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Synthesis of a vinylchlorine-containing 1,3-diol from a marine cyanophyte

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ABSTRACT

Using epoxy 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 a 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 (Fig. 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.

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.

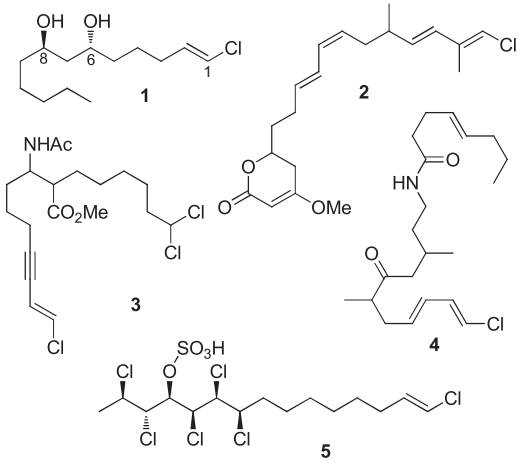

Fig. 1. The structures for some of the known vinylchlorine-containing marine natural products produced by cyanobacteria.

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

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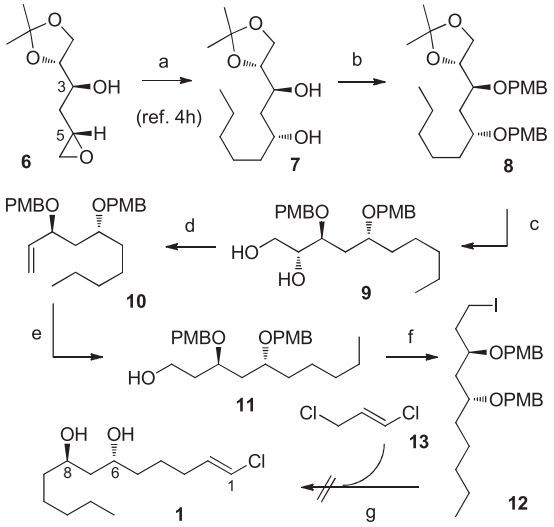
in the presence of CuI as reported[4h] in our previous work to afford the known diol **7**. Protection[7] of the hydroxyl groups with PMBCl using NaH as the base furnished the corresponding diPMB ether **8** in 90% isolated yield.



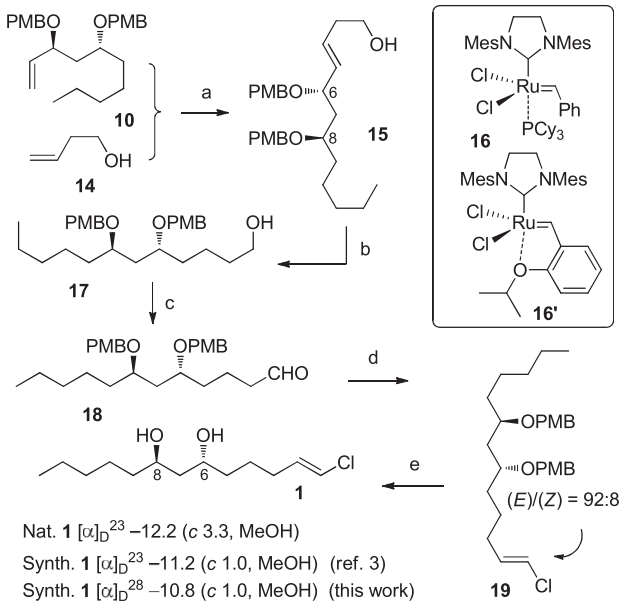
Scheme 1. Reagents and conditions. (a) ^{n}BuLi, CuI, THF, −78 °C 3 h, 96%; (b) PMBCl, NaH, DMF, $^{n}Bu_4NI$, RT, 5 h, 90%; (c) PPTS, MeOH, RT, 12 h, 85% for **9** along with 15% recovered **8**, (d) Ph_3P, imidazole, I_2, THF, 80 °C, 1 h, 97%; (e) (i) BH_3, THF, 0 °C, 3 h, (ii) NaOH, H_2O_2, RT, 2 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.

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 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.

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.

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 vinylchlorine 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



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.

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**.

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

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).