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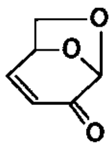
SYNTHESIS OF 1,6-ANHYDRO-2-CHLORO-2,3,4-TRIDEOXY-β-D-*erythro*-HEX-3-ENOPYRANOSE AND ITS STEREOSPECIFIC S$_N$2' SUBSTITUTION

Masakatsu Matsumoto*, Hiromi Ishikawa, Yoshihiro Soya, and Takayuki Ozawa
Department of Materials Science, Kanagawa University
Tsuchiya, Hiratsuka, Kanagawa 259-12, Japan

Abstract-------The chlorination of 1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (2) with $SOCl_2$ and pyridine gives predominantly 1,6-anhydro-2-chloro-β-D-*erythro*-hex-3-enopyranose (3). The chloride (3) takes place exclusively the suprafacial S$_N$2' substitution with a variety of nucleophiles in DMF. "Cerny epoxides" are conveniently synthesized by using the reaction of 3 with $PhCH_2ONa$.

Levoglucosenone (1) is a pyrolytic product of cellulose and is now attracting considerable interests as a chiral source of both carbohydrate and non-carbohydrate derivatives.[1] The reduction of the carbonyl of **1** leads stereospecifically to 1,6-anhydro-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose (2), which has been used to the synthesis of carbohydrates such as D-allosan.[2] We describe here that a) the alcohol (2) is predominantly chlorinated to 1,6-anhydro-2-chloro-β-D-*erythro*-hex-3-enopyranose (3), b) the chloride (3) undergoes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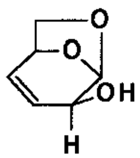
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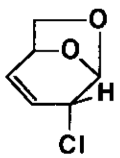
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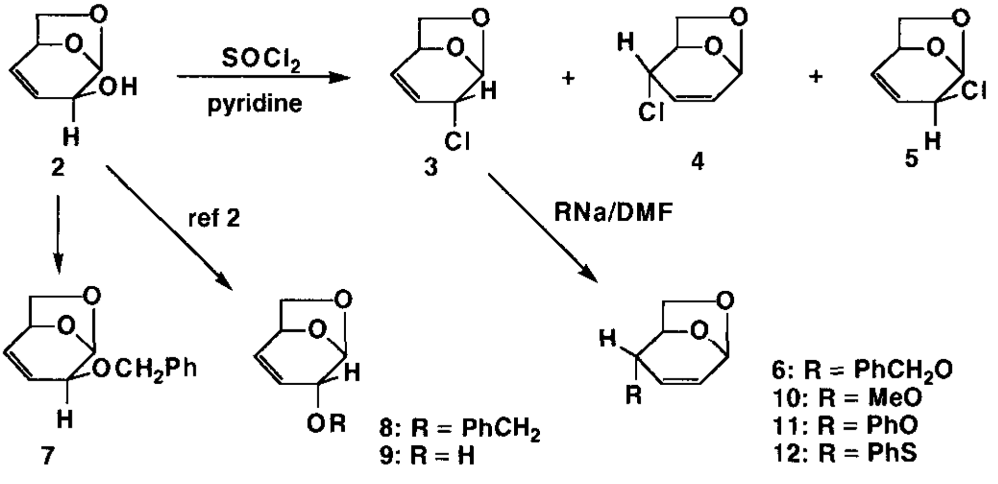
stereospecific S_N2' substitution with various nucleophiles, and c) by means of the present reaction "Cerny epoxides" are easily synthesized.

When the alcohol (2) (5.0 g, 39.1 mmol) was stirred with pyridine (12.4 g, 0.16 mol) and $SOCl_2$ (4.3 ml, 58.7 mmol) in $CHCl_3$ (20 ml) at refluxing temperature for 1 h, a mixture of 1,6-anhydro-2-chloro-β-D-*erythro*-hex-3-enopyranose (3) and its isomers (4) and (5) was produced in 72% yield (**3** : **4** : **5** = 74 : 20 : 6).[3] These chlorides were easily separated by chromatography on silica gel. The structures of the chlorides (3-5) were determined by decoupling experiments of ^{1}Hnmr and ^{13}Cnmr.[4] The chlorination of **3** with $SOCl_2$ was further examined under various conditions using $CHCl_3$, ether, THF, or CH_2Cl_2 as a solvent, and pyridine, triethylamine or 4-(*N,N*-dimethylamino)pyridine as a base; among them, the combination of THF and pyridine gave the most stereospecific chlorination to **3** (**3** : **4** : **5** = 83 : 13 : 4), though the yield was less favorable (39%). The chlorination without base gave scarcely fruitful results to yield **5** through S_Ni substitution.

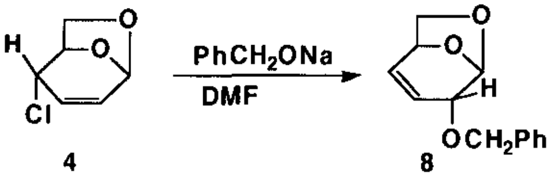


When the chloride (3) (1.00 g, 6.8 mmol) was reacted with benzyl alcohol (1.11 g, 10.2 mmol) in the presence of NaH (60%, 10.2 mmol) in DMF (10 ml) under a nitrogen atmosphere at room temperature for 2 h, a benzyl ether (6) formed as the sole product in 97% isolated yield. The structure was determined by its spectral analysis[5-7] and by comparing its spectral and physical properties with those of the authentic isomers (7) and (**8**), which were not detected in the present reaction. The S_N2 substitution of **3** should lead to **7**, which is prepared by the usual benzylation of 2. If the substitution proceeds through the corresponding allylic carbocation, the chloride (3) should afford more or less the ether (8), which is synthesized from 2 through an isomeric alcohol (9) obtained by the use of Mitsunobu reaction.[2] Thus the results revealed that the nucleophile $PhCH_2O^-$ attacks the chloride (3) completely from its *exo* site in S_N2' mode.

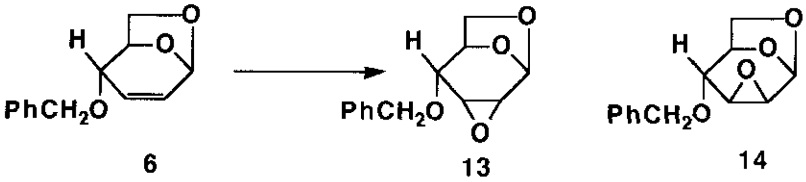
The substitution of 3 was further examined by using MeONa and PhONa. Both cases gave also exclusively the corresponding suprafacial S_N2' products (**10**) and (**11**). The treatment of 3 with t-BuOK resulted in the recovery of the starting material. The anion of thiophenol reacted similarly with 3 to afford the substitution products (**12**) in 55% isolated yield.

The racemic Br-analogue of 3 has already been synthesized and reported[8] to react with the nucleophiles such as OH^- and MeO^-; unlike the chloride (3), the bromide undergoes the nucleophilic substitution at the 2-position as well as the 4-position through an allylic carbocation. On the other hand, an unstable tosylate of 9 has been reported to undergo S_N2' substitution with $PhCH_2O^-$ to afford 6 in moderate yield.[9]

The regio- and stereospecificity for the nucleophilic substitution of the chloride (3) are well explained as follows; the S_N2 substitution of the quasiaxial chloride is hindered by the 1,6-anhydro bridge, and/or by the oxygens of the acetal group.[9] Here, we found an interesting fact in the substitution of the isomeric chloride (4). When the chloride (4) (100 mg, 0.68 mmol) was treated with $PhCH_2ONa$ (benzyl alcohol 0.11 g, 1.0 mmol and 60% NaH, 1.0 mmol) in DMF (1 ml) under a nitrogen atmosphere at room temperature for 2 h, the benzyl ether (8) was produced in 95% isolated yield. Thus, the substitution of 4 takes place also completely with suprafacial allylic rearrangement. The fact is significantly different from the case of ethyl 2,3-dideoxy-4,6-di-*O*-methylsulfonyl-α-D-*erythro*-hex-2-enopyranoside,[10] for which the substitution occurs with Walden inversion (S_N2), and from the case of 1,6-anhydro-2-*O*-methylsulfonyl-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose,[11] whose nucleophilic substitution proceeds sluggishly at the 2-position. The difference between the case of 4 and the former is due to that the β- (*endo*) site of bicyclic 4 is more congested than the case of ethyl 2,3-dideoxy-4,6-di-*O*-methylsulfonyl-α-D-*erythro*-hex-2-enopyranoside. The fact that the S_N2' substitution takes place smoothly at the 2-position of 4 suggests that the acetal oxygens do not essentially prevent a nucleophile from attacking at the 2-carbon; in the case of **4**, the carbon at the 2-position is sp^2 so that it is less hindered than the 2-carbon (sp^3) of 1,6-anhydro-2-*O*-methylsulfonyl-3,4-dideoxy-β-D-*threo*-hex-3-enopyranose.



The present results disclosed a convenient synthesis of 1,6-anhydro-2-chloro-β-D-*erythro*-hex-3-enopyranose and its stereospecific nucleophilic substitution. Last, we should like to note that the epoxidation of benzyl ether (**6**) leads to the Cerny epoxides (**13**) and (**14**) which are versatile intermediates to synthesize a variety of carbohydrates.[12-14]



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REFERENCES AND NOTES

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2. K. Matsumoto, T. Ebata, K. Koseki, H. Kawakami, and H. Matsushita, *Heterocycles*, 1991, **32**, 2225.
3. The ratio of the chlorides(**3**, **4**, and **5**)was measured by ^{1}Hnmr.
4. **3**: colorless oil; $[\alpha]_D^{25}$ -252° (c 0.1, CHCl$_3$); ^{1}Hnmr (400 MHz, CDCl$_3$) δ 3.77 (d,J=0.98 Hz, 1H), 3.78 (s, 1H), 4.08 (dd, J=3.90 and 0.98 Hz, 1H), 4.77 (ddd, J=4.88, 3.90, and 1.96 Hz, 1H), 5.63 (br s, 1H), 5.82 (ddd, J=9.76, 3.90, and 1.96 Hz, 1H), 6.18

(ddd, J=9.76, 4.88, and 0.98 Hz, 1H) ppm; ir (liq. film) 2971, 2894, 1639 cm^{-1}; mass (m/z, %) 146 (M$^+$, 1), 117 (19), 83 (78), 81 (100). **4**: colorless needles melted at 37°C (from ether-hexane); $[\alpha]_D^{25}$ +366° (c 0.07, $CHCl_3$); ^{1}Hnmr (400 MHz, $CDCl_3$) δ 3.56 (dd, J=8.30 and 1.96 Hz, 1H), 4.02 (dd, J=8.30 and 6.35 Hz, 1H), 4.17 (dt, J=4.40 and 0.98Hz, 1H), 4.78 (dtd, J=6.35, 1.96, and 0.98 Hz,1H), 5.60 (dd, J=3.42 and 0.98Hz, 1H), 5.85 (dddd, J=9.28, 4.40, 1.96, and 0.98 Hz, 1H), 6.05 (ddd, J=9.28, 3.42, and 0.98 Hz, 1H) ppm. **5**: colorless oil; $[\alpha]_D^{25}$ +2.6° (c 0.07, $CHCl_3$); ^{1}Hnmr (400 MHz, $CDCl_3$) δ 3.97 (ddd, J=8.30, 5.86, and 1.47 Hz, 1H), 4.30 (dd, J=8.30 and 1.96 Hz, 1H), 4.63 (m, 1H), 5.01 (m, 1H), 5.53 (d, J=2.93 Hz, 1H), 5.73 (dt, J=9.77 and 1.96 Hz, 1H), and 5.94 (ddd, J=9.77, 2.93, and 1.96 Hz, 1H) ppm.

5. **6**: colorless leaflets melted at 55.5 °C (lit.,[6] 56-57°C) (from ether-hexane); $[\alpha]_D^{25}$ +155° (lit.,[6] +155°, lit.,[7] +149°).
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7. H. B. Mereyala, K. C. Venkataramanaiah, and V. S. Dalvoy, *Carbohydr. Res.*, 1992, **225**, 151.
8. K. Ranganayakulu and R. K. Brown, *J. Org. Chem.*, 1974, **39**, 3941.
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10. R. J. Ferrier and N. Vethaviyaser, *J. Chem. Soc. C*, **1971**, 1907.
11. The substitution of the mesylate of **2** with a nucleophile such as $PhCH_2O^-$, MeO^-, and PhO^- occurred scarcely in DMF at elevated temperature. On the other hand, the Mitsunobu reaction[2] of **2** and the present chlorination proceed smoothly.
12. M. Cerny, T. Trnka, P. Beran, and J. Pacak, *Coll. Czech. Chem. Comm.*, 1969, **34**, 3377.
13. G. Lauer and F. Oberdorfer, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 272. See also ref. therein.
14. We also carried out the epoxidation of **6** with *m*-chloroperbenzoic acid in CH_2Cl_2 to give **13** in 62% yield.

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