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Synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-Epoxynonadec-18-ene-7,10-diol, a Marine Epoxy Lipid Isolated from the Brown Alga, *Notheia anomala*, by an Oxiranyl Anion Strategy

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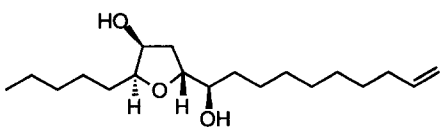
Abstract

The stereocontrolled synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol, isolated from the brown alga, *Notheia anomala*, has been achieved. The key 2,3,5-trisubstituted tetrahydrofuran ring was constructed by alkylation of the sulfonyl-stabilized oxiranly anion followed by 5-*endo* cyclization.

Keywords: Carbanions; Cyclization; Marine metabolites; Oxiranes

The southern Australian marine brown alga, *Notheia anomala*, produced an array of novel epoxy lipids, exemplified by (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**1**) [1] and accompanying methylene-interrupped bisepoxides [2] and trisepoxides [3]. The structure of **1** was unambiguously confirmed by single-crystal X-ray analysis and revealed to have a 3-oxygenated *trans*-2,5-dialkyltetrahydrofuran core [1]. The functionalized tetrahydrofuran structure has been the target of considerable synthetic efforts and several stereocontrolled syntheses of **1** have been achieved by the methods of NBS oxidation of a substituted 1,3-dioxolane [4], selenoetherification of a substituted bishomoallylic alcohol [5], transformation from D-glucose [6], cyclodehydration of a 1,4-diol [7], and an asymmetric dihydroxylation approach [8].



1

2 (relative stereochemistry)

The tetrahydrofuran **1** has been considered to be biosynthesized via a somewhat truncated version of the polyepoxide cyclization of bisepoxide co-metabolite **2** [2] and, in this context, a biomimetic transformation of **2** to **1** was recently reported by the Capon group [9,10]. Our

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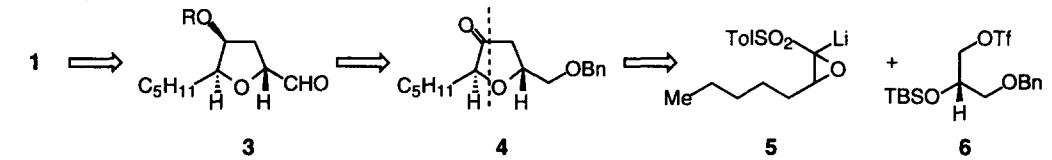
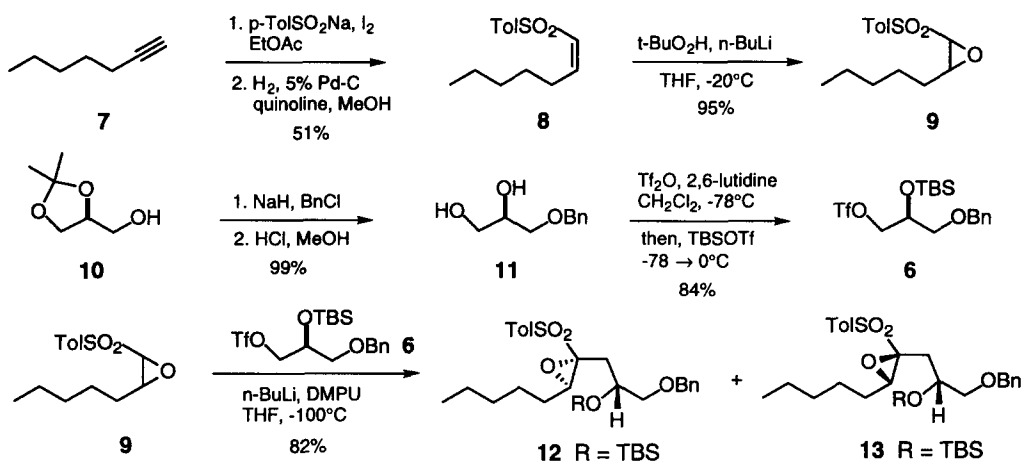
interest in this field came about during investigation of biomimetic polytetrahydropyran synthesis based on an oxiranyl anion strategy [11-13]. In this paper, we describe a unique approach to the synthesis of 2,3,5-trisubstituted tetrahydrofuran **1** by 5-*endo* cyclization.

Scheme 1



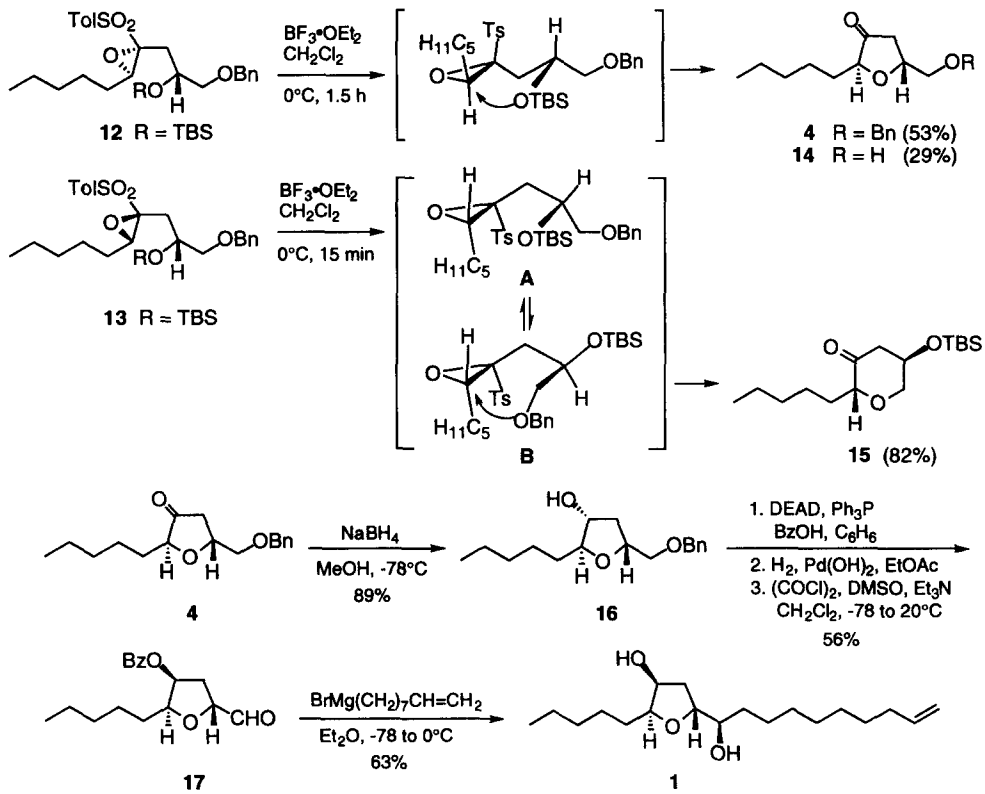
The retrosynthetic analysis is illustrated in Scheme 1. Disconnection of the C10-C11 bond of the side chain in the target molecule would provide the key tetrahydrofuran unit **4** via **3**, which could be available by a strategy based upon alkylation of the sulfonyl-stabilized oxiranyl anion **5** [14-16] with **6** followed by the sulfonyl-assisted 5-*endo* cyclization.

Reaction of 1-heptyne (**7**) with sodium *p*-toluenesulfinate in the presence of iodine and hydrogenolysis gave (*Z*)-vinyl sulfone **8** in 51% yield [17]. Epoxidation with *n*-BuLi-*t*-BuO_2H afforded the racemic epoxy sulfone **9** in 95% yield [18]. Triflate **6** was prepared from the commercially available (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (**10**). Regioselective activation and protection of the diol **11** obtained from **10** were carried out using a one-pot process. Thus, treatment of a solution of **11** in 2,6-lutidine and CH_2Cl_2 with one equivalent of triflic anhydride at -78°C for 30 min followed by the addition of a slight excess of *t*-butyldimethylsilyl triflate (-78°→ 0°C) gave the triflate **6** in 84% yield.



Alkylation of the oxiranyl anion **5** was accomplished by the addition of *n*-BuLi to a mixture of **6** and **9** in THF-DMPU at -100°C [16], providing a 1:1 diastereomeric mixture of epoxy sulfones **12** and **13** in 82% yield, which were separated by HPLC (silica gel 60, 14% EtOAc in hexane). ^1H NMR analysis did not allow for the unambiguous assignment of stereochemistry of epoxide for these isomers at this stage. However, the stereochemistry was

assigned based upon the stereospecific cyclization reaction of each diastereoisomer (*vide infra*). Treatment of the polar isomer **12** with *p*-TsOH (1.5 equiv) in $CHCl_3$ at 55°C for 8 h led to the desilylation and the subsequent stereospecific 5-*endo* cyclization to afford the key *trans*-2,5-disubstituted tetrahydrofuranyl ketone **4** in 63% yield, but the reproducibility of this cyclization was found to be poor. Exposure of **12** to excess BF_3•OEt_2 (10 equiv) in CH_2Cl_2 at 0°C for 1.5 h led to its clean cyclization to **4** in 53% yield along with the debenzylated product **14** in 29% yield. On the other hand, cyclization of the less polar isomer **13** with BF_3•OEt_2 (1.2 equiv) proceeded within 15 min in CH_2Cl_2 at 0°C in a 6-*endo* mode to give the tetrahydropyranyl ketone **15** in 82% yield as a single isomer. Compounds **4** and **15** showed IR absorption at 1755 and 1726 cm^{-1}, diagnostic to 5- and 6-membered ketones, respectively, and their structures were determined by ^1H NMR spectral analysis, involving COSY and NOE experiments.



Our previous studies on polytetrahydropyran synthesis revealed that the 6-*endo* cyclization of hydroxy epoxy sulfones proceeded with inversion of configuration at the epoxide carbon [11]. This mechanistic feature suggested that compound **15** was formed from the isomer **13**. Thus, in a presumed 5-*endo* cyclization transition state **A** for the isomer **13**, the pentyl,

sulfonyl, and benzyloxymethyl substituents should be arrayed on the same side of a forming ring, which causes the serious steric interactions and prevents the cyclization of 5-*endo* mode. The sterically less crowded 6-*endo* transition state **B** led to the exclusive formation of the tetrahydropyranyl ketone **15**.

Reduction of **4** with sodium borohydride proceeded with high selectivity (94:6) to give alcohol **16** in 89% isolated yield. NOE studies on **16** revealed that the hydroxyl was oriented α and, therefore, in a configuration unnatural to the target molecule. Then, the hydroxyl group of **16** was inverted into the β-benzoyloxy group using Mitsunobu conditions. Debenzylation and Swern oxidation gave the aldehyde **17** in 56% overall yield. Elaboration of the olefinic side chain was carried out in a fashion similar to that described by Williams [4]. Addition of excess 1-nonenylmagnesium bromide to **17** afforded the desired **1** as the major product (63%) and the C10 epimer (12%) in a 5:1 ratio. Optical rotation [$[\alpha]^{25}_D$ +15.5° (c 0.3, $CHCl_3$)] and spectral properties of synthetic **1** were identical to those of the natural product, $[\alpha]^{21}_D$ +15.0° (c 1.0, $CHCl_3$) [1].

In summary, we have described a unique synthesis of a marine tetrahydrofuran (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,9-diol based on an oxiranyl anion strategy. The advantages of using the sulfonyl-stabilized oxiranyl anion are the efficiency of the C-C bond formation, control of the 5-*endo* cyclization, and generation of the carbonyl group, which enable a stereocontrolled construction of 2,3,5-trisubstituted tetrahydrofurans.

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