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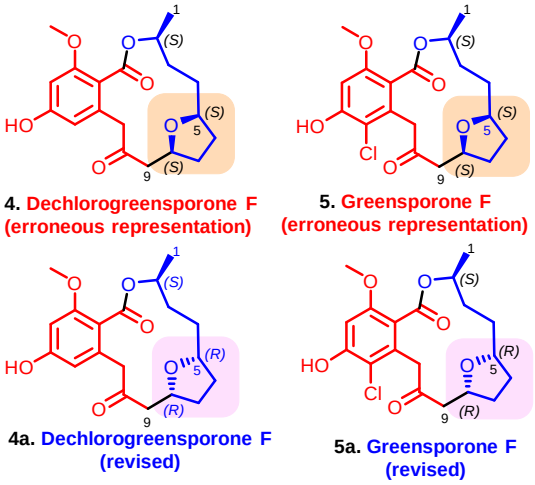
Total Synthesis and Structural Revision of Greensporone F and Dechlorogreensporone F

Janardhan Gaddam,[†,§,≠] Aedula Vishnu V. Reddy,[†,§,≠] Akella V. S. Sarma,[‡] Jhillu S. Yadav[†,§,‼] and Debendra K. Mohapatra*[†,§]

[†]*Department of Organic Synthesis and Process Chemistry and* [‡]*Centre for NMR and Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India;* [§]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh-201002, India.* [‼]*School of Science, Indrashil University, Kadi, Gujarat, India,* mohapatra@iict.res.in



ABSTRACT: The first asymmetric total syntheses of the real isolation product (2*S*,5*R*,8*R*)-greensporone F and (2*S*,5*R*,8*R*)-dechlorogreensporone F, a 14-membered resorcylic acid lactones (RALs) with a *cis*-2,5-disubstituted tetrahydrofuran ring system, was accomplished. The synthesis features a late-stage Lewis acid-catalyzed stereoselective intramolecular oxa-Michael reaction, *E*-selective ring-closing metathesis (RCM), De Brabander's esterification and Jacobsen's hydrolytic kinetic resolution as the key steps. Synthesis of both real isolation and erroneously proposed structure necessitated the revision of the absolute configuration of greensporone F and dechlorogreensporone F. The erroneous representation of (2*S*,5*S*,8*S*)-configuration in greensporone F and dechlorogreensporone

F was assigned to be (2*S*,5*R*,8*R*) by comparison with the NMR data and specific rotation of the synthetic compounds with that of the reported data.

INTRODUCTION

Fungi are known to be one of the potential sources of major antibiotic-producing organisms. These are the most diversified kingdoms of life and 95% of these are not well investigated. The novelty of freshwater fungi derived compounds and their wide spectrum of applications may find way in getting solutions to many dreadful diseases like AIDS, cancer, Alzheimer's disease and arthritis which are difficult to be cured. Resorcylic acid lactones[1] are 14-membered macrolides, exhibiting wide spectrum of biological properties such as anti-fungal, anti-microbial, anti-malarial, anti-bacterial, estrogenic, anti-cancer, anti-parasitic and anti-fouling activity. Oberlies et al in 2014 isolated 14 new 14-membered resorcylic acid lactones from fresh water aquatic fungus *Halenospora* sp. collected in North Carolina. During the isolation of the natural products dihydrogreensporone C (**1**), greensporone D (**2**), dechlorogreensporone D (**3**), they have also isolated three new compounds dechlorogreensporone F (**4**), greensporone F (**5**) and greensporone G (**6**) which are not natural products but are the artefacts arising from the intramolecular oxa-Michael addition reaction (Figure 1).[2] The absolute configuration of the stereogenic center at the C2-position in the lactone **1** was assigned as *R* based on the single-crystal X-ray diffraction analysis of the bromobenzoyl derivative of 8,9-dihydrogreensporone C **1a**. The stereochemistry at the C5-position was assigned to be *S* in the lactones **1-3** based on extensive NMR analysis. While stereochemistry at the C5-position is *S* in the lactones **2-3**, the stereochemistry at the C5 position in the THF containing lactones **4-6** would be *R* owing to the change in priorities of the substituents on the asymmetric carbon at C5. Structures of **4-6** were elucidated through various

spectroscopic techniques. While assigning the absolute stereochemistry of the THF containing lactones **4-6**, they might have inadvertently depicted the stereocenter at C5-position as *S* although the stereochemistry would be *R* as a consequence of the change in priorities of the substituents with the THF formation from the lactones **2-3**. Except greensporone D and greensporone F, all other isolated compounds were tested for their in vitro activity against two cancer cell lines HT-29 (Colon) and MDA-MB-435 (Melanoma). Among these, greensporone C was found to be potent with IC_{50} values of 2.9 and 7.5 μM against HT-29 and MDA-MB-435, respectively.

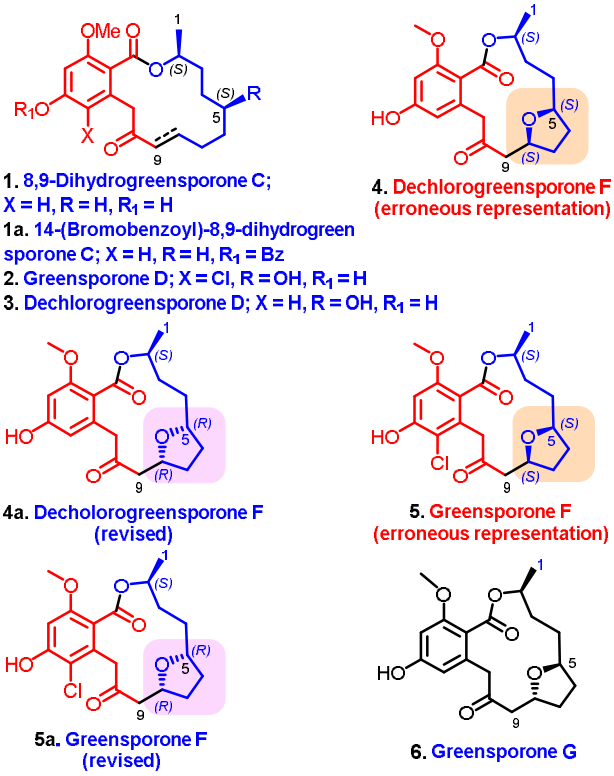


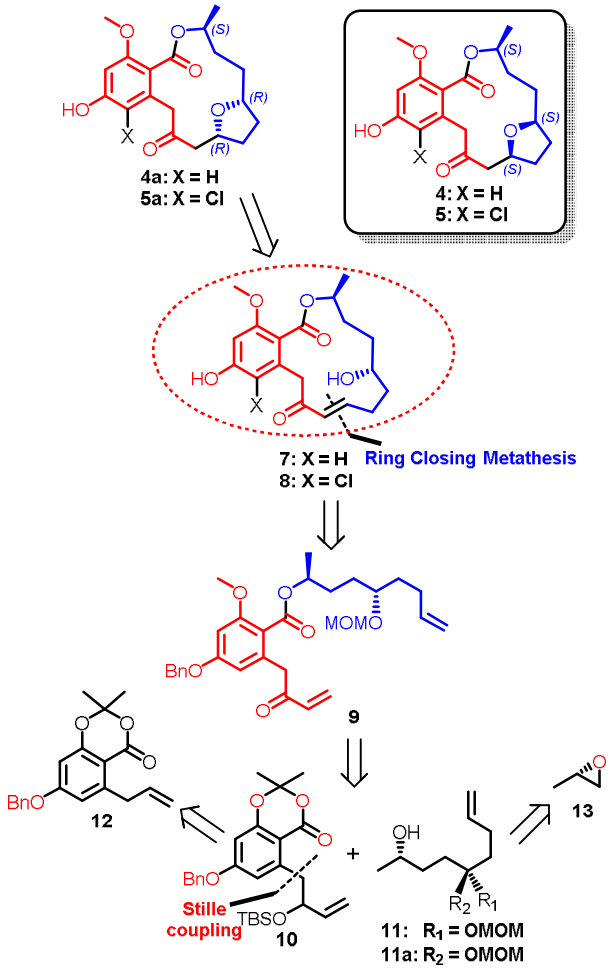
Figure 1. Representative structures of 14-membered Resorcylic Acid Lactones (RALs).

Coupled with our continuing interest in the total synthesis of resorcylic acid lactones and in THF containing natural products, we aimed initially at the total synthesis of dechlorogreensporone F (**4a**) and greensporone F (**5a**). Herein, we describe our efforts in the first asymmetric total synthesis of the

greensporone F and dechlorogreensporone F and confirmation of the structure and absolute configuration of dechlorogreensporone F and greensporone F.

The proposed convergent retrosynthetic strategy for the synthesis of **4a** and **5a** is outlined in Scheme 1. To make these two products efficiently with full control of all stereocenters, we envisioned a late-stage diastereoselective intramolecular oxa-Michael reaction of intermediate **7** to construct the

Scheme 1. R**etrosynthetic Plan**



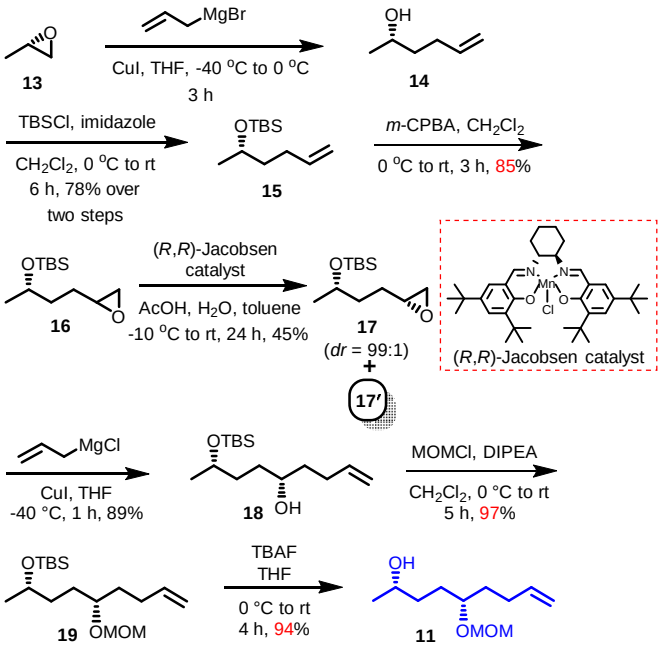
cis-2,5-disubstituted tetrahydrofuran scaffold.[3] Synthesis of 7 was planned by *E*-selective ring-closing metathesis (RCM) reaction of ester **9** which can be obtained by coupling of acid fragment **10** and alcohol fragment **11** by esterification using De Brabander's reaction conditions. Synthesis of fragment

10 was envisaged from **12**, while the alcohol fragment **11** could be synthesized from the known chiral epoxide **13**. In a similar reaction sequence, greensporone F (**5**) could also be synthesized *via* macrolactone **8**.

RESULTS AND DISCUSSION

With the general synthetic plan in hand, regioselective opening of the enantiopure (*S*)-propylene oxide **13**[4] (prepared from corresponding racemic epoxide by treating with (*S*,*S*)-Jacobsen catalyst**)** with allyl Grignard reagent and CuI at –40 °C furnished the alcohol **14** which was immediately used in the next step without any further purification/characterization (Scheme 2). The secondary alcohol in **14** was protected with TBSCl in presence of imidazole in CH_2Cl_2 at 0 °C to give the TBS ether **15** in 78% yield over two steps.[5] Epoxidation of compound **13** with *m*-CPBA in CH_2Cl_2 provided **16** as a mixture

Scheme 2. Synthesis of Alcohol Fragment 12



of diastereomers (1:1) in 85% yield.[6] Compound **16** was then subjected to hydrolytic kinetic resolution using (*R*,*R*)-Jacobsen's catalyst to yield the optically active epoxide **17** in 45% yield.[7] Epoxide **17** was

treated with allylmagnesium chloride in presence of CuI at – 40 °C to produce the requisite secondary alcohol fragment **18** in 89% yield. The stereochemistry of the secondary hydroxy attached at the C5

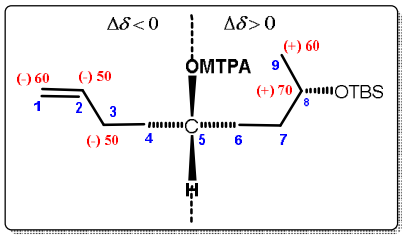
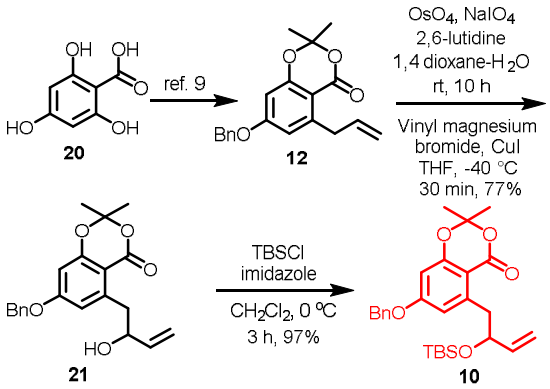


Figure 2. $(\Delta\delta) = (\delta_S - \delta_R) \times 10^3$ for (*S*)- and (*R*)-MTPA ester of alcohol compound **18**.

carbon was determined by following the modified Mosher's ester method (Figure 2).[8] Esterification of the alcohol **18** with both (*S*)- and (*R*)-methoxy-(trifluoromethyl)phenylacetic acid (MTPA) revealed negative chemical shift difference [$\Delta\delta = (\delta_S - \delta_R) \times 10^3$] for protons on C6 through C9 (Figure S1 in SI), while protons on C1 through C4 showed positive chemical shift differences, which is consistent with C5 bearing an *S*-configuration.

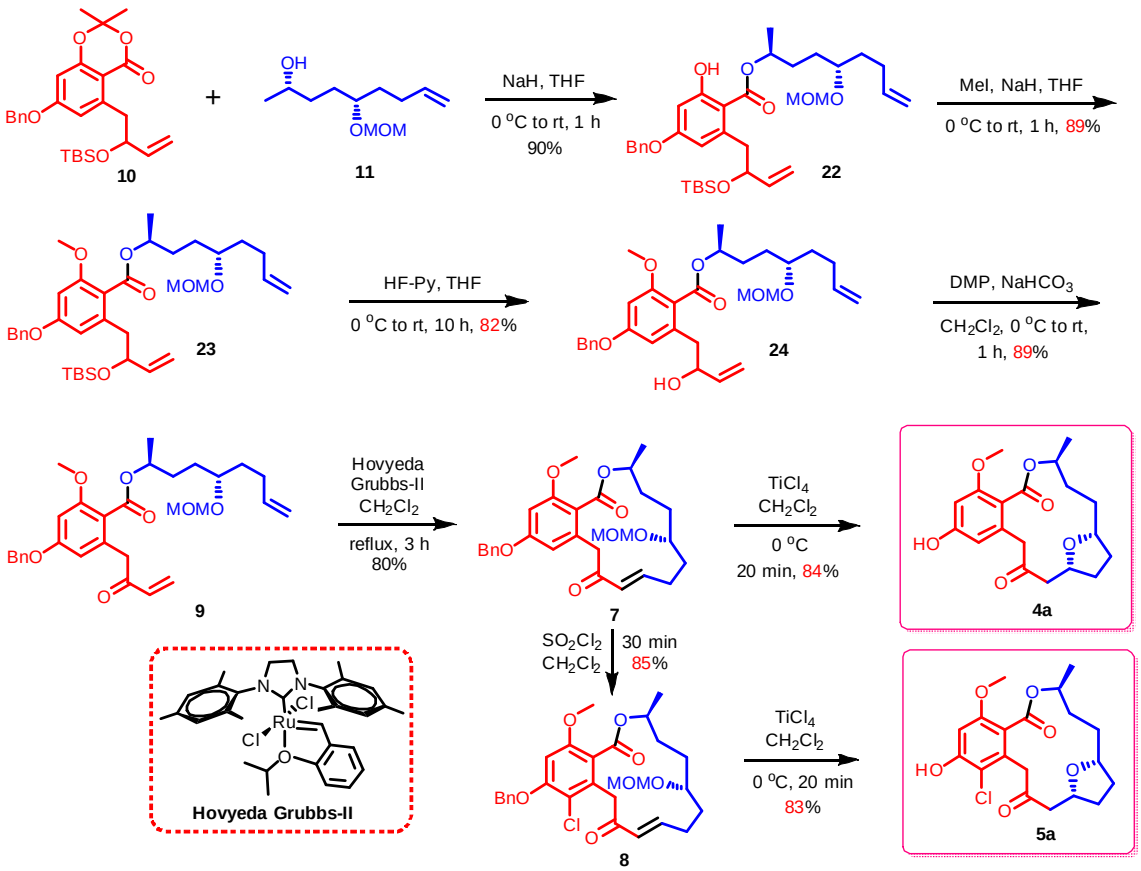
After confirming the absolute configuration at C5, the hydroxyl group in compound **18**, it was protected as MOM ether using MOMCl and *N*,*N*-diisopropylethylamine (DIPEA) to obtain compound **19** in 97% yield. The TBS group in **19** was removed smoothly using tetrabutylammonium fluoride (TBAF)[9] to provide **11** in 94% yield.

Scheme 3. Synthesis of Fragment 10



The synthesis of compound **10** commenced from the known compound **12**,[10] in which the terminal double bond was cleaved following Jin's protocol[11] of one-pot dihydroxylation-oxidation reaction using OsO_4, 2,6-lutidine, $NaIO_4$ in 1,4-dioxane-H_2O (3:1) to furnish the desired aldehyde in 86% yield which was immediately used in the next step without any further purification. Addition of Grignard reagent to the aldehyde with vinylmagnesium bromide at −40 °C afforded the allyl alcohol **21** in 77% yield over two steps. The secondary alcohol group in **21** was protected as the TBS ether using TBSCl in presence of imidazole in CH_2Cl_2 at 0 °C in 97% yield (Scheme 3).[5]

Scheme 4. Total Synthesis of the Proposed Structures of Dechlorogreensporone F and Greensporone F



The coupling of both the fragments **10** and **11** by employing De Brabander's protocol,[12] with NaH in THF at 0 °C furnished the ester **22** in 90% yield. The free phenolic hydroxyl group in compound **22** was protected as methoxy ether using MeI and NaH to furnish the compound **23** in 89% yield. Removal of the TBS group using HF-Py (70% v/v) in THF afforded the alcohol **24** in 82% yield.[13] The allyl alcohol **24** was oxidized to the corresponding ketone **9** with Dess–Martin periodinane[14] in CH_2Cl_2 with 89% yield. Ring-closing metathesis reaction of a 0.001 M solution of the bis-olefin **9** with 10 mol% of Hovyeda Grubbs' second-generation[15] catalyst heating under reflux conditions for 3 h in anhydrous, degassed CH_2Cl_2 provided the required 14-membered-*E*-lactone **7** as the sole product in 80% yield (Scheme 4).

Global deprotection followed by acid-catalyzed intramolecular transannular oxa-Michael cyclization was achieved by treating **7** with excess $TiCl_4$ in CH_2Cl_2 to complete the total synthesis of **4a** in 84% yield.[16] Pleasingly, the spectral data (^{1}H and ^{13}C NMR) of synthetic dechlorogreensporone F (**4a**) matched exactly with the data reported for the natural product (see comparison of the NMR data of natural dechlorogreensporone F and **4a** in Table S1 in the Supporting Information). The specific rotation of the synthetic dechlorosporone F (**4a**) was the same in sign and comparable magnitude {$[\alpha]_D^{20}$ –29.8 (*c* 1.0, MeOH); lit. {$[\alpha]_D^{20}$ –31.0 (*c* 0.11, MeOH)}, confirming the synthesis of the real isolation product. Therefore, the absolute configuration of the real isolated dechlorogreensporone F was determined to be (2*S*,5*R*,8*R*) as depicted in **4a** in Scheme 4 and Figure 1.

Table 1. Comparison of ^{13}C NMR data of the Natural Products with the Synthetic Samples

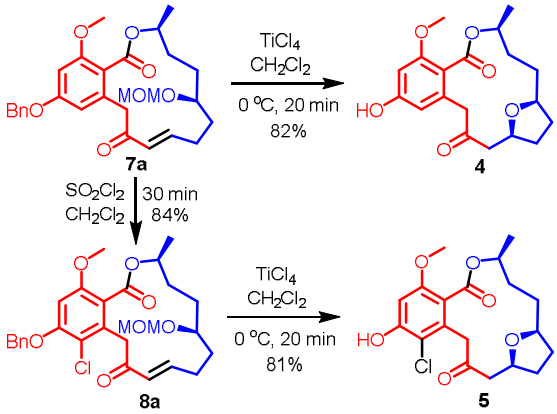
Position	Dechloro-greensporone F in ppm	Synthetic Product **4a** in ppm	Δ (lit-Dechlorogreen sporone F **4a**)[a]	Greensporone F in ppm	Synthetic Product **5a** in ppm	Δ (lit-Greensporone F **5a**)[a]
1	20.9	20.8	+0.13	21.5	21.5	+0.04
2	72.7	72.6	+0.11	73.4	73.4	−0.01
3	33.0	32.9	+0.10	33.8	33.8	0.00

4	31.3	31.3	+0.04	34.7	34.7	−0.02
5	79.5	79.4	+0.12	79.3	79.3	0.00
6	33.5	33.3	+0.16	31.6	31.5	+0.09
7	30.5	30.4	+0.09	29.8	29.8	+0.03
8	76.1	76.1	+0.04	76.3	76.3	+0.01
9	47.9	47.9	+0.04	46.6	46.6	+0.02
10	207.7	207.7	−0.01	203.9	204.0	−0.16
11	49.0	48.8	+0.18	48.6	48.6	+0.02
12	134.2	134.1	+0.13	132.1	132.0	+0.11
13	109.2	109.2	+0.05	113.1	113.1	+0.01
14	157.7	157.7	0.00	153.3	153.3	−0.05
15	98.3	98.3	0.00	99.1	99.1	0.00
16	159.0	159.0	−0.01	157.0	157.0	+0.04
17	117.3	117.2	+0.09	119.2	119.1	+0.14
18	167.7	167.6	+0.10	166.9	166.9	−0.02
19	56.0	55.9	+0.09	56.4	56.3	+0.08

With the corrected structure of dechlorogreensporone F (**4a**) in hand, our attention was then focused on the synthesis of greensporone F (**5a**). To this end, we introduced the chlorine group in the aromatic ring following regioselective electrophilic chlorination using sulfuryl chloride in CH_2Cl_2 at 0 ^oC to afford compound **8** in 85% yield.[17] Global deprotection followed by acid-catalyzed intramolecular transannular oxa-Michael cyclization of **8** with excess $TiCl_4$ in CH_2Cl_2 furnished **5a** in 83% yield. The NMR spectral data (δ_H, δ_C and couplings from ^1H and ^{13}C NMR spectra) for **5a** were identical with that reported for the real isolated greensporone F (see comparison of the NMR data of natural greensporone and **5a** in Table S2 in the Supporting Information) (Table 1). The specific rotation value of the synthetic greensporone F {$[\alpha]_D^{20}$ –35.2 (*c* 0.25, MeOH)} was quite close to that of the natural product {$[\alpha]_D^{20}$ –38.0 (*c* 0.01, MeOH)}. To further ascertain the correct structure of greensporone F

and dechlorogreensporone F, we reasoned that the configuration at the THF can be *cis* and considered the synthesis of erroneously represented (5*S*,8*S*)-disubstituted THF containing analogues **4** and **5**.

Scheme 5. Completion of Synthetic Samples 4 and 5



Thus, synthesis of **4** and **5** was started from the chiral alcohol **11a** (fragment having inverted C5 hydroxy stereocenter which was converted into antipodal THF ring, see the Supporting Information) following the sequence of reactions that are described in Scheme 4. However, the spectroscopic (^{1}H and ^{13}C{^{1}H} NMR spectral data) and analytical data of synthetic compound **4** and **5** (see the comparison of NMR data in Table S3 and S4 in the Supporting Information) were found to be different from those reported for greensporone F and dechlorogreensporone F, respectively. In particular, the reported ^{1}H NMR data for greensporone F contained four multiplets at 2.02 (m, 1H), 1.79 (m, 1H), 1.55 (m, 1H), 1.38 (m, 1H), whereas, for the synthesized sample, the peaks due to the resonance of those four protons appeared at 1.66 (m, 2H), 1.48 (m, 2H) ppm, respectively (Table S4). In ^{13}C{^{1}H} NMR spectra, resonances for C1 to C4, C6, C10 and C11 appeared at 21.5, 73.4, 33.8, 34.7, 31.6, 203.9 and 48.6 ppm for the reported compound, whereas, for the synthetic compound, they appeared at 18.5, 71.0, 31.7, 31.7, 30.2, 204.9 and 47.7 ppm (Table 2). The specific rotation value of

Table 2. Comparison of $^{13}C\{^{1}H\}$ NMR data of the Reported Products with the Synthetic Samples

Position	Dechloro-greensporone F in ppm	Synthetic Product **4** in ppm	Δ (lit-Dechlorogreen sporone F **4**)[a]	Greensporone F in ppm	Synthetic Product **5** in ppm	Δ (lit-Greensporone F **5**)[a]
1	20.9	18.6	+2.31	21.5	18.5	+2.96
2	72.7	70.7	+2.02	73.4	71.0	+2.37
3	33.0	31.6	+1.44	33.8	31.7	+2.11
4	31.3	31.7	−0.41	34.7	31.7	+2.96
5	79.5	79.4	+0.12	79.3	79.1	+0.24
6	33.5	30.5	+2.99	31.6	30.2	+1.37
7	30.5	30.3	+0.18	29.8	29.6	+0.15
8	76.1	77.1	−1.00	76.3	76.9	−0.55
9	47.9	47.7	+0.24	46.6	46.3	+0.33
10	207.7	208.5	−0.83	203.9	204.9	−1.03
11	49.0	49.2	−0.21	48.6	47.7	+0.88
12	134.2	133.5	+0.73	132.1	131.3	+0.79
13	109.2	109.0	+0.21	113.1	112.6	+0.51
14	157.7	157.8	−0.14	153.3	152.9	+0.45
15	98.3	98.3	0.00	99.1	98.8	+0.33
16	159.0	158.3	+0.70	157.0	156.1	+0.90
17	117.3	117.8	−0.47	119.2	119.4	−0.24
18	167.7	167.7	0.00	166.9	166.7	+0.20
19	56.0	55.8	+0.19	56.4	56.0	0.35

the synthetic greensporone F (**5**) {$[\alpha]_D^{20}$ +30.5 (*c* 0.12, MeOH)} was different from that of the reported value {$[\alpha]_D^{20}$ –38.0 (*c* 0.01, MeOH)}. 2D (DQF-COSY, HMBC, HSQC and NOESY) NMR data were also not in agreement with the reported data,[2] which clearly indicated that the correct structure of the real isolation products dechlorogreensporone F and greensporone F should be **4a** and **5a**, respectively.

Extensive NMR studies on synthetic compounds **5** and **5a** were carried out in $CDCl_3$ using 2D (DQF-COSY, HMBC, HSQC and NOESY) NMR experiments. DQF-COSY and HSQC spectra confirmed the assignment made by Oberlies et al.[2] Further confirmation of the assignment was obtained by the HMBC data. The spectra displayed the characteristic correlations; H_2-6 to C-4 and C-8, H_2-7 to C-5 C-9, H_2-9 to C-7, C-10 and C-11 (only with the proton with δ_H = 2.55 ppm), H_2-11 to C-13 and C-17, H-15 to C-13, C-17 and C-18 and O-Me to C-16 (Figure 3b). Finally, the presence of H-5/H-8 correlation in the NOESY spectrum proved beyond doubt the *cis*-configuration at C-5 and C-8 in the tetrahydrofuran ring (see Supporting Information) of all four compounds. Consequently, the absolute configuration of the greensporone F is most likely to be (2*S*,5*R*,8*R*) as portrayed for **5a** in Scheme 4 and Figure 1.

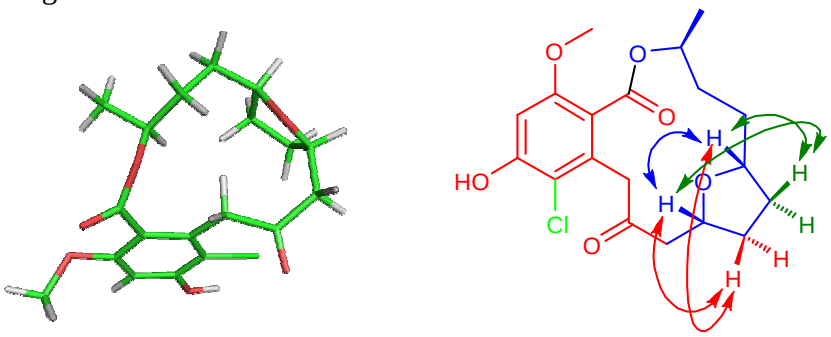


Figure 3. (a) Energy-minimized structure of **5a**. (b) Key NOE correlations in **5a**.

CONCLUSIONS

In summary, the first asymmetric total synthesis of erroneously represented structures of greensporone (**5**) and dechlorogreensporone F (**4**) as well as corrected structures of greensporone F (**5a**) and dechlorogreensporone F (**4a**) were achieved. The key reactions such as transannular acid-catalyzed oxa-Michael cyclization, ring-closing metathesis (RCM) reaction, and De Brabander's esterification were employed. The spectral and analytical data for the reported compounds were

exactly matching with the synthetic samples **4a** and **5a**, led to the revision of the real isolated structure for greensporone F and dechlorogreensporone F. The erroneously represented absolute configuration (2*S*,5*S*,8*S*)-greensporone F and dechlorogreensporone were revised to (2*S*,5*R*,8*R*)-greensporone F and dechlorogreensporone F, respectively. We believe that the methodologies and strategies described herein will find wide application in the asymmetric synthesis of other natural products of this family for further biological evaluations.

EXPERIMENTAL SECTION

General Information: All air and/or moisture sensitive reactions were carried out in anhydrous solvents under an inert atmosphere in flame-dried glassware. All commercially available starting materials and reagents were used as received without further purification. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; DMF, CH_2Cl_2 from CaH_2; MeOH from Mg cake. Column chromatography was carried out by using silica gel (60–120 mesh). Thin layer chromatography (TLC) was run on plates (0.25 mm) with pre-coated silica gel GF254, for monitoring the reactions. Specific rotations $[\alpha]_D$ were recorded with Anton Paar MCP 200 digital polarimeter at 20 ^oC and reported in deg dm^{-1} cm^3 g^{-1}. Diastereomeric ratio was analyzed by Shimadzu LC-MS-8040 instrument. Infrared spectra were recorded in $CHCl_3$ and reported in wave number (cm^{-1}). HRMS spectra were recorded by using Waters Q-TOF mass spectrometer. ^1H and $^{13}C\{^1H\}$ NMR chemical shifts were reported in ppm downfield from tetramethylsilane relative to the $CDCl_3$, 7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR, respectively and coupling constants (*J*) were reported in hertz (Hz). Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. The following abbreviations were used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*S*)-Hex-5-en-2-ol (14): A mixture of purified epoxide **13** (10.0 g, 172.4 mmol), copper (I) iodide (3.26 g, 17.14 mmol,) in THF (100 mL), was vigorously stirred under argon at −40 °C for 20 min. Allyl magnesium bromide (344.8 mL, 344.8 mmol) was added dropwise at −40 °C and the mixture allowed to slowly warm to room temperature. The dark brown solution was quenched with NH_4Cl (150 mL) and diluted with ethyl acetate (200 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure to give the crude product **14** which was used immediately without further characterization.

(*S*)-*tert*-Butyl(hex-5-en-2-yloxy)dimethylsilane (15): To a cold solution (0 ºC) of crude alcohol **14** (15.0 g, 150.0 mmol), imidazole (15.3 g, 225.0 mmol), and DMAP (1.68 g, 15.0 mmol) in CH_2Cl_2 (200 mL) was added TBSCl (37.75 g, 225.0 mmol). The reaction mixture was warmed to room temperature for 6 h and quenched with saturated NH_4Cl solution (100 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated to leave a residue which was purified by silica gel column chromatography (ethyl acetate/hexane = 1:49) to afford **15** (21.42 g 78% over two steps) as a colorless liquid. $[\alpha]_D^{20}$ = +15.94 (*c* 0.32, $CHCl_3$); IR (neat) ν_{max} 2922, 2854, 1629, 1458, 1380, 1218, 1087, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.08–4.94 (m, 2H), 3.80 (m, 1H), 2.18–1.99 (m, 2H), 1.58–1.42 (m, 2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 138.93, 114.2, 68.1, 38.9, 30.0, 25.90, 25.9, 23.7, −4.4, −4.7 ppm; EI-MS: *m/z* Calcd. for $C_{12}H_{27}OSi$ $[M + H]^+$: 215.

***tert*-Butyldimethyl(((2*S*)-4-(oxiran-2-yl)butan-2-yl)oxy)silane (16):** To a stirred solution of olefin **15** (13.5 g, 63.06 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C, was added slowly *m*-chloroperbenzoic acid (16.2 g, 94.59 mmol) as a solid and the reaction mixture was stirred for 3 h. The solution was washed thoroughly with cold aqueous NaOH solution (6.3 g, 157.65 mmol) and the organic layer was

separated. The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the crude epoxide, which on purification by silica gel column chromatography (ethyl acetate/hexane = 1:9) furnished **16** (12.38 g, 85%) as a viscous liquid. $[\alpha]_D^{20}$ = +13.78 (*c* 0.37, $CHCl_3$); IR (neat) ν_{max} 2852, 2648, 1632, 1465, 1312, 1283, 1061, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (m, 1H), 2.91 (m, 1H), 2.74 (m, 1H), 2.46 (td, *J* = 4.7, 2.7 Hz, 1H), 1.64–1.48 (m, 4H), 1.13 (ddd, *J* = 8.0, 5.1, 2.9 Hz, 3H), 0.88 (d, *J* = 0.8 Hz, 9H), 0.05–0.03 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 68.2, 68.0, 52.5, 52.3, 47.1, 47.1, 35.8, 35.4, 28.9, 28.4, 25.9, 25.8, 23.8, 23.6, 18.1, −4.4, −4.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{26}O_2SiNa$: 253.1600, Found: 253.1598.

***tert*-Butyldimethyl((*S*)-4-((*R*)-oxiran-2-yl)butan-2-yloxy)silane (17):** A mixture of (*R*,*R*)-(-)-*N*-*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamino-cobalt-II (0.196 g, 0.32 mmol) toluene (2 mL) and acetic acid (0.15 mL, 2.5 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The oxirane **16** (15 g, 65.21 mmol) was added in one portion, and the stirred mixture was cooled in an ice water bath. Water (0.64 mL, 35.5 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 ^oC. After 1 h, addition was complete. The ice bath was removed and the reaction mixture was stirred for 36 h. The crude reaction mixture was purified by column chromatography to afford the chiral epoxide **17** (6.75 g, 45%) as colorless oil. $[\alpha]_D^{20}$ = −4.76 (*c* 0.9, $CHCl_3$); IR (neat) ν_{max} 2932, 2858, 1632, 1465, 1375, 1253, 1061, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (m, 1H), 2.92 (m, 1H), 2.74 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.59 – 1.49 (m, 4H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 2.4 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 68.0, 52.3, 47.1, 35.4, 28.4, 25.9, 25.8, 23.6, -4.3, -4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{27}O_2Si$: 231.1780, Found: 231.1775.

(5*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)non-1-en-5-ol (18): A mixture of purified epoxide **17** (3.0 g, 13.02 mmol), copper (I) iodide (2.64 mg, 1.3 mmol) in THF (40 mL) was vigorously stirred under argon at −40 °C for 20 min. Allyl magnesium bromide (1M, 21.96 mL, 21.96 mmol) was added dropwise and the mixture was allowed to warm room temperature slowly (ca. 1 h). The dark brown solution was quenched with NH_4Cl (30 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 3:17) to afford the fragment **18** (3.16 g, 89%) as a colorless liquid. $[\alpha]_D^{20}$ = +15.2 (*c* 0.25 $CHCl_3$); IR (neat) ν_{max} 3448, 2927, 2857, 1637, 1457, 1374, 1254, 1047, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.08- 4.94 (m, 2H), 3.85 (m, 1H), 3.62 (m, 1H), 2.26–2.07 (m, 2H), 1.86 (br s 1H), 1.59-1.45 (m, 6H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (d, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.7, 144.6, 71.1, 68.5, 36.4, 35.0, 32.9, 30.1, 25.9, 23.5, 18.1, −4.4, −4.7 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{33}O_2Si$ $[M + H]^+$ 273.2250, Found: 273.2246.

Determination of absolute stereochemistry of hydroxyl group in compound (18):

(*S*)-((5*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)non-1-en-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (18′): To a stirred solution of alcohol **18** (20 mg, 0.07 mmol) in CH_2Cl_2 (2 mL), were added *N*,*N*-dicyclohehylcarbodiimde (DCC) (19 mg, 0.09 mmol), (*S*)-(−)-*α*-methoxy-*α*-(trifluoromethyl) phenylacetic acid (*S*-MTPA) (22 mg, 0.11 mmol) and catalytic amount of DMAP (2 mg) and the reaction was allowed to stir at room temperature for 10 h. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane =

1:19) to afford (*S*)-MTPA ester **18′** (27 mg, 77%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 2H), 7.42 – 7.37 (m, 3H), 5.72 (ddt, *J* = 16.3, 9.7, 6.6 Hz, 1H), 5.11 (m, 1H), 4.98–4.90 (m, 2H), 3.78 (m, 1H), 3.56 (d, *J* = 1.2 Hz, 3H), 2.02 – 1.89 (m, 2H), 1.78 (m, 1H), 1.72–1.60 (m, 3H), 1.49–1.35 (m, 2H), 1.10 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 5.5 Hz, 6H) ppm.

(*R*)-((5*S*,8*S*)-8-(*tert*-butyldimethylsilyloxy)non-1-en-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (18″): (*R*)-MTPA ester **18″** was obtained from the reaction of alcohol **18** with (*R*)-(+)-α-methoxy-α-(trifluoromehtyl)phenylacetic acid (*R*-MTPA) by following the above mentioned procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 5H), 5.77 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.11 (m, 1H), 5.05 – 4.95 (m, 2H), 3.71 (m, 1H), 3.55 (d, *J* = 0.9 Hz, 3H), 2.11 – 1.99 (m, 2H), 1.85 – 1.69 (m, 2H), 1.58 (m, 1H), 1.36 – 1.28 (m, 2H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.02 (d, *J* = 2.7 Hz,6H) ppm.

(5*S*,8*S*)-5-(But-3-en-1-yl)-8,10,10,11,11-pentamethyl-2,4,9-trioxa-10-siladodecane (19): To a stirred solution of alcohol **18** (1.2 g, 4.41 mmol) in CH_2Cl_2 (20 mL) under nitrogen atmosphere, was added diisopropylethylamine (2.3 mL, 17.83 mmol) followed by MOMCl (0.7 mL, 8.32 mmol) at 0 ^{o}C and allowed to stir for 5 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with water (20 mL) and diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was quickly washed with 1N HCl (40 mL) to remove excess diisopropylethylamine. The organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which on purification by silica gel column chromatography (ethyl acetate/hexane = 1:19) furnished the desired MOM ether **19** (1.35 g, 97%) as a colorless liquid. $[\alpha]_D^{20}$ = +2.14 (*c* 1.08, $CHCl_3$); IR (neat) ν_{max} 2930, 1453, 1219, 1042, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.08 – 4.92 (m, 2H), 4.65 (q, *J* = 6.7 Hz, 2H), 3.79 (m, 1H), 3.57(m, 1H), 3.38 (s, 3H), 2.23-2.02 (m, 2H), 1.66 – 1.54 (m, 3H), 1.53 – 1.37 (m, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.08 (s,

9H), 0.05 (d, J = 2.9 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 138.5, 114.4, 95.4, 76.9, 68.5, 55.4, 34.9, 33.5, 30.0, 29.5, 25.8, 23.7, 18.0, −4.3, −4.7 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{36}NaO_3Si$ $[M + Na]^+$ 339.2326, Found: 339.2341.

(2*S*,5*S*)-5-(Methoxymethoxy)non-8-en-2-ol (11): To a solution of TBS-ether **19** (1.0 g, 3.16 mmol) in THF (20 mL), was added TBAF (3.79 mL of a 1 M solution in THF) at 0 ^oC. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched by addition of saturated NH_4Cl solution (15 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography (ethyl acetate/hexane = 1:2) gave alcohol **11** (602 mg, 94%) as a colorless liquid. $[\alpha]_D^{20}$ = +12.75 (*c* 1.44, $CHCl_3$); IR (neat) ν_{max} 3412, 2950, 1638, 1371, 1052, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.07 – 4.94 (m, 2H), 4.66 (s, 2H), 3.81 (m, 1H), 3.59 (m, 1H), 3.39 (s, 3H), 2.19 – 2.04 (m, 2H), 1.96 (br s, 1H), 1.68 –1.56 (m, 4H), 1.55-1.49 (m, 2H), 1.20 (d, J = 6.8 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.4, 114.6, 95.4, 77.0, 67.8, 55.6, 34.5, 33.3, 30.1, 29.5, 23.5 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_{22}O_3Na$ $[M + Na]^+$ 225.1461, Found: 225.1452.

5,7-Dihydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (20a): To a stirred solution of 2,4,6-trihydroxybenzoic acid monohydrate (**20**) (15.0 g, 88.2 mmol) in 1,2-dimethoxy ethane (250 mL), were added $SOCl_2$ (19.2 mL, 264 mmol), DMAP (2.1 g, 17.6 mmol), and acetone (19.6 mL, 264 mmol) at 0 ^oC. The reaction mixture was slowly brought to room temperature and stirred for 6 h. After completion of the reaction (monitored by TLC), volatiles were removed under reduced pressure, poured into a saturated aqueous $NaHCO_3$ solution (300 mL) and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column

chromatography over silica gel (ethyl acetate/hexane = 1:9) to afford compound **20a** (15.2 g, 82%) as light yellow solid. R_f 0.52 (ethyl acetate/hexane = 1:4); Mp. 203–205 ^{o}C; IR ($CHCl_3$) ν_{max} 3765, 3182, 2920, 1635, 1540, 1265, 1060 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 10.29 (s, 1H), 6.01 (d, J = 2.1 Hz, 1H), 5.94 (d, J = 2.1 Hz, 1H), 1.66 (s, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 166.3, 163.5, 162.1, 156.9, 106.4, 97.3, 95.3, 91.8, 25.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}O_5$: 211.0601, found: 211.0601.

7-(Benzyloxy)-5-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (20b): To a stirred solution of compound **20a** (8.0 g, 38.1 mmol) and benzyl alcohol (4.3 mL, 41.9 mmol) in THF (80 mL) at 0 °C, were added triphenyl phosphine (11.0 g, 41.9 mmol) and DIAD (8.2 mL, 41.9 mmol). The reaction mixture was warmed to room temperature and stirred for 4 h. After completion of the reaction (monitored by TLC), it was quenched with water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (70 mL), brine (70 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to furnish compound **20b** (9.6 g, 84 %) as white solid. R_f 0.55 (ethyl acetate/hexane = 1:9); Mp. 145–147 ^{o}C; IR ($CHCl_3$) ν_{max} 3200, 3021, 1684, 1640, 1586, 1501, 1275, 1160, 1105 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (s, 1H), 7.42–7.39 (m, 4H), 7.36 (m, 1H), 6.23 (d, J = 2.3 Hz, 1H), 6.08 (d, J = 2.3 Hz, 1H), 5.06 (s, 2H), 1.73 (s, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 165.1, 163.0, 156.8, 135.5, 128.7, 128.4, 127.5, 106.9, 96.5, 95.3, 93.2, 70.4, 25.6 ppm .; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{16}O_5Na$: 323.0895, found: 323.0894.

2,2-Dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl trifluoromethanesulfonate (20c): Anhydrous Et_3N (12.4 mL, 90.0 mmol) and trifluolomethanesulfonic anhydride (7.5 mL, 45.0 mmol) were successively added to a solution of compound **20b** (9.0 g, 30.0 mmol) in anhydrous dichloromethane (50 mL) and the mixture was stirred at 0 ºC for 2 h. The reaction was quenched with water (50 mL)

and the reaction mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:9) to afford compound **20c** (11.7 g, 90%) as a white solid. R_f 0.6 (ethyl acetate/hexane = 1:4); Mp. 87–89 ^oC; IR ($CHCl_3$) ν_{max} 3020, 1692, 1574, 1436, 1385, 1106, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.35 (m, 5H), 6.60 (d, J = 2.3 Hz, 1H), 6.56 (d, J = 2.3 Hz, 1H), 5.10 (s, 2H), 1.74 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.6, 158.8, 157.0, 149.9, 134.6, 128.9, 128.8, 127.6,123.5, 120.3, 117.1, 113.9, 106.6, 105.8, 102.0, 71.2, 25.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}F_3O_7S$: 433.0568, Found: 433.0572.

5-Allyl-7-(benzyloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (12): To a stirred solution of triflate **21c** (8.0 g, 18.51 mol) in anhydrous DMF (80 mL), LiCl (1.55 g, 36.90 mmol), $Pd(PPh_3)_4$ (1.06 g, 0.91 mmol) and allyltributyltin (8.6 mL, 25.98 mmol) were added at room temperature. The resulting mixture was heated (oil bath) to 80 ^oC and stirred for 4 h. After completion of the reaction (monitored by TLC), it was quenched with H_2O (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (150 mL), brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by column chromatography (ethyl acetate/hexane = 1:11) to obtain **12** (4.92 g, 82%) as a colorless liquid. R_f 0.7 (ethyl acetate/hexane = 1:4); IR (neat): ν_{max} = 2927, 1725, 1612, 1355, 1283, 1165, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.37 (m, 5H), 6.6 (d, J = 2.4 Hz, 1H), 6.4 (d, J = 2.4 Hz, 1H), 6.02 (m, 1H), 5.09–5.05(m, 4H), 3.86 (d, J = 6.5 Hz, 2H), 1.69 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0, 160.0, 159.0, 147.2, 136.4, 135.7, 128.7, 128.3, 127.6, 127.5, 116.3, 112.7, 105.0, 100.3, 70.4, 70.2, 38.4, 25.6 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}O_4$: 325.1434, Found: 325.1438.

7-(Benzyloxy)-5-(2-hydroxybut-3-enyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (21): 2,6-Lutidine (2.75 mL, 25.66 mmol), OsO_4 (2.1 mL, 0.21 mmol, 0.1M in toluene), and $NaIO_4$ (9.2 g, 43.19 mmol) were added to a stirred solution of compound **12** (3.5 g, 10.8 mmol) in dioxane and water (3:1, 60 mL) and stirred at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (30 mL). The organic solvent was removed under reduced pressure and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with 1N HCl (100 mL), water (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude mass was purified by silica gel chromatography (ethyl acetate/hexane = 1:5) to afford the resulting aldehyde (3.14 g, 89%) as a colorless viscous liquid, which was used for the next reaction without characterization.

To a stirred solution of resulting aldehyde (3.0 g, 9.2 mmol) in anhydrous THF (50 mL), was added vinyl magnesium bromide (13.8 mL, 13.8 mmol, 1M in THF) in THF at −40 ^{o}C and stirred for 30 min. After completion of the reaction (monitored by TLC), it was quenched with saturated ammonium chloride solution (30 mL) and diluted with ethyl acetate (60 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:4) to furnish the desired allylic alcohol **21** (2.83 g, 87%). IR (neat): ν_{max} = 3451, 2933, 1717, 1410, 1202, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 6.60 (d, J = 2.5 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 5.97 (ddd, J = 17.1, 10.5, 5.6 Hz, 1H), 5.26 (dt, J = 17.2, 1.5 Hz, 1H), 5.10 (dt, J = 10.5, 1.4 Hz, 1H), 4.39 (dt, J = 8.1, 5.7 Hz, 1H), 3.33 (dd, J = 13.0, 4.5 Hz, 1H), 3.23 (dd, J = 13.0, 8.1 Hz, 1H), 2.67 (br s, 1H), 1.69 (d, J = 5.5 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9, 161.5, 159.0, 145.1, 140.5, 135.6, 128.7, 128.4, 127.5, 114.5, 114.4, 105.8, 105.2, 101.0, 73.7, 70.3, 41.8, 25.8, 25.3 ppm; HRMS: *m/z* calcd for $C_{21}H_{23}O_5$ $[M + H]^+$ 355.1545, Found 355.1561.

7-(Benzyloxy)-5-(2-(*tert*-butyldimethylsilyloxy)but-3-enyl)-2,2-dimethyl-4*H*-enzo[*d*][1,3]-dioxin-4-one (10): To a stirred solution of alcohol **21** (2.0 g, 5.64 mmol), imidazole (500 mg, 7.35 mmol), and DMAP (34 mg, 0.27 mmol) in CH_2Cl_2 (40 mL), was added TBSCl (1.27 g, 8.46 mmol) at 0 ºC. The reaction mixture was warmed to room temperature, stirred for 3 h and quenched with saturated NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes = 1:5) to afford **10** (2.57 g, 97%) as a colorless liquid. IR (neat): ν_{max} = 2942, 1729, 1613, 1283, 1165, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.41-7.35 (m, 5H), 6.6 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 5.93 (ddd, J = 17.1, 10.4, 5.5 Hz, 1H), 5.21 (dt, J = 17.2, 1.6 Hz, 1H), 5.08 – 5.00 (m, 3H), 4.44 (m, 1H), 3.53 (dd, J = 12.4, 3.9 Hz, 1H), 2.86 (dd, J = 12.4, 8.4 Hz, 1H), 1.69 (d, J = 9.9 Hz, 6H), 0.83 (s, 9H), −0.10 (s, 3H), −0.24 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4, 160.3, 158.9, 145.8, 141.5, 135.8, 128.7, 128.3, 127.5, 115.6, 105.1, 104.9, 100.9, 73.4, 70.1, 43.7, 25.8, 25.5, 18.1, −4.7, −5.2 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{37}O_5Si$ $[M + H]^+$ 469.2410, Found: 469.2428.

(2*S*,5*S*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-(2-(*tert*-butyldimethyl)silyloxy)-but-3-enyl)-6-hydroxybenzoate (22): To a suspension of NaH (0.047 g, 47.52 mmol) (washed with anhydrous hexane twice to remove mineral oil and dried under vacuum) in dry THF (10 mL), alcohol **11** (0.4 g, 1.98 mmol) was added at 0 ^oC under nitrogen atmosphere and stirred for 30 min. The 1,3-benzodioxin derivative **10** (0.74 g, 1.58 mmol) was added in THF (5 mL) to the reaction mixture at 0 ^oC. The suspension was stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with cold water (10 mL) at 0 ^oC and diluted with ethyl acetate (30 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under

reduced pressure. The crude mass was purified by silica gel chromatography (ethyl acetate/hexane = 1:9) to obtain **22** (1.09 g, 90%) as a colorless liquid. $[\alpha]_D^{20}$ = +17.34 (*c* 0.28, $CHCl_3$); IR (neat) ν_{max} 3462, 2925, 1629, 1219, 1052, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 5H), 6.43 (s, 2H), 5.93 (m, 1H), 5.80 (m, 1H), 5.34 – 5.22 (m, 2H), 5.10 (m,1H), 5.06 (d, *J* = 1.5 Hz, 2H), 5.01 (m, 1H), 4.96 (m, 1H), 4.67 – 4.61 (m, 2H), 4.30 (m, 1H), 3.59 (m, 1H), 3.51 (dd, *J* =12.9, 2.6 Hz, 1H), 3.37 (s, 3H), 3.34 (m, 1H), 2.79 (dd, *J* = 12.9, 9.5 Hz, 1H), 2.61 (dd, *J* = 12.9, 9.7 Hz, 1H), 2.15 – 2.04 (m, 2H), 1.87 (m, 1H), 1.74 – 1.60 (m, 3H), 1.39 (d, *J* = 6.1 Hz, 3H), 0.79 (d, 9H), −0.18 (d, 3H), −0.38 (d, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.1, 171.0, 165.6, 165.3, 162.6, 143.4, 143.4, 141.4, 138.2, 136.3, 128.6, 128.1, 127.4, 114.8, 114.2, 113.9, 113.7, 105.8, 105.3, 100.5, 100.4, 95.6, 76.5, 76.5, 73.9, 73.8, 72.6, 72.5, 69.8, 55.6, 44.8, 44.4, 33.5, 33.4, 31.6, 31.4, 30.2, 30.2, 29.5, 29.4, 25.8, 25.8, 20.2, 20.2, 18.1, −4.8, −4.9, −5.4, −5.5 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{35}H_{52}O_7NaSi$ $[M + Na]^+$ 635.3375, Found: 635.3380.

(2*S*,5*S*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-(2-(*tert*-butyldimethyl)silyloxy) but-3-enyl)-6-methoxybenzoate (23): To a suspension of NaH (0.078 g, 3.25 mmol) (washed with hexane twice to remove mineral oil and dried under vacuum) in anhydrous THF (5 mL), phenolic compound **22** (0.5 g, 0.81 mmol) was added in THF (5 mL) at 0 ^oC under nitrogen atmosphere and stirred for 30 min. Methyl iodide (0.07 mL, 0.49 mmol) was added at the same temperature. The reaction mixture was warmed to room temperature and stirring was continued for 1 h. After completion of the reaction (monitored by TLC), it was quenched with cold water (15 mL) at 0 ^oC and diluted with ethyl acetate (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:15) to obtain **23** (0.455 g, 89%) as a colorless liquid. $[\alpha]_D^{20}$ = +6.09 (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 2926, 2856, 1717, 1598, 1457, 1155, 1038, 775 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.44-7.30 (m, 5H), 6.47 (dd, J = 3.9, 2.2 Hz, 1H), 6.41 (d, J = 1.95 Hz, 1H), 5.87 – 5.76 (m, 2H), 5.20 – 5.12 (m, 2H), 5.09 – 4.99 (m, 4H), 4.95 (m, 1H), 4.65 (s, 2H), 4.35 (m, 1H), 3.75 (s, 3H), 3.60 (m, 1H), 3.38 (s, 3H), 2.80 (m, 1H), 2.63 (m, 1H), 2.19 – 2.04 (m, 2H), 1.82 – 1.54 (m, 6H), 1.34 (t, J = 5.0 Hz, 3H), 0.84 (s, 9H), −0.11 (s, 3H), −0.21 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 167.9, 159.7, 157.8, 141.1, 141.1, 138.5, 138.4, 136.6, 128.6, 128.1, 127.5, 114.6, 113.8, 109.1, 109.0, 97.8, 95.5, 74.0, 73.9, 71.7, 70.0, 55.8, 55.5, 42.6, 33.6, 31.4, 29.9, 29.8, 29.5, 25.9, 20.2, 20.1, 18.1, −4.9, −5.2 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{36}H_{55}O_7Si$ $[M + H]^+$ 627.3712, Found: 627.3717.

(2*S*,5*S*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-(2-hydroxybut-3-enyl)-6-methoxy benzoate (24): The HF·pyridine complex (70% HF, 3.0 mL) was added dropwise to a stirred solution of compound **23** (300 mg, 0.48 mmol) in THF (7.0 mL, in a plastic test tube) at 0 ^oC. The reaction mixture was allowed to warm to room temperature. After 10 h, the mixture was partitioned between an ice-cooled mixture of ethyl acetate (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:4) to furnish **24** (201 mg, 82%) as a colorless liquid. $[\alpha]_D^{20}$ = +9.1 (*c* 0.6, $CHCl_3$); IR (neat) ν_{max} 3352, 2856, 1717, 1598, 1457, 1264, 1155, 1038, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 6.48 – 6.42 (m, 2H), 5.96 – 5.75 (m, 2H), 5.28 (m, 1H), 5.19 (ddd, J = 7.5, 6.2, 4.2 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 5.07 (s, 3H), 5.02 (m, 1H), 4.96 (d, J = 10.2 Hz, 1H), 4.65 (d, J = 2.8 Hz, 1H), 4.31 (m, 1H), 3.77 (s, 1H), 3.59 (m, 1H), 3.38 (d, J = 2.0 Hz, 1H), 2.85 (dd, J = 13.7, 4.4 Hz, 1H), 2.68 (ddd, J = 13.7, 8.8, 4.9 Hz, 1H), 2.13 (m, 1H), 1.82 – 1.62 (m, 4H), 1.59 – 1.53 (m, 2H), 1.34 (dd, J = 6.2, 4.4 Hz, 1H)ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 168.5, 160.5, 158.3, 140.5, 140.5, 138.6, 138.4, 136.4, 128.6, 128.1, 127.5, 117.6, 116.8, 114.6, 114.5, 107.6, 98.1, 95.5, 73.1, 72.3, 70.1, 55.7,

55.6, 41.5, 41.5, 33.6, 33.5, 31.5, 29.9, 29.7, 29.5, 20.3, 20.1 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{30}H_{40}NaO_7$ $[M + Na]^+$ 535.2666, Found: 535.2681.

(2*S*,5*S*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-methoxy-6-(2-oxobut-3-enyl) benzoate (9): To a stirred solution of allyl alcohol **24** (190 mg, 0.38 mmol) in CH_2Cl_2 (20 mL), was added Dess-Martin periodinane (230 mg, 0.57 mmol) at 0 ^oC. The resulting reaction mixture was stirred at same temperature for 1 h. After completion of the reaction (monitored by TLC), it was filtered through a small bed of Celite and washed with CH_2Cl_2 (20 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude reaction mass by column chromatography on silica gel (ethyl acetate/hexane = 3:17) afforded the ketone **9** (169 mg, 89%) as a colorless liquid. $[\alpha]_D^{20}$ = +7.97 (*c* 0.32, $CHCl_3$); IR (neat) ν_{max} 2924, 1649, 1582, 1219, 1027, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 6.47 (d J = 2.2 Hz, 1H), 6.44 – 6.37 (m, 2H), 6.29 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.86 – 5.77 (m, 2H), 5.13 (m, 1H), 5.04 (s, 2H), 5.01 (m, 1H), 4.95 (m, 1H), 4.64 (s, 2H), 3.89 (dd, *J* = 16.2 Hz, 2H), 3.78 (s, 3H), 3.59 (m, 1H), 3.37 (s, 3H), 2.17 – 2.06 (m, 2H), 1.76 – 1.57 (m, 6H), 1.30 (d, *J* = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (100 MHz, $CDCl_3$) δ 196.6, 167.4, 160.7, 158.7, 138.4, 136.3, 135.3, 134.8, 129.0, 128.6, 128.1, 127.5, 114.6, 107.8, 98.6, 95.5, 76.6, 72.0, 70.2, 55.8, 55.6, 45.2, 33.5, 31.4, 29.8, 29.5, 20.1 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{30}H_{38}NaO_7$ $[M + Na]^+$ 533.2510, Found: 533.2504.

(3*S*,6*S*,*E*)-14-(Benzyloxy)-16-methoxy-6-(methoxymethoxy)-3-methyl-3,4,5,6,7,8-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,11(12*H*)-dione (7): Hovyeda Grubbs second generation catalyst (27 mg, 0.03 mmol) was dissolved in dry, deoxygenated CH_2Cl_2 (80 mL) under argon atmosphere. After the solution was heated (oil bath) to reflux, diene **9** (140 mg, 0.3 mmol) dissolved in anhydrous and deoxygenated CH_2Cl_2 (30 mL) was added slowly via syringe (ca. 30 min) to the reaction mixture.

It was then stirred under reflux conditions (oil bath) for an additional 3 h. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:4) to obtain macrolactone **7** (106 mg, 80%) as a colorless liquid. $[\alpha]_D^{20}$ = +31.1 (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 2923, 2314, 1612, 1218, 1157, 1035, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 6.77 (m, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 6.47 (d, *J* = 2.1, 1H), 6.10 (d, *J* = 15.5 Hz, 1H), 5.16 (m, 1H), 5.05 (s, 2H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.28 (d, *J* = 15.5 Hz, 1H), 3.78 (s, 3H), 3.53 (m, 1H), 3.47 (d, *J* = 15.5 Hz, 1H), 3.37 (s, 3H), 2.30 – 2.24 (m, 2H), 1.94 (m, 1H), 1.86 – 1.68 (m, 3H), 1.65-1.57 (m, 2H), 1.36 (d, *J* = 6.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.9, 167.7, 160.8, 159.3, 147.5, 136.2, 135.7, 129.4, 128.6, 128.2, 127.6, 116.9, 107.7, 98.8, 95.4, 75.0, 70.4, 70.2, 56.0, 55.5, 45.4, 31.4, 30.8, 28.7, 27.7, 20.0 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{28}H_{34}NaO_7$ $[M + Na]^+$ 505.2197, Found: 505.2173.

(2*S*,5*R*,8*R*)-Dechlorogreensporone F (4a) (Revised Structure):To a stirred solution of **7** (18 mg, 0.036 mmol) in CH_2Cl_2 (5 mL), $TiCl_4$ (0.36 mL, 0.36 mmol, 1 M in CH_2Cl_2) was added at 0 °C and the reaction mixture stirred at room temperature for 20 min. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:1) to afford compound **4** (11 mg, 84%) as a white amorphous solid. $[\alpha]_D^{20}$ = −29.8 (*c* 1.0, MeOH); IR (neat) ν_{max} 3446, 2922, 1746, 1456, 1220, 1157, 1036, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, *J* = 1.8 Hz, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 5.90 (br s, 1H), 5.27 (m, 1H), 4.13 (m, 1H), 4.02 (d, *J* = 16.9 Hz, 1H), 3.91 (d, *J* = 16.9 Hz, 1H), 3.82 (m, 1H), 3.77 (s, 3H), 2.64 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.55 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.98 (m, 1H), 1.93 (m, 1H),1.84 (m, 2H), 1.65 (m, 1H), 1.54 (m,

1H), 1.50 (m, 2H), 1.32 (d, *J* = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 207.7, 167.6, 159.0, 157.7, 134.1, 117.2, 109.2, 98.3, 79.4, 76.1, 72.6, 55.9, 48.8, 47.9, 33.3, 32.9, 31.3, 30.4, 20.8 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{25}O_6$ $[M + H]^+$ 349.1651.1646, Found: 349.1652.

(3*S*,6*S*,*E*)-14-(Benzyloxy)-13-chloro-16-methoxy-6-methoxymethoxy)-3-methyl-3,4,5,6,7,8-hexa hydro-1*H*-benzo[*c*][1]oxacyclo-tetradecine-1,11(12*H*)-dione (8): To the solution of compound **7** (40 mg, 0.08 mmol) in dry CH_2Cl_2 (5 mL), was added SO_2Cl_2 (0.01 mL, 0.13 mmol)) in CH_2Cl_2 (2 mL) at 0 °C. After 30 min the reaction was quenched by the addition of 5% aqueous NH_4Cl solution (5 mL), diluted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:3) to give compound **8** (36.5 mg, 85%) as a colorless liquid. $[\alpha]_D^{20}$ = +5.20 (*c* 2.0, CH_3OH); IR (neat) ν_{max} 2816, 2305, 1425, 1213, 1029, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.32 (m, 5H), 6.78 (dt, *J* = 15.7, 8.0 Hz, 1H), 6.53 (s, 1H), 6.09 (d, *J* = 15.4 Hz, 1H), 5.20 (s, 2H), 5.11 (m, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.14 (d, *J* = 16.9 Hz, 1H), 3.98 (d, *J* = 16.9 Hz, 1H), 3.78 (s, 3H), 3.42 (m, 1H), 3.35 (s, 3H), 2.28– 2.20 (m, 2H), 2.07 – 1.90 (m, 2H), 1.77 – 1.60 (m, 4H), 1.33 (d, *J* = 6.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 195.0, 166.9, 156.7, 156.0, 147.2, 135.9, 133.2, 128.7, 128.3, 128.2, 127.0, 118.2, 116.7, 97.7, 95.3, 75.7, 71.4, 71.1, 56.3, 55.5, 44.0, 31.4, 31.0, 28.9, 27.9, 19.8 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{28}H_{33}O_7ClNa$ $[M + Na]^+$ 539.1813, Found: 539.1813.

(2*S*,5*R*,8*R*)-Greensporone F (5a) (Revised Structure): To a stirred solution of **8** (30 mg, 0.057 mmol) in CH_2Cl_2 (5 mL), $TiCl_4$ (1.14 mL, 1.14 mmol, 1 M in CH_2Cl_2) was added at 0 °C and the reaction mixture stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (10 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure,

and the residue purified by silica gel column chromatography (ethyl acetate/hexane = 1:1) to afford compound **5** (18.5 mg, 83%) as a white amorphous solid. $[\alpha]_D^{20}$ = −35.2 (*c* 0.25, MeOH); IR (neat) ν_{max} 3341, 2714, 1525, 1213, 1083, 1029, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.87 (br s, 1H), 5.23 (m, 1H), 4.35 (m, 1H), 4.13 (d, *J* = 18.5 Hz, 1H), 4.0 (d, *J* = 18.4 Hz, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 2.81 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.55 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.02 (m, 1H), 1.91 (m, 1H), 1.90 (m, 1H), 1.80 (m, 1H),1.75 (m, 1H),1.71 (m, 1H), 1.55 (m, 1H), 1.39 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.0, 166.9, 157.0, 153.3, 132.0, 119.1, 113.1, 99.1, 79.3, 76.3, 73.4, 56.3, 48.6, 46.6, 34.7, 33.8, 31.5, 29.8, 21.45 ppm. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{23}O_6ClNa$ $[M + Na]^+$ 405.1081, Found: 405.1088.

***tert*-Butyldimethyl((*S*)-4-((*S*)-oxiran-2-yl)butan-2-yloxy)silane (17a):** A mixture of (*S*,*S*)-(-)-*N*-*N*'-bis(3,5-di-*tert*-butyl salicylidene)-1,2-cyclohexanediamino-cobalt-II (0.131 g, 0.21 mmol) toluene (4 mL) and acetic acid (0.1 mL, 1.78 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The oxirane **16** (10.0 g, 43.47 mmol) was added in one portion, and the stirred mixture was cooled in an ice water bath. Water (0.43 mL, 23.88 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 ^oC. After addition was complete (1 h), the ice bath was removed and the reaction mixture was stirred at room temperature for 24 h. The crude reaction mixture was purified by silica gel column chromatography to afford the chiral epoxide **17a** (4.5 g, 45%) as a colorless viscous liquid. $[\alpha]_D^{20}$ = +9.2 (*c* 1.2, $CHCl_3$); IR (neat) 2962, 2633, 1647, 1435, 1389, 1057, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (m, 1H), 2.91 (m, 1H), 2.74 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.66–1.48 (m, 4H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 4.8 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 68.2, 52.5, 47.1, 35.8, 28.9, 26.0, 25.9, 23.9, 19.0, 18.1, −4.4, −4.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{27}O_2Si$: 231.1780, Found: 231.1778.

(5*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)non-1-en-5-ol (18a): Compound **18a** (2.9 g, 89%) was prepared from **17a** by following the similar procedure described for the synthesis of compound **18**. $[\alpha]_D^{20}$ = +7.4 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3394, 2939, 2862, 1461, 1373, 1254, 1135, 1059, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.07– 4.94 (m, 2H), 3.88 (m, 1H), 3.58 (m, 1H), 2.25–2.08 (m, 2H), 1.61–1.49 (m, 6H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.7, 114.6, 71.5, 68.7, 36.6, 35.8, 33.2, 30.1, 25.9, 23.2, 18.1, −4.5, −4.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{33}O_2Si$: 273.2250, Found: 273.2255.

Determination of absolute stereochemistry of hydroxyl group in compound (18a):

(*S*)-((5*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)non-1-en-5-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (18a′): (*S*)-MTPA ester **18a′** was prepared as a colorless liquid from **18a** following the similar protocol utilized for the synthesis of **18′**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 5H), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.09 (m, 1H), 5.04 – 4.96 (m, 2H), 3.69 (dd, *J* = 11.9, 6.0 Hz, 1H), 3.56 (d, *J* = 1.2 Hz, 3H), 2.12 – 2.03 (m, 2H), 1.83 – 1.67 (m, 3H), 1.52 (m, 1H), 1.32 – 1.25 (m, 2H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.01 (d, *J* = 6.2 Hz, 3H) ppm.

(*R*)-((5*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)non-1-en-5-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (18a″): (*R*)-MTPA ester **18a″** was prepared as a colorless liquid from **18a** following the similar protocol utilized for the synthesis of **18′**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 5H), 5.72 (ddt, *J* = 16.3, 9.6, 6.6 Hz, 1H), 5.09 (m, 1H), 4.98–4.92 (m, 2H), 3.76 (dd, *J* = 11.9, 6.0 Hz, 1H), 3.55 (d, *J* = 1.0 Hz, 3H), 2.02–1.89 (m, 2H), 1.80 (m, 1H), 1.73–1.59 (m, 3H), 1.45–1.39 (m, 2H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 6.9 Hz, 3H) ppm.

(5*R*,8*S*)-5-(But-3-enyl)-8,10,10,11,11-pentamethyl-2,4,9-trioxa-10-siladodecane (19a): Compound **19a** (1.5 g, 98%) was prepared from **18a** by following the similar procedure described for the synthesis of compound **19**. $[\alpha]_D^{20}$ = +11.5 (*c* 1.9, $CHCl_3$); IR (neat) ν_{max} 2943, 1459, 1373, 1216,1158,

1063, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.93 (m, 2H), 4.65 (q, *J* = 6.7 Hz, 2H), 3.77 (m, 1H), 3.54 (m, 1H), 3.38 (s, 3H), 2.18 – 2.05 (m, 2H), 1.69 – 1.51 (m, 4H), 1.48 – 1.42 (m, 2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 1.0 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$) *δ* 138.6, 114.5, 95.5, 77.1, 68.8, 55.5, 35.1, 33.6, 30.4, 29.6, 25.9, 23.9, 18.1, −4.4, −4.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{36}O_3SiNa$: 339.2331, Found: 339.2339.

(2*S*,5*R*)-5-(Methoxymethoxy)non-8-en-2-ol (11a): Compound **11a** (0.75 g, 91%) was prepared from **19a** by following the similar procedure described for the synthesis of compound **11**. $[\alpha]_D^{20}$ = +7.4 (*c* 0.6, $CHCl_3$); IR (neat) ν_{max} 3482, 2937, 1645, 1378, 1043, 953, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06 – 4.93 (m, 2H), 4.67 (s, 2H), 3.79 (m, 1H), 3.61 (m, 1H), 3.40 (s, 3H), 2.18 – 2.06 (m, 2H), 1.71 – 1.50 (m, 6H), 1.20 (d, *J* = 6.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 138.4, 114.6, 95.6, 77.1, 68.1, 55.6, 34.6, 33.4, 30.5, 29.6, 23.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{22}O_3Na$: 225.1467, Found: 225.1474.

(2*S*,5*R*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-(2-(*tert*-butyldimethyl)silyloxy)-but-3-enyl)-6-hydroxybenzoate (22a): Compound **22a** (0.82 g, 90%) was obtained from the coupling of **10** and **11a** by following the similar procedure used for the synthesis of compound **22**. $[\alpha]_D^{20}$ = +21.06 (*c* 0.85, $CHCl_3$); IR (neat) ν_{max} 3448, 2938, 1646, 1255, 1036, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.41 – 7.32 (m, 5H), 6.44 (s, 2H), 5.92 (m, 1H), 5.81 (m, 1H), 5.30 – 5.21 (m, 2H), 5.11 – 5.06 (m, 3H), 5.05 – 4.94 (m, 2H), 4.67 – 4.62 (m, 2H), 4.31 (m, 1H), 3.56 (m, 1H), 3.37 (d, *J* = 2.4 Hz, 3H), 2.81 (dd, *J* = 13.0, 9.6 Hz, 1H), 2.60 (dd, *J* = 12.9, 9.8 Hz, 1H), 2.15 – 2.06 (m, 2H), 1.80 – 1.75 (m, 1H), 1.68 – 1.53 (m, 5H), 1.39 (dd, *J* = 6.3, 0.7 Hz, 3H), 0.80 (d, *J* = 4.8 Hz, 9H), -0.18 (d, *J* = 2.1 Hz, 3H), −0.37 (d, *J* = 8.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 165.6, 165.3, 162.6, 162.5, 143.4, 141.4, 141.3, 138.2, 136.2, 128.6, 128.1, 127.4, 114.8, 114.2, 113.9, 113.7, 105.7, 105.3, 100.5, 100.4, 95.7, 95.6, 73.9, 73.7, 72.8, 72.7, 69.8, 55.6, 44.8, 44.3, 33.6, 33.4, 31.8, 31.7,

30.4, 30.3, 29.5, 29.4, 25.8, 20.2, 20.1, 18.1, −4.86, −4.9, −5.4, −5.5, ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{35}H_{52}O_7SiNa$ $[M + Na]^+$ 635.3380, Found: 635.3388.

(2*S*,5*R*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-(2-(*tert*-butyldimethyl)silyloxy) but-3-enyl)-6-methoxybenzoate (23a): Compound **23a** (0.81 g, 88%) was prepared from **22a** by following the similar procedure described for the synthesis of compound **23**. $[\alpha]_D^{20}$ = +10.67 (*c* 0.3, $CHCl_3$); IR (neat) ν_{max} 2940, 2892, 1722, 1602, 1462, 1274, 1159, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 5H), 6.47 (dd, *J* = 5.2, 2.2 Hz, 1H), 6.42 (dd, *J* = 2.6, 1.9 Hz, 1H), 5.86 – 5.77 (m, 2H), 5.19 – 5.12 (m, 2H), 5.09 – 4.99 (m, 4H), 4.96 (m, 1H), 4.67 – 4.62 (m, 2H), 4.36 (m, 1H), 3.76 (s, 3H), 3.57 (m, 1H), 3.37 (d, *J* = 0.7 Hz, 3H), 2.81 (ddd, *J* = 24.1, 13.4, 4.5 Hz, 1H), 2.64 (ddd, *J* = 13.4, 11.0, 8.7 Hz, 1H), 2.17 – 2.06 (m, 2H), 1.73 – 1.69 (m, 2H), 1.66– 1.54 (m,4H), 1.34 (t, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), −0.10 (d, *J* = 2.4 Hz, 3H), −0.21 (d, *J* = 1.8 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 167.8, 159.7, 157.8, 141.1, 141.0, 138.4, 138.3, 136.6, 129.7, 128.6, 128.05, 127.5, 117.8, 115.2, 114.6, 113.8, 109.1, 108.9, 97.7, 95.5, 73.9, 73.8, 72.0, 70.0, 55.8, 55.5, 42.6, 33.6, 31.7, 30.2, 30.1, 29.5, 25.9, 20.2, 20.1, 18.1, −4.9, −5.2 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{36}H_{55}O_7Si$ $[M + H]^+$ 627.3717, Found: 627.3723.

(2*S*,5*R*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-(2-hydroxybut-3-enyl)-6-methoxy-benzoate (24a): Compound **24a** (0.55 g, 85%) was prepared from **23a** by following the similar procedure described for the synthesis of compound **24**. $[\alpha]_D^{20}$ = +7.19 (*c* 0.32, $CHCl_3$); IR (neat) ν_{max} 3451, 2932, 1756, 1647, 1457, 1284, 1162, 1044, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.44 – 7.34 (m, 5H), 6.45 (m, 2H), 5.95 – 5.76 (m, 2H), 5.28 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.17 (dd, *J* = 12.0, 6.0 Hz, 1H), 5.11 – 4.94 (m, 5H), 4.68 – 4.63 (m, 2H), 4.31 (m, 1H), 3.77 (s, 3H), 3.58 (m, 1H), 3.37 (d, *J* = 3.5 Hz, 3H), 2.84 (m, 1H), 2.69 (ddd, *J* = 13.6, 8.8, 3.4 Hz, 1H), 2.18 – 2.07 (m, 2H), 1.75 – 1.69 (m, 2H), 1.65 – 1.56 (m, 4H), 1.34 (dd, *J* = 6.2, 4.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 168.6, 168.5, 160.6, 158.3, 140.6, 140.5, 138.6, 138.4, 136.4, 128.6, 128.1, 127.51, 117.6, 114.7,

114.5, 107.6, 98.1, 95.5, 76.8, 73.2, 73.1, 72.6, 72.5, 70.1, 55.7, 55.6, 41.5, 33.6, 31.6, 30.0, 29.5, 20.1, 20.0 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{30}H_{40}O_7Na$ $[M + Na]^+$ 535.2672, Found: 535.2671.

(2*S*,5*R*)-5-(Methoxymethoxy)non-8-en-2-yl-4-(benzyloxy)-2-methoxy-6-(2-oxobut-3-enyl) benzoate (9a): Compound **9a** (0.32 g, 91%) was prepared from **24a** by following the similar procedure described for the synthesis of compound **9**. $[\alpha]_D^{20}$ = +4.6 (c 0.5, $CHCl_3$); IR (neat) ν_{max} 2915, 1642, 1524, 1348, 1212, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H), 6.48 (d, *J* = 2.2 Hz, 1H), 6.45 – 6.37 (m, 2H), 6.29 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.85 – 5.76 (m, 2H), 5.10 (dd, *J* = 12.3, 6.2 Hz, 1H), 5.04 (s, 2H), 5.02 – 4.93 (m, 2H), 4.64 (d, *J* = 0.6 Hz, 2H), 3.89 (q, *J* = 16.3 Hz, 2H), 3.78 (s, 3H), 3.55 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.37 (s, 3H), 2.12 (dt, *J* = 22.4, 7.9 Hz, 2H), 1.71 – 1.55 (m, 6H), 1.30 (d, *J* = 6.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.6, 167.4, 160.7, 158.7, 138.4, 136.3, 135.3, 134.7, 129.0, 128.6, 128.1, 127.5, 117.3, 114.6, 107.8, 98.6, 95.5, 72.2, 70.1, 55.8, 55.6, 45.2, 33.6, 31.7, 30.1, 29.5, 20.0.1 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{30}H_{38}O_7Na$ $[M + Na]^+$ 533.2515, Found: 533.2518.

(3*S*,6*R*,*E*)-14-(Benzyloxy)-16-methoxy-6-(methoxymethoxy)-3-methyl-,4,5,6,7,8-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,11(12*H*)-dione (7a): Compound **7a** (0.21 g, 80%) was prepared from **9a** by following the similar procedure described for the synthesis of compound **7**. $[\alpha]_D^{20}$ = −9.2 (*c* 0.55, $CHCl_3$); IR (neat) ν_{max} 2874, 2402, 1430, 1215, 1025, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 5H), 6.81(m, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.21 (m, 1H), 5.06 (q, *J* = 11.4 Hz, 2H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.27 (d, *J* = 14.9 Hz, 1H), 3.77 (s, 3H), 3.54 (m , 1H), 3.45 (d, *J* = 14.9 Hz, 1H), 3.33 (m, 3H), 2.42 (m, 1H), 2.18 (m, 1H), 1.88 (m, 1H), 1.84 – 1.61 (m, 5H), 1.34 (d, *J* = 6.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.12, 167.7, 160.6, 149.0, 136.3, 134.6, 130.7, 128.6, 128.1, 127.7, 117.1, 107.7, 98.6, 95.3, 77.5, 73.0, 70.2, 60.4, 55.8, 55.5, 43.5, 31.4, 31.2, 30.6, 29.0, 20.3 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{28}H_{34}O_7Na$ $[M + Na]^+$ 505.2202, Found: 505.2201.

(2*S*,5*S*,8*S*)-Dechlorogreensporone (4) (proposed structure): Compound **4** (7 mg, 82%) was prepared from **7a** by following the similar procedure described for the synthesis of compound **4**. $[\alpha]_D^{20}$ = +26.25 (*c* 0.16, CH_3OH); IR (neat) ν_{max} 3435, 2925, 1720, 1283, 1163, 1097, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (br s, 1H), 6.31 (d, *J* = 2.1 Hz, 1H), 6.12 (d, *J* = 2.0 Hz, 1H), 5.38 (m, 1H), 4.33 (qd, *J* = 7.2, 4.2 Hz, 1H), 4.00 (d, *J* = 17.1 Hz, 1H), 3.93 (m,1H), 3.76 (s, 3H), 3.75 (d, *J* = 17.1 Hz, 1H), 2.53 (qd, *J* = 12.8, 6.0 Hz, 2H), 2.02 (m, 1H), 1.97 (m, 2H), 1.77 (m, 1H), 1.66 (m, 1H), 1.62 (m, 1H), 1.53 (m, 2H), 1.28 (d, *J* = 6.5 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.5, 167.7, 158.3, 157.8, 133.5, 117.8, 109.0, 98.3, 79.4, 77.1, 70.7, 55.8, 49.2, 47.7, 31.7, 31.6, 30.5, 30.3, 18.6 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{25}O_6$ $[M + H]^+$ 349.1651, Found: 349.1643.

(3*S*,6*R*,*E*)-14-(Benzyloxy)-13-chloro-16-methoxy-6-(methoxymethoxy)-3-methyl-3,4,5,6,7,8-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,11(12*H*)-dione (8a): Compound **8a** (30 mg, 84%) was prepared from **7a** by following the similar procedure described for the synthesis of compound **8**. $[\alpha]_D^{20}$ = −7.1 (*c* 0.6, $CHCl_3$); IR (neat) ν_{max} 2839, 2402, 1430, 1215, 1025, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.31 (m, 5H), 6.81 (ddd, *J* = 15.8, 9.6, 6.1 Hz, 1H), 6.52 (s, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.20 (s, 2H), 5.09 (3, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 4.12 (d, *J* = 17.1 Hz, 1H), 4.01 (d, *J* = 17.1 Hz, 1H), 3.76 (s, 3H), 3.42 (m, 1H), 3.36 (s, 3H), 2.49 (m, 1H), 2.13 (m, 1H), 1.93 (m, 1H), 1.78 – 1.61 (m, 3H), 1.52–1.41 (m, 2H), 1.29 (d, *J* = 6.3 Hz, 1H ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.8, 166.9, 156.2, 155.8, 149.0, 136.0, 132.5, 130.0, 128.7, 128.2, 127.1, 118.5, 116.8, 97.6, 95.1, 78.3, 73.4, 71.1, 56.2, 55.5, 42.3, 32.5, 31.7, 31.5, 29.4, 20.8 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{34}O_7Cl$: 517.1993, Found: 517.1993.

(2*S*,5*S*,8*S*)-Greensporone (5) (proposed structure): Compound **5** (6 mg, 81%) was prepared from **8a** by following the similar procedure described for the synthesis of compound **5**. $[\alpha]_D^{20}$ = +30.5 (*c* 0.12, CH_3OH); IR (neat) ν_{max} 3325, 2835 , 1520, 1163, 1063, 1098, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.83 (br s, 1H), 5.36 (m, 1H), 4.38 (m, 1H), 4.04 (d, *J* = 0.7 Hz, 2H), 3.91 (m, 1H), 3.78

(s, 3H), 2.84 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.46 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.04 (m, 1H), 1.95 (m, 1H),1.91 (m, 1H), 1.66 (m, 2H), 1.48 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 204.9, 166.7, 156.1, 152.9, 131.3, 119.4, 112.6, 98.8, 79.1, 76.9, 71.0, 56.0, 47.7, 46.3, 31.7, 31.7, 30.2, 29.6, 18.5 ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{24}O_6Cl$ $[M + H]^+$ 383.1261, Found: 383.1254.

Supporting Information Available: Copies of ^{1}H, ^{13}C NMR spectra for all new compounds and 2D NMR spectra for **4**, **5**, **4a**, and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

Author Contributions: ≠J.G. and A.V.V.R. contributed equally.

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