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A Novel and Highly Stereoselective Synthesis of 2-Substituted Perhydrofuro[2,3-*b*]pyran Derivatives

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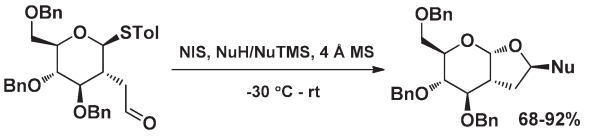
ABSTRACT



An effective and facile method for the synthesis of 2-substituted perhydrofuro[2,3-*b*]pyran derivatives is described. The cyclization of 2-*C*-aldehydo-2-deoxy-D-thioglucoside in the presence of *N*-iodosuccinimide (NIS) is highly stereoselective. 2-Substituted cyclization products were obtained in good to excellent yields.

Perhydrofuro[2,3-*b*]pyran subunits have been found in a variety of biologically important natural products such as tetrahydroaplysulphurin-1;[1] novaxenicins A, B, C;[2] penifulvin A, B, C;[3] stemona alkaloids;[4] euplotin C;[5] azadirachtin;[6] and cadlinolide A, B.[7] A range of methods have been developed for the synthesis of these fascinating motifs.[8] Classical routes include reactions such as radical cyclization,[8a−c] intramolecular dehydration,[8d] double intramolecular cyclizations from an acyclic precursor,[8e] *N*-iodosuccinimide (NIS) mediated ring opening of 1,2-cyclopropanated sugar derivatives,[8f] or the hetero-Diels−Alder reaction.[8g−i] While these methods have contributed greatly to this area, the highly stereoselective installation of a heteroatom substituent or an active functional group at the C(2) of perhydrofuro[2,3-*b*]pyrans still represents a great challenge.

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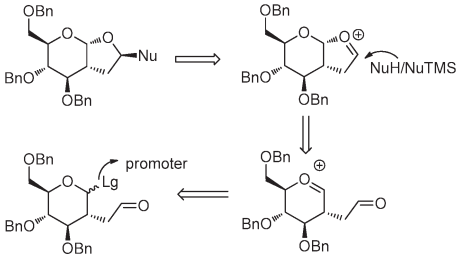
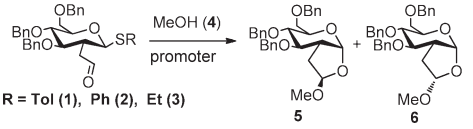
Traditionally, 2-*O*-acyl groups have been used as neighboring assistant groups for the stereoselective construction of 1,2-*trans* glycosides and the synthesis of 1,2-sugar orthoesters. In continuation of our previous work in the stereoselective synthesis of *C*-glycosides,[9] we conceived that 2-*O*-acetyl could be replaced with a 2-formylmethyl group, and an appropriate leaving group was installed at anomeric carbon; under the help of a promoter, this might generate fused perhydrofuro[2,3-*b*]pyran ring systems by trapping six-five fused ring oxonium ion intermediates (Scheme 1). Herein, we report our recent attempts to effect this transformation.

Scheme 1. Proposed Synthetic Route for 2-Substituted Perhydrofuro[2,3-*b*]pyran Derivatives



A preliminary experiment was performed with *p*-tolyl thioglucopyranoside **1** and MeOH **4** as model substrates, and the reaction was mediated by NIS in the presence of 5% mmol AgOTf in CH_2Cl_2 at −30 °C, whereafter the reactants were warmed to room temperature for 1 h. To our delight, the desired perhydrofuro[2,3-*b*]pyran derivatives **5** and **6** were obtained in 32% combined yield (Table 1, entry 1). The stereochemistries of **5** and **6** were extensively studied by ^1H NMR, $^1H-^1H$ COSY, and NOESY (Figure 1), and the structure of **5** was further unambiguously determined by X-ray crystallography (Figure 2). With this promising result in hand, the reaction conditions were then optimized. By choosing the additive TMSOTf, the yield was increased to 53% (Table 1, entry 2). $CuBr_2$ and Bu_4NBr as promoters afforded an unsatisfactory result (Table 1, entry3). The presence of TfOH provided a good result (Table 1, entry 4). In order to reveal optimal conditions for this transformation, *p*-tolyl thioglucopyranoside **1** and MeOH were directly treated with thiophilic reagents including NIS, NBS, NCS, I_2, Br_2, and ICl (Table 1, entries 5−10). It was found that all of these thiophilic reagents promoted the reaction except for NCS. NBS, I_2, and ICl furnished the bicyclo-products in high yield but with lower stereoselectivity. By way of contrast, when NIS was employed as a promoter, the perhydrofuro-[2,3-*b*]pyran derivative was obtained in excellent yield with good diastereoselectivity (Table 1, entry 5). Further screening of the glycosyl donors with phenyl thioglucopyranoside **2** and ethyl thioglucopyranoside **3** (Table 1, entries 11 and 12) indicated that the *p*-tolyl thioglucopyranoside **1** was the best substrate for this NIS-promoted reaction.

Table 1. Reaction of Thioglucosides **1**, **2**, **3** with MeOH[a]



entry	donor	promoter[b]	yield[c] (%)	**5/6**[d]
1	1	NIS+AgOTf	32	2:1
2	1	NIS + TMSOTf	53	3:1
3	1	$CuBr_2$+ Bu_4NBr	trace	/
4	1	NIS + TfOH	85	3:1
5	**1**	**NIS**	**92**	**5:1**
6	1	NBS	92	3:1
7	1	NCS	trace	/
8	1	I_2	83	1:2
9	1	Br_2	69	1:1
10	1	ICl	89	1:3
11	2	NIS	83	1:1
12	3	NIS	trace	/

[a] All reactions were performed with thioglucosides **1**, **2**, or **3** (0.1 mmol), MeOH **4** (0.2 mmol), promoter 0.15 mmol, in CH_2Cl_2 (2 mL) at −30 °C - rt for 1 h. [b] For NIS promoted reactions, 0.15 mmol NIS and 5 mol % additive were used; while for $CuBr_2$ pomoted reaction, 0.35 mmol $CuBr_2$ and 0.22 mmol Bu_4NBr were used. [c] Isolated yield. [d] Values were determined by ^1H NMR.

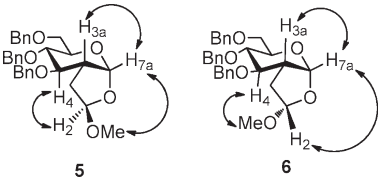


Figure 1. Key NOEs of perhydrofuro[2,3-*b*]pyran derivatives **5** and **6**.

To investigate the scope of the reaction, a number of primary, secondary, and tertiary alcohols; hydroxybenzenes; and $TMSN_3$ were reacted with *p*-tolyl thioglucopyranoside **1** (Table 2). The NIS-promoted reaction shows wide applicability for the synthesis of various alkyl or aryl *O*-substituted perhydrofuro[2,3-*b*]pyran derivatives (Table 2). When simple alcohols and hydroxybenzenes were used as nucleophiles, the desired perhydrofuro[2,3-*b*]pyran derivatives were formed in 68−83% yields (Table 2, entries 1, 4−9), while, with *i*-PrOH **9** and *t*-BuOH **11** (Table 2, entries 2, 3) as nucleophiles, the reactions were not complete, giving lower conversions (70%, 60% respectively), but with good yields. Altering the reaction conditions by elevating the reaction temperature, increasing the quantity of NIS to 2 equiv, and using the acceptors as solvent gave similar results. When monosaccharides **25** and **27** (Table 2, entries 10 and 11) were used as nucleophiles, the perhydrofuro-[2,3-*b*]pyran derivatives **26** and **28** were obtained in high yields. Interestingly, when $TMSN_3$ **29** (Table 2, entry 12)

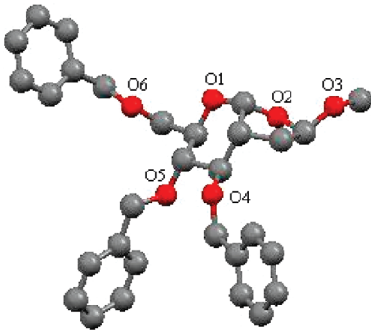
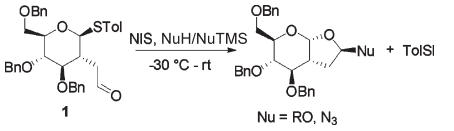


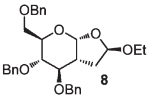
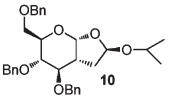
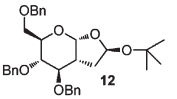
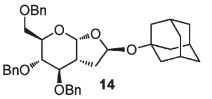
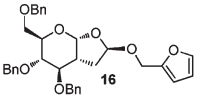
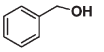
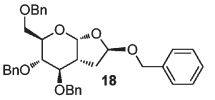
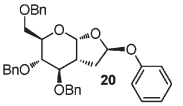
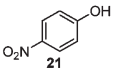
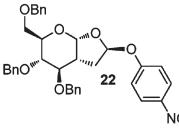
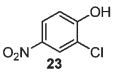
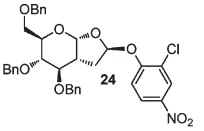
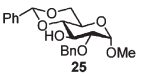
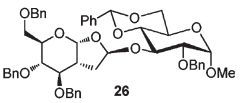
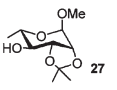
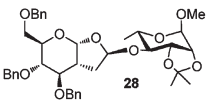
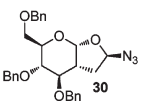
Figure 2. X-ray crystal structure of **5** (CCDC 828091). The hydrogen atoms are deleted for clarity.

was employed as a nucleophile the N_3-substituted perhydrofuro[2,3-*b*]pyran derivative **30** was formed in 78% yield. This result is of particular significance because this compound is an analogue of Thiamet-G, which exhibits excellent *O*-GlcNAcase inhibition activity.[10]

On the basis of the above results, a plausible mechanism is proposed for the formation of hemiketal under the NIS-mediated conditions (Scheme 2). First, the thiophilic NIS coordinates to the anomeric sulfur atom to give a tolylthionium cation. This is followed by the generation of a six-five fused ring oxocarbenium ion via participation of the carbonyl oxygen of the 2-acetaldehyde. Then, the resulting highly reactive five-membered oxocarbenium ion intermediate is trapped by nucleophiles, giving the fused ring products.[11] The stereoselectivity of the NIS-promoted reaction can be rationalized by evaluation of the face selectivity in the transition state. In order to accommodate the optimal chair conformer of the six-membered ring, we propose that the five-membered ring oxocarbenium ion adopts an envelope conformation, with the C=O$^+$-unit connected to the flattened portion of the envelope,[12] which produces a

Table 2. Cyclization Reaction of 2-*C*-Acetaldehyde-D-thioglucoside **1** with Different Nucleophiles[a]



entry	nucleophile	product	yield (%)[b]
1[c]	 7	 8	83
2[d]	 9	 10	87
3[e]	 11	 12	82
4	 13	 14	78
5	 15	 16	71
6	 17	 18	69
7	 19	 20	68
8	 21	 22	79
9	 23	 24	73
10	 25	 26	88
11	 27	 28	85
12	 29	 30	78

[a] All reactions were carried out using 1.5 equiv of NIS and 1.2 equiv of acceptor in 2 mL CH_2Cl_2 unless otherwise noted. [b] Isolated yield. [c] 3.0 equiv of acceptor was used. [d] Conversion rate 70%. [e] Conversion rate 60%.

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(11) It is presumed that initial activation of sulfur by iodization released succinimide anion, and then with the assistance of oxygen from the acetaldehyde and/or pyranoid ring oxygen-assisted departure of TolSI, generated the six-five fused ring or monocyclic pyran oxocarbenium ions. The nucleophiles attacked the six-five fused ring oxocarbenium ions and would offer the perhydrofuro[2,3-*b*]pyrans. However, if the nucleophiles intercepted the pyran oxocarbenium species, the glycosylation products will be obtained. Because the intramolecular reactions are faster than the intermolecular reactions, it is no surprise that, under our reaction conditions, the major products were perhydrofuro-[2,3-*b*]pyrans. In some cases, the presence of the glycosylation reaction would complicate the reaction which resulted in the decrease of the yield (Table 1, entry 12). In addition, it is possible that more than one accessible bicyclic oxocarbenium ion was formed in which the steric hindrance from the sugar backbone had been partially reduced; therefore, the nucleophiles had almost equal opportunity to attack the oxocarbenium ions from the two faces which did not influence the yield, but would decrease the stereoselectivity. For different species of bicyclic oxocarbenium ions, see: (a) Whitfielda, D. M.; Nukada, T. *Carbohydr. Res.* **2007**, *342*, 1291. (b) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497. (c) Bohé, L.; Crich, D. *Chim. C. R.* **2011**, *14*, 3. (d) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144.

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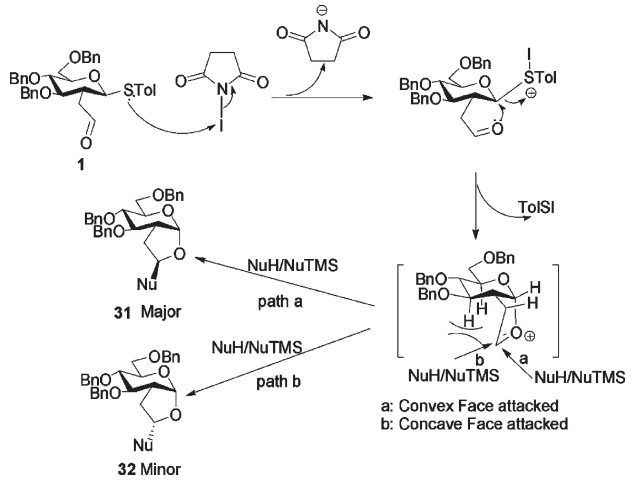
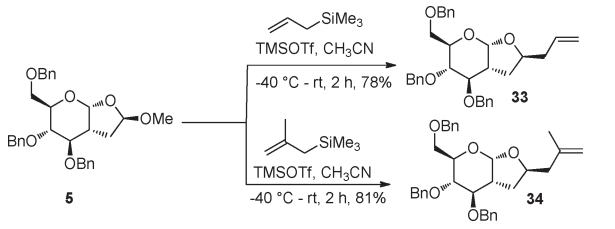
Scheme 2. Plausible Mechanism of NIS-Promoted Cyclization via Oxocarbenium Ion Intermediates



convex and concave face. Theoretically, the nucleophile can approach the cation from either the convex face (path a) or the concave face (path b), which will lead to the products in two different conformations. However, the concave face is blocked by the sugar backbone.[13] Therefore, compared with its concave face, the convex face of this six-five fused ring oxocarbenium ion is less sterically hindered, which facilitates the nucleophile to capture the electrophilic oxocarbenium ion from the convex face to offer the major product **31**.

Meanwhile, modification of these 2-heteroatom substituted fused ring building blocks was demonstrated by the synthesis of the 2-*C*-substituted perhydrofuro[2,3-*b*]pyran derivatives **33** and **34**. Under the standard allylation conditions, **5** was treated with allyltrimethylsilane and 2-methyl allyltrimethylsilane in the presence of TMSOTf in CH_3CN (Scheme 3),[14] providing 2-*C*-substituted perhydrofuro[2,3-*b*]pyran derivatives in high yield and diastereoselectivity.[15]

Scheme 3. Modification of Perhydrofuro[2,3-*b*]pyran Derivatives



In conclusion, we have developed an effective and facile method for the highly stereoselective synthesis of 2-substituted perhydrofuro[2,3-*b*]pyran derivatives by NIS-mediated cyclization of 2-*C*-aldehydo-D-thioglucoside. In the future, this method may also be expanded to other analogues.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds and ^{1}H, ^{1}H−COSY, NOESY for **5**, **6**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Other convex face attack examples, see: (a) Chen, S.; Patrick, B. O.; Scheffer, J. R. *J. Org. Chem.* **2004**, *69*, 2711. (b) Beignet, J.; Tiernan, J.; Woo, C. H.; Kariuki, B. M.; Cox, L. R. *J. Org. Chem.* **2004**, *69*, 6341. (c) Banoub, J.; Boullanger, P.; Potier, M.; Descotes, G. *Tetrahedron Lett.* **1986**, *27*, 4145.

(14) The reactions were carried out using 0.10 mmol of **5**, 0.08 mmol of TMSOTf, and 0.20 mmol of nucleophiles in 1.0 mL of acetonitrile.

(15) The stereochemistry of the product **33** was determined by extensive ^{1}H NMR and NOESY studies.