Stereocontrolled Preparation of Cyclic Xanthate; a Novel Synthetic Route to 4-Thiofuranose and 4′-Thionucleoside

Jun'ichi Uenishi,* Mitsuhiro Motoyama, Yoshitaka Nishiyama and Shoji Wakabayashi

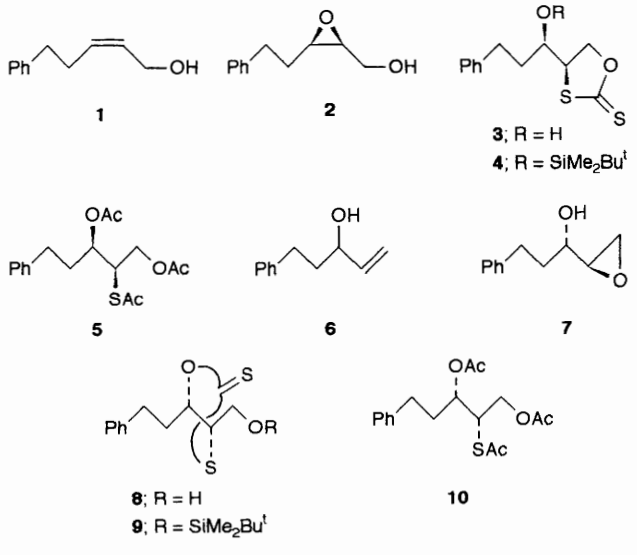
Department of Chemistry, Okayama University of Science, Ridaicho, Okayama 700, Japan

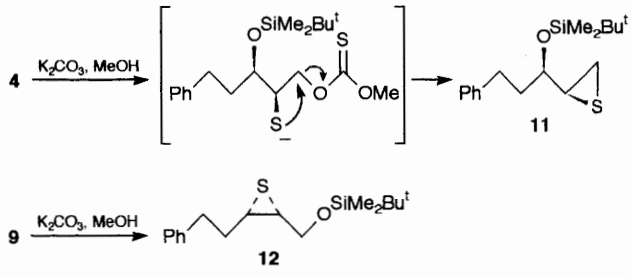
Optically active cyclic xanthate was prepared by the reaction of an epoxy alcohol with NaH and CS_2, and was found to be a useful intermediate for synthesis of 4-thio-2-deoxyribose and 4′-thio-2′-deoxyribonucleoside.

Since optically active epoxy alcohols have been obtained easily by the asymmetric epoxidation of allylic alcohol,[1] regio- and stereo-specific ring opening reactions to 2,3-epoxy alcohol by various types of nucleophiles, intramolecularly[2] or intermolecularly,[3] have provided useful synthetic tools as an optically active form.[4]

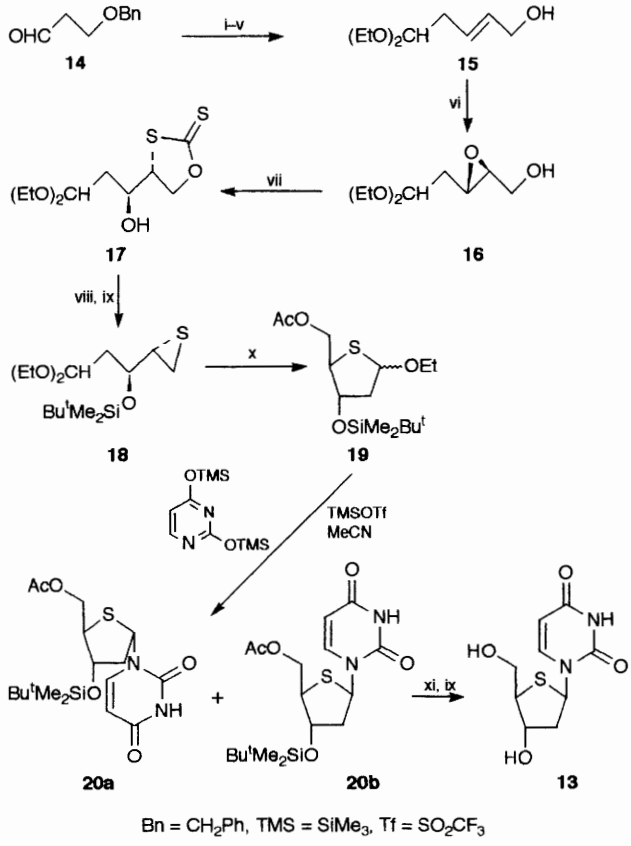
We now report a novel ring opening reaction of optically active epoxy alcohol by xanthate anion to give α-hydroxy cyclic xanthate, which provides a new method to introduce sulphur functions to epoxy alcohols, for example 2-mercapto-1,3-diols and α-hydroxyepisulphides, as optically active forms. Synthesis of 4-thio-2-deoxyribose was accomplished using this methodology.

The Sharpless epoxidation of *cis*-allylic alcohol **1** was carried out by the reaction of (+)-diethyl tartrate, $Ti(OPr^i)_4$ and Bu^tO_2H to give epoxy alcohol **2**† in 80% yield with 95% e.e.‡ Treatment of **2** with NaH or KH in CS_2 and tetrahydrofuran (THF) (1 : 2) at −78 °C, followed by warming up the reaction to −30 °C for 30 min gave cyclic xanthate **3** in 73% yield as a single stereoisomer. This stereospecific reaction involves initial formation of a sodium or potassium xanthate anion followed by the epoxide ring opening from the back side of the epoxide in a 5-*exo*-tetragonal fashion. Silylation of secondary alcohol **3** with trimethylsilyl trifluoromethane-sulphonate (TMSOTf) gave silyl ether **4** in 79% yield. Then the following four steps from **4**, (*i*) reductive hydrogenolysis with $LiAlH_4$; (*ii*) acetylation by Ac_2O in pyridine; (*iii*) desilylation with Bu^n_4NF; (*iv*) acetylation by Ac_2O in pyridine, afforded triacetate **5** ($[\alpha]_D^{24}$ +6.1°, *c* 1.0, chloroform) in 35% yield. However, the kinetic resolution[1] of allylic alcohol **6** with (+)-diethyl tartrate, $Ti(OPr^i)_4$ and Bu^tO_2H gave epoxy alcohol **7** in 35% yield with 85% e.e. The ring opening reaction of **7** by KH and CS_2 gave cyclic xanthate **8** in 81% yield. Taking the same reaction sequence as described for the synthesis of **5**, the xanthate **8** afforded triacetate **10** ($[\alpha]_D^{24}$ −5.9°, *c* 1.0, chloroform) in five steps, which corresponded to an enantiomer of **5**. Methanolysis of





Scheme 1



Scheme 2 *Reagents and conditions*: i, $(EtO)_3CH$, $ZnCl_2$, room temp.; ii, Li, liq. NH_3, −78 °C; iii, the Swern oxidation; iv, Ph_3PCHCO_2Me, benzene, room temp. and separation of *E*- and *Z*-isomers by silica gel column chromatography; v, diisobutylaluminium hydride, CH_2Cl_2, −78 °C; vi, Bu^tO_2H, $Ti(OPr^i)_4$, (+)-diethyl tartrate, CH_2Cl_2, −20 ~0 °C; vii, KH, CS_2, THF, −78 ~ −40 °C; viii, $TfOSiMe_2Bu^t$, 2,6-lutidine, CH_2Cl_2, room temp.; ix, K_2CO_3, MeOH, room temp.; x, AcONa, AcOH, 100 °C; xi, Bu^n_4NF, THF, room temp.

† All new compounds reported here gave satisfactory spectroscopic data (NMR, IR, mass and optical rotation).

‡ Enantiomeric excess (e.e.) was determined by NMR spectroscopy or HPLC analysis after transformation of the epoxy alcohol to the corresponding (+)-MTPA esters (MTPA = α-methoxy-α-trifluoromethylphenylacetic acid).

cyclic xanthate **4** in the presence of anhydrous potassium carbonate in methanol gave terminal episulphide **11** quantitatively *via* the thiolate anion intermediate shown in Scheme 1. Internal episulphide **12** was also obtained from cyclic xanthate **9** in 80% yield.

In searching for new antiviral drugs, the structure–activity relationships of nucleoside type compounds have been studied. Particularly, chemical modifications of the furanose part in nucleosides to other heterocycles have recently been made.[5] Tetrahydrothiophene is an example of this class of compounds. However, no attention has been given to the optically active thia analogue of 2-deoxyribonucleoside except for the recent one,[6] since a practical method to obtain the optically active 2-mercapto-1,3-diols unit had not been established. The above result now allows a practical synthesis of optically active 4′-thio-2′-deoxyribouridine **13**. Allylic alcohol **15** was obtained from 3-benzyloxypropanal **14** in five steps (63%) by general procedures *via* 3,3-bisethoxypropanal. The Sharpless asymmetric epoxydation afforded epoxy alcohol **16** ($[\alpha]_D^{24}$ −44.7°, *c* 1.0, chloroform) in 69% yield with more than 95% e.e. Epoxide opening by KH and CS_2 gave the key cyclic xanthate **17** ($[\alpha]_D^{24}$ −40.9°, *c* 1.0, chloroform) in 86% yield. Silylation and episulphide formation provided **18** in 90% yield by two steps. Treatment of γ,γ-diethoxy episulphide with sodium acetate in acetic acid at 100 °C afforded **19** in 87% yield as a 1:1 mixture of diastereoisomers at the C-1 anomeric position, which were separable on silica gel column chromatography. TMSOTf mediated glycosidation[7] of **19** (α:β = 1:1) with bis(trimethylsilyloxy)pyrimidine was carried out in CH_2Cl_2 at room temperature to give diastereoisomers, **20a** ($[\alpha]_D^{24}$ −30.1°, *c* 1.0, ethanol) and **20b** ($[\alpha]_D^{24}$ +22.1°, *c* 1.0, ethanol) in 23 and 35% yields, respectively. Removal of protecting groups in the β-isomer **20b** was performed in two steps, desilylation by Bu^n_4NF in THF and hydrolysis by K_2CO_3 in methanol, furnishing the synthesis of **13** ($[\alpha]_D^{24}$ +61.5°, *c* 1.0, ethanol) in 75% yield.

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References

1 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974; V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.
2 N. Minami, S. S. Ko and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 1109; W. R. Roush and R. J. Brown, *J. Org. Chem.*, 1982, **47**, 1371.
3 M. Caron and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 1557; C. H. Behrens and K. B. Sharpless, *Aldrichimica Acta*, 1983, **16**, 67.
4 A. Pfenninger, *Synthesis*, 1986, 89.
5 R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17; M. F. Jones, S. A. Noble, C. A. Robertson and R. Storer, *Tetrahedron Lett.*, 1991, **32**, 247; M. J. Bamford, D. C. Humber and R. Storer, *Tetrahedron Lett.*, 1991, **32**, 271; D. M. Huryn, B. C. Sluboski, S. Y. Tam, L. J. Tadaro and M. Weigele, *Tetrahedron Lett.*, 1989, **30**, 6259; D. W. Norbeck, S. Spanton, S. Broder and H. Mitsuya, *Tetrahedron Lett.*, 1989, **30**, 6263.
6 Just before submitting this manuscript, Professor R. T. Walker published the synthesis of 4′-thio-2′-deoxyribonucleoside; see M. R. Dyson, P. L. Coe and R. T. Walker, *J. Chem. Soc., Chem. Commun.*, 1991, 741 and the reference 6.
7 H. Vorbruggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234.