A Highly Stereoselective Synthesis of 2-Deoxy-β-glycosides Using 2-Deoxy-2-iodo-glucopyranosyl Acetate Donors

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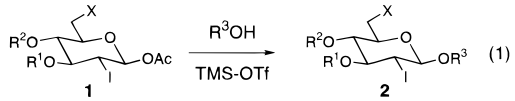
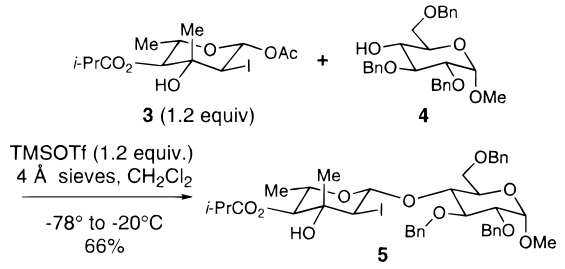
2-Deoxy glycosides are important structural components of many natural products.[2] Although 2-deoxy-α-glycosides are generally easily prepared from glycals or activated 2-deoxysugar precursors,[3−5] the synthesis of 2-deoxy-*b*-glycosides has proven to be a much more challenging undertaking.[4,6−8] There are relatively few methods for the synthesis of this important glycosidic linkage directly from 2-deoxy glycosyl precursors, and those procedures that have been reported lack generality and often do not proceed with high selectivity.[9−13] The most extensively developed strategy for synthesis of 2-deoxy-β-glycosides utilizes donors with equatorial C(2) heteroatom substituents (e.g., -Br,[14] -SR,[7,8,15−20] -SePh,[21] -OAc,[22] -NHCHO,[22] and 1,2-epoxy[23]) that are removed reductively after the glycosylation event. However, most of these methods also lack broad generality, and highly specialized syntheses of the donors are often required.[7,8,14]

We report herein a new, highly stereoselective synthesis of 2-deoxy-β-glucosides that utilizes 2-deoxy-2-iodo-glucopyranosyl acetates as the glycosyl donors, as illustrated by eq 1. This

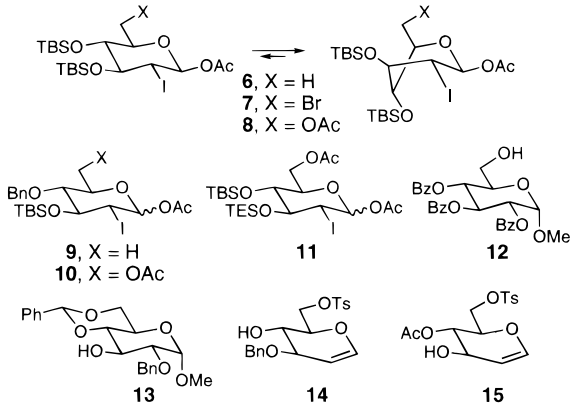


(1)

methodology evolved from earlier studies on the synthesis of the α-L-olivomycoside linkage present in the aureolic acid antitumor antibiotics. During these studies we examined a single example of the glycosidation reaction of the β-L-2-iodo-olivomycosyl acetate **3** using glucopyranose **4** as the acceptor.[24] Recognizing that the sole product obtained in this reaction, **5**, is in fact a latent 2-deoxy-β-glycoside, we sought to generalize and broaden the scope of this reaction.



Results of glycosidation reactions of donors **6**−**11** with monosaccharide acceptors **4** and **12**−**15** are summarized in Table



1. These reactions were performed in CH_2Cl_2, usually in the presence of activated 4 Å molecular sieves, using either TMS-OTf or TBS-OTf as the promoter. Typically 2 equiv. of the less reactive donors **8**−**11** are employed, while the more reactive donors **6** and **7** may be used as the limiting reagent.[25] Remarkably, these glycosylations are highly stereoselective, and provide the 2-deoxy-2-iodo-β-disaccharides **16**−**29** in 62−92% yield. The only cases in which α-glycosides were observed were experiments using primary alcohol **12** as the acceptor, and the least selective example (**7** + **12**) still proceeds with a 9:1 preference favoring the β-disaccharide. Given the high selectivity of these glycosidations and the ease with which the 2-iodo substituent is reduced with Bu_3SnH,[24] we anticipate that 2-iodo-glycosyl donors will find widespread application in the synthesis of 2-deoxy-β-glycosides.

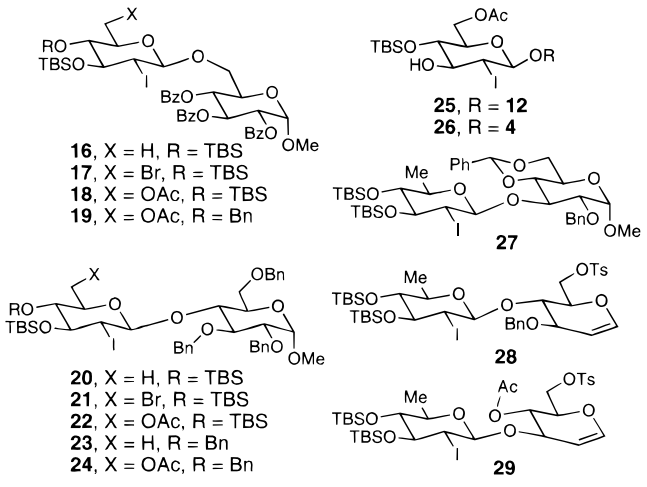


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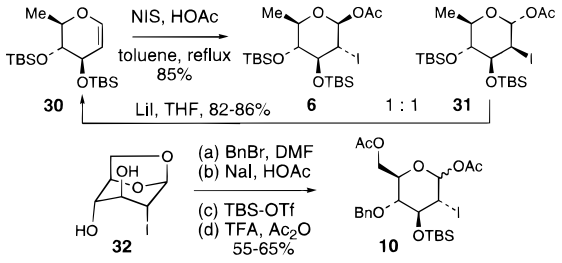
Table 1. Glycosidation Reactions of 2-Deoxy-2-iodo-glucopyranosyl Acetates

β:α donor	glycosyl donor	acceptor	promoter (equiv)	reaction conditions[a]	product glycoside	isolated yield[b] (%)	β:α selectivity[c]
β	**6** (0.8 equiv)	**12**	TMS-OTf (0.5 eq)	−78 °C, 40 min	**16**	92	95:5
β	**7** (0.8 equiv)	**12**	TMS-OTf (0.5 eq)	−78 °C to −30 °C, 2 h	**17**	83	90:10
87:13	**8** (2 equiv)	**12**	TMS-OTf (0.15 eq)	−35 °C, 25 min[d]	**18**	93	98:2
60:40	**10** (2 equiv)	**12**	TBS-OTf (0.25 eq)	0 °C, 0.5 h	**19**	74	92:8
96:4	**11** (2 equiv)	**12**	TMS-OTf (0.15 eq)	−35 °C, 0.5 h[d]	**25**[e]	86	98:2
β	**6** (0.7 equiv)	**4**	TMS-OTf (0.5 eq)	−78 °C, 5 min	**20**	90	β only
β	**7** (0.5 equiv)	**4**	TMS-OTf (0.5 eq)	−78 °C to −45 °C, 2 h	**21**	93	β only
87:13	**8** (2 equiv)	**4**	TMS-OTf (0.15 eq)	−35 °C, 0.75 h[d]	**22**	89	β only
88:12	**9** (2 equiv)	**4**	TMS-OTf (0.15 eq)	−35 °C, 1 h[d]	**23**	81	β only
60:40	**10** (2 equiv)	**4**	TMS-OTf (0.25 eq)	0 °C, 0.25 h	**24**	62	β only
96:4	**11** (2 equiv)	**4**	TMS-OTf (0.05 eq)	−35 °C, 2.25 h[d]	**26**[e]	78	β only
β	**6** (0.7 equiv)	**13**	TMS-OTf (0.5 eq)	−78 °C, 10 min	**27**	82	β only
β	**6** (0.8 equiv)	**14**	TMS-OTf (0.05 eq)	−78 °C, 10 min	**28**	80	β only
β	**6** (0.7 equiv)	**15**	TMS-OTf (0.2 eq)	−78 °C, 10 min	**29**	74	β only

[a] All reactions were performed in CH_2Cl_2 in the presence of activated 4 Å molecular sieves, unless indicated otherwise. [b] Yield of product(s) isolated chromatographically, calculated based on the limiting component of the reaction. [c] Product ratios determined by 500 MHz ^{1}H NMR analysis of the crude reaction products. The detection limit of these determinations is such that ca. 2−3% of the α-anomer could have escaped detection in those experiments where only the β anomer was observed. [d] Molecular sieves were not used in this experiment. [e] These experiments were quenched with Et_3N (10 equiv), and then $Et_3N{\cdot}3HF$ (10 equiv, 3 h, 0 °C) was added to deprotect the TES ether, which was partially cleaved under the original reaction conditions.

The 2-deoxy-2-iodo-glucosyl acetate donors can be prepared by two different routes. One approach, illustrated here by the synthesis of **6**, involves the reaction of a glucal (**30**) with NIS and HOAc in toluene at reflux. Although this method provided a ca. 1:1 mixture of the β-gluco (**6**) and α-manno (**31**) isomers,[26] the α-manno isomer can be reduced back to the starting glycal **30** by treatment with LiI in THF. The second route is stereospecific at C(2), and originates from the readily available iodo ether **32**.[27,28] The two hydroxyl groups of **32** are easily differentiated, with monosilylation or benzylation occurring selectively at C(4). Application of this method to the synthesis of **8** and **11** is summarized in the Supporting Information.



The remarkable stereoselectivity of these glycosylation reactions is virtually unparalleled in the 2-deoxy-β-glycoside arena. The factors that cause the 2-iodo substituent to be such a powerful stereodirecting group, far superior to the extensively studied C(2)-SAr and -SePh substituents,[8,15−19,21] remain to be clarified. However, an observation that may have mechanistic significance is that donors **6** and **8** containing C(3) and C(4) silyl ether protecting groups are considerably more reactive than **9** and **10** (comparable entries for **6** vs **9** and **8** vs **10**). Donors **6** and **8** (as well as **7** and **11**) exist in twist-boat conformations, as determined by ^{1}H NMR analysis which reveals $J_{1,2} = 7.4$ Hz, $J_{3,4} = 3.7$ Hz, and $J_{2,3} = J_{4,5} < 1$ Hz. This conformation is adopted in order to minimize the gauche interactions between the bulky silyl substituents.[29,30] On the other hand, donors **9** and **10** adopt the usual $^4C_1$ chair conformation. Although the ground-state conformational preferences of the donors strikingly influences their reactivity, the reaction stereoselectivity is independent of this feature.

Applications of the 2-deoxy-2-iodo-glucopyranosyl glycosidation methodology reported herein to the synthesis of biologically important 2-deoxyoligosaccharides is in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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