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The Cyclodehydration Route to the Asymmetric Total Synthesis of the Marine Natural Product Isolated from the Brown Alga, *Notheia Anomala*

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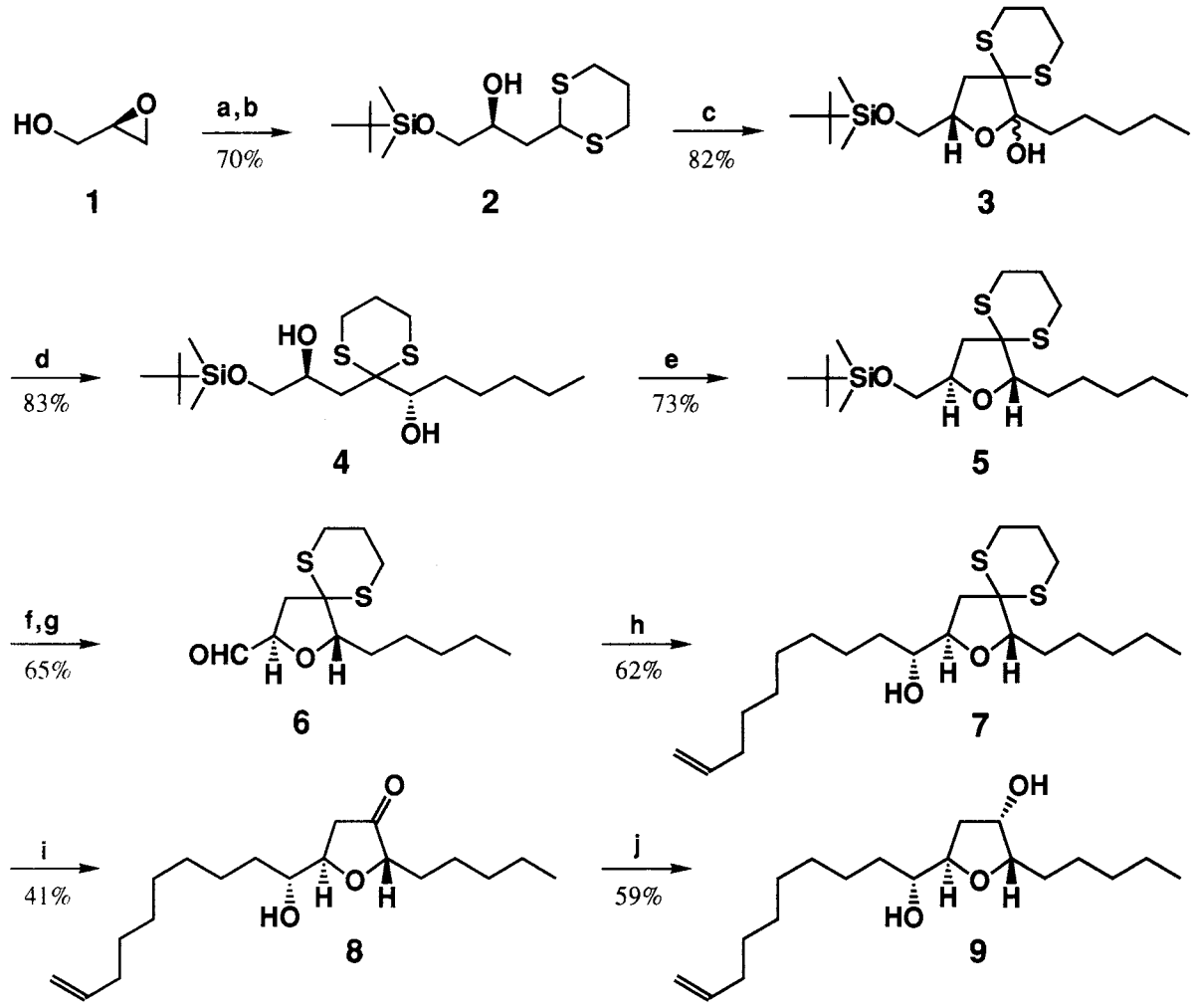
The asymmetric total synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxy-nonadec-18-ene-7,10-diol, which is a lipid diol component of the brown alga, *Notheia anomala*, was performed *via* the stereocontrolled $LiAlH_4$ reduction of the cyclic hemiketal intermediate followed by the stereospecific one-step cyclodehydration of the resulting *anti* 1,4-diol.

Tetrahydrofuran structures are frequently found on a variety of biologically interesting natural products such as macrolides, antitumor antibiotics, marine toxins, pheromones, and most commonly, polyether antibiotics, and it still continues to attract considerable attention in recent years. Although many elegant methodologies for the stereocontrolled construction of substituted tetrahydrofuran skeletons have been developed and have led to the total synthesis of these natural products, these methodologies are generally based on several fixed types of reactions[1] and have remained relatively undeveloped.[2] The stereoselective direct cyclodehydration of a 1,4-diol seems to be a natural synthetic strategy for substituted tetrahydrofurans, but such an approach has not so far been generally employed[3] because of difficulties of stereoselective facile synthesis of 1,4-diols[4] and problems on the discrimination between two secondary hydroxyl groups in a 1,4-diol molecule at the cyclization stage.[5] We have recently reported a new stereocontrolled asymmetric route to both *trans* and *cis* 2,5-substituted tetrahydrofurans based on the stereocontrolled hydride addition of cyclic hemiketals followed by the stereospecific one-step cyclodehydration of the resulting 1,4-diols.[6] In this paper, we wish to report the first example of the natural product synthesis based on this methodology, the total synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol, which is a lipid diol component of the brown alga, *Notheia anomala*.[7]

The present route to the natural product starting with (*S*)-glycidol **1** is illustrated in Scheme 1.[8] The alkylation of **1** with 2 equiv. of 2-lithio-1,3-dithiane in THF at -78 °C to 0 °C proceeded smoothly to give (*S*)-2-



Scheme 1.

a; 2-lithio-1,3-dithiane, HMPA, THF: **b**; TBDMS-Cl, imidazole, CH_2Cl_2: **c**; (i) *n*-BuLi, TMEDA, THF, (ii) HMPA, $C_5H_{11}CO_2Me$, THF: **d**; $LiAlH_4$, THF, -78 °C: **e**; *p*-TsCl, pyridine, r.t.: **f**; AcOH, acetone-water: **g**; DMSO, $(COCl)_2$, CH_2Cl_2: **h**; $C_9H_{17}MgBr$, ether, -78 °C: **i**; HgO, $BF_3 \cdot OEt_2$: **j**; $NaBH_4$, EtOH, -78 °C.

(2',3'-dihydroxypropyl)-1,3-dithiane. The terminal hydroxyl group of this diol could be selectively protected as a *tert*-butyldimethylsilyl (TBDMS) ether by the treatment with TBDMS-Cl and imidazole in CH_2Cl_2 at room temperature to afford the alcohol **2** in 70% yield from **1**. The optical purity of **2** was determined to be 92% e.e. by ^1H NMR analysis of the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester.[9] The dianion[10] produced from **2** by treating with 2.2 equiv. of *n*-BuLi was acylated with methyl hexanoate in the

presence of HMPA to give the cyclic hemiketal **3** in 62% yield. To obtain the *anti* diol **4**, we examined the reduction of **3** with $LiAlH_4$ in THF at -78 °C. As expected from our previous work,[6] the *anti* product **4** was obtained in excellent stereoselectivity (11.2:1). The relative stereochemistry of **4** was disclosed to be *anti* after its transformation into the corresponding tetrahydrofuran by employing the stereospecific one-step cyclodehydration with *p*-TsCl in pyridine at room temperature.[6] The *trans* isomer **5** was thus obtained from **4** in 73% yield without epimerization and racemization. The desilylation of **5** with acetic acid in aqueous acetone followed by the Swarn oxidation of the resulting alcohol gave the aldehyde **6** in 65% overall yield. The alkylation of **6** with 1-nonenyl magnesium bromide[11] in THF at -78 °C gave the alcohol **7** with the desired stereochemistry as the major product in 3.5:1 selectivity,[12] which was then hydrolyzed with HgO and BF_3•OEt_2 in aqueous THF to afford the hydroxy ketone **8** in 41% yield. Finally, the $NaBH_4$ reduction of **8** in ethanol at -78 °C gave the diol **9** with the desired stereochemistry as the major product in 4.2:1 selectivity.[12] Spectroscopic data of this compound were in good agreement with the reported ones.[13] Specific rotation of the diol **9**, $[a]_D^{23}$ +14.1° (c 0.2, $CHCl_3$), showed a somewhat smaller value than the reported one, $[a]_D^{21}$ +15.0° (c 1.00, $CHCl_3$).[13] Based on these findings, the optical purity of the synthesized **9** was estimated to be 94% e.e. which is comparable to that of the alcohol **2** (92% e.e.).

In summary, we have described a novel and convenient route for the total synthesis of the natural product, (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol, *via* the stereocontrolled $LiAlH_4$ reduction of the dithioacetal-functionalized chiral cyclic hemiketal **3** followed by the stereospecific one-step cyclodehydration of the resulting dithioacetal-functionalized chiral *anti* 1,5-diol **4** to the *trans* tetrahydrofuran **5**. It should be noted that the reliability of the stereoselectivity and the stereospecificity of our methodology previously reported was reconfirmed by the results of the present asymmetric total synthesis.

References

1) The methods with acyclic substrates can be fundamentally classified into either an intramolecular addition of γ,δ-unsaturated alcohols or an intramolecular substitution of γ,δ-epoxy alcohols: See also, Ref. 2.

2) As reviews, see: A. S. Rao, S. K. Paknikar, and J. G. Kirtane, *Tetrahedron*, **39**, 2323 (1983); T. L. B. Boivin, *ibid.*, **43**, 3309 (1987); D. S. Brown, S. V. Ley, and M. Bruno, *Heterocycles*, **28**, 773 (1989).

3) As an exception, stereospecific cyclodehydration of 1,4-diols has been efficiently utilized for the synthesis of highly substituted tetrahydrofurans: D. R. Williams, J. G. Phillips, and B. A. Barner, *J. Am. Chem. Soc.*, **103**, 7398 (1981); D. R. Williams and J. G. Phillips, *Tetrahedron*, **42**, 3013 (1986).

4) 1,4-Asymmetric induction by nucleophilic additions to chiral alkoxy aldehydes would be a convenient, useful, and standard route for the stereoselective construction of 1,4-diols, but an efficiently controlled method based on this methodology is rare: M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.*, **22**, 989 (1983).

5) Although cyclodehydration processes of 1,n-diols to the corresponding cyclic ethers have been previously reported, these procedures are not exempted from these problems: J. C. Martin, J. A. Franz, and R. J. Arhart, *J. Am Chem. Soc.*, **96**, 4604 (1974); A. Molnar, K. Felfoldi, and M. Martok, *Tetrahedron*, **37**, 2149 (1981); D. Kotkar, S. W. Mahajan, and A. K. Mandal, and P. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1749.

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8) (*S*)-Glycidol **1** was prepared from (*S*)-malic acid according to the literature procedure: D. L. Boger and J. S. Panek, *J. Org. Chem.*, **46**, 1208 (1981).

9) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

10) We have already used a similar dianion of 1-(1,3-dithiane-2-yl)-2-propanol in the stereoselective synthesis of insect pheromone isomers: H. Chikashita, E. Kittaka, Y. Kimura, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 833 (1989).

11) 9-Bromo-1-nonene was prepared from commercially available 6-bromo-1-hexanol *via* allylation with allyl magnesium bromide catalyzed by Li_2CuCl_4 (M. Tamura and J. Kochi, *Synthesis*, **1971**, 303) and bromination with PBr_3.

12) Selectivities of these reactions have not yet been optimized.

13) D. R. Williams, Y. Harigaya, J. L. Moore, and A. D'sa, *J. Am. Chem. Soc.*, **106**, 2641 (1984).

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