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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of the new marine epoxy lipid, (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diol

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Abstract—An efficient and stereocontrolled process is described for the preparation of (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diol, a marine epoxy lipid isolated from the brown alga, *Notheia anomala*. The key 2,3,5-trisubstituted tetrahydrofuran ring was constructed by stereoselective hydrogenation of the hemiketal derivative elaborated through nucleophilic addition of Grignard reagent in the presence of $CeCl_3$ to the highly functionalized lactone derived from L-galactono-1,4-lactone.

The tetrahydrofuran backbone is among the most common heterocyclic units found in natural products. Structurally complex substituted tetrahydrofurans feature in many biologically potent compounds such as pheromones,[1] polyether antibiotics[2] and marine epoxy lipids.[3] Due to their interesting activity and unique structural characteristics, they have been the subject of extensive synthetic efforts which have culminated in numerous syntheses.[4] Noteworthy members among this class of compounds are optically active tri- and tetrasubstituted tetrahydrofuran derivatives. They serve as good templates for the construction of pharmacologically important furanoid groups and exhibit various degrees of potency and specificity.[5] In connection with this we have recently accomplished the asymmetric total syntheses of (−)-sesaminone (trisubstituted tetrahydrofuran lignan)[6] and (−)-virgatusin (tetrasubstituted tetrahydrofuran lignan),[7] employing Lewis acid-induced deoxygenation of the lactol precursors (Fig. 1).

On the other hand, new trisubstituted tetrahydrofuran-type marine epoxy lipids, (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diol **1**[8] and its stereoisomer, (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol **2**,[9] possessing a characteristic substitution pattern in their ring system have recently been isolated from the southern Australian brown alga *Notheia anomala*, a member of the Notheiaceae family. These are considered to be biosynthesized via a cyclization of a natural methylene-interrupted bisepoxide and within this context a

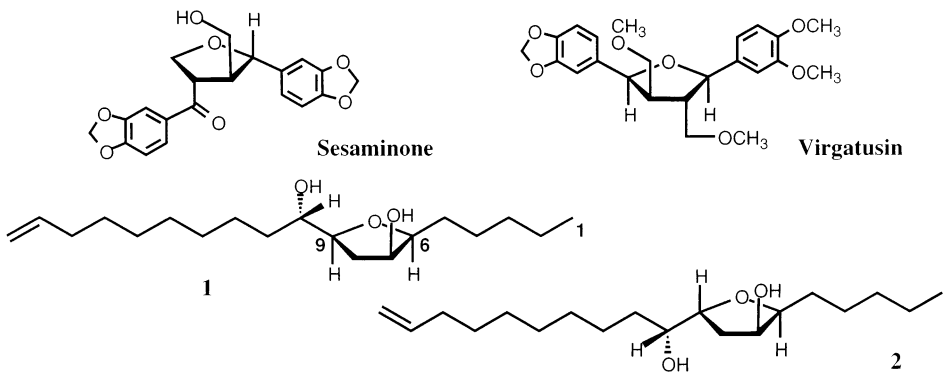

Figure 1.

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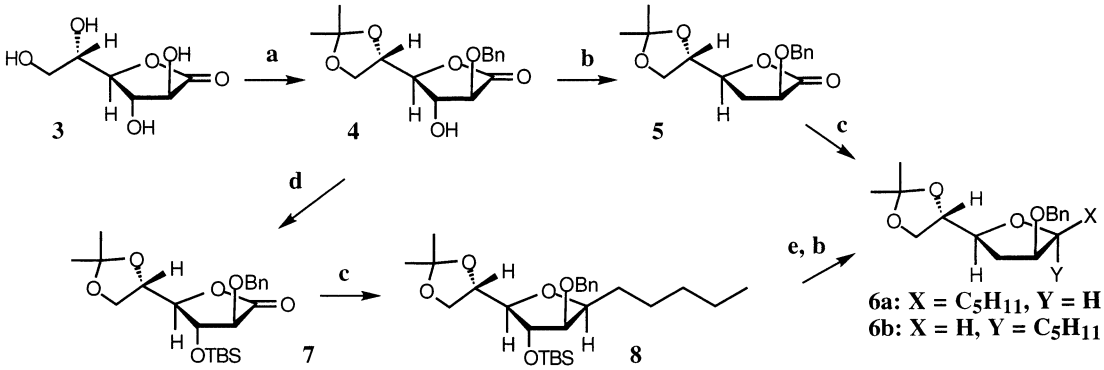
biomimetic synthesis of (±)-**2** has been reported.[10] In addition, since it became apparent that these compounds are potent and selective inhibitors of the larval development of parasitic nematodes,[8] considerable efforts have been directed toward the synthesis of **2**,[11] some of which require multi-step reactions or are non-stereoselective. Herein we communicate a novel and efficient asymmetric synthesis of **1** based on Lewis acid-promoted deoxygenation of the hemiketal intermediate elaborated from L-galactono-1,4-lactone with complete stereoselectivity. To the best of our knowledge, only one approach to the synthesis of **1** has been reported[12] recently based on Sharpless asymmetric dihydroxylation during the course of our studies.

As shown in Scheme 1, commercially available and conveniently functionalized L-(+)-galactono-1,4-lactone **3** was selected as a starting material. Acetonide formation of **3** and successively regioselective benzylation with Ag_2O–BnBr was performed to give the mono-protected hydroxylactone **4** in moderate yield. To begin with, we attempted the direct conversion of the lactone **5** derived from **4** to the corresponding trisubstituted tetrahydrofuran framework via Lewis acid-induced reductive deoxygenation. Thus, **4** was subjected to reaction with phenyl chlorothionoformate followed by radical elimination with Bu_3SnH, leading to the desired compound **5**.[13] Treatment of **5** with pentylmagnesium bromide in the presence of $CeCl_3$[7,14] at low temperature provided the labile hemiketal intermediate, which was readily effected by $BF_3{\cdot}OEt_2$-promoted hydrogenation with Et_3SiH[15] at −78°C to afford the trisubstituted tetrahydrofuran **6** in moderate yield. However, the reaction occurred with unsatisfactory selectivity (the ratio of the stereoisomers **6a** and **6b** was almost 1:1 as determined by ^{13}C NMR). Enhancement of the selectivity was not observed under any conditions.

Next, we turned our attention and researched an alternative synthetic strategy towards **1**. When the lactone **7** obtained from the TBS-protection of **4** was treated with *n*-pentyl Grignard reagent also in the presence of $CeCl_3$, followed by subsequent hydrogenation with Et_3SiH under the same conditions as above, it rapidly yielded the *cis*-tetrasubstituted tetrahydrofuran **8** with the desired stereochemistry[16] as a sole product (determined by ^{13}C NMR and HPLC analysis). Highly substituted five-membered ring oxocarbenium ions sometimes exhibit opposite stereoselectivities to what would be expected based upon a consideration of simple steric effects alone. In this case, steric destabilization of the transition state leading to the *trans*-2,3-stereochemistry is presumably being observed due to the presence of the β-OTBS group (Fig. 2).[15a] Consequently it could proceed through the exclusive attack of Et_3SiH to the oxocarbenium ion intermediate from the opposite side of the large α-OBn and γ-substituent.[7,14b] With the above stereochemical outcome in hand, deprotection of **8** and thiocarbonate formation followed by radical elimination were performed again, smoothly providing the optically pure tetrahydrofuran **6a** in three steps (56% yield).

The remaining C(8) side unit was then easily introduced as follows: acetonide deprotection of **6a** afforded the diol **9**, which was in turn subjected to regioselective tosylation in the presence of Bu_2SnO[17] and subsequent cyclization under mildly basic conditions, leading to epoxide **10** ($[\alpha]_D^{25} = +44.9$ (*c* 0.97, $CHCl_3$)) in high yield. Exchange of the benzyl ether protecting group in **10** to



Scheme 1. *Reagents and conditions*: (a) 1, $(CH_3)_2C(OCH_3)_2$, CH_3COCH_3, cat. *p*-TsOH; 92%; 2, BnBr, Ag_2O, CH_3COOEt; 50%; (b) 1, $ClC(S)OC_6H_5$, pyridine, DMAP, CH_3CN; 2, Bu_3SnH, cat. AIBN, toluene, 90°C; 45% (**5**) (two steps yield from **4**); 57% (**6a**) (two steps yield from **8**); (c) 1, $C_5H_{11}MgBr$, $CeCl_3$, −78°C, THF; 2, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C; 36% (**6a** and **6b**) (two steps yield from **5**); 41% (**8**) (two steps yield from **7**); (d) TBSCl, imidazole, CH_2Cl_2; 92%; (e) Bu_4NF, THF; 98%.

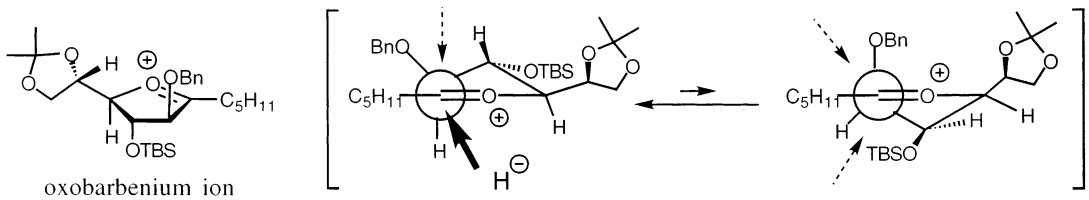
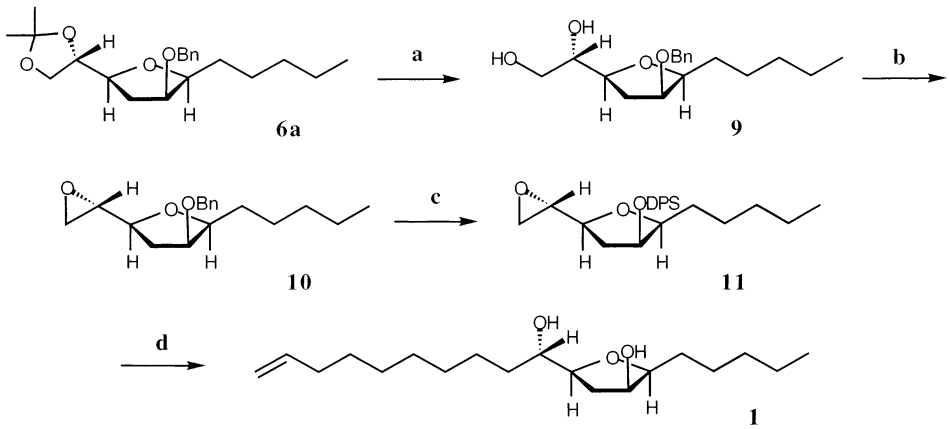


Figure 2. Mechanistic origin of the stereoselective reduction with Et_3SiH.



Scheme 2. *Reagents and conditions*: (a) cat. *p*-TsOH, MeOH; 50%; (b) 1, TsCl, Bu_2SnO, Et_3N, CH_2Cl_2; 90%; 2, K_2CO_3, MeOH; 90%; (c) 1, Pd (black), 4.4% HCOOH–MeOH; 87%; 2, DPSCl, imidazole, CH_2Cl_2; quant.; (d) $CH_2CH(CH_2)_6MgBr$, cat. CuI, THF, −50°C; 2, Bu_4NF, THF; 68% (two steps).

a *tert*-butyldiphenylsilyl (DPS) ether[18] was necessary to avoid the use of hydrogenation conditions after introduction of the octenyl chain. The was carried out to give the furan **11** in 87% yield. Finally, **11** was subjected to a coupling reaction in the presence of CuI with octenylmagnesium bromide reagent followed by desilylation to complete the total synthesis of the marine epoxy lipid **1** ($[\alpha]_D^{23.2}=+23.7$ (*c* 0.42, $CHCl_3$))[19] in high yield. The spectral data of synthesized **1** were completely identical with those of the reported natural compound[8] (Scheme 2).

In summary, this work constitutes an efficient and straightforward pathway for the asymmetric synthesis of a marine epoxy lipid based on the stereoselective Lewis acid-induced hydrogenation of a hemiketal derivative and will serve for the synthesis of other polysubstituted tetrahydrofuran natural products.

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16. The absolute configuration of the generated stereogenic center was determined based on its spectral data of synthetic (+)-**1** and in this case β-elimination of the TBSO-group also took place as an accompanying reaction.

    Experimental procedure for the synthesis of **8** from **7**: To a suspension of well-dried cerium chloride (0.176 g, 0.473 mmol) in THF (3 mL) was added a solution of lactone **7** (0.200 g, 0.473 mmol) in THF (1 mL) at −20°C and stirred for 1 h under nitrogen. Then, the reaction mixture was cooled to −78°C and pentylmagnesium bromide (1.5 M in THF, 1.0 mL, 1.5 mmol) was added. After the solution was stirred for 2 h at the same temperature, it was quenched by the addition of water (3 mL) and filtered through a pad of Celite followed by the extraction with ether (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an oil of the crude hemiketal. A solution of the product in CH_2Cl_2 (2.5 mL) was cooled to −78°C and Et_3SiH (0.550 g, 4.730 mmol) was added. After the mixture was stirred for 5 min, $BF_3{\cdot}OEt_2$ (0.167 g, 1.182 mmol) was slowly added. The solution was further stirred for 2 h at the same temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried (Na_2SO_4) followed by the concentration in vacuo. The residue was chromatographed (10:1 hexane–ethyl acetate) to give the tetrasubstituted furan **8** as a colorless oil (0.091 g, 0.189 mmol, 41%).

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18. The direct coupling reaction between the debenzylated hydroxyl tetrahydrofuran with octenylmagnesium bromide did not proceed even at room temperature.
19. Although the naturally isolated compound **1** is reported to be a colorless oil ($[\alpha]_D = +74.5$ (*c* 0.4, $CHCl_3$)),[8] our synthetic **1** was a waxy oil and has a different specific rotation in analogy with the product described in the preceding synthetic report ($[\alpha]_D^{25} = +20.5$ (*c* 0.4, $CHCl_3$)).[12] This would be due to impurities present in the natural compound.