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HIGHLY STEREOSELECTIVE SYNTHESIS OF α-D-GLUCOPYRANOSIDES BY THE N-IODOSUCCINIMIDE-PROMOTED INTERNAL CYCLIZATION

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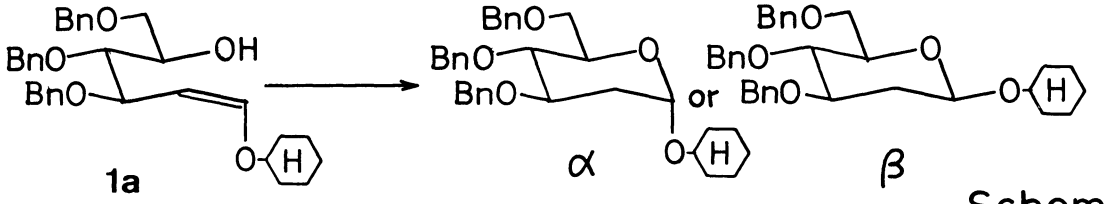
Highly stereoselective cyclizations of hydroxy enol ethers are effected by N-iodosuccinimide to result in the exclusive formation of 2'-deoxy-2'-iodo-α-D-glucopyranosides. An analog of glycolipid is also successfully synthesized according to the present method.

Stereoselective synthesis of glycosides has been one of the current interests in synthetic organic chemistry as a result of isolation and structure elucidation of a number of biologically important glycosidic compounds. The synthesis of glycosides is usually accomplished by the coupling reactions between the C-1 activated sugars and the suitably protected nucleophilic components such as alcohols.[1] In spite of many investigations on this problem, the stereoselective formation of the glycosidic linkage still remains a problem of different difficulty for each case and the exploitation of a new and efficient method of glycoside synthesis is strongly needed.

In a previous communication,[2] we described a novel approach toward the synthesis of glycosidic compounds by the stereoselective internal cyclization of the hydroxy enol ether precursor 1a promoted by the electrophilic activating agents.

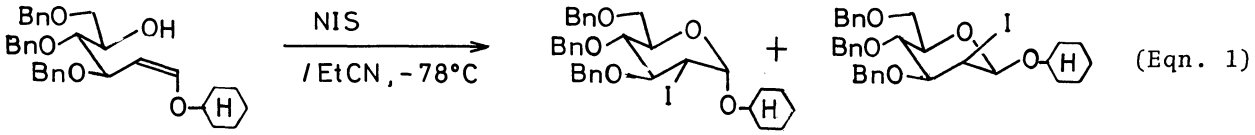


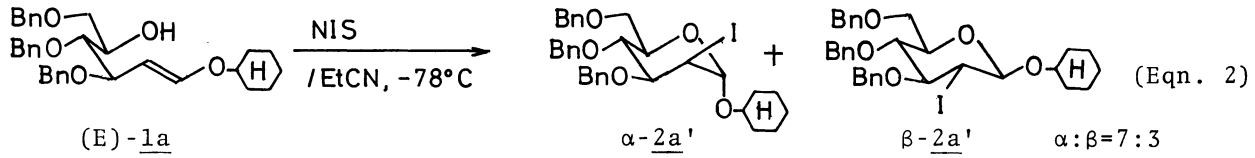
Scheme 1

Therein, the proper choice of the promotor has the decisive influence on the stereochemical course of reaction, that is, the α-selective cyclization took place by $Hg(OCOCF_3)_2$, while the β-selective cyclization was favored by PhSeCl (Scheme I).

In this communication, we wish to describe an improvement of the α-selectivity in the cyclization by the use of N-iodosuccinimide (NIS) as the promotor,[3] and a successful synthesis of a glycolipid analog *via* the present method. When the hydroxy enol ether (Z)-1a was treated with 1.2 equivalent of N-iodosuccinimide in propionitrile at -78 °C, a facile ring closure took place to result in the exclusive formation of the α-anomer in 95% yield. Under the same reaction conditions,

the (E)-isomer of 1a gave a separable 7:3 mixture of the α and β glycosides (α-2a' and β-2a'), each of which was in full accordance with the α and β glycosides prepared from 3,4,6-tri-O-benzyl-D-glucal[4] by the method of J. Thiem *et al.*[3]

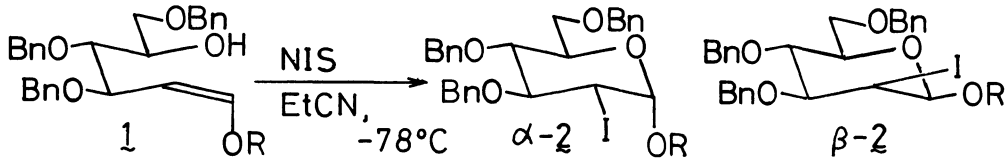


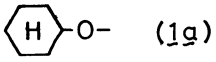
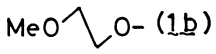
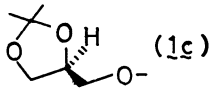
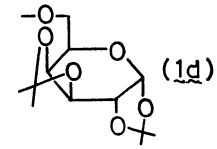
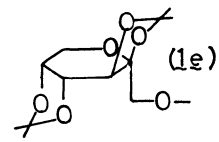


From the HPLC analysis of the crude products of the Eqn. 1, neither α-2a' nor β-2b' was detected, and *vice versa* for the Eqn. 2. Thus, it was confirmed that the present cyclization reaction proceeded through the clean *trans*-addition of iodide and the internal hydroxyl group to the olefinic linkage.[5]

Then, the method was further applied to the synthesis of several glycosides and the results are summarized in Table 1.

Table 1. Synthesis of Glycosides by NIS Promoted Cyclizations



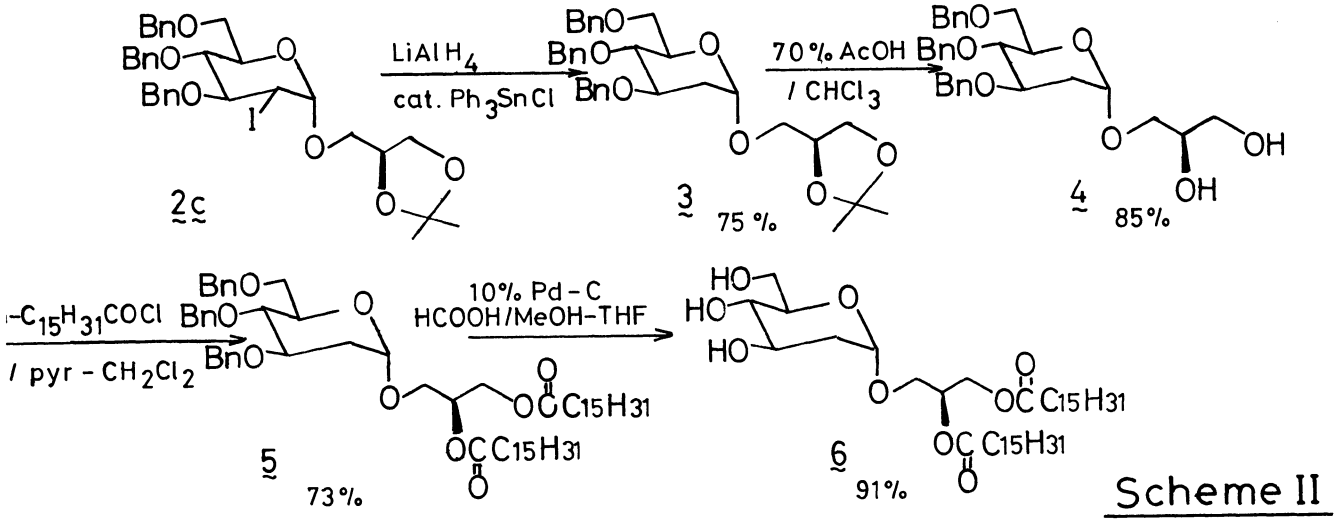
Entry	RO-[6]	Yield (%)[a]	α / β[b]
1	 (1a)	95	120/1
2	 (1b)	92	98/2
3	 (1c)	97	99/1
4	 (1d)	96	>99/1
5	 (1e)	89	>99/1

a) Isolated yield. Product gave satisfactory spectroscopic properties and elemental analysis.[7]
b) Determined by HPLC analysis (Merck LiChrosorb SI 60, hexane-AcOEt).[8]

As shown in the Table, the present cyclizations proceed with uniformly excellent α-selectivity irrespective of the substrate and the highly pure 2'-deoxy-2'-iodo-α-D-glucopyranosides (2a - 2e) were obtained in excellent yields. Since the 2'-iodo group could be subjected to further manipulations such as reduction or displacements, the present method offers a new entry into the α-glycosides syntheses.

A typical procedure for the preparation of cyclohexyl-3,4,6-O-benzyl-2-deoxy-2-iodo-α-D-glucoside (2a) is as follows: Under an argon atmosphere with protection from light, to a propionitrile (5 ml) solution of (Z)-1a (206 mg, 0.4 mmol) was added a propionitrile (5 ml) solution of NIS (113 mg, 0.5 mmol) at -78°C and the reaction mixture was kept standing for 3 hr at the temperature. The solvent was evaporated at reduced pressure and the resulting residue was dissolved in AcOEt. The solution was washed with 1M $Na_2S_2O_3$ and brine and dried over anhydrous Mg_2SO_4. After the evaporation of the solvent, the residue was purified on silica-gel TLC (hexane-AcOEt) to give the glycoside (2a) (240 mg, 95% yield).[7), 10)]

Further, the *syn*-glyceryl adduct 2c was converted to a glycolipid analog 6 as depicted in the Scheme II. Reduction of the iodide 2c with $LiAlH_4$ in the presence



Scheme II

of cat. Ph_3SnCl (rt, 12 hr) gave the glycoside 3[9)] (75%), which in turn was hydrolyzed with 70% AcOH-$CHCl_3$ (rt, 16 hr) to afford diol 4[10,11)] (85% yield). The diol 4 was esterified by the action of palmitoyl chloride (4 equiv.) in pyridine-CH_2Cl_2 to afford the diester 5[10,12)] (73% yield), which was debenzylated under a catalytic transfer hydrogenation conditions.[13)] Purification by the silica-gel flash chromatography gave the desired glycolipid analog 6,[14)] a substance of biological interests,[15)] in 91% yield.

Thus, it is noted that the NIS promoted cyclization of the hydroxy enol ethers proceeded in a stereoselective manner to furnish the highly pure α-glycosides in excellent yields. The present method opens a novel and efficient access to the syntheses of the α-glycosides.

References

1) a) A. F. Bochkov and G. E. Zaikov, 'Chemistry of the O-Glycosidic Bond. Formation and Cleavage', Engl. Ed., Pergamon Press (1979). b) H. Paulsen, Angew. Chem., Int. Ed. Engl., 21, 155 (1982).

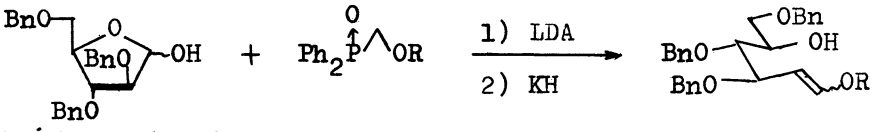
2) K. Suzuki and T. Mukaiyama, Chem. Lett., 1982, 683.

3) It was reported that the addition of various alcohols to tri-O-acetyl-D-glucal is effected by NIS. J. Thiem, H. Karl, and J. Swentner, Synthesis, 1978, 696.

4) I. D. Blackburne, P. M. Fredericks, and R. D. Guthrie, Aust. J. Chem., 29, 381 (1976).

5) In contrast, the PhSeCl promoted ring closure was not stereospecific and concomitant *anti* and *syn* additions proceeded as briefly stated in ref. 2).

6) The hydroxy enol ether precursors were prepared by the method described in ref. 2).



The acid labile phosphine oxides were prepared by the similar procedure of S. David *et al.*, starting from the MTM ether of the parent alcohols; S. David, J. Eustache, and A. Lubineau, J. Chem. Soc., Perkin I, 1974, 2274. The separation of the E, Z isomers of the enol ether was accomplished by silica-gel flash chromatography (entry 1,3,4) or HPLC (entry 2,5).

7) The properties of the cyclized products are presented: 2a: mp 91 - 92 °C (pentane), $[\alpha]_D^{22}$ +104° (c 0.43, CH_2Cl_2); 2b: oil, $[\alpha]_D^{23}$ +111° (c 0.7, CH_2Cl_2); 2c: mp 63 - 65 °C (pentane-Et_2O), $[\alpha]_D^{22}$ +105° (c 0.3, CH_2Cl_2); 2d: oil, $[\alpha]_D^{22}$ +47° (c 0.5, CH_2Cl_2); 2e: amorphous solid, $[\alpha]_D^{21}$ +76° (c 1.8, CH_2Cl_2).

8) The α/β ratio was also examined after the reductive removal of the iodides. The authentic sample was prepared by the method in ref. 2).

9) $[\alpha]_D^{22}$ +69° (c 2.2, CH_2Cl_2); NMR($CDCl_3$): δ=1.35(s, 3H), 1.40(s, 3H), 1.7(ddd, J_1=3Hz, J_2=11Hz, J_3=13Hz, 1H), 2.35(ddd, J_1=1.5Hz, J_2=4.5Hz, J_3=13Hz, 1H), 3.2 - 5.05(m, 17H), 7.0 - 7.5(m, 15H); IR(neat): 2900, 1450, 740, and 700 cm^{-1}.

10) Satisfactory spectroscopic properties were obtained.

11) Oil, $[\alpha]_D^{21}$ +63° (c 0.6, CCl_4).

12) mp 57 - 58 °C (EtOH); $[\alpha]_D^{21}$ +40° (c 0.8, CCl_4); Found: C, 75.77; H, 9.65%; Calcd for $C_{62}H_{96}O_9$: C, 75.57, H, 9.82%.

13) V. S. Rao and A. S. Perlin, Carbohydr. Res., 83, 175 (1980).

14) mp 66 - 68 °C (pentane); $[\alpha]_D^{20}$ +35° (c 0.4, CH_2Cl_2); Found: C, 68,63; H, 10.71%; Calcd for $C_{41}H_{78}O_9$: C, 68.87; H, 11.00 %; NMR($CDCl_3$): δ=0.6 - 1.8 (m, 59H), 1.95 - 2.1(m, 1H), 2.3(t, J=7Hz, 4H), 2.5 - 3.3(broad, 3H), 3.3 - 4.3 (m, 9H), 4.85(dd, J_1=3Hz, J_2=1Hz, 1H), 5.0 - 5.3(m, 1H); IR(KBr disk): 3420, 2960, 2910, 2850, 1735, 1465 cm^{-1}.

15) P. S. Sastry, Adv. Lipid Res., 12, 251 (1974).

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