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The first synthesis of a 12-membered macrolide natural product via a RCM protocol: determination of absolute stereochemistry

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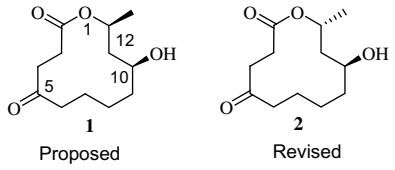
Abstract—The first synthesis of (10*S*,12*R*)-10-hydroxy-12-methyl-1-oxacyclododecane-2,5-dione and its C12 epimer is reported, thereby assigning the absolute stereochemistry of the natural product. The strategy utilizes a *syn* selective reduction, Yamaguchi esterification, and ring-closing metathesis as the key steps.

1. Introduction

The (10*S*,12*R*)-10-hydroxy-12-methyl-1-oxacyclododecan-2,5-dione **2**, whose absolute stereochemistry of the two hydroxyl functionalities at C10 and C12 was originally assigned as depicted in structure **1**, was isolated from the endophytic fungal strain *Cladosporium tenuissimum* LR463 of *Maytenus hookeri*,[1] and is found to rapidly induce the systematic defense responses in plants, that is, the production of peroxidase, phenylalanine ammonia lyase, ligin, and salicylic acid. As part of our interest in the synthesis of bioactive natural products,[2] herein, we report the synthesis of macrolides **1** and **2** and revise the absolute stereochemistry of the natural product as **2**. Our strategy involves the esterification of the two appropriately functionalized components under Yamaguchi conditions, followed by the Grubbs' catalyst-mediated ring-closing metathesis to afford the macrocycle first and its subsequent elaboration to the target compound.



2. Results and discussion

The synthesis of **1** (Scheme 1) began with the conversion of commercially available 1,4-butane diol into **9**. Thus, mono-protection (DHP/PTSA/CH_2Cl_2/rt), Swern oxidation followed by the Barbier reaction (Zn/allyl bromide/aq NH_4Cl/THF/rt), benzylation (NaH/BnBr/THF/rt) of the ensuing alcohol **9a**, and THP deprotection (PTSA/MeOH/rt) furnished **9**. The required acid **8** was obtained in two consecutive steps. Alcohol **9** was first oxidized to an aldehyde under Swern conditions; the crude aldehyde thus obtained was then oxidized to acid **8** (80% over two steps) under sodium chlorite oxidation ($NaClO_2$–NH_2PO_4/$2H_2O$–*t*-BuOH–2-methyl-2-butene) conditions.

Simultaneously, another intermediate **3** was synthesized from the known homoallylic alcohol[2a,6] **12** whose hydroxyl functionality was protected as its TPS ether (TPSCl/imidazole/CH_2Cl_2) and then the benzyl ether was deprotected (Li/liq. NH_3/THF) to give alcohol **3** (68%). Later, the esterification of **8** with **3** under Yamaguchi conditions[3] furnished bis-olefin **4** (67%). Subsequently, the Grubbs' catalyst-mediated ring-closing metathesis[4] (Grubbs' catalyst **II**/CH_2Cl_2/reflux) of **4** afforded the cyclic ester **5** (72%), which upon treatment with Pd/C in MeOH afforded **6** (82%), wherein two reactions of benzyl deblocking as well as the reduction of the double bond were addressed in one-pot. The ensuing secondary hydroxyl was oxidized using Dess–Martin periodinane in CH_2Cl_2 to give ketone **7** (90%), and consequently deprotection of the TPS ether by HF–py in THF afforded compound **1** (85%) as a white solid, mp: 70–72 °C; $[\alpha]_D^{25} = +68.1$ (*c* 0.25, MeOH) {lit.[1]

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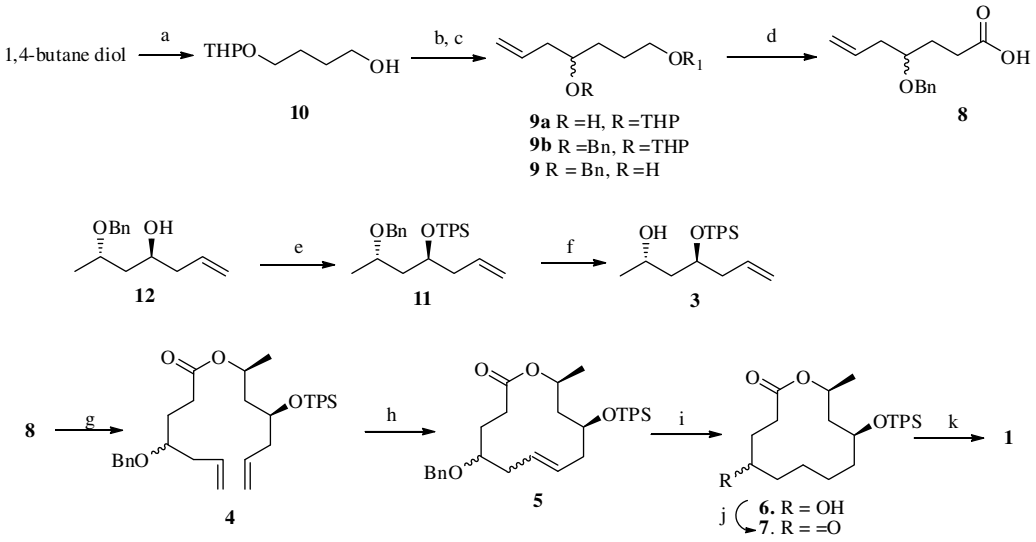
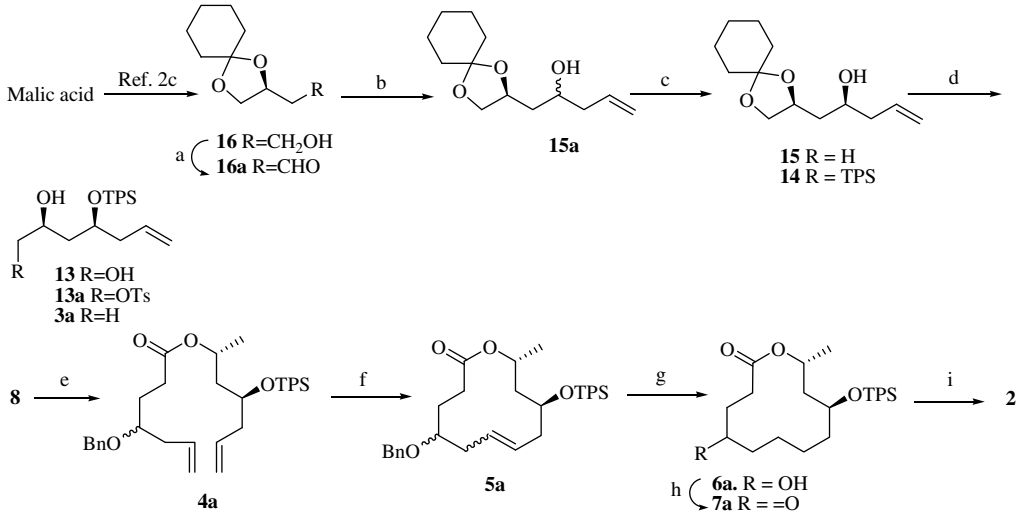


Scheme 1. Reagents and conditions: (a) DHP, PTSA, CH_2Cl_2, 2 h; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 2 h, (ii) Zn, allyl bromide, aq NH_4Cl, THF, 4 h, 90%, (c) (i) NaH, benzyl bromide, THF, 2 h, (ii) PTSA, MeOH, rt, 4 h; (d) (i) $(COCl)_2$ DMSO, Et_3N, CH_2Cl_2, 2 h, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, 6 h, (80% over two steps); (e) imidazole, CH_2Cl_2, 0 °C to rt, 98%; (f) Li, liq. NH_3, −78 °C, 68%; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF DMAP, toluene, **3**, 67%; (h) Grubbs-II (10 mol %), CH_2Cl_2, reflux, 12 h, 72%; (i) Pd/C, MeOH, 6 h, 82%; (j) Dess–Martin periodinane, CH_2Cl_2, 2 h, 90%; (k) HF·py, THF, 4 h, 85%.

$[\alpha]_D^{25} = -54.5$ (*c* 0.91, MeOH)}. Moreover, the physical and spectroscopic data of **1** were different to the reported values of the natural product.[1]

This synthesis thus implies that the proposed structure for macrolide **1** is incorrect. Hence, to arrive at the first synthesis of the macrolide natural product and to determine the absolute stereochemistry as well, another synthesis was planned.

Accordingly, the synthesis of **2** (Scheme 2) was achieved by adopting a related stratagem from the known[2c] alcohol **16** prepared from commercially available L-malic acid. The primary alcohol in **16** was oxidized under Swern conditions to afford aldehyde **16a**, which on Barbier reaction (Zn/allyl bromide/aq NH_4Cl/THF) afforded homoallyl alcohol **15a** (90%). This mixture of alcohols was converted to the desired (10*S*)-diastereomer via an oxidation/selective reduction sequence. Thus, alcohol **15a** was oxidized using IBX, DMSO in CH_2Cl_2 to afford the ketone, which upon treatment with LiI, LAH at −40 to −78 °C gave the *syn*-alcohol **15** (72%, 95% de).[5] The ensuing hydroxyl was protected (TPSCl/imidazole/CH_2Cl_2) as a TPS ether, followed by deprotection (PTSA/MeOH/rt) of the cyclohexylidene



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 2 h; (b) Zn, allyl bromide, aq NH_4Cl, THF, 4 h, 90%; (c) (i) IBX, DMSO, CH_2Cl_2, 2 h, 89%, (ii) LiI, LAH, diethyl ether, −40 to −78 °C, 72%; (d) (i) TPSCl, imidazole, CH_2Cl_2, 95%, (ii) PTSA, MeOH, 2H, 85%, (iii) TsCl, CH_2Cl_2, 2 h, 95%, (iv) LAH, THF, 1 h, reflux, 73%; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 3a, 69%; (f) Grubbs'-II (10 mol %), CH_2Cl_2, reflux, 12 h, 70%; (g) Pd/C, MeOH, 6 h, 85%; (h) Dess–Martin periodinane, CH_2Cl_2, 2 h, 92%; (i) HF·py, THF, 4 h, 85%.

group to afford diol **13** (85%), mono tosylation (TsCl/Et_3N/CH_2Cl_2) of which gave tosylate **13a** (75%), which upon treatment with LAH in THF gave alcohol **3a** (73%). Further reactions such as esterification and RCM, adopted are similar to those described in Scheme 1 to afford macrolide **2** as a colorless oil with $[\alpha]_D^{25} = -52.2$ (*c* 0.25, MeOH) {lit.[1] $[\alpha]_D^{25} = -54.5$ (*c* 0.91, MeOH)}. The physical and spectroscopic data of **2** were identical to the reported values of the natural product.[1] Thus, the absolute stereochemistry assigned was (10*S*,12*R*) (Table 1).

3. Conclusions

Thus in summary, the stereoselective total synthesis of the 12-membered macrolide natural product **2** was accomplished by the strategy wherein a *syn* selective reduction, Yamaguchi esterification, and ring-closing metathesis are the key steps and its absolute stereochemistry was revised as (10*S*,12*R*).

4. Experimental

4.1. General methods

Varian Gemini 200 MHz, Bruker Avance-300 MHz spectrometers with 7–10 mM solutions in deuteriochloroform, tetramethylsilane as internal standard. *J* values are given in Hertz. Optical rotations were measured with a JASCO P-1020 instrument and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1} at 25 °C. IR spectra were taken with a Perkin–Elmer 1310 spectrometer. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system and ESI-MS was measured using ion-trap mass spectrometer. Elemental analysis was recorded on ELEMENTAR (Vario EL, Germany). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. The software ACD/Name Version 1.0, developed by M/s Advanced Chemistry Development Inc., Toronto, Canada, assisted nomenclature used in the experimental section.

4.1.1. 7-Tetrahydro-2*H*-2-pyranyloxy-1-hepten-4-ol 9a. To a stirred solution of oxalyl chloride (2.73 mL, 31.2 mmol) in CH_2Cl_2 (20 mL) at −78 °C, DMSO (4.4 mL, 61.4 mmol) was added followed by the alcohol (4.6 g, 28.4 mmol) in CH_2Cl_2 (30 mL) and the reaction mixture stirred for 1 h at −78 °C, quenched with Et_3N (23.9 mL, 170.3 mmol), and extracted with CH_2Cl_2 (2 × 120 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the aldehyde (4.2 g, 95%) as a colorless liquid, which was directly used for further reaction.

To a stirred solution of aldehyde (4.6 g, 28.7 mmol) in THF (50 mL), Zn (3.7 g, 56.5 mmol), and allyl bromide (4.8 mL, 57.5 mmol) were added at 0 °C. Then satd aq NH_4Cl (15 mL) was added slowly and stirred for 4 h. Later, quenched with satd aq NH_4Cl (40 mL), extracted with EtOAc (2 × 50 mL), and the organic layer was separated. The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 4:21) to afford **9a** (5.4 g, 90%) as a light yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.90–5.73 (m, 1H), 5.14–5.03 (m, 2H), 4.58 (t, *J* 3.7 Hz, 2H), 3.88–3.72 (m, 2H), 3.66 (sept, *J* 12.0, 8.3, 4.5 Hz, 1H), 3.52–3.33 (m, 2H), 2.30–2.12 (m, 2H), 1.88–1.41 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.2, 118.2, 98.6, 71.6, 67.2, 66.9, 38.5, 30.6, 25.5 and 25.3, 19.4; IR (neat) *v*: 3452, 2925, 2861, 1229, 950 cm^{-1}; ESI-MS; 223 $[M+Na]^+$; Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.93; H, 9.95.

Table 1. Comparative NMR values for natural product and synthetic compounds

Position	Natural product		Compound **1**		Compound **2**	
	H^1	^{13}C	H^1	^{13}C	H^1	^{13}C
1	—	—	—	—	—	—
2	—	171.4	—	172.0	—	171.1
3	2.57–2.55 (m) 2.61–2.58 (m)	30.5	2.60–2.53 (m)	29.8	2.60–2.15 (m)	30.1
4	2.58–2.55 (m) 2.93–2.91 (m)	38.2	2.94–2.63 (m)	38.8	3.00–2.66 (m)	37.7
5	—	210.2	—	209.9	—	210.1
6	2.04–2.02 (m) 2.61–2.58 (m)	41.8	2.42 (t, *J* 5.12)	44.0	2.60–2.15 (m)	41.3
7	1.19–1.17 (m) 1.38–1.33 (m)	23.5	1.89–1.36 (m)	23.2	1.89–1.35 (m)	23.4
8	1.19–1.17 (m) 1.38–1.33 (m)	35.3	1.89–1.36 (m)	36.1	1.89–1.35 (m)	34.3
9	1.38–1.33 (m) 1.67–1.66 (m)	23.2	1.89–1.36 (m)	21.8	1.89–1.35 (m)	23.2
10	3.82–3.78 (m)	67.0	3.75 (p, *J* 6.75)	68.6	3.79 (p, *J* 5.12)	, 67.5
11	1.67–1.66 (m) 1.67–1.66 (m)	41.4	1.89–1.36 (m)	41.5	1.89–1.35 (m)	40.4
12	5.04–4.98 (m)	69.0	4.98–4.81 (m)	70.9	5.10 (sext, *J* 13.18, 5.85)	68.5
12-Me	1.19 (d, *J* 6.4)	20.4	1.21 (d, *J* 6.58)	21.0	1.25 (d, *J* 6.42)	20.0

4.1.2. 2-{[4-(Benzyloxy)-6-heptenyl]oxy}tetrahydro-2*H*-pyran 9b. To a stirred solution of alcohol **9a** (1.0 g, 4.6 mmol) in THF (10 mL), NaH (0.3 g, 13.0 mmol) was added at 0 °C and stirred for 30 min. Then, benzyl bromide (0.7 mL, 5.6 mmol) was added and stirred for 2 h. Later, the reaction was quenched with satd aq NH_4Cl (10 mL) and then extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford **9b** (1.3 g, 95%) as a light yellow syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69–7.25 (m, 5H), 5.90–5.75 (m, 1H), 5.16–5.05 (m, 2H), 4.58 (dd, *J* 10.98 Hz, 3H), 3.85–3.70 (m, 2H), 3.54–3.34 (m, 3H), 2.32–2.11 (m, 2H), 1.82–1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.4, 132.7, 130.0, 129.5, 128.2, 127.7, 98.8, 67.5, 67.1, 66.9, 62.3, 38.6, 30.6, 30.3, 25.5, 25.4 and 19.5; IR (neat) *v*: 2925, 2851, 1221, 939 cm^{-1}; ESI-MS; 304 $[M+NH_4]^+$; Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.93; H, 9.25.

4.1.3. 4-(Benzyloxy)-6-hepten-1-ol 9. To a stirred solution of alcohol **9b** (1.3 g, 4.2 mmol) in MeOH (10 mL), PTSA (0.02 g) was added at 0 °C and stirred for 4 h at room temperature. The reaction mixture was quenched with satd aq $NaHCO_3$ solution (2 mL), extracted with EtOAc (2 × 15 mL) and the organic layer separated. The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford **8** (0.84 g, 90%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.24 (m, 5H), 5.90–5.75 (m, 1H), 5.16–5.05 (m, 2H), 4.52 (dd, *J* 11.33 Hz, 2H), 3.57 (t, *J* 6.04 Hz 2H), 3.54–3.43 (m, 1H), 2.46–2.28 (m, 2H), 1.72–1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.1, 128.5, 128.0, 127.9, 117.0, 78.8, 70.8, 62.9, 38.0, 30.9 and 28.2; IR (neat) *v*: 3480, 2930, 2860, 1215, 952 cm^{-1}. ESI-MS; 243 $[M+Na]^+$; Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.09.

4.1.4. 4-(Benzyloxy)-6-heptenoic acid 8. To a stirred solution of oxalyl chloride (0.34 mL g, 3.9 mmol) in CH_2Cl_2 (120 mL) at −78 °C, DMSO (0.55 mL, 7.8 mmol) was added followed by alcohol **9** (0.73 g, 3.5 mmol) in CH_2Cl_2 and the reaction mixture stirred for 1 h at −78 °C, quenched with Et_3N (3.0 mL, 21.4 mmol), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford the aldehyde (0.7 g, 97.2%) as a colorless liquid, which was directly used for further reaction.

To a stirred solution of aldehyde (0.7 g, 3.4 mmol) in *t*-BuOH/2-methyl 2-butene (2:1, 6 mL), $NaClO_2$ (0.62 g, 6.8 mmol), and NaH_2PO_4 (1.1 g, 6.8 mmol) [dissolved in water (2 mL)] were added and stirred for 6 h at room temperature. Solvent was removed under reduced pressure and extracted with EtOAc (2 × 5 mL), the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford acid **8** (0.58 g, 78%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.21 (s, 5H), 5.92–5.74 (m, 1H), 5.20–5.06 (m, 2H), 4.53 (dd, *J* 11.25 Hz, 2H), 3.49 (p, *J* 11.8, 8.2 Hz, 1H), 2.44–2.23 (m, 4H), 1.91–1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0, 134.1, 129.2, 128.4, 127.9, 127.9, 117.8, 77.9, 71.1, 38.1, 30.2 and 28.1; IR (neat) *v*: 3580, 2932, 2870, 1701, 1280, 689 cm^{-1}; ESI-MS; 234 $[M+Na]^+$; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.69; H, 7.71.

4.1.5. {(1*S*)-1-[(2*S*)-2-(Benzyloxy)propyl]-3-butenyloxy}-(*tert*-butyl)diphenylsilane 11. To a stirred solution of alcohol **12** (2.5 g, 11.3 mmol) in CH_2Cl_2 (25 mL), imidazole (1.93 g, 28.3 mmol) was added at 0 °C and stirred for 30 min followed by TPSCl (3.56 mL, 15.0 mmol) and then stirred for an additional 2 h at room temperature. After completion of the reaction (TLC), the reaction mixture was diluted with CH_2Cl_2 (20 mL), the organic layer was washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:49) to afford **11** (0.58 g, 78%) as a light yellow syrup. $[\alpha]_D^{25} = +11.2$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72–7.60 (m, 4H), 7.45–7.10 (m, 11H), 5.80–5.59 (m, 1H), 5.00–4.80 (m, 2H), 4.37 (d, *J* 9.75 Hz, 1H), 4.10–4.00 (m, 2H), 3.68–3.50 (m, 1H), 2.21–2.10 (m, 2H), 1.80–1.48 (m, 2H), 1.07 (s, 9H), 1.05 (d, *J* 6.03 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.6, 134.0, 132.7, 129.8, 129.7, 129.5, 128.2, 127.5, 117.4, 71.8, 70.3, 69.8, 43.2, 42.0, 41.3, 27.0, 23.5 and 19.5; IR (neat) *v*: 2915, 2851, 1221 cm^{-1}; ESI-MS; 481 $[M+Na]^+$; Anal. Calcd for $C_{30}H_{38}O_2Si$: C, 78.55; H, 8.35; Si, 6.12. Found: C, 78.48; H, 8.29; Si, 6.07.

4.1.6. (2*S*,4*S*)-4-{[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}-6-hepten-2-ol 3. To a solution of THF (3 mL) and liq. NH_3 (10 mL), Li (0.16 g, 23.3 mmol) was added and the reaction mixture was stirred for 30 min at −78 °C. Then, compound **11** (2.5 g, 5.88 mmol) was added and further stirred for 1 h at the same temperature. Later, the reaction mixture was quenched with satd NH_4Cl (50 mL), extracted with EtOAc (2 × 30 mL), and the organic layer was washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:24) to afford alcohol **3** (1.3 g, 68%) as a light yellow liquid. $[\alpha]_D^{25} = +41.3$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75–7.61 (m, 4H), 7.42–7.30 (m, 6H), 5.60–5.38 (m, 1H), 4.94–4.75 (m, 2H), 4.13–3.90 (m, 2H), 2.42–2.09 (m, 2H), 1.63–1.42 (m, 2H), 1.08 (s, 9H), 1.07 (d, *J* 6.04 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0, 134.2, 130.1, 127.9, 127.9, 117.5, 96.2, 72.1, 64.0, 43.4, 41.0, 27.2, 27.2 and 23.8; IR (neat) *v*: 3441, 3015, 2898, 1855, 1268, 1251, 695 cm^{-1}; ESI-MS; 369 $[M+1]^+$; Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75; Si, 7.62. Found: C, 74.89; H, 8.70; Si, 7.56.

4.1.7. (1*S*,3*S*)-3-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-1-methyl-5-hexenyl-4-(benzyloxy)-6-heptenoate 4. To a stirred solution of acid **8** (0.8 g, 3.6 mmol) in dry THF (6 mL), Et_3N (1.5 mL, 10.9 mmol) was added at room temperature and stirred for 1 h. Then, 2,4,6-trichlorobenzoyl

chloride (1.14 mL, 7.3 mmol) was added and stirred for 2 h at room temperature. The solvent was evaporated, the residue diluted with toluene (6 mL), treated with DMAP (1.12 g, 9.16 mmol) and alcohol **3** (1.2 g, 3.6 mmol). After 6 h, the toluene was evaporated in vacuo and the crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:24) to afford ester **4** (1.2 g, 67%) as a colorless syrup. $[\alpha]_D^{25} = +25.3$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.68–7.60 (m, 4H), 7.38–7.20 (m, 11H), 5.86–5.54 (m, 2H), 5.11–4.82 (m, 5H), 4.58–4.37 (m, 2H), 3.78–3.68 (m, 1H), 3.45–3.34 (m, 1H), 2.40–2.09 (m, 6H), 1.82–1.50 (m, 4H), 1.07 (s, 9H), 1.06 (d, *J* 6.39 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 143.1, 140.9, 135.8, 134.3, 134.2, 139.1, 38.5, 137.5, 137.4, 137.3, 117.8, 117.5, 71.0, 69.6, 68.0, 42.2, 40.9, 38.2, 30.0, 29.0, 27.1, 22.9, 22.5 and 20.8; IR (neat) *v*: 2928, 2890, 1718, 1085, 1060 cm^{-1}; ESI-MS; 585 $[M+1]^+$; Anal. Calcd for $C_{37}H_{48}O_4Si$: C, 75.98; H, 8.27; Si, 4.80. Found: C, 75.88; H, 8.21; Si, 4.75.

4.1.8. (10*S*,12*S*)-5-[1-(Benzyloxy)]-10-[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy-12-methyl-1-oxa-7-cyclododecen-2-one 5. To a solution of bis-olefin **4** (0.2 g, 0.37 mmol) and Grubbs' second generation catalyst (0.03 g, 10 mol %) in CH_2Cl_2 (20 mL) was stirred at reflux temperature for 12 h. Later, the solvent was removed under reduced pressure and the crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:49) to afford cyclized product **5** (0.13 g, 72%) as a light yellow liquid. $[\alpha]_D^{25} = +9.5$ (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.59 (m, 4H), 7.45–7.18 (m, 11H), 5.88–5.64 (m, 1H), 5.40–5.24 (m, 1H), 5.18–4.93 (m, 1H), 4.54–4.88 (m, 2H), 3.72–3.48 (m, 1H), 3.42–3.16 (m, 1H), 2.50–2.21 (m, 6H), 1.51–1.24 (m, 4H), 1.09 (s, 9H), 1.07 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 143.5, 140.0, 135.8, 135.6, 134.3, 131.2, 127.8, 130.1, 127.4, 127.4, 70.5, 69.5, 68.2, 66.7, 42.2, 30.9, 30.7, 26.5, 26.3, 22.8 and 19.3; IR (neat) *v*: 2920, 2885, 1721, 1095, 1080 cm^{-1}; ESI-MS; 579 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{44}O_4Si$: C, 75.50; H, 7.96; Si, 5.04. Found: C, 75.45; H, 7.91; Si, 4.98.

4.1.9. (10*S*,12*S*)-10-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-5-hydroxy-12-methyl-1-oxacyclododecan-2-one 6. To a stirred solution of **5** (0.1 g, 0.19 mmol) in MeOH (1 mL), 10% Pd/C (catalytic) was added under hydrogen atmosphere and stirred for 6 h. Later, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The crude residue so obtained was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford cyclic alcohol **6** (0.06 g, 82%) as a colorless liquid. $[\alpha]_D^{25} = +2.8$ (*c* 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.61–7.48 (m, 4H), 7.40–7.22 (m, 6H), 5.14–5.08 (m, 1H), 3.95–3.80 (m, 1H), 3.78–3.60 (m, 1H), 2.52–2.31 (m, 2H), 1.61–1.25 (m, 12H), 1.06 (s, 9H), 1.05 (d, *J* 6.46 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 135.8, 130.0, 127.5, 127.4, 70.3, 70.2, 66.7, 42.0, 30.7, 28.7, 28.5, 27.9, 26.8, 26.5, 26.1, 22.9 and 19.1; IR (neat) *v*: 3482, 2920, 1718, 1462, 1262 cm^{-1}; ESI-MS; 486 $[M+NH_4]^+$; Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60; Si, 5.99. Found: C, 71.66; H, 8.49; Si, 5.85.

4.1.10. (10*S*,12*S*)-10-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-12-methyl-1-oxacyclododecane-2,5-dione 7. To a stirred solution of alcohol **6** (0.06 g, 0.14 mmol) in CH_2Cl_2 (2 mL), DMP (0.08 g, 0.18 mmol) was added and stirred for 2 h at room temperature. Then, the reaction was quenched with aq solution of $NaHCO_3$:hypo (1:1, 1 mL) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford ketone **7** (0.05 g, 90%) as a light yellow syrup. $[\alpha]_D^{25} = +23.2$ (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.59 (m, 4H), 7.43–7.30 (m, 6H), 4.48–4.31 (m, 1H), 3.61–3.50 (p, *J* 11.35, 6.81 Hz, 1H), 2.60–2.32 (m, 4H), 2.21 (t, *J* 5.0 Hz, 2H), 1.80–1.21 (m, 8H), 1.05 (s, 9H), 1.04 (d, *J* 6.49 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 171.7, 135.8, 129.6, 127.5, 70.9, 70.7, 42.9, 41.3, 37.9, 35.5, 29.7, 26.9, 22.3, 21.9, 20.9 and 19.8; IR (neat) *v*: 2929, 1721, 1678, 1250 cm^{-1}; ESI-MS; 489 $[M+Na]^+$; Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21; Si, 6.02. Found: C, 71.92; H, 8.09; Si, 5.91.

4.1.11. (10*S*,12*S*)-10-Hydroxy-12-methyl-1-oxacyclododecane-2,5-dione 1. To a stirred solution of **7** (0.05 g, 0.11 mmol) in dry THF (2 mL), HF·py (0.3 mL, 0.3 mmol) was added and stirred for 4 h at room temperature. The reaction mixture was quenched with $CuSO_4$ solution and extracted with EtOAc (2 × 2 mL), and the organic layer was washed with brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 3:7) to afford **1** (0.02 g, 85%) as a white solid. Mp 70–72 °C; $[\alpha]_D^{25} = +68.1$ (*c* 0.25, MeOH); ^1H NMR (200 MHz, $CDCl_3$): δ 4.98–4.81 (m, 1H), 3.75 (p, *J* 6.75 Hz, 1H), 2.94–2.63 (m, 2H), 2.60–2.53 (m, 3H), 2.42 (t, *J* 5.12 Hz, 2H), 1.89–1.36 (m, 7H), 1.21 (d, *J* 6.58 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 172.0, 70.9, 68.6, 44.0, 41.5, 38.8, 36.1, 29.8, 23.2, 21.8 and 21.0; IR (neat): 3444, 2920, 1710, 1662, 1251 cm^{-1}; ESI-MS; 251 $[M+Na]^+$; Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.07; H, 8.73.

4.1.12. 1-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-4-penten-2-ol 15a. To a stirred solution of oxalyl chloride (1.91 mL, 21.8 mmol) in CH_2Cl_2 (30 mL) at −78 °C, DMSO (3.1 mL, 43.7 mmol) was added followed by compound **17** (3.7 g, 19.8 mmol) in CH_2Cl_2 and the reaction mixture stirred for 1 h at −78 °C, then quenched with Et_3N (8.3 mL, 59.6 mmol), and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the aldehyde (3.62 g, 99%) as a colorless liquid, which was directly used for further reaction.

To a stirred solution of the above aldehyde (3.62 g, 20.1 mmol) in THF (40 mL), Zn (2.6 g, 39.7 mmol), and allyl bromide (3.3 mL, 40.0 mmol) were added at 0 °C followed by the slow addition of satd NH_4Cl (11 mL) and stirred for 4 h. Later, the reaction mixture was quenched with satd aq solution of NH_4Cl (30 mL), extracted with EtOAc (2 × 30 mL), and the organic layer separated. The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo.

The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford **15a** (4.1 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = +2.8$ (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90–5.73 (m, 1H), 5.13–5.04 (m, 1H), 4.29–4.18 (m, 1H), 4.15–3.98 (m, 1H), 3.96–3.80 (m, 1H), 3.50 (t, *J* 6.79 Hz, 1H), 3.10 (m, 1H), 2.32–2.14 (m, 2H), 1.74–1.51 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 118.1, 75.5, 70.4, 69.1, 42.0, 40.1, 36.5, 35.1, 25.4, and 23.9; IR (thin film): 3448, 3059, 2918, 1580, 1050 cm^{-1}; ESI-MS; 226 $[M+H]^+$; Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.95; H, 9.70.

4.1.13. (2*S*)-1-[(2*S*)-1,4-Dioxaspiro[4.5]dec-2-yl]-4-penten-2-ol 15. To a stirred solution of oxalyl chloride (0.42 mL g, 4.8 mmol) in CH_2Cl_2 (10 mL) at −78 °C, DMSO (0.69 mL, 9.6 mmol) was added followed by compound **15a** (1 g, 4.4 mmol) in CH_2Cl_2 and the reaction mixture stirred for 1 h at −78 °C, then quenched with Et_3N (1.86 mL, 12.8 mmol), and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the ketone (0.94 g, 95%) as a colorless liquid, which was directly used for further reaction.

To a stirred solution of ketone (0.94 g, 4.1 mmol), in dry ether (10 mL), lithium iodide (1.68 g, 12.5 mmol) was added at 0 °C and stirred for 10 min. Then at −78 °C, lithium aluminum hydride (0.48 g, 12.5 mmol) was added and the mixture stirred for 10 min after which the temperature was decreased to −100 °C and stirred for 30 min. Later, the reaction was quenched with satd aq KOH (10 mL) solution and extracted with ether (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford **15** (0.67 g, 72%) as a colorless syrup. $[\alpha]_D^{25} = +12.2$ (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90–5.73 (m, 1H), 5.13–5.04 (m, 1H), 4.29–4.18 (m, 1H), 4.05 (q, *J* 8.3, 6.0 Hz, 1H), 3.9–3.8 (m, 1H), 3.52 (t, *J* 6.79 Hz, 1H), 3.10 (br s, 1H), 2.32–2.14 (m, 2H), 1.74–1.51 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 118.1, 75.5, 70.4, 69.1, 42.0, 40.1, 36.5, 35.1, 25.4, and 23.9; IR (thin film): 3440, 3050, 2920, 1590, 1054 cm^{-1}; ESI-MS; 226 $[M+H]^+$; Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.90; H, 9.78.

4.1.14. *tert*-Butyl (1*S*)-1-[(2*S*)-1,4-dioxaspiro[4.5]dec-2-ylmethyl}-3-butenyloxy diphenylsilane 14. To a stirred solution of alcohol **15** (1.9 g, 8.4 mmol) in CH_2Cl_2 (20 mL), imidazole (1.4 g, 20.5 mmol) was added at 0 °C and stirred for 30 min, then TPSCl (2.6 mL, 10.0 mmol) was added and the mixture stirred for 2 h at room temperature. After the completion of the reaction (TLC), the reaction mixture was diluted with CH_2Cl_2 (20 mL), the organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford **14** (3.7 g, 95%) as a colorless liquid. $[\alpha]_D^{25} = +30.9$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.69–7.60 (m, 4H), 7.40–7.26 (m, 6H), 5.83–5.61 (m, 1H), 4.98–4.83 (m, 2H), 4.19–4.05 (m, 1H), 3.86 (p, *J* 10.93, 5.47 Hz, 1H), 3.74 (dd, *J* 6.25 Hz, 1H), 3.25 (t, *J* 7.03 Hz, 1H), 2.39–2.10 (m, 2H), 1.81–1.34 (m, 12H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.4, 129.8, 129.8, 117.5, 72.1, 70.4, 69.2, 41.0, 39.5, 36.7, 35.2, 27.6, 25.2, 23.9 and 23.9; IR (neat) *v*: 3020, 2900, 1850, 1275, 1250, 751 cm^{-1}; ESI-MS; 465 $[M+1]^+$; Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68; Si, 6.04. Found: C, 74.88; H, 8.61; Si, 5.95.

4.1.15. (2*S*,4*S*)-4-{[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}-6-hepten-1,2-ol 13. To a stirred solution of **14** (1.0 g, 2.1 mmol) in MeOH (10 mL), PTSA (0.02 g) was added at 0 °C and stirred for 4 h at room temperature. The reaction mixture was quenched with satd aq $NaHCO_3$ solution (2 mL), extracted with EtOAc (2 × 15 mL), the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 2:3) to afford **13** (0.7 g, 85%) as a colorless syrup. $[\alpha]_D^{25} = +94.8$ (*c* 0.45, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.77–7.65 (m, 4H), 7.49–7.34 (m, 6H), 5.67–5.45 (m, 1H), 4.94–4.76 (m, 2H), 3.97 (q, *J* 12.75, 6.71 Hz, 1H), 3.87–3.73 (m, 1H), 3.44 (dd, *J* 3.35 Hz, 1H), 3.27 (dd, *J* 6.04 Hz, 1H), 2.18–2.10 (m, 2H) 1.63–1.56 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 133.8, 129.9, 129.7, 127.7, 127.7, 127.6, 117.6, 72.6, 70.4, 66.8, 41.8, 38.9, 26.9 and 19.2; IR (neat) *v*: 3450, 3020, 2895, 1850, 1275, 1250, 750 cm^{-1}; ESI-MS; 402 $[M+NH_4]^+$; Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39; Si, 7.30. Found: C, 71.80; H, 8.34; Si, 7.22.

4.1.16. (2*S*,4*S*)-4-{[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}-2-hydroxy-6-heptenyl-4-methyl-1-benzenesulfonate 13a. To a stirred solution of diol **13** (0.2 g, 0.52 mmol) in CH_2Cl_2 (4 mL), Et_3N (0.22 mL, 1.5 mmol) was added at 0 °C and stirred for 1 h. Then, tosyl chloride (0.11 g, 0.57 mmol) was added and stirred for further 5 h at room temperature. Later, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford **13a** (0.24 g, 87%) as a light yellow liquid. $[\alpha]_D^{25} = +56.5$ (*c* 0.15, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, *J* 8.3 Hz, 2H), 7.67–7.65 (m, 4H), 7.47–7.32 (m, 8H), 5.66–5.51 (m, 1H), 4.99–4.81 (m, 2H), 4.01–3.86 (m, 3H), 3.74 (dd, *J* 6.04 Hz, 1H), 2.48 (s, 3H), 2.25–2.10 (m, 2H), 1.62–1.56 (m, 2H), 1.06 (s, 9H); IR (neat) *v*: 2941, 1709, 1661, 1241 cm^{-1}; ESI-MS; 561 $[M+Na]^+$; Anal. Calcd for $C_{30}H_{38}O_5SSi$: C, 66.88; H, 7.11; S, 5.95; Si, 5.21. Found: C, 66.81; H, 7.02; S, 5.90; Si, 5.10.

4.1.17. (2*R*,4*S*)-4-{[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}-6-hepten-2-ol 3a. To a stirred solution of lithium aluminum hydride (0.01 g, 0.26 mmol) in dry THF (1 mL), compound **14** dissolved in dry THF (1 mL) was added at 0 °C, the reaction mixture brought to reflux temperature and stirred for 1 h, quenched with satd aq Na_2SO_4 solution filtered through a pad of Celite, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford **3a** (0.09 g, 73%) as a light yellow syrup. $[\alpha]_D^{25} = -3.3$ (*c* 2.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$):

δ 7.74–7.65 (m, 4H), 7.46–7.32 (m, 6H), 5.87–5.71 (m, 1H), 5.12–5.05 (m, 2H), 4.11 (q, *J* 6.04 Hz, 1H), 3.90–3.79 (m, 1H), 2.17 (t, *J* 6.04 Hz, 2H), 1.80–1.51 (m, 2H), 1.07 (s, 9H), 1.02 (d, *J* 6.04 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 134.8, 129.7, 127.7, 127.4, 117.5, 70.0, 69.6, 45.5, 41.9, 26.9, 26.5 and 23.9; IR (neat) *v*: 3445, 3010, 2895, 1860, 1268, 1251, 695 cm^{-1}; ESI-MS; 391 [M+Na]$^+$; Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75; Si, 7.62. Found: C, 74.90; H, 8.66; Si, 7.59.

4.1.18. (1*R*,3*S*)-3-[1-(*tert*-Butyl)]-1,1-diphenylsilyl]oxy-1-methyl-5-hexenyl-4-(benzyloxy)-6-heptenoate 4a. To a stirred solution of acid **8** (0.6 g, 2.7 mmol) in dry THF (6 mL), Et_3N (1.14 mL, 8.2 mmol) was added at room temperature and stirred for 1 h. Then, 2,4,6-trichlorobenzoyl chloride (0.85 mL, 5.4 mmol) was added and the reaction mixture was further stirred for 2 h at room temperature. The solvent was evaporated, residue diluted with toluene (6 mL), treated with DMAP (0.84 g, 6.8 mmol) and alcohol **3a** (0.92 g, 2.7 mmol). After 6 h, the toluene was evaporated in vacuo and the crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:24) to afford bis-olefin **4a** (0.96 g, 69%) as a colorless liquid. $[\alpha]_D^{25} = +36.5$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69–7.57 (m, 4H), 7.35–7.21 (m, 11H), 5.88–5.50 (m, 2H), 5.09–4.89 (m, 5H), 4.46 (q, 2H, *J* 11.72 Hz), 3.88–3.70 (m, 1H), 3.51–3.33 (m, 1H), 2.32–2.08 (m, 6H), 1.88–1.48 (m, 4H), 1.14–0.96 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 138.9, 136.0, 135.5, 134.3, 133.5, 129.4, 128.3, 127.6, 127.5, 118.0, 117.4, 77.5, 71.1, 70.3, 66.7, 43.1, 38.9, 38.1, 30.1, 28.9, 27.0, 23.0 and 19.0; IR (neat) *v*: 2927, 2896, 1720, 1095, 1060 cm^{-1}; ESI-MS; 607 [M+Na]$^+$; Anal. Calcd for $C_{37}H_{48}O_4Si$: C, 75.98; H, 8.27; Si, 4.80. Found: C, 75.91; H, 8.19; Si, 4.71.

4.1.19. (10*S*,12*R*)-5-[1-(Benzyloxy)]-10-[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy-12-methyl-1-oxa-7-cyclododecen-2-one 5a. A solution of bis-olefin **4a** (0.1 g, 0.18 mmol) and Grubbs' second generation catalyst (0.02 g, 10 mol %) in CH_2Cl_2 (15 mL) was stirred at reflux temperature for 12 h. Later, the solvent was removed under reduced pressure and the crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:49) to afford cyclized product **5a** (0.06 g, 70%) as a light yellow liquid. $[\alpha]_D^{25} = +45.9$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66–7.60 (m, 4H), 7.42–7.21 (m, 11H), 5.56–5.24 (m, 2H), 5.03–4.84 (m, 1H), 4.57–4.45 (m, 2H), 3.84 (q, 1H, *J* 6.25 Hz), 3.65–3.47 (m, 1H), 2.50–2.16 (m, 2H), 2.09–1.48 (m, 4H), 1.39–1.25 (m, 4H), 1,12 (d, 3, *J* 6.25H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 142.0, 140.5, 135.3, 135.6, 134.1, 131.5, 130.1, 127.6, 127.4, 70.6, 69.3, 68.2, 66.9, 42.2, 30.9, 30.5, 26.5, 26.3, 22.6 and 19.0; IR (neat) *v*: 2925, 2895, 1719, 1090, 1050 cm^{-1}; ESI-MS; 579 [M+Na]$^+$; Anal. Calcd for $C_{35}H_{44}O_4Si$: C, 75.50; H, 7.96; Si, 5.04. Found: C, 75.39; H, 7.89; Si, 4.90.

4.1.20. (10*S*,12*R*)-10-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-5-hydroxy-12-methyl-1-oxacyclododecan-2-one 6a. To a stirred solution of **5a** (0.15 g, 0.29 mmol) in MeOH (2 mL), 10% Pd/C (catalytic) was added under hydrogen atmosphere and stirred for 6 h. Later, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The crude residue thus obtained was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford cyclic alcohol **6a** (0.1 g, 85%) as a colorless syrup. $[\alpha]_D^{25} = +37.2$ (*c* 0.15, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69–7.49 (m, 4H), 7.41–7.19 (m, 6H), 5.19–5.11 (m, 1H), 4.13–3.98 (m, 1H), 3.81–3.70 (m, 1H), 2.50–2.28 (m, 2H), 1.75–1.31 (m, 12H), 1.12–1.05 (m, 12H); IR (neat) *v*: 3480, 2925, 1720, 1475, 1250 cm^{-1}; ESI-MS; 469 [M+1]$^+$; Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60; Si, 5.99. Found: C, 71.71; H, 8.55; Si, 5.91.

4.1.21. (10*S*,12*R*)-10-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-12-methyl-1-oxacyclododecane-2,5-dione 7a. To a stirred solution of alcohol **6a** (0.09 g, 0.18 mmol) in CH_2Cl_2 (2 mL), DMP (0.13 g, 0.31 mmol) was added and stirred for 2 h at room temperature. Then, the reaction was quenched with aq solution of $NaHCO_3$:hypo (1:1, 1 mL), extracted with CH_2Cl_2 (2 mL), and the organic layer was washed with brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue so obtained was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) to afford ketone **7a** (0.08 g, 92%) as a colorless syrup. $[\alpha]_D^{25} = -12.9$ (*c* 0.36, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62–7.45 (m, 4H), 7.40–7.22 (m, 6H), 5.28–5.11 (m, 1H), 3.95–3.81 (m, 1H), 2.80–2.42 (m, 4H), 2.32–2.05 (m, 2H), 1.92–1.55 (m, 4H), 1.50–1.13 (m, 4H), 1.06–0.98 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.0, 171.1, 135.8, 129.6, 127.5, 70.7, 70.6, 42.8, 41.3, 37.7, 35.5, 29.6, 26.7, 22.1, 21.8, 20.9, 19.9; IR (neat) *v*: 2928, 1729, 1670, 1252 cm^{-1}; ESI-MS; 489 [M+Na]$^+$; Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21; Si, 6.02. Found: C, 72.01; H, 8.18; Si, 5.99.

4.1.22. (10*S*,12*R*)-10-Hydroxy-12-methyl-1-oxacyclododecane-2,5-dione 2. To a stirred solution of **7a** (0.06 g, 0.14 mmol) in dry THF (2 mL), HF·py (0.4 mL, 0.41 mmol) was added and stirred for 4 h at room temperature. The reaction mixture was quenched with $CuSO_4$ solution, extracted with EtOAc (2 mL), and the organic layer was washed with brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 3:7) to afford **2** (0.02 g, 85%) as a colorless oil. $[\alpha]_D^{25} = -52.2$ (*c* 0.25, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (sext, *J* 13.18, 5.86 Hz, 1H), 3.79 (p, *J* 10.25, 5.12 Hz, 1H), 3.00–2.66 (m, 3H), 2.60–2.15 (m, 5H), 1.89–1.35 (m, 6H), 1.25 (d, *J* 6.42 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.1, 171.1, 68.5, 67.5, 41.3, 40.4, 37.7, 34.3, 30.1, 23.4, 23.2, 20.0; IR (neat): 3431, 2931, 1716, 1665, 1460, 1255 cm^{-1}; ESI-MS; 251 [M+Na]$^+$; Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.10; H, 8.79.

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