ChemPubSoc Europe

DOI: 10.1002/ejoc.201600625

EurJOC European Journal of Organic Chemistry

Full Paper

Stereodivergence in Synthesis

Synthesis of Ophiocerins A, B and C, Botryolide E, Decarestrictine O, Stagonolide C and 9-*epi*-Stagonolide C Employing Chiral Hexane-1,2,3,5-tetraol Derivatives as Building Blocks

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Abstract: An organocatalytic approach to the synthesis of (2*R*,3*S*)-hexane-1,2,3,5-tetraol (**11**) derivatives (in the forms of different stereoisomers and bearing different protecting groups) has been developed. The key chiral intermediates **11** were prepared with complete stereocontrol through the proline-catalyzed intermolecular aldol reaction between acetone and D-glyceraldehyde acetonide. The synthetic utility of the intermediates was demonstrated by their transformation into the title hydroxylated pyrans and a variety of unsaturated lactones through standard synthetic protocols.

Introduction

Despite extensive research, development of efficient and simple protocols for the synthesis of complex organic molecules always poses a challenge to the synthetic organic chemist.[1] Among these challenges, one of the most vital is to construct a versatile and stereodivergent route that leads to various potent compounds from a common starting material.[2] Simple chiral synthons containing high functional density and multiple stereogenic centres are of common interest in this regard. In continuation of our interest in organocatalysis[3] and the enantioselective synthesis of naturally occurring unsaturated lactones,[4] we have taken up the asymmetric synthesis of bioactive molecules such as **1**–**7** (Figure 1), by employing (2*R*,3*S*)-hexane-1,2,3,5-tetraol derivatives **11** (in the form of different stereoisomers and bearing different protecting groups) as important building blocks and general structural motifs for the syntheses. Here we have developed a conceptually new and efficient strategy for the synthesis of the common chiral intermediates **11** by employing the proline-catalyzed intermolecular aldol reaction between acetone and D-glyceraldehyde acetonide as the key step. We used various stereoisomers based on the common intermediates **11** for the asymmetric synthesis of the following molecules.

(i) Ophiocerins A, B and C (**1**, **2**, **3**), each based on a tetrahydropyran ring, with an interesting array of substituents, were isolated from freshwater aquatic fungi *Ophioceras venezuelense* and are found in a wide variety of natural products that show broad spectrum biological activity.[5]

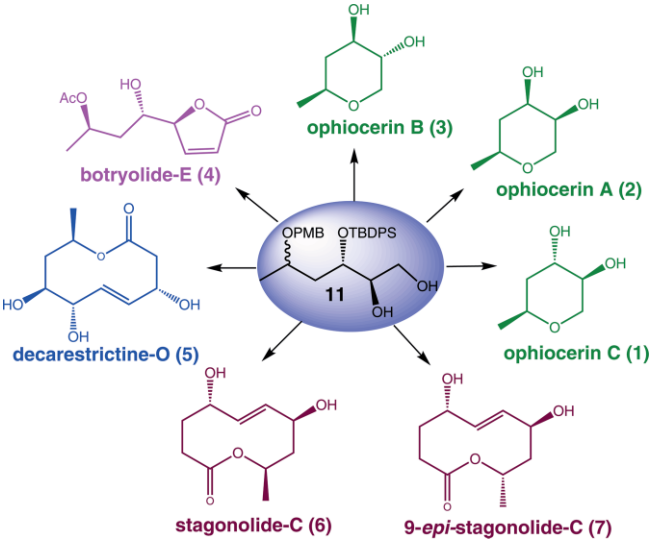

Figure 1. Structures of hydroxylated pyrans **1**–**3** and unsaturated lactones **4**–**7**.

(ii) Botryolide E (**4**) was isolated from cultures of fungicolous *Botryotrichum sp.* (NRRL 38180) and showed promising antibacterial activity against *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96) and *Escherichia coli* (MTCC 443), as well as antifungal activity against *Aspergillus niger* (MTCC 1344) and *Saccharomyces cerevisiae* (MTCC 171).[6]

(iii) Decarestrictine O (**5**), a secondary metabolite, was isolated from various *Penicillium* strains and showed interesting activity against cell line tests with HEP-G2 liver cells, having an inhibitory effect on cholesterol biosynthesis. Thanks to this property, decarestrictine O has been marked as a new class of cholesterol-lowering drug.[7]

(iv) Stagonolide C (**6**) was isolated from the liquid culture filtrate of *Stagonospora cirsii* (a pathogen of *Cirsium arvense*),

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600625.

which has attracted considerable attention due to its potential mycoherbicide properties, acting by causing necrotic leison on leaves.[8]

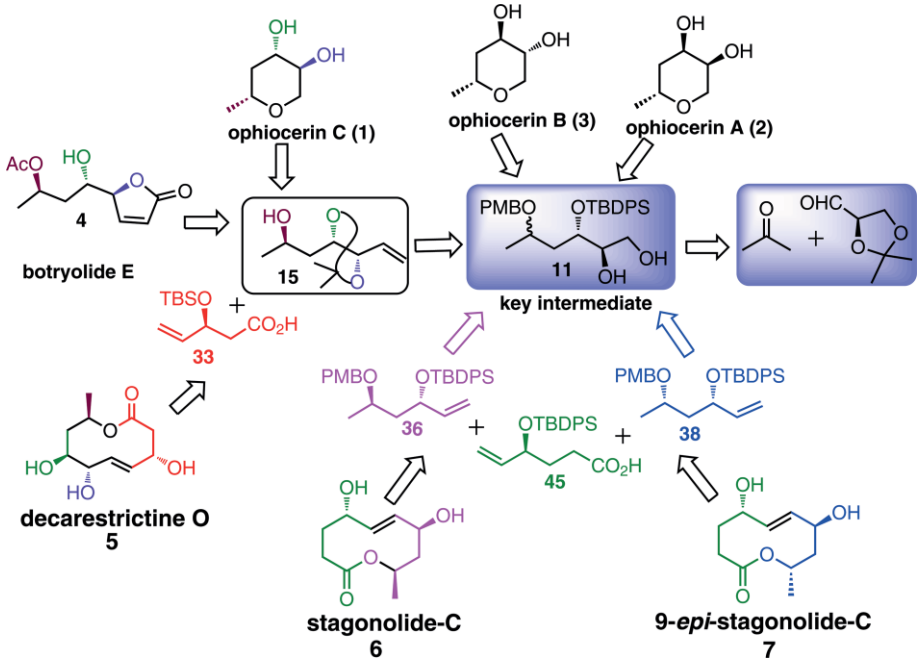
Due to their wide variety of biological activities and interesting structural features with an array of functionalities, such as stereochemically pure hydroxy appendages and/or olefinic moieties placed in strictly defined locations and having well-defined geometries, the above compounds have attracted the attention of synthetic chemists as prominent synthetic targets, and therefore a great deal of interest has been devoted to their synthesis. The previously described synthetic approaches to botryolide E involve either a chiral pool approach or the asymmetric transformation of chiral propylene oxide or allylation of acetaldehyde.[9] The previously reported syntheses of ophiocerins A, B and C used chiral-pool sources such as carbohydrates, (*R*)-(–)-pent-4-en-2-ol or tartaric acid, asymmetric transformation of chiral epoxides or Sharpless kinetic resolution.[10] Likewise, a few comparatively tedious and lengthy syntheses of decarestrictine O have been reported, either from a chiral building block or through asymmetric dihydroxylation.[11] There are some reports on the synthesis of stagonolide C by employing the well-established RCM protocol, a chiral-pool approach or combined metal/enzyme DKR strategies.[12]

Results and Discussion

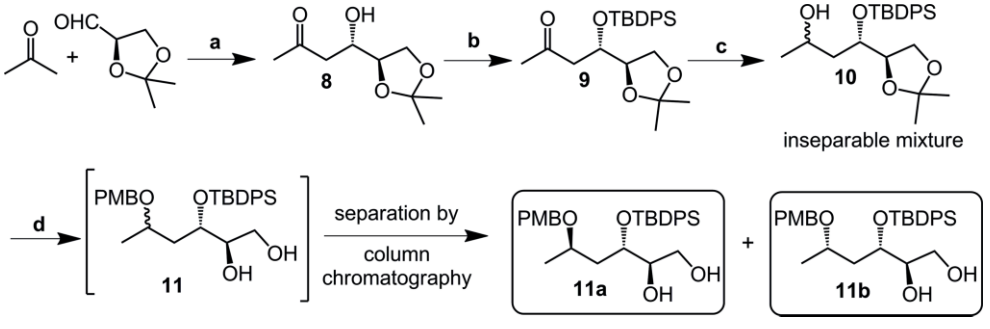
In this study, we report our successful attempts directed towards the total synthesis of all these molecules (Figure 1, **1**–**7**) by way of a common building block derived from a proline-catalyzed diastereoselective intermolecular aldol reaction[13] and α-aminoxylation of aldehydes[14] as the key steps. Our approach to the synthesis of hydroxylated pyrans **1, 2** and **3** and to unsaturated lactones **4, 5**, **6** and **7** was envisioned by the retrosynthetic route shown in Scheme 1.

Preparation of Key Intermediate 11

The key intermediate **11** was synthesised by the reaction sequence shown in Scheme 2. D-Glyceraldehyde acetonide was treated with acetone in the presence of D-proline to give the β-hydroxy ketone aldol product **8** (*de* > 99 % by NMR and HPLC).



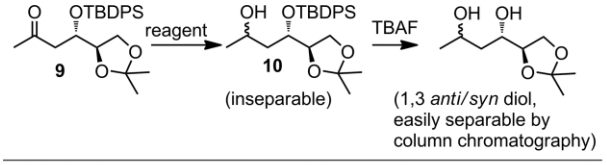
Scheme 1. Retrosynthetic analysis for the synthesis of target molecules **1**–**7**.



Scheme 2. Reagents and conditions: (a) 30 mol-% D-proline, 5 h, room temp., 65 %; (b) imidazole, TBDPSCl, room temp., 8 h, 95 %; (c) $CeCl_3 \cdot 7 H_2O$, $NaBH_4$, MeOH, –78 °C, 2 h, 80 %; (d) (1) PMBCl, NaI, DIPEA, 150 °C, 3 h; (2) PPTS (catalytic), MeOH, 12 h, room temp., 90 % (over two steps).

Protection of the alcohol as a *tert*-butyldiphenylsilyl (TBDPS) ether provided compound **9** in good yield. We then examined the *anti*-selective reduction of **9** to give protected 1,3-*anti*-diol **10** directly (Table 1). The use of bulky reducing agents such as $LiAl(OtBu)_3H$, LS-Selectride or either (*R*)- or (*S*)-Alpine Hydride (combination with $LiEt_3BH$) furnished inseparable diastereoisomeric mixtures of protected 1,3-*anti*- and -*syn*-diols **10** with moderate selectivity (in each case the *anti*/*syn* ratio was determined by in situ desilylation of inseparable **10** with TBAF to afford the corresponding easily separable 1,3-*anti*- and -*syn*-diols). After examination of several reducing agents, it was observed that a combination of $NaBH_4$ and $CeCl_3 \cdot 7\,H_2O$ in methanol provided compound **10** in a ratio in favour of the *anti* isomer (*anti*/*syn* 3:1) in 80 % yield. Under weakly basic conditions,[15a] the free hydroxy group in the diastereoisomeric mixture **10** was protected as a PMB ether, followed by acetonide removal with PPTS (pyridinium *p*-toluenesulfonate) in methanol to produce the easily separable diastereoisomers **11**. Flash column chromatography separation of **11** afforded *anti* diastereoisomer **11a** in 67.5 % yield along with *syn* diastereoisomer **11b** in 22.5 % yield.[15b,15c]

Table 1. Optimization of stereoselective keto reduction of **9**.

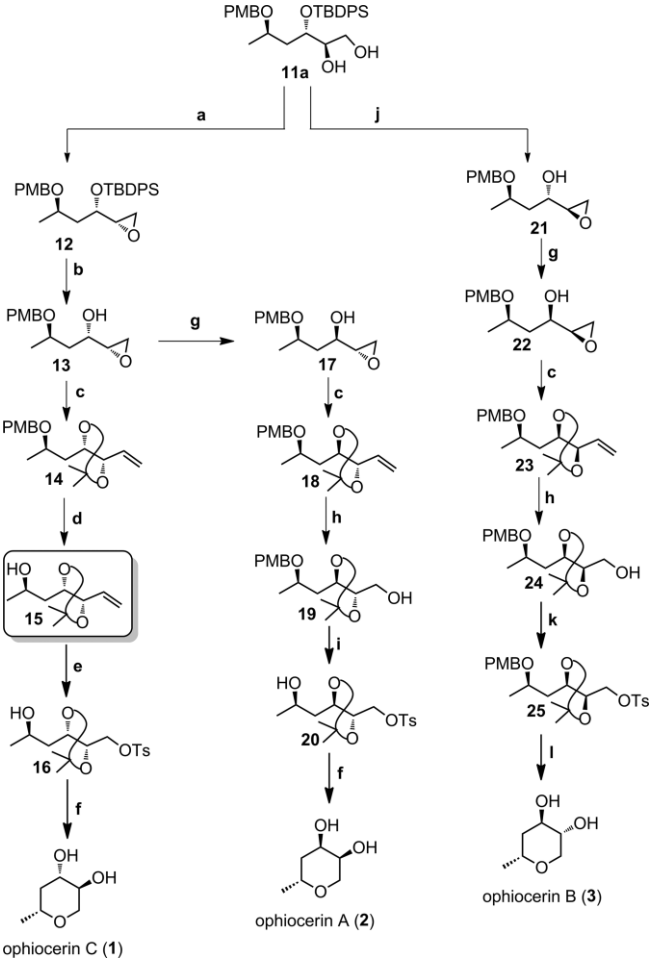


No.	Solvent	Reagent	Yield (%)	*syn*:*anti*
1.	THF	LS-Selectride[a,b]	86%	5:1
2.	THF	$LiAl(OtBu)_3H$[c]	88%	4.5:1
3.	THF	(*S*)-Alpine-Hydride[c,d]/$LiBH_4$[e]	82%	5:1
4.	THF	(*R*)-Alpine-Hydride[c,d]/$LiBH_4$[e]	85%	5:1
5.	THF	K-Selectride[c]/$LiBEt_3H$[f]	84%	3:1
6.	MeOH	$NaBH_4$[c]/$LiBEt_3H$[f]	83%	3:2
7.	MeOH	$NaBH_4$[g]	81%	1.2:1
8.	MeOH	$NaBH_4/CeCl_3 \cdot 7H_2O$[h]	80%	1:3

[a] LS-Selectride: lithium triisoamylborohydride. [b] –78 °C for 8 h. [c] –78 °C for 2 h. [d] Alpine-Hydride: lithium B-isopinocampheyl-9-borabicyclo-[3.3.1]nonyl hydride. [e] Room temp., for 2 h. [f] Room temp., for 1 h. [g] 0 °C for 1 h. [h] –78 °C for 1 h.

Synthesis of Ophiocerins A, B and C

According to the retrosynthetic analysis shown in Scheme 1, compound **11** was envisioned as a common intermediate for the synthesis of ophiocerins A, B and C, by the fine modulation of the two free hydroxy groups of **11**. The synthesis of ophiocerin C (**1**) from intermediate **11a** is presented in Scheme 3. The diol **11a** was converted into the desired *syn* epoxide **12** in 70 % yield by a three-step sequence involving chemoselective monobenzoylation of the diol followed by mesylation of the secondary alcohol and subsequent internal nucleophilic substitution of the secondary mesylate by treatment with base (K_2CO_3 in MeOH). Desilylation of compound **12** (TBAF in THF at room temp.) furnished **13** in 85 % yield. Ring opening of epoxide **13** mediated by dimethylsulfonium methylide (generated from trimethylsulfonium iodide and *n*BuLi), followed by protection of the diol as its acetonide with 2,2-dimethoxypropane in the presence of catalytic amount of PPTS in dry CH_2Cl_2 afforded **14** in 80 % yield. Subsequent removal of the PMB group with DDQ furnished hydroxy alkene **15** in 82 % yield. Ozonolysis of **15** followed by reduction with $NaBH_4$ and selective monotosylation of the primary alcohol gave monotosylate **16** in 70 % yield, and this, upon base-induced cyclization under known conditions,



Scheme 3. Reagents and conditions: (a) (1) Bu_2SnO, BzCl, NEt_3, CH_2Cl_2; (2) MsCl, NEt_3, CH_2Cl_2; (iii) K_2CO_3, MeOH, room temp., 1 h, 70 % (three steps); (b) TBAF, THF, room temp., 2 h, 85 %; (c) (1) $(CH_3)_3S^+I^-$, *n*BuLi, THF, –20 °C; (2) 2,2-DMP, PPTS (catalytic), dry CH_2Cl_2, 3 h; (d) DDQ, CH_2Cl_2/H_2O (18:1), room temp., 1 h, 82 %; (e) (1) O_3, CH_2Cl_2, –78 °C,1 h; (2) $NaBH_4$, MeOH, room temp., 0.5 h; (3) TsCl, NaH, THF, 2 h, 70 % (three steps); (f) (1) $tBuO^-K^+$, Et_2O, 2 h; (2) *p*TsA, MeOH, room temp., 2 h; (g) (1) Ph_3P, DIAD, PNBA, THF, 0 °C to room temp., 6 h; (2) K_2CO_3, MeOH; (h) (1) OsO_4, $NaIO_4$, dioxane/H_2O (3:1), 12 h, room temp.; (2) $NaBH_4$, MeOH, room temp., 0.5 h; (i) (1) DDQ, CH_2Cl_2/H_2O (18:1), room temp., 1 h; (2) TsCl, NEt_3, CH_2Cl_2, 3 h, 83 %; (j) (1) Bu_2SnO, TsCl, NEt_3, CH_2Cl_2; (2) K_2CO_3, MeOH; (3) TBAF, THF, room temp., 2 h, 79 % (three steps); (k) TsCl, NEt_3, CH_2Cl_2, 3 h, 86 %; (l) (1) DDQ, CH_2Cl_2/H_2O (18:1), room temp., 1 h; (2) $tBuO^-K^+$, Et_2O, 2 h; (3) *p*TsA, MeOH, room temp., 2 h, 82 % (after three steps).

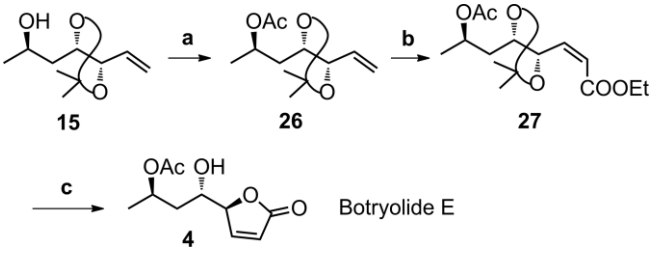
furnished ophiocerin C **(1)** in 92 % yield as a white solid. The physical and spectroscopic data were in full agreement with literature data. $[\alpha]_D^{25}$ = +42.4 (*c* = 0.1, CH_2Cl_2); ref.[5] $[\alpha]_D^{25}$ = +45.0 (*c* = 0.1, CH_2Cl_2).

For the synthesis of ophiocerin A (**2**), we followed almost the same reaction sequence as for the synthesis of ophiocerin C. To this end, the required *anti*-epoxy alcohol **17** was achieved in 79 % yield by inversion of stereochemistry at the carbon atom bearing the unprotected hydroxy group in *syn* epoxy alcohol **13** by use of the Mitsunobu reaction,[16] followed by basic hydrolysis (K_2CO_3 in MeOH). Epoxide **17** was then opened with excess dimethylsulfonium methylide followed by acetonide protection to provide **18** in 80 % yield. Oxidative cleavage of olefin **18** (OsO_4/$NaIO_4$) followed by $NaBH_4$ reduction gave the corresponding alcohol **19** in good yield. Treatment of **19** with tosyl chloride and the subsequent removal of the PMB group with DDQ furnished tosylate **20**. Finally, base-mediated cyclization with potassium *tert*-butoxide followed by acetonide removal furnished ophiocerin A (**2**) as a white solid. The spectroscopic data for the synthetic compound were in full agreement with literature values $[\alpha]_D^{25}$ = –23.4 (*c* = 0.1, CH_2Cl_2); ref.[5] $[\alpha]_D^{25}$ = –24.0 (*c* = 0.1, CH_2Cl_2).

The synthesis of ophiocerin B (**3**) began with intermediate **11a**. In order to obtain the *anti*-epoxy alcohol **21** from diol **11a**, we applied a three-step sequence: firstly regioselective primary monotosylation[17] (Bu_2SnO, tosyl chloride, NEt_3) of diol **11a**, followed by base-induced epoxide formation through intramolecular nucleophilic displacement of the tosyl group and then TBAF-mediated removal of the TBDPS group. Inversion of the stereochemistry of the free hydroxy group of **21** under Mitsunobu reaction conditions followed by basic hydrolysis provided the required *syn* epoxy alcohol **22**. Opening of the epoxide with excess trimethylsulfonium iodide and *n*BuLi produced a *syn*-diol, which upon treatment with 2,2-dimethoxypropane and catalytic amounts of PPTS provided acetonide compound **23** in good yield. OsO_4/$NaIO_4$-mediated oxidative cleavage of olefin **23** followed by $NaBH_4$ reduction gave primary alcohol **24**. Esterification of **24** with tosyl chloride afforded the *O*-tosyl derivative **25**. Finally, PMB removal from **25** with DDQ and base-mediated cyclization followed by acetonide removal gave ophiocerin B (**3**) in 82 % yield as a pale yellow oil. The correct stereochemistry of the three stereogenic centres was confirmed by comparison of its specific rotation value and spectroscopic data with those reported. $[\alpha]_D^{25}$ = –35.2 (*c* = 1.0, CH_2Cl_2); ref.[5] $[\alpha]_D^{25}$ = –37.0 (*c* = 0.1, CH_2Cl_2).

Synthesis of Botryolide E

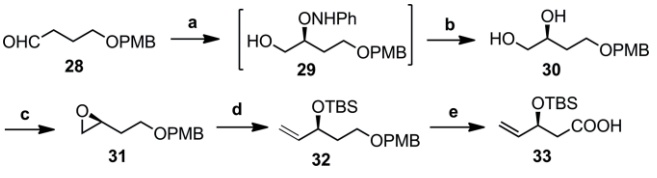
From the retrosynthetic analysis shown in Scheme 1, we envisioned hydroxy olefin **15** as a common intermediate both for ophiocerin C (Scheme 3) and for botryolide E. For the synthesis of botrylide E (Scheme 4), the hydroxy group of **15** was protected as an acetyl ester by use of acetic anhydride in pyridine to provide acetylated compound **26**. Ozonolysis of the olefin followed by modified Horner–Emmons olefination with electrophilic bis(trifluoroethyl)phosphono ester $(CF_3CH_2O)_2P(O)CH_2CO_2Et$ and KHMDS/18-crown-6 gave the Wittig product **27** in 88 % yield with *Z*/*E* ratio 95:5.[18] The *cis* isomer was easily separated by flash column chromatography, and upon treatment with 1 M HCl in THF at 0 °C for 2 h it provided botryolide E (**4**) in 65 % yield. The physical and spectroscopic data of **4** were in full agreement with the reported data. $[\alpha]_D^{25}$ = –37.1 (*c* = 2.5, $CHCl_3$); ref.[6] $[\alpha]_D^{25}$ = –36.7 (*c* = 0.05, $CHCl_3$).



Scheme 4. Reagents and conditions: (a) Ac_2O, pyr, room temp., 4 h, 90 % (b) (1) O_3, DMS; (2) $(CF_3CH_2O)_2P(O)CH_2CO_2Et$, KHMDS/18-crown-6, –78 °C, 6 h, 88 % (over two steps); (c) 1 M HCl in THF, 0 °C to room temp., 1 h, 65 %.

Synthesis of Decarestrictine O

Our retrosynthetic analysis of decarestrictine O (Scheme 1) is based on a convergent approach. We envisioned that the target molecule could be accessed by the esterification of acid **33** with hydroxy olefin **15**, followed by cyclization of diene by the Grubbs RCM protocol. The acid fragment **33** could be prepared by sequential α-aminoxylation of 4-(4-methoxybenzyloxy)-butanal (**28**, Scheme 5) whereas the alcohol fragment **15** was also the common intermediate for ophiocerin C and for botryolide E, easily obtained from **11a** (Scheme 3).



Scheme 5. Reagents and conditions: (a) (1) D-proline, PhNO, DMSO; (2) $NaBH_4$, MeOH, room temp., 0.5 h; (b) $CuSO_4$•5 H_2O, MeOH, 10 h, 78 % (over three steps); (c) (1) Bu_2SnO, TsCl, NEt_3, CH_2Cl_2; (2) K_2CO_3, MeOH, 0.5 h, room temp., 80 % (over two steps); (d) (1) $(CH_3)_3S^+I^-$, *n*BuLi, THF, –20 °C; (2) TBSCl, imidazole, CH_2Cl_2, 82 % (over two steps); (e) (1) DDQ, CH_2Cl_2/H_2O (18:1), room temp.,1 h; (2) TEMPO (catalytic), BAIB, CH_3CN/H_2O (3:1), room temp., 7 h. 75 % (over two steps).

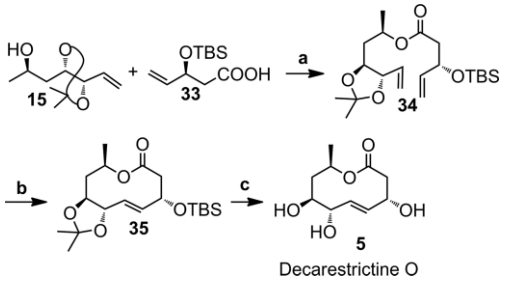
Synthesis of Acid Fragment 33

The synthesis of acid fragment **33** started from 4-(4-methoxybenzyloxy)butanal (**28**) as illustrated in Scheme 5. α-Aminoxylation of **28** in the presence of D-proline followed by reduction with $NaBH_4$ provided unstable anilinoxy compound **29**. This was further treated with 30 mol-% $CuSO_4$•5 H_2O in methanol, which eventually led to the cleavage of the O–N bond, affording diol **30** in 78 % yield. Regioselective primary monotosylation of diol **30** and subsequent base treatment furnished epoxide **31** in 80 % yield.

Opening of the epoxide by use of excess dimethylsulfonium methylide followed by protection of the hydroxy group as a TBS ether gave olefin **32** in 82 % yield. Finally, DDQ-mediated removal of the PMB group followed by one-pot oxidation of the primary alcohol with TEMPO/BAIB provided the required acid **33**.

Synthesis of Decarestrictine O by Coupling of Acid Fragment 33 and Alcohol Fragment 15 through RCM

With both fragments **15** and **33** to hand, we proceeded with the coupling of the two components by use of the Shiina esterification[19] protocol to provide the diene ester **34** (Scheme 6) in 95 % yield. The diene ester was then subjected to ring closing metathesis[20] under high-dilution conditions (0.001 M in dry CH_2Cl_2) in the presence of the second-generation Grubbs catalyst (10 mol-%) to give the unsaturated macrocyclic lactone **35** in 75 % yield and exclusively as the *E* isomer. Compound **35**, upon exposure to 1 M HCl in THF, underwent removal of both TBS ether and acetonide groups to provide decarestrictine O (**5**) in 68 % yield. All the spectroscopic and physical data of the synthesized compound were in full agreement with literature data. $[\alpha]_D^{25}$ = –20.2 (*c* = 0.2, MeOH); ref.[11b] $[\alpha]_D^{25}$ = –19.6 (*c* = 0.2, MeOH).



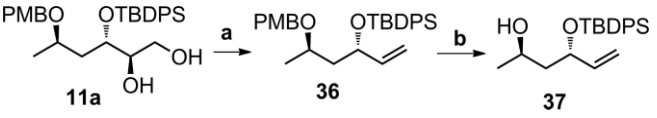
Scheme 6. Reagents and conditions: (a) 2-methyl-6-nitrobenzoic anhydride, NEt_3, DMAP, CH_2Cl_2, 12 h, 95 %; (b) second-generation Grubbs catalyst (10 mol-%), CH_2Cl_2, reflux, 12 h, 75 %; (c) 1 M HCl in THF, CH_2Cl_2, room temp., 1 h, 68 %.

Synthesis of Stagonolide C and 9-*epi*-Stagonolide C

Analogously, by a similar strategy, stagonolide C and its 9-epimer could be obtained by coupling of olefinic acid **45** (Scheme 9, below) with olefinic alcohols **37** (Scheme 7, below) and **39** (Scheme 8, below), respectively, and subsequent cyclization of the diene by the Grubbs RCM protocol. The olefinic alcohol fragment **37** could easily be obtained from the common intermediate **11a** (Scheme 7), whereas the other alcoholic fragment **39** could be prepared from the diol isomer **11b** by the same reaction sequence (Scheme 8). Similarly, the acid fragment **45** could be prepared from 5-(4-methoxybenzyloxy)-pentanal (**40**) through α-aminoxylation and epoxide ring opening.

Synthesis of Alcohol Fragment 37

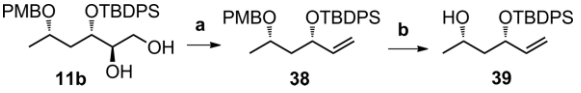
To synthesize the alcohol fragment, the diol **11a** was subjected to direct reductive elimination[21] with iodine, Ph_3P and imidazole at reflux for 4 h to give olefin **36** in 83 % yield. Cleavage of the PMB protecting group with DDQ furnished the target alcohol **37** in 80 % yield (Scheme 7).



Scheme 7. Reagents and conditions: (a) Ph_3P, I_2, imidazole, THF, reflux, 4 h, 83 %; (b) DDQ, CH_2Cl_2/H_2O (18:1), room temp.,1 h, 80 %.

Synthesis of Alcohol Fragment 39

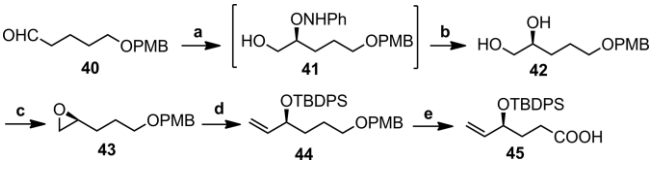
For the synthesis of 9-*epi*-stagonolide C, the required alcohol fragment **39** (Scheme 8) was synthesized from the diol intermediate **11b** by the same reaction sequence as described in Scheme 7.



Scheme 8. Reagents and conditions: (a) Ph_3P, I_2, imidazole, THF, reflux, 4 h, 82 %; (b) DDQ, CH_2Cl_2/H_2O (18:1), room temp., 1 h, 84 %.

Synthesis of Common Acid Fragment 45 for Both Stagonolide C and Its Epimer

The synthesis of acid fragment **45** commenced from 5-(4-methoxybenzyloxy)pentanal as illustrated in Scheme 9. D-Proline-catalyzed α-aminoxylation of aldehyde **40** under a set of reaction conditions similar to those described in Scheme 5 (synthesis of acid fragment for decarestrictine O) afforded diol **42** in 77 % yield. Selective primary monotosylation of the diol and subsequent base treatment gave the epoxide **43** in 81 % yield. Epoxide ring opening mediated by dimethylsulfonium methylide, followed by protection of the secondary hydroxy group (TBDPSCl/imidazole), afforded TBDPS ether **44** in 78 % yield. Removal of the PMB group (DDQ) then furnished the primary alcohol, which upon one-pot oxidation (TEMPO/BAIB) gave the acid **45** in 70 % yield.

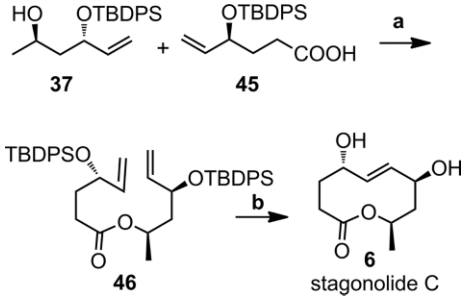


Scheme 9. Reagents and conditions: (a) (1) D-proline, PhNO, DMSO; (2) $NaBH_4$, MeOH, room temp., 0.5 h; (b) $CuSO_4 \cdot 5H_2O$, MeOH, 10 h, 77 % (over three steps); (c) (1) Bu_2SnO, TsCl, NEt_3, CH_2Cl_2; (2) K_2CO_3, MeOH, 0.5 h, room temp., 81 % (over two steps); (d) (1) $(CH_3)_3S^+I^-$, *n*BuLi, THF, –20 °C; (2) TBDPSCl, imidazole, CH_2Cl_2, 78 % (over two steps); (e) (1) DDQ, CH_2Cl_2/H_2O (18:1), room temp., 1 h; (2) TEMPO (catalytic), BAIB, CH_3CN/H_2O (3:1), room temp., 7 h, 75 % (over two steps).

Synthesis of Stagonolide C through RCM

With substantial amounts of alcohol **37** and acid **45** to hand, the stage was set to couple the two fragments for the diene ester formation (Scheme 10). To this end, the alcohol **37** was coupled with acid **45** under the Shiina protocol[19] to give diene

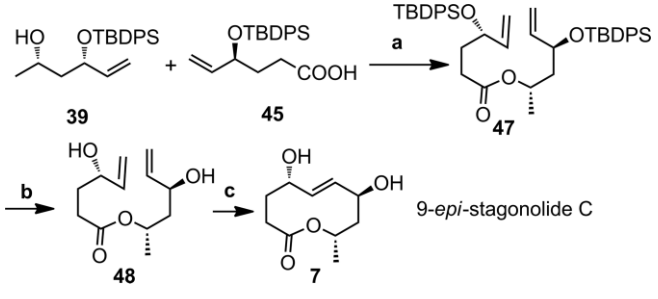
46 in 93 % yield. Removal of both TBDPS group with NH_4F in methanol[22] gave the required diol, which was immediately subjected to RCM in the presence of the second-generation Grubbs catalyst (10 mol-%) to afford the target molecule stagonolide C (**6**) in 78 % yield. The constitution and configuration of the assigned structure were in full agreement with the literature data. $[\alpha]_D^{25}$ = +46.2 (*c* = 0.08, MeOH); ref.[12c] $[\alpha]_D^{25}$ = +43.9 (*c* = 1.0, MeOH).



Scheme 10. Reagents and conditions: (a) 2-methyl-6-nitrobenzoic anhydride, NEt_3, DMAP, CH_2Cl_2, 6 h, 93 %; (b) (i) NH_4F, MeOH, 40 °C, 24 h; (ii) second-generation Grubbs catalyst (10 mol-%), CH_2Cl_2, reflux, 48 h, 78 % (over two steps).

Completion of the Synthesis of 9-epi-Stagonolide C through RCM

For the synthesis of the 9-*epi* isomer, coupling of acid fragment **45** with alcohol **39** was carried out under Shiina's esterification conditions followed by removal of both TBDPS groups (NH_4F in methanol[22]) to give the diene **48** in 73 % yield (Scheme 11). On treatment with the second-generation Grubbs catalyst (10 mol-%), compound **48** furnished 9-*epi*-stagonolide C (**7**) as the sole product. The geometry of the newly formed double bond was unambiguously determined by the olefinic J_{trans} coupling constant (16.14 Hz between the protons at δ = 5.98 and 5.62 ppm).



Scheme 11. Reagents and conditions: (a) 2-methyl-6-nitrobenzoic acid anhydride, NEt_3, DMAP, CH_2Cl_2, 6 h, 92 %; (b) NH_4F, MeOH, 40 °C, 24 h, 70 %; (c) second-generation Grubbs catalyst (10 mol-%), CH_2Cl_2, reflux, 48 h, 73 %.

Conclusions

In summary, we have successfully synthesized key precursors for the synthesis of ophiocerins A, B and C, botryolide E, decarestrictine O, stagonolide C and 9-*epi*-stagonolide C by employing proline-catalyzed aldol reaction as the key step. This route demonstrates coupling of two different fragments through sequential esterification and RCM. We believe that this synthetic sequence should be employable for several other hydroxylated pyrans and for 10-membered unsaturated lactones and macrolides.

Experimental Section

General Experimental Methods: All reactions were carried out under anhydrous conditions, with use of flame-dried glassware under a positive pressure of argon unless otherwise mentioned. CH_2Cl_2, Et_3N and iPr_2NEt were distilled from CaH_2; Et_2O and THF were distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. Air-sensitive reagents and solutions were transferred by syringe or cannula and were introduced into the apparatus through rubber septa. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or $KMnO_4$ followed by heating with a heat gun for ca. 15 s. Flash chromatography was performed on silica gel (230–400 mesh). All ^1H NMR and ^{13}C NMR spectra were obtained with a 200, 400 or 500 MHz spectrometer in $CDCl_3$ or CD_3OD. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS, with use of the residual solvent peak as a reference standard. The following abbreviations are used to describe the multiplicities: s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet and br = broad. HRMS (ES^+) were recorded with an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded with a FTIR spectrometer as thin films with use of NaCl plates; wavenumbers are in cm^{-1}. Optical rotations were measured with a polarimeter with a 1 dm path length. Chemical nomenclature was generated with Chem. Bio Draw Ultra 14.0.

(*S*)-4-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-hydroxybutan-2-one (8): D-Proline (0.046 g, 0.40 mmol) was added to a solution of D-glyceraldehyde acetonide (0.260 g, 2.00 mmol) in acetone (4 mL) and chloroform (1 mL) and the mixture was stirred at room temperature for 5 h. Subsequently, the mixture was diluted with water (5 mL) and diethyl ether (5 mL) and partitioned. The aqueous layer was washed with diethyl ether (3 × 5 mL), and the combined organic layers were dried with Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 30 %) afforded the desired product **8** as a pale yellow liquid (0.244 g, 65 %, *de* > 99 % by ^1H NMR and HPLC, Kromasil Rp-18, MeOH/H_2O 20:80; major isomer 9.36 min, minor isomer 8.00 min). $[\alpha]_D^{25}$ = –24.40 (*c* = 4.0, $CHCl_3$); ref.[23] $[\alpha]_D^{25}$ = –27.00 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.13–4.05 (m, 1 H), 4.00–3.88 (m, 3 H), 3.21 (br. s, 1 H), 2.89–2.80 (dd, *J* = 1.6, 17.5 Hz, 1 H), 2.61 (dd, *J* = 8.1, 17.9 Hz, 1 H), 2.21 (s, 3 H), 1.40 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 209.7, 109.4, 69.0, 66.8, 46.2, 30.8, 26.6, 25.1 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3492, 3018, 2954, 2901, 1720, 1363, 1299, 1205, 1069, 859 cm^{-1}.

(*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]butan-2-one (9): TBDPSCl (0.8 mL, 3.30 mmol) was added dropwise at 0 °C to a stirred solution of compound **8** (0.517 g, 2.75 mmol) and imidazole (0.375 g, 5.50 mmol) in dry CH_2Cl_2, and the reaction mixture was stirred for 8 h at room temperature. After completion of the reaction, water was added to quench the reaction mixture and the organic layer was washed with excess water and brine. The organic layer was dried with Na_2SO_4 and concentrated to afford the crude silylated compound, which was puri-

fied by silica gel chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to afford **9** (1.110 g, 95 %) as a viscous liquid. $[\alpha]_D^{25}$ = –10.37 (*c* = 3.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.77–7.64 (m, 4 H), 7.47–7.34 (m, 6 H), 4.32–4.17 (m, 1 H), 4.14–4.01 (m, 1 H), 3.92 (dd, *J* = 6.4, 8.3 Hz, 1 H), 3.64 (dd, *J* = 6.3, 8.3 Hz, 1 H), 2.60 (dd, *J* = 3.4, 5.7 Hz, 2 H), 1.91 (s, 3 H), 1.29 (s, 6 H), 1.03 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 206.1, 135.92, 135.9, 135.2, 134.8, 133.5, 133.3, 129.9, 129.8, 129.6, 127.7, 127.65, 127.63, 109.3, 78.7, 70.6, 66.9, 48.3, 30.6, 26.9, 26.5, 26.2, 25.1, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3392, 3008, 2558, 1732, 1458, 1263, 1099, 759 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{34}O_4SiNa$ $[M + Na]^+$ 449.2119; found 449.2120.

(4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]butan-2-ol (10): $CeCl_3 \cdot 7\ H_2O$ (0.057 g, 0.16 mmol) and $NaBH_4$ (0.006 g, 0.15 mmol) were added at –78 °C to a stirred solution of β-hydroxy ketone **9** (0.063 g, 0.15 mmol) in MeOH (1 mL) in a 25 mL flask, and the mixture was allowed to warm to room temperature. It was then stirred for 1 h until analysis of the mixture by TLC (silica gel) indicated completion of reaction. The reaction was diluted with aq. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL), washed with brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure provided the crude hydroxy compound, which was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 20 %) to afford **10** (0.051 g, 80 %) as a pale yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.74–7.64 (m, 4 H), 7.50–7.34 (m, 6 H), 4.17 (qd, *J* = 6.7, 13.2 Hz, 1 H), 4.05–3.96 (m, 1 H), 3.91–3.76 (m, 1 H), 3.63 (ddd, *J* = 7.0, 8.4, 15.7 Hz, 1 H), 2.76 (br. s, 1 H), 1.77–1.61 (m, 2 H), 1.34–1.18 (m, 5 H), 1.10–1.04 (m, 9 H), 1.01–0.96 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 135.9 (135.94), 135.9 (135.91), 135.9 (135.85), 135.8, 133.6, 133.3, 133.1, 130.1, 130.0, 129.9, 129.9, 127.9, 127.8, 127.7, 127.7, 127.6, 109.4, 109.3, 78.63, 78.58, 74.3, 73.9, 72.4, 71.9, 67.8, 67.7, 64.8, 64.1, 63.7, 63.4, 43.9, 43.6, 41.3, 30.9, 27.0, 26.99, 26.94, 26.3, 25.31, 25.30, 24.0, 23.7, 23.5, 19.4 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3382, 3068, 2893, 1632, 1435, 1250, 1136, 889, 743 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{36}O_4SiNa$ $[M + Na]^+$ 451.2275; found 451.2268.

(2*R*,3*S*,5*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-5-[(4-methoxybenzyl)oxy]hexane-1,2-diol (11a) and (2*R*,3*S*,5*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-5-[(4-methoxybenzyl)oxy]hexane-1,2-diol (11b): Alcohol **10** (0.428 g, 1.00 mmol), *p*-methoxybenzyl chloride (0.172 g, 0.15 mL, 1.10 mmol), NaI (10 mol-%), and DIPEA (0.34 mL, 2.00 mmol) were placed under argon in a reaction vessel equipped with a magnetic stirring bar. The mixture was heated at reflux in a 150 °C bath for 3 h. Consumption of the starting material was monitored by TLC. The resulting mixture was diluted with ethyl acetate (5 mL) and aqueous sodium bisulfate (10 %, 5 mL) and extracted twice with EtOAc (2 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. The crude PMB-protected product was used for the next step without further purification.

PPTS (0.021 g, 0.08 mmol) was added to a stirred solution of the crude PMB-protected compound (0.450 g, 0.82 mmol) in MeOH (10 mL) and the mixture was then stirred overnight at room temperature. After completion of the reaction, a saturated aqueous $NaHCO_3$ solution (10 mL) was added to the reaction mixture, which was then concentrated under reduced pressure and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. Solvent was concentrated under vacuum. The crude residue was purified by column chromatography on silica gel (230–400 mesh. eluent: EtOAc/petroleum ether 45 %) to give the major product **11a** (0.281 g, 67.5 %) along with minor product **11b** (0.093 g, 22.5 %) as a colourless liquid.

Stereoisomer 11a: $[\alpha]_D^{25}$ = –12.59 (*c* = 3.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.70 (m, 4 H), 7.48–7.33 (m, 6 H), 7.05 (d, *J* = 8.1 Hz, 2 H), 6.82 (d, *J* = 8.1 Hz, 2 H), 4.29 (d, *J* = 10.8 Hz, 1 H), 3.96 (d, *J* = 4.6 Hz, 1 H), 3.87 (d, *J* = 11.0 Hz, 1 H), 3.80 (s, 3 H), 3.74–3.61 (m, 3 H), 3.11–2.97 (m, 1 H), 2.55 (br. s, 2 H), 1.78 (ddd, *J* = 5.9, 9.5, 15.2 Hz, 1 H), 1.57 (td, *J* = 3.4, 15.2 Hz, 1 H), 1.07 (s, 9 H), 0.90 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 135.9, 133.8, 133.1, 129.9, 129.9, 129.8, 129.4, 127.8, 127.7, 113.7, 75.0, 73.7, 72.8, 70.0, 63.3, 55.2, 42.2, 27.0, 19.4,19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3479, 2978, 1554, 1358, 1063, 851, 742 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{40}O_5SiNa$ $[M + Na]^+$ 531.2537; found 531.2537.

Stereoisomer 11b: $[\alpha]_D^{25}$ = +38.20 (*c* = 2.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4 H), 7.49–7.36 (m, 6 H), 7.26–7.19 (m, *J* = 8.2 Hz, 2 H), 6.92–6.85 (m, *J* = 8.5 Hz, 2 H), 4.53–4.50 (m, 1 H), 4.35–4.33 (m, 1 H), 3.94–3.87 (m, 1 H), 3.84–3.80 (m, 4 H), 3.79–3.75 (m, 1 H), 3.68–3.63 (m, 1 H), 3.45 (dd, *J* = 7.0, 11.0 Hz, 1 H), 2.66 (br. s, 2 H), 1.82 (ddd, *J* = 2.3, 8.8, 15.2 Hz, 1 H), 1.53 (dd, *J* = 4.3, 15.3 Hz, 1 H), 1.07 (s, 9 H), 0.97 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 135.9, 134.0, 133.2, 129.9, 129.8, 129.7, 129.6, 128.6, 127.7, 127.6, 113.9, 113.7, 73.6, 71.7, 70.5, 70.3, 64.1, 55.2, 39.9, 27.0, 19.4, 19.2 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3379, 2988, 1546, 1308, 1136, 987, 842 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{40}O_5SiNa$ $[M + Na]^+$ 531.2537; found 531.2538.

***tert*-Butyl{(1*S*,3*R*)-3-[(4-methoxybenzyl)oxy]-1-[(*S*)-oxiran-2-yl]butoxy}diphenylsilane (12):** Bu_2SnO (0.007 g, 0.03 mmol) was added under argon to a stirred solution of diol **11a** (0.665 g, 1.31 mmol) in dry CH_2Cl_2 (2 mL), followed by addition of benzoyl chloride (0.18 mL, 1.44 mmol) and Et_3N (0.22 mL, 1.57 mmol). The resulting mixture was stirred at room temperature for 2 h, quenched with water and then extracted with CH_2Cl_2. Removal of volatiles under reduced pressure gave an oily crude monobenzoyl ester. This compound was then dissolved in dry CH_2Cl_2 (10 mL) under argon and treated with MsCl (0.11 mL, 1.44 mmol), Et_3N (0.22 mL, 1.57 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 2 h and then diluted with water. The water layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give a crude product, which was dissolved in MeOH (10 mL) and treated with K_2CO_3 (0.180 g, 1.31 mmol). The mixture was stirred for 1 h at room temperature and then filtered through celite. Removal of the volatiles under reduced pressure, followed by column chromatography on silica gel (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) produced the epoxide **12** (0.449 g, overall yield 70 %) as a yellow liquid. $[\alpha]_D^{25}$ = –43.50 (*c* = 1.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.66 (m, 4 H), 7.43–7.30 (m, 6 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 4.28–4.25 (m, 1 H), 3.92 (d, *J* = 10.8 Hz, 1 H), 3.80 (s, 3 H), 3.68–3.48 (m, 2 H), 3.03 (ddd, *J* = 2.7, 4.1, 6.9 Hz, 1 H), 2.65 (t, *J* = 4.5 Hz, 1 H), 2.43 (dd, *J* = 2.7, 4.9 Hz, 1 H), 1.84–1.61 (m, 2 H), 1.10 (s, 9 H), 1.06 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 136.1, 136.0, 133.9, 133.8, 130.8, 129.6, 129.1, 127.5, 127.4, 113.6, 73.1, 71.4, 70.0, 56.0, 55.2, 45.0, 42.6, 27.0, 19.9, 19.5 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2818, 1632, 1521, 1498, 1332, 1063, 809 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{38}O_4Si$ Na $[M + Na]^+$ 513.2432; found 513.2435.

(1*S*,3*R*)-3-[(4-Methoxybenzyl)oxy]-1-[(*S*)-oxiran-2-yl]butan-1-ol (13): TBAF in THF (1 M, 0.52 mL, 0.52 mmol) was added at room temperature to a stirred solution of epoxide **12** (0.170 g, 0.35 mmol) in dry THF (10 mL) and the mixture was stirred for 4 h. It was then diluted with saturated aq. NH_4Cl (20 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine and then dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography

(100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to give **13** (0.074 g, 85 %) as a light yellow oil. $[\alpha]_D^{25}$ = –28.75 (*c* = 3.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.22 (d, *J* = 8.5 Hz, 2 H), 6.95–6.83 (d, *J* = 8.5 Hz, 2 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 4.40 (d, *J* = 11.0 Hz, 1 H), 3.98–3.88 (m, 1 H), 3.85–3.76 (m, 4 H), 2.99 (dt, *J* = 2.9, 4.2 Hz, 1 H), 2.80–2.73 (m, 2 H), 2.72 (d, *J* = 5.8 Hz, 1 H), 1.78 (ddd, *J* = 2.4, 4.4, 7.5 Hz, 2 H), 1.27 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 130.5, 129.3, 113.8, 71.9, 70.4, 68.2, 55.3, 55.2, 44.4, 40.8, 19.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3410, 3118, 2584, 1638, 1239 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}O_4Na$ $[M + Na]^+$ 275.1254; found 275.1255.

(4*S*,5*S*)-4-{(*R*)-2-[(4-Methoxybenzyl)oxy]propyl}-2,2-dimethyl-5-vinyl-1,3-dioxolane (14): Trimethylsulfonium iodide (1.230 g, 6.05 mmol) was added at –20 °C to stirred dry THF, followed by *n*BuLi (3.8 mL, 1.6 M, 6.05 mmol). The reaction mixture was stirred for 1 h, after which epoxide **13** (0.300 g, 1.21 mmol) in THF was added dropwise. The reaction mixture was stirred at –20 °C for 3 h and completion of the reaction was monitored by TLC. The mixture was diluted with saturated ammonium chloride solution and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine, dried with Na_2SO_4 and concentrated. The crude diol was used for the next step without further purification.

2,2-DMP (0.25 mL, 2.00 mmol) and PPTS (0.023 g, 0.10 mmol) were added to a solution of crude diol (0.280 g, 1.00 mmol) in dry CH_2Cl_2 (30 mL), and the mixture was stirred for 4 h and then quenched with satd. aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to give **14** (0.290 g, 80 %) as a pale yellow oil. $[\alpha]_D^{25}$ = –3.70 (*c* = 3.5, $CHCl_3$); ref.[11a] $[\alpha]_D^{25}$ = –4.40 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.9 Hz, 2 H), 5.85–5.74 (m, 1 H), 5.40–5.31 (m, 1 H), 5.29–5.15 (m, 1 H), 4.55 (d, *J* = 11.3 Hz, 1 H), 4.41 (d, *J* = 11.6 Hz, 1 H), 4.08–3.88 (m, 2 H), 3.81 (s, 3 H), 3.78–3.70 (m, 1 H), 1.81–1.73 (m, 1 H), 1.62–1.55 (m, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 135.1, 131.0, 129.2, 129.1, 118.8, 113.7, 108.5, 82.9, 77.3, 71.8, 70.4, 55.2, 39.5, 27.4, 27.3, 26.9, 20.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3092, 2954, 1658, 1563, 1412, 1099, 829 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}O_4Na$ $[M + Na]^+$ 329.1723; found 329.1718.

(*R*)-1-[(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]propan-2-ol (15): Compound **14** (0.168 g, 0.55 mmol) was dissolved in CH_2Cl_2/H_2O (18:1, 10 mL). DDQ (0.187 g, 0.82 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with $NaHCO_3$ solution (5 %), water and brine and was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) afforded the pure compound **15** (0.083 g, 82 %) as a light yellow oil. $[\alpha]_D^{25}$ = –11.91 (*c* = 2.2, $CHCl_3$); ref.[11b] $[\alpha]_D^{25}$ = –12.25 (*c* = 0.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.77 (ddd, *J* = 7.3, 10.2, 17.2 Hz, 1 H), 5.34 (d, *J* = 17.1 Hz, 1 H), 5.24 (d, *J* = 10.4 Hz, 1 H), 4.08–3.99 (m, 2 H), 3.90 (dt, *J* = 3.4, 8.4 Hz, 1 H), 2.71 (br. s, 1 H), 1.70–1.67 (m, 1 H), 1.65–1.58 (m, 1 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.20 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.8, 119.1, 108.8, 82.3, 77.7, 64.9, 39.4, 27.2, 26.8, 23.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3414, 2987, 2918, 1736, 1408 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{18}O_3$ $[M + Na]^+$ 209.1148; found 209.1149.

{(4*S*,5*S*)-5-[(*R*)-2-Hydroxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl 4-Methylbenzenesulfonate (16): Olefin **15** (0.084 g, 0.45 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C. Ozone was passed through the solution until a blue tint was observed, and dimethyl sulfide (3 mL) was added to this resulting blue solution. The reaction mixture was allowed to warm to room temperature and stirred for 12 h, at which point the reaction mixture was concentrated and the crude aldehyde was used for the next step without purification. The residue was redissolved in MeOH (10 mL), and $NaBH_4$ (0.045 g) was added. After 30 min, the mixture was concentrated and the residue was partitioned between EtOAc (50 mL) and H_2O (20 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated, and the residue was purified by silica gel column chromatography. NaH (0.010 g, 0.45 mmol) was added to a stirred solution of this alcohol in dry THF cooled to 0 °C, and after 10 min TsCl (0.086 g, 0.45 mmol) was added and the reaction mixture was stirred at same temperature for another 3 h, at which point TLC analysis of the reaction mixture shows consumption of starting material. The reaction mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried with Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography with EtOAc/petroleum ether 15 % as eluent to furnish compound **16** (0.108 g, 70 %) as a colourless oil. $[\alpha]_D^{25}$ = +3.20 (*c* = 0.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 4.14–4.11 (m, 2 H), 4.09–4.05 (m, 1 H), 4.02–3.99 (m, 1 H), 3.88–3.85 (m, 1 H), 2.47 (s, 3 H), 1.71–1.68 (m, 2 H), 1.37 (s, 3 H),1.31 (s, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.1, 132.6, 129.9, 127.9, 109.5, 78.0, 75.3, 68.9, 65.0, 41.0, 27.2, 26.6, 23.8, 21.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3455, 2903, 1445, 1185, 790 cm^{-1}.

Ophiocerin C (1): *t*BuOK (0.087 g, 0.78 mmol) was added at 0 °C to a stirred solution of tosylate **16** (0.089 g, 0.26 mmol) in dry Et_2O (3 mL), and the mixture was stirred for 1 h at 0 °C and monitored by TLC. After completion of the reaction the mixture was diluted with saturated aq. NH_4Cl (10 mL) and extracted with Et_2O (4 × 5 mL). The combined organic layers were washed with H_2O and brine, concentrated in vacuo and then treated with PTSA (0.003 g) and MeOH (5 mL) with stirring at room temperature for another 2 h. The reaction was quenched with saturated aq. $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to furnish ophiocerin C (**3**, 0.028 g, 82 %) as a white solid. $[\alpha]_D^{25}$ = +42.40 (*c* = 1.3, CH_2Cl_2); ref.[5] $[\alpha]_D^{25}$ = +45.00 (*c* = 0.1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.97 (dd, *J* = 5.0, 11.3 Hz, 1 H), 3.65–3.45 (m, 3 H), 3.16 (dd, *J* = 9.9, 11.0 Hz, 1 H), 2.00 (ddd, *J* = 1.8, 4.3, 12.6 Hz, 1 H), 1.38 (ddd, *J* = 11.1, 11.1, 12.8 Hz, 1 H), 1.22 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 73.3, 72.7,72.2, 69.6, 40.5, 21.2 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3392, 3018, 2854, 1458, 1263, 1099, 759 cm^{-1}.

(1*R*,3*R*)-3-[(4-Methoxybenzyl)oxy]-1-[(*S*)-oxiran-2-yl]butan-1-ol (17): DIAD (diisopropyl azodicarboxylate, 0.36 mL, 1.86 mmol) was added to a precooled (0 °C) solution of alcohol **13** (0.116 g, 0.46 mmol), triphenylphosphine (0.366 g, 1.39 mmol) and *p*-nitrobenzoic acid (0.386 g, 2.32 mmol) in dry THF (2 mL). The reaction mixture was stirred at room temperature for 5 h and monitored by TLC. After completion of the reaction, the solvent was removed and the crude residue was purified by silica gel column chromatography with petroleum ether/EtOAc (9:1) to give *p*-nitrobenzoate as a yellow oil along with DIAD as an impurity. K_2CO_3 (0.190 g, 1.38 mmol) was added to the solution of *p*-nitrobenzoate (obtained above) in

MeOH (3 mL), and the mixture was stirred at room temperature for 1 h, at which point it was filtered through Celite and washed with ethyl acetate (20 mL). The solvent was concentrated in vacuo, and the crude residue was purified by column chromatography with EtOAc/petroleum ether 15 % as eluent to furnish compound **17** (0.091 g, 79 %) as a colourless oil. $[\alpha]_D^{25}$ = –53.13 (*c* = 1.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.60 (d, *J* = 11.0 Hz, 1 H), 4.36 (d, *J* = 11.0 Hz, 1 H), 3.92–3.82 (m, 1 H), 3.82–3.77 (s, 3 H), 3.70–3.64 (m, 1 H), 2.94–2.87 (m, 1 H), 2.81–2.71 (m, 2 H), 1.84–1.76 (m, 2 H), 1.28 (d, *J* = 5.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 40.6, 45.2, 54.3, 55.2, 70.0, 71.0, 74.9, 113.9, 129.4, 129.9, 159.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3402, 3108, 2564, 1618, 1219 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}O_4Na$ $[M + Na]^+$ 275.1254; found 275.1251.

(4*R*,5*S*)-4-{(*R*)-2-[(4-Methoxybenzyl)oxy]propyl}-2,2-dimethyl-5-vinyl-1,3-dioxolane (18): Compound **18** was synthesized by the same procedure as described for compound **14**, in 82 % yield. $[\alpha]_D^{25}$ = +69.90 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.85–5.71 (m, 1 H), 5.27–5.17 (m, 2 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.42–4.35 (m, 2 H), 4.27 (td, *J* = 5.6, 8.6 Hz, 1 H), 3.81 (s, 3 H), 3.67–3.56 (m, 1 H), 1.91 (ddd, *J* = 6.2, 8.3, 14.1 Hz, 1 H), 1.53–1.49 (m, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 1.22 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 134.4, 130.9, 129.3, 118.4, 113.8, 108.2, 79.8, 75.0, 71.6, 69.8, 55.3, 37.1, 28.3, 25.7, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3102, 2964, 1668, 1573, 1422, 1199, 839 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}O_4Na$ $[M + Na]^+$ 329.1723; found 329.1721.

((4*S*,5*R*)-5-{(*R*)-2-[(4-Methoxybenzyl)oxy]propyl}-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (19): 2,6-Lutidine (0.19 mL, 1.62 mmol) was added to a stirred solution of compound **18** (0.248 g, 0.81 mmol) in dioxane/water (3:1, 8 mL), followed by OsO_4 (0.165 g, 0.02 mmol) and $NaIO_4$ (0.695 g, 3.25 mmol). The mixture was stirred at room temperature for 12 h. After completion of the reaction (checked by TLC), water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed, and the crude aldehyde was used for the next step immediately. The aldehyde was dissolved in MeOH (10 mL), and $NaBH_4$ (0.030 g) was added. After 30 min the mixture was concentrated and the residue was partitioned between EtOAc (50 mL) and H_2O (20 mL). The organic layer was dried with Na_2SO_4 and concentrated, and the residue was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to afford the pure compound **19** as a colourless liquid in 80 % (0.200 g) yield. $[\alpha]_D^{25}$ = +48.20 (*c* = 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.39 (d, *J* = 11.2 Hz, 1 H), 4.36–4.26 (m, 1 H), 4.11–4.07 (m, 1 H), 3.81 (s, 3 H), 3.73–3.64 (m, 1 H), 3.62–3.54 (m, 2 H), 1.96 (ddd, *J* = 5.5, 8.4, 13.8 Hz, 1 H), 1.80 (br. s, 1 H), 1.69–1.56 (m, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.26 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 130.6, 129.3, 113.8, 108.0, 77.9, 73.6, 71.9, 70.0, 61.7, 55.3, 35.5, 28.2, 25.5, 19.0 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3392, 3018, 2854, 1458, 1263, 1099, 759 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{26}O_5Na$ $[M + Na]^+$ 333.1672; found 333.1670.

{(4*S*,5*R*)-5-[(*R*)-2-Hydroxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl 4-Methylbenzenesulfonate (20): Et_3N (1.0 mL, 7.2 mmol) and DMAP (0.044 g, 0.40 mmol) were added at room temperature to a stirred solution of alcohol **19** (1.100 g, 3.60 mmol) in dry CH_2Cl_2, and the mixture was stirred for 10 min. TsCl (0.900 g, 4.80 mmol) was added and stirring was continued at room temperature for another 3 h. The mixture was diluted with saturated aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated in vacuo. The crude tosylate product was used in the next step without further purification. Crude tosylate (1.100 g, 2.37 mmol) was dissolved in CH_2Cl_2/H_2O (18:1, 15 mL). DDQ (0.805 g, 3.55 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with $NaHCO_3$ solution (5 %), water and brine and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) afforded the pure compound **20** (1.00 g, 83 %). $[\alpha]_D^{25}$ = –6.20 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.2 Hz, 2 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 4.40–4.22 (m, 2 H), 4.05–3.88 (m, 3 H), 2.46 (s, 3 H), 1.73–1.49 (m, 2 H), 1.35 (s, 3 H),1.32 (s, 3 H),1.18 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 145.0, 132.5, 129.9, 127.9, 109.2, 74.3, 71.8, 68.7, 64.7, 34.0, 29.8, 22.0, 21.6, 19.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3455, 2903, 1445, 1185, 790 cm^{-1}. $C_{16}H_{24}O_6S$ (344.42): calcd. C 55.80, H 7.02; found C 55.69, H 6.99.

Ophiocerin A (2): Ophiocerin A was synthesized from **20** by the same procedure as described for ophiocerin C. $[\alpha]_D^{25}$ = –23.40 (*c* = 0.1, CH_2Cl_2); ref.[3] $[\alpha]_D^{25}$ = –24.00 (*c* = 0.1, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.10 (m, 1 H), 3.83 (ddq, *J* = 2.0, 6.4, 11.3 Hz, 1 H), 3.71–3.78 (m, 2 H), 3.60–3.53 (m, 1 H), 1.89 (ddd, *J* = 2.1, 3.5, 14.3 Hz, 1 H), 1.53 (ddd, *J* = 2.5, 11.0,13.9 Hz, 1 H), 1.16 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 67.3, 67.1, 67.0, 65.9, 39.0, 20.8 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3401, 2930, 1454, 1389, 1185, 1011 cm^{-1}.

(1*S*,3*R*)-3-[(4-Methoxybenzyl)oxy]-1-[(*R*)-oxiran-2-yl]butan-1-ol (21): Dibutyltin oxide (0.009 g, 0.04 mmol) was added under argon to a mixture of diol **11a** (0.900 g, 1.77 mmol) in dry CH_2Cl_2 (2 mL), followed by *p*-toluenesulfonyl chloride (0.337 g, 1.77 mmol) and Et_3N (0.25 mL, 1.77 mmol). The resulting mixture was stirred at room temperature for 2 h, quenched with water and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give a crude monotosylate product, which was dissolved in MeOH (10 mL) and treated with K_2CO_3 (0.500 g, 3.61 mmol). This mixture was stirred for 1 h at room temperature and then filtered through celite. Removal of the volatiles under reduced pressure gave the crude epoxide. TBAF in THF (1 M, 2.5 mL, 2.60 mmol) was added at room temperature to the stirred soln. of crude epoxide in dry THF (10 mL) and the mixture was stirred for 4 h. It was then diluted with saturated aq. NH_4Cl (20 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to give **21** (0.352 g, 79 %) as a light yellow oil. $[\alpha]_D^{25}$ = –32.30 (*c* = 0.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.39 (d, *J* = 11.3 Hz, 1 H), 3.99–3.86 (m, 2 H), 3.81 (s, 3 H), 3.02–2.94 (m, 1 H), 2.80–2.68 (m, 2 H), 1.87–1.66 (m, 2 H), 1.27 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 129.4, 113.9, 71.9, 70.3, 67.1, 55.3, 54.3, 44.4, 39.8, 19.4 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3420, 3128, 2594, 1648, 1249 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}O_4Na$ $[M + Na]^+$ 275.1254; found 275.1248.

(1*R*,3*R*)-3-[(4-Methoxybenzyl)oxy]-1-[(*R*)-oxiran-2-yl]butan-1-ol (22): Compound **22** was synthesized from **21** by the same procedure as described for compound **17**, in 75 % yield. $[\alpha]_D^{25}$ = –42.4 (*c* = 2.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.36 (d, *J* = 11.2 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.80 (s, 3 H), 3.75–3.67 (m, 1 H), 3.37 (d, *J* = 2.7 Hz, 1 H), 3.02–2.94 (m, 1 H), 2.78–2.72 (m, 1 H), 2.70–

2.60 (m, 1 H), 1.86 (td, *J* = 9.2, 14.4 Hz, 1 H), 1.74–1.61 (m, 1 H), 1.26 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 130.0, 129.4, 113.9, 74.1, 70.7, 69.9, 55.2, 54.9,44.3, 40.3, 19.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3410, 3118, 2584, 1638, 1239 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}O_4Na$ $[M + Na]^+$ 275.1254; found 275.1249.

(4*R*,5*S*)-4-{(*R*)-2-[(4-Methoxybenzyl)oxy]propyl}-2,2-dimethyl-5-vinyl-1,3-dioxolane (23): Compound **23** was synthesized from **22** by the same procedure as described for compound **14**. $[\alpha]_D^{25}$ = –8.47 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.79 (ddd, *J* = 7.3, 10.1, 17.3 Hz, 1 H), 5.36 (d, *J* = 17.1 Hz, 1 H), 5.24 (d, *J* = 10.3 Hz, 1 H), 4.50 (d, *J* = 11.2 Hz, 1 H), 4.38 (d, *J* = 11.0 Hz, 1 H), 4.05 (t, *J* = 7.8 Hz, 1 H), 3.81 (s, 3 H), 3.80–3.77 (m, 1 H), 3.76–3.66 (m, 1 H), 1.96 (td, *J* = 7.1, 14.0 Hz, 1 H), 1.68 (ddd, *J* = 4.4, 6.5, 14.1 Hz, 1 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.24 (d, *J* = 5.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 135.2, 130.9, 129.2, 119.0, 113.7, 108.6, 82.8, 77.6, 71.8, 69.9, 55.3, 38.5, 27.3, 26.9, 19.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3082, 2964, 1648, 1573, 1402, 1119, 789 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}O_4Na$ $[M + Na]^+$ 329.1723; found 329.1725.

((4*S*,5*R*)-5-{(*R*)-2-[(4-Methoxybenzyl)oxy]propyl}-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (24): Compound **24** was synthesized from **23** by the same procedure as described for compound **19**. $[\alpha]_D^{25}$ = +0.81 (*c* = 5.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 4.51 (d, *J* = 11.2 Hz, 1 H), 4.38 (d, *J* = 11.0 Hz, 1 H), 4.06–3.96 (m, 1 H), 3.80 (s, 3 H), 3.74 (m, 2 H), 3.66–3.56 (m, 1 H), 2.09–1.92 (m, 2 H), 1.76–1.65 (m, 2 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.26 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 130.6, 129.3, 129.2, 113.8, 108.5, 81.4, 74.1, 71.8, 69.9, 61.9, 55.3, 39.6, 27.3, 27.0, 19.4 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3412, 3018, 2854, 1458, 1263, 1099, 759 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{26}O_5Na$ $[M + Na]^+$ 333.1672; found 333.1674.

((4*S*,5*R*)-5-{(*R*)-2-[(4-Methoxybenzyl)oxy]propyl}-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-Methylbenzenesulfonate (25): Et_3N (0.5 mL, 3.60 mmol) and DMAP (0.022 g, 0.20 mmol) were added at room temperature to a stirred solution of alcohol **24** (0.560 g, 1.80 mmol) in dry CH_2Cl_2, and the mixture was stirred for 10 min. TsCl (0.900 g, 4.80 mmol) was added and stirring was continued at room temperature for another 3 h. The reaction mixture was diluted with saturated aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated in vacuo. The crude tosylate product was purified by column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to give the tosyl ester **25** (0.720 g, 86 %) as a yellow liquid. $[\alpha]_D^{25}$ = –12.3 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83–7.72 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.91–6.85 (d, *J* = 8.5 Hz, 2 H), 4.56–4.46 (m, 1 H), 4.35 (d, *J* = 11.3 Hz, 1 H), 4.14–4.02 (m, 2 H), 3.96 (dt, *J* = 4.9, 7.5 Hz, 1 H), 3.91–3.85 (m, 1 H), 3.81 (s, 3 H), 3.73–3.67 (m, 1 H), 2.44 (s, 3 H), 1.93 (td, *J* = 6.8, 13.9 Hz, 1 H), 1.74–1.62 (m, 1 H), 1.37 (s, 3 H), 1.30 (s, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 144.9, 132.7,130.7, 129.8, 129.1, 127.9, 113.7, 109.3, 78.3, 74.6, 71.5, 69.8, 69.0, 55.3, 39.5, 27.3, 26.6, 21.6, 13.4 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3392, 2754, 1858, 1463, 1009, 959 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{32}O_7SNa$ $[M + Na]^+$ 487.1761; found 487.1762.

Ophiocerin B (3): Compound **25** (0.255 g, 0.55 mmol) was dissolved in CH_2Cl_2/H_2O (18:1, 15 mL), and DDQ (0.187 g, 0.83 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with $NaHCO_3$ solution (5 %), water and brine and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude residue was used for the next step without further purification. *t*BuOK (0.248 g, 2.20 mmol) was added at 0 °C to the stirred solution of crude tosylate in dry Et_2O (3 mL), and the mixture was stirred for 1 h at 0 °C and monitored by TLC. After completion of the reaction it was diluted with satd. aq. NH_4Cl (10 mL) and extracted with Et_2O (4 × 5 mL). The combined organic layers were washed with H_2O and brine, concentrated in vacuo and then treated with PTSA (0.003 g) and MeOH (5 mL) with stirring at room temperature for another 2 h. The reaction was quenched with saturated aq. $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to produce ophiocerin B (**3**, 0.059 g, overall yield 82 %) as a yellow oil. $[\alpha]_D^{25}$ = –35.20 (*c* = 1.3, CH_2Cl_2); ref.[5] $[\alpha]_D^{25}$ = –37.00 (*c* = 0.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.01–3.94 (m, 2 H), 3.91–3.81 (m, 1 H), 3.73 (dd, *J* = 12.5, 1.8 Hz, 1 H), 3.48 (m, 1 H), 2.27 (br. s, 2 H), 1.81 (ddd, *J* = 3.2, 10.9, 14.3 Hz, 1 H), 1.63–1.60 (m, 1 H), 1.19 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 68.4, 68.3, 67.4, 67.3, 36.0, 21.2 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3398, 1467, 1389, 1287, 1104, 987 cm^{-1}. HRMS (ESI): calcd. for $C_6H_{12}O_3Na$ $[M + Na]^+$ 155.0679; found 155.0680.

(*R*)-1-[(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]propan-2-yl Acetate (26): Acetic anhydride (1.0 mL, 7.74 mmol) and DMAP (cat.) were added to a precooled (0 °C) solution of **15** (0.725 g, 3.90 mmol) in dry pyridine (5 mL), and the mixture was stirred at room temperature for 4 h. After completion of the reaction, the mixture was diluted with aq. $CuSO_4$•5 H_2O solution (10 %) and extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine solution and dried with Na_2SO_4, and the solvents were evaporated under vacuum to furnish the crude residue, which was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to give acetate compound **26** (0.800 g, 90 %) as a yellow oil. $[\alpha]_D^{25}$ = –16.48 (*c* = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.71 (m, 1 H), 5.38 (d, *J* = 17.1 Hz, 1 H), 5.27 (d, *J* = 10.3 Hz, 1 H), 5.14–4.97 (m, 1 H), 4.01–3.90 (m, 1 H), 3.80–3.61 (m, 1 H), 2.03 (s, 3 H), 1.92–1.79 (m, 1 H), 1.74–1.64 (m, 1 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.27 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 134.9, 119.2, 108.8, 82.7, 77.2, 68.6, 38.2, 27.2, 26.9, 21.3, 20.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3081, 2854, 1685, 1458, 1263, 1009, 917 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{20}O_4Na$ $[M + Na]^+$ 251.1254; found 251.1254.

Ethyl (*Z*)-3-{(4*S*,5*S*)-5-[(*R*)-2-Acetoxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (27): Olefin **26** (0.251 g, 1.10 mmol) was dissolved in CH_2Cl_2 (10 mL), and the mixture was cooled to –78 °C. Ozone was passed through the solution until a blue tint was observed (ca. 3 min), and dimethyl sulfide (6 mL) was added to this resulting blue solution. The reaction mixture was allowed to warm to room temperature and stirred for 12 h, at which point it was concentrated and the crude aldehyde was used for the next step without purification. Ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]-acetate (0.320 g, 1.40 mmol) and 18-crown-6 (2.470 g, 9.36 mmol) were taken up in dry THF (10 mL) at –78 °C, KHMDS (0.670 g, 2.93 mmol) was added, and the reaction mixture was stirred for 1 h. Then, the above crude aldehyde (0.179 g, 0.95 mmol) dissolved in THF (5 mL) was added, and stirring was continued for another 6 h at –78 °C, at which point it showed complete consumption of starting material. Then the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo, and the residue was purified over silica gel (100–200 mesh, eluent EtOAc/hexane 10 %) to give the product **27** (0.290 g, 88 %) as a colourless syrup. $[\alpha]_D^{25}$ = –7.10 (*c* = 1.2,

$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.11 (dd, J = 8.8, 11.7 Hz, 1 H), 5.95 (d, J = 12.2 Hz, 1 H), 5.28–5.23 (m, 1 H), 5.14–4.94 (m, 1 H), 4.18 (q, J = 7.3 Hz, 2 H), 3.84–3.66 (m, 1 H), 2.00 (s, 3 H), 1.91–1.69 (m, 2 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.24 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 165.4, 145.2, 123.3, 109.5, 77.9, 76.4, 68.5, 60.5, 38.2, 29.6, 27.3, 26.9, 21.3, 14.1 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2975, 2940, 1732, 1645, 1357, 1263, 1199, 1019 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{24}O_6Na$ $[M + Na]^+$ 323.1465; found 323.1460.

Botryolide E (4): The ester **27** (0.150 g, 0.50 mmol) was dissolved in THF, HCl solution (1 M, 1 mL) was added, and the mixture was stirred for 2 h at 0 °C. After consumption of starting material (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ and extracted into EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide crude lactone, which was purified by column chromatography (silica gel 100–200 mesh, EtOAc/petroleum ether 40 %) to afford pure lactone **4** (0.069 g, 65 %). $[\alpha]_D^{25}$ = –37.10 (c = 2.5, $CHCl_3$); ref.[6] $[\alpha]_D^{25}$ = –36.70 (c = 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (dd, J = 1.5, 6.1 Hz, 1 H), 6.19 (dd, J = 2.1, 5.8 Hz, 1 H), 5.18–5.08 (m, 1 H), 5.07–4.98 (m, 1 H), 3.96–3.84 (m, 1 H), 2.04 (s, 3 H), 1.95–1.88 (m, 1 H), 1.80–1.73 (m, 1 H), 1.31 (d, J = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 170.8, 153.7, 122.8, 85.3, 69.0, 68.7, 39.1, 21.3, 20.0 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3432, 3008, 2844, 1743, 1720, 1658, 1256 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}O_5Na$ $[M + Na]^+$ 237.0733; found 237.0733.

(*S*)-4-[(4-Methoxybenzyl)oxy]butane-1,2-diol (30): D-Proline (0.187 g, 1.63 mmol) was added at room temperature to a solution of PMB-protected butanal **28** (1.130 g, 5.43 mmol) and nitrosobenzene (0.581 g, 5.43 mmol) in anhydrous DMSO (29 mL), turning the solution green. The reaction mixture was vigorously stirred for 1 h under argon (the colour changed from green to yellow during this time). Then the temperature was lowered to 0 °C, followed by addition of methanol and sodium borohydride to the reaction mixture. After completion of the reaction (monitored by TLC), the resulting mixture was diluted with water and extracted with EtOAc (4 × 20 mL), and the combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated to give the crude aminoxy alcohol, which was used directly for the next step without purification. $CuSO_4$•5 H_2O (1.350 g, 5.43 mmol) was added to a well-stirred solution of this aminoxy alcohol in methanol, and the mixture was stirred overnight at room temp. The reaction mixture was filtered through celite and concentrated in vacuo. The compound was purified by column chromatography (silica gel mesh 100–200, EtOAc/petroleum ether 40 %) to afford diol **30** in 78 % yield (0.958 g). $[\alpha]_D^{25}$ = –4.80 (c = 1.7, $CHCl_3$); ref.[24] $[\alpha]_D^{25}$ = –5.20 (c = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.44 (s, 2 H), 3.91–3.82 (m, 1 H), 3.79 (s, 3 H), 3.68–3.54 (m, 3 H), 3.50–3.41 (m, 1 H), 3.17 (br. s, 2 H), 1.81–1.68 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 129.8, 129.3, 113.8, 72.8, 71.0, 67.6, 66.4, 55.2, 32.7 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3446, 2980, 2932, 2853, 1623, 1533 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{18}O_4Na$ $[M + Na]^+$ 249.1097; found 249.1095.

(*S*)-2-{2-[(4-Methoxybenzyl)oxy]ethyl}oxirane (31): Dibutyltin oxide (0.009 g, 0.04 mmol) was added under argon to a mixture of diol **30** (0.4 g, 1.77 mmol) in dry CH_2Cl_2 (20 mL), followed by addition of *p*-toluenesulfonyl chloride (0.337 g, 1.77 mmol) and Et_3N (0.25 mL, 1.77 mmol). The resulting mixture was stirred at room temperature for 2 h, quenched with water and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water, dried (Na_2SO_4) and concentrated to give a crude monotosylate product, which was dissolved in MeOH (10 mL) and treated with K_2CO_3 (0.500 g, 3.61 mmol). This mixture was stirred for 1 h at room temperature and then filtered through celite. Removal of the volatiles under reduced pressure gave crude epoxide, which was purified by column chromatography (silica gel mesh 100–200, EtOAc/petroleum ether 20 %) to provide epoxide **31** (0.295 g, 80 % yield). $[\alpha]_D^{25}$ = –13.5 (c = 2.5, $CHCl_3$); ref.[25] $[\alpha]_D^{25}$ = –13.1 (c = 0.58, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 4.47 (s, 2 H), 3.81 (s, 3 H), 3.62–3.57 (m, 2 H), 3.09–3.03 (m, 1 H), 2.78 (t, J = 4.5 Hz, 1 H), 2.52 (dd, J = 2.7, 4.9 Hz, 1 H), 1.95–1.84 (m, 1 H), 1.77 (qd, J = 6.0, 14.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 130.3, 129.2, 113.7, 72.7, 66.6, 55.2, 50.0, 47.0, 32.9 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3036, 2987, 2915, 2870, 1643 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}O_3Na$ $[M + Na]^+$ 231.0992; found 231.0988.

(*S*)-*tert*-Butyl({5-[(4-methoxybenzyl)oxy]pent-1-en-3-yl}oxy)-dimethylsilane (32): Trimethylsulfonium iodide (1.230 g, 6.05 mmol) was added at –20 °C to stirred dry THF, followed by *n*BuLi (3.8 mL, 1.6 M, 6.05 mmol). The reaction mixture was stirred for 1 h, after which epoxide **31** (0.251 g, 1.21 mmol) in THF was added dropwise. The reaction mixture was stirred at –20 °C for 3 h, and completion of the reaction was monitored by TLC. The reaction mixture was diluted with saturated ammonium chloride solution and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine, dried with Na_2SO_4 and concentrated. The crude alcohol was used for the next step without further purification. *tert*-Butylchlorodimethylsilane (0.212 g, 1.41 mmol) was added slowly at 0 °C to the stirred solution of crude alcohol and imidazole (0.129 g, 1.90 mmol) in dry CH_2Cl_2, and the reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, water was added to quench the reaction mixture, and the organic layer was washed with excess water and brine, dried with Na_2SO_4 and concentrated to afford the crude silylated compound, which was purified by silica gel column chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to afford **32** (0.330 g, 82 %) as a viscous liquid. $[\alpha]_D^{25}$ = +3.5 (c = 1.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.2 Hz, 2 H), 6.89 (d, J = 8.5 Hz, 2 H), 5.81 (ddd, J = 6.1, 10.5, 16.9 Hz, 1 H), 5.16 (d, J = 17.1 Hz, 1 H), 5.02 (d, J = 10.4 Hz, 1 H), 4.48–4.36 (m, 2 H), 4.30 (q, J = 6.0 Hz, 1 H), 3.82 (s, 3 H), 3.59–3.43 (m, 2 H), 1.78 (q, J = 5.7 Hz, 2 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 141.6, 130.7, 129.3, 113.7, 72.6, 70.8, 66.4, 55.3, 38.1, 25.9, 18.2, –4.4, –4.9 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3072, 3028, 2967, 2912, 1709, 1613, 1485, 1203, 1099 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{32}O_3Si$ Na $[M + Na]^+$ 359.2013; found 359.2014.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]pent-4-enoic Acid (33): Olefin **32** (0.250 g. 0.74 mmol) was dissolved in CH_2Cl_2/H_2O (18:1, 15 mL). DDQ (0.253 g, 1.12 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with $NaHCO_3$ solution (5 %), water and brine and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude alcohol was used for the next step without further purification. TEMPO (0.029 g, 0.10 mmol) and BAIB (0.900 g, 2.8 mmol) were added at 0 °C to a stirred solution of crude primary alcohol (0.194 g, 0.90 mmol) in CH_3CN (3 mL) and H_2O (1 mL) with monitoring by TLC. The reaction mixture was stirred for 7 h, until TLC indicated the complete consumption of starting material. The reaction mixture was diluted by the addition of saturated aqueous Na_2SO_3 (20 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (EtOAc/hexane 25 %) to give **33** (0.128 g, 75 %) as a light yellow oil. $[\alpha]_D^{25}$ = +2.8 (*c* = 1.8, $CHCl_3$); ref.[11b] $[\alpha]_D^{25}$ = +2.1 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 6.2, 10.5, 17.0 Hz, 1 H), 5.27 (dd, *J* = 1.1, 17.2 Hz, 1 H), 5.13 (dd, *J* = 1.1, 10.4 Hz, 1 H), 4.69–4.50 (m, 1 H), 2.56 (dd, *J* = 2.7, 6.1 Hz, 2 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 139.4, 115.4, 70.6, 43.0, 25.7, 18.1, –4.4, –5.2 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2954, 2856, 1741, 1446, 812 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{22}O_3Si$ Na $[M + Na]^+$ 253.1230; found 253.1231.

(*R*)-1-[(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]propan-2-yl (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]pent-4-enoate (34): DMAP (0.003 g, 0.020 mmol) was added to a stirred solution of triethylamine (0.066 g, 0.65 mmol) in dry CH_2Cl_2 (5 mL), followed by 2-methyl-6-nitrobenzoic anhydride (0.083 g, 0.24 mmol) and acid **33** (0.056 g, 0.24 mmol). The reaction mixture was stirred for another 45 min, hydroxy olefin **15** (0.037 g, 0.2 mmol) in dry CH_2Cl_2 was then added, and the progress of the reaction was monitored by TLC. This reaction mixture was then stirred for 12 h and quenched by addition of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with petroleum ether/EtOAc (80:20) as an eluent to afford **34** (0.075 g, 95 %) as a colourless liquid. $[\alpha]_D^{25}$ = –6.92 (*c* = 1.1, $CHCl_3$); ref.[11b] $[\alpha]_D^{25}$ = –5.25 (*c* = 0.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.90–5.71 (m, 2 H), 5.37 (d, *J* = 17.1 Hz, 1 H), 5.29–5.17 (m, 2 H), 5.13–4.98 (m, 2 H), 4.63–4.52 (m, 1 H), 4.02–3.90 (m, 1 H), 3.78–3.60 (m, 1 H), 2.52 (dd, *J* = 7.0, 15.0 Hz, 1 H), 2.41 (dd, *J* = 5.8, 14.6 Hz, 1 H), 1.95–1.79 (m, 1 H), 1.77–1.59 (m, 1 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.27 (d, *J* = 6.1 Hz, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 140.2, 134.8, 119.3, 114.6, 108.9, 82.8, 77.2, 68.9, 43.8, 38.4, 27.2, 26.9, 25.8, 20.6, 18.1, –4.4, –4.5 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3023, 2909, 2875, 1773, 1664, 1436, 1337, 1252 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{38}O_5Si$ Na $[M + Na]^+$ 421.2381; found 421.2381.

(3*S*,5*R*,9*S*,11*S*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,2,5-trimethyl-4,5,8,9-tetrahydro-3-[1,3]dioxolo[4,5]oxecin-7-one (35): The second-generation Grubbs catalyst (0.027 g, 10 mol-%) was added to a solution of diene **34** (0.125 g, 0.31 mmol) in freshly distilled CH_2Cl_2 (250 mL, degassed for 15 min by argon bubbling), and the solution was then again degassed for 1 h. The reaction mixture was heated at reflux at 45 °C for 24 h (completion of the reaction was checked by TLC). The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (silica gel, 230–400 mesh, EtOAc/petroleum ether 30 %) to afford compound **35** (0.087 g, 75 %) as a colourless oil. $[\alpha]_D^{25}$ = –9.81 (*c* = 1.5, $CHCl_3$); ref.[11b] $[\alpha]_D^{25}$ = –8.10 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.97–5.87 (m, 1 H), 5.70–5.58 (m, 1 H), 5.04–4.92 (m, 1 H), 4.72–4.63 (m, 1 H), 4.10 (t, *J* = 8.8 Hz, 1 H), 3.63 (t, *J* = 8.8 Hz, 1 H), 2.46 (d, *J* = 3.4 Hz, 2 H), 2.06–1.85 (m, 2 H), 1.41 (s, 6 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 138.1, 122.8, 107.9, 84.1, 81.6, 69.0, 67.9, 45.2, 38.5, 27.0, 26.9, 25.7, 21.8, 18.3, –5.0, –5.2 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2919, 2837, 1753, 1126, 1087 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{34}O_5Si$ Na $[M + Na]^+$ 393.2068; found 393.2064.

Decarestrictine O: The protected lactone **35** (0.087 g, 0.24 mmol) was dissolved in THF, HCl solution (1 M, 1 mL) was added, and the mixture was stirred for 2 h at 0 °C. After consumption of starting material (monitored by TLC), the reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted into EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide crude lactone, which was purified by column chromatography (silica gel 100–200 mesh, EtOAc/petroleum ether 40 %) to afford pure lactone **5** (0.034 g, 68 %) as a colourless thick liquid. $[\alpha]_D^{25}$ = –20.2 (*c* = 0.8, MeOH); ref.[11b] $[\alpha]_D^{25}$ = –19.6 (*c* = 0.2, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 5.89 (dd, *J* = 3.1, 15.8 Hz, 1 H), 5.52 (dd, *J* = 10.8, 15.8 Hz, 1 H), 4.80–4.69 (m, 1 H), 4.63–4.62 (m, 1 H), 3.75 (t, *J* = 9.2 Hz, 1 H), 3.38 (t, *J* = 9.3 Hz, 1 H), 2.52 (dd, *J* = 3.8, 11.9 Hz, 1 H), 2.43 (dd, *J* = 3.5, 11.9 Hz, 1 H), 1.95–1.88 (m, 1 H), 1.75 (d, *J* = 15.9 Hz, 1 H), 1.20 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 171.9, 137.6, 127.1, 80.0, 77.2, 70.9, 68.1, 44.5, 44.2, 23.4 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3412, 2918, 1754, 1485 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}O_5Na$ $[M + Na]^+$ 239.0890; found 239.0889.

***tert*-Butyl({(3*S*,5*R*)-5-[(4-methoxybenzyl)oxy]hex-1-en-3-yl}oxy)-diphenylsilane (36):** Triphenylphosphine (3.000 g, 11.40 mmol) and imidazole (1.560 g, 22.90 mmol) were added at 0 °C to a stirred solution of compound **11a** (1.930 g, 3.80 mmol) in dry THF (150 mL), followed by iodine (2.900 g, 11.40 mmol). Then the reaction mixture was heated at reflux for 4 h and allowed to cool to room temperature, after which it was diluted with saturated aqueous $Na_2S_2O_3$ (100 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with brine and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (100–200 mesh silica gel, EtOAc/hexane 5 % as an eluent) to afford olefin **36** (1.500 g, 83 %) as a colourless oil. $[\alpha]_D^{25}$ = +13.45 (*c* = 5.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 4 H), 7.46–7.32 (m, 6 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 6.85 (d, *J* = 8.2 Hz, 2 H), 5.85–5.75 (m, 1 H), 4.95–4.85 (m, 2 H), 4.40–4.29 (m, 2 H), 4.15 (d, *J* = 10.7 Hz, 1 H), 3.81 (s, 3 H), 3.63–3.54 (m, 1 H), 1.81 (td, *J* = 6.5, 13.5 Hz, 1 H), 1.74–1.64 (m, 1 H), 1.09–1.05 (m, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 141.0, 136.0, 135.9, 134.3, 131.1, 129.5, 129.4, 129.1, 129.0, 127.5, 127.3, 114.5, 113.6, 72.5, 71.7, 69.8, 55.3, 45.6, 27.0, 19.9, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3072, 2932, 2866, 1614, 1459, 1426, 1377, 1260, 1106, 1046, 992 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{38}O_3SiNa$ $[M + Na]^+$ 497.2482; found 497.2479.

(2*R*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-en-2-ol (37): Olefin **36** (0.150 g, 0.32 mmol) was dissolved in CH_2Cl_2/H_2O (18:1, 15 mL), and DDQ (0.108 g, 0.47 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with $NaHCO_3$ solution (5 %), water and brine and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (100–200 mesh silica gel, EtOAc/hexane 15 % as an eluent) to afford olefin **37** (0.089 g, 80 %) as a colourless oil. $[\alpha]_D^{25}$ = –6.25 (*c* = 1.2, $CHCl_3$); ref.[12c] $[\alpha]_D^{25}$ = –5.30 (*c* = 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.64 (m, 4 H), 7.49–7.36 (m, 6 H), 5.86 (ddd, *J* = 5.9, 10.7, 16.9 Hz, 1 H), 5.12–4.99 (m, 2 H), 4.47 (q, *J* = 5.1 Hz, 1 H), 4.11–4.03 (m, 1 H), 1.69 (ddd, *J* = 4.4, 9.8, 14.4 Hz, 1 H), 1.55–1.47 (m, 1 H), 1.10 (s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 136.0, 135.9, 133.3, 133.2, 129.9, 129.8, 127.7, 127.5, 115.0, 73.8, 64.6, 44.8, 27.0, 23.4, 19.2 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3479, 2924, 2845, 1436, 1471, 1206, 1119, 969, 942, 812, 716 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{30}O_2SiNa$ $[M + Na]^+$ 377.1907; found 377.1904.

***tert*-Butyl({(3S,5S)-5-[(4-methoxybenzyl)oxy]hex-1-en-3-yl}oxy)-diphenylsilane (38):** Compound **38** was synthesized from **11b** by the same procedure as described for the synthesis of compound **36**, in 82 % yield. $[\alpha]_D^{25}$ = +22.58 (*c* = 8.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.67 (m, 4 H), 7.48–7.35 (m, 6 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 6.83 (d, *J* = 8.2 Hz, 2 H), 5.86–5.75 (m, 1 H), 4.93 (d, *J* = 10.4 Hz, 1 H), 4.84 (d, *J* = 17.7 Hz, 1 H), 4.41–4.30 (m, 2 H), 4.24 (d, *J* =

11.3 Hz, 1 H), 3.82 (s, 3 H), 3.58–3.48 (m, 1 H), 2.04–1.95 (m, 1 H), 1.59–1.50 (m, 1 H), 1.08 (s, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 140.7, 136.0, 135.9, 134.2, 134.1, 131.1, 129.5, 129.4, 129.0, 127.5, 127.3, 114.6, 113.6, 72.6, 71.3, 69.5, 55.2, 45.2, 27.0, 19.8, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3052, 2922, 2836, 1617, 1449, 1416, 1317, 1267, 1162, 1056 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{38}O_3SiNa$ [M + Na]$^+$ 497.2482; found 497.2476.

(2*S*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-en-2-ol (39): Compound **39** was synthesized by the same procedure as described for the synthesis of compound **37**, in 84 % yield. $[\alpha]_D^{25}$ = –2.87 (*c* = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.61 (m, 4 H), 7.48–7.33 (m, 6 H), 5.79 (ddd, *J* = 6.7, 10.4, 17.1 Hz, 1 H), 4.95–4.85 (m, 2 H), 4.40 (q, *J* = 6.3 Hz, 1 H), 4.04–3.96 (m, 1 H), 2.13 (br. s, 1 H), 1.71 (ddd, *J* = 6.7, 9.0, 14.3 Hz, 1 H), 1.53 (ddd, *J* = 2.9, 5.9, 14.2 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 136.0, 135.9, 133.8, 133.7, 129.8, 129.6, 127.6, 127.4, 114.9, 74.3, 65.8, 46.3, 27.0, 23.7, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3472, 2942, 2855, 1466, 1451, 1216, 1039, 869, 802, 746 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{30}O_2SiNa$ [M + Na]$^+$ 377.1907; found 377.1907.

(*S*)-5-[(4-Methoxybenzyl)oxy]pentane-1,2-diol (42): Compound **42** was synthesized from **40** in 77 % yield by the same procedure as described for the synthesis of compound **30**. $[\alpha]_D^{25}$ = –2.51 (*c* = 4.2, $CHCl_3$); ref.[24] $[\alpha]_D^{25}$ = –2.00 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.14 (m, *J* = 8.6 Hz, 2 H), 6.84–6.78 (m, *J* = 8.6 Hz, 2 H), 4.37 (s, 2 H), 3.73 (s, 3 H), 3.64–3.55 (m, 1 H), 3.51 (dd, *J* = 3.1, 11.1 Hz, 1 H), 3.45–3.31 (m, 3 H), 2.90 (br. s, 2 H), 1.74–1.59 (m, 2 H), 1.58–1.45 (m, 1 H), 1.43–1.34 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 129.9, 129.4, 113.8, 72.7, 71.9, 70.1, 66.7, 55.2, 30.7, 26.1 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3412, 2924, 2872, 1602, 1522, 1236, 1076, 809 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{20}O_4Na$ [M + Na]$^+$ 263.1254; found 263.1252.

(*S*)-2-{3-[(4-Methoxybenzyl)oxy]propyl}oxirane (43): Compound **43** was synthesized from **42** in 81 % yield by the same procedure as described for the synthesis of compound **31**. $[\alpha]_D^{25}$ = –5.2 (*c* = 3.5, $CHCl_3$); ref.[26] $[\alpha]_D^{25}$ = –4.5 (*c* = 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.22 (m, *J* = 8.6 Hz, 2 H), 6.89–6.84 (m, *J* = 8.6 Hz, 2 H), 4.42 (s, 2 H), 3.79 (s, 3 H), 3.54–3.41 (m, 2 H), 2.96–2.87 (m, 1 H), 2.73 (t, *J* = 4.5 Hz, 1 H), 2.45 (dd, *J* = 2.8, 5.0 Hz, 1 H), 1.79–1.55 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 130.5, 129.2, 113.7, 72.5, 69.4, 55.2, 52.1, 47.0, 29.3, 26.1 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2913, 2836, 1652, 1510, 1266, 1074, 1034, 811 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{18}O_3Na$ [M + Na]$^+$ 245.1148; found 245.1145.

(*S*)-*tert*-Butyl({6-[(4-methoxybenzyl)oxy]hex-1-en-3-yl}oxy)-diphenylsilane (44): Trimethylsulfonium iodide (2.460 g, 12.10 mmol) was added at –20 °C to stirred dry THF, followed by *n*BuLi (7.6 mL, 1.6 M, 12.10 mmol). The reaction mixture was stirred for 1 h, after which epoxide **43** (0.537 g, 2.42 mmol) in THF was added dropwise. The reaction mixture was stirred at –20 °C for 3 h, and completion of the reaction was monitored by TLC. The reaction mixture was diluted with saturated ammonium chloride solution and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine, dried with Na_2SO_4 and concentrated. The crude alcohol was used for the next step without further purification. TBDPSCl (0.6 mL, 2.60 mmol) was added dropwise to a stirred solution of alcohol (0.510 g, 2.16 mmol) and imidazole (0.294 g, 4.32 mmol) in dry CH_2Cl_2 at 0 °C, and the reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, water was added to quench the reaction mixture, and the organic layer was washed with excess water and brine. The organic layer was dried with Na_2SO_4 and concentrated to afford the crude silylated compound, which was purified by silica gel chromatography (100–200 mesh, eluent: EtOAc/petroleum ether 5 %) to afford **44** (0.890 g, 78 %) as a viscous liquid. $[\alpha]_D^{25}$ = +16.9 (*c* = 3.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 4 H), 7.48–7.37 (m, 6 H), 7.25 (s, 2 H), 6.91 (d, *J* = 8.5 Hz, 2 H), 5.83 (ddd, *J* = 6.3, 10.5, 17.1 Hz, 1 H), 5.07–4.97 (m, 2 H), 4.41 (s, 2 H), 4.28–4.20 (m, 1 H), 3.84 (s, 3 H), 3.40–3.31 (m, 2 H), 1.68–1.55 (m, 4 H), 1.12 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 140.5, 135.9, 135.8, 134.4, 134.2, 129.5, 129.4, 129.1, 127.4, 127.3, 114.5, 113.7, 74.3, 72.3, 70.0, 55.2, 34.0, 27.0, 24.6, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3408, 3049, 2912, 2867, 1632, 1445, 1406, 1372, 1351, 1109, 1031, 963, 851, 717, 652 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{38}O_3SiNa$ [M + Na]$^+$ 497.2482; found 497.2482.

(*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-enoic Acid (45): Compound **45** was synthesized in 70 % yield by the same procedure as described for the synthesis of compound **33**. $[\alpha]_D^{25}$ = +15.2 (*c* = 2.5, $CHCl_3$); ref.[10c] $[\alpha]_D^{25}$ = +14.5 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.66 (m, 4 H), 7.47–7.30 (m, 6 H), 5.76 (ddd, *J* = 5.8, 10.6, 16.9 Hz, 1 H), 5.12–4.95 (m, 2 H), 4.28 (d, *J* = 4.9 Hz, 1 H), 2.46–2.26 (m, 2 H), 1.86–1.72 (m, 2 H), 1.09 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.7, 139.6, 135.9, 135.8, 133.9,133.8, 129.7,129.5, 127.5, 127.4, 115.4, 73.2, 31.8, 28.8, 27.0, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3460, 3051, 2941, 2869, 1721, 1637, 1453, 1412, 1215, 1119, 947 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{28}O_3SiNa$ [M + Na]$^+$ 391.1700; found 391.1696.

(2*R*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-en-2-yl (*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-enoate (46): Compound **46** was synthesized in 93 % yield by the same procedure as described for the synthesis of compound **34**. $[\alpha]_D^{25}$ = –44.26 (*c* = 3.0, $CHCl_3$); ref.[12c] $[\alpha]_D^{25}$ = 48.30 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77–7.63 (m, 8 H), 7.49–7.34 (m, 12 H), 5.85–5.68 (m, 2 H), 5.10–4.79 (m, 5 H), 4.32–4.19 (m, 1 H), 4.17–4.04 (m, 1 H), 2.25–2.13 (m, 2 H), 1.86–1.63 (m, 4 H), 1.11 (s, 9 H), 1.09 (s, 9 H), 1.05 (d, *J* = 5.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 140.2, 139.8, 136.0, 135.9, 135.8, 134.1, 134.0, 133.9, 129.6, 129.5, 129.4, 129.5, 127.5, 127.4, 127.38, 127.3, 115.1, 115.0, 73.5, 72.4, 67.8, 44.2, 32.2, 29.5, 27.0, 26.9, 20.2, 19.4, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3079, 2942, 2891, 2837, 1744, 1617, 1417, 1334, 1265, 1027, 957, 830, 682 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{56}O_4Si_2Na$ [M + Na]$^+$ 727.3609; found 727.3581.

Stagonolide C (6): A solution of **46** (0.138 g, 0.20 mmol) and NH_4F (0.110 g, 2.94 mmol) in MeOH (5 mL) was stirred at 40 °C for 24 h and monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and immediately filtered through a small pad of silica gel (60–120 mesh, eluent: EtOAc/petroleum ether 50 %) to give RCM precursor diene, which was used for the subsequent RCM reaction. The second-generation Grubbs catalyst (0.015 g, 10 mol-%) was added to a solution of crude diene (0.040 g, 0.18 mmol) in freshly distilled CH_2Cl_2 (250 mL, degassed for 15 min by argon bubbling), and the solution was then again degassed for 1 h. The reaction mixture was heated at reflux at 45 °C for 24 h (completion of the reaction was checked by TLC). The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (silica gel, 230–400 mesh, EtOAc/petroleum ether 50 %) to afford compound **6** (0.03 g, 78 % over two steps) as a colourless oil. $[\alpha]_D^{25}$ = +46.2 (*c* = 0.08, MeOH); ref.[12c] $[\alpha]_D^{25}$ = +43.9 (*c* = 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.60 (dd, *J* = 9.3, 15.4 Hz, 1 H), 5.44 (dd, *J* = 9.2, 15.3 Hz, 1 H), 5.21–5.10 (m, 1 H), 4.18–4.02 (m, 2 H), 2.32–2.28 (m, 1 H), 2.24–2.14 (m, 2 H), 2.09–2.01 (m, 3 H), 1.90 (dd, *J* = 2.6, 13.9 Hz, 1 H), 1.78 (td, *J* = 11.1, 13.7 Hz, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4, 135.8, 133.0, 74.4, 72.1, 67.7, 43.3, 34.4, 31.5, 21.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3389, 2918, 2854, 1725, 1453, 1367, 1213, 1023 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}O_4Na$ [M + Na]$^+$ 223.0941; found 223.0943.

(2*S*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-en-2-yl (*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]hex-5-enoate (47): Compound **47** was synthesized in 92 % yield by the same procedure as described for the synthesis of compound **46**. $[\alpha]_D^{25}$ = +18.48 (*c* = 2.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.60 (m, 8 H), 7.44–7.31 (m, 12 H), 5.81–5.65 (m, 2 H), 5.03–4.83 (m, 5 H), 4.20 (q, *J* = 5.8 Hz, 1 H), 4.17–4.10 (m, 1 H), 2.24–2.05 (m, 2 H), 1.85 (ddd, *J* = 4.6, 8.9, 13.7 Hz, 1 H), 1.74–1.63 (m, 2 H), 1.56–1.53 (m, 1 H), 1.07 (s, 18 H), 1.05 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 139.8, 139.7, 135.94, 135.92, 135.89, 135.8, 134.1, 134.06, 134.0, 133.9, 129.7, 129.6, 129.5, 127.6, 127.5, 127.4, 127.3, 115.1, 115.0, 73.5, 72.0, 67.6, 43.8, 32.1, 29.4, 27.1, 27.0, 20.5, 19.4, 19.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3077, 2937, 2899, 1749, 1626, 1423, 1343, 1255, 1020, 977, 840 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{56}O_4Si_2Na$ $[M + Na]^+$ 727.3609; found 727.3610.

(2*S*,4*S*)-4-Hydroxyhex-5-en-2-yl (*S*)-4-Hydroxyhex-5-enoate (48): A solution of **47** (0.069 g, 0.10 mmol) and NH_4F (0.055 g, 1.47 mmol) in MeOH (5 mL) was stirred at 40 °C for 24 h and monitored by TLC. After completion of the reaction, the reaction mixture was concentrated. The crude diol was purified by silica gel column chromatography (60–120 mesh, EtOAc/petroleum ether 40 %) to afford compound **48** (0.016 g, 70 %) as a colourless oil. $[\alpha]_D^{25}$ = +12.4 (*c* = 1.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.93–5.76 (m, 2 H), 5.31–5.06 (m, 5 H), 4.18 (qd, *J* = 6.1, 12.1 Hz, 2 H), 2.45–2.37 (m, 2 H), 2.30 (br. s, 2 H), 1.93–1.80 (m, 3 H), 1.70–1.62 (m, 1 H), 1.26 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6, 140.3, 136.2, 115.1, 115.0, 72.2, 70.6, 69.0, 43.0, 31.6, 30.6, 20.3 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3411, 3071, 2837, 1779, 1403, 1313, 1020, 907, 841 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{20}O_4Na$ $[M + Na]^+$ 251.1254; found 251.1253.

9-*epi*-Stagonolide C (7): The second-generation Grubbs catalyst (0.006 g, 10 mol-%) was added to a solution of diene **48** (0.016 g, 0.07 mmol) in freshly distilled CH_2Cl_2 (100 mL, degassed for 15 min by argon bubbling), and the solution was then again degassed for 1 h. The reaction mixture was heated at reflux at 45 °C for 24 h (completion of the reaction was checked by TLC). The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (silica gel, 230–400 mesh, EtOAc/petroleum ether 30 %) to afford compound **7** (0.010 g, 73 %) as a colourless oil. $[\alpha]_D^{25}$ = +164.28 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.98 (d, *J* = 16.1 Hz, 1 H), 5.62 (d, *J* = 16.1 Hz, 1 H), 5.46–5.29 (m, 1 H), 4.61–4.53 (m, 2 H), 2.54–2.40 (m, 1 H), 2.22 (t, *J* = 13.7 Hz, 1 H), 2.06 (ddd, *J* = 2.4, 5.4, 14.1 Hz, 1 H), 1.98–1.85 (m, 3 H), 1.68 (br. s, 2 H), 1.23 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 130.6, 127.4, 69.0, 68.2, 64.5, 42.0, 32.9, 28.0, 21.1 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3402, 2981, 2864, 1735, 1413, 1347, 1231, 1033 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{16}O_4Na$ $[M + Na]^+$ 223.0941; found 223.0940.

Acknowledgments

K. S. thanks the University Grants Commission (UGC), New Delhi for generous financial support in the form of a senior research fellowship (S.R.F.). The financial support from the Council of Scientific and Industrial Research (CSIR), New Delhi, in the form of 12th five year project (Origin CSC0108) is gratefully acknowledged.

Keywords: Asymmetric synthesis · Aldol reactions · Metathesis · α-Aminoxylation

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Received: May 20, 2016
Published Online: ■

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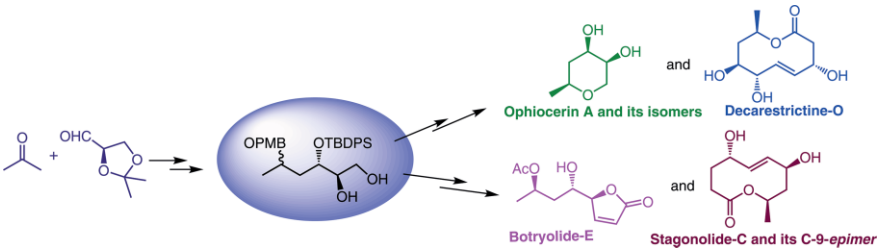

An organocatalytic approach to the synthesis of (2*R*,3*S*)-hexane-1,2,3,5-tetraol derivatives (in the forms of different stereoisomers and bearing different protecting groups) has been developed. The synthetic utility of the intermediates was demonstrated by their transformation into hydroxylated pyrans and a variety of unsaturated lactones through standard synthetic protocols.

DOI: 10.1002/ejoc.201600625