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A NOVEL METHOD FOR THE SYNTHESIS OF 2-DEOXYDISACCHARIDE BY STEREOSELECTIVE CYCLIZATION OF THE ACYCLIC PRECURSOR

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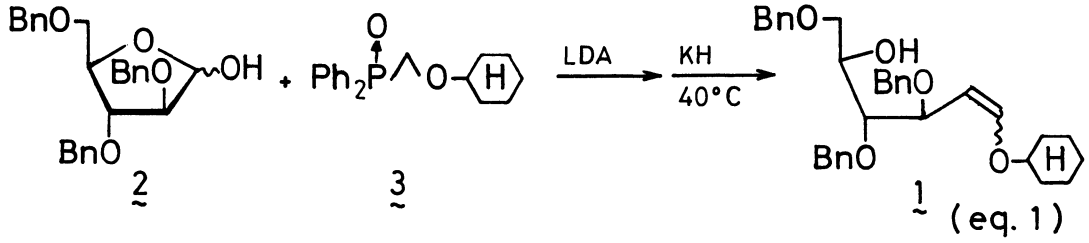
Stereoselective cyclization of (Z)-(2R,3R,4R)-6-cyclohexyloxy-1,3,4-tribenzyloxy-5-hexen-2-ol (1) promoted by $Hg(OCOCF_3)_2$, followed by reductive work up gave the 2-deoxy-α-hexopyranoside derivative almost exclusively. On the other hand, a predominant formation of the β-anomer was achieved by the treatment of 1 with PhSeCl, and the successive deselenation.

There have been isolated a number of natural products containing 2-deoxyglycoside moiety, some of which have pronounced antitumor or antibiotic activities. While most of them have the α-linkage, such as anthracyclines,[1a] orthosomycin[1b] or macrolide antibiotics,[1c] the compounds with β-linkage are also known, such as everninomicins.[1d] For this reason, the stereoselective synthesis of 2-deoxyglycoside is one of the current interests in synthetic organic chemistry, and various methods for this structural unit have been reported. Since the absence of the neighboring group at C-2 renders the common glycosidation reaction non-stereospecific,[2] most of the methods for the synthesis of this linkage known to date are based on the addition of the alcohols to glycals resulting in the predominant formation of the α-glycosides.[3]

In this communication we wish to describe a novel method of 2-deoxyglycoside synthesis by way of the stereoselective cyclization of the acyclic precursor, (Z)-(2R,3R,4R)-6-cyclohexyloxy-1,3,4-tribenzyloxy-5-hexen-2-ol (1), leading to the selective formation of the α- and β-anomers by the proper choice of the reagent for the activation of the enol ether.

The model precursor 1 was prepared from 2,3,5-tri-O-benzyl-D-arabinose (2)[3] according to the following procedure (eq. 1). Cyclohexyloxymethyldiphenylphosphine



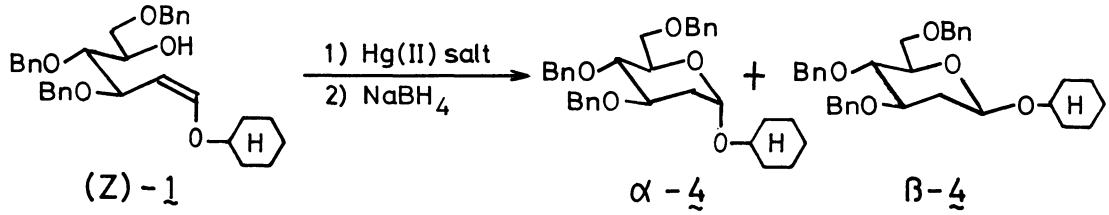
oxide[4] (3) was lithiated[5] with LDA in THF (0°C, 10 min), and admixed with lithium salt of 2 at -78°C, and then stirred at 0°C for further 3 hr. After usual work-up, the resulting phosphine oxide adduct was treated with excess (∿ 4

equiv.) KH in THF (40°C, 30 min) to afford the enol ether 1 as an E-Z mixture, which was separated with silica-gel Lobar column chromatography (hex-AcOEt, 75% Z:E = 2:1).[6]

Using the model compound 1 thus prepared, we investigated the cyclization reaction promoted by electrophilic activating agent. Among the various reagent examined, Hg(II) and $PhSe^+$ induced cyclizations showed a marked contrast in their stereoselectivity.

In the first place, the Hg(II) induced cyclization was investigated. The enol ether (Z)-1 was treated with several kinds of Hg salts, and reductively worked up with $NaBH_4$. The results are summarized in Table 1.

Table 1. Hg(II) Induced Cyclization of (Z)-1



(Z)-1 α-4 β-4

Entry[a]	Hg(II) salt	Temp.(°C)	Yield(%)	α/β [c]
1	$Hg(OAc)_2$	0	48	85/15
2		-42	55	90/10
3		-78	25	91/ 9
4	$Hg(OCOCF_3)_2$	-42	60	93/ 7
5		-78	70	96/ 4
6	$HgBr_2$	-78	40	39/61

a) All reactions were carried out in THF under an argon atmosphere and protected against light.
b) Products gave satisfactory IR and NMR spectra.[8]
c) Ratio was determined by HPLC analysis.

It is noted that the extremely rapid cyclization takes place even at the temperature as low as -78°C, due to the proximity effect of the internal nucleophile. Concerning the stereoselectivity, $Hg(OCOCF_3)_2$ gave better result than $Hg(OAc)_2$, and cyclohexyl-3,4,6-arabino-2-deoxy-α-D-hexopyranoside (α-4) was obtained in high stereoselectivity. In all run except for entry 6, a small amount of oxygenated product was isolated, which is possibly ascribable to a side reaction shown in ref. 7).

Typical procedure of the $Hg(OCOCF_3)_2$ induced cyclization is as follows: Under an argon atmosphere with protection from light, to a THF (5 ml) solution of (Z)-1 (103 mg, 0.2 mmol) was added a THF (5 ml) solution of $Hg(OCOCF_3)_2$ (89 mg, 0.21 mmol) at -78°C, and the resulting mixture was stirred for 3 hr. To this solution was added a 1 N NaOH solution of $NaBH_4$ (15 mg, 0.4 mmol) and stirred for a further 3 hr at r.t. The solution was dried over anhydrous Na_2SO_4 and filtered through a Celite pad. After evaporation of the solvent, the resulting mixture was purified with silica-gel thin layer chromatography to afford the glycoside 4 (72 mg, 70%).

Thus, the α-glycoside was obtained stereoselectively from the precursor (Z)-1.

On the other hand, cyclization of (E)-1 was less stereoselective under any condition examined to result in the predominant formation of α-4 (α/β = 1/1 ∿ 7/3). From these observations, the stereochemical course of the reaction may rationalized in terms of two factors, i) the conformation of the intermediates and ii) the anomeric effect. Namely, the intermediate "mercurinium ion" prefers a chair-like form, and the anomeric effect is co-operative when starting from (Z)-1 (Fig. A) leading

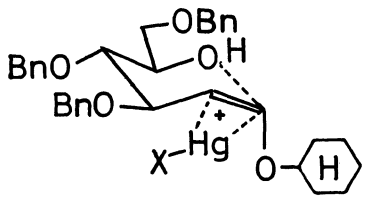


Fig. A

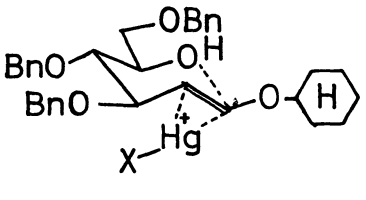
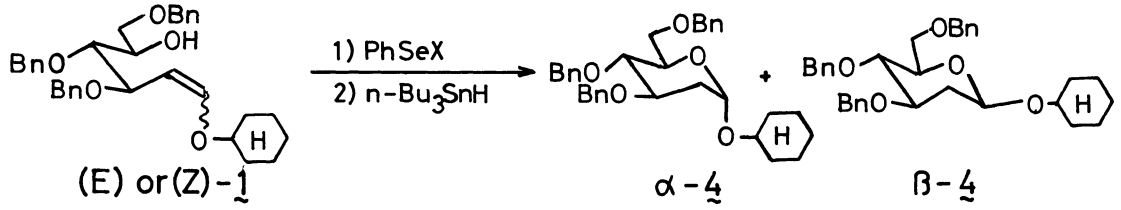


Fig. B

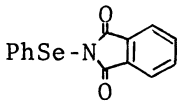
to the highly stereoselective cyclization, while it is not the case for (E)-1 (Fig. B). In addition, it was shown that the α-anomer becomes the predominant product also in the case of (E)-1. This suggests that the transition state is rather product-like and the dominant factor in controlling the stereochemistry is the anomeric effect.

Next, the "$PhSe^+$" induced cyclization was examined. The precursor 1 was treated with several kinds of organoselenium reagents, and the resulting seleno-adduct was reduced with n-Bu_3SnH. The results are shown in Table 2.

Table 2. PhSeX Induced Cyclization of 1



(E) or (Z)-1 α-4 β-4

Entry	1	PhSeX	Yield(%)	α/β
1	E	 9)	81	85/15[a]
2	Z		83	60/40[a]
3	E	PhSeCl	70	86/14[b]
4	Z		75	20/80[b]
5	Z		71	30/70[c]
6	Z		63	53/47[c]
7	Z		44	70/30[d]
8	Z	PhSeBr	75	30/70[b]

a) Reaction was carried out in acetonitrile at r.t.
b) Reaction was carried out in CH_2Cl_2 at -78°C.
c) Reaction was carried out in the presence of CsF (-78°C, entry 5) and 2,6-lutidine (0°C, entry 6) in CH_2Cl_2.
d) Reaction was carried out in THF at -78°C.

In contrast with the case of Hg(II), described above, the $PhSe^+$ induced cyclizations furnished α-4 from (E)-1 and β-4 from (Z)-1, with good stereospecificity (entry 3, 4), formally through the boat-like transition state. However, the case is not so simple and the selenoadducts which are not anticipated from anti-addition were also isolated, depending on the reaction conditions. The presence of the acid captors (entry 5, 6) had no marked effect on the stereoselectivity. Although the precise mechanism is far from clear at present, the PhSeCl induced cyclization of 1 gave α or β adduct stereospecifically depending on the configuration of the precursor 1.

Thus, in the cyclization of (Z)-1, the nature of the reaction promotors has a great influence on the stereochemical outcome to result in the selective formation of the α glycoside, or the β anomer which is not accessible by the glycal methods. These ring closure processes open a new possibility of the 2-deoxy-disaccharide synthesis, and extensive work along this line is underway in our laboratory.

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1) a) F. Arcamone, "Topics in Antibiotic Chemistry" Vol. 2, P.G. Samms Ed., p. 100, Ellis Horwood, Sussex. b) D.E. Wright, Tetrahedron, 35, 1207 (1979). c) S. Umezawa, MTP Int. Rev. Sci. Org. Chem. Ser. Two, 7, 145 (1976). d) A.K. Ganguly, pp. 59-98 in ref. 1a).

2) A.F. Bochkov and G.E. Zaikov, "Chemistry of the O-Glycosidic Bond", Pergamon, 1979, and references cited therein.

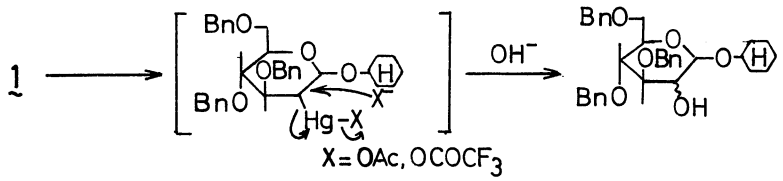
3) For example, R.U. Lemieux and S. Levine, Can. J. Chem., 42, 1473 (1964); S. Honda, K. Kakei, H. Takei, and K. Takiura, Carbohydr. Res., 29, 477 (1973); S. Honda, K. Kakei, and K. Takiura, ibid., 29, 488 (1973); K. Tatsuta, K. Fujimoto, M. Kinoshita, and S. Umezawa, Carbohydr. Res., 54, 85 (1977); G. Jaurand, J.-M. Bean, and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 1981, 572.

4) Prepared by the reaction of chloromethyl cyclohexyl ether and triphenylphosphine, followed by alkaline hydrolysis, see ref. 5). NMR (δ, $CDCl_3$): 0.8-2.1 (m, 10H), 3.0-3.6 (m, 1H), 4.15 (d, J=8 Hz, 2H), and 7.0-8.2 (m, 10H). IR (KBr, cm^{-1}): 2920, 2850, 1435, 1180, 1120, 1090, 745, 715, and 695. M.p. 55-56°C.

5) C. Earnshaw, C.J. Wallis, and S. Warren, J. Chem. Soc., Perkin I, 1979, 3099.

6) (E)-1: NMR (δ, $CDCl_3$); 1.0-2.1 (m, 10H), 3.0 (broad, 1H), 3.6-4.2 (m, 6H), 4.3-5.1 (m, 7H), 6.25 (d, J=13 Hz, 1H), and 7.1-7.3 (m, 15H). IR (neat, cm^{-1}): 3400, 3025, 1690, 1500, 1455, 740, and 700. $[\alpha]_{365}^{23}$ +32° (c 0.53, CH_2Cl_2).
(Z)-1: NMR (δ, $CDCl_3$); 1.0-2.0 (m, 10H), 3.0 (broad, 1H), 3.4-3.8 (m, 4H), 3.9-4.2 (m, 2H), 4.25-4.8 (m, 7H), 6.25 (d, J=6 Hz, 1H), and 7.15-7.3 (m, 15H). IR (neat, cm^{-1}): 3430, 3020, 1655, 1495, 1450, 1070, 735, and 700. $[\alpha]_{365}^{23}$ -14° (c 0.52, CH_2Cl_2).

7)



8) α-4: NMR (δ, $CDCl_3$); 1.0-2.0 (m, 11H), 2.2 (ddd, J_1=13 Hz, J_2=5 Hz, J_3=1 Hz, 1H), 3.3-4.2 (m, 6H), 4.3-4.6 (m, 5H), 4.85 (d, J=10 Hz, 1H), 5.1 (dd, J_1=3 Hz, J_2=1 Hz, 1H), 7.0-7.5 (m, 15H). IR (neat, cm^{-1}): 2900, 2835, 1490, 1445, 1355, 1090, 730, 695. $[\alpha]_D^{22}$ +76° (c 1.1, CH_2Cl_2). ^{13}C-NMR (δ, $CDCl_3$): 95.0.
β-4: NMR (δ, $CDCl_3$); 1.0-2.05 (m, 11H), 2.3 (ddd, J_1=12 Hz, J_2=4 Hz, J_3=2 Hz, 1H), 3.3-3.8 (m, 6H), 4.4-4.6 (m, 6H), 4.90 (d, J=10 Hz, 1H), 7.2-7.4 (m, 15H). IR (neat, cm^{-1}); 2900, 2840, 1590, 1085. $[\alpha]_D^{22}$ -24.3° (c 0.65, CH_2Cl_2). ^{13}C-NMR (δ, $CDCl_3$): 97.7.

9) The reaction proceeded smoothly without any acid catalyst. cf. K.C. Nicolau, D.A. Calaremon, W.E. Barnette, and S.P. Seitz, J. Am. Chem. Soc., 101, 3704 (1979).

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