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Graphical Abstract

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Xiao-Long Wang[a,b], Yang-Yang Yang[b], Hui-Jun Chen[b], Yikang Wu[b], and Dong-Sheng Ma[a]
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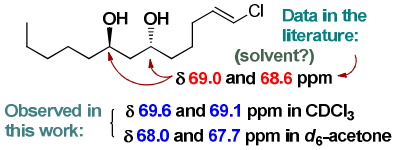

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ABSTRACT

Using expoxy chiral building blocks readily derived from D-gluconolactone as the source of the stereogenic centers, both (6*R*,8*R*)- and (6*R*,8*S*)- isomers of (*E*)-1-chlorotridec-1-ene-6,8-diol were synthesized. The vinylchloro unit was installed onto the substrate carbon chain in an approximately 9:1 (*E*)/(*Z*) ratio via a condensation of $CrCl_2/CHCl_3$ with an terminal aldehyde. A tosylation protocol featuring addition of H_2O was also developed for a highly polar tetraol. The synthetic products allowed for re-acquisition of the NMR spectra of better quality and revealed some delicate yet unignorable discrepancies in the ^{13}C NMR for the natural isomer obtained by synthesis and that isolated some 30 years ago from the marine cyanophyte. The puzzling discrepancies were eventually shown to be caused by deuteration of the hydroxyl groups.

1. Introduction

Marine cyanobacteria are known to be prolific producers of bioactive secondary metabolites.[1] Among the numerous structurally interesting compounds generated by cyanobacteria, those that contain a vinylchlorine moiety (Figure 1, **1**-**5**[2]) comprise a unique class. One of them, (–)-(*E*)-(6*R*,8*S*)-1-chlorotridec-1-ene-6,8-diol (**1**) was disclosed[2a] in 1978, with its first synthesis[3] briefly communicated in 1998.

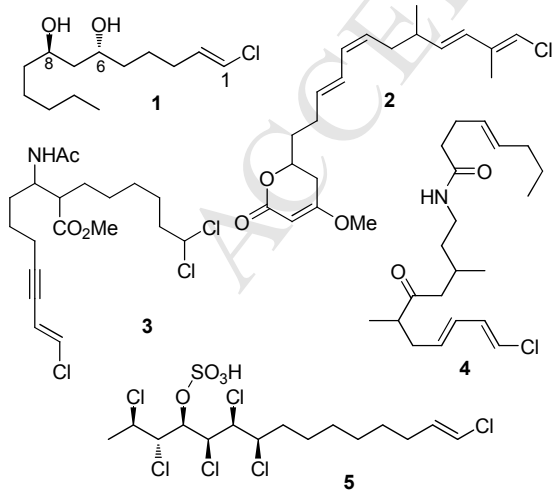

Figure 1. The structures for some of the known vinylchlorine-containing marine natural products produced by cyanobacteria.

In connection with our studies[4] on synthesis of 1,3-diol motif-containing natural products[5] using the epoxy chiral building blocks[6] readily accessible from the inexpensive D-gluconolactone as the source of the stereogenic centers, we also completed a synthesis of **1**, which allowed for collection of spectral data of better quality (thanks to the modern instruments compared with those three decades ago) and revealed some unexpected discrepancies that may puzzle many investigators who need the data for comparison yet have no access to any authentic sample of **1**. Here below are the details of this endeavor.

2. Results and Discussion

The initial route to **1** we examined is shown in Scheme 1. The starting enantiopure epoxy building block **6** was treated with *n*BuLi in the presence of CuI as reported[4h] in our previous work to afford the known diol **7**. Protection[7] of the hydroxyl groups with PMBCl using NaH as the base furnished the corresponding diPMB ether **8** in 90% isolated yield.

Removal[8] of the acetonide protecting group in **8** was then realized via exposure to MeOH at ambient temperature in the presence of PPTS. The resulting vicinal diol **9** was treated with Ph_3P/I_2/imidazole[9] at 80 °C gave the desired vinyl species **10** in 97% yield. It is noteworthy that the reactants concentration appeared to play a critical role in this reaction. With a fixed reactant ratio (cf. the experimental section), a substrate concentration of > 0.2 M seemed to be essential to secure a

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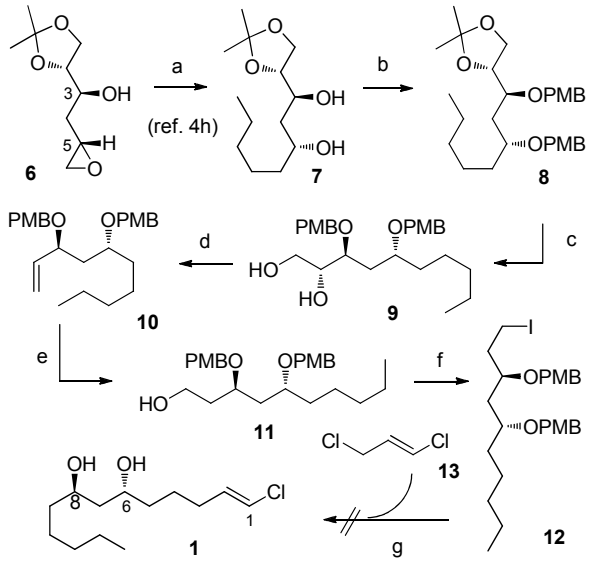
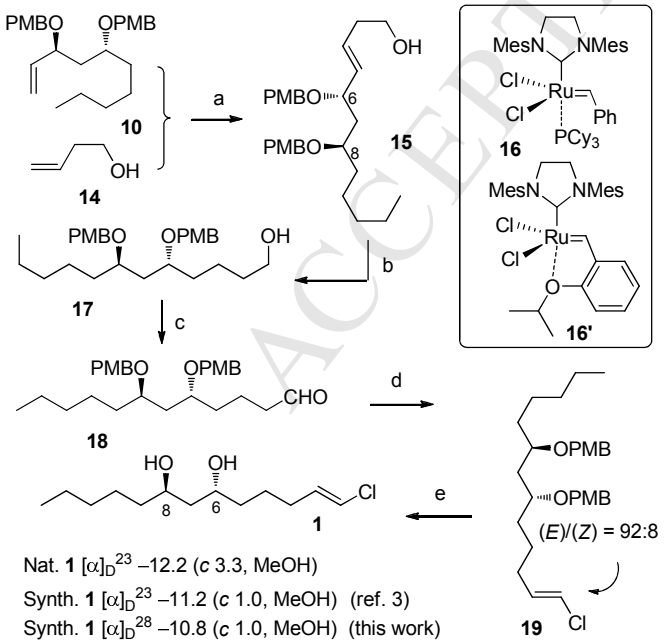
successful conversion, while at concentrations < 0.1 M the intermediate iodoalcohol (with primary hydroxyl group in **9** being replaced by an iodine atom) was almost always the major product.



Scheme 1. Reagents and conditions. a) *n*BuLi, CuI, THF, –78 °C 3 h, 96%; b) PMBCl, NaH, DMF, *n*Bu$_4$NI, RT, 5 h, 90%; c) PPTS, MeOH, RT, 12 h, 85% for **9** along with 15% recovered **8**, d) Ph_3P, imidazole, I_2, THF, 80 °C, 1 h, 97%; e) (i) BH_3, THF, 0 °C, 3 h, (ii) NaOH, H_2O_2, RT, 2 h, 60% from **10**; f) Ph_3P, imidazole, I_2, THF, RT, 2 h, 100%; g) Zn dust, CuCN, TMSCl, LiCl, DMF. THF = tetrahydrofuran. PMBCl = *p*-methoxybenzyl chloride. DMF = *N*,*N*'-dimethylformamide. PPTS = Pyridium *p*-toluenesulfonate. TMS = Trimethylsilyl.

Installation of the (*E*)-vinylchlorine unit was first planned to use a coupling reaction of a suitable carbanion species with the known allyl chloride **13**, because that the desired (*E*)-configuration might be secured from the beginning. To this end, the terminal alkene was converted into the primary alcohol **11** via a standard hydroboration. The hydroxyl group was then transformed into an iodide in high yield by exposure to Ph_3P/I_2/imidazole[10] at ambient temperature.



Nat. **1** $[\alpha]_D^{23}$ –12.2 (*c* 3.3, MeOH)

Synth. **1** $[\alpha]_D^{23}$ –11.2 (*c* 1.0, MeOH) (ref. 3)

Synth. **1** $[\alpha]_D^{28}$ –10.8 (*c* 1.0, MeOH) (this work)

Scheme 2. Reagents and conditions. a) **16** (10 mol%), Et_2O, RT, 2 h, 51%; b) H_2 (1 atm), Skeletal Ni, RT, 1 h, 49% overall from **10**; c) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2 RT, 2 h, 85% along with 10% of recovered **17**; d) $CrCl_2$, $CHCl_3$, THF, 65 °C, 4 h, 63%; e) CAN, MeCN-H_2O (10:1, v/v), RT, 1 h, 89%. CAN = cerium ammonium nitrate.

The coupling of iodide **12** with dichloride **13** under the Zn dust/CuCN/LiCl/TMSCl[11] conditions did not occur as expected. The only product that could be identified was the alkane derived from **12** via de-iodination, although a model reaction using allyl chloride (i.e., without the vinyl chlorine in the molecule) instead of **13** did generate the corresponding coupling product as a 1:1 inseparable mixture with the deiodination product.

As the Cu-mediated coupling did not seem to be feasible, we next turned to a CM (cross metathesis) based approach. As shown in Scheme 2, the alkene **10** was treated with homoallyl alcohol **14** in the presence of Grubbs II catalyst (**16**) to afford **15**. Because the self-coupling of the homoallyl alcohol occurred very rapidly, repeated further addition of **14** was essential for the formation of the desired **15**. The solvent also made a difference here. Initially, the coupling was carried out in CH_2Cl_2 in the presence of catalyst **16** as in most literature CM cases. However, the desired **15** was obtained in only ca. 21% yield. Use of Et_2O[12] to replace CH_2Cl_2 as the reaction solvent led to significantly improved yields. Thus, under otherwise the same conditions, the **15** was obtained in 51% yield. Attempt to use Hoveyda-Grubbs II catalyst (**16'**) instead of **16** under comparable conditions resulted in **15** in only 10% yield.

Saturation of the C-C double bond in **15** by atmospheric hydrogenation over the commercially available Skeletal Ni (from Aldrich) gave **17** as a colorless oil; the often inseparable traces of dark impurities related to the CM catalyst were also readily removed at this stage. The resulting alcohol was oxidized into the corresponding aldehyde **18** with Dess-Martin[13] periodinane, which on treatment with $CrCl_2/CHCl_3$/THF[14] furnished vinyl chloride 19 in 63% yield with a 92:8 (*E*)/(*Z*) ratio. Finally, the PMB protecting group were cleaved smoothly with CAN to afford end product **1**.

Table 1. Comparison of the ^{13}C NMR for the natural and synthetic **1** .

Natural **1**[a]	Synth **1**[b]	Synth **1**[c]	Synth **1**[d]
133.4 (C-2)	133.6	134.3	133.7
116.9 (C-1)	117.2	116.6	117.1
69.0 (C-8)	69.6	68.0	69.3
68.6 (C-6)	69.1	67.7	68.8
42.4 (C-7)	42.4	44.0	42.3
37.4 (C-9)	37.5	37.9	37.4
36.6 (C-5)	36.8	37.2	36.6
31.8 (C-11)	31.8	31.8	31.9
30.7 (C-3)	30.8	30.5	30.8
25.4 (C-10)	25.4	25.3	25.5
25.1 (C-4)	25.1	25.0	25.1
22.6 (C-12)	22.6	22.4	22.7
14.0 (C-13)	14.0	13.4	14.0

[a]Data taken from ref 2a along with the assignments, recorded at 25 MHz without specifying the solvent. [b]This work, measured at 125 MHz in $CDCl_3$. [c]This work, measured at 125 MHz in d_6-acetone. [d]This work, measured at 125 MHz in $CDCl_3$-CD_3OD (0.6 mL/0.01 mL)

The ^{1}H and ^{13}C NMR for **1** were then acquired in $CDCl_3$. The data were generally compatible with those reported for the natural **1**. However, delicate yet unignorable discrepancies occurred at the C-6 and C-8 (δ 69.0 and 68.6 vs 69.6 and 69.1 ppm, respectively), the two oxygenated carbon atoms (Table 1). The original report[2a] did not specify the solvent for the ^{13}C NMR, but the ^{1}H NMR was recorded in $CDCl_3$ and d_6-acetone,

respectively. Therefore, we next recorded the ^{13}C NMR in d_6-acetone.

Somewhat to our surprise, the ^{13}C NMR in d_6-acetone (Table 1, column 3 from the left) turned out to be even more incompatible with that for the natural **1** than that recorded in $CDCl_3$. As the previous synthesis did not provide any NMR information, the spectroscopic data reported for the isolated natural **1** were the only available ones that can be used for comparison. Given the simple structure of **1**, especially with a previous synthesis already published in the literature, there was really no reason to doubt about the correctness of the assigned structure. However, the identity of our sample was just as unequivocal; we were stuck in the middle of nowhere.

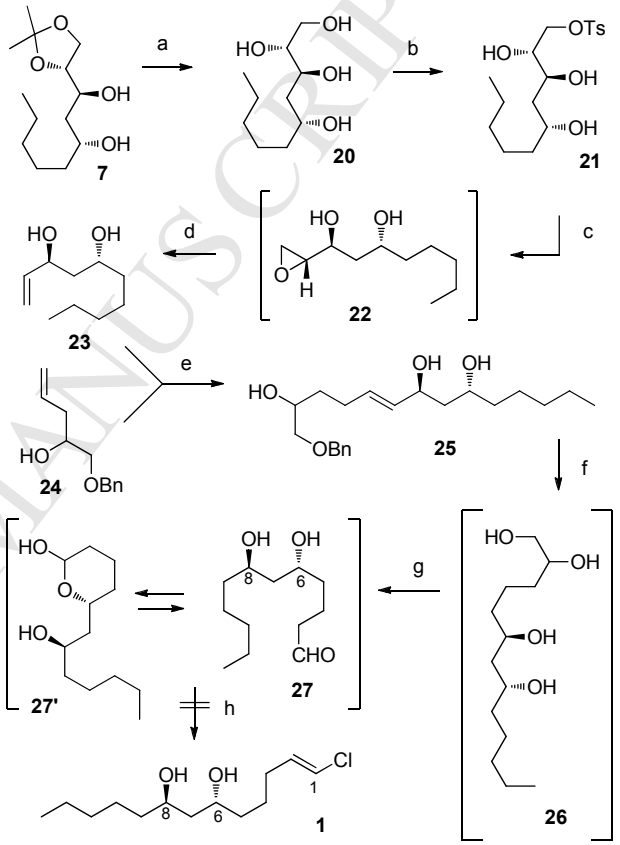
Then we recalled that in a previous[4g] case, similar discrepancies in the ^{13}C NMR were proven to be caused by deuteration of the hydroxyl groups. In the present case, the discrepancies also occurred at those oxygenated carbon atoms and chemical shifts for the involved carbon atoms of the synthetic sample were also larger in value than those reported for the natural ones. Could the present discrepancies also stem from deuteration of the hydroxyl groups? Although there were no traces of clues for the possibility of deuteration of the natural **1** in the original[2a] report, under the given circumstances we really did not have any other choices but looking into the deuteration of the hydroxyl groups.

The synthetic **1** was dissolved in CD_3OD. And a ^{13}C NMR was recorded. However, the data were apparently incompatible with those for the natural **1**. The solvent (CD_3OD) in the NMR sample solution was then removed by rotary evaporation. The residue was re-dissolved in CD_3OD and stirred overnight. The process was repeated three times before the residue was eventually dissolved in $CDCl_3$ to acquire another ^{13}C NMR.

Entirely to our surprise, the ^{13}C NMR of the "deuterated" **1** in $CDCl_3$ turned out to be exactly the same as the one without the deuteration treatment. Because of the structural similarity between the previous[4g] diol and compound **1** here (both are 1,3-diols with the hydroxyl groups located in the middle of an alkyl chain), it appears impossible to explain why deuteration of the hydroxyl groups in **1** would not cause any changes in the ^{13}C NMR. This forced us to consider that the deuterium might be lost in the $CDCl_3$. Indeed, a brief estimation suggested that only a fraction of 1 mg of H_2O in the $CDCl_3$ may suffice for washing out the deuterium in diol **1** in the NMR sample solution. To exclude this possibility, we re-recorded the ^{13}C NMR of the deuterated **1** in $CDCl_3$ in the presence of a very small amount of CD_3OD (which nevertheless was still in large molar excess with respect to the dissolved **1** and thus ensured its deuteration). To our gratification, the data acquired under such conditions (Table 1, the first column from the right) were indeed in full consistence with those reported for the natural **1** and thus provided the ultimate answer to the otherwise "mysterious" discrepancies[15] in the ^{13}C NMR.

While working on the data discrepancies, efforts were also made in exploring another route to **1**, which did not involve protection of the 1,3-diol functionality. As shown in Scheme 3, the acetonide protecting group in the aforementioned diol **7** was removed by treatment with propan-1,3-dithiol in the presence of BF_3-Et_2O. To convert the terminal diol into a vinyl group in the presence of the unmasked 1,3-diol functionality, the strategy employed in Scheme 1 was apparently not applicable. Therefore, an alternative via the corresponding epoxide **22** was devised, which demanded selective activation of the primary hydroxyl group and subsequent epoxidation exploiting the kinetic advantage of the epoxidation process compared with formation of an oxetane or a THP ring.

The primary hydroxyl group in the resulting tetraol **20** was then selectively tosylated to afford tosylate **21**. Because of the poor solubility of **20** in CH_2Cl_2, the most commonly employed solvent for tosylation, was not applicable here. Addition of MeCN did not result in any discernible improvements. THF, which was employed in one of our previous studies[16] to solve a similar problem, could fairly dissolve the added the tetraol **20**.and thus made it possible to execution of the tosylation under the *p*TsCl/Et_3N/DMAP/ *n*Bu_2SnO[17] conditions. However, the desired product **21** (71%) was unavoidably accompanied by the undesired di-tosylated product (29%), which was observed even well before the starting **20** was substantially consumed.



Scheme 3. Reagents and conditions. a) $HS(CH_2)_3SH$, BF_3-Et_2O, CH_2Cl_2, RT, 1 h, 96%; b) *p*TsCl, Et_3N, DMAP, THF, H_2O, *n*Bu_2SnO, RT, 3 h, 87%; c) K_2CO_3, MeOH, RT, 20 min; d) KSeCN MeOH-H_2O, 65 °C, 22 h, 83% overall from **21**; e) **16** (10 mol%), CH_2Cl_2, PhOH, RT, 2 h, 41% (or 35% if with Et_2O as the solvent instead of CH_2Cl_2) along with recovered **23** (29%); f) H_2 (1 atm), Pd-C, EtOH, RT, 22 h, 87% from **25**; g) $NaIO_4$, MeOH-H_2O (1:1, v/v), RT, 40 min; h) $CrCl_2$, $CHCl_3$, THF, 65 °C, 4 h, see the text.

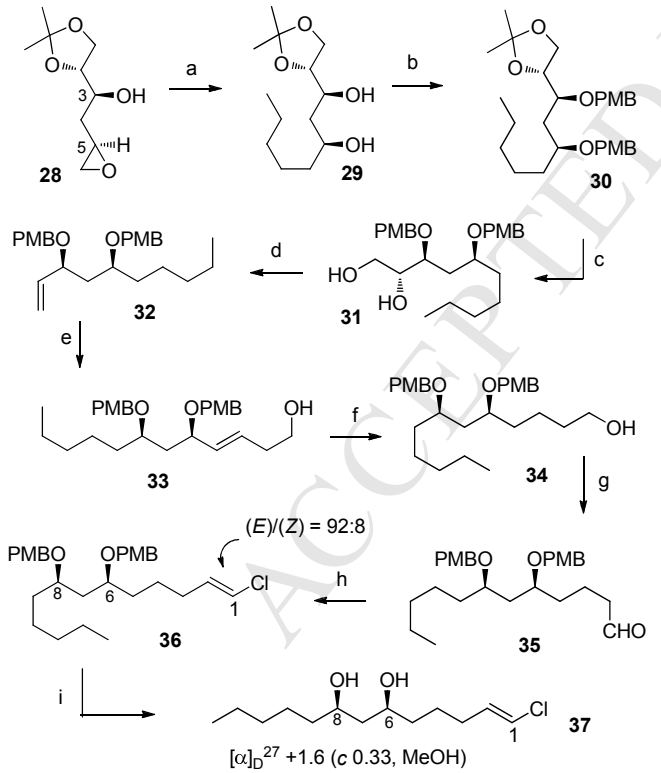
In light of the experience from a previous over-tosylation case,[18] we reasoned that the undesired di-tosylate(s) might be a consequence of the better solubility of the primary product **21** compared with that of tetraol **20**. However, all conventional solvents compatible with tosylation all failed to effect better solvation. Addition of H_2O (which normally should be depleted) to the THF solution of **20** was then tried. Interestingly, the presence of traces of water indeed improved the solubility of **20** and significantly suppressed formation of the over-tosylation. However, the reaction stopped well before full consumption of the starting **20**, because of full consumption of the *p*-TsCl by hydrolysis. Increasing the added *p*-TsCl to 1.5 mol. equiv. (with respect to **20**) provided the desired mono tosylate **21** in 87% yield, along with 7% of di-tosylates and 6% of recovered **20**.

The functions of nBu$_2$SnO and DMAP were also briefly examined in the THF-H_2O system. In the absence of either species the reaction proceeded apparently much slower (incomplete even after several days), while the di-tosylate formation was evidently facilitated without nBu$_2$SnO.

Conversion of the mono tosylate **21** to furnish epoxide **22** by treatment with K_2CO_3/MeOH proceeded without event. However, the resulting epoxide was rather unstable, which began to decompose even during work-up/chromatographic purification and decomposed largely after standing at ambient temperature overnight); subsequent reaction with KSeCN in tBuOH-H_2O at reflux according to the literature[19] failed to give any acceptable results because of extensive formation of side products.

Then, we next tried to combine the two reactions into a "one-flask" conversion using MeOH-H_2O as the solvent (required for the first step). Under such modified conditions, the desired alkene **23** formed in good yields (65%). Even better results (80% overall from **21**) were later obtained by portionwise additions of the reaction mixture of newly formed epoxide **22** to a solution of KSeCN in MeOH-H_2O and minimizing the reaction (heating) time.

A CM reaction between **23** and the known **24** was performed in the presence of catalyst **16** and phenol (to suppress the rather facile allylol re-arrangement[4h] of **23** to the corresponding ethyl ketone). The product **25** was rather difficult to purify because of contamination of the dark catalyst-related species. Fortunately, colored species could be readily removed after exposure of the mixture to H_2/Pd-C, the conditions for the simultaneous removal of the benzyl protecting group and the saturation of the C-C double bond.



Scheme 4. Reagents and conditions. a) cf. ref. 4h, 98%; b) PMBCl, NaH, DMF, nBu$_4$NI, RT, 5 h, 63%, or La(OTf)$_3$, PMBOC(=NH)CCl$_3$, DMF, RT, 12 h, 64%; c) PPTS, MeOH, RT, 12 h, 83% for **31** along with 17% recovered **30**, d) Ph$_3$P, imidazole, I$_2$, THF, 80 °C, 1 h, 100%; e) **16** (10 mol%), Et$_2$O, RT, 2 h; f) H$_2$ (1 atm), skeletal Ni, RT, 1 h, 50% from **32**; g) Dess-Martin periodinane, NaHCO$_3$, CH$_2$Cl$_2$ RT, 2 h, 93% along with 7% of recovered **34**; h) (i) CrCl$_3$, LiAlH$_4$, THF, 0 °C, (ii) CHCl$_3$, THF, 65 °C, 3 h, 73%; i) CAN, MeCN-H$_2$O (10:1, v/v), RT, 1 h, 83%.

The terminal vic-diol in the resulting tetraol **26** was then oxidatively cleaved with $NaIO_4$ to cleanly afford the intermediate aldehyde **27**. However, subsequent reaction with $CrCl_2$/$CHCl_3$ failed to give any desired **1**, presumably because of the strong interference of cyclic hemiacetal formation.

For the purpose of direct comparison, we also synthesized the cis diol **37** as shown in Scheme 4, which was similar to that in Schemes 2-3, except that at the final step of this route, use of the inexpensive and readily available $CrCl_3$ as a precursor of the air-sensitive $CrCl_2$ was examined. To this end, we first tried to employ the French protocol[20] with Zn/NaI as the reducing agent. However, although the outcomes in the literature were very encouraging, this method failed to give acceptable results in our case; the product was always accompanied by undesired iodine-containing side product(s). It thus seemed that the presence of NaI in the reaction system should be avoided. Use of $LiAlH_4$ in THF[21] was then examined (with $CHCl_3$ to replace the CHI_3). To our gratification, this reaction led to the desired vinyl intermediate **36** smoothly, which on removal of the PMB protecting groups with CAN gave the end product **37** in 83% yield. The ^{13}C NMR for **37** is indeed significantly different from that for **1** (for quick comparison, cf. Table S1, Supplementary information)

3. Conclusion

Using expoxy chiral building blocks readily derived from inexpensive D-gluconolactone as the source of the stereogenic centers, both (6*R*,8*R*)-(*E*)-1-chlorotridec-1-ene-6,8-diol (a natural product isolated from marine cyanophytes some 30 years ago) and its (6*R*,8*S*) isomer were synthesized. The vinylchloro unit was installed onto the substrate carbon chain in an approximately 9:1 (*E*)/(*Z*) ratio via a condensation of $CrCl_2$/$CHCl_3$ with an terminal aldehyde, using either commercially available $CrCl_2$ or that formed *in situ* from $CrCl_3$ and a reducing agent. Different approaches for extending the carbon chain from the epoxy building blocks were also explored. An abnormal tosylation of a highly polar tetraol was developed featuring use of THF as the reaction solvent in the presence of small amounts of added water to suppress the unwanted over tosylation. The synthetic samples allowed for re-acquisition of the NMR spectra and thus revealed some delicate yet unignorable discrepancies in the ^{13}C NMR for the natural isomer obtained by synthesis and that isolated some 30 years ago from the marine cyanophyte. Although in retrospect probably the hidden discrepancies (caused by the lack of an explicit description of the NMR solvent employed for the natural **1**) were already noticed by the previous investigators back in the late 1990's when they published the first synthesis of **1** (with only optical rotation without any NMR data), the mysterious smaller shifts of the C-6 and C-8 reported for the natural sample were finally reproduced in this work by deuteration (or partial deuteration) of the hydroxyl groups.

4. Experimental

4.1. General.

The NMR spectra were recorded on a Bruker Avance NMR spectrometer operating at 400 MHz for ^{1}H unless otherwise stated. IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. ESI-HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. EI-MS were recorded on an Agilent Technologies 5973N spectrometer. EI-HRMS were acquired using a Waters Micromass GCT Premier instrument. Optical rotations were measured on a Jasco P-1030 polarimeter. Melting points were

uncorrected (measured on a hot stage melting point apparatus equipped with a microscope). Dry THF was obtained by distillation over Na/Ph_2CO under argon prior to use. Dry toluene and CH_2Cl_2 were acquired via drying over activated 4Å MS (molecular sieves). All reagents were of reagent grade and used as purchased. Column chromatography was performed on silica gel (300-400 mesh) under slightly positive pressure. PE (chromatography solvent) stands for petroleum ether (b.p. 60-90 °C).

*4.2. PMB protection of diol **7** to afford **8**.*

NaH (60% suspension in mineral oil, 159 mg, 3.98 mmol) was added in portions to a solution of diol **7** (196 mg, 0.80 mmol) and *n*Bu_4NI (29 mg, 0.08 mmol) in dry DMF (1.6 mL) stirred under N_2 (balloon) in an ice-water bath. After completion of the addition, the bath was removed. The mixture was stirred at ambient temperature for 1 h. Then with cooling (ice-water bath), PMBCl (0.49 mL, 3.59 mmol)) was added slowly. Stirring was continued at ambient temperature for 5 h. Crushed ice was added to the reaction system, followed by Et_2O (30 mL) and water (5 mL). The phases were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10:1 PE/EtOAc) on silica gel gave **8** as a colorless oil (348 mg, 0.720 mmol, 90% from **7**). $[\alpha]_D^{28}$ –57.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 10.9 Hz, 1H), 4.19 (d, *J* = 11.1 Hz, 1H), 4.13 (dt, *J* = 3.8, 7.1 Hz, 1H), 3.98 (dd, *J* = 7.8, 6.6 Hz, 1H), 3.88(t, *J* = 7.7 Hz, 1H), 3.85-3.81 (m, 1H), 3.77 (s, 6H), 3.63-3.55 (m, 1H), 1.70-1.46 (m, 4H), 1.44 (s, 3H), 1.35 (s, 3H), 1.34-1.22 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 159.0, 131.0, 130.9, 129.33, 129.26, 113.71, 113.68, 108.9, 78.8, 75.1, 75.0, 73.0, 70.1, 65.4, 55.20, 55.18, 37.1, 33.7, 32.0, 26.4, 25.2, 24.5, 22.6, 14.0 ppm; FT-IR (film): 2932, 2861, 1613, 1514, 1464, 1379, 1301,1248, 1173, 1069, 1036, 820 cm^{-1}. ESI-MS *m/z* 509.7 ($[M+Na]^+$). ESI-HRMS calcd for $C_{29}H_{42}O_6Na$ ($[M+Na]^+$): 509.2874; found: 509.2869.

*4.3. Hydrolysis of the acetonide in **8** to afford diol **9**.*

A solution of acetonide **8** (163 mg, 0.335 mmol) and PPTS (169 mg, 0.671 mmol) in MeOH (6.7 mL) was stirred at ambient temperature overnight. The solvent was removed on a rotary evaporator. The residue was dissolved in EtOAc (30 mL) and washed with water (5 mL). The phases were separated. The aqueous layer was back extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:1 PE/EtOAc) on silica gel gave diol **9** as a colorless oil (126 mg，0.285mmol, 85% from **8**) along with recovered starting **8** (24 mg, 0.050 mmol, 15%). Data for **9**: $[\alpha]_D^{27}$ –57.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.862 (d, *J* = 8.5 Hz, 2H), 6.857 (d, *J* = 8.4 Hz, 2H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76-3.71 (m, 1H), 3.70-3.59 (m, 3H), 3.58-3.50 (m, 1H), 2.56-2.19 (br s, 2H, OH), 1.78-1.58 (m, 3H), 1.58-1.47 (m, 1H), 1.40-1.27 (m, 6H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 159.2, 130.4, 130.3, 129.52, 129.46, 113.86, 113.83, 78.0, 75.9, 73.2, 72.2, 70.2, 63.4, 55.2, 36.3, 33.5, 32.0, 24.4, 22.6, 14.0 ppm; FT-IR (film): 3442, 2931, 2859, 1612, 1586, 1514, 1465, 1302, 1248, 1173, 1073, 1035, 820 cm^{-1}. ESI-MS *m/z* 469.7 ($[M+Na]^+$). ESI-HRMS calcd for $C_{26}H_{38}O_6Na$ ($[M+Na]^+$): 469.2561; found: 469.2557.

*4.4. Conversion of diol **9** into alkene **10**.*

A mixture of diol **9** (217 mg, 0.487 mmol), Ph_3P (511 mg, 1.948 mmol), imidazole (256 mg, 3.895 mmol) and I_2 (493 mg, 1.948 mmol) in THF (1.5 mL) was stirred in a 60-80 °C bath for 1 h with precaution to exclude direct light. After cooling to ambient temperature, the mixture was diluted with Et_2O (10 mL), washed in turn with aq. sat. $Na_2S_2O_3$ (2 mL) and water (2 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (15:1 PE/EtOAc) on silica gel afforded alkene **10** as a colorless oil (195 mg, 0.472 mmol, 97% from **9**). $[\alpha]_D^{28}$ –74.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.75 (ddd, *J* = 17.7, 14.4, 7.5, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.2 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 1H), 3.99 (td, *J* = 8.3, 4.0 Hz, 1H), 3.742 (s, 3H), 3.737 (s, 3H), 3.68-3.60 (m, 1H), 1.76-1.60 (m, 2H), 1.59-1.41 (m, 2H), 1.39-1.20 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.01, 158.97, 139.2, 131.1, 130.7, 129.4, 129.2,116.3, 113.62, 113.59, 76.7, 75.0, 70.7, 69.7, 55.08, 55.07, 41.3, 34.1, 32.0, 24.5, 22.5, 14.0 ppm; FT-IR (film): 2931, 2859, 1613, 1586, 1513, 1465, 1301, 1247, 1172, 1068, 1036, 924, 820 cm^{-1}. ESI-MS *m/z* 435.6 ($[M+Na]^+$). ESI-HRMS calcd for $C_{26}H_{38}O_6Na$ ($[M+Na]^+$): 435.2506; found: 435.2486.

*4.5. Hydroboration of alkene **10** to afford alcohol **11**.*

BH_3 (0.2 M solution in THF, 3.38 mL, 6.735 mmol) was added via a syringe to a solution of alkene **10** (150 mg, 0.364 mmol) in dry THF (14 mL) stirred under N_2 (balloon) in an ice-water bath. After completion of the addition, the cooling bath was removed. The mixture was stirred at ambient temperature for 3.5 h. With cooling (ice-water bath), EtOH (2 mL) was added slowly to decompose the excess BH_3, followed by aq. NaOH (3 M, 2 mL) and H_2O_2 (2 mL, added very slowly). The mixture was stirred at ambient temperature for 2 h. White precipitates formed. The mixture was diluted with EtOAc (20 mL), washed with water (3 mL). The aq. layer was back extracted with EtOAc (10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (3:1 PE/EtOAc) on silica gel furnished alcohol **11** as a colorless oil (93 mg, 0.218 mmol, 60% from **10**) along with a side product with one of the two PMB group removed (14 mg, 0.045 mmol, 12 % from **10**). Data for **11**: $[\alpha]_D^{27}$ –42.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.217 (d, *J* = 8.6 Hz, 2H), 7.204 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 4H), 4.464 (d, *J* = 11.0 Hz, 1H), 4.456 (d, *J* = 11.0 Hz, 1H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.25 (d, *J* = 11.0 Hz, 1H), 3.83-3.72 (m, 2H), 3.761 (s, 3H), 3.756 (s, 3H), 3.70-3.62 (m, 1H), 3.61-3.52 (m, 1H), 2.71-2.40 (br s, 1H, OH),1.91-1.80 (m, 1H), 1.80-1.45 (m, 5H), 1.40-1.27 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.13, 159.06, 130.8, 130.5, 129.39, 129.35, 113.72, 113.68, 75.4, 74.6, 70.8, 70.3, 59.8, 55.1, 39.6, 36.2, 33.8, 32.0, 24.4, 22.5, 14.0 ppm; FT-IR (film): 3441, 2930, 2857, 1613, 1586, 1514, 1465, 1354, 1302, 1248, 1173, 1035, 820 cm^{-1}. ESI-MS *m/z* 453.8 ($[M+Na]^+$). ESI-HRMS calcd for $C_{26}H_{38}O_5Na$ ($[M+Na]^+$): 453.2612; found: 453.2606.

*4.6. Conversion of alcohol **11** into iodide **12**.*

I_2 (39 mg, 0.154mmol) was added to a solution of **11** (33 mg, 0.077 mmol), Ph_3P (41 mg, 0.154 mmol) and imidazole (21 mg,

0.308 mmol) in THF (0.4 mL) stirred in an ice-water bath with precaution to exclude light. Then, stirring was continued for 2 h before being diluted with Et_2O (10 mL), washed with aq. sat. NaS_2SO_3 (1 mL) and water (2 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10:1 PE/EtOAc) on silica gel afforded iodide **12** as a colorless oil (39 mg, 0.077 mmol, 100% from **11**).$[\alpha]_D^{27}$ –30.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 6.858 (d, *J* = 8.4 Hz, 2H), 6.853 (d, *J* = 8.5 Hz, 2H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 10.9 Hz, 1H), 4.27 (d, *J* = 10.6 Hz, 1H), 3.77 (s, 6H), 3.70-3.63 (m, 1H), 3.58-3.51 (m, 1H), 3.27-3.16 (m, 2H), 2.12-2.02 (m, 2H), 1.74-1.67 (m, 1H), 1.64-1.45 (m, 3H), 1.37-1.23 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 159.1, 130.9, 130.6, 129.4, 113.8, 113.7, 75.9, 75.3, 71.2, 70.3, 55.2, 39.6, 39.2, 33.9, 32.0, 24.5, 22.6, 14.0, 2.2 ppm; FT-IR (film): 2930, 2857, 1612, 1586, 1513, 1464, 1355, 1301, 1248, 1172, 1064, 1036, 820 cm^{-1}. ESI-MS *m/z* 563.6 ([M+Na]$^+$). ESI-HRMS calcd for $C_{26}H_{37}O_4INa$ ([M+Na]$^+$): 563.1629; found: 563.1627.

*4.7. Synthesis of **17** via cross metathesis between **10** and **14** followed by hydrogenation.*

A solution of 3-buten-1-ol (**14**, 0.15 mL, 1.663 mmol) in dry Et_2O (1 mL) was added slowly over 1 h (with the aid of a syringe pump) to a mixture of alkene **10** (137 mg, 0.333 mmol) and catalyst **16** (42 mg, 0.05 mmol) in dry Et_2O (2 mL) stirred at ambient temperature under N_2 (balloon). After completion of the addition, the mixture was stirred at the same temperature for 3 h before another portion of **14** (0.15 mL, 1.663 mmol) was added. Stirring was continued at the same temperature overnight. The flask was then open to air with stirring continued for 5 h to oxidize the catalyst. The mixture was then concentrated on a rotary evaporator. The residue was chromatographed (2:1 PE/EtOAc) on silica gel to give **15** (79 mg, 0.17mmol, 51% from **10**) as a dark oil (due to contamination of traces of the catalyst-related impurities), from which the following data were acquired: $[\alpha]_D^{27}$ –64.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.68-5.54 (m, 1H), 5.54-5.41 (m, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.22 (d, *J* = 11.0 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 1H), 3.96 (dt, *J* = 3.5, 8.9 Hz, 1H), 3.761 (s, 3H), 3.755 (s, 3H), 3.62 (t, *J* = 6.4 Hz, 3H), 2.41-2.22 (m, 2H), 1.94-1.79 (br s, 1H, OH), 1.75-1.58 (m, 2H), 1.58-1.41 (m, 2H), 1.37-1.19 (m, 6H), 0.88 (t, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.12, 159.09, 134.0, 131.2, 130.9, 129.5, 129.4, 129.1, 113.8, 113.7, 76.3, 75.2, 70.8, 69.7, 62.0, 55.27, 55.25, 41.6, 35.7, 34.2, 32.1, 24.6, 22.7, 14.1 ppm; FT-IR (film): 3412, 2931, 2859, 1612, 1586, 1513, 1465, 1301, 1248, 1173, 1036, 970, 820 cm^{-1}. ESI-MS *m/z* 479.7 ([M+Na]$^+$). ESI-HRMS calcd for $C_{28}H_{40}O_5Na$ ([M+Na]$^+$): 479.2768; found: 479.2775.

A mixture of the **15** obtained as the above (combined from two parallel runs, 121 mg, 0.265 mmol) and skeletal Ni (30 mg) in MeOH (1.5 mL) was stirred under atmospheric H_2 for 1 h. The catalyst was removed by filtration. The conbined filtrate and EtOAc washings were concentrated on a rotary evaporator. The residue was chromatographed (2:1 PE/EtOAc) on silica gel to furnish **17** as a colorless oil (115 mg, 0.26mmol, 49% overall from **10**). Data for **17**: $[\alpha]_D^{26}$ –65.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.1 Hz, 4H), 6.85 (d, *J* = 8.5 Hz, 4H), 4.47 (d, *J* = 8.1 Hz, 1H), 4.44 (d, *J* = 8.1 Hz, 1H), 4.27 (d, *J* = 8.3 Hz, 1H), 4.25 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 6H), 3.63-3.56 (m, 4H), 1.65-1.46 (m, 8H), 1.44-1.24 (m, 8H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 131.13, 131.07, 129.32, 129.30, 113.7, 75.53, 75.47, 70.6, 70.4, 62.8, 55.2, 40.1, 34.0, 33.9, 32.9, 32.1, 24.6, 22.6, 21.1, 14.0 ppm; FT-IR (film): 3431, 2931, 2859, 2363, 1612, 1586, 1513, 1464, 1354, 1301, 1248, 1173, 1064, 1036, 820 cm^{-1}. ESI-MS *m/z* 481.8 ([M+Na]$^+$). ESI-HRMS calcd for $C_{28}H_{42}O_5Na$ ([M+Na]$^+$): 481.2925; found: 481.2935.

*4.8. Oxidation of alcohol **17** to afford aldehyde **18**.*

Dess-Martin periodinane (185 mg, 0.436 mmol) was added to a mixture of alcohol **17** (100 mg，0.218 mmol) and $NaHCO_3$ (183 mg，2.18 mmol) in dry CH_2Cl_2 (4.3 mL) stirred in an ice-water bath. After completion of the addition, the bath was removed. Stirring was continued at ambient temperature for 2 h. Aq. sat. $Na_2S_2O_3$ (1 mL) was added, followe by EtOAc (20 mL) and water (3 mL). The phases were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5:1 PE/EtOAc) on silica gel gave aldehyde **18** as a colorless oil (85 mg, 0.185mmol, 85%), along with recovered starting **17** (10 mg, 0.022 mmol, 10 %). Data for **18**: $[\alpha]_D^{28}$ –62.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.74 (s, 1H), 7.22 (d, *J* = 8.9 Hz, 4H), 6.85 (d, *J* = 8.4 Hz, 4H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 4.25 (d, *J* = 10.8 Hz, 1H), 3.78 (s, 6H), 3.65-3.55 (m, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.73-1.52 (m, 8H), 1.38-1.27 (m, 6H), 0.89 (t, *J* = 6.0Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5, 159.1, 159.07, 131.1, 130.9, 129.4, 129.3, 113.75, 113.73, 75.5, 75.1, 70.7, 70.5, 55.2, 43.9, 39.9, 34.0, 33.5, 32.1, 24.5, 22.6, 17.5, 14.0 ppm; FT-IR (film): 2930, 2857, 1725, 1611, 1513, 1466, 1301, 1248, 1172, 1067, 1035, 820 cm^{-1}. ESI-MS *m/z* 479.6 ([M+Na]$^+$). ESI-HRMS calcd for $C_{28}H_{40}O_5Na$ ([M+Na]$^+$): 479.2768; found: 479.2764.

*4.9. Conversion of aldehyde **18** into chroroalkene **19**.*

A solution of aldehyde **18** (61 mg, 0.131 mmol) and $CHCl_3$ (26 μL, 0.263 mmol) in dry THF (1.0 mL) was added via a syringe to a mixture of $CrCl_2$ (160 mg, 1.31 mmol) in dry THF (1.5 mL) placed in a screw-capped (with a septum) test tube stirred at ambient temperature under argon (balloon). The resulting dark-red mixture was heated at 65 °C for 4 h. After cooling to ambient temperature, the mixture was diluted with Et_2O (10 mL), washed in turn with water (1 mL), aq. sat. $NaHCO_3$, water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (17:1 PE/EtOAc) on silica gel gave **19** as a colorless oil (a 92:8 inseparable (*E*)/(*Z*) mixture, 40 mg, 0.083mmol, 65% from **18**). $[\alpha]_D^{25}$ –47.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.02 (dt, *J* = 7.0, 1.3 Hz, 0.08H), 5.92 (d, *J* = 13.3 Hz, 0.92H), 5.88 (dt, *J* = 13.4, 6.6 Hz, 0.92H), 5.73 (q, *J* = 14.5, 7.2 Hz, 0.08H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.25 (d, *J* = 11.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.64-3.55 (m, 2H), 2.03 (q, *J* = 13.9, 7.1 Hz, 2H), 1.65-1.39 (m, 8H), 1.38-1.26 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.14, 159.12, 133.8, 131.2, 131.1, 129.37, 129.35, 117.0, 113.8, 75.6, 75.3, 70.7, 70.5, 55.3, 40.1, 34.1, 33.5, 32.1, 31.2, 24.6, 24.2, 22.7, 14.1 ppm; FT-IR (film): 2931, 2858, 2063, 1613, 1586, 1514, 1464, 1442, 1353, 1302, 1248, 1172, 1070, 1037, 936, 821, 754 cm^{-1}. ESI-MS *m/z* 511.7 ([M+Na]$^+$). ESI-HRMS calcd for $C_{26}H_{37}O_4INa$ ([M+Na]$^+$): 511.2586; found: 511.2599.

*4.10. Removal of the PMB protecting groups in **19** to afford **1**.*

A mixture of **19** (49 mg, 0.10mmol) and CAN (137 mg, 0.25mmol) in MeCN-H_2O (10:1, v/v, 1.65 mL) was stirred at ambient temperature for 1 h. The mixture was diluted with CH_2Cl_2 (5 mL), washed with aq. sat. $NaHCO_3$ and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4:1 PE/EtOAc) on silica gel gave **1** as a white powder (22 mg, 0.089 mmol, 89% from **19**). M.p. 49-51 °C. $[\alpha]_D^{28}$ –10.8 (*c* 1.0, MeOH), $[\alpha]_D^{28}$ = –11.2 (*c* = 0.33, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.95 (d, *J* = 13.0 Hz, 1H), 5.91 (dt, *J* = 13.1, 6.9 Hz, 1H), 3.99-3.91 (2H, m), 2.10 (q, *J* = 14.1, 7.6 Hz, 2H), 1.96-1.72 (br s, 2H, OH), 1.94-1.82 (m, 2H), 1.64-1.25 (m, 12H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{1}H NMR (400 MHz, d_6-acetone): δ = 6.12 (dt *J* = 13.2, 1.0 Hz, 1H), 5.94 (dt, *J*=13.2, 7.2 Hz, 1H), 3.90-3.81 (m, 2H), 3.66 (d, *J*=5.1 Hz, 1H), 3.60 (d, *J* = 5.1 Hz, 1H), 2.15-2.06 (m, 2H), 1.52-1.23 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ^{1}H NMR (500 MHz, CD_3OD): δ = 6.06 (d, *J* = 13.2 Hz, 1H), 5.91 (dt, *J* = 13.2, 7.3 Hz, 1H), 3.84-3.74 (m, 2H), 2.15-2.02 (m, 2H), 1.51-1.13 (m, 14H), 0.91 (t, *J* = 6.5 Hz, 3H) ppm; ^{1}H NMR (500 MHz, $CDCl_3$-CD_3OD (6:0.1, v/v)): δ = 5.96 (d, *J* = 13.5 Hz, 1H), 5.89 (dt, *J* = 13.2, 6.9 Hz, 0.8H), 3.86-3.95 (2H, m), 2.09 (q, *J* = 14.4 , 7.0 Hz, 2H), 1.99-1.87 (br s, 2H, OH), 1.28-1.60 (m, 16H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 135.1, 118.1, 69.3, 69.0, 45.6, 39.2, 38.4, 33.1, 31.7, 26.5, 26.2, 23.2, 14.4 ppm; for ^{13}C NMR in $CDCl_3$, d_6-acetone or $CDCl_3$-CD_3OD (6/0.1, v/v), see Table 1; FT-IR (film of a conc. solution in CH_2Cl_2): 3341, 2919, 2857, 1710, 1631, 1459, 1070, 935, 827 cm^{-1}. ESI-MS *m/z* 271.4 ([M+Na]$^+$). ESI-HRMS calcd for $C_{13}H_{25}ClO_2Na$ ([M+Na]$^+$): 271.1435; found: 271.1430.

*4.11. Removal of the acetonide group in **7** to afford tetraol **20**.*

A solution of **7** (730 mg, 2.967 mmol), $HS(CH_2)_2SH$ (0.75 mL, 7.418 mmol) and $BF_3{\cdot}OEt_2$ (28 µL, 0.223 mmol) in CH_2Cl_2 (15 mL) was stirred at ambient temperature for 2 h. The mixture was concentrated on a rotary evaporator. The residue was chromatographed (1:6 MeOH/CH_2Cl_2) on silica gel to give tetraol **20** as a white powder (588 mg, 2.85 mmol, 96% from **7**). M.p. 54-56 °C. $[\alpha]_D^{24}$ –22.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.87-3.77 (m, 2H), 3.71 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.57 (dd, *J* = 11.2, 6.5 Hz, 1H), 3.48 (dt, *J* = 4.0, 6.3 Hz, 1H), 1.67 (ddd, *J* = 14.7, 9.8, 2.3 Hz, 1H), 1.54 (ddd, *J* = 14.1, 9.6, 2.2 Hz, 1H), 1.51-1.43 (m, 3H), 1.41-1.24 (m, 5H), 0.92 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 76.4, 70.6, 69.2, 64.5, 41.1, 39.2, 33.1, 26.5, 23.7, 14.4 ppm; FT-IR (film of a conc. solution in CH_2Cl_2): 3283, 2954, 2921, 2852, 1675, 1465, 1379, 1202, 1131, 1062, 1030, 908, 875, 669, 650 cm^{-1}. EI-MS *m/z* (%) 207 (M$^+$ + 1, 3.0), 157 (8.0), 145 (20.2), 127 (21.0), 117 (65.7), 109 (97.2), 101 (31,4), 99 (30.9), 83 (71.0), 55 (100). EI-HRMS calcd for $C_9H_{17}O_2$ (M$^+$ – CH_2OH and H_2O): 157.1231; found: 157.1229.

*4.12. Tosylation of tetraol **20** to afford monotosylate **21**.*

nBu_2SnO (18mg, 0.071mmol) was added to a solution of tetraol **20** (146 mg, 0.709 mmol) in THF (6.5 mL) and H_2O (0.7 mL), followed by DMAP (9 mg, 0.071 mmol) and Et_3N (0.15 mL, 1.06 mmol). The mixture was stirred at ambient temperature for 15 min. *p*TsCl (202 mg, 1.06 mmol) was added. The mixture was stirred at the same temperature for another 5 h. The solids were filtered off (washing with EtOAc). The combined filtrate and washings were concentrated on a rotary evaporator. The residue was chromatographed (1:2 PE/EtOAc) on silica gel to furnish the desired mono tosylate **21** as a white powder (222 mg, 0.62mmol, 87% from **20**), along with an undesired ditosylate (26 mg, 0.05 mmol, 7% from **20**). Data for **21**: M.p. 58-60 °C. $[\alpha]_D^{22}$ +1.8 (*c* 1.0, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.20-4.15 (m, 2H), 3.98-3.84 (m, 2H), 3.78-3.71 (m, 1H), 3.42-3.36 (br s, 3H, OH), 2.44 (s, 3H), 1.63 (t, *J* = 6.0 Hz, 2H), 1.54-1.22 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.1, 132.3, 130.0, 128.0, 72.5, 71.6, 69.1, 68.8, 38.7, 37.6, 31.7, 25.3, 22.5, 21.6, 14.0 ppm; FT-IR (film of a conc. solution in CH_2Cl_2): 3399, 2929, 2859, 1598, 1456, 1356, 1190, 1175, 1096, 1065, 974, 814, 668, 555cm^{-1}. ESI-MS *m/z* 383.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{17}H_{28}O_6SNa$ ([M+Na]$^+$): 383.1499; found: 383.1502.

*4.13. Conversion of tosylate **21** into alkene **23** via epoxide **22**.*

K_2CO_3 (137 mg, 0.99 mmol) was added to a solution of **21** (236 mg, 0.660 mmol) in MeOH (1.2 mL) stirred in an ice-water bath. After stirring at the same temperature for 30 min, the mixture was cooled to –78 °C (bath). Solids were filtered through Celite (washing with dry-ice cooled MeOH, 3 mL). The combined filtrate and washings (cooled in a –78 °C bath before the addition to KSeCN to avoid decomposition of the unstable intermediate epoxide) were added (in ca. 0.5 mL portions through a pipette over 3 h) to a solution of KSeCN(380 mg, 2.64 mmol) in MeOH (1.0 mL) and H_2O (0.22 mL) stirred at refluxing temperature. The resulting mixture was refluxed for 3h before being cooled to ambient temperature. The solids were filtered through Celite (washing with CH_2Cl_2). The combined filtrate and washings were concentrated on a rotary evaporator. The residue was dissolved in CH_2Cl_2, washed with water, and 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 known alkene **23** as a colorless oil (94 mg, 0.55 mmol, 83% from **21**), with all data in full consistence with those[4h] in the literature. (The ^{1}H and ^{13}C NMR are alsoprovided in the Supporting Information).

*4.14. Cross metathesis between **23** and **24** and subsequent hydrogenation leading to **26**.*

A mixture of **23** (20 mg, 0.116 mmol), **24** (111 mg, 0.58 mmol), PhOH (5.0 mg, 0.058 mmol), and catalyst **16** (10 mg, 0.012 mmol) in dry CH_2Cl_2 (2.5 mL) was heated at reflux under argon (balloon) for 3 h. The mixture was then concentrated on a rotary evaporator. The residue was chromatographed (1:1 PE/EtOAc) on silica gel to give **25** as a dark-brown oil (due to contamination by traces of the catalyst-related impurities, 16 mg, 0.048 mmol, 41% from **23**), together with recovered **23** (5.0 mg, 0.029 mmol, 25%). (The dark impurity made it impossible to measure [α]). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.27(m, 4H), 5.75-5.66 (m, 1H), 5.66-5.60 (m, 1H), 4.54(s, 2H), 4.39 (q, *J* = 10.6, 4.8 Hz, 1H), 3.91-3.83 (m, 2H), 3.52-3.46 (m, 1H), 3.40-3.33 (m, 1H), 2.82-2.50 (br s, 3H, OH), 2.29-2.17(m, 2H), 1.65 (q, *J* = 10.5, 5.3 Hz, 2H), 1.55-1.36 (m, 3H), 1.36-1.22 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.93, 137.91, 135.93, 135.84, 128.49, 127.83, 127.78, 126.75, 126.59, 73.95, 73.91, 73.4, 70.47, 70.39, 69.90, 69.88, 69.21, 69.18, 42.68, 42.54, 37.60, 37.58, 36.24, 36.21, 31.9, 25.3, 22.6, 14.0 ppm; FT-IR (film): 3382, 2929, 2858, 1454, 1363, 1094, 1028, 971, 736 698 cm^{-1}. ESI-MS *m/z* 359.1 ([M+Na]$^+$). ESI-HRMS calcd for $C_{20}H_{32}O_4Na$ ([M+Na]$^+$): 359.2193; found: 359.2200.

A mixture of the above obtained **25** (14 mg, 0.042mmol) and 10% Pd-C (5 mg) in EtOH (1 mL) was stirred at ambient temperature under atmospheric H_2 for 22 h. The solids were filtered off. The filtrate and washings were concentrated by rotary evaporation. The residue was chromatographed (1:5 CH_2Cl_2/MeOH) on silica gel to furnish tetraol **26** (9 mg, 0.037 mmol, 87% from **25**) as a white wax. $[\alpha]_D^{24}$ –8.4 (*c* 1.0, CH_3OH).

^{1}H NMR (500 MHz, CD_3OD): δ = 3.86-3.77 (m, 2H), 3.62-3.54 (m, 1H), 3.52-3.39 (m, 2H), 1.71-1.20 (m, 16H), 0.92 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 73.23, 73.21, 69.3, 69.20, 69.17, 67.38, 67.36, 45.57, 45.54, 39.20, 39.18, 34.42, 34.38, 33.1, 26.5, 23.7, 22.8, 14.4 ppm; FT-IR (film of a conc. solution in CH_2Cl_2): 3315, 2931, 2857, 1459, 1409, 1376, 1351, 1176, 1064, 1030, 901, 831, 737 cm^{-1}. EI-MS *m/z* (%) 199 (6.7, (M^+ – CH_2OH and H_2O), 185 (2.1), 181 (3.3), 115 (58.2), 109 (34.6), 97 (38.5), 55 (100). EI-HRMS calcd for $C_{12}H_{23}O_2$ (M^+ – CH_2OH and H_2O): 199.1698; found: 199.1702.

*4.15. PMB protection of diol **29** to afford **30**.*

The same procedure given above for conversion of **7** into **8** was employed (with **29** to place of **7**). Data for **30** (a colorless oil, 1.490 g, 63% from **29**): $[\alpha]_D^{27}$ +3.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 9.1 Hz, 2H), 7.21 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.59 (d, *J* = 11.1 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.41 (s, 2H), 4.12 (dt, *J* = 4.6, 6.9 Hz, 1H), 4.01 (dd, *J* = 8.4, 6.7Hz, 1H), 3.86 (t, *J* = 7.4 Hz, 1H), 3.79 (s, 6H), 3.60-3.65 (m, 1H), 3.51 (quint, *J* = 6.0 Hz, 1H), 1.85 (dt, *J* = 14.7, 6.8 Hz, 1H), 1.65-1.59 (m, 1H), 1.50-1.44 (m, 2H), 1.43 (s, 3H), 1.35 (s, 3H), 1.31-1.17 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 131.0, 130.6, 129.5, 129.3, 113.69, 113.67, 109.0, 78.6, 75.6, 75.5, 72.2, 70.2, 66.0, 55.24, 55.21, 36.3, 33.9, 32.0, 26.5, 25.3, 24.8, 22.6, 14.0 ppm; FT-IR (film): 2933, 2860, 1612, 1514, 1464, 1370, 1301, 1248, 1173, 1069, 1036, 821 cm^{-1}. ESI-MS *m/z* 509.7 ([M+Na]$^+$). ESI-HRMS calcd for $C_{29}H_{42}O_6Na$ ([M+Na]$^+$): 509.2874; found: 509.2884.

*4.16. Hydrolysis of the acetonide in **30** to afford diol **31**.*

The same procedure described above for the conversion of **8** to **9** was employed (with **30** to replace **8**). Data for **31** (a colorless oil, 709 mg, 1.59 mmol, 83% from **30**): $[\alpha]_D^{23}$ +59.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 4H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.48 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 12.4 Hz, 1H), 4.36 (d, *J* = 10.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.74 (dd, *J* =10.1, 2.4Hz, 1H), 3.71-3.56 (m, 4H), 1.93-1.86 (m, 1H), 1.85-1.79 (m, 1H), 1.64-1.49 (m, 2H), 1.37-1.24 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 130.2, 130.0, 129.6, 129.5, 113.85, 113.83, 77.3, 75.2, 72.3, 71.3, 70.5, 63.9, 55.2, 34.0, 33.3, 31.9, 24.5, 22.6, 14.0 ppm; FT-IR (film): 3478, 2931, 2858, 1849, 1612, 1514, 1464, 1301, 1248, 1173, 1073, 1035, 821 cm^{-1}. ESI-MS *m/z* 469.5 ([M+Na]$^+$). ESI-HRMS calcd for $C_{26}H_{38}O_6Na$ ([M+Na]$^+$): 469.2561; found: 469.2568.

*4.17. Conversion of diol **31** into alkene **32**.*

The same procedure described above for conversion of **9** to **10** was employed (with **31** to replace **9**). Data for **32** (a colorless oil, 576 mg, 1.40 mmol, 100% from **31**): $[\alpha]_D^{21}$ –23.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 5.71 (ddd, *J* = 18.2, 10.2, 8.0 Hz, 1H), 5.22 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.15 (dd, *J* = 17.1, 1.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 10.9 Hz, 1H), 4.26 (d, *J* = 11.7 Hz, 1H), 3.88 (q, *J* = 14.5, 7.3 Hz, 1H), 3.79 (s, 6H), 3.45 (dq, *J* = 6.8, 5.5 Hz, 1H), 2.01 (quint, *J* = 6.7 Hz, 1H), 1.62-1.54 (m, 1H), 1.54-1.41 (m, 2H), 1.38-1.17 (m, 6H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 138.9, 131.1, 130.7, 129.4, 129.3, 117.5, 113.68, 113.65, 77.5, 75.4, 70.1, 69.6, 55.22, 55.19, 40.13, 33.8, 31.9, 24.7, 22.6, 14.0 ppm; FT-IR (film): 2931, 2858, 1736, 1612, 1513, 1465, 1301, 1247, 1172, 1074, 1036, 926, 820 cm^{-1}. ESI-MS *m/z* 435.4 ([M+Na]$^+$). ESI-HRMS calcd for $C_{26}H_{38}O_6Na$ ([M+Na]$^+$): 435.2506; found: 435.2519.

*4.18. Synthesis of **34** via cross metathesis between **32** and **14** followed by hydrogenation.*

The same procedure described above for coupling of **10** with **14** followed by hydrogenation to afford **17** was employed (with **32** to replace **10**). Data for **34** (a colorless oil, 250 mg, 0.54 mmol, 50% for two steps from **32**): $[\alpha]_D^{24}$ +6.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.7 Hz, 4H), 6.85 (d, *J* = 8.1 Hz, 4H), 4.47-4.34 (m, 4H), 3.79 (s, 6H), 3.59 (t, *J* = 6.1 Hz, 2H), 3.49-3.39 (m, 2H), 2.01-1.88 (m, 1H), 1.76-1.19 (m, 16H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.06, 159.03, 131.0, 130.9, 129.4, 113.7, 75.6, 75.5, 70.2, 70.1, 62.8, 55.23, 55.22, 38.6, 34.0, 33.8, 32.8, 32.0, 24.8, 22.6, 21.4, 14.0 ppm; FT-IR (film): 3460, 2932, 2859, 1734, 1612, 1586, 1513, 1464, 1364, 1302, 1248, 1173, 1061, 1036, 820 cm^{-1}. ESI-MS *m/z* 481.5 ([M+Na]$^+$). ESI-HRMS calcd for $C_{28}H_{42}O_5Na$ ([M+Na]$^+$): 481.2925; found: 481.2934.

*4.19. Oxidation of alcohol **34** to afford aldehyde **35**.*

The same procedure described above for oxidation of **17** to give **18** was employed (with **34** to replace **17**). Data for 35 (a colorless oil, 85 mg, 0.19 mmol, 93% from **34**): $[\alpha]_D^{27}$ +13.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (t, *J* = 1.9 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 4H), 6.85 (d, *J* = 8.6 Hz, 4H), 4.48-4.33 (m, 4H), 3.80 (s, 6H), 3.51-3.38 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.99-1.89 (m, 1H), 1.80-1.17 (m, 13H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.6, 159.18, 159.15, 131.0, 130.9, 129.5, 113.78, 113.76, 75.5, 75.2, 70.28, 70.22, 55.3, 43.8, 38.5, 34.0, 33.4, 32.0, 24.9, 22.7, 17.9, 14.1 ppm; FT-IR (film): 2932, 2859, 1725, 1612, 1513, 1464, 1301, 1248, 1173, 1064, 1036, 821 cm^{-1}. ESI-MS *m/z* 479.6 ([M+Na]$^+$). ESI-HRMS calcd for $C_{28}H_{40}O_5Na$ ([M+Na]$^+$): 479.2768; found: 479.2779.

*4.20. Conversion of **35** into **36**.*

A solution of $LiAlH_4$ (1.0 M, in THF, 0.27 mL, 0.27 mmol) was added dropwise to a solution of $CrCl_3$ (166 mg, 1.05 mmol) in dry THF (0.5 mL) stirred in an ice-water bath under argon (balloon). The initially purple solution turned light green, with a lot of gas bubbles evolved. After completion of the addition, the cooling bath was removed. The mixture was heated to reflux (still under argon), while a solution of aldehyde **35** (48 mg, 0.105 mmol) and $CHCl_3$ (21µL, 0.21 mmol) in dry THF (1.5 mL) was introduced. The solution turned dark-red. The mixture was then heated with stirring for 3 h. The heating bath was removed. The reaction was quenched by addition of water. The reaction mixture was diluted with EtOAc (10 mL), washed water (3 mL), aq. sat. $NaHCO_3$ 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 gave **36** as a colorless oil (a 92:8 inseparable (*E*)/(*Z*) mixture, 37 mg, 0.077 mmol, 73% from **35**). $[\alpha]_D^{26}$ +13.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22(d, *J* = 8.3 Hz, 4H), 6.85 (d, *J* = 7.7 Hz, 4H), 6.01(d, *J* = 6.4 Hz, 0.08H), 5.90 (d, *J* = 13.0 Hz, 0.92H), 5.85 (dt, *J* = 13.2, 7.4 Hz, 0.92H), 5.71 (q, *J* = 14.3, 7.3 Hz, 0.08H), 4.48-4.33 (m, 4H), 3.80 (s, 6H), 3.49-3.38 (m, 2H), 2.07-1.87 (m, 2H), 1.57-1.40 (m, 6H), 1.40-1.18 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.13, 159.10, 133.8, 131.0, 130.9, 129.5, 129.4, 116.9, 113.74, 113.72, 75.5, 75.3, 70.3, 70.2, 55.3, 38.6, 34.0, 33.4, 32.0, 30.9, 24.9, 24.6, 22.7, 14.1 ppm; FT-IR (film): 2932, 2858, 1612, 1586, 1513, 1464, 1441, 1301, 1247, 1172, 1067, 1037, 935, 820cm^{-1}.

ESI-MS *m/z* 511.6 ([M+Na]$^+$). ESI-HRMS calcd for $C_{26}H_{37}O_4INa$ ([M+Na]$^+$): 511.2586; found: 511.2589.

*4.21. Removal of the PMB protecting groups in **36** to afford **37**.*

The same procedure described above for the conversion of **19** to **1** was employed (with **36** to replace **19**) Data for **37** (a colorless oil, 4.0 mg, 0.02 mmol, 83% from **36**) $[\alpha]_D^{27}$ +1.6 (*c* 0.33, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.96 (d, *J* = 13.0 Hz, 1H), 5.89 (dt, *J* = 13.2, 6.7 Hz, 1H), 3.92-3.81 (2H, m), 2.55-2.14 (br s, 2H, OH), 2.13-2.02 (m, 2H), 1.64–1.51 (m, 2H), 1.51-1.37 (m, 6H), 1.36-1.27 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.6, 117.1, 73.4, 72.7, 42.9, 38.4, 37.4, 31.8, 30.8, 25.0, 24.7, 22.6, 14.0 ppm; FT-IR (film): 3336, 2931, 2858, 2097, 1846, 1779, 1458, 1090, 847 cm^{-1}. ESI-MS *m/z* 271.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{13}H_{25}ClO_2Na$ ([M+Na]$^+$): 271.1435; found: 271.1432.

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Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra, FT-IR spectra for all new compounds

References and Notes

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