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2-Deoxy-2-iodo-β-glucopyranosyl Fluorides: Mild and Highly Stereoselective Glycosyl Donors for the Synthesis of 2-Deoxy-β-glycosides from β-Hydroxy Ketones

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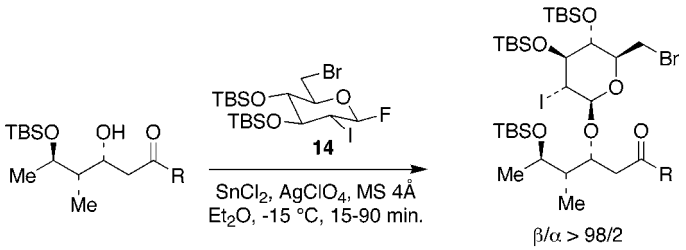
ABSTRACT



2-Deoxy-2-iodo-β-glucopyranosyl fluoride 14 is a highly stereoselective glucopyranosyl donor that may be activated under mild conditions. Application of this new glycosyl donor to the glycosidation reactions of a variety of acceptors including β-hydroxy ketones affords β-glycosides with high efficiency and stereoselectivity.

2-Deoxy-glycosides are important structural units found in numerous natural and biologically active compounds such as the angucycline family of antibiotics (landomycin A), the aureolic acid antibiotics (olivomycin A, chromomycin A_3), the enediynes (calicheamycin γ_1[I], esperamicins A_1 and C), the avermectins (avermectin B_{1a}, ivermectin), some cholestane glycosides (OSW-1), and cardiac glycosides.[1] Although some general methods have been developed for the stereoselective construction of 2-deoxy-α-glycosidic linkages (mainly by electrophilic addition to glycals),[2] preparation of the corresponding β-linkage has proved to be much more difficult. Our group has been involved in the development of new methods of synthesis of this challenging 2-deoxy-β-glycosidic linkage.[3−5] We previously reported that 2-deoxy-2-iodo-β-glucopyranosyl acetates **1**[4] and 2-deoxy-2-iodo-α-glucopyranosyl trichloroacetimidates **2**[5] are highly reactive glycosyl donors for establishing β-linked glycosides. The C(2)-iodo unit can then be reductively removed[6] under mild

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(3) Leading references: (a) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990. (b) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825, 8837. (c) Roush, W. R.; Briner, K.; Kesler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098.

(4) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541.

(5) (a) Roush, W. R.; Chong, P. *Org. Lett.* **2002**, *4*, 4523. (b) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891.

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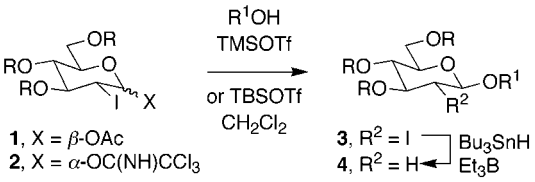
Scheme 1. Glycosidation Reaction of 2-Iodo-2-deoxy-glycoside Acetates **1** and Trichloroacetimidates **2**



conditions, leading to the desired 2-deoxy-β-glycosidic unit in high yield (Scheme 1).

During the course of our studies directed toward the total synthesis of formamicin (Figure 1),[7] a complex member of the plecomacrolide family of antibiotics, we anticipated the need to perform a β-selective glycosidation reaction of a late-stage β-hydroxy ketone (aldol) intermediate. We report herein the results of our studies of this key glycosidation reaction using model substrates, which led to the development of a highly selective synthesis of 2-deoxy-β-glycosides using 2-deoxy-2-iodo-β-glycosyl fluorides as the glycosyl donors.

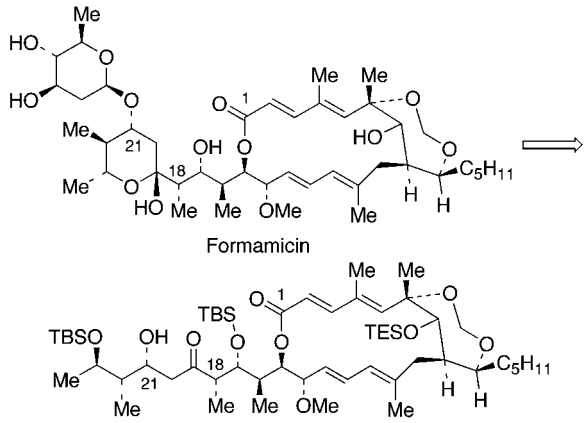


Figure 1. Formamicin and the targeted late stage β-hydroxy ketone (aldol) glycosidation substrate.

Although β-selective glycosidation reactions of β-hydroxy carbonyl compounds are known in the literature,[9,11,12] a general method proceeding in good yield and selectivity is not yet available. An intrinsic limitation in the glycosidation of β-hydroxy ketones is the weakened reactivity of the acceptor, due to intramolecular hydrogen bonding of the hydroxyl hydrogen to the carbonyl moiety.[8] Selected relevant examples of β-selective glycosidation reactions of aldol acceptors with 2-deoxy donors have been reported by Tastuta and Kinoshita.[9] Glycosidation of a β-hydroxy ketone with a 2-deoxy glycosyl fluoride under modified Mukaiyama's conditions[10] proceeded in 30% yield and unreported anomeric selectivity. Upon reinvestigation of this reaction in connection with a total synthesis of concanamycin A, Paterson[11] obtained the glycoside product in only 12% yield and a β:α ratio of 1:1.4. After screening a variety of 2-deoxyglycosyl donors, Paterson determined that the 2-deoxy-glycosyl bromide was the most β-selective of those examined. The desired 2-deoxy-β-glycoside was obtained with 2.5:1 β:α selectivity in 21% yield.[11] In Evans' total synthesis of cytovaricin,[12] the glycosidation of a β-hydroxy Weinreb amide derivative with a 2-deoxy glycosyl acetate using trityl perchlorate activation provided the β-glycoside product in 70% yield with a β: α selectivity of 4:1. This glycosidation reaction was extremely sensitive to variation of protecting groups, solvents, and temperatures.

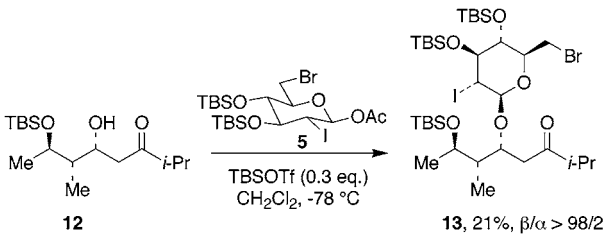
The lack of general methods available to efficiently glycosidate aldols in a β-selective manifold presented a unique opportunity to test our highly reactive and stereoselective 2-deoxy-2-iodo-glucopyranosyl acetate (**1**) and trichloroacetimidate (**2**) methodology.

Glycosidation reactions of β-hydroxy ketone **12** (corresponding to the C18−C24 fragment of formamicin) with 2-iodo-2-deoxy glycosyl acetates (**5**−**7**), imidates (**8**−**10**), or phosphate[13] **11** in the presence of a variety of promoters (TMSOTf, $BF_3{\cdot}OEt_2$, $TrClO_4$,[12] K10 clay,[14] $LiClO_4$,[15] LiOTf[16]) led only to decomposition of the acceptor (Scheme 2). Control experiments showed that in the presence of 0.3 equiv of TMSOTf, the acceptor **12** was not stable for more than 20 min at low temperature (−78 to −30 °C). Optimization of the glycosidation with TBSOTf (0.3 equiv) as the promoter led to a disappointing 21% yield of the desired glycosylated product **13** but with excellent anomeric selectiv-

Scheme 2. Glycosidation Reaction of β-Hydroxy Ketone **12**

5, X = Br, R^1 = TBS
6, X = Br, R^1 = TBDPS
7, X = H, R^1 = TBS

8, X = Br, R^1 = R^2 = TBS, R^3 = C(NH)CCl_3
9, X = Br, R^1 = R^2 = TBDPS, R^3 = C(NH)CCl_3
10, X = H, R^1 = R^2 = TBDPS, R^3 = C(NH)CCl_3
11, X = Br, R^1 = ClAcO, R^2 = TES, R^3 = P(O)$(OBn)_2$



12

13, 21%, β/α > 98/2

(7) (a) Igarashi, M.; Kinoshita, N.; Ikeda, T.; Nakagawa, E.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 926. (b) Igarashi, M.; Nakamura, H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 932. Correction: *J. Antibiot*. **1998**, *51*, C1.

(8) A similar hydrogen-bonding pattern has been reported to increase the nucleophilicity of hydrogen-bound hydroxyl acceptors: Mitchell, S. A.; Pratt, M. R.; Hruby, V. J.; Polt, R. *J. Org. Chem.* **2001**, *66*, 2327. However, our data indicate that hydrogen-bound aldols such as **12** and **16** are considerably less reactive than acceptors **19** and **21**.

(9) Toshima, K.; Misawa, M.; Ohta, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett*. **1989**, *30*, 6417.

(10) Mukaiyama, T.; Murai, Y.; Shoda, S.-i. *Chem. Lett.* **1981**, 431.

(11) Paterson, I.; McLeod, M. D. *Tetrahedron Lett*. **1995**, *36*, 9065.

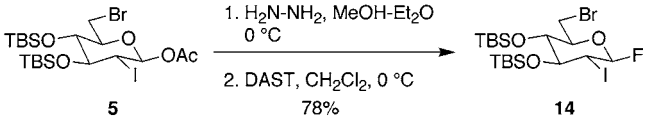
(12) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

ity (β:α > 98: 2).[17] This example further confirms that TBSOTf is superior to TMSOTf for the glycosidation reactions of sensitive substrates.[2b,5,18] However, to achieve a synthetically useful glycosidation procedure with aldol acceptors, it was clear that almost neutral activation conditions of the donor would be required.[19]

We anticipated that a donor combining a C(2)-iodo substituent, which we have shown to be a very efficient β-directing group,[4,5] with an anomeric fluoride leaving group might help to circumvent the stability problems noted above. 2-Iodo-2-deoxy glycosyl fluorides were first reported by Wood et al. in 1966,[20] and have continued to be targets of methodological studies for the past 30 years.[21] However, only one report of glycosidation reactions involving this class of donor has been disclosed, in which cyclohexanol was used as the acceptor.[22] Therefore, we decided to explore the potential of 2-iodo-2-deoxy-β-glycosyl fluorides in the glycosidation reactions of β-hydroxy ketones.

2-Iodo-2-deoxy-glycosyl fluorides are easily prepared in two steps starting from the corresponding 2-iodo-2-deoxy-β-glycosyl acetate (Scheme 3). For the present purposes, we

Scheme 3. Synthesis of 2-Iodo-2-deoxy-β-glycosyl Fluoride **14**

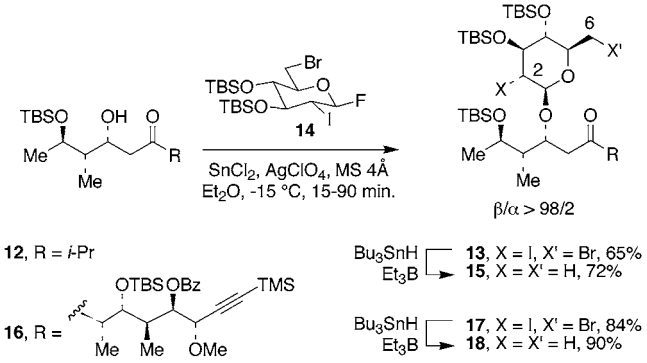


5 **14**

elected to use the readily accessible glycosyl acetate **5**[4] as starting material. Use of a substrate with a C(6)-bromo substituent simplifies the overall synthetic sequence, in that the C(2)-iodo and C(6)-bromo substituents can be reduced in the same step to give the targeted 2,6-dideoxy-β-glycosides (vide infra). Thus, cleavage of the anomeric acetate unit of **5** with hydrazine followed by transformation of the mixture of hemiacetals to the glycosyl fluoride **14** by using DAST[23] proceeded in 78% yield and excellent anomeric stereoselectivity (β:α > 98: 2). The configuration of the anomeric center was determined by measurement of the coupling constant (J_{1-2} = 8.4 Hz)[17] after desilylation (HF·NEt$_3$, CH$_3$CN, 60 °C).[24] Donor **14** is relatively stable and could be stored at −20 °C for more than two weeks without any noticeable decomposition.

With the glycosyl donor **14** in hand, we turned our attention toward the glycosidation reaction of the β-hydroxy ketone **12**. To our delight, slow addition of donor **14** to a solution of β-hydroxy ketone **12**, stannous chloride, and silver perchlorate in diethyl ether at −15 °C according to Mukaiyama's general procedure[10] provided the coupled product **13** in 65% yield with excellent stereoselectivity (β:α > 98: 2)[17] (Scheme 4). Silver triflate proved equally effective

Scheme 4. Glycosidation Reactions of 2-Iodo-2-deoxy-β-glycosyl Fluoride **14** and Aldols **12** and **16**

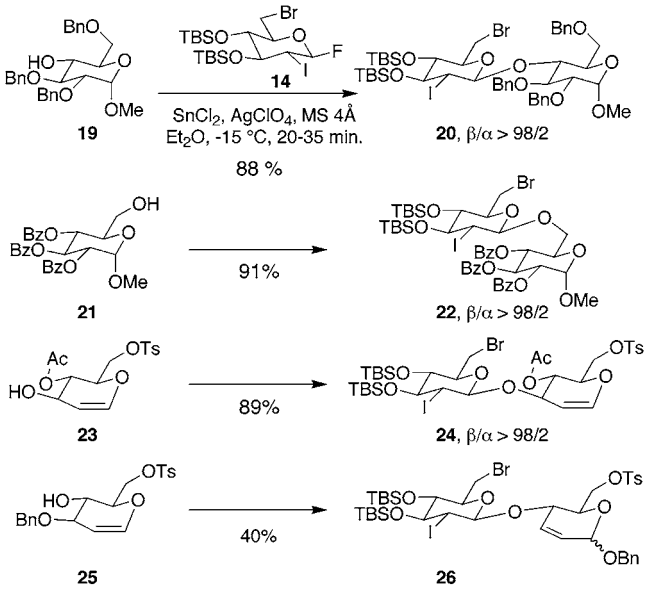


as the activating agent (58% isolated yield of **13**) whereas addition of a base (2,6-lutidine)[25] led to a lower yield (24%). Other promoters ($AgClO_4/Cp_2HfCl_2$,[26] $AgClO_4/Cp_2ZrCl_2$,[27] $AgSbF_6/SnCl_2$) or incorporation of a more labile protecting group on the aldol acceptor (TES instead of TBS ether) resulted in unsuccessful glycosidation reactions. More elaborated β-hydroxy ketones (e.g., **16**) can also be glycosylated with the 2-iodo-2-deoxy-β-glycosyl fluoride **14** in very good yield and selectivity (84%, β:α > 98: 2).[17] Reductive removal of the C(2)-iodo and the C(6)-bromo substituents under mild conditions[6] led to the desired 2-deoxy-glycoside units **15** and **18** in 72% and 90%, respectively.

(13) Lee, J.; Coward, J. K. *J. Org. Chem.* **1992**, *57*, 4126.
(14) Nagai, H.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2002**, *43*, 847.
(15) Waldmann, H.; Böhm, G.; Schmid, U.; Röttele, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1944.
(16) Lubineau, A.; Drouillat, B. *J. Carbohydr. Chem.* **1997**, *16*, 1179.
(17) Determined by 500-MHz ^{1}H NMR analysis of the crude reaction mixture.
(18) Roush, W. R.; Narayan, S. *Org. Lett.* **1999**, *1*, 899.
(19) Activation of a glycal donor in the presence of **12** was also attempted, but none of the literature methods examined (e.g., PPh$_3$·HBr, NBS) led to formation of the β-glycoside product. The acceptor was recovered in these cases. *PPh$_3$·HBr activation*: Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812. *NBS activation*: Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369.
(20) Wood, K. R.; Kent, P. W.; Fisher, D. *J. Chem. Soc. (C)* **1966**, 912.
(21) (a) Evans, R. D.; Schauble, J. H. *Synthesis* **1987**, 551. (b) Campbell, J. C.; Dwek, R. A.; Kent, P. W.; Prout, C. K. *Carbohydr. Res.* **1969**, *10*, 71. (c) Hall, L. D.; Manville, J. F. *Can. J. Chem.* **1969**, *47*, 361. (d) Hall, L. D.; Manville, J. F. *Carbohydr. Res.* **1968**, *8*, 295. (e) Hall, L. D.; Manville, J. F. *Chem. Commun.* **1968**, *35*, 37.
(22) Nishimura, S.; Washitani, K. (Sumitomo Pharmaceuticals Co., Ltd., Japan), Stereoselective Production of Glycosyl Compound, Japanese Patent 09241288, 1997.
(23) (a) Rosenbrook, Wm., Jr.; Riley, D. A.; Lartey, P. A. *Tetrahedron Lett.* **1985**, *26*, 3. (b) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5.
(24) Determination of the anomeric configuration of **14** by measurement of the $J_{1,2}$ coupling constant was not possible since this donor exists in a twist-boat conformation to relieve the gauche interactions between the two bulky silyl ethers at C3 and C4.
(25) Nicolaou, K. C.; Caulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910.
(26) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1988**, *29*, 3571.
(27) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1988**, *29*, 3567.

To test the scope of this glycosylation procedure, we subjected a variety of acceptors to glycosidation reactions with **14**. The results are presented in Scheme 5.

Scheme 5. Glycosidation Reactions of Various Acceptors with 2-Iodo-2-deoxy-β-glycosyl Fluoride **14**



We have previously shown that the primary and secondary alcohols **19** and **21** are glycosylated in high yields and β-selectivities with donors such as **5**, under TMSOTf activation.[4] The 2-iodo-2-deoxy-β-glycosyl fluoride **14** proved equally effective, with even greater selectivity in the case of the acceptor **21** (β:α > 98: 2 compared to β:$\alpha \geq$ 90:10 for the experiment with **5**[4]). Acid-sensitive acceptors such as **23** are not stable above −50 °C in the presence of a strong Lewis acid such as TMSOTf.[18] Consequently, the glycosidation of **23** in the presence of catalytic amounts of TMSOTf with the 2-iodo-2-deoxy-β-glycosyl acetate **5** proceeds in less than 11% yield (β:α > 98: 2).[28] Donor **14**, however, undergoes this challenging glycosidation and permits disaccharide **24** to be obtained in 89% yield, the β-anomer being the only detectable diastereomer in this reaction.[17] Increasing the sensitivity of the acceptor as in the case of **25** led to several products, the major arising from Ferrier rearrangement.[29] The rearranged coupled product **26** was isolated in 40% yield.

It is interesting to note that the conditions for activation of donors **1**, **2**, and **14** can be controlled such that it should be possible to use 6-heteroatom-substituted 2-iodo-glycosyl acetates or 2-iodo-glycosyl fluorides as acceptors in glycosidation reactions with 2-iodo-glycosyl trichloroacetimidates as the donors. The differential reactivity of these three classes of glycosyl donors should be of considerable utility in the synthesis of oligosaccharides containing 2-deoxy-glycoside units.

In summary, we have shown that 2-iodo-2-deoxy-β-glycosyl fluoride **14** is a synthetically useful glycosyl donor for establishing β-glycosidic linkages with a variety of acceptors. In particular, donor **14** gave excellent results in the glycosidation reaction of aldol acceptors **12** and **16**. Application of this methodology to the total synthesis of formamicin is currently underway and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM 38436) for support of this research. N.B. also acknowledges the Ministère Français des Affaires Etrangères for a Lavoisier Fellowship. We also thank Dr. Brad Savall for initial studies of the glycosidation reactions of aldol acceptors.

Supporting Information Available: Experimental procedures and spectral data for compounds **12**−**18**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027257H

(28) Bennett, C. E. Ph.D. Thesis, Indiana University, Bloomington, IN, 2000.

(29) We suspect that **26** arises via Ferrier-type decomposition of **25** to give an equivalent of Lewis acid complexed benzyloxide, which then undergoes standard Ferrier substitution with the cation generated from **25**. The resulting 3,4-unsaturated sugar then presumably undergoes subsequent, slower, glycosidation with **14** to give the observed product, **26**. It is of course conceivable that the order of these steps could be reversed. For additional examples of this process, see ref 28.