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Synthesis and stereochemical assignment of (+)-Cladospolide D

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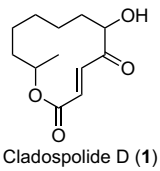
ABSTRACT

Cladospolides A–D are 12-membered, α,β-unsaturated lactones isolated from various species of *Cladosporium*. Cladospolide D is unique in its γ-keto functionality and possesses antifungal activity; however, the stereochemistry of Cladoapolide D was unknown. We report the asymmetric syntheses to generate both possible diastereomers of Cladospolide D. Two regioselective cross-metatheses were applied to form the carbon skeleton, and the two olefins were differentiated by Michael addition, hydrogenation, and elimination. Later, the macrocycle was achieved through the Yamaguchi protocol. After comparing the spectroscopic data of the synthetic Cladospolide D with the reported values, the stereochemistry of Cladospolide D is confirmed as (2*E*,5*R*,11*S*).

1. Introduction

Cladopsolide D (**1**) was isolated from the fermentation broth of *Cladosporium* sp. FT0012 in 2001.[1] All the reported Cladopsolides (A–D) are 12-membered α,β-unsaturated lactones,[2] but only Cladospolide D has the γ-keto functionality and possesses antifungal activity against *Mucor racemosus*.[1] Indeed, many α,β-unsaturated-γ-keto lactones, such as 12-membered Patulolide A and 16-membered A26771B, have been synthetic targets because these compounds hold antifungal, antibacterial, and antiinflammatory activities.[3,4] Although Cladospolides A, B, and C have been synthesized and reported,[5–7] the synthesis of Cladospolide D remained elusive probably due to the unknown stereochemistry at C5 and C11. Here, we report our work in asymmetrically synthesizing the two possible diastereomers of Cladospolide D. After comparing the reported spectroscopic data with that of the synthetic counterparts, the absolute stereochemistry of **1** is determined.



Cladospolide D (**1**)

2. Results and discussion

The synthesis of Cladospolide D started with the monoprotection of the C_2-symmetric (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**2**) as the silyl ether **3**.[8] Cross-metathesis (CM) between the diene **3** and methyl acrylate was catalyzed by the second generation Grubbs catalyst[9] (**4**) to give the (*E*)-α,β-unsaturated ester **5** in 66% yield. The regioselectivity of CM in this case is consistent with Michaelis and Blechert's observation,[10] and the regioselective reaction of the olefin with an allylic hydroxy group for cross-metathesis has directed the following steps of the synthesis. Thus, the hydroxy group of **5** was further protected as (2-methoxyethoxy)methyl (MEM) ether **6**, and the *tert*-butyldimethylsilyl group was removed to facilitate the second metathesis at the terminal olefin.[11] The second cross-metathesis between the allylic alcohol **7** and both enantiomerically pure (*R*)- and (*S*)-2-(6-heptenyl) acetates[12] (**8a** and **8b**, respectively) proceeded well to form **9a** and **9b**. The large coupling constant (15.0 Hz) between the new formed vinylic hydrogens indicates the formation of an *E*-olefin. Thus, the required carbon skeleton for Cladospolide D was assembled (Scheme 1).

We found that the selective hydrogenation of the allylic alcohol in **9** is difficult to achieve,[13] and attempted to utilize Michael addition to differentiate the two olefins here. However, no Michael adduct directly derived from the ester **9** and 1-butanethiol could be obtained. We suspected that the alkoxide anion, generated from **9** under the basic condition, leads to the undesired reaction channels and byproducts at 80 °C. On the other hand, the Michael addition of the re-protected **10** and 1-butanethiol went smoothly to give the sulfides **11** in good yields.[14] The remaining olefin was hydrogenated, and the (*E*)-α,β-unsaturated ester was regenerated after oxidation of sulfide **12**, and then elimination.[15] This route is more efficient than regenerating the α,β-unsaturated ester by

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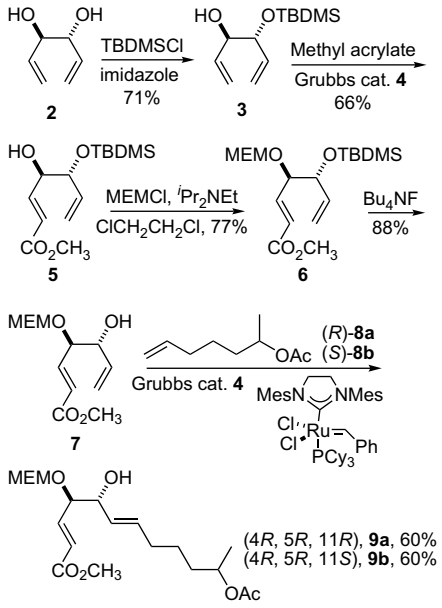
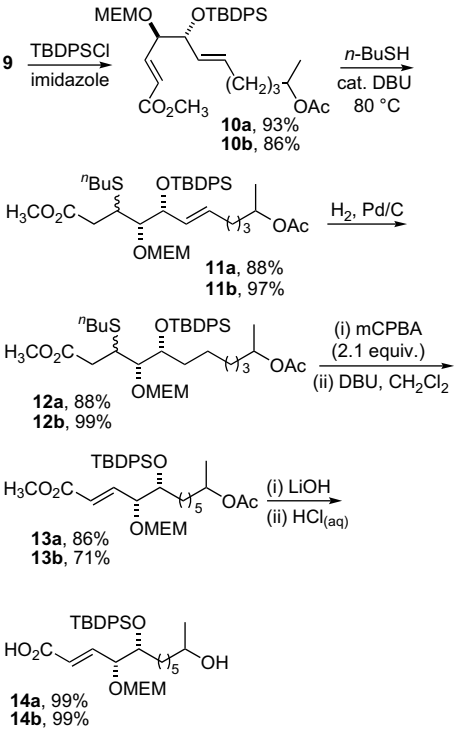


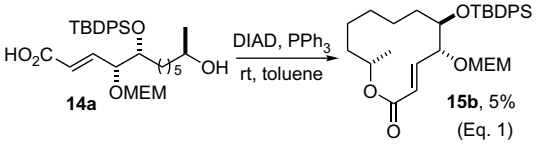
Scheme 1. Two cross-metatheses to form **9**.

selenylation/deselenylation in our hands.[7c] Both ester groups were hydrolyzed under basic conditions to give acid **14** (Scheme 2).

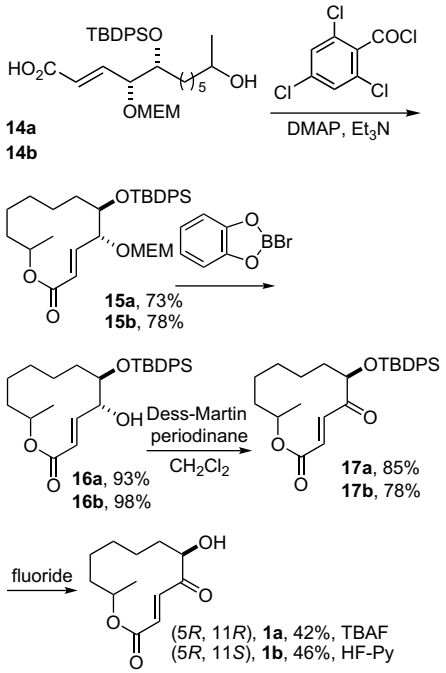


Scheme 2. Formation of **14**.

Lactone formation and further modifications to achieve Cladospolide D are summarized in Scheme 3. The Yamaguchi protocol was applied to form the 12-membered lactone **14**.[16] The MEM group was removed with *B*-bromocatechol-borane,[17] and the resulting alcohol was oxidized by Dess–Martin periodinane to give the γ-keto lactone **17**.[18] Diastereomers **1a** and **1b** were produced after removing the *tert*-butyldiphenyl silyl (TBDPS) groups by tetrabutylammonium fluoride (TBAF) or hydrogen fluoride/pyridine (HF/Py).[19,20] Although the product **1a** could be formed by both reagents with reasonable yields (42 and 30%, respectively), we noticed that the diastereomer **1b** is only generated by HF-Py (46%). The diastereomer **1b**, whose methyl and hydroxyl groups are located on the opposite face of the macrolactone, seems more susceptible under the basic condition of TBAF. Indeed, the ^{1}H NMR of the crude product showed the presence of aldehyde, probably generated from the retro-Aldol condensation. The overall yields in synthesizing the two diastereomers **1a** and **1b** are 3%. We also attempted to apply the Mitsunobu reaction[21] to form the macrolide; however, the yield is much lower when preparing the C11 inverted product **15b** from **14a** (Eq. 1).



(1)



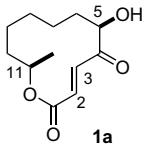
Scheme 3. Lactonization to form Cladospolide D.

The key spectroscopic data to identify the natural Cladospolide D as **1b** are shown in Table 1. The diastereomer **1b** not only matches the reported Cladopolide D well in NMR, but it is also consistent with its optical rotation. Thus, both the relative and absolute configurations of (+)-Cladospolide D is established as (5*R*,11*S*).

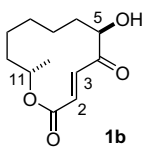
3. Conclusions

We have achieved the first synthesis of Cladospolide D by applying two cross-metatheses to provide the carbon skeleton, Michael addition/elimination to generate the α,β-unsaturated ester, and the Yamaguchi protocol to form the macrolide. Comparing to our previous synthesis of Cladospolide C,[7c] the protecting groups applied in this synthesis allow selective deprotection and oxidation to form the γ-ketone. The stereochemistry of Cladospolide D is established after comparing the reported characterization data with that of both diastereomers **1a** and **1b**.

Table 1
Spectroscopic data of natural Cladospolide D, **1a** and **1b**



1a



1b

	Cladospolide D[1]		**1a**		**1b**	
$[\alpha]_D$	+56.0 (*c* 0.1, methanol)		−6.2 (*c* 0.20, methanol)		+56.9 (*c* 0.15, methanol)	
NMR (δ)	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
2-CH	130.9	6.31	130.2	6.21	130.9	6.31
3-CH	133.3	6.41	134.6	6.56	133.3	6.41
5-CH	73.46	4.66	75.9	4.96	73.5	4.67
11-CH	71.50	5.23	73.9	4.44	71.5	5.22
12-CH_3	20.59	1.31	21.5	1.27	20.6	1.30

4. Experimental section

4.1. (3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-1,5-hexadien-4-ol (3)[8c,22]

tert-Butyldimethylsilyl chloride (TBSCl, 10.14 g, 67.29 mmol) was added to a solution of diol **2** (5.12 g, 44.9 mol), imidazole (4.57 g, 67.29 mmol), and dichloromethane (256 mL) at 0 °C. The solution was refluxed for 16 h, quenched with water (150 mL), and diluted with ether (300 mL). The aqueous layer was further extracted with ether (50 mL×3), and the combined organic layer was washed with $HCl_{(aq)}$ (0.1 N, 250 mL), satd $NaCl_{(aq)}$ (250 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:9; R_f 0.60) to give **3** (7.27 g, 31.85 mmol, 71%) as a colorless oil. $[\alpha]_D^{20}$ +8.9 (*c* 2.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 2.52 (d, 1H, *J*=4.5 Hz), 3.88–3.97 (m, 2H), 5.14–5.34 (m, 4H), 5.74–5.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.9, −4.2, 18.2, 25.8, 75.7, 77.5, 116.5, 117.0, 136.9, 137.8; IR (neat): 3465, 3080, 2930, 2857, 1245, 836 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{12}H_{24}NaO_2Si$) 251.1443, found 251.1440.

4.2. *E*-(4*R*,5*R*)-Methyl 5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-2,6-heptadienoate (5)

Grubbs catalyst second generation (74.0 mg, 0.09 mmol) was added to the solution of diene **3** (400.0 mg, 1.75 mmol), 2,6-di-*tert*-butyl-4-methylphenol (BHT, 193.0 mg, 0.88 mmol), and methyl acrylate (1.51 g, 17.53 mmol) in toluene (4 mL). After being heated at reflux for 3 h, the reaction mixture was concentrated and the crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.40) to give **5** (331 mg, 1.16 mmol, 66%) as a light yellow oil. $[\alpha]_D^{20}$ +14. 8 (*c* 2.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 2.61 (d, 1H, *J*=5.0 Hz), 3.72 (s, 3H), 3.99 (dd, 1H, *J*=5.8, 6.7 Hz), 4.11 (ddd, 1H, *J*=9.0, 4.0 and 2.0 Hz), 5.22 (dd, 1H, *J*=10.5 and 1.0 Hz), 5.26 (dd, 1H, *J*=17.5 and 1.0 Hz), 5.80 (ddd, 1H, *J*=17.5, 10.5 and 7.0 Hz), 6.11 (dd, 1H, *J*=15.5 and 2.0 Hz), 6.90 (dd, 1H, *J*=15.5 and 4.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.0, −4.2, 18.1, 25.7, 51.6, 74.0, 76.8, 118.0, 121.5, 137.1, 146.6, 166.7; IR (neat): 3495, 3081, 2953, 2857, 1726, 1255 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$($C_{14}H_{27}O_4Si$) 287.1679, found 287.1673.

4.3. *E*-(4*R*,5*R*)-Methyl 5-(*tert*-butyldimethylsilyloxy)-4-((2-methoxyethoxy)methoxy)-2,6-heptadienoate (6)

Methoxyethoxylmethyl chloride (MEMCl, 433.0 mg, 3.49 mmol) was added to the solution of **5** (500.0 mg, 1.75 mmol), diisopropylethylamine (1.13 g, 8.74 mmol), and 1,2-dichloroethane (4 mL) in a sealable tube at 0 °C. The reaction mixture was sealed, microwave irradiated (120 °C, 150 W) for 40 min. After cooled to room temperature, the reaction mixture was added with satd $NaHCO_{3(aq)}$ (4 mL) and water (16 mL), extracted with dichloroethane (20 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.40) to give **6** (503 mg, 1.35 mmol, 77%) as a light brown oil. $[\alpha]_D^{20}$ +18.8 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 3.34 (s, 3H), 3.50 (t, 2H, *J*=5.0 Hz), 3.60–3.65 (m, 1H), 3.70 (s, 3H), 3.71–3.75 (m, 1H), 4.18–4.23 (m, 2H), 4.70 (d, 1H, *J*=6.9 Hz), 4.76 (d, 1H, *J*=6.9 Hz), 5.13 (dd, 1H, *J*=10.5 and 1.5 Hz), 5.22 (dd, 1H, *J*=17.5 and 1.5 Hz), 5.77 (ddd, 1H, *J*=16.0 Hz, 10.5 and 5.0 Hz), 5.99 (dd, 1H, *J*=15.0 and 1.0 Hz), 6.86 (dd, 1H, *J*=15.0 and 5.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.0, −4.7, 18.2, 25.8, 51.5, 59.0, 67.2, 71.6, 75.0, 78.9, 94.6, 116.7, 122.4, 136.6, 145.0, 166.5;IR (neat): 3093, 2953, 1728, 1271, 1136, 1032 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{18}H_{34}NaO_6Si$) 397.2022, found 397.2023.

4.4. *E*-(4*R*,5*R*)-Methyl 5-hydroxy-4-((2-methoxyethoxy)-methoxy)-2,6-heptadienoate (7)

Compound **6** (190.0 mg, 0.51 mmol) in THF (6 mL) was added with TBAF (1.5 mL, 1.52 mmol, 1 M in THF). After stirred at room temperature for 2 h, the reaction mixture was added with water (5 mL) and extracted with ethyl acetate (10 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.60) to give **7** (117 mg, 0.45 mmol, 88%) as a light yellow oil. $[\alpha]_D^{20}$ −55.1 (*c* 1.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.05 (d, 1H, *J*=4.0 Hz), 3.35 (s, 3.0H), 3.51 (t, 2H, *J*=5.0 Hz), 3.64–3.68 (m, 1H), 3.71 (s, 3H), 3.78–3.82 (m, 1H), 4.04–4.10 (m, 1H), 4.11–4.14 (m, 1H), 4.69 (d, 1H, *J*=7.0 Hz), 4.74 (d, 1H, *J*=7.0 Hz), 5.21 (dd, 1H, *J*=10.5 and 1.5 Hz), 5.34 (dd, 1H, *J*=17.0 and 1.0 Hz), 5.79 (ddd, 1H, *J*=17.0 Hz, 10.5 and 6.0 Hz), 6.02 (dd, 1H, *J*=16.0 and 1.0 Hz), 6.79 (dd, 1H, *J*=16.0 and 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7, 58.9, 67.7, 71.6, 74.5, 79.7, 94.3, 117.7, 123.6, 135.9, 144.0, 166.2; IR (neat): 3446, 3081, 2950, 1725, 1278, 1114, 1023 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{12}H_{20}NaO_6$) 283.1158, found 283.1157.

4.5. (2*E*,6*E*)-(4*R*,5*R*,11*R*)-Methyl 11-acetoxy-5-hydroxy-4-((2-methoxyethoxy)methoxy)-2,6-dodecadienoate (9a)

Grubbs catalyst **4** (17 mg, 0.02 mmol) was added to the solution of compound **7** (100.0 mg, 0.38 mmol), (*R*)-**8a** (90.0 mg, 0.58 mmol), and *p*-cresol (20.0 mg, 0.19 mmol) in dichloromethane (2 mL). The reaction mixture was refluxed for 16 h under nitrogen, concentrated, and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1;

R_f 0.35) to give **9a** (90.0 mg, 0.23 mmol, 60%) as a light brown oil. $[\alpha]_D^{20}$ −43.3 (*c* 1.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, 3H, *J*=6.5 Hz), 1.31–1.55 (m, 4H), 2.00 (s, 3H), 2.00–2.05 (m, 2H), 3.02 (d, 1H, *J*=4.0 Hz), 3.36 (s, 3H), 3.52 (t, 2H, *J*=4.5 Hz), 3.65–3.70 (m, 1H), 3.72 (s, 3H), 3.77–3.82 (m, 1H), 4.00–4.03 (m, 1H), 4.08–4.11 (m, 1H), 4.70 (d, 1H, *J*=7.0 Hz), 4.75 (d, 1H, *J*=7.0 Hz), 4.82–4.87 (m, 1H), 5.39 (dd, 1H, *J*=15.0 and 6.5 Hz), 5.68–5.76 (m, 1H), 6.00 (dd, 1H, *J*=16.0 and 1.5 Hz), 6.76 (dd, 1H, *J*=16.0 and 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9, 21.3, 24.7, 32.0, 35.3, 51.7, 59.0, 67.8, 70.8, 71.7, 74.4, 80.1, 94.4, 123.4, 127.9, 134.6, 144.3, 166.2, 170.8; IR (neat): 3446 (br), 2937, 1730, 1653, 1247, 1023 cm^{-1}; HRMS (APCI) calcd for $[M+Na]^+$ ($C_{19}H_{32}NaO_8$) 411.1995, found 411.1992.

4.6. (2*E*,6*E*)-(4*R*,5*R*,11*S*)-Methyl 11-acetoxy-5-hydroxy-4-((2-methoxyethoxy)methoxy)-2,6-dodecadienoate (9b)

The procedure to prepare **9a** was followed. Starting with compound **7** (100.0 mg, 0.38 mmol), *p*-cresol (20.0 mg, 0.19 mmol), (*S*)-**8b** (90.0 mg, 0.58 mmol) and Grubbs catalyst **4** (17.0 mg, 0.02 mmol), the diene **9b** (90.0 mg, 0.23 mol, 60%) was prepared. $[\alpha]_D^{20}$ −29.9 (*c* 2.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (d, 3H, *J*=6.0 Hz), 1.28–1.56 (m, 4H), 1.98 (s, 3H), 2.00–2.05 (m, 2H), 3.08 (d, 1H, *J*=3.5 Hz), 3.35 (s, 3H), 3.51 (t, 2H, *J*=4.0 Hz), 3.63–3.68 (m, 1H), 3.70 (s, 3H), 3.76–3.81 (m, 1H), 3.96–4.02 (m, 1H), 4.06–4.11 (m, 1H), 4.68 (d, 1H, *J*=7.0 Hz), 4.73 (d, 1H, *J*=7.0 Hz), 4.80–4.86 (m, 1H), 5.38 (dd, 1H, *J*=16.5 and 8.0 Hz), 5.66–5.74 (m, 1H), 5.99 (dd, 1H, *J*=16.0 and 1.5 Hz), 6.75 (dd, 1H, *J*=16.0 and 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.8, 21.3, 24.6, 31.9, 35.2, 51.6, 58.9, 67.7, 70.6, 71.6, 74.3, 80.0, 94.3, 123.3, 127.9, 134.5, 144.3, 166.2, 170.7; IR (neat): 3447 (br), 2916, 1727, 1247, 1022 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{19}H_{32}NaO_8$) 411.1995, found 411.1996.

4.7. (2*E*,6*E*)-(4*R*,5*R*,11*R*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-4-((2-methoxyethoxy)methoxy)-2,6-dodecadienoate (10a)

The solution of compound **9a** (358.0 mg, 0.92 mmol) in dichloromethane (8.3 mL) was added with *tert*-butyldiphenylchlorosilane (506.8 mg, 1.84 mmol) and imidazole (188.0 mg, 2.77 mmol) at 0 °C. The reaction mixture was refluxed for 16 h, quenched with water (15 mL), and extracted with ether (15 mL×3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.46) to give **10a** (539.0 mg, 0.86 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}$ −2.9 (*c* 2.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9H), 1.14 (d, 3H, *J*=6.0 Hz), 1.15–1.22 (m, 2H), 1.29–1.47 (m, 2H), 1.81–1.89 (m, 2H), 2.00 (s, 3H), 3.30 (s, 3H), 3.38 (t, 2H, *J*=5.0 Hz), 3.50 (t, 2H, *J*=5.0 Hz), 3.72 (s, 3H), 4.08–4.12 (m, 1H), 4.22 (t, 1H, *J*=5.5 Hz), 4.53 (d, 1H, *J*=7.0 Hz), 4.56 (d, 1H, *J*=7.0 Hz), 4.77–4.83 (m, 1H), 5.27–5.33 (m, 2H), 5.97 (dd, 1H, *J*=15.5 and 1.5 Hz), 6.95 (dd, 1H, *J*=15.5 and 5.0 Hz), 7.30–7.42 (m, 6H), 7.60–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 19.9, 21.4, 24.7, 27.0, 31.8, 35.3, 51.5, 59.0, 67.1, 70.8, 71.5, 75.4, 78.6, 94.4, 122.5, 127.4, 127.6, 128.1, 129.6, 129.8, 133.7, 133.7, 133.9, 135.9, 136.0, 145.3, 166.6, 170.7; IR (neat): 3071, 2933, 1730, 1245, 1111 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{35}H_{50}NaO_8Si$) 649.3173, found 649.3174.

4.8. (2*E*,6*E*)-(4*R*,5*R*,11*S*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-4-((2-methoxyethoxy)methoxy)-2,6-dodecadienoate (10b)

The procedure to prepare **10a** was followed. Starting with **9b** (615.0 mg, 1.58 mmol in 15 mL dichloromethane), *tert*-butyldiphenylchlorosilane (871.0 mg, 3.17 mmol), and imidazole (323.0 mg, 4.75 mmol), compound **10b** (850.0 mg, 1.36 mol, 86%) was prepared as a colorless oil. $[\alpha]_D^{20}$ −7.6 (*c* 1.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9H), 1.14 (d, 3H, *J*=6.5 Hz), 1.17–1.24 (m, 2H), 1.28–1.48 (m, 2H), 1.81–1.88 (m, 2H), 2.00 (s, 3H), 3.30 (s, 3H), 3.38 (t, 2H, *J*=5.0 Hz), 3.51 (t, 2H, *J*=5.0 Hz), 3.72 (s, 3H), 4.10–4.12 (m, 1H), 4.22 (t, 1H, *J*=5.5 Hz), 4.53 (d, 1H, *J*=7.0 Hz), 4.56 (d, 1H, *J*=7.0 Hz), 4.77–4.83 (m, 1H), 5.26–5.35 (m, 2H), 5.97 (dd, 1H, *J*=16.0 and 1.5 Hz), 6.95 (dd, 1H, *J*=16.0 and 5.5 Hz), 7.30–7.40 (m, 6H), 7.59–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 19.9, 21.4, 24.6, 26.9, 31.8, 35.2, 51.5, 58.9, 67.0, 70.8, 71.5, 75.3, 78.6, 94.4, 122.5, 127.4, 127.6, 128.0, 129.6, 129.8, 133.7, 133.8, 133.9, 135.9, 135.9, 145.2, 166.6, 170.7; IR (neat): 3052, 2930, 1731, 1245, 1111, 1044 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{35}H_{50}NaO_8Si$) 649.3173, found 649.3188.

4.9. *E*-(4*S*,5*R*,11*R*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-3-(butylthio)-4-((2-methoxyethoxy)methoxy)-6-dodecenoate (11a)

A reaction mixture of **10a** (489.0 mg, 0.78 mmol), 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU, 24.0 mg, 0.16 mmol), and 1-butanethiol (211.0 mg, 2.34 mmol) was heated in a 80 °C oil bath for 3 h. The excess reagents were removed under vacuum, and the crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.46) to give **11a** (491 mg, 0.69 mmol, 88%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, 3H, *J*=7.0 Hz), 1.00 and 1.03 (s, 9H), 1.13 (d, 3H, *J*=6.5 Hz), 1.21–1.51 (m, 8H), 1.63–1.80 (m, 2H), 1.99 (s, 3H), 2.33–2.50 (m, 2H), 2.33–2.50 and 2.70–2.76 (m, 2H), 3.32 and 3.35 (s, 3H), 3.36–3.40 (m, 1H), 3.40–3.59 (m, 4H), 3.64 and 3.66 (s, 3H), 3.68–3.73 (m, 1H), 3.76–3.83 (m, 1H), 4.68 (d, 1H, *J*=7.0 Hz), 4.12 (d, 1H, *J*=7.0 Hz), 4.73–4.81 (m, 1H), 5.19–5.35 (m, 2H), 7.29–7.40 (m, 6H), 7.60–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 19.3, 19.9, 21.3, 21.9, 24.4, 27.0, 31.5, 31.7, 31.9, 35.4, 36.5, 41.8, 51.6, 59.0, 67.3, 70.8, 71.7, 75.5, 83.3, 96.8, 127.2, 127.3, 127.5, 127.5, 128.8, 129.5, 129.7, 133.5, 135.9, 136.0, 136.0, 136.1, 170.7, 172.5; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{39}H_{60}NaO_8SSi$) 739.3676, found 739.3683.

4.10. *E*-(4*S*,5*R*,11*S*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-3-(butylthio)-4-((2-methoxyethoxy)methoxy)-6-dodecenoate (11b)

The procedure to prepare **11a** was followed. Starting with **10b** (784.0 mg, 1.25 mmol), DBU(38.0 mg, 0.25 mmol), and 1-butanethiol (339.0 mg, 3.76 mmol), compound **11b** (872.0 mg, 1.22 mol, 97%) was harvested. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84 (t, 3H, *J*=7.0 Hz), 1.00 and 1.03 (s, 9H), 1.13 and 1.11(d, 3H, *J*=6.5 Hz), 1.25–1.50 (m, 8H), 1.71–1.78(m, 2H), 1.99(s, 3H), 2.33–2.50 (m, 2H), 2.33–2.50 and 2.70–2.76 (m, 2H), 3.32 and 3.35 (s, 3H), 3.35–3.40 (m, 1H), 3.40–3.60 (m, 4H), 3.64 and 3.66 (s, 3H), 3.69–3.71 (m, 1H), 3.77–3.82 (m, 1H), 4.68 (d, 1H, *J*=7.0 Hz), 4.81 (d, 1H, *J*=7.0 Hz), 4.74–4.80 (m, 1H), 5.19–5.34 (m, 2H), 7.29–7.40 (m, 6H), 7.61–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 19.3, 19.9, 21.3, 21.9, 24.4, 27.0, 31.5, 31.7, 31.9, 35.4, 36.5, 41.8, 51.6, 59.0, 67.3, 70.7, 71.7, 75.5, 83.2, 96.8, 127.2, 127.3, 127.4, 127.5, 128.8, 129.5, 129.7, 133.5, 135.9, 136.0, 136.0, 136.0, 170.7, 172.5; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{39}H_{60}NaO_8SSi$) 739.3676, found 739.3669.

4.11. (4*S*,5*R*,11*R*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-3-(butylthio)-4-((2-methoxyethoxy)methoxy)-dodecanoate (12a)

The suspension of palladium (5% on activated carbon, 414 mg) and compound **11a** (491.0 mg, 0.69 mmol) in methanol (5 mL) was stirred under hydrogen (1 atm) for 30 h. The suspension was filtered, and the filtrate was concentrated to give **12a** (432.0 mg, 0.60 mmol, 88%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, 3H, *J*=7.0 Hz), 1.02 (s, 9H), 1.02–1.05 (m, 3H), 1.18 (d, 3H,

J=6.0 Hz), 1.20–1.42 (m, 6H), 1.42–1.50 (m, 2H), 1.98 (s, 3H), 2.45–2.56 (m, 2H), 2.45–2.56 and 2.76–2.82 (m, 2H), 3.35 (s, 3H), 3.39–3.44 (m, 1H), 3.44–3.64 (m, 4H), 3.66 and 3.68 (s, 3H), 3.70–3.73 (m, 1H), 3.73–3.82 (m, 1H), 4.71 (d, 1H, J=7.0 Hz), 4.82 (d, 1H, J=7.0 Hz), 4.72–4.79 (m, 1H), 7.31–7.41 (m, 6H), 7.61–7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6, 19.4, 19.9, 21.3, 22.0, 24.9, 25.1, 27.1, 29.3, 31.2, 31.6, 33.0, 35.7, 37.2, 42.4, 51.6, 59.0, 67.6, 70.9, 71.7, 74.0, 82.1, 97.0, 127.4, 127.4, 127.5, 129.5, 129.6, 133.6, 134.6, 135.9, 135.9, 136.0, 170.7, 172.6; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{39}H_{62}NaO_8SSi$) 741.3832, found 741.3835.

4.12. (4*S*,5*R*,11*S*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-3-(butylthio)-4-((2-methoxyethoxy)methoxy)-dodecanoate (12b)

The procedure to prepare **12a** was followed. Starting with **11b** (859.0 mg, 1.19 mmol) and palladium (359.0 mg), compound **12b** (854.0 mg, 1.19 mmol, 99%) was produced. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, 3H, J=7.0 Hz), 1.02 (s, 9H), 1.02–1.06 (m, 3H), 1.12 (d, 3H, J=6.5 Hz), 1.20–1.42 (m, 6H), 1.42–1.51 (m, 2H), 1.99 (s, 3H), 2.45–2.56 (m, 2H), 2.45–2.56 and 2.75–2.81 (m, 2H), 3.35 (s, 3H), 3.38–3.42 (m, 1H), 3.44–3.64 (m, 4H), 3.66 and 3.68 (s, 3H), 3.70–3.72 (m, 1H), 3.77–3.83 (m, 1H), 4.71 (d, 1H, J=7.0 Hz), 4.82 (d, 1H, J=7.0 Hz), 4.72–4.79 (m, 1H), 7.30–7.40 (m, 6H), 7.60–7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 19.4, 19.9, 21.4, 22.0, 24.8, 25.1, 27.0, 29.2, 31.2, 31.6, 33.0, 35.7, 37.2, 42.4, 51.7, 59.0, 67.5, 71.0, 71.7, 74.0, 82.0, 97.0, 127.4, 127.4, 127.5, 129.5, 129.6, 133.6, 134.6, 135.9, 136.0, 170.7, 172.6; HRMS (FAB) calcd for $[M]^+$ ($C_{39}H_{62}O_8SSi$) 718.3933, found 718.3938.

4.13. *E*-(4*R*,5*R*,11*R*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-4-((2-methoxyethoxy)methoxy)-2-dodecenoate (13a)

m-Chloroperbenzoic acid (312.0 mg, 1.26 mmol) in dichloromethane (3.2 mL) was added to the solution of **12a** (432.0 mg, 0.60 mmol) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 min, at room temperature for another 1 h, quenched with satd $NaHCO_{3(aq)}$ (10 mL), and extracted with dichloromethane (10 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give the sulfone intermediate (450.0 mg, 0.60 mmol, 99%). The crude sulfone was redissolved in dichloromethane (30 mL), cooled to 0 °C, and added with 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU, 274.0 mg, 1.80 mmol). After stirred at 0 °C for 1 h, the reaction mixture was concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.40) to give **13a** (325 mg, 0.52 mmol, 86%) as a colorless oil. $[\alpha]_D^{20}$ +14.2 (c 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02–1.12 (m, 4H), 1.04 (s, 9H), 1.14 (d, 3H, J=6.0 Hz), 1.15–1.34 (m, 4H), 1.35–1.47 (m, 2H), 1.99 (s, 3H), 3.32 (s, 3H), 3.39 (t, 2H, J=5.0 Hz), 3.51 (t, 2H, J=5.0 Hz), 3.74 (s, 3H), 3.76–3.80 (m, 1H), 4.17–4.21 (m, 1H), 4.49 (d, 1H, J=7.0 Hz), 4.51 (d, 1H, J=7.0 Hz), 4.75–4.82 (m, 1H), 6.00 (dd, 1H, J=16.0 and 1.5 Hz), 7.04 (dd, 1H, J=16.0 and 5.0 Hz), 7.32–7.43 (m, 6H), 7.63–7.67(m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 19.9, 21.4, 25.1, 25.4, 27.1, 29.3, 32.3, 35.7, 51.6, 59.0, 67.1, 71.0, 71.5, 74.5, 78.3, 94.4, 122.5, 127.5, 127.6, 129.5, 129.6, 129.7, 129.8, 133.5, 133.9, 135.9, 136.0, 145.5, 166.6, 170.7; IR (neat): 2933, 1730, 1245, 1010 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{35}H_{52}NaO_8Si$) 651.3329, found 651.3320.

4.14. *E*-(4*R*,5*R*,11*S*)-Methyl 11-acetoxy-5-(*tert*-butyldiphenylsilyloxy)-4-((2-methoxyethoxy)methoxy)-2-dodecenoate (13b)

The procedure to prepare **13a** was followed. Starting with **12b** (80.0 mg, 0.11 mmol) and *m*-chloroperbenzoic acid (58.0 mg, 0.23 mmol), the sulfone intermediate (82.2 mg, 0.109 mmol, 98%) was produced. Then, the elimination of the sulfone (82.21 mg, 0.109 mmol) by DBU (50.88 mg, 0.33 mmol) provided **13b** (50.0 mg, 0.08 mmol, 71%) as a colorless oil. $[\alpha]_D^{20}$ +9.4 (c 2.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97–1.12 (m, 4H), 1.04 (s, 9H), 1.13 (d, 3H, J=6.0 Hz), 1.16–1.32 (m, 4H), 1.35–1.45 (m, 2H), 1.99 (s, 3H), 3.32 (s, 3H), 3.39 (t, 2H, J=5.5 Hz), 3.50 (t, 2H, J=5.5 Hz), 3.73 (s, 3H), 3.75–3.80 (m, 1H), 4.17–4.21 (m, 1H), 4.91 (d, 1H, J=7.0 Hz), 4.51 (d, 1H, J=7.0 Hz), 4.74–4.81 (m, 1H), 6.00 (dd, 1H, J=16.0 and 1.5 Hz), 7.04 (dd, 1H, J=16.0 and 5.0 Hz), 7.31–7.44 (m, 6H), 7.63–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 19.9, 21.3, 25.1, 25.4, 27.0, 29.4, 32.3, 35.7, 51.6, 59.0, 67.0, 71.0, 71.4, 74.4, 78.2, 94.4, 122.0, 127.3, 127.4, 127.6, 129.6, 129.7, 133.4, 133.8, 135.8, 135.9, 135.9, 145.5, 166.6, 170.7; IR (neat): 3073, 2932, 1730, 1245, 1011 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{35}H_{52}NaO_8Si$) 651.3329, found 651.3315.

4.15. *E*-(4*R*,5*R*,11*R*)-5-(*tert*-Butyldiphenylsilyloxy)-11-hydroxy-4-((2-methoxyethoxy)methoxy)-2-dodecenoic acid (14a)

The solution of **13a** (93.0 mg, 0.15 mmol) and lithium hydroxide (62.2 mg, 1.48 mmol) in THF/water (1:1, 2.4 mL) was stirred at room temperature for 16 h. The reaction mixture was neutralized (pH ~ 4) by adding $HCl_{(aq)}$ (1 N), and extracted with ethyl acetate (5 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give the acid **14a** (85.0 mg, 0.15 mmol, 99%) as a colorless oil. $[\alpha]_D^{20}$ +12.6 (c 1.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99–1.09 (m, 4H), 1.04 (s, 9H), 1.12 (d, 3H, J=6.0 Hz), 1.14–1.34 (m, 6H), 3.32 (s, 3H), 3.40 (t, 2H, J=5.0 Hz), 3.51(t, 2H, J=5.0 Hz), 3.65–3.73(m, 1H), 3.76–3.84 (m, 1H), 4.18–4.23 (m, 1H), 4.50 (d, 1H, J=7.0 Hz), 4.51 (d, 1H, J=7.0 Hz), 6.01 (dd, 1H, J=16.0 and 1.5 Hz), 7.15 (dd, 1H, J=16.0 and 4.5 Hz), 7.32–7.45 (m, 6H), 7.63–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 20.7, 23.2, 25.3, 27.0, 29.4, 32.3, 39.0, 59.0, 67.1, 68.1, 71.4, 74.4, 78.3, 94.5, 121.7, 127.4, 127.6, 129.6, 129.7, 133.4, 133.8, 135.9, 135.9, 147.7, 170.5; IR (neat) 3404 (br), 3071, 2929, 1702, 1110, 1040 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{32}H_{48}NaO_7Si$) 595.3067, found 595.3078.

4.16. *E*-(4*R*,5*R*,11*S*)-5-(*tert*-Butyldiphenylsilyloxy)-11-hydroxy-4-((2-methoxyethoxy)methoxy)-2-dodecenoic acid (14b)

The procedure to prepare **14a** was followed. Starting with **13b** (258.0 mg, 0.41 mmol) and lithium hydroxide (172.0 mg, 4.10 mmol, in water and THF, 3 mL each), the acid **14b** (235.0 mg, 4.10 mmol, 99%) was produced. $[\alpha]_D^{20}$ +15.3 (c 1.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03–1.07 (m, 4H), 1.04 (s, 9H), 1.12 (d, 3H, J=6.0 Hz), 1.15–1.36 (m, 6H), 3.32 (s, 3H), 3.40 (t, 2H, J=5.0 Hz), 3.52 (t, 2H, J=5.0 Hz), 3.66–3.73 (m, 1H), 3.78–3.83 (m, 1H), 4.19–4.23 (m, 1H), 4.50 (d, 1H, J=7.0 Hz), 4.52 (d, 1H, J=7.0 Hz), 6.02 (dd, 1H, J=16.0 and 1.5 Hz), 7.15 (dd, 1H, J=16.0 and 4.5 Hz), 7.32–7.44 (m, 6H), 7.63–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 23.2, 25.4, 27.0, 27.0, 29.4, 32.3, 39.0, 58.9, 67.1, 68.1, 71.5, 74.4, 78.4, 94.5, 121.8, 127.3, 127.5, 127.6, 129.6, 129.8, 133.4, 133.8, 135.8, 135.9, 136.0, 147.8, 170.6; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{32}H_{48}NaO_7Si$) 595.3067, found 595.3067.

4.17. *E*-(5*R*,6*R*,12*R*)-6-(*tert*-Butyldiphenylsilyloxy)-5-((2-methoxyethoxy)methoxy)-12-methyloxacyclododec-3-en-2-one (15a)

2,4,6-Trichlorobenzoyl chloride (54.90 mg, 0.23 mmol) was added to the solution of **14a** (85.0 mg, 0.15 mmol), triethylamine (23.0 mg, 0.23 mmol), and THF (2.4 mL). The solution was stirred at room temperature for 3 h, diluted with toluene (6 mL), and added into a refluxing solution of 4-dimethylaminopyridine (91 mg, 0.74 mmol) and toluene (20 mL). The reaction mixture was refluxed

for 3 h, cooled to room temperature, added with satd $NaHCO_{3(aq)}$ (10 mL). The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with satd $CuSO_{4(aq)}$, water (10 mL), and satd $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.60) to give **15a** (60 mg, 0.11 mmol, 73%) as a colorless oil. $[\alpha]_D^{20}$ −0.4 (*c* 1.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01–1.22 (m, 6H), 1.06 (s, 9H), 1.25 (d, 3H, *J*=6.5 Hz), 1.22–1.50 (m, 4H), 3.31 (s, 3H), 3.38 (t, 2H, *J*=5.0 Hz), 3.45 (t, 2H, *J*=5.0 Hz), 3.93–3.98 (m, 1H), 4.03–4.08 (m, 1H), 4.45 (d, 1H, *J*=7.0 Hz), 4.50 (d, 1H, *J*=7.0 Hz), 5.07–5.16 (m, 1H), 6.09 (dd, 1H, *J*=16.0 and 1.5 Hz), 6.89 (dd, 1H, *J*=16.0 and 6.5 Hz), 7.32–7.42 (m, 6H), 7.59–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 19.3, 22.2, 23.7, 26.9, 28.5, 30.0, 32.8, 58.9, 66.9, 71.4, 72.9, 74.5, 79.4, 94.0, 123.2, 127.5, 127.6, 129.6, 129.7, 133.7, 133.8, 135.7, 135.8, 145.4, 167.4; IR (neat): 3071, 2932, 1719, 1212, 1042 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{32}H_{46}NaO_6Si$) 577.2961, found 577.2965.

4.18. *E*-(5*R*,6*R*,12*S*)-6-(*tert*-Butyldiphenylsilyloxy)-5-((2-methoxyethoxy)methoxy)-12-methyloxacyclododec-3-en-2-one (15b)

The procedure to prepare **15a** was followed. Starting with **14b** (235.0 mg, 0.41 mmol), triethylamine (62.2 mg, 0.62 mmol), 2,4,6-trichlorobenzoyl chloride (149.0 mg, 0.62 mmol), and DMAP (250.0 mg, 2.05 mmol) in toluene (72 mL), the lactone **15b** (178.0 mg, 0.32 mmol, 78%) was harvested as a colorless oil. $[\alpha]_D^{20}$ −1.7 (*c* 1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04–1.25 (m, 6H), 1.07 (s, 9H), 1.27 (d, 3H, *J*=6.5 Hz), 1.36–1.55 (m, 4H), 3.32 (s, 3H), 3.41 (t, 2H, *J*=5.0 Hz), 3.57 (t, 2H, *J*=5.0 Hz), 3.75–3.82 (m, 1H), 4.15–4.21 (m, 1H), 4.56 (d, 1H, *J*=7.0 Hz), 4.59 (d, 1H, *J*=7.0 Hz), 4.94–5.02 (m, 1H), 6.02 (dd, 1H, *J*=16.0 and 2.0 Hz), 7.05 (dd, 1H, *J*=16.0 and 4.0 Hz), 7.33–7.42 (m, 6H), 7.62–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 19.8, 22.6, 23.8, 27.0, 27.9, 31.8, 32.7, 58.9, 67.1, 71.5, 73.1, 76.0, 80.8, 94.8, 121.7, 127.5, 127.6, 129.7, 129.7, 133.6, 134.1, 135.8, 135.8, 146.5, 166.9; IR (neat): 3071, 2931, 1715, 1212, 1039 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{32}H_{46}NaO_6Si$) 577.2961, found 577.2964.

4.19. *E*-(5*R*,6*R*,12*R*)-6-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-12-methyloxacyclododec-3-en-2-one (16a)

B-Bromocatechol-borane (3.9 mL, 0.78 mmol, 0.2 M in DCM) was added to the solution of **15a** (42.0 mg, 0.08 mmol) and dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 20 h, quenched with water (5 mL), and extracted with dichloromethane (5 mL×3). The combined organic layer was washed with satd $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.60) to give **16a** (33 mg, 0.07 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}$ +25.0 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.08–1.22 (m, 4H), 1.24 (d, 3H, *J*=6.5 Hz), 1.26–1.46 (m, 6H), 2.07–2.12 (br, 1H), 3.70–3.76 (m, 1H), 4.07–4.13 (m, 1H), 4.96–5.04 (m, 1H), 6.05 (dd, 1H, *J*=16.0 and 1.5 Hz), 6.83 (dd, 1H, *J*=16.0 and 7.5 Hz), 7.35–7.45 (m, 6H), 7.63–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 20.0, 22.7, 24.0, 26.5, 26.9, 31.0, 33.1, 73.4, 76.4, 77.6, 123.2, 127.6, 127.9, 129.8, 129.9, 133.5, 134.7, 135.7, 135.7, 145.4, 167.3; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{28}H_{38}NaO_4Si$) 489.2437, found 489.2431.

4.20. *E*-(5*R*,6*R*,12*S*)-6-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-12-methyloxacyclododec-3-en-2-one (16b)

The procedure to prepare **16a** was followed. Starting with **15b** (70.0 mg, 0.13 mmol) and *B*-bromocatechol-borane (3.16 mL, 0.63 mmol, 0.2 M in DCM) in dichloromethane (4 mL), alcohol **16b** (57.6 mg, 0.12 mmol, 98%) was produced. $[\alpha]_D^{20}$ −7.8 (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.08–1.22 (m, 4H), 1.24 (d, 3H, *J*=7.0 Hz), 1.30–1.57 (m, 6H), 2.40 (br, 1H), 3.39–3.46 (m, 1H), 4.22–4.27 (m, 1H), 4.98–5.06 (m, 1H), 6.03 (dd, 1H, *J*=16.0 and 2.0 Hz), 6.94 (dd, 1H, *J*=16.0 and 4.5 Hz), 7.35–7.44 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0, 19.3, 22.8, 23.8, 27.0, 27.9, 32.5, 33.0, 72.7, 77.2, 79.8, 121.6, 127.7, 127.9, 129.8, 130.0, 133.3, 133.6, 135.7, 135.7, 146.9, 166.9; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{28}H_{38}NaO_4Si$) 489.2437, found 489.2434.

4.21. *E*-(6*R*,12*R*)-6-(*tert*-Butyldiphenylsilyloxy)-12-methyloxacyclododec-3-ene-2,5-dione (17a)

Dess–Martin periodinane (60.0 mg, 0.14 mmol) was added to the solution of **16a** (33.0 mg, 0.07 mmol) and dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 2.5 h, added with satd $NaHCO_{3(aq)}$ (5 mL), and extracted with dichloromethane (5 mL×3). The combined organic layer was washed with water (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.80) to give **17a** (28 mg, 0.06 mmol, 85%) as a colorless oil. $[\alpha]_D^{20}$ −21.4 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 9H), 1.21–1.36 (m, 6H), 1.20 (d, 3H, *J*=6.0 Hz), 1.39–1.48 (m, 2H), 1.58–1.73 (m, 2H),4.36–4.40 (m, 1H), 4.83–4.90 (m, 1H), 6.62 (d, 1H, *J*=16.0 Hz), 6.99 (d, 1H, *J*=16.0 Hz), 7.32–7.46 (m, 6H), 7.60–7.66 (m, 4H); ^{13}C NMR($CDCl_3$, 125 MHz) δ 19.2, 20.6, 24.0, 26.5, 26.9, 27.6, 34.0, 35.0, 75.4, 78.8, 127.7, 127.7, 127.8, 130.0, 130.0, 131.1, 132.7, 133.3, 134.8, 135.7, 135.9, 137.9, 166.7, 200.1; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{28}H_{36}NaO_4Si$) 487.2281, found 487.2274.

4.22. *E*-(6*R*,12*S*)-6-(*tert*-Butyldiphenylsilyloxy)-12-methyloxacyclododec-3-ene-2,5-dione (17b)

The procedure to prepare **17a** was followed. Starting with Dess–Martin periodinane (58.0 mg, 0.14 mmol) and **16b** (32.0 mg, 0.07 mmol) in dichloromethane (2 mL), the ketone **17b** (25.0 mg, 0.05 mmol, 78%; R_f 0.80, EtOAc/hexanes) was produced as a colorless oil. $[\alpha]_D^{20}$ −13.2 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 9H), 1.17–1.47 (m, 6H), 1.33 (d, 3H, *J*=6.0 Hz), 1.47–1.57 (m, 2H), 1.60–1.81 (m, 2H), 4.36–4.40 (m, 1H), 4.48–4.57 (m, 1H), 6.73 (d, 1H, *J*=16.5 Hz), 7.34 (d, 1H, *J*=16.5 Hz), 7.32–7.46 (m, 6H), 7.52–7.57 (m, 2H), 7.61–7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 20.5, 21.5, 24.0, 26.9, 27.2, 33.9, 34.6, 74.8, 76.7, 127.7, 127.8, 130.0, 130.1, 131.4, 132.4, 133.0, 134.6, 135.6, 135.7, 167.3, 200.7; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{28}H_{36}NaO_4Si$) 487.2281, found 487.2287.

4.23. *E*-(6*R*,12*R*)-6-Hydroxy-12-methyloxacyclododec-3-ene-2,5-dione (1a)

Tetrabutylammonium fluoride (0.16 mL, 0.16 mmol, 1 M in THF) was slowly added to the solution of **17a** (25.0 mg, 0.05 mmol), acetic acid (32.0 mg, 0.54 mmol), and THF (1 mL) in 6 h. The reaction mixture was stirred at room temperature for another 16 h and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.40) to give **1a** (5.0 mg, 0.02 mmol, 42%) as a colorless oil. $[\alpha]_D^{20}$ −27.2 (*c* 0.2, $CHCl_3$); $[\alpha]_D^{20}$ −6.2 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15–1.35 (m, 6H), 1.27 (d, 3H, *J*=6.5 Hz), 1.51–1.73 (m, 4H), 2.90 (br, 1H),4.41–4.47 (m, 1H), 4.92–5.02 (m, 1H), 6.21 (d, 1H, *J*=13.0 Hz), 6.57 (d, 1H, *J*=13.0 Hz); ^{13}C NMR($CDCl_3$, 125 MHz) δ 18.7, 18.8, 21.5, 27.3, 31.0, 31.2, 74.0, 76.0, 130.3, 134.8, 164.6, 203.2; IR (neat): 3445 (br), 2925, 2855, 1717, 1625, 1259, 1114 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{12}H_{18}NaO_4$) 249.1103, found 249.1103.

4.24. *E*-(6*R*,12*S*)-6-Hydroxy-12-methyloxacyclododec-3-ene-2,5-dione (1b)

Hydrogen fluoride/pyridine (65–70%, 0.05 mL) diluted with acetonitrile (0.5 mL) was added to the solution of compound **17b** (9.0 mg, 0.02 mmol) and acetonitrile (0.25 mL) in a 5 mL plastic vial. The reaction mixture was stirred at room temperature for 16 h, quenched with satd $NaHCO_3$(aq) (10 mL), and extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with satd $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.40) to give **1b** (2 mg, 0.013 mmol, 46%) as a colorless oil. $[\alpha]_D^{20}$ +56.9 (*c* 0.15, MeOH); $[\alpha]_D^{20}$ +22.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR($CDCl_3$, 500 MHz) δ 1.30 (d, 3H, *J*=6.0 Hz), 1.32–1.52 (m, 6H), 1.63–1.75 (m, 4H), 3.18 (d, 1H, *J*=5.5 Hz), 4.63–4.69 (m, 1H), 5.20–5.26 (m, 1H), 6.31 (d, 1H, *J*=13.5 Hz), 6.41 (d, 1H, *J*=13.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6, 21.5, 21.6, 23.0, 31.0, 33.2, 71.5, 73.5, 130.9, 133.3, 165.4, 203.5; IR (neat): 3458 (br), 2928, 2855, 1721, 1623, 1226, 1083 cm^{-1}; HRMS (FAB) calcd for $[M]^+$ ($C_{12}H_{18}O_4$) 226.1205, found 226.1206.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for all the synthesized compounds are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.059.

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