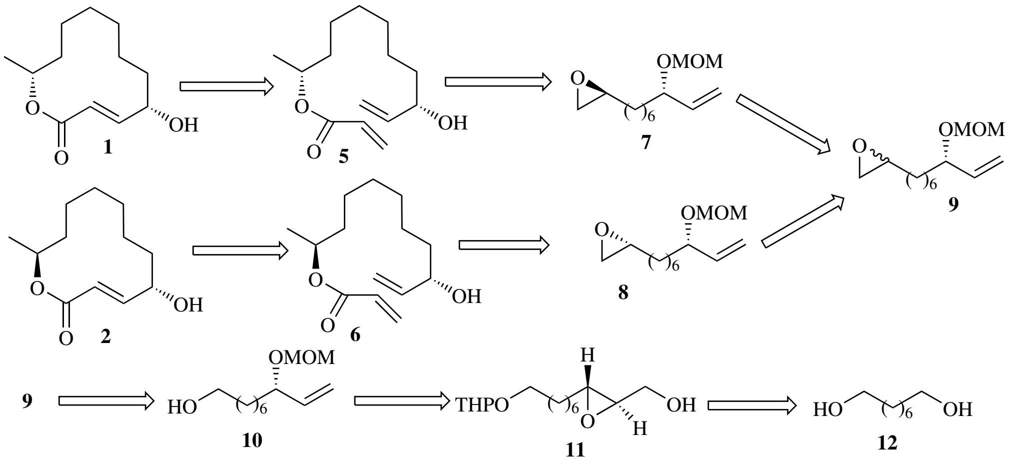
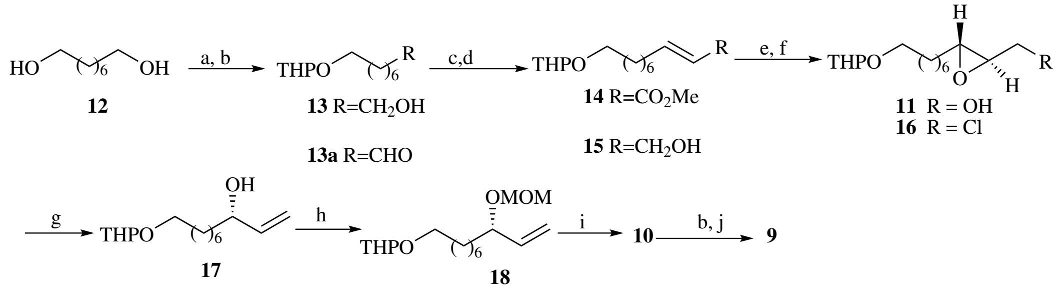


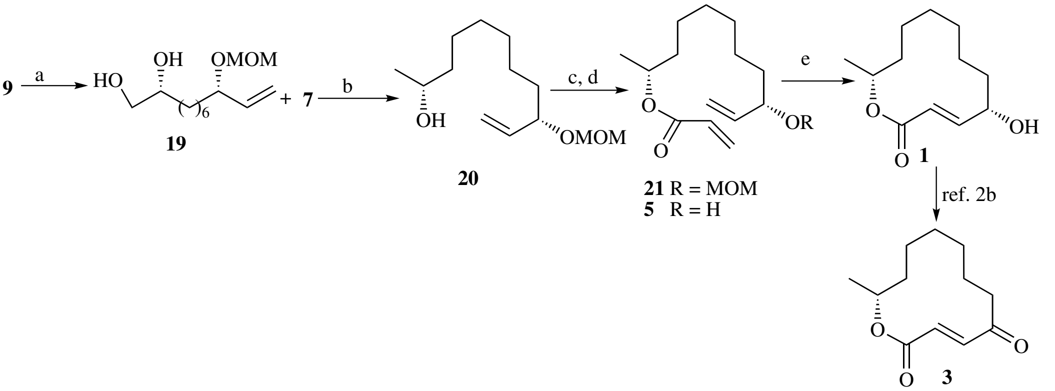
Scheme 1. The retrosynthesis of patulolide C and 11-epipatulolide C.



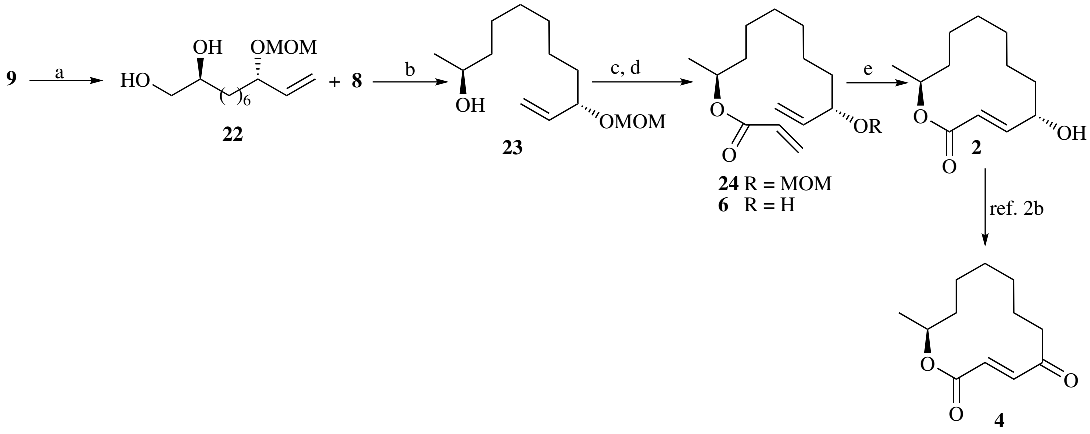
Scheme 2. Reagents and conditions: (a) 2,3-dihydro-2*H*-pyran, cat. PTSA, CH_2Cl_2, 0 °C, 1 h; (b) $(COCl)_2$, DMSO, −78 °C, 2 h; (c) $Ph_3P{=}CHCOOCH_3$, benzene, reflux, 2 h; (d) DIBAL-H, CH_2Cl_2, 0 °C to rt, 4 h; (e) (+)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, dry CH_2Cl_2, −20 °C, 5 h; (f) Ph_3P, CCl_4, cat. $NaHCO_3$, reflux, 4 h; (g) Na, dry ether, 0 °C to rt, 12 h; (h) MOMCl, DIPEA, CH_2Cl_2, rt, 6 h; (i) cat. PPTS, methanol, 5 h; (j) trimethylsulfonium iodide, DMSO, NaH, THF, 0 °C to rt, 4 h.

which on treatment with Na in dry ether for 12 h afforded **17** (86%). Etherification of **17** with MOMCl and DIPEA in CH_2Cl_2 at room temperature for 6 h furnished ether **18** in 94% yield. Thus, the allylic alcohol segment and creation of the (4*S*)-hydroxy group has been outlined from **12**. The remaining stereocentre was obtained by Jacobsen kinetic resolution of the racemic epoxide.

Accordingly, deprotection of the THP group with PPTS (cat.) in methanol at room temperature for 3 h afforded alcohol **10** in 91% yield, which was oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with NaH in DMSO, trimethylsulfonium iodide[5] in THF to afford the corresponding epoxide **9** in 62% yield. Epoxide **9** was subjected to Jacobsen's hydro-



Scheme 3. Reagents and conditions: (a) (*S*,*S*) Jacobsen catalyst, H_2O, rt, 12 h; (b) LAH, THF, 0 °C to rt, 1 h; (c) acryloyl chloride, diisopropylethylamine, CH_2Cl_2, rt, 3 h; (d) PPTS, *n*-butanol, reflux, 3 h; (e) Grubbs catalyst II, CH_2Cl_2, reflux, 24 h.



Scheme 4. Reagents and conditions: (a) (*R*,*R*) Jacobsen catalyst, H_2O, rt, 12 h; (b) LAH, THF, 0 °C to rt, 2 h; (c) acryloyl chloride, DIPEA, CH_2Cl_2, rt, 3 h; (d) PPTS, *n*-butanol, reflux, 3 h; (e) Grubbs catalyst II, CH_2Cl_2, reflux, 24 h.

lytic kinetic resolution[6] using (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) to give diol **19** (46%) and chiral epoxide **7** (43%). The reduction of **7** with LAH in THF at room temperature for 1 h afforded **20** in 91% yield, which on further treatment with acryloyl chloride and DIPEA in CH_2Cl_2 at room temperature for 3 h afforded acrylate ester **21** (93%). MOM deprotection in **21** on treatment with PPTS in *n*-butanol at reflux temperature for 3 h furnished alcohol **5** in 83% yield. Finally, the treatment of **5** with Grubb's catalyst II[7] in CH_2Cl_2 at reflux temperature for 24 h afforded patulolide C **1** in 47.5% yield, $[\alpha]_D^{25} = +6.0$ (*c* 0.5, EtOH), whose spectral data were comparable with the reported data (Scheme 3).

Epoxide **9** was subjected to Jacobsen's hydrolytic kinetic resolution[6] using (*R*,*R*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) to give diol **22** (44%) and chiral epoxide **8** (43%). Epoxide **8** on treatment with LAH in THF at room temperature for 1 h afforded **23** in 89% yield. The treatment of **23** with acryloyl chloride and DIPEA in CH_2Cl_2 at room temperature for 3 h afforded ester **24** (91%). MOM deprotection of **24**, on reaction with PPTS in *n*-butanol at reflux temperature for 3 h furnished alcohol **6** (84%), which finally on treatment with Grubb's catalyst II[7] in CH_2Cl_2 at reflux temperature for 24 h afforded 11-epipatulolide C **2** in 45% yield. Since the conversion of **1** and **2** on oxidation to give the respective enones **3** and **4** is reported[2b] in the literature, synthesis of **1** and **2** also completes the formal synthesis of **3** and **4** (Scheme 4).

3. Conclusion

In conclusion, the present report that describes an efficient total synthesis of patulolide C **1** and 11-epipatulolide C **2**, formal syntheses of patulolide A **3** and epipatulolide A **4** with high enantioselectivity. Important features of this approach include (a) the two stereocentres, one was established by Sharpless asymmetric epoxidation and the other one by Jacobsen's hydrolytic kinetic resolution and (b) ring-closing metathesis strategy for the construction of the C-2 and C-3 *trans* double bond. Thus, this flexible protocol developed in the present study paves the way for the construction of related 12-membered macrolides 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 the internal standard for solutions in deuteriochloroform. *J* values are given in Hertz. 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. 8-(Tetrahydro-2*H*-2-pyranyloxy)-1-octanol 13. To a cooled (0 °C) solution of 1,8-octane diol (5 g, 34.25 mmol) in dry CH_2Cl_2 (100 mL), 3,4-dihydro-2*H*-pyran (2.87 g, 34.25 mmol) and catalytic amount of PTSA were added and stirred at 0 °C for 1 h. The reaction mixture was quenched with Et_3N (1 mL), evaporated the residue under reduced pressure and purified by column chromatography (silica gel, EtOAc/hexane, 7:13) to afford **13** (6.46 g, 82%) as a yellow syrup. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34–1.86 (m, 18H, 9 × CH_2), 3.23–3.52 (m, 2H, –OCH_2), 3.61 (t, 2H, $J = 6.1$ Hz, –OCH_2), 3.63–3.87 (m, 2H, –OCH_2), 4.53–4.56 (m, 1H, –OCH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.6, 25.4, 25.6, 26.1, 29.2, 29.3, 29.6, 30.6, 32.6, 62.2, 62.8, 67.6, 98.7; IR (neat): 3454, 2930, 2857, 1461 cm^{-1}; HRMS *m/z* [M+Na]$^+$ found 253.1426; calculated 253.1415 for $C_{13}H_{26}O_3Na$.

4.1.2. Methyl (*E*)-10-(tetrahydro-2*H*-2-pyranyloxy)-2-decenoate 14. To a solution of oxalyl chloride (2.8 g, 22.1 mmol) in dry CH$_2$Cl$_2$ (30 mL) at −78 °C, dry DMSO (2.12 g, 27.1 mmol) was added dropwise. After 30 min, alcohol **13** (3.9 g, 16.9 mmol) in CH$_2$Cl$_2$ (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at −78 °C, Et$_3$N (6.9 g, 67.8 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (50 mL) and CH$_2$Cl$_2$ (100 mL). The organic layer was separated and washed with water (20 mL), brine (20 mL) and dried (Na$_2$SO$_4$). Solvent was evaporated to give aldehyde **13a**, which was used for the reaction.

The above crude aldehyde was dissolved in benzene (70 mL) and treated with (methoxycarbonylmethylene)triphenyl phosphorane (7.2 g, 20.5 mmol) at reflux. After 2 h, the solvent was evaporated and the residue purified by column chromatography (silica gel, EtOAc/hexane, 5:95) to furnish **14** (4.4 g, 90.8%) as a yellow syrup. ^{1}H NMR (CDCl$_3$, 200 MHz): δ 1.33–1.85 (m, 16H, 8 × CH$_2$), 2.18 (q, 2H, $J = 6.6$ Hz, –CH$_2$), 3.26–3.51 (m, 2H, –OCH$_2$), 3.63–3.87 (m, 2H, –OCH$_2$), 4.16 (s, 3H, –OCH$_3$), 4.52–4.56 (m, 1H, –OCH), 5.76 (dt, 1H, $J = 1.5$, 2.9 Hz, olefinic), 6.91 (dt, 1H, $J = 6.9$, 13.9 Hz, olefinic); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.6, 25.4, 26.1, 27.9, 28.9, 29.1, 29.6, 30.7, 32.1, 51.3, 62.3, 67.5, 98.8, 120.8, 149.6, 167.2; IR (neat): 2932, 2858, 1722, 1441 cm^{-1}; HRMS *m/z* [M+Na]$^+$ found 307.1881; calculated 307.1885 for $C_{16}H_{28}O_4Na$.

4.1.3. (*E*)-10-(Tetrahydro-2*H*-2-pyranyloxy)-2-decen-1-ol 15. To a cooled (0 °C) solution of **14** (4.4 g, 15.5 mmol) in dry CH$_2$Cl$_2$ (20 mL), DIBAL-H (4.42 g, 31.1 mmol, 20% solution in toluene) was added slowly for 15 min. The reaction mixture was stirred at room temperature for 4 h, cooled to 0 °C, quenched with methanol (1 mL) and sodium potassium tartarate solution (5 mL). The reaction mixture was passed through a short pad of Celite. The filtrate was concentrated and purified the residue by column chromatography (silica gel, EtOAc/hexane, 1:3) to furnish **15** (3.2 g, 80.7%) as a yellow syrup. ^{1}H NMR (CDCl$_3$, 200 MHz): δ 1.22–1.86 (m, 16H, 8 × –CH$_2$), 1.99–2.05 (m, 2H, –CH$_2$), 3.25–3.52 (m, 2H, –OCH$_2$), 3.63–3.87 (m, 2H, –OCH$_2$), 4.03–4.05 (m, 2H, –OCH$_2$), 4.53–4.56 (m, 1H, –OCH), 5.59–5.65 (m, 2H, olefinic); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.5, 25.3, 26.0, 28.9, 29.1, 29.5, 30.6, 32.0, 62.1, 63.4, 67.5, 98.6, 128.8, 132.9; IR (neat): 3454, 2929, 2856, 1028 cm^{-1}; HRMS *m/z* [M+Na]$^+$ found 279.1926; calculated 279.1936 for $C_{15}H_{28}O_3Na$.

4.1.4. (2*S*,3*S*)-3-[7-(Tetrahydro-2*H*-2-pyranyloxy)heptyl]-oxiran-2-ylmethanol 11. To a stirred solution of (+) DIPT (1.62 g, 6.9 mmol) in CH$_2$Cl$_2$ (15 mL) at −20 °C containing MS 4 Å (0.3 g), sequentially Ti(O^{i}Pr)$_4$ (1.64 g, 5.76 mmol) and cumenehydroperoxide (3.55 g, 23.0 mmol) were added and stirred for 20 min. A solution of **15** (2.95 g, 11.5 mmol) in CH$_2$Cl$_2$ (15 mL) was added and stirred for 5 h at −20 °C. The reaction mixture was quenched with 10% KOH solution (1.5 g in 15 mL brine), stirred for 3 h and filtered. The organic layers were dried (Na$_2$SO$_4$), evaporated and the residue obtained was purified by column chromatography (silica gel, EtOAc/hexane, 2:3) to furnish **11** (2.82 g, 90.1%) as a yellow syrup. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.28–1.86 (m, 18H, 9 × –CH$_2$), 2.83–2.92 (m, 2H, 2 × –OCH), 3.29–3.50 (m, 2H, –OCH$_2$), 3.56–3.72 (m, 2H, –OCH$_2$), 3.78–3.87 (m, 2H, –OCH$_2$), 4.53–4.57 (m, 1H, –OCH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.6, 23.4, 25.8, 26.1, 29.2, 29.6, 30.6, 31.6, 55.9, 58.6, 61.8, 62.4, 63.4, 67.5, 98.8; HRMS *m/z* [M+Na]$^+$ found 295.1878; calculated 295.1885 for $C_{15}H_{28}O_4Na$.

4.1.5. 2-(7-[(2*S*,3*R*)-3-(Chloromethyl)oxiran-2-yl]heptyloxy)-tetrahydro-2*H*-pyran 16. To a stirred solution of **11** (2.63 g, 9.67 mmol) in CCl$_4$ (30 mL), Ph$_3$P (2.79 g, 10.64 mmol) and NaHCO$_3$ (cat.) were added and heated at reflux for 4 h. The reaction mixture was evaporated and the residue purified by column chromatography (silica gel, EtOAc/hexane, 5:95) to afford **16** (2.61 g, 93%) as a yellow syrup. ^{1}H NMR (CDCl$_3$, 200 MHz): δ 1.26–1.91 (m, 18H, 9 × –CH$_2$), 2.76–2.96 (m, 2H, 2 × –OCH), 3.25–3.87 (m, 6H, 2 × –OCH$_2$, –CH$_2$Cl), 4.49–4.55 (m, 1H, –OCH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.6, 25.3, 25.7, 26.2, 29.1, 29.6, 30.7, 31.3, 44.7, 57.0, 59.0, 62.3, 63.4, 67.5, 98.8; IR (neat): 2929, 2856, 1459 cm^{-1}.

4.1.6. (3*S*)-10-(Tetrahydro-2*H*-2-pyranyloxy)-1-decen-3-ol 17. To a suspension of Na (0.42 g, 17.9 mmol) in dry ether (10 mL), a solution of **16** (2.61 g, 8.98 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 **17** (1.96 g, 86%) as a yellow syrup. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.34–1.87 (m, 18H, 9 × –CH$_2$), 3.28–3.49 (m, 2H, –OCH$_2$), 3.63–3.85 (m, 2H, –OCH$_2$), 4.04 (q, 1H, $J = 6.1$ Hz, –OCH), 4.53–4.55 (m, 1H, –OCH), 5.06–5.18 (m, 2H, olefinic), 5.78–5.89 (m, 1H, olefinic); ^{13}C NMR (75 MHz, CDCl$_3$): δ 19.6, 25.2, 25.4, 26.1, 29.3, 29.5, 29.7, 30.7, 36.9, 62.3, 67.6, 73.2, 98.8, 114.5, 141.3; HRMS *m/z* [M+Na]$^+$ found 279.1937; calculated 279.1936 for $C_{15}H_{28}O_3Na$.

4.1.7. 2-[(8*S*)-8-(Methoxymethoxy)-9-decenyl]oxytetrahydro-2*H*-pyran 18. To a cooled (0 °C) solution of **17** (1.37 g, 5.39 mmol) in CH$_2$Cl$_2$ (15 mL), DIPEA (1.395 g, 10.8 mmol) and MOMCl (0.65 g, 8.1 mmol) were added sequentially and stirred at room temperature for 6 h. The reaction mixture was evaporated and the residue purified by column chromatography (silica gel, EtOAc/hexane, 1:19) to afford **18** (1.52 g, 94%) as a yellow syrup. ^{1}H NMR (CDCl$_3$, 200 MHz): δ 1.26–1.89 (m, 18H, 9 × –CH$_2$), 3.26–3.51 (m, 2H, –OCH$_2$), 3.33 (s, 3H, –OCH$_3$) 3.60–3.98 (m, 3H, –OCH$_2$, –OCH), 4.4 (d, 1H, $J = 6.9$ Hz, –OCH), 4.52–4.55 (m, 1H, –OCH), 4.62 (d, 1H, $J = 6.9$ Hz, –OCH), 5.12–5.20 (m, 2H, olefinic), 5.54–5.71 (m, 1H, olefinic); ^{13}C NMR (75 MHz, CDCl$_3$):

δ 19.6, 25.2, 25.5, 26.1, 29.3, 29.5, 29.7, 30.7, 35.3, 55.3, 62.3, 67.6, 77.3, 93.6, 98.8, 116.9, 138.4; IR (neat): 2929, 2855, 1460, 1032 cm^{-1}; HRMS *m/z* $[\text{M+Na}]^+$ found 323.2199; calculated 323.2198 for $C_{17}H_{32}O_4Na$.

4.1.8. (8*S*)-8-(Methoxymethoxy)-9-decen-1-ol 10. To a stirred solution of **18** (1.5 g, 5.04 mmol) in methanol (15 mL), PPTS (cat.) was added and stirred at room temperature for 5 h. The reaction mixture was quenched with Et_3N (1 mL), evaporated and purified the residue by column chromatography (silica gel, EtOAc/hexane, 1:4) to afford **10** (0.989 g, 91%) as a yellow syrup. $[\alpha]_D^{25} = -148.2$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25–1.56 (m, 12H, 6 × $-CH_2$), 3.34 (s, 3H, $-OCH_3$), 3.60 (t, 2H, $J = 6.4$ Hz, $-OCH_2$), 3.94 (q, 1H, $J = 6.8$ Hz, –OCH), 4.45 (d, 1H, $J = 6.4$ Hz, –OCH), 4.63 (d, 1H, $J = 6.4$ Hz, –OCH), 5.14–5.19 (m, 2H, olefinic), 5.56–5.68 (m, 1H, olefinic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 25.6, 29.2, 29.3, 32.6, 35.2, 55.2, 62.6, 77.2, 93.5, 116.9, 138.3; IR (neat): 3431, 2930, 2856, 1462 cm^{-1}; HRMS *m/z* $[\text{M+Na}]^+$ found 239.1614; calculated 239.1623 for $C_{12}H_{24}O_3Na$.

4.1.9. 2-[(7*S*)-7-(Methoxymethoxy)-8-nonenyl]oxirane 9. To a solution of oxalyl chloride (0.732 g, 5.76 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C, dry DMSO (0.601 g, 7.69 mmol) was added dropwise. After 30 min, alcohol **10** (0.830 g, 16.9 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at −78 °C, Et_3N (1.6 g, 15.4 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was separated and washed with water (5 mL) and brine (5 mL), and dried (Na_2SO_4). Solvent was evaporated to give the aldehyde, which was used as such for the next reaction.

A solution of NaH (0.133 g, 5.75 mmol) in DMSO (2 mL) was stirred at 70–75 °C for 30 min and cooled to room temperature. THF (4 mL), followed by suspension of TMSI (1.25 g, 6.13 mmol) in DMSO (2.5 mL) were added at −5 °C and stirred for 5 min. Then, a solution of the above aldehyde in THF (4 mL) was added to the reaction mixture and stirred for 2 h at −5 °C, allowed to room temperature and stirred for 2 h. The reaction mixture was quenched with water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with water (2 × 5 mL), brine (5 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by column chromatography (silica gel, EtOAc/hexane, 8:92) to afford **9** (0.540 g, 61.8%) as a yellow syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34–1.59 (m, 12H, 6 × $-CH_2$), 2.38–2.41 (m, 1H, –OCH), 2.67–2.70 (m, 1H, –OCH), 2.81–2.83 (m, 1H, –OCH), 3.33 (s, 3H, $-OCH_3$), 3.94 (q, 1H, $J = 7.2$ Hz, –OCH), 4.47 (d, 1H, $J = 6.8$ Hz, –OCH), 4.65 (d, 1H, $J = 6.8$ Hz, –OCH), 5.13–5.19 (m, 2H, olefinic), 5.56–5.68 (m, 1H, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 25.9, 29.3, 29.4, 32.4, 35.3, 47.1, 52.3, 55.3, 77.3, 93.7, 116.9, 138.5; IR (neat): 2929, 2856, 1462, 1035 cm^{-1}; HRMS *m/z* $[\text{M+Na}]^+$ found 251.1616; calculated 251.1623 for $C_{13}H_{24}O_3Na$.

4.1.10. (2*R*,9*S*)-9-(Methoxymethoxy)-10-undecene-1,2-diol 19 and (2*S*)-2-[(7*S*)-7-(methoxymethoxy)-8-nonenyl]oxirane 7. A mixture of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt[7] (**II**) (0.007 g, 0.011 mmol) in toluene (0.25 mL) and acetic acid (0.29 g, 4.83 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 **9** (0.5 g, 2.19 mmol) was added in one portion at 0 °C and water (0.021 mL, 1.21 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The residue was purified by column chromatography. First eluted (silica gel, EtOAc/hexane, 1:9) was (*S*)-oxirane **7** (0.215 g, 43%) as a yellow syrup $[\alpha]_D^{25} = -179.5$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35–1.59 (m, 12H, 6 × $-CH_2$), 2.40 (dd, 1H, $J = 2.6$, 4.9 Hz, –OCH), 2.67–2.71 (m, 1H, –OCH), 2.81–2.86 (m, 1H, –OCH), 3.34 (s, 3H, $-OCH_3$), 3.94 (q, 1H, $J = 7.2$ Hz, –OCH), 4.47 (d, 1H, $J = 6.8$ Hz, –OCH), 4.66 (d, 1H, $J = 6.8$ Hz, –OCH), 5.14–5.19 (m, 2H, olefinic), 5.57–5.68 (m, 1H, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 25.9, 29.3, 29.4, 32.4, 35.4, 47.1, 52.3, 55.4, 77.3, 93.7, 116.9, 138.5; IR (neat): 2925, 2854, 1462, 1036 cm^{-1}; HRMS *m/z* $[\text{M+Na}]^+$ found 251.1618; calculated 251.1623 for $C_{13}H_{24}O_3Na$.

The second eluted (silica gel, EtOAc/hexane, 4:1) was diol **19** (0.247 g, 46%) $[\alpha]_D^{25} = -188.27$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25–1.59 (m, 12H, 6 × $-CH_2$), 3.34 (s, 3H, $-OCH_3$), 3.35–3.42 (m, 1H, –OCH), 3.60–3.66 (m, 2H, –OCH), 3.94 (q, 1H, $J = 7.2$ Hz, –OCH), 4.47 (d, 1H, $J = 6.8$ Hz, –OCH), 4.64 (d, 1H, $J = 6.8$ Hz, –OCH), 5.14–5.19 (m, 2H, olefinic), 5.57–5.68 (m, 1H, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 25.5, 29.4, 29.5, 35.3, 55.3, 77.4, 93.7, 117.0, 138.4; IR (neat): 3393, 2929, 2856, 1461, 1036 cm^{-1}; HRMS *m/z* $[\text{M+Na}]^+$ found 269.1724; calculated 269.1728 for $C_{13}H_{26}O_4Na$.

4.1.11. (2*R*,9*S*)-9-(Methoxymethoxy)-10-undecen-2-ol 20. To a suspension of LAH (0.032 g, 0.834 mmol) in THF (2 mL), a solution of **7** (0.190 g, 0.834 mmol) in THF (2 mL) was added at 0 °C and stirred at room temperature for 1 h. It was quenched with Na_2SO_4 solution (1 mL), filtered and washed with ethyl acetate (20 mL). Combined organic layers were dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc/hexane, 1:4) to furnish **20** (0.175 g, 91.3%) as a yellow syrup. $[\alpha]_D^{25} = -177.6$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 1.24–1.59 (m, 12H, 6 × $-CH_2$), 3.34 (s, 3H, $-OCH_3$), 3.70–3.78 (m, 1H, –OCH), 3.93 (q, 1H, $J = 6.1$ Hz, –OCH), 4.45 (d, 1H, $J = 6.8$ Hz, –OCH), 4.66 (d, 1H, $J = 6.8$ Hz, –OCH), 5.13–5.19 (m, 2H, olefinic), 5.57–5.68 (m, 1H, olefinic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 25.3, 25.7, 29.4, 29.5, 35.3, 39.2, 55.4, 68.1, 77.3, 93.6, 117.1, 138.4; IR (neat): 3431, 2929, 2856, 1034 cm^{-1}; HRMS *m/z* $[\text{M+Na}]^+$ found 253.1771; calculated 253.1779 for $C_{13}H_{26}O_3Na$.

4.1.12. (1*R*,8*S*)-8-(Methoxymethoxy)-1-methyl-9-decenyl acrylate 21. A solution of DIPEA (0.295 g, 2.28 mmol) and **20** (0.175 g, 0.761 mmol) in CH_2Cl_2 (4 mL) at 0 °C was treated with acryloyl chloride (0.10 g, 1.14 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, 4:96) to afford **21** (0.199 g, 93%) as a yellow syrup. $[\alpha]_D^{25} = -122.5$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25 (d, 3H, $J = 6.2$ Hz, $-CH_3$), 1.30–1.67 (m, 12H, $6 \times -CH_2$), 3.33 (s, 3H, $-OCH_3$), 3.94 (q, 1H, $J = 6.6$ Hz, –OCH), 4.47 (d, 1H, $J = 6.6$ Hz, –OCH), 4.66 (d, 1H, $J = 6.6$ Hz, –OCH), 4.96 (sextet, 1H, $J = 6.2$ Hz, –OCH), 5.12–5.20 (m, 2H, olefinic), 5.53–5.72 (m, 1H, olefinic), 5.79 (dd, 1H, $J = 1.8$, 10.3 Hz olefinic), 5.99–6.13 (m, 1H, olefinic), 6.36 (dd, 1H, $J = 1.8$, 17.3 Hz olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 25.2, 25.3, 29.4, 29.5, 35.4, 35.9, 55.4, 71.2, 77.3, 93.7, 116.9, 129.1, 130.0, 138.5, 165.8; IR (neat): 2932, 2857, 1723, 1199, 1037 cm^{-1}; HRMS *m*/*z* $[M+Na]^+$ found 307.1883; calculated 307.1885 for $C_{16}H_{28}O_4Na$.

4.1.13. (1*R*,8*S*)-8-Hydroxy-1-methyl-9-decenyl acrylate 5. To a solution of **21** (0.178 g, 0.63 mmol) in *n*-butanol (4 mL), PPTS (0.473 g, 1.88 mmol) was added and stirred at reflux for 4 h. Then reaction mixture was concentrated, residue dissolved in EtOAc (20 mL), washed with water (2 mL), brine (2 mL) and dried (Na_2SO_4). Solvent was evaporated and residue purified by column chromatography (silica gel, EtOAc/hexane, 1:4) to afford **5** (0.125 g, 83%) as a yellow syrup. $[\alpha]_D^{25} = +11.5$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.23 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 1.27–1.67 (m, 12H, $6 \times -CH_2$), 4.05 (q, 1H, $J = 6.1$ Hz, –OCH), 4.93 (sextet, 1H, $J = 6.1$ Hz, –OCH), 5.08 (td, 1H, $J = 1.5$, 10.6 Hz, olefinic), 5.18 (td, 1H, $J = 1.5$, 16.9 Hz, olefinic), 5.77 (dd, 1H, $J = 1.5$, 10.2 Hz, olefinic), 5.76–5.88 (m, 1H, olefinic), 6.02–6.12 (m, 1H, olefinic), 6.36 (dd, 1H, $J = 1.5$, 16.9 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 25.2, 25.3, 29.3, 29.4, 35.9, 36.9, 71.2, 73.2, 114.5, 129.1, 130.1, 141.3, 165.9; IR (neat): 3443, 2926, 2856, 1723, 1199 cm^{-1}; HRMS *m*/*z* $[M+F]^+$ found 259.1717; calculated 259.1709 for $C_{14}H_{24}O_3F$.

4.1.14. Patulolide C 1. To a solution of **5** (0.05 g, 0.208 mmol) in CH_2Cl_2 (125 mL), 5 mol % Grubbs catalyst II (8.9 mg, 0.0104 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 air bubbling 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 **1** as a colourless syrup (21 mg, 47.5%). $[\alpha]_D^{25} = +6.0$ (*c* 0.5, EtOH); lit.[2c] $[\alpha]_D = +6.6$ (*c* 0.42, EtOH); lit.[2b] $[\alpha]_D = +6.8$ (*c* 0.15, EtOH); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.13–1.67 (m, 12H, $6 \times -CH_2$), 1.23 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 4.31 (q, 1H, $J = 4.5$ Hz, –OCH), 4.99–5.05 (m, 1H, –OCH), 6.03 (dd, 1H, $J = 1.5$, 15.5 Hz, olefinic), 6.91 (dd, 1H, $J = 4.5$, 15.9 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 23.9, 24.2, 28.1, 28.6, 34.7, 36.5, 70.9, 71.1, 120.5, 149.9, 166.6; IR (neat): 3416, 2919, 2845, 1718 cm^{-1}; HRMS *m*/*z* $[M-H]^+$ found 211.1344; calculated 211.1334 for $C_{12}H_{19}O_3$.

4.1.15. (2*S*,9*S*)-9-(Methoxymethoxy)-10-undecene-1,2-diol 22 and (2*R*)-2-[(7*S*)-7-(methoxymethoxy)-8-nonenyl]oxirane 8. A mixture of (*R*,*R*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt[7] (**II**) (0.006 g, 0.009 mmol) in toluene (0.25 mL) and acetic acid (0.23 g, 3.86 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 **9** (0.4 g, 1.75 mmol) was added in one portion at 0 °C and water (0.018 mL, 0.97 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The residue was purified by column chromatography. First eluted (silica gel, EtOAc/hexane, 1:9) was (*R*)-oxirane **8** (0.172 g, 43%) as a yellow syrup $[\alpha]_D^{25} = -23.3$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33–1.59 (m, 12H, $6 \times -CH_2$), 2.41 (dd, 1H, $J = 2.6$, 5.1 Hz, –OCH), 2.67–2.71 (m, 1H, –OCH), 2.80–2.86 (m, 1H, –OCH), 3.34 (s, 3H, $-OCH_3$), 3.94 (q, 1H, $J = 7.2$ Hz, –OCH), 4.47 (d, 1H, $J = 6.6$ Hz, –OCH), 4.66 (d, 1H, $J = 6.6$ Hz, –OCH), 5.13–5.19 (m, 2H, olefinic), 5.57–5.68 (m, 1H, olefinic); IR (neat): 2926, 2854, 1461, 1036 cm^{-1}; HRMS *m*/*z* $[M+Na]^+$ found 251.1616; calculated 251.1623 for $C_{13}H_{24}O_3Na$.

The second eluted (silica gel, EtOAc/hexane, 4:1) was diol **22** (0.189 g, 44%) $[\alpha]_D^{25} = -29.4$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.23–1.59 (m, 12H, $6 \times -CH_2$), 3.34 (s, 3H, $-OCH_3$), 3.35–3.40 (m, 1H, –OCH), 3.59–3.66 (m, 2H, –OCH), 3.94 (q, 1H, $J = 7.1$ Hz, –OCH), 4.47 (d, 1H, $J = 6.6$ Hz, –OCH), 4.64 (d, 1H, $J = 6.6$ Hz, –OCH), 5.14–5.19 (m, 2H, olefinic), 5.57–5.68 (m, 1H, olefinic); IR (neat): 3394, 2927, 2856, 1461, 1036 cm^{-1}; HRMS *m*/*z* $[M+Na]^+$ found 269.1721; calculated 269.1728 for $C_{13}H_{26}O_4Na$.

4.1.16. (2*S*,9*S*)-9-(Methoxymethoxy)-10-undecen-2-ol 23. Compound **23** was prepared from **8** (0.17 g, 0.48 mmol) following the procedure described for compound **20** in 89% yield as a colourless liquid. $[\alpha]_D^{25} = -2.6$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.15 (d, 3H, $J = 6.3$ Hz, $-CH_3$), 1.23–1.67 (m, 12H, $6 \times -CH_2$), 3.34 (s, 3H, $-OCH_3$), 3.66–4.16 (m, 2H, $2 \times$ –OCH), 4.48 (d, 1H, $J = 6.6$ Hz, –OCH), 4.66 (d, 1H, $J = 6.6$ Hz, –OCH), 5.09–5.21 (m, 2H, olefinic), 5.52–5.71 (m, 1H, olefinic); IR (neat): 3428, 2926, 2854 cm^{-1}; HRMS *m*/*z* $[M+Na]^+$ found 253.1774; calculated 253.1779 for $C_{13}H_{26}O_3Na$.

4.1.17. (1*S*,8*S*)-8-(Methoxymethoxy)-1-methyl-9-decenyl acrylate 24. Compound **24** was prepared from **23** (0.10 g, 0.44 mmol) following the procedure described for compound **21** in 91% yield as a colourless liquid. $[\alpha]_D^{25} = -33.5$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (d, 3H, $J = 6.2$ Hz, $-CH_3$), 1.26–1.74 (m, 12H, $6 \times -CH_2$), 3.33 (s, 3H, $-OCH_3$), 3.94 (q, 1H, $J = 6.2$ Hz, –OCH), 4.40 (d, 1H, $J = 6.6$ Hz, –OCH), 4.62 (d, 1H, $J = 6.6$ Hz, –OCH), 4.93 (sextet, 1H, $J = 6.6$ Hz, –OCH), 5.10–5.20 (m, 2H, olefinic), 5.53–5.71

(m, 1H, olefinic), 5.77 (dd, 1H, $J = 1.8$, 10.3 Hz olefinic), 5.99–6.13 (m, 1H, olefinic), 6.34 (dd, 1H, $J = 1.8$, 17.3 Hz olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 25.1, 25.2, 29.1, 29.2, 35.2, 35.7, 55.2, 70.9, 77.1, 93.5, 116.8, 128.9, 129.9, 138.3, 165.7; IR (neat): 2933, 2858, 1723, 1200, 1036 cm^{-1}; HRMS *m/z* $[M+Na]^+$ found 307.1884; calculated 307.1885 for $C_{16}H_{28}O_4Na$.

4.1.18. (1*S*,8*S*)-8-Hydroxy-1-methyl-9-decenyl acrylate 6. Compound **6** was prepared from **24** (0.11 g, 0.39 mmol) following the procedure described for compound **5** in 84% yield as a colourless liquid. $[\alpha]_D^{25} = -12.7$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (d, 3H, $J = 6.1$ Hz, $-CH_3$), 1.25–1.69 (m, 12H, $6 \times -CH_2$), 4.04 (q, 1H, $J = 6.4$ Hz, –OCH), 4.93 (sextet, 1H, $J = 6.1$ Hz, –OCH), 5.06 (td, 1H, $J = 1.5$, 10.5 Hz, olefinic), 5.18 (td, 1H, $J = 1.5$, 16.9 Hz, olefinic), 5.78 (dd, 1H, $J = 1.9$, 10.5 Hz, olefinic), 5.77–5.88 (m, 1H, olefinic), 6.02–6.11 (m, 1H, olefinic), 6.36 (dd, 1H, $J = 1.9$, 17.3 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 25.1, 25.2, 29.2, 29.3, 35.8, 36.8, 71.1, 73.1, 114.4, 128.9, 130.1, 141.2, 165.9; IR (neat): 3443, 2925, 2854, 1720, 1200 cm^{-1}; HRMS *m/z* $[M+F]^+$ found 259.1714; calculated 259.1709 for $C_{14}H_{24}O_3F$.

4.1.19. 11-Epipatulolide C 2. Compound **2** was prepared from **6** (0.05 g, 0.21 mmol) following the procedure described for compound **1** in 45% yield as a colourless liquid. $[\alpha]_D^{25} = +3.6$ (*c* 0.25, EtOH); lit.[2b] $[\alpha]_D = +3.4$ (*c* 0.05, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.13–1.70 (m, 12H, $6 \times -CH_2$), 1.23 (d, 3H, $J = 6.4$ Hz, $-CH_3$), 4.23–4.36 (m, 1H, –OCH), 4.90–5.05 (m, 1H, –OCH), 6.02 (dd, 1H, $J = 5.3$, 15.1 Hz, olefinic), 6.92 (dd, 1H, $J = 5.6$, 15.1 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 24.7, 24.9, 28.7, 28.9, 35.6, 36.4, 71.1, 71.2, 120.9, 149.8, 166.3; IR (neat): 3416, 2919, 2845, 1718 cm^{-1}; HRMS *m/z* $[M-H]^+$ found 211.1342; calculated 211.1334 for $C_{12}H_{19}O_3$.

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