Supporting information

Synthetic Studies toward the Bicyclic Peroxylactone Core of Plakortolides

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**Experimental section**

**General methods**

All reactions were carried out under atmosphere of dry nitrogen. All chemicals purchased from commercial sources were used as received without further purification. Reagents and solvents were purified by standard means. Tetrahydrofuran was distilled from sodium wire/benzophenone and stored under a nitrogen atmosphere. Toluene, dichloromethane, dichloroethane and methanol were distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates. Flash chromatography was performed on silica gel (230–400 mesh) from Macherey Nagel. Preparative thin-layer chromatography (PTLC) was performed on Silicycle plates (F-254, 1000 microns). \([\alpha]_D\) were measured on Perkin Elmer 343 apparatus at the sodium D line (598 nm). NMR spectra were recorded on Bruker AC 300, AM 300 and AM 400 instruments. Multiplicity is described by the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts are given in ppm. \(^1H\) NMR spectra were referenced to the residual solvent peak at \(\delta = 7.26\) (CDCl\(_3\)). \(^13C\) NMR spectra were referenced to the solvent peak at \(\delta = 77.16\) (CDCl\(_3\)). Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrometer and are reported in wave numbers (cm\(^{-1}\)). High resolution mass spectrometry (HRMS) analyses were conducted using a Thermofinigan- MAT 95 XL instrument.

\(\text{(1R,4R,6R)-6-Methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one (11).}\)

![Chemical structure of 11](image)

To a solution of the lactone 7 (2.28 g, 6.95 mmol) in MeOH (100 mL) was added H\(_2\)O\(_2\) (35 %, 2.13 mL, 24.3 mmol) and 6 N NaOH (0.7 mL, 4.17 mmol) at 0°C. After 10 min, a precipitate was formed. The reaction mixture was stirred for 30 min at 0°C, then warmed to room temperature and stirred until the solution became clear (~3h). Et\(_2\)O (100 mL) and H\(_2\)O (100 mL) were added and the solution was acidified with HCl (35 %) to pH ~ 3. Water phase was extracted with Et\(_2\)O (5x20 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\) and evaporated. The residue was chromatographed on silica gel (Et\(_2\)O/Petroleum ether = 1:1) to furnish 11 (1.96 g, 82 %) as an amorphous powder.

\([\alpha]_D^{20} +33.0\) (c 0.9, CH\(_2\)Cl\(_2\)); \(^1H\) NMR (300 MHz): 1.26 (m, 14 H), 1.50 (s, 3H), 1.60 (m, 4H), 1.91 (dd, \(J=11.7\ Hz, 15\ Hz, 1H\)), 2.18 (dd, \(J=3\ Hz, 15\ Hz, 1H\)), 2.60 (t, \(J=7.5\ Hz, 2H\)), 3.39 (s, 1H), 4.48 (m, 1H), 7.17-7.30 (m, 5H); \(^13C\) NMR (75 MHz): 20.3, 25.0, 29.4-29.6 (6C), 31.7, 34.7, 34.8, 36.1, 55.6, 59.4, 75.0, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 168.5; IR (neat): 1735, 2851, 2919; HRMS (ESI) calculated for C\(_{22}H\(_{33}\)O\(_3\) (MH\(^+\)) 345.2424, found 345.2422.

**Methyl (2R, 3R)-3-methyl-3-(2-oxo-12-phenyldeceyl)oxirane-2-carboxylate (14).**
To a solution of epoxylactone 11 (110 mg, 0.32 mmol) in MeOH (6 mL) was added NaOH (6 M, 0.1 mL, 0.64 mmol) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in H2O (7 mL) and RuCl₃ (4 mg, 16 µmol) and K₂CO₃ (88 mg, 0.64 mmol) were added sequentially followed by addition of an aqueous NaIO₄ solution (10 %, 2.01 mL, 0.96 mmol) by portions (0.3 mL). When the reaction was finished (~3-4 h) the reaction mixture was acidified with HCl (2 M) to pH 3-4, and extracted with EtOAc (6x3 mL). The combined organic extracts was treated with a solution of CH₂N₂ in Et₂O until persistent slightly yellow color, and then dried over Na₂SO₄. Solvents were evaporated and the residue was chromatographed on silica gel (Et₂O/petroleum ether = 1:9) to give 14 (114 mg, 96 %) as a colorless oil.

[α]D²⁰ -39.5 (c 1.2, CHCl₃); ¹H NMR (300 MHz): 1.25 (br m, 12H), 1.43 (s, 3H), 1.56 (br m, 4H), 2.37 (t, J=7.5 Hz, 2H), 2.59 (t, J=7.5 Hz, 2H), 2.94 (s, 2H), 3.42 (s, 1H), 3.74 (s, 3H), 7.16-7.29 (m, 5H); ¹³C NMR (75 MHz): 22.9, 23.7, 29.2-29.6 (6C), 31.6, 36.1, 43.4, 46.0, 52.5, 58.2, 59.8, 125.6, 128.3 (2C), 128.5 (2C), 143.0, 169.1, 207.6; IR (neat): 1604, 1715, 1751, 2854, 2927, 3026, 3062; HRMS (ESI) calculated for C₂₃H₃₄NaO₄ (MNa⁺) 397.2349, found 397.2344.

Methyl (2R, 3R)-3-methyl-3-(2-methylene-12-phenyldodecyl)oxirane-2-carboxylate (15).

Nysted reagent (20 % in THF, 3.51 mL, 1.83 mmol) was added to a stirred solution of ketone 14 (0.219 g, 0.585 mmol) in dry THF (8 mL) at 0°C. TiCl₄(OiPr)₂, prepared from TiCl₄ (1 M in dichloromethane, 0.73 mL, 0.73 mmol) and Ti(OiPr)₄ (0.217 mL, 0.73 mmol), was added dropwise. The reaction mixture was then allowed to reach 15 °C and stirred for 15 min. The reaction mixture was cooled to 0 °C, treated carefully with water (1 ml) and extracted with ether (5x8 ml). The combined organic layers were washed with saturated NaHCO₃ solution and brine. The ethereal solution was filtered through a small pad of silica gel to remove metal species, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed on silica gel (ether/petroleum ether = 1:5) to provide 15 (0.153 g, 70 %) as a colorless oil.

[α]D²⁰ -29.2 (c 1, CH₂Cl₂); ¹H NMR (300 MHz): 1.26 (br m, 14 H), 1.38 (s, 3 H), 1.60 (m, 2 H), 1.95 (m, 2H), 2.35 (d, J=15 Hz, 1 H), 2.41 (d, J=15 Hz, 1H), 2.59 (t, J=7.6 Hz, 2 H), 3.37 (s, 1H), 3.76 (s, 3H), 4.79 (s, 1H), 4.85 (s, 1H), 7.16-7.29 (m, 5 H); ¹³C NMR (75 MHz): 21.8, 27.6, 29.4-29.7 (6C), 31.6, 36.1, 36.3, 39.0, 52.3, 59.0, 62.2, 112.2, 125.6, 128.3 (2C), 128.5 (2C), 143.0, 145.3, 169.0; IR (neat): 1646, 1736, 1757, 2854, 2927, 3026. HRMS (ESI) calculated for C₂₄H₃₆NaO₃ (MNa⁺) 395.2557, found 395.2557.

(2R, 3S)-2-Methyl-2-(2-methylene-12-phenyldodecyl)-3-vinylxirane (6).
To a cooled (-90 °C) solution of 15 (26 mg, 0.07 mmol) in toluene (1 mL) was added slowly a solution of DIBAL (1 M in hexanes, 0.35 mL, 0.35 mmol). After stirring for 30-40 min at -78 °C, the reaction mixture was treated with MeOH (0.2 mL) and saturated aqueous Rochelle salt solution (1 mL). The mixture was warmed to room temperature, stirred for 20 min and extracted with Et2O (5x2 mL). Combined extracts were washed with brine, dried over Na2SO4 and evaporated to yield crude aldehyde.

\[ n\text{-BuLi (2.4 M, 0.12 mL, 0.28 mmol) was added dropwise to the suspension of Ph3PMeBr (125 mg, 34.9 mmol) in THF (1.3 mL) cooled at -78 °C. After the temperature was raised to 0 °C the mixture was stirred for 30 min and the solution of aldehyde in THF (2 mL) was added dropwise. After 30 min, H2O (3 mL) was added and the mixture was extracted with Et2O/petroleum ether = 1:2 (5x4 mL). Combined extracts were dried with Na2SO4 and evaporated. Purification of the residue by flash chromatography on silica gel (Et2O/petroleum ether = 3:97) gave 6 (19.6 mg, 83 %) as a colorless oil. \]

\[ \left[\alpha\right]\text{D}^{20} \text{ -3.2 (c 0.7, CH2Cl2); } ^1\text{H NMR (300 MHz): } \delta \text{(ppm) 1.26 (br m, 14 H), 1.31 (s, 3H), 1.60 (m, 2H), 1.99 (m, 2H), 2.18 (d, J=15 Hz, 1H), 2.31 (d, J=15 Hz, 1H), 2.59 (t, J=7.5 Hz, 2H), 3.23 (d, J=7.2 Hz, 1H), 4.78 (s, 1H), 4.83 (s, 1H), 5.33 (d, J=10.5 Hz, 1H), 5.45 (d, J=17.1 Hz, 1H), 5.78 (d, J=17.2 Hz, 10.5 Hz, 17.1 Hz, 1H), 7.16-7.32 (m, 5H); } ^{13}\text{C NMR (75 MHz): } \delta \text{(ppm) 22.1, 27.8, 29.5-29.7 (6C), 31.7, 36.1, 36.5, 39.5, 62.2, 64.2, 112.1, 120.1, 125.7, 128.3 (2C), 128.5 (2C), 133.6, 143.1, 146.1; } \text{IR (neat): 1643, 2854, 2927, 3026, 3070; HRMS (ESI) calculated for C24H36NaO (MNa+) 363.2658, found 363.2656.} \]

\[ (1S)-1-[(3R,5RS)-3,5-Dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl]prop-2-en-1-ol (17). \]

To a solution of (2R, 3S)-2-methyl-2-(2-methylene-12-phenyldodecyl)-3-vinyloxirane 6 (13 mg, 38 μmol) in dichloroethane (0.5 mL) was added Co(II) bis(2,2,6,6-tetramethylheptane-3,5-dienoate) [Co(thd)2] (1.6 mg, 3.8 μmol) and the flask was charged with O2. Et3SiH (7.3 μl, 45.8 μmol) was added. The reaction mixture was stirred under O2 atmosphere for 4 h, filtered through silica gel and evaporated. The residue was dissolved in dichloromethane (1 mL) and amberlyst-15 (4.7 meq/g, 8.1 mg) was added. After stirring for 2 h at room temperature, the reaction mixture was filtered and evaporated. The residue was chromatographed on silica gel (Et2O/petroleum ether = 1:3) to provide 17 (mixture of 1/1 diastereomers) (7.3 mg, 51 %) as a colorless oil.

\[ ^1\text{H NMR(CDCl}_3, \text{ 400 MHz): } \delta \text{(ppm) 1.26-1.43 (br m, 20H), 1.57 (br m, 4H), 2.00 (d, J=12.2 Hz, 0.5H), 2.12 (d, J=12.3 Hz, 0.5H), 2.32 (d, J=12.3 Hz, 0.5H), 2.38 (d, J=12.2 Hz, 0.5H), 2.53 (d, J=2.7 Hz, 0.5H), 2.54 (d, J=2.7 Hz, 0.5H), 2.60 (t, J=6 Hz, 2H), 4.19 (m, 1H), 5.27 (br d, J=10.5, 1H), 5.39 (dd, J=17.2, 1.5 Hz, 0.5H), 5.40 (dd, J=17.2, 1.5 Hz, 0.5H), 5.81 (m, 1H), 7.17-7.29 (m, 5H); } ^{13}\text{C NMR(CDCl}_3, \text{ 101 MHz): } \delta \text{(ppm) 18.2, 22.4, 24.6, 25.2, 25.2, 29.5-29.7 (6C), 31.7, 36.1, 38.3, 39.9, 52.8, 53.2, 76.3, 76.4, 87.0, 87.3, 87.9, 88.2, 118.3, 125.7, 128.4 (2C), 128.5 (2C), 135.2, 135.3, 143.1; } \]
IR (neat): 1722, 2854, 2927, 3026, 3521; HRMS (ESI) calculated for C$_{24}$H$_{38}$NaO$_3$ (MNa$^+$) 397.2713, found 397.2707.

Methyl (2R,3R)-3-methyl-3-{(2RS)-2-methyl-12-phenyl-2-[(triethylsilyl)peroxy]dodecyl}oxirane-2-carboxylate (18).

To a solution of 15 (118 mg, 0.32 mmol) in dichloroethane (3 mL) was added Co(thd)$_2$ (13.5 mg, 32 µmol) and the flask was charged with O$_2$. Et$_3$SiH (101 µl, 0.63 mmol) was added and the reaction mixture was stirred for 2 h under O$_2$ atmosphere. Evaporation of the reaction mixture and chromatography of the residue on silica gel (Et$_2$O/Petrol = 1:10) afforded 18 (mixture of 1/1 diastereomers) (142 mg, 86 %) as a colorless oil.

$^1$H NMR (300 MHz): 0.67 (q, $J$=7.8 Hz, 6H), 0.98 (t, $J$=7.8 Hz, 9H), 1.07 (s, 1.5H), 1.26 (m, 15.5H), 1.51 (s, 1.5H), 1.52 (s, 1.5H), 1.61 (m, 4H), 1.98 (s, 1H), 2.00 (s, 1H), 2.59 (t, $J$=7.5 Hz, 2H), 3.24 (s, 0.5H), 3.27 (s, 0.5H), 3.76 (s, 3H), 7.16-7.29 (m, 5H); $^{13}$C NMR (75 MHz): 3.94, 6.86, 21.7, 22.2, 23.4, 23.5, 23.8, 29.5-29.7 (6C), 30.28, 30.30, 31.7, 36.1, 37.2, 37.7, 38.1, 38.5, 52.26, 52.27, 59.6, 59.7, 61.9, 62.1, 84.1, 84.3, 125.63, 125.65, 128.3 (2C), 128.5 (2C), 143.02, 143.05, 169.2, 169.3; IR: 1737, 1756, 2854, 2926, 3026; HRMS (ESI) calculated for C$_{30}$H$_{52}$NaO$_5$Si (MNa$^+$) 543.3476, found 543.3492.

Methyl (1R)-2-((3R,5R and 5S)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxyolan-3-yl)-2-hydroxy acetate (19a and 19b). To an ice-cooled solution of 18 (140 mg, 0.269 mmol) in MeOH (5 mL) was added K$_2$CO$_3$ (11 mg, 80.7 µmol). The reaction mixture was stirred at 0°C for 5 h, water (10 mL) was added and the resulting mixture was extracted with Et$_2$O (5x5 mL). The combined organic extracts were dried with Na$_2$SO$_4$ and evaporated. The crude mixture was purified by preparative TLC (Et$_2$O/petroleum ether = 1:2, 2 elutions) to give 19a (40 mg, 36 %) and 19b (42 mg, 39 %) as colorless oils.

Compound 19a (5R).

[α]$_D^{20}$ +51.3 (c 1.65, CHCl$_3$); $^1$H NMR (400 MHz): 1.26 (m, 14H), 1.34 (s, 3H), 1.37 (s, 3H), 1.55 (br m, 4H), 2.03 (d, J = 12.3 Hz, 1H), 2.59 (t, J = 7.5 Hz, 2H), 2.78 (d, J = 12.3 Hz, 1H), 3.01 (d, J = 5.7, 1H), 3.79 (s, 3H), 4.23 (d, J = 5.7, 1H), 7.16-7.29 (m, 5H); $^{13}$C NMR(CDCl$_3$, 101 MHz): δ (ppm) 20.2, 24.8, 25.2, 29.4-29.6 (5C), 30.2, 31.6, 36.1, 37.9, 52.4, 52.7, 74.7, 86.9, 87.3, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 172.5; IR (neat): 1733, 1738, 2854, 2927, 3498; HRMS (ESI) calculated for C$_{26}$H$_{38}$NaO$_5$ (MNa$^+$) 429.2611, found 429.2623.
Compound 19b (55).

\[
\begin{array}{c}
\text{HO} \\
\text{COOMe} \\
\text{19b}
\end{array}
\]

\([\alpha]_D^{20} +46.8 (c 2.31, \text{CHCl}_3); \ ^1H \text{ NMR}(\text{CDCl}_3, 400 \text{ MHz}): \delta (\text{ppm}) 1.25 (s, 3H), 1.27 (br s, 14H), 1.50-1.76 (br m, 4H), 2.13 (d, \text{J}=12.6 \text{ Hz}, 1H), 2.59 (t, \text{J}=7.7 \text{ Hz}, 2H), 2.72 (d, \text{J}=12.6 \text{ Hz}, 1H), 3.00 (br s, 1H), 3.80 (s, 3H), 4.24 (s, 1H), 7.16 – 7.29 (m, 5H); \ ^{13}C \text{ NMR}(\text{CDCl}_3, 101 \text{ MHz}): \delta (\text{ppm}) 20.3, 21.8, 24.5, 29.4-29.7 (5C), 30.1, 31.6, 36.1, 39.8, 52.6, 52.8, 74.8, 87.0, 87.2, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 172.6; \text{IR (neat): 1736, 2854, 2926, 3498; HRMS (ESI) calculated for C}_{24}H_{38}NaO_5 (MNa^+) 429.2611, found 429.2609.} \]
C\(_2\)H\(_2\)O
C\(_3\)H\(_3\)
BB5032
LCO1V / BB5032 / HMBC / 400MHz