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Synthesis of the structures proposed for natural butanolides piliferolides A and C

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ABSTRACT

The structures proposed for natural butanolides piliferolides A and C have been synthesized. The allylic and lactone stereogenic centers in the target structures were derived from D-mannitol, while that near the side-chain terminal was taken from (*R*)-propylene oxide. The synthetic samples helped to reveal that a signal at around δ 2.0 ppm was missing in the ^{1}H NMR data listing for the structures proposed for natural piliferolides, whereas the δ 29.7 ppm signal in the ^{13}C NMR reported for the structure proposed for natural piliferolide C most likely stemmed from the impurities in the chromatography solvent.

1. Introduction

The butanolides piliferolides A–C (**1a**–**c**, Fig. 1) were isolated[1] in 1994 by Ayer and Khan from *Ophiostoma piliferum* (*Fr*) H.P. Sydow (=*Ceratocystis pilifera*), a blue strain fungus known to cause staining of aspen logs and chips. The structures of these compounds were determined mainly by spectroscopic means, with the absolute configurations of the lactone and allylic stereogenic centers assigned on the basis of circular dichroism (CD) analysis.[1]

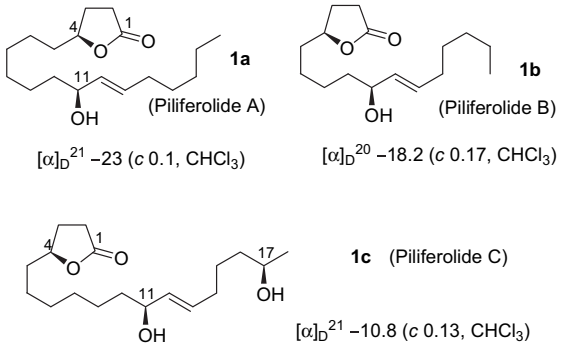

Fig. 1. The structures *proposed* for natural piliferolides A–C (**1a**–**c**) and the corresponding optical rotation data measured on the natural samples.

In continuation of our work on enantioselective synthesis of biologically active butanolides performed in recent years,[2] we conducted a total synthesis of piliferolides A and C, which have not been synthesized to date. Although because of the unexpected partial discrepancy of the spectroscopic data between those reported for the natural samples and their synthetic counterparts made in this work the genuine structures of the 'natural piliferolides' are still to be further investigated, additions and corrections have been reliably made to the data for the structures proposed for piliferolides A and C. Herein we wish to present the results of this study.

2. Results and discussion

The general features of our synthetic plan are outlined in Fig. 2. Close inspection of the molecular architecture suggested that the C-4 and C-11 stereogenic centers of desired absolute configurations in **1c** could be built up from a bis-epoxide (**5**) and the C-17 stereogenic center might be taken from (*R*)-propylene oxide (**8**). Accordingly, the framework of **1c** could be disconnected at the carbon–carbon double bond, leading to fragments **2** and **3b**.

Using a simpler alkene **3a** in place of **3b** would allow for synthesis of target structure **1a**. The fragment common to both targets (the larger fragment **2**) in turn could be disconnected into a one-carbon

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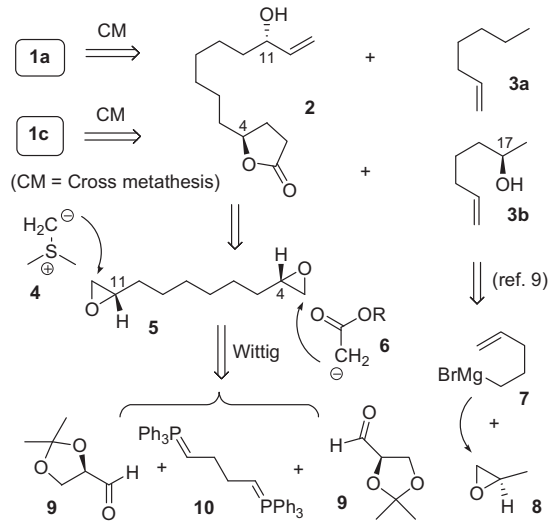
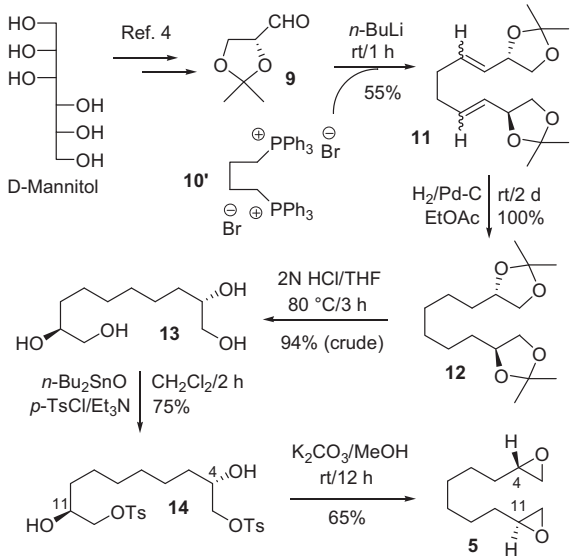


Fig. 2. The retrosynthetic analysis of this work.

unit (sulfur ylid **4**), a known bis-epoxide **5**,[3] and a proper two-carbon carbanion species (**6**). The smaller fragment (**3a**) needed for synthesis of **1a** was commercially available reagent, while that for **1c** (**3b**) was planned to be built up via a ring-opening reaction of epoxide **8** with Grignard reagent **7**. The bis-epoxide **5** could be derived from aldehyde **9** and the Wittig reagent **10**.

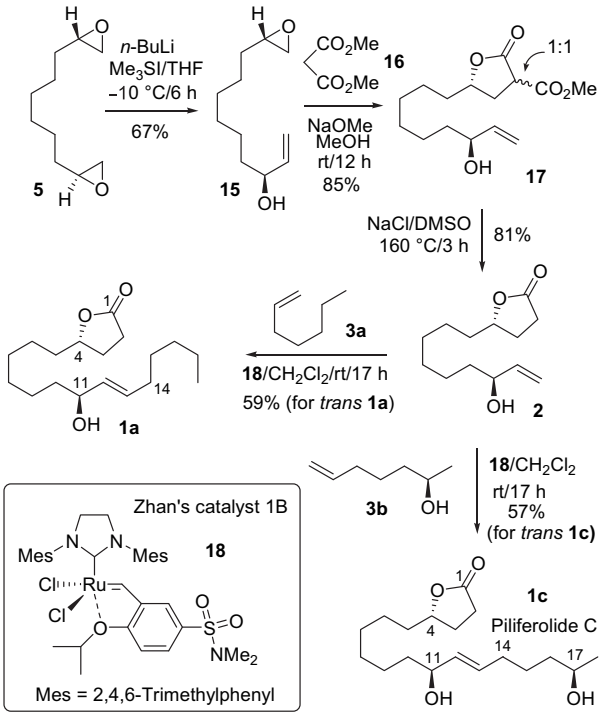
The detailed synthesis is shown in Scheme 1. Following the literature[4] procedure, aldehyde **9** ($[\alpha]_D^{28}$ +59.7 (*c* 4.1, $CHCl_3$)) was readily prepared from D-mannitol in two steps. Subsequent treatment of this aldehyde with the known[5] Wittig reagent **10** (derived in situ from its precursor **10′**) gave diene species **11** as a mixture of the (*E*)- and (*Z*)-isomers of the C–C double bonds, which on hydrogenation over Pd/C afforded the bis-acetonide **12** in an enantiopure form.



Scheme 1.

The acetonide protecting groups in bis-acetonide **12** were removed by treatment of **12** with 2 N HCl in THF at 80 °C for 3 h to afford tetraol **13**. Because of its highly polar/water soluble nature, the crude tetraol, after removal of all volatiles by repeated co-evaporation first with toluene and with EtOH was directly treated with *n*-Bu_2SnO/*p*-TsCl/Et_3N[6] in CH_2Cl_2 at ambient temperature to deliver bis-tosylate **14**, which on subsequent exposure to K_2CO_3/MeOH resulted in the desired bis-epoxide **5**.

Introduction of the vinyl group, which was required in the coupling with alkenes either **3a** or **3b** by a cross metathesis at a later stage, was effected through a selective ring-opening[7] reaction (Scheme 2) of only one epoxy ring in **5** with $Me_2S{=}CH_2$ (generated in situ from Me_3SI and *n*-BuLi). The remaining epoxy ring was then transformed into the γ-lactone unit by reaction with dimethyl malonate in the presence of NaOMe. Finally, removal of the superfluous ester group in the lactone ring by heating the resultant 1:1 epimers of **17** at 160 °C (bath temperature) in DMSO containing NaCl delivered the common fragment **2** in 81% yield.



Scheme 2.

The cross coupling reaction between the common fragment **2** and the linear alkene **3a** was achieved in CH_2Cl_2 with the aid of the Zhan's catalyst 1B[8] (**18**). After stirring at ambient temperature for 17 h, **1a** was formed in 59% yield. Similarly, the reaction of **2** with **3b**[9] instead of **3a** under otherwise the same conditions delivered **1c** in 57% yield. In both cases the newly formed C–C double bonds isomers could be cleanly separated from each other and the double bond geometry was reliably established on the basis of the coupling constant in the ^1H NMR.

With both **1a** and **1c** in hand, our endeavor seemed to approach to an end. The only remaining thing to do was to compare the spectroscopic data with those reported for the natural ones. Because both piliferolides A and C are rather simple compounds, we did not expect any discrepancies between the two sets of data. The ^{13}C data for synthetic **1a** did agree very well with those reported for the natural piliferolide A. However, among all those signal lines in the δ 37.3–14.0 ppm region (those methylene groups in the chain), the only one that is much higher than the remainder (of more or less the same height) occurred at δ 28.9 ppm, rather than 29.3 ppm. Because those methylene groups have very similar surroundings and consequently more or less the same relaxation time, they should give lines of similar heights in ^{13}C NMR. The one that is much higher than the remainder must stem from two different carbons. On the basis of this line of reasoning, the two carbons overlapped in ^{13}C NMR should be at δ 28.9 ppm, rather than 29.3 ppm as suggested[1] in the literature.

More distinct differences were then observed between the ^{1}H NMR for **1a** and piliferolide A—a quartet at δ 2.02 ppm (J=7.3 Hz, 2H) in the ^{1}H NMR of synthetic **1a** was missing in the data listing for the natural piliferolide A, while two more protons were reported for the latter in the δ 1.7–1.2 ppm region (Table 1).

Table 1
Comparison of the ^{1}H NMR (in $CDCl_3$) data for natural piliferolide A and **1a** as well as **1a**′ synthesized in this work

Natural[1] (360 MHz)	**1a** (500 MHz)	**1a**′ (300 MHz)
5.65 (dt, J=16.0, 7.0 Hz, 1H, H-13)	5.63 (dt, J=15.5, 6.9 Hz, 1H)	5.62 (dt, J=15.3, 6.3 Hz, 1H)
5.45 (ddt, J=16.0, 7.0, 2.0 Hz, 1H, H-12)	5.45 (dd, J=15.2, 6.9 Hz, 1H)	5.44 (dd, J=15.0, 7.1 Hz, 1H)
4.48 (m, 1H, H-4)	4.48 (br quint, J=7.0 Hz, 1H)	4.48 (br quint, J=6.8 Hz, 1H)
4.08 (q, J=7.0 Hz, 1H, H-11)	4.03 (q, J=6.3 Hz, 1H)	4.02 (q, J=6.5 Hz, 1H)
2.52 (dd, J=6.8, 9.0 Hz, 2H, H-2)	2.53 (dd, J=8.3, 7.8 Hz, 2H)	2.53 (dd, J=9.4, 7.2 Hz, 2H)
2.32 (ddt, J=12.0, 6.8, 6.8 Hz, 1H, H-3a)	2.31 (ddt, J=12.8, 6.4, 6.4 Hz, 1H)	2.34 (ddt, J=12.9, 6.5, 6.5 Hz, 1H)
(No signal given here)	2.03 (br q, J=7.3 Hz, 2H)	2.02 (br q, J=6.8 Hz, 2H)
1.85 (m, 1H, H-3b)	1.88–1.81 (m, 1H)	1.91–1.81 (m, 1H)
1.2–1.7 (m, 21H, H-5 to 10 and H-14 to 17)	1.76–1.25 (m, 19H)	1.82–1.11 (m, 19H)
0.88 (t, J=6.2 Hz, 3H, H-18)	0.88 (t, J=6.9 Hz, 3H)	0.86 (t, J=7.1 Hz, 3H)

Similar data disagreements were also observed between the synthetic and the natural **1c**: in the ^{13}C NMR of the synthetic **1c** no signal appeared at δ 29.7 ppm as reported for the natural one (Tables 2 and 3). And the two-proton quartet at δ 2.07 ppm in the ^{1}H NMR of synthetic **1c** was, as in the case of **1a**, not in the data listing for the natural **1c**.

Table 2
Comparison of the ^{13}C NMR (in $CDCl_3$) data for natural piliferolide C and **1c** synthesized in this work

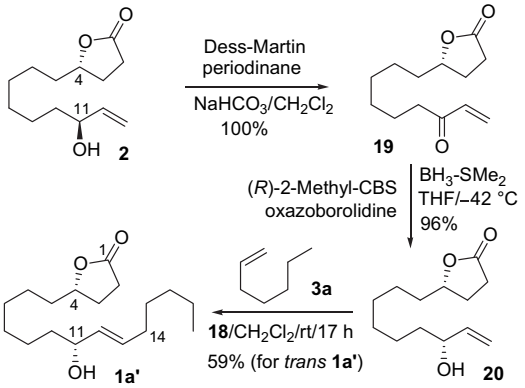
Natural[1] (125 MHz)	Synthetic **1c** (100 MHz)	Natural[1] (125 MHz)	Synthetic **1c** (100 MHz)
177.2 (C-1)	177.4	32.2 (C-14)	32.1
133.5 (C-12)	133.4	29.7 (C-15)	—[a]
131.7 (C-13)	131.7	29.4 (C-8)	29.371
81.0 (C-4)	81.1	29.3 (C-7)	29.286
73.1 (C-11)	73.0	28.9 (C-2)	28.8[b]
68.1 (C-17)	67.9	28.1 (C-3)	28.0
38.8 (C-16)	38.7	25.4 (C-9)	25.3
37.3 (C-10)	37.2	25.2 (C-6)	25.2
35.6 (C-5)	35.6	23.6 (C-18)	23.5

[a] To our experience the high-boiling residue (which can be removed by re-distillation prior to use) in the chromatography solvent petroleum ether (consisting of mainly *n*-hexane) normally gave a signal at δ 29.7 ppm in ^{13}C NMR taken in $CDCl_3$.
[b] Two carbons here (C-2 and C-15, the same as observed with **1a** and **1a**′).

Table 3
Comparison of the ^{1}H NMR (in $CDCl_3$) data for the natural piliferolide C and **1c** synthesized in this work

Natural[1] piliferolide C (360 MHz)	Synthetic **1c** (400 MHz)
5.65 (dt, J=16.0, 7.0 Hz, 1H, H-13)	5.63 (dt, J=15.3, 6.7 Hz, 1H)
5.45 (ddt, J=16.0, 7.0, 2.0 Hz, 1H, H-12)	5.46 (dd, J=15.3, 7.1 Hz, 1H)
4.48 (m, 1H, H-4)	4.48 (br quint, J=6.9 Hz, 1H)
4.08 (q, J=7.0 Hz, 1H, H-11)	4.03 (q, J=6.4 Hz, 1H)
3.78 (m, 1H, H-17)	3.81–3.78 (m, 1H)
2.52 (dd, J=6.8, 9.0 Hz, 2H, H-2)	2.53 (dd, J=9.1, 7.2 Hz, 2H)
2.32 (ddt, J=12.0, 6.8, 6.8 Hz, 1H, H-3a)	2.33 (ddt, J=12.8, 6.8, 6.8 Hz, 1H)
(No signal given here)	2.07 (br q, J=7.2 Hz, 2H)
1.85 (m, 1H, H-3b)	1.90–1.80 (m, 1H)
1.2–1.7 (m, 21H, H-5 to10 and H-14 to 17)	1.80–1.25 (m, 18H)
1.17 (d, J=6.0 Hz, 3H, H-18)	1.21 (d, J=5.9 Hz, 3H)

To exclude the any unexpected effects (causing an upfield shift of the allylic methylene group) associated with different relative configurations of the two stereogenic centers in **1a**, we also synthesized a diastereomer of **1a** as shown in Scheme 3. The alcohol **2** was first oxidized into ketone **19** with Dess–Martin periodinane. The carbonyl group was then stereo-selectively reduced under the CBS[11] (Corey–Bakshi–Shibata) conditions. Finally, the resulting **20** was coupled with alkene **3a** in the presence of the Zhan catalyst 1B[8] (**18**) to deliver the C-14 epimer of **1a** (**1a**′).



Scheme 3.

The protons for an allylic methylene group without any other functional groups in close vicinity (similar to the C-14 in **1a** and **1c**) normally[10] appear at around δ 2.0 ppm and can never go down to δ 1.7 ppm. Therefore, the two-proton broadened quartet at δ 2.03/2.07 ppm in the ^{1}H NMR for synthetic **1a**/**1c** is quite normal, while the absence of such a signal in the data listing for the natural piliferolides is very unusual.

The ^{1}H NMR of **1a**′ was then recorded to see if the different relative configuration might lead to the unusual appearance of the allylic methylene group (C-14) at δ 1.7 ppm as reported for the natural piliferolides. The results turned out to be negative; the δ 2.02 ppm quartet still remained unshifted. In fact, no significant differences could be found between the ^{1}H and ^{13}C NMR for **1a** and **1a**′. These results unequivocally confirmed that in any case the methylene group at the allylic position in a structure closely related to that of **1a** and **1c** should appear at around δ 2.0 ppm (rather than 1.7 ppm) in ^{1}H NMR.

As the synthetic **1a** and **1c** were constructed through an unambiguous route with all stereogenic centers derived from well-established enantiopure chiral building blocks and the spectroscopic analyses were performed with care to eliminate/reduce the artifacts caused by solvent impurities and the errors associated with low sample concentrations, the NMR as well as rotation data collected on the synthetic samples should better represent the structures **1a** and **1c** than those given in the previous paper.

As for the genuine structures for natural piliferolides A and C, although at this stage no conclusion can be reached with absolute confidence, judging from the otherwise excellent agreements between the NMR data for the synthetic and natural piliferolides, also taking into account the reliability of the well-established methodologies utilized for determination of the configurations in that work along with the additional support from the IR and MS data, the structures proposed for the natural piliferolides are likely to be correct.

3. Conclusions

In summary, the structures proposed for natural piliferolides A and C have been synthesized for the first time through an efficient and enantioselective route. The ^{1}H and ^{13}C NMR data for the

synthetic **1a** and **1c** are in excellent agreement with those reported for their natural counterparts, except that a δ 2.03/2.07 ppm signal was absent in the ^{1}H NMR for both natural piliferolides and an extra δ 29.7 ppm signal in ^{13}C NMR was reported for the natural piliferolide C. Besides, the two overlapped carbons in the ^{13}C NMR for **1a** are now re-assigned to δ 28.9 ppm. Although the natural piliferolides are not accessible to us and direct comparison is thus not possible, judging from the available information the originally assigned structures are likely to be correct though the accompanying data listing contained some minor errors.

4. Experimental section

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using a Varian Mercury or a Bruker Avance instrument operating at 300 or 400 MHz for proton as indicated in each individual case. The FTIR spectra were scanned with a Nicolet Avatar 360 FT-IR. EIMS and EIHRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESI-MS and ESI-HRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 T) FTMS mass spectrometer, respectively. Dry THF was distilled from Na/Ph_2CO under N_2. Unless otherwise specified, all other solvents and reagents were commercially available and used as received without any further purification. PE (chromatography solvent) stands for petroleum ether (60–90 °C). Optical rotations were recorded on a Jasco P-1030 Polarimeter. Melting points were taken on a micro melting point apparatus equipped with a microscope and were uncorrected.

4.2. (*E*/*Z*)-1,6-Di-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-hex-1,5-diene (11)

n-BuLi (2.5 M, in hexanes, 24 mL, 60 mmol) was added to a solution of phosphonium salt **10′** (22.2 g, 30 mmol) in dry THF (150 mL) stirred in an ice-water bath. After completion of the addition, stirring was continued at ambient temperature for 20 min. The resulting red-brown mixture was cooled in an ice-water bath. again. Freshly prepared aldehyde **9** ($[\alpha]_D^{28}$ +59.7 (*c* 4.1, $CHCl_3$), neat, 7.7 g, 59 mmol) was added. The mixture was stirred at ambient temperature for 1 h. Aq satd NH_4Cl (200 mL) was added. The mixture was extracted with Et_2O (3×200 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20:1 PE/EtOAc) on silica gel gave **11** (a mixture of double bonds isomers, 4.8 g, 17 mmol, 56.4%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76–5.71 (m, 0.3H), 5.61–5.53 (m, 1.7H), 5.47–5.36 (m, 2H), 4.78 (dt, *J*=8.1, 6.5 Hz, 1.7H), 4.42 (dt, *J*=7.8, 6.4 Hz, 0.3H), 4.02 (dd, *J*=6.2, 1.6 Hz, 2H), 3.55–3.45 (m, 2H), 2.29–2.06 (m, 4H), 1.39 (s, 6H), 1.36 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 128.1, 128.0, 127.7, 109.0, 71.8, 71.7, 69.3 (2C′s), 32.0, 27.5, 27.0, 26.7, 26.6, 25.9 (2C′s); FTIR (film) 2986, 2934, 2869, 1655, 1455, 1379, 1370, 1248, 1156, 1059, 861, 510 cm^{-1}; EIMS *m*/*z* 267 ([M−CH_3]$^+$, 4.25), 72 (100), 43 (97), 59 (39), 101 (27), 55 (24), 83 (24), 105 (24), 41 (19); EIHRMS calcd for $C_{16}H_{26}O_4$ (M^+) 282.1831, found 282.1825.

4.3. 1,6-Di-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-hexane (12)

A mixture of **11** (4.8 g, 17 mmol) and 10% Pd/C (480 mg) in EtOAc (30 mL) was stirred at ambient temperature under atmospheric H_2 for 48 h. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (10:1 PE/EtOAc) on silica gel to afford **12** (4.9 g, 17 mmol, 100%) as a colorless oil. $[\alpha]_D^{24}$ +24.5 (*c* 2.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06–3.95 (m, 4H), 3.44 (br t, *J*=6.8 Hz, 2H), 1.68–1.35 (m, 12H), 1.30 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.5, 76.0, 69.4, 33.5, 29.4, 26.9, 25.7, 25.6; FTIR (film) 2985, 2934, 2861, 1458, 1378, 1369, 1250, 1217, 1157, 1061, 857, 792, 513 cm^{-1}; EIMS *m*/*z* 271 (100) ([M−CH_3]$^+$), 43 (96), 72 (70), 95 (34.96), 59 (31), 101 (29.4), 67 (27); EIHRMS calcd for $C_{16}H_{30}O_4$ ([M]$^+$) 286.2144, found 286.2141.

4.4. (2*S*,9*S*)-1,10-Di-tosyloxy-decan-2,9-diol (14)

A solution of bis-acetonide **12** (4.9 g, 17 mmol) in 6 N HCl (10 mL) and EtOH (20 mL) was stirred at 80 °C for 3 h. After being cooled to ambient temperature, the mixture was transferred to a large flask containing EtOH (100 mL) and toluene (50 mL) and concentrated on a rotary evaporator to remove water. The residual solution was dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left the crude tetraol **13** (3.3 g, 16 mmol, 94% from **12**) as a white solid.

A mixture of crude tetraol **13** (382 mg, 1.87 mmol), Bu_2SnO (21 mg, 0.08 mmol), *p*-TsCl (715 mg, 3.75 mmol), and Et_3N (379 mg, 3.75 mmol) in dry CH_2Cl_2 (8 mL) was stirred at ambient temperature for 2 h, when TLC showed completion of the reaction. Water was added. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2:1 PE/EtOAc) on silica gel gave the bis-tosylate **14** (721 mg, 1.40 mmol, 75% from **13**, 71% from **12**) as a white solid. Mp 75–76 °C. $[\alpha]_D^{23}$ +6.2 (*c* 2.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.0 Hz, 4H), 7.35 (d, *J*=8.0 Hz, 4H), 3.99 (dd, *J*=10.0, 3.2 Hz, 2H), 3.88 (dd, *J*=10.0, 7.2 Hz, 2H), 3.80–3.79 (m, 2H), 2.44 (s, 6H), 1.42–1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 132.6, 130.0, 127.9, 74.0, 69.2, 32.6, 29.13, 25.0, 21.6; FTIR (film) 3527, 2934, 2858, 1598, 1455, 1356, 1308, 1176, 1097, 968, 815, 667, 555 cm^{-1}; EIMS *m*/*z* 172 (*p*-TsO$^+$, 92), 155 (8), 107 (45), 91(100), 77 (20), 65 (31); EIHRMS calcd for $C_{17}H_{27}O_5S$ ([M−OTs]$^+$) 343.1579, found 343.1584.

4.5. 1,6-Di-((*S*)-oxiran-2-yl)-hexane (5)

Finely powdered K_2CO_3 (129 mg, 0.94 mmol) was added to a solution of bis-tosytlate **14** (241 mg, 0.47 mmol) in MeOH (15 mL) stirred at ambient temperature. Stirring was continued at the same temperature for 8 h. Water (2 mL) and Et_2O (50 mL) were added. The mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10:1 PE/EtOAc) on silica gel afforded the known bis-epoxide **5** (53 mg, 0.31 mmol, 66.6%) as a colorless oil. $[\alpha]_D^{23}$ −17.0 (*c* 2.45, $CHCl_3$) (lit.[3] $[\alpha]_D^{27}$ −17.0 (*c* 0.79, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (m, 2H), 2.74 (br t, *J*=4.5 Hz, 2H), 2.47 (dd, *J*=5.1, 2.8 Hz, 2H), 1.60–1.35 (m, 12H).

4.6. (*S*)-9-((*S*)-Oxiran-2-yl)-non-1-ene-3-ol (15)

n-BuLi (2.5 M, in hexanes, 2.1 mL, 5.25 mmol) was added to a solution of Me_3SI (1.078 g, 5.28 mmol) in dry THF (10 mL) stirred at −10 °C under N_2 (balloon). The mixture was stirred at the same temperature for 1 h before being transferred dropwise to a solution of bis-epoxide **5** (300 mg, 1.81 mmol) in dry THF (3 mL) stirred at 0 °C under N_2 (balloon). The mixture was stirred at 0 °C for 6 h, when TLC showed completion of the reaction. Aq satd NH_4Cl (15 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5:1 PE/EtOAc) on silica gel afforded alcohol **15** (217 mg, 1.17 mmol, 64.6%) as a colorless oil. $[\alpha]_D^{26}$ −2.6 (*c* 0.35, $CHCl_3$). ^{1}H NMR

(300 MHz, $CDCl_3$) δ 5.87 (ddd, J=17.1, 10.5, 6.3 Hz, 1H), 5.22 (d, J=17.5 Hz, 1H), 5.11 (d, J=10.4 Hz, 1H), 4.10 (q, J=6.1 Hz, 1H), 2.91 (s, 1H), 2.76 (t, J=4.5 Hz, 1H), 2.47 (dd, J=4.8, 2.7 Hz, 1H), 1.62–1.25 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 114.5, 73.1, 52.4, 47.1, 36.9, 32.4, 29.4, 29.3, 25.8, 25.2; FTIR (film) 3433, 2982, 2931, 2856, 1645, 1465, 1427, 1410, 1250, 992, 918, 832 cm^{-1}; ESI-MS m/z 207.2 ([M+Na]$^+$). ESI-HRMS calcd for $C_{11}H_{20}O_2Na$ ([M+Na]$^+$) 207.1356, found 207.1357.

4.7. (*S*)-9-((5*S*)-3-Methyloxycarbonyl-2-oxo-tetrahydrofuran-5-yl)-non-1-en-3-ol (17)

A mixture of methanolic MeONa (1 M, 1.9 mL) and dimethyl malonate (257 mg, 1.95 mmol) was stirred at ambient temperature for 5 min being cooled in a 0 °C bath. A solution of alcohol **15** (120 mg, 0.65 mmol) in THF (2 mL) was then added. The mixture was stirred at ambient temperature overnight. The mixture was acidified to pH 5 with 2 N HCl. Water (10 mL) was added, followed by CH_2Cl_2 (10 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (6:1 CH_2Cl_2/EtOAc) on silica gel afforded a 1:1 mixture of diastereomers of lactone **17** (157 mg, 0.55 mmol, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, J=17.1, 10.4, 6.2 Hz, 1H), 5.23 (d, J=17.5 Hz, 1H), 5.11 (d, J=10.5 Hz, 1H), 4.67 (quint, J=7.5, 6.7 Hz, 0.5H), 4.45 (quint, J=7.8, 6.1 Hz, 0.5H), 4.13–4.05 (m, 1H), 3.82 and 3.81 (two singlets, 3H altogether), 3.69–3.60 (m, 1H), 2.75–2.67 (m, 0.5H), 2.60–2.51 (m, 0.5H), 2.39–2.28 (m, 0.5H) 1.85–1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (2C′s), 168.4, 141.4, 114.4, 80.4, 79.6, 73.0, 53.1, 53.0, 47.2, 46.8, 36.9, 35.3, 35.2, 32.2, 31.9, 29.3, 29.3, 29.1, 25.1 (2C′s); FTIR (film) 3521, 2933, 2857, 1777, 1741, 1644, 1455, 1438, 1357, 1264, 1168, 992, 925, 726, 673 cm^{-1}; EIMS m/z 269 ([M−CH_3]$^+$), 110 (100), 55 (92). EIHRMS calcd for $C_{15}H_{24}O_5$ (M$^+$) 284.1624, found 284.1624.

4.8. (*S*)-9-((5*S*)-2-Oxo-tetrahydrofuran-5-yl)-non-1-en-3-ol (2)

A solution of ester **17** (88 mg, 0.31 mmol), NaCl (36 mg, 0.62 mmol), and H_2O (0.178 mL, 9.92 mmol) in DMSO (5 mL) was heated in a 160 °C bath with stirring for 3 h. After being cooled to ambient temperature, water (10 mL) and Et_2O (10 mL) were added. The mixture was diluted with Et_2O (3×30 mL). The combined organic layers were washed with water and brine before being dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation and column chromatography (3:1 PE/EtOAc) on silica gel afforded lactone **2** (57 mg, 0.25 mmol, 81%) as a colorless oil. $[\alpha]_D^{23}$ −21.2 (c 1.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, J=17.5, 10.0, 6.1 Hz, 1H), 5.18 (d, J=17.4 Hz, 1H), 5.07 (d, J=10.2 Hz, 1H), 4.50–4.41 (m, 1H), 4.03 (q, J=6.3 Hz, 1H), 2.50 (t, J=7.4 Hz, 2H), 2.29 (ddt, J=13.2, 6.6, 6.2 Hz, 1H), 1.88–1.22 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 141.2, 114.5, 81.0, 73.1, 36.8, 35.5, 29.3, 29.2, 28.8, 27.9, 25.1 (2C′s); FTIR (film) 3449, 2932, 2857, 1774, 1460, 1422, 1350, 1283, 1184, 992, 917 cm^{-1}; EIMS m/z 85 ([M−CH_2CHCH_2OH]$^+$) 57 (100), 85 (71), 55 (61), 41 (38), 69 (34), 84 (33), 67 (29), 83 (28); EIHRMS calcd for $C_{13}H_{22}O_3$ (M$^+$) 226.1569, found 226.1564.

4.9. (8*S*,6*E*)-14-((5*S*)-2-Oxo-tetrahydrofuran-5-yl)-tetradec-6-en-8-ol (1a)

A mixture of **2** (17 mg, 0.075 mmol), alkene **3a** (29 mg, 0.30 mmol), and Zhan's catalyst 1B (9 mg, 0.012 mmol) in dry CH_2Cl_2 (3 mL) was stirred at ambient temperature under N_2 (balloon) for 17 h before being concentrated on a rotary evaporator and chromatographed (3:1 PE/EtOAc) on silica gel to give **1a** (15 mg, 0.05 mmol, 67.6% from **2**) as a colorless oil. $[\alpha]_D^{26}$ −26.3 (c 0.53, $CHCl_3$) (lit.[1] $[\alpha]_D^{21}$ −23 (c 0.1, $CHCl_3$)). For ^{1}H NMR, see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 133.0, 132.3, 81.0, 73.1, 37.3, 35.6, 32.1, 31.4, 29.4, 29.3, 28.9 (2C′s), 28.0, 25.4, 25.2, 22.5, 14.0; FTIR (film) 3460, 2929, 2856, 1775, 1461, 1354, 1286, 1220, 1182, 1018, 971, 914, 726, 652 cm^{-1}; ESI-MS m/z 319.2 ([M+Na]$^+$). ESI-HRMS calcd for $C_{18}H_{32}O_3Na$ ([M+Na]$^+$) 319.2248, found 319.2244.

4.10. (2*R*,8*S*,6*E*)-14-((5*S*)-2-Oxo-tetrahydrofuran-5-yl)-tetradec-6-en-2,8-diol (1c)

A mixture of **2** (21 mg, 0.095 mmol), alkene **3b** (43 mg, 0.38 mmol), and Zhan's catalyst 1B (9 mg, 0.012 mmol) in dry CH_2Cl_2 (3 mL) was stirred at ambient temperature under N_2 (balloon) for 17 h before being concentrated on a rotary evaporator and chromatographed (1:1 PE/EtOAc) on silica gel to give **1c** (17 mg, 0.054 mmol, 56.8% from **2**) as a colorless oil. $[\alpha]_D^{23}$ −22.9 (c 0.35, $CHCl_3$) (lit.[1] $[\alpha]_D^{21}$ −10.8 (c 0.13, $CHCl_3$)). FTIR (film) 3410, 2929, 2856, 1770, 1462, 1185, 1016, 969, 652 cm^{-1}; ESI-MS m/z 335.2 ([M+Na]$^+$); ESI-HRMS calcd for $C_{18}H_{32}O_4Na$ ([M+Na]$^+$): 335.2193; found: 335.2200 (for NMR, see Tables 2 and 3).

4.11. (*S*)-9-((5*S*)-2-Oxo-tetrahydrofuran-5-yl)-non-1-en-3-one (19)

Dess–Martin periodinane (135 mg, 0.32 mmol) and $NaHCO_3$ (40 mg, 0.48 mmol) were added to a solution of alcohol **2** (37 mg, 0.17 mmol) in dry CH_2Cl_2 (3 mL) at ambient temperature. Stirring was continued at the same temperature for 3 h. Et_2O (8 mL) was added. The solids precipitated were filtered off through Celite (washing with Et_2O). The filtrate and washings were combined and concentrated on a rotary evaporator. The residue was chromatographed (3:1 PE/EtOAc) on silica gel to give ketone **19** (37 mg, 0.17 mmol, 100%) as a colorless oil. $[\alpha]_D^{24}$ +49.7 (c 0.450, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (dd, J=17.7, 10.5 Hz, 1H), 6.22 (dd, J=17.6, 0.8 Hz, 1H), 5.83 (dd, J=10.5, 0.9 Hz, 1H), 4.48 (quint, J=6.8 Hz, 1H), 2.59 (t, J=7.3 Hz, 2H), 2.53 (dd, J=9.5, 6.9 Hz, 2H), 2.32 (ddt, J=13.2, 6.6, 6.6 Hz, 1H), 1.90–1.80 (m, 1H), 1.78–1.67 (m, 1H) 1.67–1.27 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 177.2, 136.5, 128.0, 81.0, 39.5, 35.5, 29.1, 29.0, 28.8, 28.0, 25.1, 23.7; FTIR (film) 2927, 2856, 1778, 1749, 1678, 1615, 1460, 1372, 1228, 1136, 1025, 960, 908, 778, 727, 652, 601 cm^{-1}; ESI-MS m/z 247.1 ([M+Na]$^+$); ESI-HRMS calcd for $C_{13}H_{20}O_3Na$ ([M+Na]$^+$) 247.1305, found 247.1303.

4.12. (*R*)-9-((5*S*)-2-Oxo-tetrahydrofuran-5-yl)-non-1-en-3-ol (20)

A solution of (*R*)-2-methyl-CBS-oxazaborolidine (66 mg, 0.24 mmol) in dry THF (2 mL) was added to a solution of ketone **20** (27 mg, 0.12 mmol) in dry THF (2 mL) and stirred at −40 °C under argon. The mixture was stirred at the same temperature for 10 min. $BH_3{\cdot}SMe_2$ (2 M, in THF, 0.3 mL, 0.6 mmol) was added. Stirring was continued at −40 °C for 1.5 h. EtOH (5 mL) was added. The mixture was stirred at ambient temperature for 15 min. Water (10 mL) was added, followed by Et_2O (10 mL). The phases were separated. The aq layer was extracted with Et_2O (3×15 mL). The combined organic layers were washed with water and brine before being dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation and column chromatography (3:1 PE/EtOAc) on silica gel afforded alcohol **20** (26 mg, 0.12 mmol, 96%) as a colorless oil. $[\alpha]_D^{23}$ +11.2 (c 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, J=16.9, 10.4, 6.2 Hz, 1H), 5.22 (d, J=17.2 Hz, 1H), 5.10 (d, J=10.4 Hz, 1H), 4.60–4.40 (m, 1H), 4.09 (q, J=6.2 Hz, 1H), 2.53 (dd, J=9.4, 7.4 Hz, 2H), 2.32 (ddt, J=13.3, 6.6, 6.2 Hz, 1H), 1.88–1.20

(m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 141.3, 114.6, 81.0, 73.2, 36.9, 35.6, 29.3, 29.3, 28.9, 28.0, 25.2 (2C′s); FTIR (film) 3463, 2930, 2857, 1774, 1645, 1461, 1422, 1182, 1015, 916, 704 cm^{-1}; ESI-MS m/z 249.2 ([M+Na]$^+$); ESI-HRMS calcd for $C_{13}H_{22}O_3Na$ ([M+Na]$^+$) 249.1461, found 249.1465.

4.13. (8*R*,6*E*)-14-((5*S*)-2-Oxo-tetrahydrofuran-5-yl)-tetradec-6-en-8-ol (1a′)

A mixture of **20** (34 mg, 0.15 mmol), alkene **3a** (58 mg, 0.59 mmol), and Zhan's catalyst 1B (18 mg, 0.024 mmol) in dry CH_2Cl_2 (3 mL) was stirred at ambient temperature under N_2 (balloon) for 22 h before being concentrated on a rotary evaporator and chromatographed (1:1 PE/EtOAc) on silica gel to give **1a′** (20 mg, 0.05 mmol, 45% from **20**) as a colorless oil. $[\alpha]_D^{26}$ −13.1 (*c* 0.13, $CHCl_3$). For ^{1}H NMR, see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 133.0, 132.3, 81.0, 73.1, 37.2, 35.5, 32.1, 31.3, 29.3, 29.2, 28.8 (2C′s), 28.0, 25.3, 25.1, 22.5, 14.0; FTIR (film) 3469, 2927, 2856, 1775, 1462, 1346, 1278, 1182, 1018, 970, 912, 809, 710 cm^{-1}; EIMS m/z 252 ([M−CO_2]$^+$) 57 (100), 43 (92), 71 (84), 55 (71), 41 (64), 85 (61), 69 (55), 83 (40); EIHRMS calcd for $C_{18}H_{32}O_3$ (M$^+$) 296.2351, found 296.2354.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.12.037.

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