Stereoselective Total Synthesis of Iso-Cladospolide B and the 12 Membered-Macrolactone (6*S*,12*R*)-6-Hydroxy-12-methyloxacyclododecane-2,5-dione

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Total syntheses of iso-cladospolide B (**1**) and the 12-membered macrolactone (6*S*,12*R*)-6-hydroxy-12-methyloxacyclododecane-2,5-dione (**2**), a non-natural product, were achieved from a common intermediate starting from commercially available 1,9-nonane diol.

Introduction. – Natural products from marine-derived fungi or soil-derived fungi are the source of many drugs showing diverse biological and pharmacological properties [1]. Cladospolides A–D [2–4] structurally resemble marine-derived hexaketide macrolactones, but differ in the position of OH functional groups. They are isolated from *Cladosporium sp.* and exhibit plant growth retardant activity towards rice seedlings. Amongst all, Cladospolide D [5] isolated from *Cladosporium sp.* FT-0012 shows antimicrobial activity against *Mucor racemosus* and *Pyricularia oryzae* with IC_{50} values of 0.15 and 29 μg ml^{-1}. A γ-butenolide skeleton containing iso-cladospolide B (*Fig.*) was isolated along with cladospolide B by *Ireland* and co-workers from marine fungi isolate I96S215 [6]. Another polyketide metabolite (6*R*,12*S*)-6-hydroxy-12-methyloxacyclododecane-2,5-dione, a 12-membered macrolactone, which structurally resembles cladospolides was isolated from the endophytic fungal strain *Cladosporium tenuissimum* LR463 of *Maytenus hookeri* [7]. Based on the significant activity of this class of molecules, several syntheses were reported for iso-cladospolide B ((4*S*,5*S*,11*S*) as well as (4*S*,5*S*,11*R*)) [8]. All these diastereomers are commonly referred to as iso-cladospolides due to the smaller ring-size compared to the ring-size of the parent compound cladospolide. Some inconsistencies in the optical rotational values are noted in the literature, *e.g.*, *Prasad et al.* [8g][8j] have synthesized both the (4*S*,5*S*,11*S*)-isomer and its enantiomer and hence they share opposite sign of optical rotation with

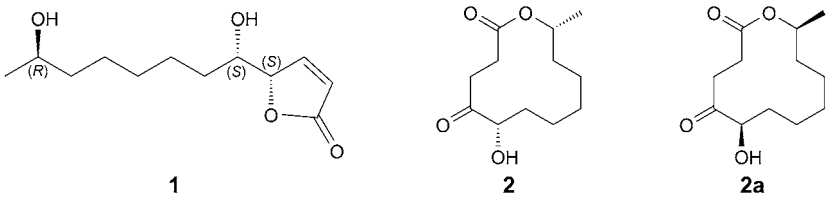


Figure. *Structures of natural products and a non-natural product*

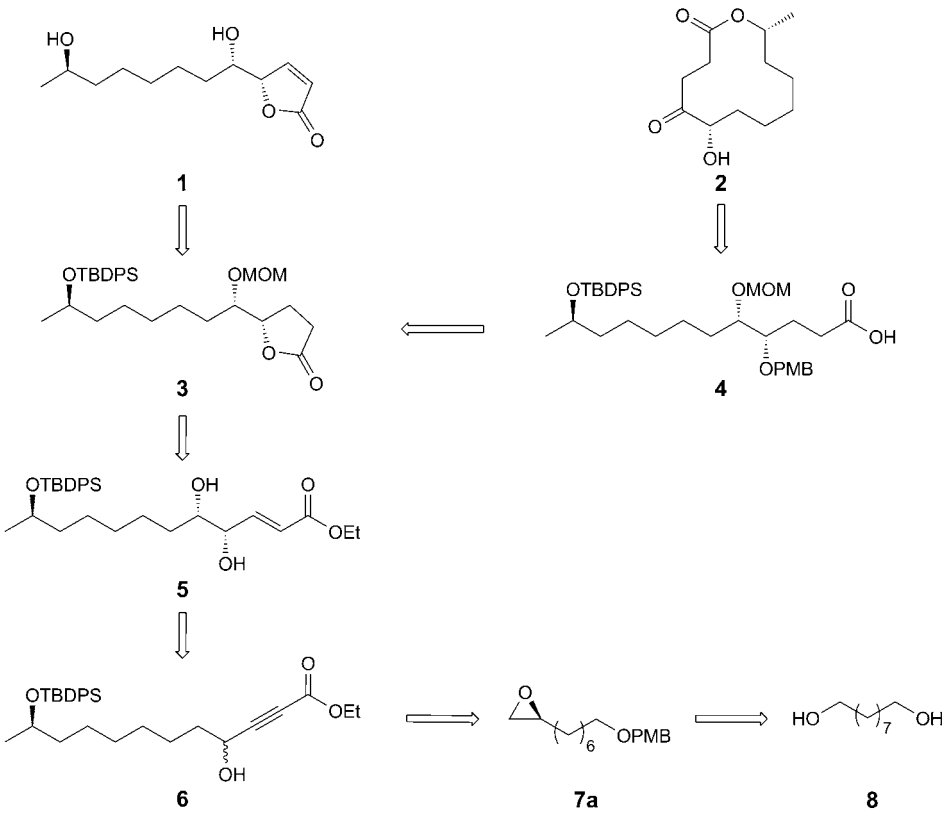
almost same numerical values. However, others [8a][8f] report low negative values for the (4*S*,5*S*,11*R*)-isomer maybe due to the low optical purity. More recently, *González et al.* [8l] described the synthesis of both the diastereoisomers ((4*S*,5*S*,11*S*) and its 11-epimer), assigned their configurations and recorded their individual optical rotation values.

As part of our interest in the synthesis of lactone-containing molecules [9], we have recently accomplished the first stereoselective total synthesis of (6*R*,12*S*)-6-hydroxy-12-methyl-1-oxacyclododecane-2,5-dione (**2a**) [10]. Herein, we report the total synthesis of iso-cladospolide B (**1**) with (4*S*,5*S*,11*R*) configuration and of a non-natural product and enantiomer of (6*R*,12*S*)-6-hydroxy-12-methyl-1-oxacyclododecane-2,5-dione (**2a**), *i.e.*, (6*S*,12*R*)-6-hydroxy-12-methyloxacyclododecane-2,5-dione (**2**) [11]. The strategy for the synthesis of **1** described herein is general, using commercially available inexpensive starting materials. Compound **2** was synthesized from a common intermediate thus emphasizing the multiple usefulness of the intermediates.

Results and Discussion. – Retrosynthetic analysis of both iso-cladospolide B (**1**) and the 12-membered macrolide **2** were encompassed in *Scheme 1*. Accordingly, compounds **1** and **2** could be prepared from γ-butyrolactone **3**, identified as the common intermediate, through their respective chemical conversions. γ-Butyrolactone **3** in turn could be synthesized from diol **5** by the saturation of the C=C bond, spontaneous cyclization to form a hydroxylactone followed by the protection of the ensuing OH group as its MOM-ether. Diol **5** could be derived from **6** by the conversion of the alkynol into a conjugated diene and subsequent regioselective *Sharpless* asymmetric dihydroxylation of the distal C=C bond. Compound **6** could be derived from optically pure **7a** by its ring-opening reaction, followed by the protection of the ensuing OH group as TBDPS ether, deprotection of the PMB ether oxidation of the primary alcohol into the aldehyde, followed by ethyl propynoate anion addition. Epoxide **7a** could be derived from commercially available inexpensive starting material nonane-1,9-diol (**8**) by adopting standard functional group conversions such as: selective mono protection of one of its OH groups as PMB ether, conversion of the other into an olefinic functionality by an oxidation/*Wittig* reaction-set, followed by *m*-CPBA oxidation and resolution of the thus obtained racemic epoxide under *Jacobsen*'s (Hydrolytic kinetic resolution) conditions.

Firstly, synthesis of **1** was initiated from nonane-1,9-diol (**8**; *Scheme 2*). Thus, selective monoprotection of diol **8** (PMBBr, NaH, THF, 0°) gave the known compound **9** [12] (76%). The latter was converted into its iodide (TPP, I_2, imidazole, THF, 0°) and subsequently into a terminal C=C bond (*t*-BuOK, THF, 0° – r.t.) through an elimination reaction to afford **10** (89%). Epoxide **7** (84%) was formed from **10** (*m*-CPBA, $CHCl_3$, 0° – r.t.) followed by *Jacobsen*'s hydrolic kinetic resolution [13] ((*S*,*S*)-Salen-Co(OAc) catalyst, AcOH, toluene) to furnish optically pure **7a** (44%). Ring-opening reaction of oxirane **7a** with $LiAlH_4$ (THF, 0° – r.t.) afforded **11** (80%). Silyl protection of **11** under conventional conditions ((*tert*-butyl)diphenylsilyl chloride (TBDPSCl), imidazole, CH_2Cl_2) gave **12** (88%). Deprotection of the PMB-ether group in **12** with DDQ (DDQ, CH_2Cl_2/H_2O 19:1, 0°) furnished **13** (82%). Oxidation of alcohol **13** to the corresponding aldehyde under *Swern* conditions followed by its quenching with Li-

Scheme 1. *Retrosynthetic Analysis of Compounds* **1** *and* **2**

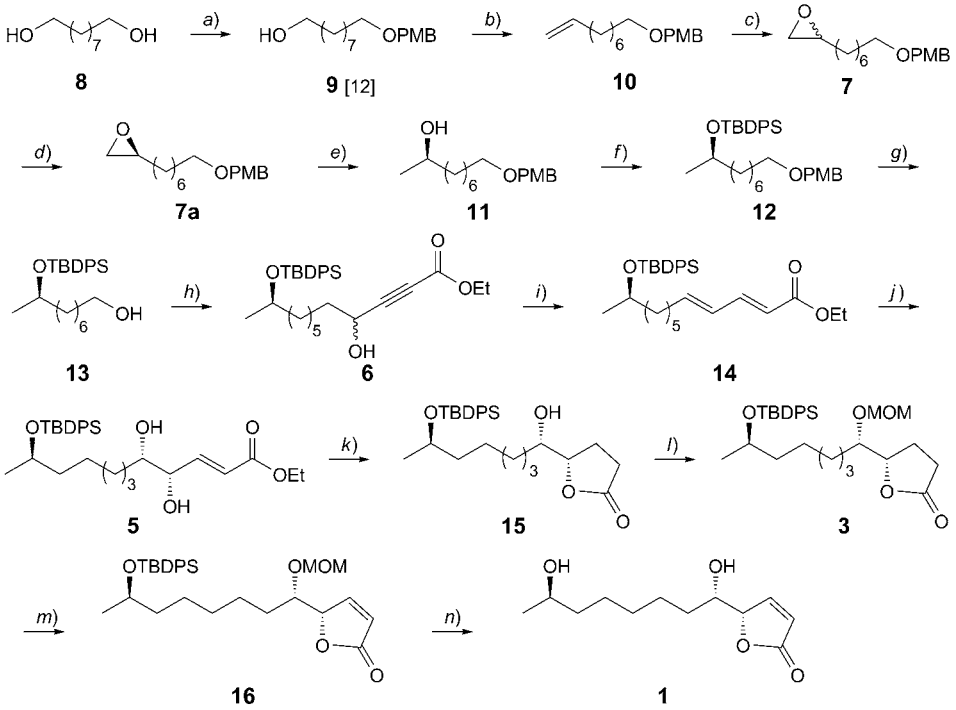


ethyl propynoate (LiHMDS, THF, $-78°$) gave alkynol **6** (57% over two steps). Next, alkynol **6** was transformed into the conjugated diene ester **14** (78%) under phosphine conditions (Ph_3P, benzene, 85°). Regioselective *Sharpless* asymmetric dihydroxylation [14] of the distal olefin in **14** (AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O 1 : 1, 0°) furnished **5** (82%).

Further, saturation of the second olefinic functionality in **5** (Pd/C, H_2, r.t.) and concomitant cyclization in one-pot led to γ-butyrolactone **15** (84%). MOM-ether protection of **15** (MOMCl, DIPEA, DMAP, CH_2Cl_2, 0° – r.t.) gave **3** (83%), which was converted to butenolide **16** by using an addition-elimination protocol (PhSeBr, LDA, THF; H_2O_2, CH_2Cl_2; 54%) [15]. Deprotection of both silyl and MOM ether groups of **16** ($TiCl_4$, CH_2Cl_2, 0° – r.t.) afforded **1** (68%). The physical and spectroscopic data of **1** matched with the reported iso-cladospolide B [6].

Next, γ-butyrolactone **3** was converted to the 12-membered macrolide **2**, a non-natural product target. As outlined in *Scheme 3*, **3** was transformed into 1,4-diol **17** ($LiBH_4$, MeOH, THF, 0° – r.t.; 85%). Selective mono-silyl protection of the primary alcohol (TBDMSCl, imidazole, CH_2Cl_2, 0° – r.t.) gave compound **18** (90%), followed

Scheme 2. *Synthesis of Iso-Cladospolide B* (**1**)

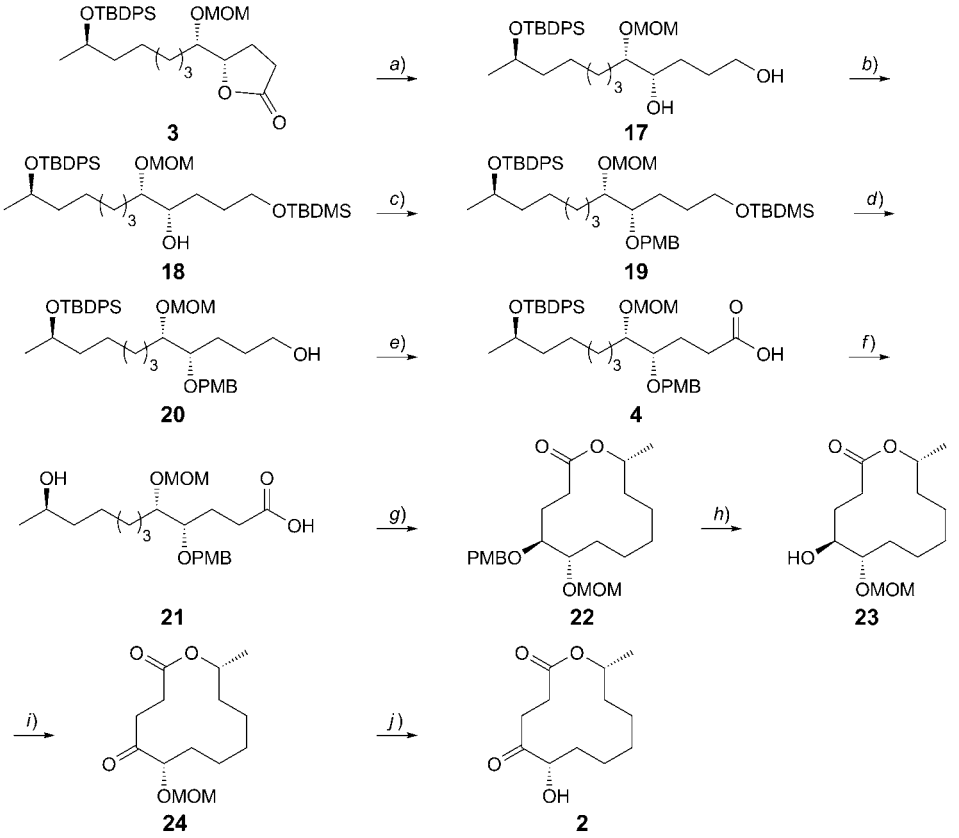


a) NaH, PMBBr, THF, 0° – r.t., 4 h; 76%. *b*) 1. TPP, I_2, imidazole, THF, 0°, 10 min; 2. *t*-BuOK, THF, 0° – r.t.; 89%. *c*) *m*-CPBA, $CHCl_3$, 0° – r.t., 3 h; 84%. *d*) (*S*,*S*)-*Jacobsen*'s catalyst, AcOH, toluene, 0° – r.t., 16 h; 44%; *e*) $LiAlH_4$, THF, 0° – r.t., 30 min; 80%. *f*) TBDPSCl, imidazole, CH_2Cl_2, 0° – r.t., 4 h; 88%. *g*) DDQ, CH_2Cl_2/H_2O 19 : 1, 0°, 20 min; 82%. *h*) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 1 h, – 78°; 81%; 2. LiHMDS, ethyl propynoate, THF, – 78°, 30 min, 72%. *i*) Ph_3P, benzene, reflux, 2 h; 78%. *j*) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O 1 : 1; 82%. *k*) Pd/C, H_2, AcOEt, 12 h; 84%. *l*) MOMCl, DIPEA, CH_2Cl_2, DMAP, 0° – r.t., 4 h; 83%. *m*) 1. PhSeBr, LDA, THF, 0° – r.t., 30 min; 2. H_2O_2, CH_2Cl_2, 2 h; 54%. *n*) $TiCl_4$, 0° – r.t., 2 h; 68%.

by PMB ether protection (PMBBr, NaH, THF, 0° – r.t.) of the secondary alcohol to give **19** (82%). Selective deprotection of the TBDMS ether (PPTS, MeOH, r.t.) in **19** afforded **20** (79%), which on subsequent oxidation (TEMPO, BAIB, H_2O/CH_2Cl_2 1 : 1, 0° – r.t.) gave acid **4** (85%). Deprotection of the TBDPS ether group (HF–Py, THF, 0° – r.t.) yielded *seco*-acid **21** (88%). Macrolactonization of **21** under *Yamaguchi* conditions [16] (Et_3N, trichlorobenzoyl chloride, THF, 0° – r.t., DMAP, toluene, 90°) gave **22** (79%), followed by PMB ether deprotection under conventional conditions (DDQ, CH_2Cl_2/H_2O 19 : 1, 0°) to yield alcohol **23** (82%).

The latter was then oxidized (*Dess–Martin* periodinane, CH_2Cl_2, 0°) [17] to furnish **24** (89%) and further deprotection of the MOM-group in **24** (TFA, CH_2Cl_2, 0° – r.t.) afforded compound **2** (72%) as colorless needles with m.p. 119 – 121° and $[\alpha]_D^{25} = -40.0$ ($c = 0.2$, MeOH).

Scheme 3. *Synthesis of the 12-Membered Macrolactone* **2**



a) $LiBH_4$, MeOH, THF, 0° – r.t., 30 min; 85%. *b*) TBDMSCl, imidazole, CH_2Cl_2, 0° – r.t., 2 h; 90%. *c*) PMBBr, NaH, THF, 0° – r.t., 4 h; 82%. *d*) PPTS, MeOH, r.t., 3 h; 79%. *e*) TEMPO, BAIB, H_2O/CH_2Cl_2 1:1, 0° – r.t., 4 h; 85%. *f*) HF–Py, THF, 0° – r.t., 2 h; 88%. *g*) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 8 h, 0° – r.t., DMAP, toluene, 90°, 20 h; 79%. *h*) DDQ, CH_2Cl_2/H_2O 19:1, 20 min; 82%. *i*) *Dess–Martin* periodinane (DMP), CH_2Cl_2, 0° – r.t., 1 h; 89%. *j*) TFA, CH_2Cl_2, 0° – r.t., 2 h; 72%.

Conclusions. – In summary, we have accomplished the stereoselective total synthesis of the iso-cladospolide B (**1**; overall yield 1.50%) and a hitherto unreported 12-membered non-natural macrolide **2** (overall yield 0.63%), wherein *Jacobsen*'s hydrolytic kinetic resolution, *Sharpless* asymmetric dihydroxylation, and *Yamaguchi* macrolactonization reactions were successfully employed for the synthesis of both the target molecules from a common intermediate.

Experimental Part

General. Org. solns. were dried (anh. Na_2SO_4) and concentrated below 40° *in vacuo*. Air sensitive reagents were transferred by double-ended needle. TLC: *Merck 60* F_{254} silica-gel plates. Column

chromatography (CC): silica gel (SiO_2, 60–120, 100–200 mesh; *Acme's*). Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogenous material. Optical rotations: *JASCO P-1020* instrument and $[\alpha]_D$ values were in units of 10^{-1} deg cm^2 g^{-1} at 25°. IR Spectra: *PerkinElmer IR-683* spectrophotometer with NaCl optics. ^{1}H-NMR Spectra: *Varian Gemini 200*, *Bruker Avance-300*, *Unity 400*, and *Inova 500* instruments; in $CDCl_3$ (7–10 mM soln.); δ in ppm rel. to Me_4Si as internal standard, J in Hz. ^{13}C-NMR Spectra (50 MHz and 75 MHz): *Varian Gemini FT-200* and *Bruker Avance 300* spectrometer in $CDCl_3$ (7–10 mM soln.); δ in ppm rel. to Me_4Si as internal standard. MS: *Finnigan Mat 1210* double focusing mass spectrometer operating at a direct inlet system and ESI-MS was measured using ion-trap mass spectrometer; in m/z. The software ACD/Name Version 1.0, developed by *M/s Advanced Chemistry Development Inc.*, Toronto, Canada, assisted nomenclature used in the experimental section.

1-Methoxy-4-[(non-8-en-1-yloxy)methyl]benzene (**10**). To the stirred soln. of primary alcohol **9** [12] (11.0 g, 39.29 mmol), in THF (110 ml), TPP (30.8 g, 117.82 mmol), imidazole (3.94 g, 58.93 mmol), and I_2 (29.8 g, 117.82 mmol) were added, and the mixture was allowed to stir for 10 min. After completion of the reaction, the mixture was diluted with AcOEt (80 ml), the org. layer was washed with H_2O (80 ml) followed by brine (80 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo* to give the corresponding iodo compound, a brown colored sticky oil, which was used for the next reaction.

To a stirred soln. of *t*-BuOK (5.28 g, 47.15 mmol) in dry THF (50 ml), the iodo compound (50 ml) was added, and the mixture stirred for 2 h. The reaction was quenched with aq. sat. NH_4Cl (60 ml) before warming to r.t. Then, the mixture was diluted with H_2O (50 ml) and extracted with AcOEt (2×50 ml). The combined org. layers were washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by CC (6% AcOEt in hexane) leading to **10** (9.18 g, 89% yield) as a colorless oil. IR (neat): 3052, 3016, 1632, 1543, 1080. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.19 (*d*, J = 9.1, 2 H); 6.81 (*d*, J = 8.3, 2 H); 5.83–5.67 (*m*, 1 H); 5.00–4.86 (*m*, 2 H); 4.38 (*s*, 2 H); 3.78 (*s*, 3 H); 3.38 (*t*, J = 6.7, 2 H); 2.02 (*q*, J = 6.7, 2 H); 1.63–1.50 (*m*, 2 H); 1.43–1.23 (*m*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 139.1; 130.7; 129.2; 114.1; 113.6; 72.4; 70.1; 55.2; 33.7; 29.7; 29.3; 29.0; 28.8; 26.1. ESI-MS: 285 ($[M+Na]^+$). HR-MS: 285.1838 ($[M+Na]^+$, $C_{17}H_{26}NaO_2^+$; calc. 285.1830).

(2S)-2-{7-[(4-Methoxybenzyl)oxy]heptyl}oxirane (**7a**). To a stirred soln. of **10** (9.13 g, 34.8 mmol) in $CHCl_3$ (60 ml) at 0°, *m*-CPBA (11.9 g, 69.6 mmol, 50% dispersion in H_2O) was added, the aq. layer was separated, dried (Na_2SO_4), anhydr. *m*-CPBA was added, and the mixture stirred for 3 h. The mixture was filtered, the filtrate washed with sat. $NaHCO_3$ (3×40 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by CC (12% AcOEt in hexane) to obtain **7** (8.14 g, 84%) as a colorless liquid, which was used as such in next step.

A mixture of (+)-(*S*,*S*)-*N*,*N*′-bis(3,5-di-(*tert*-butyl)salicylidene)-1,2-cyclohexanediaminocobalt(II) (0.095 g, 0.15 mmol) in toluene (0.5 ml) and AcOH (0.017 g, 0.29 mmol) was stirred while open to the air for 1 h at r.t. The mixture was concentrated under reduced pressure, and the brown residue ((*S*,*S*)-*N*,*N*'-bis(3,5-di-(*tert*-butyl)salicylidene)-1,2-cyclohexanediamino-Co^{III}-acetate, [Co^{III}(salen)(AcO)] complex) was dried under vacuum. The racemic epoxide **7** (8.14 g, 29.3 mmol) was added in one portion at 0°, and H_2O (0.289 ml, 0.016 mmol) was added dropwise over 5 min. The mixture was allowed to warm to r.t. and stirred for 16 h. The residue purified by CC (10% AcOEt in hexane) gave the terminal epoxide **7a** (3.90 g, 44% yield) as a colorless oil. $[\alpha]_D^{25} = -68.7$ (c = 0.2, $CHCl_3$). IR (neat): 3029, 2996, 1563, 1234, 1096. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.19 (*d*, J = 8.4, 2 H); 6.81 (*d*, J = 8.4, 2 H); 4.38 (*s*, 2 H); 3.78 (*s*, 3 H); 3.38 (*t*, J = 6.4, 2 H); 2.85–2.79 (*m*, 1 H); 2.67 (*t*, J = 3.9, 1 H); 2.41–2.36 (*m*, 1 H); 1.60–1.21 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 130.5; 129.0; 113.5; 72.3; 69.9; 55.0; 52.2; 46.9; 32.3; 29.5; 29.2; 28.1; 25.9; 25.7. ESI-MS: 301 ($[M+Na]^+$). HR-MS: 301.1783 ($[M+Na]^+$, $C_{17}H_{26}NaO_3^+$; calc. 301.1779).

(2R)-9-[(4-Methoxybenzyl)oxy]nonan-2-ol (**11**). $LiAlH_4$ (0.707 g, 20.8 mmol) was taken in a round bottomed flask and THF (10 ml) was added very slowly at 0°. To it, compound **7a** (3.86 g, 13.9 mmol) dissolved in THF (30 ml) was added at the same temp. and allowed to stir for 30 min. The reaction was quenched with sat. Na_2SO_4 and filtered through *Celite*, washed with AcOEt (40 ml). The solvent was removed under reduced pressure and purified by CC (12% AcOEt in hexane) to afford **11** (3.11 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = -101.6$ (c = 0.1, $CHCl_3$). IR (neat): 3519, 3024, 1537, 1123. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.22 (*d*, J = 8.6, 2 H); 6.84 (*d*, J = 8.6, 2 H); 4.40 (*s*, 2 H); 3.79 (*s*, 3 H); 3.78–3.72 (*m*, 1 H); 3.40 (*t*, J = 6.2, 2 H); 1.63–1.52 (*m*, 2 H); 1.50–1.23 (*m*, 10 H); 1.17 (*d*, J = 6.2, 3 H). ^{13}C-NMR

(75 MHz, $CDCl_3$): 159.0; 130.7; 129.2; 113.7; 72.4; 70.1; 68.1; 55.2; 39.2; 29.6; 29.5; 29.3; 26.1; 25.6; 23.4. ESI-MS: 303 ($[M+Na]^+$). HR-MS: 303.1936 ($[M+Na]^+$, $C_{17}H_{28}NaO_3^+$; calc. 303.1936).

tert-*Butyl({(2*R*)-9-[(4-methoxybenzyl)oxy]nonan-2-yl}oxy)diphenylsilane* (**12**). To a stirred soln. of alcohol **11** (3.07 g, 10.9 mmol) in CH_2Cl_2 (20 ml), imidazole (2.20 g, 32.9 mmol) was added at 0° and stirred for 0.5 h. Then TBDPSCl (3.39 ml, 13.08 mmol) was added, and the mixture was stirred for additional 12 h at r.t.. The mixture was diluted with CH_2Cl_2 (20 ml), the org. layer was washed with H_2O (20 ml) followed by brine (20 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo* and purified by CC (5% AcOEt in hexane) to afford **12** (5.00 g, 88%) as a colorless liquid. $[\alpha]_D^{25} = -199.4$ ($c = 0.2$, $CHCl_3$). IR (neat): 3058, 3024, 1537, 1584, 1118, 1088. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.69–7.58 (*m*, 4 H); 7.41–7.27 (*m*, 6 H); 7.20 (*d*, $J = 8.3$, 2 H); 6.81 (*d*, $J = 8.3$, 2 H); 4.39 (*s*, 2 H); 3.78 (*s*, 3 H); 3.67–3.55 (*m*, 1 H); 3.37 (*t*, $J = 6.4$, 2 H); 1.60–1.45 (*m*, 2 H); 1.40–1.12 (*m*, 13 H); 1.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 135.8; 135.5; 129.6; 129.3; 127.4; 113.7; 72.5; 70.2; 69.6; 55.3; 39.4; 29.7; 29.6; 29.4; 27.1; 26.1; 25.1; 23.2; 19.2. ESI-MS: 541 ($[M+Na]^+$). HR-MS: 541.1876 ($[M+Na]^+$, $C_{33}H_{46}NaO_3Si^+$; calc. 541.1885).

*(8*R*)-8-{[*tert-*Butyl(diphenyl)silyl]oxy}nonan-1-ol* (**13**). To a soln. of PMB ether **12** (4.96 g, 9.58 mmol) in a mixture of CH_2Cl_2 and H_2O (45 ml, 19:1), DDQ (6.52 g, 28.7 mmol) was added at 0°, and the mixture was stirred for 20 min at r.t. The reaction was quenched with sat. $NaHCO_3$ soln. (25 ml), extracted with CH_2Cl_2 (3×25 ml), washed with H_2O (25 ml) and brine (25 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (15% AcOEt in hexane) to afford **13** (3.13 g, 82%) as a colorless liquid. $[\alpha]_D^{25} = -43.6$ ($c = 0.1$, $CHCl_3$). IR (neat): 3574, 3054, 1543, 1146. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67–7.60 (*m*, 4 H); 7.41–7.29 (*m*, 6 H); 3.83–3.76 (*m*, 1 H); 3.58 (*t*, $J = 6.9$, 2 H);1.54–1.41 (*m*, 2 H); 1.38–1.09 (*m*, 13 H); 1.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.9; 129.4; 127.4; 69.6; 63.0; 39.4; 32.7; 29.7; 29.3; 27.0; 25.6; 25.1; 23.2; 19.3. ESI-MS: 421 ($[M+Na]^+$). HR-MS: 421.2531 ($[M+Na]^+$, $C_{25}H_{38}NaO_2Si^+$; calc. 421.2538).

*Ethyl (11*R*)-11-{[*tert-*Butyl(diphenyl)silyl]oxy}-4-hydroxydodec-2-ynoate* (**6**). To a stirred soln. of oxalyl chloride (1.36 ml, 15.6 mmol) in dry CH_2Cl_2 (20 ml), DMSO (2.20 ml, 31.16 mmol) was added at −78° and stirred for 30 min at same temp., followed by the addition of alcohol **13** (3.10 g, 7.79 mmol) in CH_2Cl_2 (25 ml), and the mixture was stirred for 1 h at −78°. The reaction was quenched with Et_3N (6.5 ml, 46.74 mmol) added at −78°, and stirred for further 15 min. The mixture was extracted with CH_2Cl_2 (2×20 ml), washed with H_2O (20 ml) and brine (20 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo* to give an aldehyde (2.50 g, 81%) as a pale yellow syrup, which was used for the next reaction.

To a stirred soln. of ethylpropiolate (0.680 g, 6.94 mmol) in THF (10 ml) at −78°, LiHMDS (1.0M in hexanes, 9.5 ml, 9.46 mmol) was slowly added, and the whole mixture was stirred at −78° for 1 h. Then, the aldehyde (2.50 g, 6.31 mmol) in THF (15 ml) was added dropwise to the mixture at −78°, and stirring was continued for 30 min. The reaction was quenched with aq. sat. NH_4Cl (20 ml) before warming to r.t. The mixture was diluted with H_2O (15 ml) and extracted with Et_2O (2×20 ml). The combined org. layers were washed with brine (15 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue purified by CC (10% AcOEt in hexane) resulted in the alkynol **6** (2.25 g, 72%) as colorless oil. $[\alpha]_D^{25} = -102.1$ ($c = 0.2$, $CHCl_3$). IR (neat): 3247, 3027, 2140, 1674, 1543, 1138. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67–7.61 (*m*, 4 H); 7.41–7.30 (*m*, 6 H); 4.44–4.38 (*m*, 1 H); 4.22 (*q*, $J = 6.9$, 2 H); 3.81 (*sext.*, $J = 5.9$, 1 H); 1.75–1.64 (*m*, 2 H); 1.49–1.35 (*m*, 5 H); 1.32 (*t*, $J = 6.9$, 3 H); 1.28–1.10 (*m*, 8 H); 1.04 (*s*, 9 H). ESI-MS: 517 ($[M+Na]^+$). HR-MS: 517.2757 ($[M+Na]^+$, $C_{30}H_{42}NaO_4Si^+$; calc. 517.2750).

*Ethyl (2*E*,4*E*,11*R*)-11-{[*tert-*Butyl(diphenyl)silyl]oxy}dodeca-2,4-dienoate* (**14**). A mixture of alkynol **6** (2.21 g, 4.47 mmol) and PPh_3 (1.40 g, 5.36 mmol) in benzene (20 ml) was stirred under reflux for 2 h. The solvent was removed under reduced pressure and the crude product was purified by CC (5% AcOEt in hexane) to give the conjugated diene ester **14** (1.67 g, 78% yield). $[\alpha]_D^{25} = -127.0$ ($c = 0.3$, $CHCl_3$). IR (neat): 3047, 1734, 1672, 1638, 1531, 1121. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.68–7.59 (*m*, 4 H); 7.42–7.28 (*m*, 6 H); 7.22–7.13 (*m*, 1 H); 6.17–6.00 (*m*, 2 H); 5.73 (*d*, $J = 15.3$, 1 H); 4.18 (*q*, $J = 6.9$, 2 H); 3.86–3.73 (*m*, 1 H); 2.09 (*q*, $J = 6.7$, 2 H); 1.42–1.12 (*m*, 14 H); 1.04 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.3; 145.1; 144.7; 135.8; 129.4; 128.3; 127.4; 119.1; 69.4; 60.2; 39.2; 32.9; 29.7; 27.0; 26.2; 24.9; 23.2; 19.2; 14.3. ESI-MS: 501 ($[M+Na]^+$). HR-MS: 501.2796 ($[M+Na]^+$, $C_{30}H_{42}NaO_3Si^+$; calc. 501.2801).

*Ethyl (2*E*,4*S*,5*S*,11*R*)-11-{[*tert*-Butyl(diphenyl)silyl]oxy}-4,5-dihydroxydodec-2-enoate* (**5**). Into a 100 ml round bottom flask, 16 ml of *t*-BuOH, 16 ml of H_2O, AD-mix-α (4.77 g, 1.4 g/mmol) and $MeSO_2NH_2$ (0.327 g, 3.41 mmol) were added. The mixture was stirred at r.t. for 5 min, and cooled to 0°. To this cooled soln., compound **14** (1.63 g, 3.41 mmol) was added, and the mixture was stirred for 24 h at 0°. The reaction was quenched with sat. Na_2SO_4 at r.t. The mixture was diluted with AcOEt (30 ml), and after separation of the layers, the aq. layer was further extracted with AcOEt (2 × 30 ml). The combined org. layers were washed with brine (20 ml) and dried (Na_2SO_4). The crude mixture was purified by flash CC (25% AcOEt in hexane) to give **5** (1.44 g, 82% yield) as clear colorless oil. $[\alpha]_D^{25} = -248.7$ ($c = 0.5$, $CHCl_3$). IR (neat): 3587, 3521, 3022, 1547, 1092. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67–7.58 (*m*, 4 H); 7.43–7.29 (*m*, 6 H); 6.87 (*dd*, *J* = 15.4, 4.9, 1 H); 6.09 (*d*, *J* = 15.4, 1 H); 4.19 (*q*, *J* = 7.2, 2 H); 4.09–4.00 (*m*, 1 H); 3.85–3.74 (*m*, 1 H); 3.52–3.41 (*m*, 1 H); 2.22 (br. *s*, OH), 1.85 (br. *s*, OH), 1.53–1.11 (*m*, 16 H); 1.04 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.3; 150.3; 132.6; 128.3; 127.4; 119.1; 76.2; 75.2; 69.4; 60.2; 39.2; 33.2; 30.5; 27.3; 26.2; 24.7; 23.2; 19.2; 14.3. ESI-MS: 535([*M* + Na]$^+$). HR-MS: 535.2863 ([*M* + Na]$^+$, $C_{30}H_{44}NaO_5Si^+$; calc. 535.2856).

*(5*S*)-5-[(1*S*,7*R*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-hydroxyoctyl]dihydrofuran-2(3*H*)-one* (**15**). Pd/C (10 mg, 10% wet weight) was added to a soln. of compound **5** (1.40 g, 2.73 mmol) in AcOEt (10 ml). The mixture was stirred for 12 h under H_2. After the completion of the reaction, the mixture was filtered through *Celite* and washed with AcOEt (15 ml), the filtrate was concentrated *in vacuo* and, purified by CC (22% AcOEt in hexane) to provide the hydroxylactone **15** (1.08 g, 84%) as colorless oil. $[\alpha]_D^{25} = -133.3$ ($c = 0.3$, $CHCl_3$). IR (neat): 3510, 3014, 1754, 1514, 1132. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.67–7.58 (*m*, 4 H); 7.40–7.27 (*m*, 6 H); 4.34–4.27 (*m*, 1 H); 3.84–3.76 (*m*, 1 H); 3.56–3.41 (*m*, 1 H); 2.60–2.41 (*m*, 2 H); 2.22–1.98 (*m*, 2 H); 1.53–1.10 (*m*, 13 H); 1.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.1; 135.8; 129.4; 127.4; 82.8; 73.5; 69.4; 39.2; 32.8; 29.4; 28.6; 26.9; 25.3; 24.9; 24.0; 23.2; 19.2. ESI-MS: 491([*M* + Na]$^+$). HR-MS: 491.2599 ([*M* + Na]$^+$, $C_{28}H_{40}NaO_4Si^+$; calc. 491.2593).

*(5*S*)-5-[(5*S*,11*R*)-11,14,14-Trimethyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecan-5-yl]dihydrofuran-2(3*H*)-one* (**3**). To a stirred soln. of **15** (1.04 g, 2.22 mmol) in CH_2Cl_2 (8 ml), DIPEA (1.16 ml, 6.66 mmol), MOMCl (0.54 ml, 3.33 mmol), and DMAP (cat.), were added at 0° and stirred at r.t. for 6 h. The mixture was extracted with CH_2Cl_2 (2 × 15 ml), and the combined org. layers were washed with H_2O (12 ml), brine (12 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue purified by CC (16% AcOEt in hexane) to furnish **3** (0.95 g, 83%) as a colorless oil. $[\alpha]_D^{25} = -55.3$ ($c = 0.2$, $CHCl_3$). IR (neat): 3010, 1514, 1164. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.68–7.59 (*m*, 4 H); 7.42–7.28 (*m*, 6 H); 4.86–4.79 (*m*, 2 H); 4.53–4.43 (*m*, 1 H); 3.85–3.74 (*m*, 1 H); 3.56–3.47 (*m*, 1 H); 3.36 (*s*, 3 H); 2.60–2.37 (*m*, 2 H); 2.34–2.12 (*m*, 1 H); 2.09–1.94 (*m*, 1 H); 1.60–1.12 (*m*, 13 H); 1.04 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.1; 135.8; 129.4; 127.4; 96.4; 81.3; 78.8; 69.4; 55.9; 39.3; 30.0; 29.7; 28.5; 27.0; 25.1; 24.1; 23.2; 22.7; 19.3. ESI-MS: 535 ([*M* + Na]$^+$). HR-MS: 535.2864 ([*M* + Na]$^+$, $C_{30}H_{44}NaO_5Si^+$; calc. 535.2856).

*(5*S*)-5-[(5*S*,11*R*)-11,14,14-Trimethyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecan-5-yl]furan-2(5*H*)-one* (**16**). To a soln. of LDA (prepared from diisopropyl amine (1.12 ml, 6.4 mmol) and BuLi (2.48 ml, 2.5M soln. in hexane, 6.2 mmol, at −78°) compound **3** (0.41 g, 0.80 mmol) in THF was added dropwise, under Ar at −78°. The mixture was slowly warmed up −30° and stirred for 1.5 h. It was then cooled to −78°, and a THF soln. of PhSeBr (1.23 g, 5.2 mmol) was introduced into the flask and allowed to stir for 2 h at −30°. It was quenched with aq. NH_4Cl (10 ml) and extracted with Et_2O (3 × 25 ml). The combined org. layers were washed with H_2O (12 ml), brine (12 ml), and dried (Na_2SO_4). Solvent was evaporated *in vacuo* to furnish the crude selenolactone, which was used as such in the next step.

To a soln. of crude selenolactone in CH_2Cl_2 (10 ml), H_2O_2 (2.1 ml of 30% *w*/*v* in H_2O) was added and allowed to stir for 1 h at r.t. H_2O (20 ml) was added to the mixture and extracted with CH_2Cl_2 (3 × 15 ml). The combined org. layers were washed with sat. $Na_2S_2O_3$ (15 ml), brine (15 ml), and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by CC (16% AcOEt in hexane) to furnish **16** (0.22 g, 54%) as colorless oil. $[\alpha]_D^{25} = -58.4$ ($c = 0.3$, $CHCl_3$). IR (neat): 3024, 3016, 1638, 1523, 1132. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.68–7.59 (*m*, 5 H); 7.42–7.28 (*m*, 6 H); 6.19 (*dd*, *J* = 6.0, 2.0, 1 H); 5.27–5.21 (*m*, 1 H); 4.86–4.79 (*m*, 2 H); 3.82–3.77 (*m*, 1 H); 3.74–3.68 (*m*, 1 H); 3.36 (*s*, 3 H); 1.62–1.20 (*m*, 10 H); 1.15 (*d*, *J* = 6.0, 3 H); 1.03 (*s*, 9 H). ^{13}C-NMR (150 MHz, $CDCl_3$): 174.8; 157.5; 135.7; 129.4; 127.4;

122.9; 96.6; 81.1; 79.5; 69.4; 55.9; 39.3; 32.7; 30.1; 27.0; 25.3; 24.1; 23.2; 19.3. ESI-MS: 533 ($[M+Na]^+$). HR-MS: 533.2705 ($[M+Na]^+$, $C_{30}H_{42}NaO_5Si^+$; calc. 533.2699).

*(5*S*)-5-[(1*S*,7*R*)-1,7-Dihydroxyoctyl]furan-2(5*H*)-one* (**1**). To a stirred soln. of **16** (0.18 g, 0.35 mmol) in CH_2Cl_2 (2 ml), $TiCl_4$ (0.065 g, 0.35 mmol) in CH_2Cl_2 (2 ml) was added at 0°, and the mixture was stirred for 2 h. The mixture was treated with sat. $NaHCO_3$ soln. (5 ml) and extracted with Et_2O (2 × 20 ml). The combined org. layers were washed with H_2O (20 ml), dried (Na_2SO_4), and concentrated. The crude product was purified by CC (45% AcOEt in hexane) to afford **1** (0.054 g, 68%) as colorless liquid. $[\alpha]_D^{25} = -82.3$ ($c = 0.2$, MeOH). IR (neat): 3391, 3014, 1746, 1514, 1132. ^{1}H-NMR (500 MHz, CD_3OD): 7.65 (*dd*, $J = 6.0, 1.5, 1$ H); 6.18 (*dd*, $J = 6.0, 2.0, 1$ H); 5.08 (*quint.*, $J = 2.0, 1$ H); 3.82–3.76 (*m*, 1 H); 3.74–3.69 (*m*, 1 H); 1.62–1.53 (*m*, 3 H); 1.48–1.32 (*m*, 7 H); 1.15 (*d*, $J = 6.0$, 3 H). ^{13}C-NMR (150 MHz, CD_3OD): 175.8; 157.1; 122.7; 88.2; 71.6; 68.5; 40.1; 34.2; 30.6; 26.82; 26.79; 23.51. ESI-MS: 251($[M+Na]^+$). HR-MS: 251.1263 ($[M+Na]^+$, $C_{12}H_{20}NaO_4^+$; calc. 251.1259).

*(4*S*,5*S*,11*R*)-11-{[*tert*-Butyl(diphenyl)silyl]oxy}-5-(methoxymethoxy)dodecane-1,4-diol* (**17**). To a stirred soln. of **3** (0.5 g, 0.98 mmol) in THF (5 ml) at 0° was sequentially added MeOH (0.04 ml, 0.98 mmol) and $LiBH_4$ (0.03 g, 1.18 mmol). After 30 min, the reaction was quenched with sat. aq. NH_4Cl (20 ml) and extracted with Et_2O (2 × 40 ml). The org. layers were dried (Na_2SO_4) and concentrated *in vacuo* and the crude product was purified by CC (23% AcOEt in hexane) to afford **17** (0.43 g, 85%) as colorless oil. $[\alpha]_D^{25} = -124.8$ ($c = 0.3$, $CHCl_3$). IR (neat): 3584, 3391, 3028, 1514, 1246, 1154. IR (neat): 3584, 3391, 3028, 1514, 1246, 1154. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.70–7.61 (*m*, 4 H); 7.41–7.30 (*m*, 6 H); 4.66 (*d*, $J = 6.4$, 1 H); 4.62 (*d*, $J = 6.4$, 1 H); 3.81 (*q*, $J = 5.9$, 1 H); 3.70–3.59 (*m*, 2 H); 3.51–3.45 (*m*, 1 H); 3.40 (*s*, 3 H); 3.32–3.25 (*m*, 1 H); 1.93–1.84 (*m*, 1 H); 1.78–1.56 (*m*, 3 H); 1.55–1.10 (*m*, 13 H); 1.04 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.8; 129.4; 127.4; 97.3; 83.9; 72.8; 69.5; 62.9; 55.8; 39.3; 31.0; 30.2; 29.2; 27.0; 26.2; 25.1; 23.2; 22.6; 19.2. ESI-MS: 539 ($[M+Na]^+$). HR-MS: 539.3173 ($[M+Na]^+$, $C_{30}H_{48}NaO_5Si^+$; calc. 539.3169).

*(8*S*,9*S*,15*R*)-9-(Methoxymethoxy)-2,2,3,3,15,18,18-heptamethyl-17,17-diphenyl-4,16-dioxa-3,17-disilanonadecan-8-ol* (**18**). To a stirred soln. of 1,4-diol **17** (0.4 g, 0.78 mmol) in CH_2Cl_2 (4 ml), imidazole (0.16 g, 2.34 mmol) was added at 0°, and the mixure was stirred for 0.5 h. Then, TBDMSCl (0.18 g, 1.17 mmol) was added, and the mixture was stirred for 12 h at r.t. The mixture was diluted with CH_2Cl_2 (4 ml), the org. layer was washed with H_2O (6 ml) followed by brine (6 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (12% AcOEt in hexane) to afford **18** (0.44 g, 90%) as colorless liquid. $[\alpha]_D^{25} = -98.2$ ($c = 0.2$, $CHCl_3$). IR (neat): 3497, 3036, 1525, 1258, 1137. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.65–7.56 (*m*, 4 H); 7.37–7.25 (*m*, 6 H); 4.60 (*s*, 2 H); 3.80–3.70 (*m*, 1 H); 3.60 (*t*, $J = 5.6$, 2 H); 3.48–3.38 (*m*, 1 H); 3.34 (*s*, 3 H); 3.28–3.20 (*m*, 1 H); 1.70–1.10 (*m*, 17 H); 1.03 (*s*, 9 H); 0.86 (*s*, 9 H); 0.03 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.8; 129.4; 127.4; 97.0; 82.8; 72.6; 69.5; 63.2; 55.7; 39.4; 30.8; 29.7; 27.0; 26.8; 25.9; 25.3; 25.2; 23.2; 19.3; 17.1; −5.3. ESI-MS: 653 ($[M+Na]^+$). HR-MS: 653.4027 ($[M+Na]^+$, $C_{36}H_{62}NaO_5Si_2$; calc. 653.4033).

*(5*R*,11*S*,12*S*)-12-[(4-Methoxybenzyl)oxy]-11-(methoxymethoxy)-2,2,5,17,17,18,18-heptamethyl-3,3-diphenyl-4,16-dioxa-3,17-disilanonadecane* (**19**). A soln. of alcohol **18** (0.4 g, 0.63 mmol) in dry THF (4 ml) was added to a suspension of NaH (0.75 g, 1.89 mmol) in THF (6 ml) under N_2 atmosphere at 0° and was stirred for 30 min. To this, a soln. of PMBBr (0.12 g, 0.6 mmol) in dry THF (5 ml) was added, and the mixture was allowed to stir for 6 h at r.t. The reaction was quenched with sat. aq. NH_4Cl soln. (8 ml) and extracted with AcOEt (2 × 10 ml). The org. layer was washed with H_2O (2 × 10 ml) and brine (15 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (6% AcOEt in hexane) to afford **19** (0.39 g, 82%) as a yellow oil. $[\alpha]_D^{25} = -41.1$ ($c = 0.4$, $CHCl_3$). IR (neat): 3068, 3046, 1562, 1525, 1267, 1137. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.64 (*d*, $J = 6.2$, 4 H); 7.42–7.28 (*m*, 6 H); 7.20 (*d*, $J = 8.5$, 2 H); 6.80 (*d*, $J = 8.4$, 2 H); 4.63 (*d*, $J = 6.8$, 1 H); 4.56 (*d*, $J = 6.7$, 1 H); 4.46 (2*d*, *AB* pattern, $J = 11.3, 7.7$, 2 H); 3.83–3.78 (*m*, 1 H); 3.77 (*s*, 3 H); 3.60–3.47 (*m*, 3 H); 3.41–3.34 (*m*, 1 H); 3.32 (*s*, 3 H); 1.68–1.09 (*m*, 17 H); 1.03 (*s*, 9 H); 0.87 (*s*, 9 H); 0.02 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.7; 135.9; 129.5; 129.4; 127.4; 127.3; 113.7; 96.8; 79.8; 78.7; 72.0; 69.5; 63.2; 55.6; 55.2; 39.4; 29.9; 29.8; 29.4; 27.0; 26.8; 26.2; 25.9; 25.2; 23.2; 19.2; 16.8; −5.2. ESI-MS: 773 ($[M+Na]^+$). HR-MS: 773.4614 ($[M+Na]^+$, $C_{44}H_{70}NaO_6Si_2^+$; calc. 773.4609).

*(4*S*,5*S*,11*R*)-11-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)dodecan-1-ol* (**20**). To a stirred soln. of compound **19** (0.36 g, 0.48 mmol) in MeOH (4 ml), the pyridinium

salt of *p*-toluenesulfonic acid (0.15 g, 0.6 mmol) was added at r.t., and the mixture was allowed to stir for 2 h. The solvent was removed under reduced pressure, purified by CC (15% AcOEt in hexane) to afford **20** (0.24 g, 79%) as a yellow oil. $[\alpha]_D^{25} = -74.4$ ($c = 0.5$, $CHCl_3$). IR (neat): 3557, 3029, 1527, 1142. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.64 (*d*, *J* = 6.2, 4 H); 7.41–7.29 (*m*, 6 H); 7.20 (*d*, *J* = 7.9, 2 H); 6.81 (*d*, *J* = 8.4, 2 H); 4.62 (*d*, *J* = 6.4, 1 H); 4.57 (*d*, *J* = 6.7, 1 H); 4.52 (*d*, *J* = 10.9, 1 H); 4.42 (*d*, *J* = 11.4, 1 H); 3.84–3.78 (*m*, 1 H); 3.77 (*s*, 3 H); 3.69–3.60 (*m*, 1 H); 3.60–3.52 (*m*, 2 H); 3.46–3.40 (*m*, 1 H); 3.33 (*s*, 3 H); 1.75–1.10 (*m*, 17 H); 1.04 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3; 135.9; 129.7; 129.4; 127.5; 127.4; 113.7; 96.9; 79.9; 78.5; 72.0; 69.6; 62.9; 55.7; 55.3; 39.4; 31.9; 29.7; 29.4; 27.0; 25.9; 25.2; 23.2; 22.7; 19.3. ESI-MS: 659 ($[M+Na]^+$). HR-MS: 659.3738 ($[M+Na]^+$, $C_{38}H_{56}NaO_6Si^+$; calc. 659.3744).

*(4*S*,5*S*,11*R*)-11-{[*tert*-Butyl(diphenyl)silyl]oxy}-4-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)dodecanoic Acid* (**4**). To a stirred soln. of compound **20** (0.21 g, 0.33 mmol) in CH_2Cl_2/H_2O (1:1, 2 ml) at 0°, BAIB (0.329 g, 0.99 mmol), and TEMPO (0.0155 g, 0.099 mmol) were added and stirred at r.t. for 4 h. The mixture was diluted with $CHCl_3$ (10 ml) and washed with sat. $Na_2S_2O_3$ (10 ml) and brine (20 ml), and dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (18% AcOEt in hexane) to afford **4** (0.166 g, 85%) as a yellow oil. $[\alpha]_D^{25} = -112.8$ ($c = 0.3$, $CHCl_3$). IR (neat): 3248, 3029, 1709, 1527, 1290, 1142. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67–7.59 (*m*, 4 H); 7.40–7.27 (*m*, 6 H); 7.19 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 4.61 (*d*, *J* = 6.7, 1 H); 4.55 (*d*, *J* = 6.7, 1 H); 4.51 (*d*, *J* = 11.3, 1 H); 4.40 (*d*, *J* = 10.9, 1 H); 3.87–3.78 (*m*, 1 H); 3.77 (*s*, 3 H); 3.60–3.50 (*m*, 1 H); 3.49–3.40 (*m*, 1 H); 3.32 (*s*, 3 H); 2.46–2.20 (*m*, 2 H); 1.97–1.80 (*m*, 1 H); 1.75–1.59 (*m*, 1 H); 1.57–1.09 (*m*, 13 H); 1.04 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.5; 159.2; 135.8; 129.6; 129.4; 127.4; 113.7; 96.8; 78.6; 78.2; 72.1; 69.5; 55.7; 55.2; 42.6; 39.4; 30.5; 29.7; 27.0; 26.1; 25.9; 25.1; 24.6; 23.2; 19.2. ESI-MS: 673 ($[M+Na]^+$). HR-MS: 673.3528 ($[M+Na]^+$, $C_{38}H_{54}O_7NaSi^+$; calc. 673.3536).

*(4*S*,5*S*,11*R*)-11-Hydroxy-4-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)dodecanoic Acid* (**21**). To a stirred soln. of compound **4** (0.14 g, 0.22 mmol) in dry THF, HF–Py (0.28 ml, 0.28 mmol) was added and stirred for 12 h at r.t. The reaction was quenched with $CuSO_4$ soln. (10 ml), extracted with AcOEt (2 × 5 ml), washed with H_2O (5 ml), and brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (30% AcOEt in hexane) to afford **21** (0.080 g, 88%) as colorless liquid. $[\alpha]_D^{25} = -52.3$ ($c = 0.2$, $CHCl_3$). IR (neat): 3279, 3068, 1714, 1278, 1108. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.19 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 4.61 (*d*, *J* = 6.7, 1 H); 4.55 (*d*, *J* = 6.7, 1 H); 4.51 (*d*, *J* = 11.3, 1 H); 4.40 (*d*, *J* = 10.9, 1 H); 4.04–3.98 (*m*, 1 H); 3.77 (*s*, 3 H); 3.60–3.50 (*m*, 1 H); 3.49–3.40 (*m*, 1 H); 3.32 (*s*, 3 H); 2.46–2.20 (*m*, 2 H); 1.98–1.83 (*m*, 1 H); 1.77–1.58 (*m*, 1 H); 1.55–1.09 (*m*, 13 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.5; 159.2; 129.4; 127.4; 113.7; 96.8; 78.6; 78.2; 72.1; 66.3; 55.7; 55.2; 41.4; 39.4; 30.5; 29.7; 27.0; 25.1; 24.6; 23.1. ESI-MS: 417 ($[M+Na]^+$). HR-MS: 435.2366 ($[M+Na]^+$, $C_{22}H_{36}NaO_7^+$; calc. 435.2359).

*(5*S*,6*S*,12*R*)-5-[(4-Methoxybenzyl)oxy]-6-(methoxymethoxy)-12-methyloxacyclododecan-2-one* (**22**). To a stirred soln. of acid **21** (0.065 g, 0.16 mmol) in dry THF (5 ml), Et_3N (0.066 ml, 0.48 mmol) was added at r.t., and the mixture was stirred for 0.5 h. 2,4,6-Trichlorobenzoyl chloride (0.059 ml, 0.192 mmol) was added, and the mixture was stirred for 8 h at r.t. The solvent was evaporated, the residue diluted with toluene (10 ml), then DMAP (0.195 g, 1.60 mmol) was added, and the mixture was stirred for 20 h at 90°. Toluene was evaporated, and the crude residue purified by CC (5% AcOEt in hexane) to afford cyclic ester **22** (0.049 g, 79%) as a colorless liquid. $[\alpha]_D^{25} = -13.2$ ($c = 0.4$, $CHCl_3$). IR (neat): 3023, 2872, 1728, 1131, 1062. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.19 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 5.05–5.00 (*m*, 1 H); 4.61 (*d*, *J* = 6.7, 1 H); 4.55 (*d*, *J* = 6.7, 1 H); 4.51 (*d*, *J* = 11.3, 1 H); 4.40 (*d*, *J* = 10.9, 1 H); 3.77 (*s*, 3 H); 3.60–3.50 (*m*, 1 H); 3.49–3.40 (*m*, 1 H); 3.32 (*s*, 3 H); 2.45–2.29 (*m*, 2 H); 2.15–2.05 (*m*, 1 H); 1.84–1.74 (*m*, 1 H); 1.73–1.63 (*m*, 1 H); 1.51–1.17 (*m*, 9 H); 1.12 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.5; 159.2; 129.4; 127.4; 113.7; 96.8; 72.7; 72.2; 72.1; 71.7; 55.7; 55.2; 31.7; 30.8; 29.7; 29.2; 27.1; 25.2; 20.6; 19.5. ESI-MS: 417 ($[M+Na]^+$). HR-MS: 417.2258 ($[M+Na]^+$, $C_{22}H_{34}NaO_6^+$; calc. 417.2253).

*(5*S*,6*S*,12*R*)-5-Hydroxy-6-(methoxymethoxy)-12-methyloxacyclododecan-2-one* (**23**). To a soln. of compound **22** (0.035 g, 0.09 mmol) in a mixture of CH_2Cl_2 and H_2O (5 ml, 19:1), DDQ (0.22 g, 0.98 mmol) was added at 0° and the mixture was stirred for 20 min. at r.t. The reaction was quenched with sat. $NaHCO_3$ soln. (5 ml), extracted with CH_2Cl_2 (3 × 15 ml) and washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (8% AcOEt in hexane) to afford **23** (0.02 g, 82%) as a colorless liquid. $[\alpha]_D^{25} = -11.9$ ($c = 0.1$, $CHCl_3$). IR

(neat): 3489, 1721, 1476, 1234. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.05–5.01 (*m*, 1 H); 4.61 (*d*, *J* = 6.7, 1 H); 4.55 (*d*, *J* = 6.7, 1 H); 3.87–3.79 (*m*, 1 H); 3.42–3.36 (*m*, 1 H); 3.32 (*s*, 3 H); 2.47–2.29 (*m*, 2 H); 2.16–2.07 (*m*, 1 H); 1.82–1.71 (*m*, 1 H); 1.70–1.63 (*m*, 1 H); 1.50–1.18 (*m*, 9 H); 1.12 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.5; 96.8; 74.4; 72.1; 69.6; 55.2; 31.7; 30.8; 29.7; 28.8; 27.1; 25.2; 22.9; 19.5. ESI-MS: 297 ($[M+Na]^+$). HR-MS: 297.1871 ($[M+Na]^+$, $C_{14}H_{26}NaO_5^+$; calc. 297.1885).

*(6*S*,12*R*)-6-(Methoxymethoxy)-12-methyloxacyclododecane-2,5-dione* (**24**). To a stirred soln. of alcohol **23** (0.020 g, 0.07 mmol) in dry CH_2Cl_2 (2 ml), *Dess–Martin* periodinane (0.045 g, 0.11 mmol) was added at 0°, and the mixture was allowed to stir for 2 h at r.t.. The reaction was quenched with aq. soln. of $NaHCO_3$/hypo (1:1, 1 ml) and mixture was extracted with CH_2Cl_2 (2 × 5 ml), washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (5% AcOEt in hexane) to afford ketone **24** (0.018 g, 89%) as a colorless syrup. $[\alpha]_D^{25} = -56.3$ (*c* = 0.1, $CHCl_3$). IR (neat): 1721, 1715, 1467, 1259. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.93–4.81 (*m*, 1 H); 4.61 (*d*, *J* = 6.7, 1 H); 4.55 (*d*, *J* = 6.7, 1 H); 4.18 (*t*, *J* = 5.9, 1 H); 3.48–3.34 (*m*, 1 H); 3.32 (*s*, 3 H); 2.65 (*t*, *J* = 15.7, 1 H); 2.58–2.39 (*m*, 2 H); 1.66 (*q*, *J* = 6.5, 1 H); 1.65–1.56 (*m*, 2 H); 1.48–1.35 (*m*, 1 H); 1.34–1.24 (*m*, 6 H); 1.17 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 212.3; 171.2; 95.9; 83.7; 69.6; 55.2; 38.1; 31.7; 30.2; 29.7; 29.4; 28.3; 22.9; 19.5. ESI-MS: 295 ($[M+Na]^+$). HR-MS: 295.1871 ($[M+Na]^+$, $C_{14}H_{24}NaO_5^+$; calc. 295.1885).

*(6S,12*R*)-6-Hydroxy-12-methyloxacyclododecane-2,5-dione* (**2**). A stirred soln. of **24** (0.018 g, 0.07 mmol) in CH_2Cl_2 (2 ml) was treated with TFA (0.2 ml) at 0° and stirred at r.t. for 2 h. The reaction was neutralized with solid $NaHCO_3$, and the crude mixture was extracted with AcOEt (3 × 5 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by CC (6.5% AcOEt in hexane) to furnish **2** (0.010 g, 0.07 mmol) in 72% as colorless needles. M.p. 119–121°. $[\alpha]_D^{25} = -40.0$ (*c* = 0.2, MeOH). IR (neat): 3452, 2919, 1718, 1702, 1470, 1256. ^{1}H-NMR (500 MHz, (D_6)acetone): 4.76 (*sext.*, *J* = 6.3, 1 H); 4.24–4.22 (*m*, 1 H); 3.13–3.06 (*m*, 1 H); 2.60–2.47 (*m*, 2 H); 2.44–2.40 (*m*, 1 H); 1.84–1.79 (*m*, 1 H); 1.71 (*quint.*, *J* = 6.8, 1 H); 1.46–1.37 (*m*, 2 H); 1.23–1.13 (*m*, 6 H); 1.03 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (75 MHz, (D_6)acetone): 212.6; 172.0; 77.2; 71.7; 35.0; 33.5; 32.2; 30.1; 27.9; 21.4; 20.7; 20.0. ESI-MS: 251 ($[M+Na]^+$). HR-MS: 251.1267 ($[M+Na]^+$, $C_{12}H_{20}NaO_4^+$; calc. 251.1263).

Two of the authors (*P. V. A.* and *V. S. M.*) thank the *CSIR*, New Delhi, India for financial support in the form of a fellowships.

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Received February 3, 2015