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CONCISE STEREOSELECTIVE TOTAL SYNTHESIS OF (+)-MUEGGELONE

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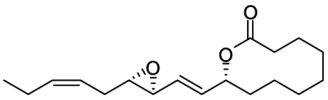
GRAPHICAL ABSTRACT



(+)Mueggelone

Abstract *A concise synthetic route has been reported for the total synthesis of (+)-mueggelone. The syntheses of fragments were initiated from commercially available and inexpensive starting materials. The synthesis involves key steps such as Sharpless epoxidation, Jacobsen resolution, lactonization, and cross metathesis.*

Keywords Jacobsen resolution; (+)-mueggelone; Sharpless epoxidation

INTRODUCTION

(+)-Mueggelone was isolated by Konig and coworkers in 1995 from the bloom-forming strain of *Aphanizomenon flos-aquae*.[1] (+)-Mueggelone is reported to show a significant ecologically important role in the inhibition of fish embryo larval development. In particular, in mueggelone at a concentration of 10 ug/mL, zebra fish larvae showed 45% mortality. Survivors showed edema in the heart region and thrombosis. The key structural features of mueggelone are a 10-membered lactone having a side chain with *cis, trans* double bonds and epoxide. The structure and unique biological activity of **1** spurred considerable interest among synthetic organic chemists. Ishigami et al. synthesized all the four possible stereoisomers of mueggelone and determined its absolute configuration. Ishigami et al.[2a] and Yadav et al.[2b] have reported the total synthesis of (+)-mueggelone in 21 and 22 steps respectively. We have planned a synthetic strategy to reduce the number of steps. The carbon skeleton of (+)-mueggelone suggests a convergent synthesis is desirable.

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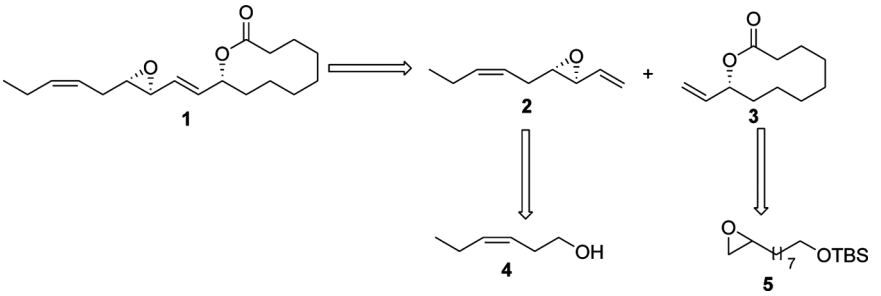
RESULTS AND DISCUSSION

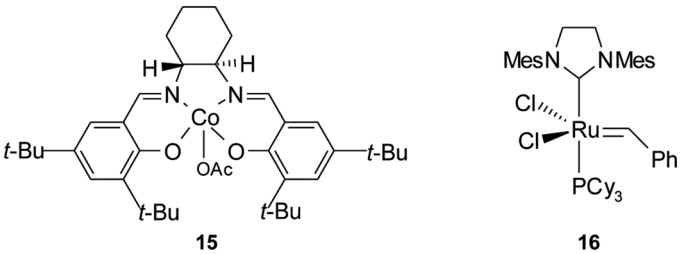
As outlined in retrosynthetic diagram in Scheme 1, the synthesis of fragment **2** commenced from commercially available (*Z*)-3-hexene1-ol **4**. Thus, the alcohol was oxidized with Dess–Martin periodinane to obtain aldehyde, which subsequently underwent Witting olefination to give **6** in 89% yield.[3]

Reduction of **6** with diisobutyl aluminium hydride gave allylic alcohol **7** in 89% yield, which was then transformed into epoxy alcohol **8** under Sharpless conditions.[4] Conversion of epoxy alcohol **8** into **2** was accomplished in good yield by Swern oxidation followed by 1C-Wittig homologation.[5]

A kinetic resolution of racemic epoxide **5** with the (*R,R*)-Jacobsen catalyst **15** (Fig. 1) furnished the optically active epoxide **9**.[6] Treatment of epoxide **9** with trimethylsulfonium iodide and *n*-BuLi cleanly afforded secondary allylic alcohol **10** in 85% yield.[7] The secondary hydroxy group protected with *tert*-butyldiphenylsilyl chloride gave the corresponding silyl ether **11**. Deprotection of TBS with PPTS resulted in to primary alcohol **12** in good yield.[8] Alcohol **12** was converted to acid **13** by treating with TEMPO and (bisiodobenzene diacetate) (BAIB) as co-oxidant.[9] Removal of the TBDPS group with HF · pyridine gave a precursor of fragment **3**. Macrolactonization of hydroxy acid using 2-methyl-6-nitrobenzoic anhydride (MNBA) under Shiina conditions gave a 10 membered lactone **3**.[10] Assembly of two terminal alkenes **2** and **3** was undertaken by cross metathesis using Grubbs catalyst[11] **16** (Fig. 1), which afforded the target molecule with desired *E*-selectivity along with the homo dimer as a side product, which was confirmed by mass spectroscopy (Scheme 3). The desired molecule was confirmed by spectral data and rotation, which are identical to the natural isomer.[2]

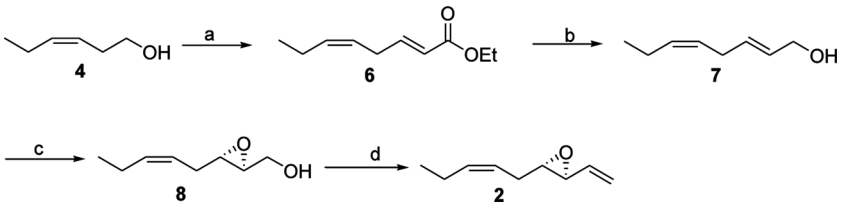


Scheme 1. Retrosynthetic analysis of (+)-muggelone (**1**).

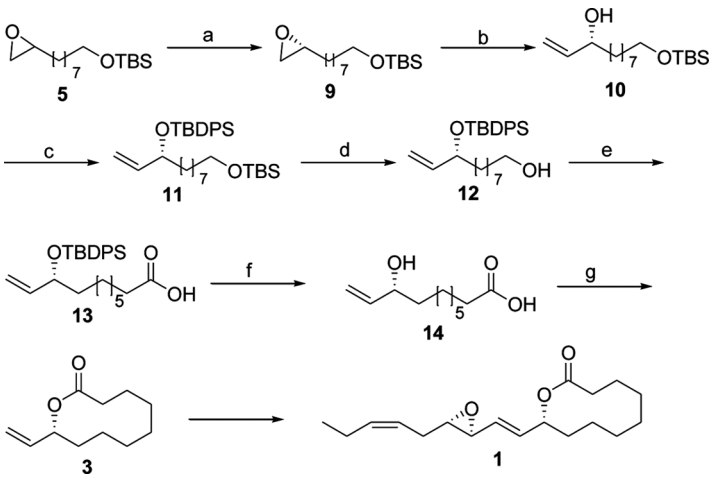


15 **16**

Figure 1. (*R,R*) Jacobsen catalyst (**15**) and second-generation Grubbs catalyst (**16**).



Scheme 2. Reagents and conditions: (a) (i) Dess–Martin oxidation, (ii) $(EtO)_2P(O)CH_2CO_2Et$, *n*-BuLi, THF, 0 °C, 89%; (b) DIBAL-H, THF, 0 °C, 89%; (c) (+)-DIPT, $Ti(iPrO)_4$, TBHP, CH_2, 4 A° MS, −20 °C, 90%; (d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 90%, (ii) PPh_3CH_3I, *t*BuOK, THF, 0–25 °C, 2 h, 70%.



Scheme 3. Reagents and conditions: (a) (*R,R*)-Co salen complex, THF, H_2O, 40%; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, −10 °C to rt, 85%; (c) TBDPSCI, imidazole, CH_2Cl_2, rt, 92%; (d) PPTS, EtOH, rt, 90%; (e) TEMPO, BAIB, CH_3CN, H_2O, 80%; (f) HF · Pyr, THF, 92%; (g) MNBA, DMAP, Et_3N, CH_2Cl_2/THF, 50 °C, 77%; (h) **2**, second-generation Grubbs catalyst, CH_2Cl_2, 25 °C, 40%.

CONCLUSION

In summary, we have synthesized (+)-mueggelone in comparably fewer steps. Both fragments were synthesized from easily available starting materials. The products are obtained in good yields. The synthesis was highlighted by Sharpless epoxidation, Jacobsen resolution, lactonization, and cross metathesis as key steps. This approach provides easy access to the synthesis of (+)-mueggelone, which has biological importance.

EXPERIMENTAL

All reactions were carried out under an inert atmosphere unless mentioned and followed standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by

thin-layer chromatography (TLC) using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60 mesh) and neutral alumina using diethyl ether, ethyl acetate, and hexane as the eluents. Optical rotation values were measured with a Perkin-Elmer P241 polarimeter and Jasco DIP-360 digital polarimeter at 25 °C. Infrared (IR) spectra were recorded with a Perkin-Elmer Fourier transform (FT)–IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini (200 MHz), Bruker Avance (300 MHz), Varian Unity (400 MHz), or Varian Inova (500 MHz) spectrometers using tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Mass spectra were recorded on a Micromass VG-7070H for electron impact (EI) and VG Autospec M for fast atom bombardment–mass spectrometry (FABMS).

(*2E,5Z*)-Octa-2,5-dienoic Acid Ethyl Ester

To a stirred solution of (*Z*)-hex-3-en1-ol **4** (1 g, 10 mmol) in dichloromethane (1 mL), Dess–Martin periodinane (6.36 g, 15 mmol) was added portionwise, and the resulting mixture was stirred for 30 min at 0 °C. The reaction mixture was diluted with ether and filtered, and the filtrate was washed with saturated aqueous sodium hydrogen carbonate and brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which, without further purification, was treated with triethyl phosphonoacetate (2.58 mL, 1.3 mmol) and *n*-butyllithium (1.6 M in *n*-hexane, 0.73 mL, 1.2 mmol) in dry THF (5 mL) for 2 h at 0 °C. After addition of saturated aqueous NH_4Cl, the mixture was extracted with diethyl ether. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography (*n*-pentane-diethyl ether, 30:1) to give **6** (1.49 g, 8.9 mmol, 89%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): (0.97 (t, 3H, $J = 7.5$ Hz, CH_3), 1.28 (t, 3H, $J = 7.2$ Hz, CH_3), 2.04–2.10 (m, 2H, CH_2), 2.94 (dd, 2H, $J = 6.3$, 7.1 Hz, CH_2), 4.18 (q, 2H, $J = 7.2$ Hz, OCH_2), 5.35–5.41 (m, 1H, olefin), 5.55–5.62 (m, 1H, olefin), 5.83 (dt, 1H, $J = 1.7$, 15.5 Hz, olefin), 6.95 (dt, 1H, $J = 6.3$, 15.5 Hz, olefin); ^{13}C NMR (75 MHz, $CDCl_3$): (13.9, 14.1, 20.4, 29.7, 60.1, 121.2, 123.5, 134.5, 147.2, 166.6; IR (KBr): 1720, 1652,1464, 1400, 1368, 1325, 1308, 1272, 1234, 1208, 1165, 1120, 1096, 1047, 993, 930, 900 cm^{-1}; EI-MS: m/z 168 [M^+]; ESI-HRMS: calculated for $C_{10}H_{16}O_2$: 168.1150; found: 168.1144.

(*2E,5Z*)-Octa-2,5-dien-1-ol (7)

Diisobutylaluminium hydride (20.6 mL, 19 mmol) was added dropwise to a stirred solution of **6** (1.49 g, 8.9 mmol) in dry diethylether (15 mL) and the resulting mixture was stirred for 1 h at 0 °C. After adding dropwise methanol–H_2O (1:3), followed by filtration of the mixture, the solvent was removed to give a residue that was purified by column chromatography (*n*-pentane–diethyl ether, 2:1) to give **7** (1.0 g, 7.92 mmol, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): (0.97 (t, 3H, $J = 7.4$ Hz, CH_3), 1.34 (brs, 1H, OH), 2.05 (dq, 2H, $J = 7.1$, 7.4 Hz, CH_2), 2.79–2.82 (m, 2H, CH_2), 4.10 (m, 2H, OCH_2), 5.40–5.51 (m, 2H, olefin), 5.68–5.79 (m, 2H, olefin); ^{13}C NMR (75 MHz, $CDCl_3$): (14.0, 20.3, 29.8, 63.3, 126.0, 129.1, 131.0, 132.6; IR (KBr): 3320, 1670, 1652, 1432, 1374, 1304, 1225, 1090, 1072, 1005, 986 cm^{-1}; EI-MS: m/z 126 [M^+]. ESI-HRMS: calculated for $C_8H_{14}O$: 126.1045; found: 126.1052.

((2S,3S)-3-((*Z*)-Pent-2-enyl)oxiran-2-yl)oxiran-2-yl)methanol (8)

To a stirred suspension of activated 4 Å molecular sieves (1.0 g) in CH_2Cl_2 (25 mL) was added L-(+)-DIPT (0.16 mL, 0.942 mmol) and Ti $(O^iPr)_4$ (0.25 mL, 0.79 mmol) with stirring, and the resulting mixture was stirred for 30 min at $-20\,^{\circ}C$. The allyl alcohol **7** (1.0 g, 7.92 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise and the resulting mixture was stirred for another 30 min at $-20\,^{\circ}C$. TBHP (5.3 mL, 3.0 M in toluene, 15.84 mmol) was then added, and the resulting mixture was stirred at the same temperature for 8 h. It was then warmed to $0\,^{\circ}C$, quenched with water (1 mL), and stirred for 2 h at room temperature. Aqueous NaOH solution 30% saturated with NaCl (3 mL) was then added, and the resulting mixture stirred vigorously for another 30 min at room temperature. The resulting mixture was filtered through celite, and the filter cake was washed well with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Combined organic layers were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure and purification by silica-gel column chromatography using ethyl acetate and hexane (2.5:7.5) afforded **8** (1.02 g, 7.12 mmol, 90%) as a colorless viscous liquid. $[(]_D + 18.0$ (c = 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): (0.98 (t, 3H, $J = 7.5$ Hz, CH_3), 1.97–2.11 (m, 2H, CH_2), 2.18–2.47 (m, 2H, CH_2), 2.56 (br s, 1H, OH), 2.87–2.96 (m, 2H, epoxide), 3.57 (dd, 1H, $J = 3.7$, 12.8 Hz, OCH), 3.85 (dd, 1H, $J = 2.2$, 12.8 Hz, OCH), 5.26–5.39 (m, 1H, olefin), 5.44–5.59 (m, 1H, olefin); ^{13}C NMR (75 MHz, $CDCl_3$): (14.1, 20.6, 29.2, 55.5, 58.3, 61.7, 122.3, 134.8; IR (KBr) $\nu = 3440$, 1590, 1257, 1450, 1050 cm^{-1}; EI-MS: m/z 142 [M^+]. ESI-HRMS: calculated for $C_8H_{14}O$: 142.0993; found: 142.0099.

(2S,3S)-2-((*Z*)-Pent-2-enyl)-3-vinyloxirane (2)

Dimethyl sulfoxide (1.13 mL, 16.0 mmol) was added to a solution of oxalyl chloride (0.82 mL, 7.5 mmol) in CH_2Cl_2 (10 mL) at $-78\,^{\circ}C$ over 20 min. The resulting mixture was stirred for an additional 15 min, and then alcohol **8** (710.9 mg, 5 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise. The mixture stirred for 30 min, and triethylamine (3.47 mL, 25 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 30 min. After completion, the reaction mixture was quenched with water (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent afforded aldehyde **(**0.560 g, 4.0 mmol, 90%) as a colorless liquid a solution of *n*-BuLi in hexane (7.5 mL, 1.6 M) was added at $0\,^{\circ}C$ to a solution of trimethylphosphonium iodide (4.84 g, 12.0 mmol) in THF (35 ml), a and solution of aldehyde (0.560 g, 4.0 mmol) in THF (15 mL) was added via cannula. Then reaction mixture was allowed to warm to rt and quenched with water after 1 h. The solution was poured into water (50 ml) and extracted with ether (3×40 mL). The combined organic extracts were washed once with brine (30 mL), dried, filtered and concentrated. The product was purified by column chromatography (10% EtOAc in hexane) to afford **2** (0.386 g, 2.8 mmol, 70%) as yellow syrup. $[\alpha]_D^{25} + 12.0$ (c = 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): (0.99 (t, 3H, $J = 7.3$ Hz, CH_3), 2.06 (quintet, 2H, $J = 7.3$ Hz, CH_2), 2.30–2.50 (m, 2H, CH_2), 2.75 (dt, 1H, $J = 5.2$, 2.0 Hz, epoxide), 3.08 (dt, 1H, $J = 7.3$, 1.3 Hz, epoxide), 5.22–5.61 (m, 5H,

olefin); ^{13}C NMR (75 MHz, $CDCl_3$): (13.5, 20.6, 29.5, 58.1, 58.5, 121.2, 122.2, 134.8, 135.3; EI-MS: m/z 161 $[M + Na]^+$. ESI-HRMS: calculated for $C_9H_{14}ONa$: 161.0942; found: 161.0950.

(*R*)-*tert*-Butyldimethyl(8-(oxiran-2-yl)octyloxy)silane (9)

A flask (100 mL) equipped with a stir bar was charged with (*R,R*)-Co salen complex (30 mg, 0.05 mmol). The catalyst was treated with racemic epoxide **5** (2.86 g, 10 mmol), AcOH (0.012 mL, 0.21 mmol), and 1 mL of THF. The reaction flask was cooled to 0 °C, and H_2O (0.1 mL, 5.5 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 16 h. The recovered epoxide was filtered through a silica plug to remove residual water, the THF was removed by rotary evaporation, and the crude mixture was passed through column chromatography using ethyl acetate and hexane (0.5:9.5) to yield (*R*)-*tert*-butyldimethyl(8-(oxiran-2-yl)silane **9** (1.14 g, 4.0 mmol, 97% *ee*, 40%). The catalyst was recovered by suspension in MeOH and vacuum filtration. $[\alpha]_D^{25} + 2.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): (0.05 [s, 6H, $Si(CH_3)_2$], 0.90 [s, 9H, $(CH_3)_3CSi$], 1.27–1.40 (m, 9H, aliphatic), 1.41–1.60 (m, 5H, aliphatic), 2.42–2.46 (m, 1H, epoxide), 2.70 (t, 1H, $J = 4.5$ Hz, epoxide), 2.83–2.90 (m, 1H, epoxide), 3.60 (t, 2H, $J = 6.7$ Hz, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): (−5.3, 25.7, 25.9, 29.2, 29.3, 29.4, 32.4, 32.8, 47.0, 52.3, 63.2; IR (KBr) $\nu = 2929$, 2856, 1426, 1252, 1098, 836, 775 cm^{-1}; EI-MS: m/z 203 $[M + H]^+$. ESI-HRMS: calculated for $C_{10}H_{23}O_2Si$: 203.1467; found 203.1470.

(*R*)-11-(*tert*-Butyldimethylsilyloxy)undec-1-3-ol (10)

n-BuLi (1.6 M in hexane, 7.43 mL, 11.9 mmol) was added to a suspension of trimethyl sulfonium iodide (2.44 g, 12 mmol) in dry THF (36 ml) at −10 °C. After 30 min, (R)-*tert*-butyldimethyl [8-(oxiran-2-yl)silane **9** (1.14 g, 4.0 mmol) in THF (8 mL) was introduced, which produced a milky suspension. The reaction was allowed to warm to 0 °C over about 30 min, then to room temperature, and stirred for 2 h. The reaction was quenched with water at 0 °C and extracted with ether, and the combined organic layers were dried over Na_2SO_4. Silica chromatography of the crude product using ethylacetate and hexane (1:9) afforded (*R*)-11-(*tert*-butyldimethylsilyloxy) undec-13-ol **10** (1.02 g, 3.4 mmol, 85%) as a colorless oil. $[\alpha]_D^{25}$ −17.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): (0.05 (s, 6H, $Si(CH_3)_2$], 0.90 [s, 9H, $(CH_3)_3CSi$], 1.32–1.41 (m, 10H, aliphatic), 1.42–1.59 (m, 4H, aliphatic), 3.60 (t, 2H, $J = 6.7$ Hz, OCH_2), 4.10 (m, 1H, OCH), 5.10 (d, 1H, $J = 10.5$ Hz, olefin), 5.20 (d, 1H, $J = 16.6$ Hz, olefin), 5.80–5.95 (m, 1H, olefin); IR (KBr) $\nu = 3377$, 2930, 2858, 1641, 1463, 1253, 1100, 837 cm^{-1}; EI-MS: m/z 216 $[M]^+$; ESI-HRMS: calculated for $C_{11}H_{24}O_4Si$: 216.1546; found: 216.1552.

(*R*)-2,2,15,15,16,16-Hexamethyl-3,3-diphenyl-5-vinyl-4,14-dioxa-3, 15 disilaheptadecane (11)

TBDPSCl (1.02 g, 3.74 mmol) was added to a stirred solution of secondary alcohol **10** (1.02 g, 3.4 mmol) and imidazole (0.57 g, 8.5 mmol) in CH_2Cl_2 (15 mL)

at 0 °C portionwise over a period of 10 min. The reaction mixture was stirred at room temperature for 3 h. The mixture was then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (0.2:9.8) to afford TBDPS-protected alcohol **11** (5.5 g, 3.12 mmol, 92%) as a colorless oil. $[\alpha]_D^{20} - 12.0$ (c = 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 [s, 6H, $Si(CH_3)_2$], 0.92 [s, 9H, $(CH_3)_3CSi$], 1.10 [s, 9H, $(CH_3)_3CSi$], 1.12–1.54 (m, 14H, aliphatic), 3.60 (t, 2H, $J = 6.7$ Hz, OCH_2), 4.10 (m, 1H, OCH), 4.95–5.05 (m, 2H, olefin), 5.72–5.84 (m, 1H, olefin), 7.25–7.45 (m, 5H, ArH), 7.62–7.71 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ−5.2, 18.3, 19.3, 24.3, 25.7, 26.0, 27.0, 29.3, 29.4, 32.9, 37.5, 63.2, 74.6, 114.1, 127.3, 124.4, 129.3, 129.4, 134.2, 134.5, 135.8, 135.9, 140.9; IR (KBr) $\nu = 3050$, 2958, 2858, 1598, 1260, 1272 cm^{-1}; EI-MS: m/z 477 $[M + Na]^+$. ESI-HRMS: calculated for $C_{27}H_{42}O_2Si_2Na$: 477.2621; found: 477.2618.

(*R*)-9-(*tert*-Butyldiphenylsilyloxy)undec-10-en-ol (12)

The bissilyl ether **11** (1.67 g, 3.12 mmol) was dissolved in absolute ethanol (16 ml), and PPTS (0.235 g, 0.93 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The organic solution was washed with saturated aqueous brine and water and then dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuum, and the crude product was purified by silica-gel column using hexane–ethyl acetate (9:l) as eluent to get pure primary alcohol **12** (1.17 g, 2.87 mmol, 90%). $[\alpha]_D^{25}$ −15.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ1.1 [s, 9H, $(CH_3)_3CSi$], 1.12–1.58 (m, 14H, aliphatic), 3.6 (t, 2H, $J = 7.0$ Hz, OCH_2), 4.02–4.16 (m, 1H, OCH), 4.90–5.02 (m, 2H, olefin), 5.56–5.83 (m, 1H, olefin), 7.26–7.43 (m, 6H, ArH), 7.58–7.74 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): (19.2, 24.2, 25.6, 26.9, 29.2, 29.3, 32.6, 37.4, 62.6, 74.5, 114.0, 127.2, 127.3, 129.3, 129.4, 134.1, 134.4, 135.7, 135.8, 140.8; IR (KBr) $\nu = 3428$, 3042, 2940, 1572, 1270, 1102 cm^{-1}; EI-MS: m/z 424 $[M]^+$. ESI-HRMS: calculated for $C_{21}H_{28}O_2Si$: 424.1859; found: 424.1866.

(*R*)-9-(*tert*-Butyldiphenylsilyloxy)undec-10-enoic acid (13)

TEMPO (0.090 g, 0.57 mmol) and BAIB (2.31 g, 7.17 mmol) were added to a vigorously stirred solution of alcohol **12** (1.17 g, 2.87 mmol) in CH_3CN (6 mL) and H_2O (3 mL). Stirring was allowed until TLC indicated complete conversion of the starting material to product. The reaction mixture was quenched by addition of saturated $Na_2S_2O_3$ solution (5 mL). The reaction mixture was then extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude acid was purified by silica-gel column chromatography using ethyl acetate and hexane (2:8) to get pure acid **13** (1.03 g, 2.43 mmol, 80%) as a colorless liquid. $[\alpha]_D^{25}$ −13.9 (c = 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ1.10 [s, 9H, $(CH_3)_3CSi$], 1.12–1.4 (m, 10H, aliphatic), 1.60 (pent, 2H, $J = 7.5$ Hz, CH_2), 2.30 [t, 2H, $J = 7.5$ Hz, $C(O)CH_2$], 4.10 (m, 1H, OCH), 4.90–5.10 (m, 2H, olefin), 5.70–5.85 (m, 1H, olefin), 7.35–7.42 (m, 6H, ArH), 7.60–7.70

(m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 19.3, 24.2, 24.5, 27.0, 28.8, 29.0, 29.1, 34.0, 37.4, 74.5, 114.1, 127.2, 127.3, 129.3, 129.4, 134.2, 134.4, 135.8, 135.9, 140.8, 179.8. IR (KBr) $\nu = 3442$, 2930, 2858, 1710, 1625, 1425, 1106 cm^{-1}; EI-MS: m/z 405 $[M + Na]^+$. ESI-HRMS: calculated for $C_{23}H_{30}O_3SiNa$: 405.1862; found: 405.1869.

9-Hydroxyundec-10-enoic acid (14)

To a solution of acid **13** (1.03 g, 2.43 mmol) in THF (8 mL), 70% HF-Py complex (1.7 mL, 12.4 mmol) was added at room temperature. The mixture was stirred for 24 h and quenched with cold water (12 mL). The resulting mixture was diluted with Et_2O (50 mL). The organic phase was successively washed with water and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate and hexane (4:6) to afford seco acid **14** (0.406 g, 2.18 mmol, 92%). $[\alpha]_D^{25}$ −15.4 (c = 1, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$): (1.23–1.64 (m, 12H, aliphatic), 2.32 [t, 2H, $J = 7.5$ Hz, $C(O)CH_2$], 4.02–4.13 (m, 2H, aliphatic), 5.06 (d, 1H, $J = 16.6$ Hz, Hz, olefin), 5.18 (d, 1H, $J = 16.6$ Hz, olefin), 5.77–5.88 (m, 1H, olefin); IR (KBr) $\nu = 3432$, 2928, 2854, 1706, 1419, 1102, 1035 cm^{-1}. EI-MS: m/z 223 $[M + Na]^+$. ESI-HRMS: calculated for $C_{17}H_{27}O_4Na$: 223.1310; found: 223.1304.

(*R*)-10-Vinyloxecan-2-one (3)

A solution of *seco*-acid **14** (100 mg, 0.543 mmol) in THF (16.3 mL) with a mechanically driven syringe was slowly added to a solution of MNBA (0.205 g, 0.597 mmol), DMAP (0.013 g, 0.108 mmol), and triethylamine (2.25 mL, 1.62 mmol) in dichloromethane (9.6 mL) at 50 °C over a 12-h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane (15 mL), and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (eluant; hexane–ethyl acetate 3/1) to afford lactone **3** (0.076 g, 0.418 mmol, 77%). $[\alpha]_D^{25}$ −10.6 (c = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): (1.27–1.81 (m, 10H, aliphatic), 2.04–2.57 (m, 4H, aliphatic), 5.17–5.36 (m, 3H), 5.83–5.94 (m, 1H, olefin); IR (KBr) $\nu = 2934$, 1728, 1469, 1229, 1069, 973 cm^{-1}; EI-MS: m/z 205 $[M + Na]^+$. ESI-HRMS: calculated for $C_{11}H_{18}O_2Na$: 205.1204; found: 205.1214.

(*R*)-10-((*E*)-2-((2S,3S)-3-((*Z*)-Pent-2-enyl)oxiran-2-yl)vinyl)oxecan-2-one (1)

To a solution of **3** (0.018 g, 0.1 mmol) and **2** (0.069 mg, 0.05 mmol) in freshly distilled degassed anhydrous CH_2Cl_2 (0.5 mL), Grubbs second-generation catalyst (0.017 mg, 0.02 mmol) was added and stirred at 40 °C for 2 h under an argon atmosphere until the complete consumption of starting material (monitored by TLC). The solvent was evaporated to a brown residue, which was purified by column chromatography (silica gel, 60–120 mesh, 10% ethyl acetate–hexane) to afford **1**

(5 mg, 0.02 mmol) as colorless oil. $[\alpha]_D^{20}$: +28.2(c = 0.6, $CHCl_3$); ^1H NMR (300 MHz, DMSO): (0.97 (t, 3H, $J = 7.5$, CH_3), 1.00–1.80 (m, 10H, aliphatic), 1.95–2.15 (m, 4H, aliphatic), 2.20 (ddd, 1H, $J = 15.5$, 11.8, 2.6 Hz, aliphatic), 2.36 (m, 2H, aliphatic), 2.52 (ddd, 1H, $J = 15.5$, 6.2, 3.0 Hz, aliphatic), 2.87 (dt, 1H, $J = 5.3$, 2.20 Hz, epoxide), 3.15 (dd, $J = 7.8$, 2.2 Hz, 1H, epoxide), 5.30–5.42 (m, 2H, olefin), 5.54 (m, 1H, olefin), 5.94 (dd, 1H, $J = 15.6$, 5.1 Hz, olefin); ^{13}C NMR (75 MHz, DMSO-d_6): (13.7, 20.9, 23.5, 23.7, 24.3, 27.2, 29.8, 33.9, 35.0, 35.3, 57.1, 58.6, 74.7, 121.5, 128.6, 132.7, 133.0, 172.6; IR (KBr) $\nu = 2931$, 1738, 1465, 1236, 1068, 969 cm^{-1}; EI-MS: 293 $[M+H]^+$; ESI-HRMS: calculated for $C_{18}H_{29}O_3$: 293.2116; found: 293.2120.

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