

Supporting Information

Racemic Total Synthesis of Dactyloidin and Demethyldactyloidin through DL-Proline-Catalyzed Knoevenagel Condensation/[4+2] Cycloaddition Cascade

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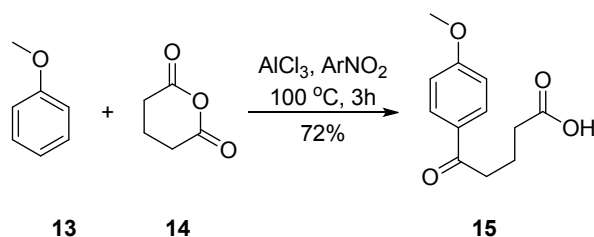
Abbreviations

Ac	Acetyl
ACN	Acetonitrile
DCE	1,2-Dichloroethane
DMSO	Dimethylsulfoxide
ESI	Electron spray ionization
HDA	Hetero Diels-Alder reaction
HRMS	High resolution mass spectroscopy
LDA	Lithium diisopropylamide
MOM	Methoxymethyl
rt	Room temperature
TBAB	Tetra- <i>n</i> -butylammonium bromide
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBS	<i>Tert</i> -butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TLC	Thin layer chromatography
THF	Tetrahydrofuran

General Information:

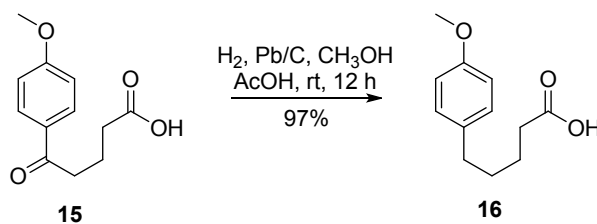
All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at high commercial quality, and used without further purification. Thin-layer chromatography (TLC) was conducted with 0.25 mm Tsingdao silica gel plates (60F-254) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Silica gel (ZCX-II, 200-300 mesh) used for flash column chromatography was purchased from Qing Dao Hai Yang Chemical Industry Co. of China. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 300 (^1H : 300 MHz, ^{13}C : 75 MHz), Bruker Advance 400 (^1H : 400 MHz, ^{13}C : 100 MHz) or Bruker Advance 500 (^1H : 500 MHz, ^{13}C : 125 MHz). Chemical shifts reported in parts per million relative to CDCl_3 (^1H NMR; 7.27 ppm, ^{13}C NMR; 77.00 ppm). Mass spectrometric data were obtained using ABI-Q Star Elite high resolution mass spectrometer. Anhydrous THF was distilled from sodium-benzophenone until a deep blue color persisted, $\text{CH}_2\text{ClCH}_2\text{Cl}$ (DCE) was distilled from calcium hydride. Yields referred to chromatographically purified products unless otherwise stated. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Total synthesis of Demethyldactyloidin and dactyloidin.



5-(4-methoxyphenyl)-5-oxopentanoic acid **15**

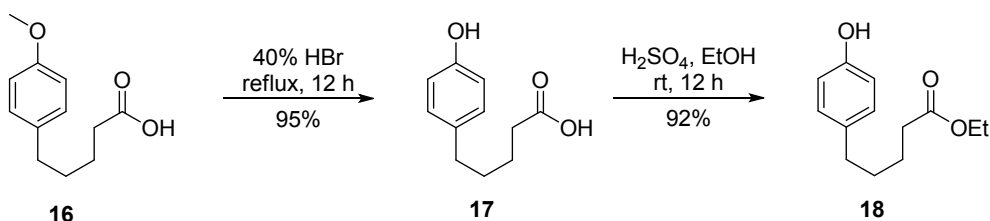
Aluminum chloride (33.3 g, 250 mmol) was slowly and carefully added to a solution of ether **13** (100 mL) and Glutaric anhydride **14** (11.4 g, 100 mmol) in nitrobenzene (100 mL) at 0 °C. After stirring at this temperature for 10 min under nitrogen atmosphere, the mixture was heated to 100 °C and kept for 3 h. Then the mixture was cooled to room temperature and quenched by pouring it into ice water (500 mL). The mixture was extracted with EtOAc (4 × 150 mL), washed with brine, concentrated in *vacuo*. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc = 1:1) afford **15** (16.0 g, 72% yield) as a white solid. The NMR data of **15** were agreed with those of the peer paper (*J. Phys. Chem. C*, **2009**, *113*, 21970-21975).



5-(4-methoxyphenyl)pentanoic acid **16**

Acid **15** (8.0 g, 36 mmol) was dissolved in methanol (150 mL) and acetic acid (50 mL). Then Pb/C (10%, 0.8 g) was added in one portion. The mixture was stirred under hydrogen atmosphere at room temperature for 12 h. Then, the mixture was filtrated and concentrated in *vacuo* to give a crude product **16** (7.3 g, 97% yield) as yellow oil. The crude product **16** was pure enough to be used directly in next step. The NMR data of **16** were agreed with those of the peer paper (*J. Am. Chem. Soc.*

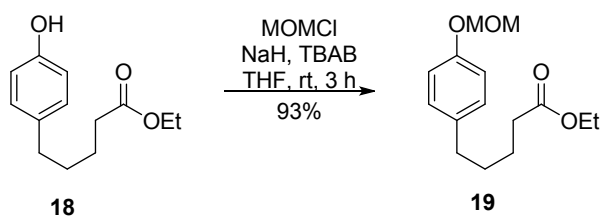
2014, 136, 11212-11215).



Ethyl 5-(4-(hydroxyl)phenyl)pentanoate 18

To a 100 mL round bottom flask, acid **16** (7.3 g, 35 mmol) and hydrobromic acid (50 mL, 40% in aqueous) were carefully added. The mixture was heated to reflux for 12 h. After cooling to room temperature, The crude mixture was poured into 150 mL water and extracted with EtOAc (4 x 200 mL), washed with brine, concentrated in *vacuo* to give a crude product **17** (6.5 g, 95% yield) as white solid. The crude product **17** was pure enough to be used directly in next step.

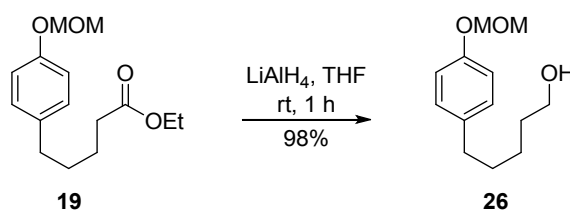
To a solution of phenol **17** (6.5 g, 33 mmol) in ethanol (50 mL), was carefully added one drop of concentrated H₂SO₄. The mixture was stirred at room temperature for 12 h, then quenched with water (100 mL) and extracted with CHCl₃ (4 x 150 mL). The combined organic phase was washed with brine, concentrated in *vacuo*. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc = 5:1) to afford **18** (6.7 g, 92% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.09 (d, *J* = 8.4 Hz, 2 H), 6.96 (dq, *J* = 2.0 Hz, *J* = 6.4 2 H), 5.16 (s, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.48 (s, 3 H), 2.58 (t, *J* = 7.2 Hz, 2 H), 2.32 (t, *J* = 7.2 Hz, 2 H), 1.61 – 1.69 (m, 4 H), 1.26 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ = 173.6, 155.4, 135.6, 129.2, 116.2, 94.6, 60.2, 55.8, 34.7, 34.2, 31.0, 24.5, 14.2.



Ethyl 5-(4-(methoxymethoxy)phenyl)pentanoate 19

NaH (8.0 g, 200 mmol, 60% in mineral oil) was slowly and carefully added to a

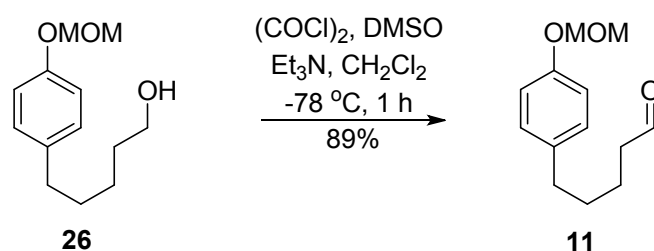
solution of phenol **18** (22.2 g, 100 mmol) in THF (250 mL) at 0 °C. After stirring at this temperature for 10 min under nitrogen atmosphere, MOMCl (12.0 g, 150 mmol) was added followed by TBAB (2.0 g, 6.2 mmol). Then the ice bath was removed, the mixture stirred at room temperature for another 6 h. The crude mixture was diluted with EtOAc (200 mL), then quenched it with saturated aqueous NH₄Cl (150 mL). The mixture was extracted with EtOAc (4 x 150 mL), washed with brine, concentrated in *vacuo*. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc = 5:1) afford **19** (24.7 g, 93% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.09 (d, *J* = 8.4 Hz, 2 H), 6.96 (dq, *J* = 2.0 Hz, *J* = 6.4 2 H), 5.16 (s, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.48 (s, 3 H), 2.58 (t, *J* = 7.2 Hz, 2 H), 2.32 (t, *J* = 7.2 Hz, 2 H), 1.61 – 1.69 (m, 4 H), 1.26 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ = 173.6, 155.4, 135.6, 129.2, 116.2, 94.6, 60.2, 55.8, 34.7, 34.2, 31.0, 24.5, 14.2. HRMS (ESI): calcd for C₁₅H₂₃O₄⁺, [M + H⁺] 267.1596, found 267.1594.



5-(4-(methoxymethoxy)phenyl)pentan-1-ol 26

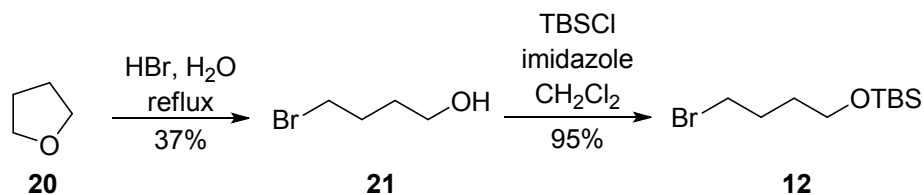
To a solution of ester **19** (13.3 g, 50 mmol) in dry THF (500 mL), LiAlH₄ (1.9 g, 50 mmol) was carefully added at 0 °C over 15 min. The solution was stirred for another 1 h at room temperature, then slowly quenched with H₂O (3 mL) at 0 °C, precipitate was formed. The resultant precipitates were filtered and washed by THF (3 x 15 mL). The combined filtrate was washed by brine and dried over Na₂SO₄. The solvent was removed in *vacuo* to give **26** (11.0 g, 98% yield) as a slight yellow-dark oil. The crude product was pure enough to use to the next step. ¹H NMR (300 MHz, CDCl₃): δ = 7.10 (d, *J* = 8.7 Hz, 2 H), 6.96 (dd, *J* = 8.7 Hz, *J* = 2.0 Hz, 2 H), 5.16 (s, 2 H), 3.64 (t, *J* = 6.6 Hz, 2 H), 2.58 (t, *J* = 7.6 Hz, 2 H), 1.62 (m, 4 H), 1.41 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃): δ = 155.3, 136.0, 129.3, 116.2, 94.6, 62.9, 55.9, 35.0, 32.6, 31.4, 25.3. HRMS (ESI): calcd for C₁₃H₂₁O₃⁺, [M + H⁺] 225.1491, found

225.1484.



5-(4-(methoxymethoxy)phenyl)pentanal **11**

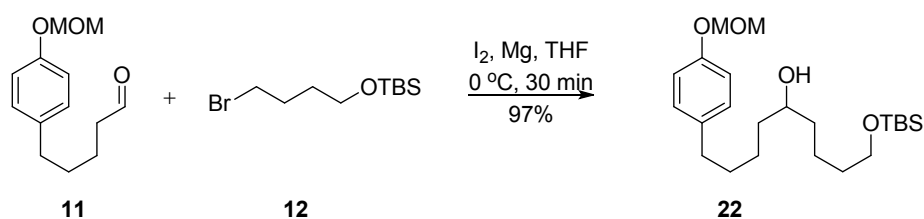
To a solution of oxalyl chloride (5.1 g, 40 mmol) in CH_2Cl_2 (100 mL) was added a solution of DMSO (6.0 mL, 80 mmol) in CH_2Cl_2 (6.0 mL) dropwise over 10 min at $-78\text{ }^\circ\text{C}$. After stirring the mixture for 15 min, the solution of alcohol **26** (4.5 g, 20 mmol) in CH_2Cl_2 (10 mL) was added to the mixture, and the resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 15 min. Triethylamine (27 mL, 200 mmol) was subsequently added, and the mixture was stirred at $-78\text{ }^\circ\text{C}$ for 10 min. The reaction was allowed to warm to ambient temperature gradually over 15 min. H_2O (50 mL) and EtOAc (150 mL) were added to quench the reaction, and the product was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated NaHCO_3 (100 mL), dried over Na_2SO_4 , and concentrated in *vacuo*. The residue was purified by flash chromatography (silica gel, hexane/EtOAc = 5:1) to afford **11** (3.96 g, 89% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 9.76 (t, J = 1.6 Hz, 1 H), 7.09 (d, J = 7.2 Hz, 2 H), 6.96 (dd, J = 2.0 Hz, J = 6.8 Hz, 2 H), 5.16 (s, 2 H), 3.48 (s, 3 H), 2.59 (t, J = 7.2 Hz, 2 H), 2.43 – 2.47 (m, 2 H), 1.62 – 1.68 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 202.5, 155.4, 135.3, 129.2, 116.2, 94.6, 55.6, 43.7, 34.7, 31.0, 21.6. HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{19}\text{O}_3^+$, $[\text{M} + \text{H}^+]$ 223.1334, found 223.1327.



(4-bromobutoxy)(tert-butyl)dimethylsilane **12**

HBr (90.6 g, 0.54 mol, 48% in water) was added dropwise to refluxing THF (135 mL). Reflux was then continued for 2 hours. Following this the reaction was cooled, H₂O (50 mL) was added. Then, the mixture was neutralized with NaHCO₃ (50 g) and the resulting yellow organic layer was then separated and washed with water (60 mL) and brine (60 mL). The aqueous layers were then extracted with CH₂Cl₂ (4 x 150 mL) and the organic extracts were combined and concentrated under vacuum to give the product **21** (29.9 g, 37% yield) as a yellow liquid which was used without further purification.

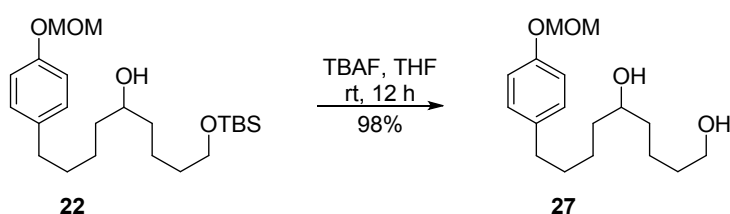
The alcohol **21** (15.3 g, 100 mmol) was dissolved in CH₂Cl₂ (500 mL), imidazole (10.2 g, 150 mmol) was added in one port followed by TBSCl (18.0 g, 120 mmol). The mixture was stirred for 3 h at room temperature. Then, the crude mixture was diluted with EtOAc (500 mL), quenched with saturated aqueous NH₄Cl (150 mL). The product was extracted with EtOAc (4 x 100 mL), washed with brine, concentrated in *vacuo*. The residue was further purified with flash column chromatography (silica gel, hexane/EtOAc = 10:1) to afford **12** (25.4 g, 95% yield) as a slight yellow oil. ¹H NMR (300 MHz, CDCl₃): δ = 3.65 (t, *J* = 6.1 Hz, 2 H), 3.54 (t, *J* = 6.9 Hz, 2 H), 1.95 (m, 2 H), 1.67 (m, 2 H), 1.60 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃): δ = 62.1, 33.9, 31.3, 29.5, 25.9, 18.3, 5.4.



1-((tert-butyldimethylsilyloxy)-9-(4-(methoxymethoxy)phenyl)nonan-5-ol 22

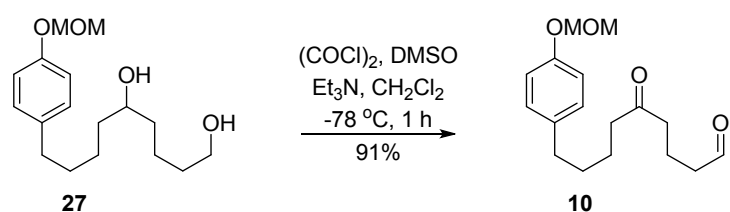
A flame-dried 50 mL flask was charged with Mg (1.44 g, 60 mmol), THF (150 mL) and (4-bromobutoxy)(tert-butyl)dimethylsilane **12** (10.7 g, 40 mmol). Two crystals of iodine in THF (1.0 mL) were added. The reaction mixture was stirred at reflux for 1 h. Then cooled it to 0 °C, a solution of aldehyde **11** (4.44 g, 20 mmol) in THF (5.0 mL) was slowly added at this temperature. The resulting yellow solution was stirred for another 30 min, AcOH (3.0 mL) and H₂O (100 mL) was added to

quench this reaction. The mixture was extracted with EtOAc (3 x 150 mL). The combined organics were washed with brine (150 mL), dried over Na₂SO₄, and filtered. Removal of solvent by rotary evaporation and purification by flash column chromatography (silica gel, hexane/EtOAc = 10:1) to afford **22** (7.95 g, 97% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.09 (d, *J* = 8.4 Hz, 2 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 5.16 (s, 2 H), 3.63 (t, *J* = 6.4 Hz, 3 H), 3.49 (s, 3 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 1.42 – 1.62 (m, 13 H), 0.90 (s, 9 H), (s, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ = 155.3, 136.1, 129.2, 116.2, 94.6, 71.8, 63.1, 55.9, 37.3, 37.3, 35.0, 32.7, 31.7, 26.0, 25.3, 21.9, 18.3, -5.3. HRMS (ESI): calcd for C₂₃H₄₃O₄Si⁺, [M + H⁺] 411.2931, found 411.2929.



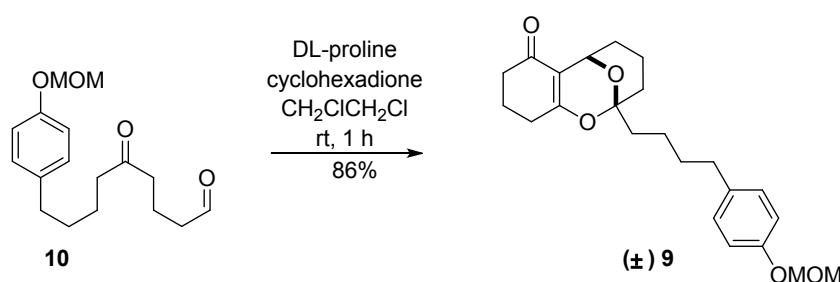
9-(4-(methoxymethoxy)phenyl)nonane-1,5-diol **27**

The alcohol **22** (7.95 g, 19.4 mmol) was dissolved in THF (100 mL), then added TBAF (5.3 g, 20.0 mmol). The resulting mixture was stirred for 12 h at room temperature. Then concentrated in *vacuo*, purified by a short flash chromatography (silica gel, hexane/EtOAc = 1:1) to afford the diol product **27** (5.63 g, 98% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.09 (d, *J* = 8.5 Hz, 2 H), 6.95 (dd, *J* = 6.5 Hz, *J* = 2 Hz, 2 H), 5.14 (s, 2 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 3.58 – 3.60 (m, 1 H), 3.48 (s, 3 H), 2.17 (br, 2 H), 1.44 – 1.63 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃): δ = 155.3, 136.0, 129.2, 116.2, 94.6, 71.6, 62.5, 55.8, 37.3, 36.9, 35.0, 32.5, 31.6, 25.2, 21.7. HRMS (ESI): calcd for C₁₇H₂₉O₄⁺, [M + H⁺] 297.2066, found 297.2060.



9-(4-(methoxymethoxy)phenyl)-5-oxononanal **10**

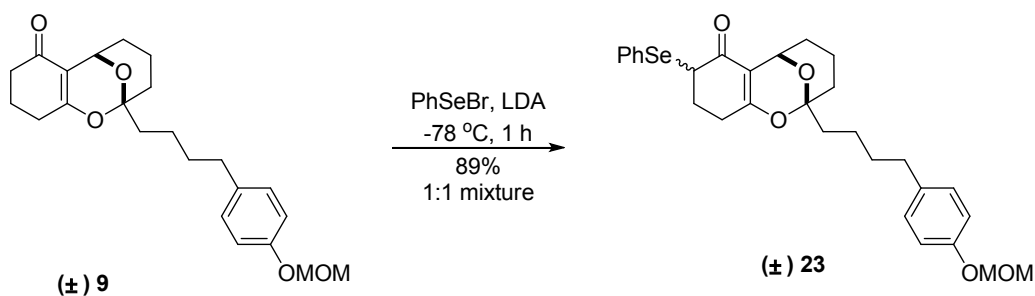
To a solution of oxalyl chloride (2.54 g, 20 mmol) in CH₂Cl₂ (50 mL) was added a solution of DMSO (3.2 mL, 40 mmol) in CH₂Cl₂ (3.0 mL) dropwise over 10 min at -78 °C. After stirring the mixture for 15 min, the solution of alcohol **27** (1.48 g, 5.0 mmol) in CH₂Cl₂ (2.0 mL) was added to the mixture, and the resulting solution was stirred at -78 °C for 35 min. Triethylamine (40 mL, 300 mmol) was subsequently added, and the mixture was stirred at -78 °C for 10 min. The reaction was allowed to warm to ambient temperature gradually over 1 h. H₂O (30 mL) and EtOAc (100 mL) were added to quench the reaction, and the product was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with saturated NaHCO₃ (50 mL), dried over Na₂SO₄, and concentrated in *vacuo*. The residue was purified by flash chromatography (silica gel, hexane/EtOAc = 3:1) to afford **10** (1.33 g, 91% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 9.75 (t, *J* = 1.4 Hz, 1 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 6.95 (dd, *J* = 2.0 Hz, *J* = 6.4 Hz, 2 H), 5.15 (s, 2 H), 3.47 (s, 3 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 2.38 – 2.49 (m, 6 H), 1.88 (m, 2 H), 1.57 – 1.60 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃): δ = 155.3, 135.5, 129.2, 116.2, 94.6, 55.9, 42.9, 42.6, 34.8, 31.1, 23.3, 16.0. HRMS (ESI): calcd for C₁₇H₂₅O₄⁺, [M + H⁺] 293.1753, found 293.1749.



2-(4-(4-(methoxymethoxy)phenyl)butyl)-3,4,5,6,9,10-hexahydro-2H-2,6-epoxybenzo[b]oxocin-7(8H)-one **9**

A flame-dried 100 mL flask was charged with aldehyde **10** (1.64 g, 5.6 mmol), DCE (60 mL) and cyclohexane-1,3-dione **6** (314 mg, 2.8 mmol). Then DL-proline (64 mg, 0.56 mmol) was added. The solution was allowed to stir at room temperature for 15 min, another part of cyclohexane-1,3-dione **6** (157 mg, 1.4 mmol) was added. 15

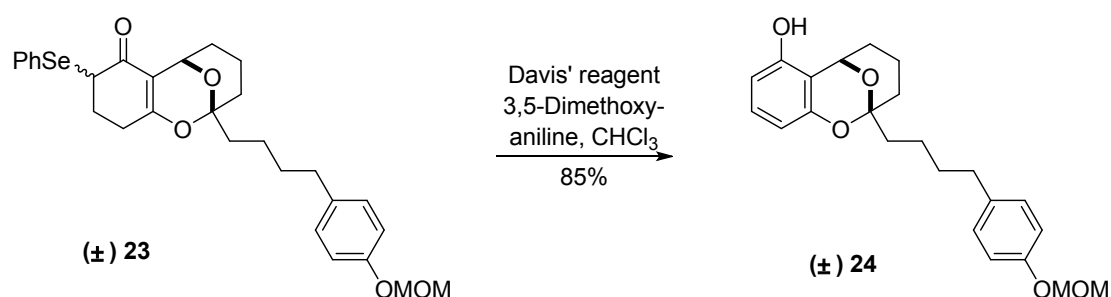
min later the last part of cyclohexane-1,3-dione **6** (157 mg, 1.4 mmol) was added. The solution was allowed to stir at room temperature for 20 min until the starting material disappeared. 10 min later, the resulting mixture was concentrated in *vacuo*. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc = 3:1) afford the corresponding product **9** (1.86 g, 86% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.08 (d, *J* = 8.8 Hz, 2 H), 6.95 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2 H), 5.15 (s, 2 H), 4.92 (d, *J* = 4.0 Hz, 1 H), 3.47 (s, 3 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 2.40 – 2.47 (m, 2 H), 2.34 – 2.38 (m, 2 H), 1.98 – 2.04 (m, 2 H), 1.84 – 1.89 (m, 2 H), 1.72 – 1.75 (m, 2 H), 1.56 – 1.71 (m, 6 H), 1.42 – 1.50 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ = 195.0, 172.1, 155.3, 135.9, 129.2, 116.1, 112.0, 103.2, 94.6, 66.6, 55.83, 40.1, 36.4, 34.9, 34.5, 31.6, 27.8, 27.3, 22.0, 21.0, 15.6. HRMS (ESI): calcd for C₂₃H₃₁O₅⁺, [M + H⁺] 387.2171, found 387.2153.



2-(4-(4-(methoxymethoxy)phenyl)butyl)-8-(phenylselenanyl)-3,4,5,6,9,10-hexahydro-2H-2,6-epoxybenzo[b]oxocin-7(8H)-one **23**

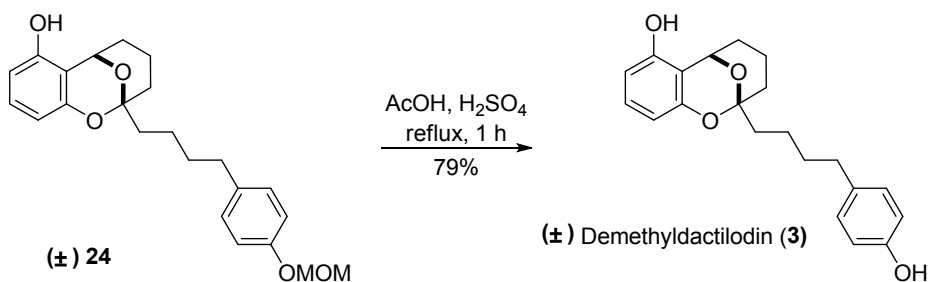
To a solution of LDA freshly prepared from *n*-BuLi (1.2 mL of 2.5 M hexane solution, 3.0 mmol) and diisopropylamine (380 mg, 3.8 mmol) in dry THF (25 mL), ketone **9** (965 mg, 2.5 mmol) was added slowly at -78 °C under a nitrogen atmosphere. 20 min later, benzeneselenenyl bromide (708 mg, 3.0 mmol) in THF (2.0 mL) was added dropwise. Kept stirring it at -78 °C for another 20 min, the mixture was allowed to reach room temperature, then quenched it with water (15 mL), extracted with EtOAc (4 x 15 mL). The organic phase was dried over Na₂SO₄, concentrated in *vacuo*. The residue was purified by flash chromatography (silica gel, hexane/EtOAc = 4:1) afford **23** (1.20 g, about 1:1 diastereoisomers, 89% yield) as a colorless oil. ¹H NMR

(300 MHz, CDCl₃): δ = 7.63 (m, 2 H), 7.30 (m, 3 H), 7.10 (m, 2 H), 6.97 (m, 2 H), 5.16 (s, 2 H), 4.93 (d, J = 2.7 Hz, 0.6 H), 4.01 (t, J = 5.2 Hz, 2 H), 3.48 (s, 3 H), 1.25-2.95 (m, 16 H); ¹³C NMR (75 MHz, CDCl₃): δ = 191.2, 191.1, 171.3, 170.6, 155.2, 135.8, 135.8, 135.6, 135.3, 129.2, 129.0, 129.0, 128.2, 127.9, 116.1, 110.9, 110.8, 103.5, 103.3, 94.5, 66.7, 66.6, 55.8, 46.4, 46.3, 40.2, 40.0, 34.9, 34.4, 31.6, 27.5, 27.3, 27.0, 26.9, 25.9, 25.4, 22.0, 21.9, 15.6, 15.5. HRMS (ESI): calcd for C₂₉H₃₅O₅Se⁺, [M + H⁺] 543.1649, found 543.1644.



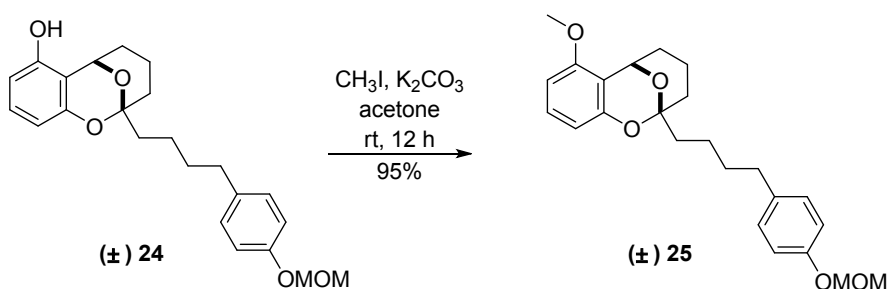
2-(4-(4-(methoxymethoxy)phenyl)butyl)-3,4,5,6-tetrahydro-2H-2,6-epoxybenzo[b]oxocin-7-ol 24

The ketone **23** (1.20 g, 2.2 mmol) was dissolved in CHCl₃ (15 mL), 3,5-dimethoxyaniline (688 mg, 4.5 mmol) and Davis reagent (725 mg, 2.6 mmol) was added. The resulting mixture was stirred for 30 min at room temperature, then concentrated in *vacuo*, purified by flash chromatography (silica gel, hexane/EtOAc = 3:1) to afford product **24** (718 mg, 85% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.11 (d, J = 8.8 Hz, 2 H), 6.95 – 7.01 (m, 3 H), 6.40 (d, J = 8.0 Hz, 1 H), 6.24 (dd, J = 0.4 Hz, J = 8.0 Hz, 1 H), 5.35 (s, 1 H), 5.29 (d, J = 2.8 Hz, 1 H), 5.17 (s, 2 H), 3.50 (s, 3 H), 2.58 (t, J = 7.2 Hz, 2 H), 1.92 – 2.08 (m, 2 H), 1.62 – 1.85 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃): δ = 155.1, 151.1, 136.3, 129.3, 128.0, 116.2, 110.5, 107.5, 105.9, 100.2, 94.6, 67.0, 55.9, 41.0, 35.0, 34.9, 31.8, 28.5, 22.1, 15.9. HRMS (ESI): calcd for C₂₃H₂₉O₅⁺, [M + H⁺] 385.2015, found 385.2010.



Demethyldactylidin 3

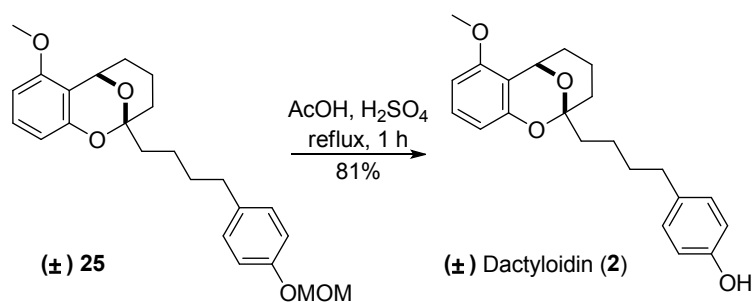
The phenol **24** (38.4 mg, 0.1 mmol) was treated with 75% aqueous acetic acid (v/v) containing a trace of sulfuric acid (1 drop/100 mL) (5 mL, purged with nitrogen) at 85 °C under nitrogen atmosphere. After 1 h, 15 mL of H₂O were added, the aqueous mixture was extracted with EtOAc (5 x 15 mL), and the organic extracts were washed with saturated sodium bicarbonate (2 x 10 mL), dried over anhydrous Na₂SO₄. Removal of the solvent, the crude product was purified by chromatography on a short column of silica gel (silica gel, hexane/EtOAc = 2:1) to give demethyldactylidin **3** (27.5 mg, 79% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 6.97 – 7.05 (m, 3 H), 6.74 (d, *J* = 7.6 Hz, 2 H), 6.43 (d, *J* = 8.4 Hz, 1 H), 6.25 (d, *J* = 8.0 Hz, 1 H), 5.27 (d, *J* = 2.8 Hz, 1 H), 4.79 – 4.91 (br, 2 H), 2.55 (t, *J* = 7.2 Hz, 2 H), 1.93 – 2.06 (m, 2 H), 1.53 – 1.80 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃): δ = 155.2, 153.4, 151.0, 134.9, 129.4, 128.0, 115.1, 110.5, 107.7, 105.9, 100.3, 67.0, 41.0, 34.9, 34.9, 31.9, 28.5, 22.1, 15.9. HRMS (ESI): calcd for C₂₁H₂₅O₄⁺, [M + H⁺] 341.1753, found 341.1748.



7-methoxy-2-(4-(4-(methoxymethoxy)phenyl)butyl)-3,4,5,6-tetrahydro-2H-2,6-epoxybenzo[b]oxocine 25

To a solution of phenol **24** (960 mg, 0.25 mmol) in dry acetone (10 mL), K₂CO₃ (345 mg, 2.5 mmol) and methyl iodine (2 mL) was added under a nitrogen

atmosphere. The solution was stirred at room temperature for 12 h, then quenched by diluting with EtOAc (30 mL). The resultant precipitates were filtered and washed by EtOAc (2 x 5 mL). The combined filtrate was concentrated in *vacuo* and purified by a very short chromatography (silica gel, hexane/EtOAc = 5:1) to afford **25** (945 mg, 95% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.12 (q, *J* = 6.8 Hz, *J* = 8.4 Hz, 3 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 6.49 (d, *J* = 8.4 Hz, 1 H), 6.40 (d, *J* = 8.4 Hz, 1 H), 5.26 (d, *J* = 3.2 Hz, 1 H), 5.17 (s, 2 H), 3.80 (s, 3 H), 3.50 (s, 3 H), 2.59 (t, *J* = 6.8 Hz, 2 H), 1.92 – 2.07 (m, 2 H), 1.71 – 1.83 (m, 4 H), 1.62 – 1.66 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ = 155.2, 155.1, 154.7, 136.2, 129.2, 127.9, 116.1, 111.4, 107.9, 101.2, 100.0, 94.6, 67.0, 55.8, 55.3, 41.0, 35.0, 35.0, 31.9, 28.4, 22.1, 16.0. HRMS (ESI): calcd for C₂₄H₃₁O₅⁺, [M + H⁺] 399.2171, found 399.2164.



Dactyloidin 2

The phenol **25** (39.8 mg, 0.1 mmol) was treated with 75% aqueous acetic acid (v/v) containing a trace of sulfuric acid (1 drop/100 mL) (5 mL, purged with nitrogen) at 85 °C under nitrogen atmosphere. After 1 h, 15 mL of H₂O were added, the aqueous mixture was extracted with EtOAc (5 x 15 mL), and the organic extracts were washed with saturated sodium bicarbonate (2 x 10 mL), dried over anhydrous Na₂SO₄. Removal of the solvent, the crude product was purified by chromatography on a short column of silica gel (silica gel, hexane/EtOAc = 4:1) to give dactyloidin **2** (28.7 mg, 81% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.12 (t, *J* = 8.4 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.74 (dd, *J* = 2.0 Hz, *J* = 6.4 Hz, 2 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 6.40 (d, *J* = 8.4 Hz, 1 H), 5.26 (d, *J* = 3.2 Hz, 1 H), 5.01 (br, 1 H), 3.80 (s, 3 H), 2.56 (t, *J* = 8.0 Hz, 2 H), 1.91 – 2.04 (m, 2 H), 1.74 – 1.81 (m, 4 H),

1.57 – 1.65 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 155.1, 154.7, 153.5, 134.9, 129.4, 128.0, 115.0, 111.4, 107.9, 101.3, 100.1, 67.1, 55.4, 41.0, 35.0, 34.9, 31.9, 28.4, 22.1, 16.0. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4^+$, $[\text{M} + \text{H}^+]$ 355.1909, found 355.1901.

Spectral Data.

