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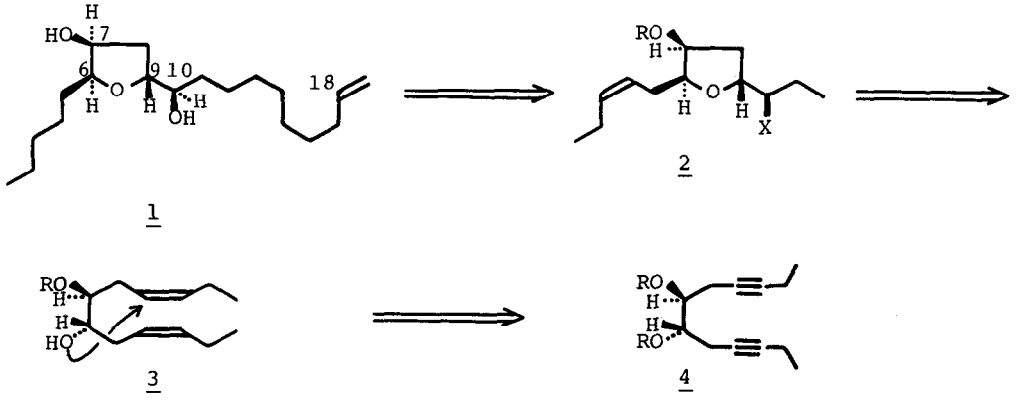
ENANTIOSELECTIVE SYNTHESIS OF (6S,7S,9R,10R)-6,9-EPOXYNONADEC-18-ENE-7,10-DIOL, A MARINE NATURAL PRODUCT

Susumi Hatakeyama, Kuniya Sakurai, Keiichi Saijo, and Seiichi Takano*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Summary: The title compound has been synthesized in enantiomerically pure form using diethyl L-tartrate as a chiral template.

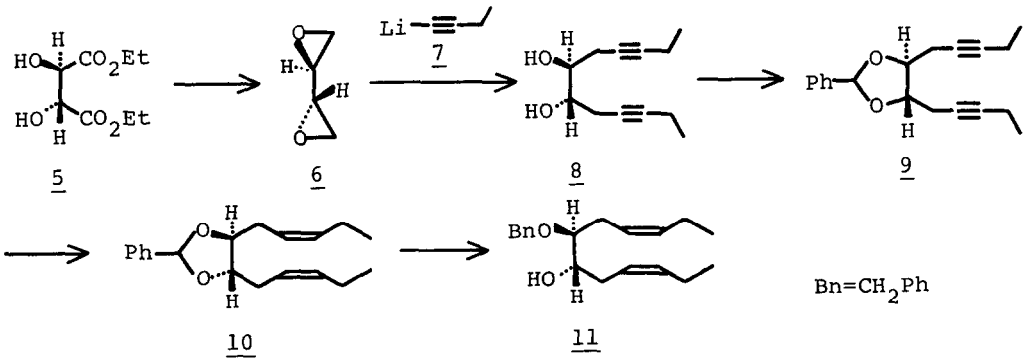
In recent years there has been an increasing interest in the synthesis of natural products possessing complex oxacyclic systems such as polyether antibiotics and marine products. One of the most challenging aspects of the synthesis of these compounds is the stereocontrolled construction of the highly substituted tetrahydrofuran units and therefore various attractive methods have been explored so far.[1] For the purpose of developing a novel chiral route to the substituted tetrahydrofuran systems, we decided to choose (6S,7S,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol (1),[2] a new lipid isolated from the brown alga (Notheia anomala),[3] as a target molecule which has a characteristic substitution pattern in its tetrahydrofuran ring system. Herein we describe an enantioselective synthesis of the marine product 1 from diethyl L-tartrate (5).

As illustrated below, our basic strategy leading to 1 centers around the compound 4. It is assumed that the C_2-symmetrical nature of 4 would allow us to construct the key tetrahydrofuran 2 having three required chiral centers through rather simple manipulations without any special tactics.



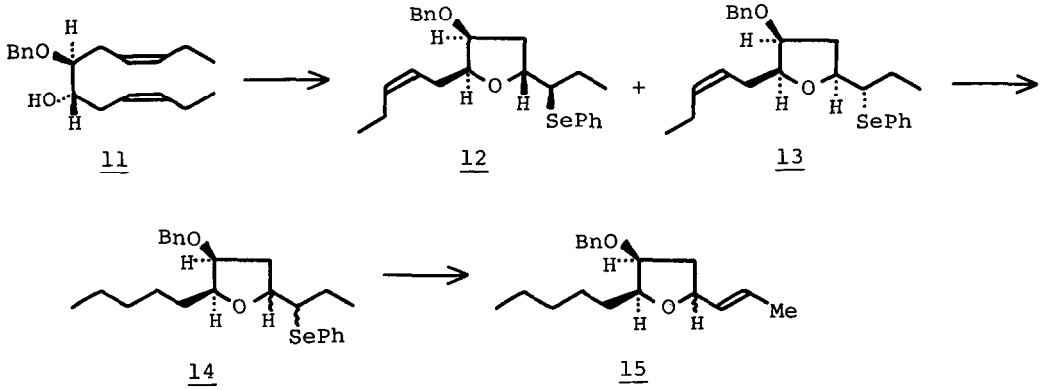
1 2 3 4

The known diepoxide 6, easily prepared from diethyl L-tartrate (5),[4] was treated with the lithium acetylide 7 in the presence of boron trifluoride etherate (THF, -78 °C)[5] to give the diol 8,[6] $[\alpha]_D$ - 13.5° (c 0.40, MeOH), which, upon benzylidene acetalization with benzaldehyde (p-TsOH, benzene, reflux), afforded the benzylidene acetal 9, $bp_{0.7}$ 170 °C (Kugelrohr), $[\alpha]_D$ + 26.4° (c 2.14, $CHCl_3$), in 72% overall yield.[7] Lindlar reduction of 9 (H_2, 5% Pd-Pb/$CaCO_3$, hexane, rt) to the cis-olefin 10, $bp_{1.0}$ 175 °C (Kugelrohr), $[\alpha]_D$ - 12.8° (c 2.64, $CHCl_3$), followed by treatment with diisobutylaluminum hydride (CH_2Cl_2, rt)[8] gave the benzyl ether 11, $bp_{0.1}$ 140 °C (Kugelrohr), $[\alpha]_D$ + 26.5° (c 1.22, $CHCl_3$) in 91% overall yield.



5 6 8 9 10 11

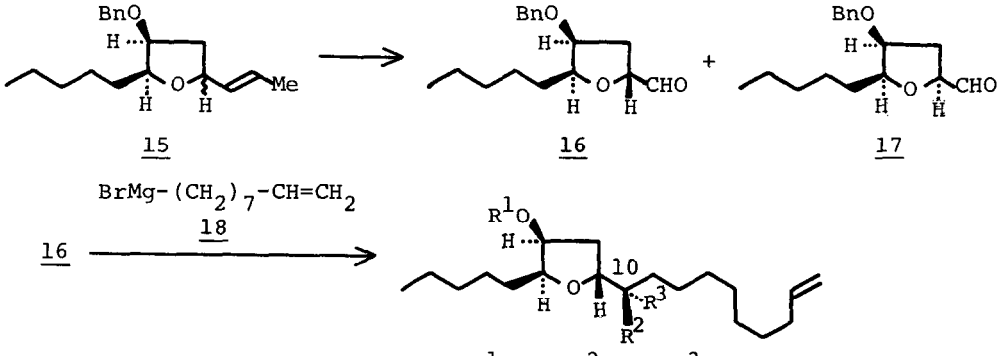
Selenoetherification[9,1a] of 11 with phenylselenyl chloride (CH_2Cl_2, -78 °C) yielded a 3 : 1 inseparable mixture of the tetrahydrofuran 12 and 13 in 89% yield.[10] Without separation, a mixture of 12 and 13 was subjected to diimide reduction using 2,4,6-triisopropylbenzenesulfonyl hydrazide[11] (THF, reflux) to give the selenide 14 which was directly converted to the olefin 15 by the conventional method[9] (30% H_2O_2, THF, rt) in 80% overall yield.



11 12 13 14 15

Since oxidative cleavage of the olefinic double bond of 15 either by ozonolysis or by Lemieux-Johnson oxidation[12] afforded the aldehyde 16 in poor yield, the following alternative route was developed. Thus, hydroxylation of the olefin 15 (10 mol % OsO_4, NMO, aq. acetone, rt)[13] followed by treatment with lead tetraacetate (THF, -30 °C) gave a 3 : 1 mixture of the aldehyde 16 and 17 in 80% overall yield. After separation of 16, $[\alpha]_D$ + 54.8° (c 0.50, $CHCl_3$), and 17,[14] $[\alpha]_D$ + 31.3° (c 0.60, $CHCl_3$), by preparative thin layer chromatography (SiO_2, 4 : 1 Et_2O-hexane), addition of excess Grignard reagent 18 (Et_2O, -78 °C)[2] led to predominant formation of the alcohol 19, $[\alpha]_D$ + 46.4° (c 1.93, $CHCl_3$), together with the 10-epi-alcohol 20, $[\alpha]_D$ + 39.1° (c 0.91, $CHCl_3$), in a ratio of 3 : 1 in 75% yield.[15] Finally, total synthesis of the marine lipid 1 was achieved by quantitative deprotection (Li, NH_3, reflux) of the benzyl ether moiety of 19. The synthetic material, mp 55-56 °C, $[\alpha]_D$ + 15.7° (c 0.69, $CHCl_3$), exhibited spectral properties (^{1}H-NMR, ^{13}C-NMR, IR, MS) in accord with those of the natural product,[3] mp 54.5-55.0 °C, $[\alpha]_D$ + 15.0° (c 1.0, $CHCl_3$).

Furthermore, the undesired 10-epi-alcohol 20 was also transformed into the desired alcohol 19 via the mesylate 21 by Corey's inversion technique[16]; (i) MsCl, Et_3N, CH_2Cl_2, rt, (ii) KO_2, DMSO, rt, in 80% overall yield.



The study outlined above demonstrates an effective chiral route to 2,5-disubstituted-3-hydroxytetrahydrofurans and further investigations for the synthesis of other natural products using this methodology are underway.

References and Notes

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Chem. Soc., 106, 2668 (1984) and references therein.

2. Recently, the synthesis of racemic 1 has been achieved brilliantly: D. R. Williams, Y. Harigaya, J. L. Moore, and A. D'sa, J. Am. Chem. Soc., 106, 2641 (1984).
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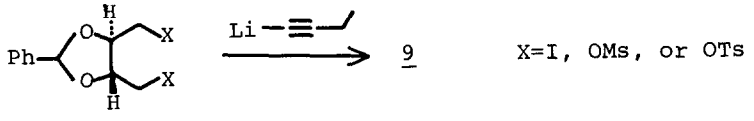
6. All new compounds gave satisfactory spectral (^{1}H-NMR, IR, MS) and analytical (high resolution MS) data.
7. The following alternative route to 9 was unsuccessfull under various conditions.



9 X=I, OMs, or OTs

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10. The ratio was determined by HPLC (column LS-320K, 2% Et_2O-hexane). The structures of 12 and 13 became certain after completion of the total synthesis of 1.
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14. Epimerization of 17 to 16 under basic conditions was unsuccessfull possibly because of instability of the aldehyde moiety.
15. In this case, the observed stereoselectivity (3 : 1) resulting from chelation-controlled Grignard reaction was somewhat low compared with the similar case reported by Williams and co-workers (6 : 1).[2]
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