Stereoselective Glycosylations of a Family of 6-Deoxy-1,2-glycals Generated by Catalytic Alkynol Cycloisomerization

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Abstract: Photolysis of 0.25 equiv of $W(CO)_6$ in the presence of tertiary amines (triethylamine or DABCO) and highly functionalized terminal alkynyl alcohols catalyzes single-step, high-yield cycloisomerization to endocyclic enol ethers. This transformation is general for each diastereomeric 3,4-bissilyl ether of 5-hydroxy-1-hexyne, leading to enantio- and diastereoselective syntheses of each isomer of 6-deoxy-1,2-glycals. Stereoselective glycosylations have also been demonstrated for each glycal diastereomer, and have been applied in the preparation of D-digitoxose-β-4-D-digitoxose glycal.

Introduction

2,6-Dideoxyglycoside substructures are found in a variety of carbohydrate-containing natural products, including many compounds exhibiting anticancer, antibiotic, and cardiotonic effects.[1] For instance, digoxin and other cardiac glycosides contain D-*ribo*-2,6-dideoxyhexoses,[2] and the family of aureolic acid anticancer natural products (olivomycin, chromomycin, mithramycin) include both D-*arabino* and D-*lyxo* diastereomers (Figure 1).[3] The D-*xylo* configuration is relatively rare but is present in the cyclopentenyl glycoside passicapsin as well as the cardenolide glycoside corchorusoside.[4] L-Antipodes are also known, such as the *lyxo*-2,6-dideoxyhexoses of elaiophylin and viriplanin.[5] These 2,6-dideoxyhexoses are not commercially available, and must be prepared either by functional group interconversion of more highly oxygenated sugars or by stereocontrolled synthetic methods from non-carbohydrate precursors.

We have previously disclosed transition metal-promoted *endo*-selective alkynol cycloisomerization protocols for the generation of simple pyranose glycals.[6] Our invention of this novel chemical transformation enabled a unique strategy for the chemical synthesis of oligosaccharides, which we first demonstrated in the preparation of di- and trisaccharides containing 2,3,6-trideoxyhexose components.[7] This work also showed that

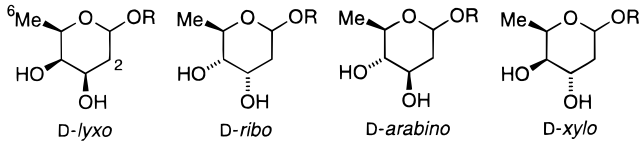

Figure 1. 2,6-Dideoxyhexose diastereomers.

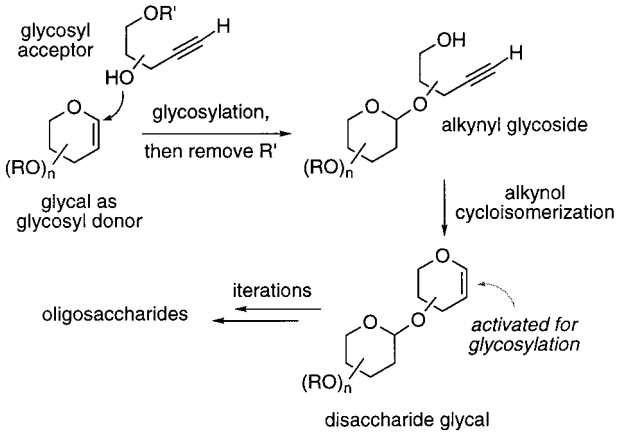

Figure 2. Alkynyl alcohol strategy for oligosaccharide construction.

acyclic alkynyl alcohols could also serve as glycosyl acceptors in glycosylation reactions of glycals, and after glycosylation could be converted into higher-order oligosaccharide glycals in a small number of steps (Figure 2). Herein we describe significant improvements in the alkynol cycloisomerization transformation, including the discovery of a high-yielding, single-step, metal-catalyzed general reaction protocol, which is applied to each diastereomeric configuration of 6-deoxy-1,2-glycals, coupled with stereoselective glycosylations of each glycal diastereomer with an alkyne-containing glycosyl acceptor.

Results and Discussion

Substrate Synthesis. The alkynyl alcohol substrates **6**−**9** were each synthesized from the common intermediate epoxy-alkynol (**2**), arising from 1-(trimethylsilyl)-hex-4-en-1-yn-3-one

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(1) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1.

(2) Cardiac Glycosides, Part 1: Experimental Pharmacology. In *Handbook Exp. Pharmacol.* **1981**, vol. *56*.

(3) (a) Wohlert, S. E.; Künzel, E.; Machinek, R.; Mendéz, C.; Salas, J. A.; Rohr, J. *J. Nat. Prod.* **1999**, *62*, 119. (b) Thiem, J.; Meyer, B. *Tetrahedron* **1981**, *37*, 551. (c) Thiem, J.; Meyer, B. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1331. (d) Berlin, Y. A.; Esipov, S. E.; Kolosov, M. N.; Shemyakin, M. M. *Tetrahedron Lett.* **1966**, *7*, 1431; 1643.

(4) (a) Olafsdottir, E. S.; Cornett, C.; Jaroszewski, J. W. *Acta Chem. Scand.* **1989**, *43*, 51. (b) Yoshikawa, M.; Murakami, T.; Shimada, H.; Fukude, N.; Matsuda, H.; Sashida, Y.; Yamahara, J. *Heterocycles* **1998**, *48*, 869.

(5) (a) Neupert-Laves, K.; Dobler M. *Helv. Chim. Acta* **1981**, *65*, 262. (b) Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Furihata, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1984**, *25*, 1937; 1941.

(6) McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061.

(7) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246.

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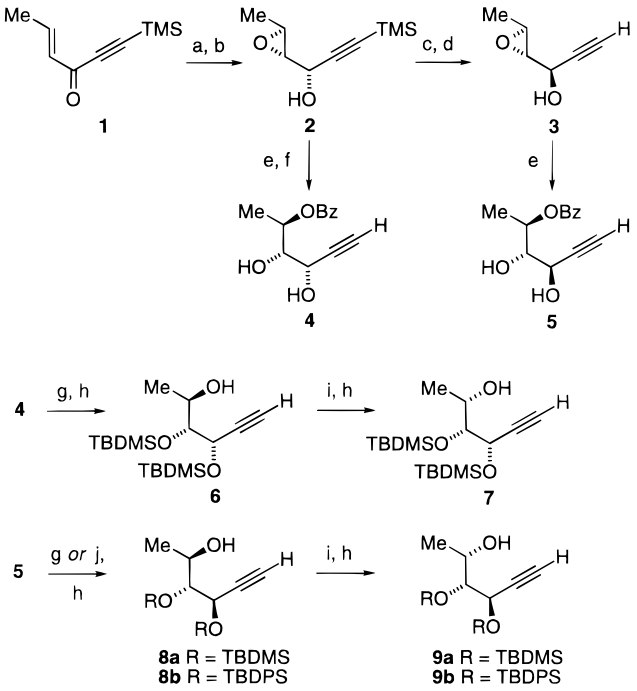
Scheme 1. Preparation of Alkynol Substrates **6**−**9**[a]

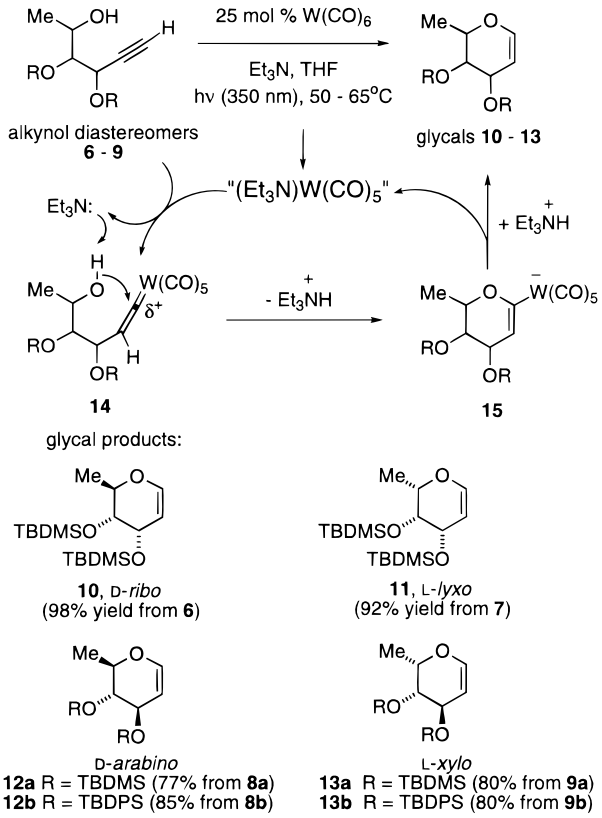


[a] Conditions: (a) BH_3-SMe_2, (*R*)-2-methyl-CBS-oxazaborolidine, THF; 91% yield, 97% ee. (b) cat. Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, $PhCMe_2OOH$, CH_2Cl_2, −20 °C; 76% yield, >99% de. (c) Ph_3P, DEAD, $PhCO_2H$, Et_2O; 94% yield. (d) 0.5 equiv of KCN, MeOH; 92% yield. (e) Ti(O-*i*-Pr)$_4$, $PhCO_2H$, benzene, 70 °C; 100% yield (from **2**), 80% yield (from **3**). (f) Bu_4NF, THF; 99% yield. (g) TBDMSCl (2.5 equiv), imidazole (5 equiv), DMF; 99% yield. (h) DIBAL, CH_2Cl_2, −70 °C; 95−98% yield. (i) Ph_3P, DEAD, *p*-nitrobenzoic acid, Et_2O; 93% yield (from **6**), 90% yield (from **8a**), 55% yield (from **8b**, +39% recovered **8b**). (j) TBDPSCl (2.5 equiv), imidazole (5 equiv), DMF; 92−99%.

(**1**)[8] via sequential enantioselective reduction[9] and epoxidation[10] transformations (Scheme 1). Enantioselective reduction promoted by (*R*)-oxazaborolidine and epoxidation with the (*R*,*R*)-tartrate−titanium catalyst were matched doubly diastereoselective processes, whereas the mismatched reactants afforded a 1:1 separable mixture of epoxyalkynol **2** and its epoxide diastereomer. We subsequently discovered that Mitsunobu inversion[11] of epoxyalkynol **2** proceeded rapidly and efficiently, affording compound **3** after cyanide-catalyzed removal[12] of both acyl and alkynylsilyl groups. Regioselective titanium-promoted anti-addition of benzoic acid[13] to each epoxyalcohol **2** or **3** gave the respective diols **4** and **5**, which after silylation of each diol and removal of the benzoyl protective group afforded alkynol substrates **6** and **8**. The remaining diastereomeric substrates were obtained by Mitsunobu inversion of **6** and **8** (with best results obtained with *p*-nitrobenzoic acid)[11b,c] followed by reductive deacylation to provide substrates **7** and **9**. This asymmetric synthesis route also permits preparation of the enantiomers of **6**−**9** from *ent*-**2**.

Catalytic Alkynol Cycloisomerization. We have previously shown that tungsten carbonyl compounds promoted *endo*-selective cyclization of terminal alkynyl alcohols to tungsten

Scheme 2. Catalytic, *endo*-Selective Alkynol Cycloisomerizations



pyranylidene compounds (six-membered cyclic oxacarbenes), which upon reaction with triethylamine were converted into dihydropyran products isomeric to the starting alkynyl alcohols. This two-step methodology was compatible with a variety of other functional groups, but gave regrettably low yields of glycal products in addition to requiring one or more equivalents of tungsten carbonyl reagent.[6,7] For instance, these conditions were suitable for cyclization of alkynol substrate **7**, but overall conversion to the cycloisomeric glycal **11** proceeded in only 45−50% isolated yield. We surmised that this transformation might be facilitated by heating the reactants, and found that a single-step cycloisomerization is achieved with catalytic amounts of $W(CO)_6$ [generally 25 mol %] when photolyzed at 350 nm at or near the reflux point of THF in the presence of the alkynol substrate and triethylamine. The success and *endo*-selectivity is highly dependent on maintaining anaerobic conditions, as the product mixture is contaminated with varying amounts of *exocyclization* products when careful technique is not used. This cycloisomerization transformation has been accomplished with alkynol substrates **6**−**9**, providing each of the corresponding glycal diastereomers **10**−**13** in excellent yields, as shown in Scheme 2.[14,15] This procedure is a significant improvement over previously reported protocols with regard to isolated yields and catalyst loading.[16] The cycloisomerization transformation likely proceeds via formation of a tungsten vinylidene intermediate

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(10) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(11) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (c) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.

(12) (a) Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **1986**, *51*, 727. (b) Alzeev, A.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 177. (c) $AgNO_3$ is not required for the removal of alkynylsilanes from our substrates.

(13) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(14) Our synthetic D-*arabino*-glycal **12a** ($[\alpha]_D = -51.6$) exhibited ^1H and ^{13}C NMR spectra identical with those of bis-TBDMS ether *ent*-**12a** ($[\alpha]_D = +53.9$) obtained in two steps from 3,4-di-*O*-acetyl-L-rhamnal: (a) NaOMe, MeOH; (b) TBDMSCl, imidazole, DMF. This also establishes the absolute configuration of all glycals **10**−**13** and confirms absolute and relative stereoinduction in the preparation of epoxyalkynol **2**.

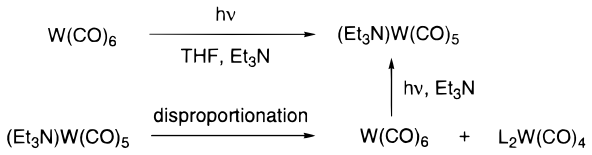


Figure 3. Formation of $(Et_3N)W(CO)_5$.

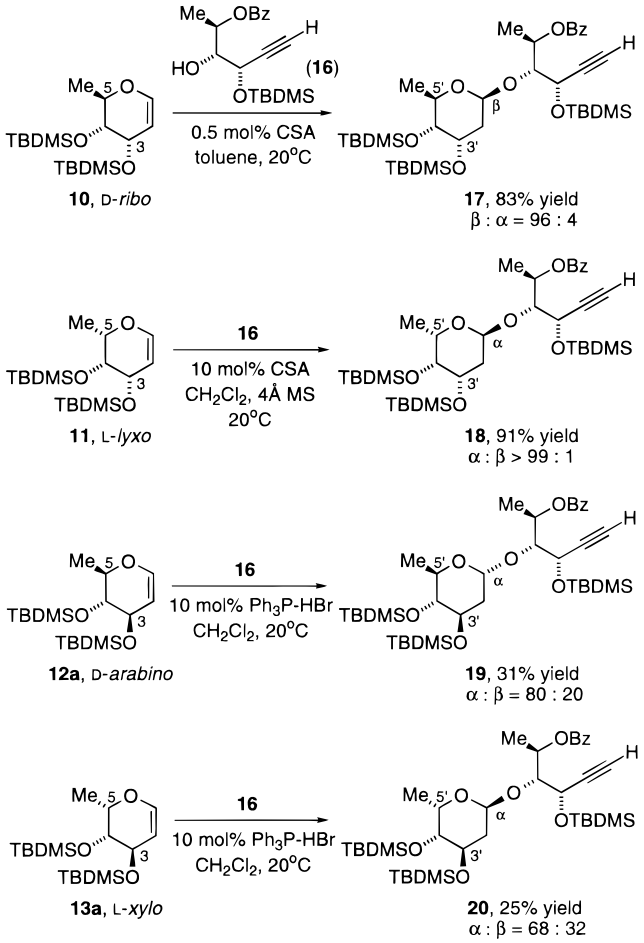
14, thus affording regioselective nucleophilic addition to the terminal carbon atom to give anionic vinyltungsten intermediate **15**. Glycal products **10**−**13** are then formed by in situ protonation of the tungsten−carbon bond with regeneration of the $(Et_3N)W(CO)_5$ catalyst.

In some cases we observe recovery of variable amounts of $W(CO)_6$, which must be arising from disproportionation of the ligand−$W(CO)_5$ catalyst species. Thus continuous irradiation of the reaction mixture may be regenerating ligand−$W(CO)_5$ catalyst from $W(CO)_6$, as shown in Figure 3.

Stereoselective Glycosylations: Acid Catalysis. Stereoselective glycosylations were explored for each glycal **10**−**13** with 1 equiv of alkynyl alcohol **16**[17] as the common glycosyl acceptor. Camphorsulfonic acid (CSA)-catalyzed glycosylation of the *ribo*-glycal **10** affords *β*-glycoside **17** with very high anomeric selectivity (83% isolated yield, Scheme 3), and the *lyxo*-glycal **11** gives completely stereoselective formation of the α-glycoside **18** (91% yield) under similar reaction conditions.[18] In both cases, the stereochemistry of the major glycoside product is consistent with alcohol addition anti to the C3-substituent, as previously predicted by Franck.[19a,b] However, acid-catalyzed glycosylations of *arabino*- and *xylo*-glycals **12a** and **13a** proceeded with much slower rates, and with relatively poor anomeric selectivity. For these glycals Ph_3P−HBr was a more effective glycosylation promoter than CSA.

Interestingly, the stereoselectivity of glycosylation in the ribo series is dependent on acid strength, as the stronger acid *p*-toluenesulfonic acid gives only a 70:30 ratio of *β*: α anomers. We have also noticed that anomeric stereoselectivity is degraded if the glycosylations of the *ribo*- and *lyxo*-glycals **10**−**11** are carried out over a longer period of time, suggesting thermodynamic equilibration at the anomeric center. Although the detailed mechanistic and/or conformational factors responsible for these selectivities is not entirely clear at this time, we note that both *ribo*- and *lyxo*-glycals exhibit a cis-relationship of the two silyloxy substituents at C3 and C4, and in both cases the major glycoside products are formed trans to the silyloxy substituents. The methyl substituent at C5 has only a minor effect on the glycosylation stereoselectivity, only slightly nonreinforcing the *ribo*-glycoside **17** under optimized conditions and reinforcing the observed α-selectivity in the *lyxo* case leading to **18**. In contrast, the *arabino*- and *xylo*-glycals undergo relatively inefficient acid-catalyzed glycosylations with lower stereoselectivity, and possess a trans relationship of the C3 and C4 silyloxy substituents. In both of these cases the major glycoside product is formed trans to the C5-methyl substituent.

Scheme 3. Acid-Catalyzed Glycosylations of Glycals **10**−**13**



Iodoacetate Formation and Glycosylation. As we could not achieve satisfactory yields or stereoselectivities in acid-catalyzed glycosylations of *arabino*- and *xylo*-glycals **12a**−**13a**, we subsequently explored formation of 2-iodo-1-acetate derivatives from these glycals, as other iodoacetates have been shown to be effective glycosyl donors for stereospecific glycosylations.[20] The stereochemistry of iodoacetate formation from *arabino*-glycals has been reported to give varying ratios of iodoacetate diastereomers depending on the choice of electrophilic reagent, although we have also noticed that some differences may also be associated with the type of *O*-protective groups utilized. Most of the work in this area to date has resulted in optimization toward the 2-deoxy-2-iodo-*manno*-α-acetate diastereomer over the *gluco*-*β*-acetate isomer, with some selectivity observed with $[Ph_3P(NR_2)]^+[I(OAc)_2]^-$ reagents,[21] and even higher selectivity demonstrated with $(NH_4)_2Ce(NO_3)_6$/NaI/HOAc.[22] Other precedents from the Roush laboratories indicated that *N*-iodosuccinimide (NIS)-promoted additions of acetic acid to glycal **12a**

(15) Cycloisomerizations of substrates **6** and **7** (leading to glycals *ribo*-**10** and *lyxo*-**11**) are facile and proceed in nearly quantitative yields, whereas the cyclization of **8a**/**b** to *arabino*-glycals **12a**/**b** is slightly slower. Substrates **9a**/**b** leading to *xylo*-glycals **13a**/**b** proceed in satisfactory yield but in all cases approximately 10% of exo-cyclization product is formed along with the major endo-cyclization products **13a**/**b**.

(16) (a) McDonald, F. E.; Bowman, J. L. *J. Org. Chem.* **1998**, *63*, 3680. (b) McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061.

(17) Prepared from **4** in 83% yield: TBDMSCl (1.0 equiv), imidazole (2.0 equiv), DMF.

(18) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369.

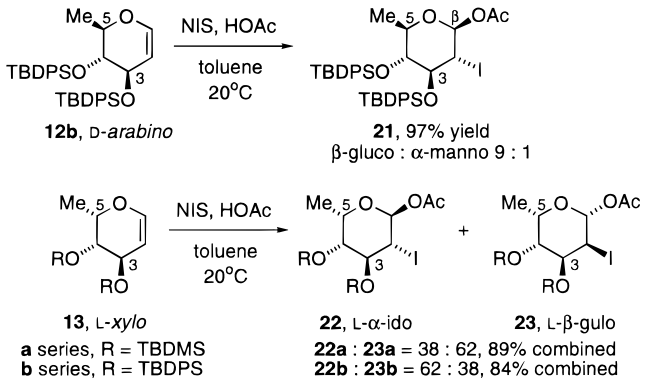
(19) (a) Kaila, N.; Blumenstein, M.; Bielawska, H.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 4576. (b) Franck, R. W.; Kaila, N.; Blumenstein, M.; Geer, A.; Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* **1993**, *58*, 5335. (c) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

(20) (a) Roush, W. R.; Briner, K.; Sebesta, D. P. *Synlett* **1993**, 264. (b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. (c) Roush, W. R.; Narayan, S. *Org. Lett.* **1999**, *1*, 899. For representative direct iodoglycosylations, see: (d) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (e) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656.

(21) (a) Kirschning, A.; Plumeier, C.; Rose, L. *Chem. Commun.* **1998**, 33. (b) Kirschning, A.; Jesberger, M.; Monenschein, H. *Tetrahedron Lett.* **1999**, *40*, 8999.

(22) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999**, *1*, 895.

Scheme 4. Iodoacetate Formation from *arabino*- and *xylo*-Glycals **12**−**13**



gave a 1:1 mixture of *β-gluco*- and α-*manno*-iodoacetates,[20a] whereas Kirschning observed that *β-gluco* anomer was the major product arising when $Bu_4NI(OAc)_2$ was utilized in glycosylation of TBDPS-glycal *ent*-**12b**.[23]

We observe that the ratios of iodoacetates produced from glycals **12a** and **12b** are essentially identical regardless of the reagent employed (NIS/HOAc, $Bu_4NI(OAc)_2$, or $I(coll)_2ClO_4$/HOAc). Although *tert*-butyldimethylsilyl (TBDMS) glycal **12a** exhibits virtually no selectivity (1.1:1) with all three reagents, the sterically bulkier *tert*-butyldiphenylsilyl (TBDPS) glycal **12b** provides *β-gluco* anomer as the major component of a 9:1 mixture with all three reagents (Scheme 4). Iodoacetate formation from both *xylo*-glycals **13a** and **13b** proceeds with poor stereoselectivity, although the major diastereomer obtained from **13a** is *β-gulo* **23a** whereas the α-*ido* isomer **22b** is the predominant product from TBDPS glycal **13b**. Minor amounts of one of the *cis*-iodoacetate diastereomers are also observed from both **13a** and **13b**.

TBDMSOTf-catalyzed glycosylation[20,24] of iodoacetate product **21** (9:1 inseparable mixture) with alkynyl alcohol **16** selectively furnishes the 2-iodo-*β*-glycoside **24** isomer in good yield with some recovery of the minor α-*manno*-2-iodo-1-acetate, thus providing pure *β*-glycoside in the *arabino* series[25] (Scheme 5). In the case of the *xylo*-derived mixture of iodoacetates **22a**/**23a**, inadvertent exposure to methanol was observed to selectively convert minor isomer **22a** to the corresponding methyl glycoside, whereas the major isomer **23a** remained unchanged. Encouraged by this serendipitous observation, we then treated the mixture of **22a**/**23a** with alkynol **16** and TBDMSOTf, and obtained only one glycoside α-**25a**, accompanied by the unreacted major iodoacetate **23a**. The TBDPS-iodoacetates **22b**/**23b** also reacted with alkynol **16** and TBDMSOTf at low temperature to afford only one glycoside α-**25b**, accompanied by quantitative recovery of the minor *β-gulo*-iodoacetate **23b**.

Analysis of coupling constants in the *arabino* glycal series suggests that **12a** with TBDMS substituents exists in a mixture of $^4H_5$ and $^5H_4$ conformations, whereas the larger TBDPS substituents of **12b** disfavor the trans-diequatorial $^4H_5$ conformation so that $^5H_4$ is the predominant ground state conformer, with C3 and C4-OTBDPS groups trans-diaxial (Figure 4).[26] In the *xylo* series **13a**,**b**, we observe little difference in the

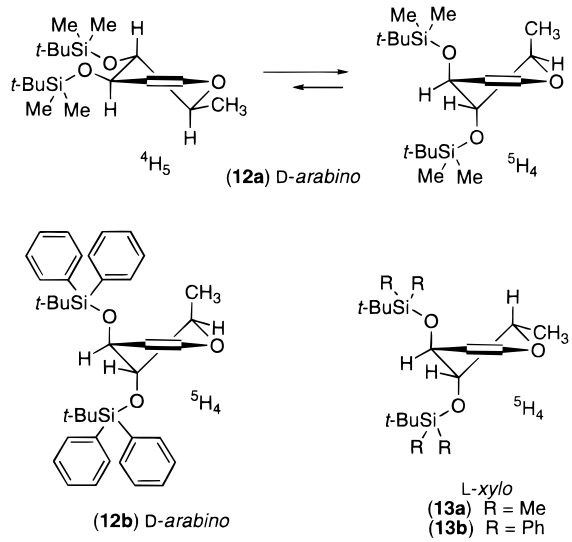
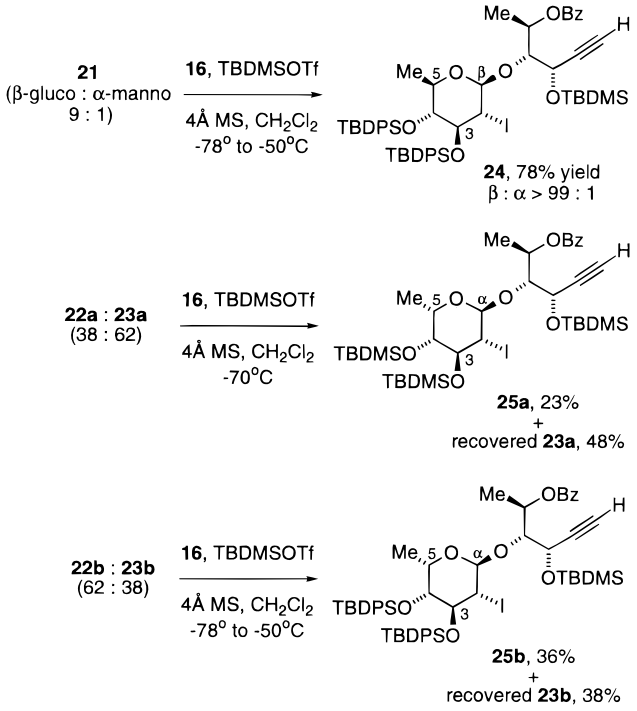


Figure 4. Conformations of glycals **12**−**13**.

Scheme 5. Stereoselective Formatin of Iodoglycosides **24**−**25**



conformations of these glycals, in line with the similar lack of selectivity in iodoacetate formation. However, it is worth noting that the more reactive α-*ido*-iodoacetates **22a** and **22b** exhibit trans-diaxial relationships between the 2-iodo and 1-acetate substituents, suggesting that such conformations are much more conducive for glycosylation transformations.

Conclusions

In summary, we have discovered an effective tungsten-catalyzed procedure for the *endo*-selective cycloisomerization of 1-alkyn-5-ols bearing silyloxy substituents at the C3 and C4 positions. Each member of the resulting family of 6-deoxyglycal diastereomers can be converted into a single *O*-glycoside anomer

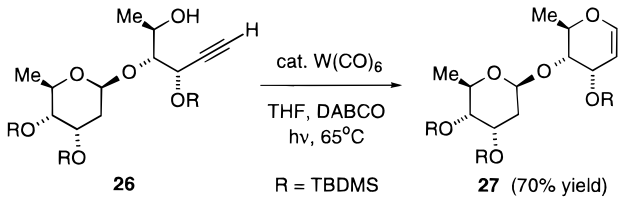
(23) Kirschning, A. *Eur. J. Org. Chem.* **1998**, *63*, *2267*.

(24) The use of TMSOTf gave slightly lower yields of glycosylation products along with byproduct arising from loss of the TBDMS protective group.

(25) Similar behavior has been observed with 2-phenylseleno-1-*O*-acetate mixtures derived from *arabino*-glycal **12a**: Dräger, G.; Garming, A.; Maul, C.; Noltemeyer, M.; Thiericke, R.; Zerlin, M.; Kirschning, A. *Chem. Eur. J.* **1998**, *4*, 1324.

(26) Similar behavior has been observed in *C*-glycosylations of 2,6-dideoxyglucosyl fluorides: Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663.

Scheme 6. Iterative Synthesis of D-*ribo*-*β*-D-*ribo*-Disaccharide Glycal **27**



26 **27** (70% yield)

with high stereoselectivity, although each diastereomeric glycal exhibits unique stereoselectivity and reactivity. One iterative application of this methodology is demonstrated from alkynol **26**, generated by DIBAL removal of the benzoate protective group from *ribo*-*β*-glycoside **17**, and the disaccharide glycal **27** is obtained in 70% isolated yield when DABCO is used rather than Et_3N for the $W(CO)_6$-catalyzed cycloisomerization (Scheme 6). Additional studies on iterative applications of this methodology to the synthesis of natural and nonnaturally occurring oligosaccharides are in progress.

Experimental Section

Representative Procedure for Alkynol Cycloisomerizations: 3,4-Bis-(*tert*-butyldimethylsilyl)-1,5-anhydro-2,6-dideoxy-L-*lyxo*-hex-1-enitol (11). An oven-dried Schlenk flask fitted with a reflux condenser and a stir bar, under nitrogen atmosphere, was charged with tungsten hexacarbonyl (0.176 g, 0.5 mmol, dried under vacuum) and alkynol substrate (**7**, 0.716 g, 2 mmol, azeotropically dried from toluene). This mixture was dissolved in freshly distilled dry THF (5 mL) and triethylamine (1.25 mL). The solution was irradiated under an inert atmosphere for 5 h at 350 nm (Rayonet photoreactor) without cooling, so that the solvent reflux point was reached. Volatile components were removed under reduced pressure and the product was purified by silica gel chromatography using an eluent mixture of pentane:triethylamine (99:1) to afford product glycal **11** (0.659 g, 92% yield) as a colorless oil. $[\alpha]^{23}_D$ +56.0 ($CHCl_3$, *c* 1.40); IR (neat) 3066, 1644, 1252, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, J = 6.2, 1.0 Hz, 1H), 4.56 (dd, J = 6.2, 3.2 Hz, 1H), 4.24−4.34 (br s, 1H), 4.05 (m, 1H, J = 6.4, 2.4, 1.2, Hz), 3.79 (app. t, J = 2.8 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 102.5, 73.7, 70.1, 26.1, 26.0, 18.4, −3.8, −4.5, −4.6, −4.7; HRMS (FAB^+) Calcd for $C_{18}H_{38}O_3Si_2Li$ [$(M + Li)^+$] 365.2520, found 365.2520. Anal. Calcd for $C_{18}H_{38}O_3Si_2$: C, 60.28; H, 10.68. Found: C, 60.42; H, 10.68.

(2*R*,3*R*,4*S*)-3-*O*-Hex-5-yn-2-benzoyloxy-[3,4-bis-(*tert*-butyldimethylsilyl)-2,6-dideoxy]-*β*-D-allopyranoside (17). A mixture of glycal **10** (0.716 g, 2 mmol) and alkynol acceptor **16** (0.696 g, 2 mmol) was azeotropically dried (twice, from toluene). Dry CSA (2.5 mg, 0.5 mol %) was introduced followed by dry toluene (2 mL) under inert atmosphere. The resulting mixture was allowed to stir for 12 h at room temperature. The reaction mixture was diluted with Et_2O (100 mL), washed with water (1 × 20 mL) and brine (1 × 20 mL), dried, and then concentrated to give crude product in a 96:4 (β:α, ^1H NMR) mixture. The major β isomer **17** was separated from the mixture by silica gel column chromatography in 83% (1.172 g) yield as a colorless oil, which solidified to a crystalline white solid upon standing. Mp 78−80 °C; $[\alpha]^{23}_D$ +14.9 ($CHCl_3$, *c* 2.04); IR (KBr) 3303, 2931, 1713, 1276, 1252, 1118, 885, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.57−7.51 (m, 1H), 7.44−7.38 (m, 2H), 5.66 (dq, J = 6.5, 2.7 Hz, 1H), 5.11 (dd, J = 9.5, 2.1 Hz, 1H), 4.78 (dd, J = 3.3, 2.1 Hz, 1H), 4.02 (app. t, J = 3.1 Hz, 1H), 3.99 (app. dd, J = 3.9, 2.1 Hz, 1H), 3.84 (app. dq, J = 6.3, 2.4 Hz, 1H), 3.23 (dd, J = 9.0, 2.4 Hz, 1H), 2.45 (d, J = 2.4 Hz, 1H), 2.04 and 2.00 (ddd, J = 13.2, 4.2, 2.1 Hz, 1H,), 1.72, 1.68, and 1.64 (ddd, J = 13.3, 3.9, 2.1 Hz, 1H), 1.42 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.83 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 132.6, 130.6, 129.5, 128.1, 98.6, 82.8, 82.0, 75.3, 73.9, 71.4, 69.9, 69.3, 65.3, 39.9, 26.2, 25.9, 25.8, 18.5, 18.3, 18.2, 18.1, 15.9, −3.3, −4.1, −4.5, −4.6, −4.8, −4.9; HRMS (FAB^+) Calcd for $C_{37}H_{66}O_7Si_3Li$ [$(M + Li)^+$] 713.4276, found 713.4271. Anal. Calcd for $C_{37}H_{66}O_7Si_3$: C, 62.84; H, 9.41. Found: C, 62.73; H, 9.41.

(2*R*,3*R*,4*S*)-3-*O*-Hex-5-yn-2-benzoyloxy-(3,4-bis-(*tert*-butyldimethylsilyl)-2-6-dideoxy)-α-L-galactopyranoside (18). A mixture of glycal **10** (50 mg, 0.139 mmol), alkynol acceptor **16** (53 mg, 0.15 mmol), and 4 Å activated powdered molecular sieves (32 mg) was suspended in dry CH_2Cl_2 (1 mL). Dry camphorsulfonic acid (3 mg, 10 mol %) was added and the reaction mixture was stirred for 6 h at room temperature. Triethylamine was added dropwise to neutralize CSA, followed by water and extraction with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated, and purification by silica gel chromatography (pentane:Et_3N, 300:1) gave β-isomer **18** (89 mg, 91%) as a colorless oil. The anomeric selectivity for **18** was determined by ^1H NMR analysis of the crude reaction mixture to be >99:1. $[\alpha]^{23}_D$ −41.7 ($CHCl_3$, *c* 1.04); IR (neat) 3310, 2117, 1722, 1272, 1256, 1106, 1067, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−7.38 (m, 5H), 5.59 (dq, J = 6.6, 2.7 Hz, 1H), 5.20 (app. d, J = 3.0 Hz, 1H), 4.43 (dd, J = 5.1, 2.1 Hz, 1H), 4.14 (ddd, J = 12.0, 4.2, 2.1 Hz, 1H), 4.06 (app. q, J = 6.6 Hz, 1H), 3.97 (dd, J = 5.1, 2.7 Hz, 1H), 3.58 (app. s, 1H), 2.42 (d, J = 2.1 Hz, 1H), 2.12 (app. td, J = 12.0, 3.6 Hz, 1H), 1.73 (app. dd, J = 12.3, 4.2 Hz, 1H), 1.37 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 132.8, 130.5, 129.6, 128.3, 99.0, 83.1, 81.0, 74.0, 73.8, 71.4, 68.4, 68.3, 64.3, 33.2, 26.2, 26.1, 25.7, 18.6, 18.5, 18.1, 17.7, 14.9, −3.7, −4.4, −4.6, −4.7, −5.3; HRMS (FAB^+) Calcd for $C_{37}H_{66}O_7Si_3Li$ [$(M + Li)^+$] 713.4276, found 713.4276. Anal. Calcd for $C_{37}H_{66}O_7Si_3$: C, 62.84; H, 9.41. Found: C, 62.76; H, 9.42.

3,4-Bis(*tert*-butyldiphenylsilyl)-2,6-dideoxy-2-iodo-*β*-D-glucopyranose, Acetate Ester (21). Glycal **12b** (0.606 g, 1 mmol) and HOAc (0.360 g, 6 mmol) were dissolved in toluene (4 mL). NIS (0.450 g, 2 mmol) was added, and the reaction mixture was placed in a 100 °C oil bath for 5 min with stirring. The reaction mixture was then allowed to cool to room temperature. Aqueous 1 M $Na_2S_2O_3$ was added to the purple solution until it became colorless, followed by $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic layers were washed with brine and dried before concentrating under reduced pressure to give crude product, which was purified by silica gel chromatography to afford an inseparable mixture of iodoacetates [(9:1 β /α, ^1H NMR), 0.768 g, 97% yield] favoring **21**. This product was a thick oil which solidified to a white solid on standing. From the β/α (9:1) mixture: IR (neat) 1768, 1229, 1212, 1112, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63−7.20 (m, 20H), 6.43 (d, J = 8.1 Hz, 1H), 4.69 (d, J = 3.3 Hz, 1H), 3.98 (d, J = 7.8 Hz, 1H), 3.94 (app. q, J = 6.9 Hz, 1H), 3.62 (d, J = 3.3 Hz, 1H), 2.13 (s, 3H), 1.08 (s, 9H), 1.02 (s, 9H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 136.0, 135.9, 135.7, 135.7, 135.5, 132.8, 132.7, 132.6, 132.5, 129.8, 129.7, 127.7, 127.60, 127.5, 94.7, 80.0, 78.8, 74.0, 27.1, 27.0, 26.3, 21.1, 19.7, 19.1; HRMS (FAB^+) Calcd for $C_{40}H_{49}IO_5Si_2Li$ [$(M + Li)^+$] 799.2280, found 799.2323. Anal. Calcd for $C_{40}H_{49}IO_5Si_2$: C, 60.59; H, 6.23. Found: C, 60.39; H, 6.06.

(2*R*,3*R*,4*S*)-3-*O*-Hex-5-yn-2-benzoyloxy-[3-4-bis-(*tert*-butyldiphenylsilyl)-2-6-dideoxy-2-iodo]-*β*-D-glucopyranoside (24). Iodoacetate **21** (β /α, 9:1 mixture, 50 mg, 0.063 mmol), alkynol acceptor **16**, (28.1 mg, 0.082 mmol), and 4 Å MS (32 mg) were mixed with dry CH_2Cl_2 (1 mL), and the mixture was stirred for 30 min at room temperature. The mixture was cooled to −70 °C and then TBDMSOTf (4.4 μL, 0.019 mmol) was added. After being stirred for 4 h between −70 and −50 °C, the reaction mixture was quenched with Et_3N (0.1 mL) at −70 °C. The cold bath was removed and saturated $NaHCO_3$ was added. Extractive workup (CH_2Cl_2/H_2O) and silica gel chromatography (hexanes:EtOAc, 19:1 to 9:1) afforded glycoside **24** (52.9 mg, 78%) as a white solid. Mp 53−55 °C; $[\alpha]^{23}_D$ +12.6 ($CHCl_3$, *c* 0.84); IR (neat) 2120, 1719, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18−7.19 (m, 25H), 5.72 (dq, J = 6.4, 2.6 Hz, 1H), 5.29 (d, J = 7.8 Hz, 1H), 4.81 (app. t, J = 2.6 Hz, 1H), 4.71 (d, J = 3.2 Hz, 1H), 3.99 (d, J = 7.8 Hz, 1H), 3.85 (app. t, J = 2.6 Hz, 1H), 3.55 (q, J = 6.8 Hz,

1H), 3.41 (d, $J = 3.2$ Hz, 1H), 2.48 (d, $J = 2.6$ Hz, 1H), 1.53 (d, $J = 6.8$ Hz, 3H), 0.98 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.61 (d, $J = 6.6$ Hz, 3H), 0.12 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 136.1, 135.9, 135.8, 133.1, 132.9, 132.9, 132.6, 132.5, 130.7, 130.0, 129.9, 129.8, 129.7, 129.7, 128.2, 127.8, 127.6, 127.5, 104.8, 83.6, 82.7, 79.7, 79.4, 74.1, 74.0, 71.6, 65.5, 31.6, 29.7, 28.7, 27.0, 26.9, 25.7, 19.6, 19.0, 18.6, 18.2, 16.0, 14.12, −4.8, −5.10; HRMS (FAB$^+$) Calcd for $C_{57}H_{73}IO_7Si_3Li$ [$(M + Li)^+$] 1087.3914, found 1087.3869. Anal. Calcd for $C_{57}H_{73}IO_7Si_3$: C, 63.31; H, 6.80. Found: C, 63.25; H, 6.74.

4-*O*-[3,4-Bis-(*tert*-butyldimethylsilyl)-2,6-dideoxy-*β*-D-allopyranosyl]-3-(*tert*-butyldimethylsilyl)-1-5-anhydro-2,6-dideoxy-D-*ribo*--hex-1-enitol (27). The representative procedure described for glycal **11** was employed except DABCO was used as the tertiary amine base instead of Et_3N. Thus a mixture of alkynol **26** (0.360 g, 0.6 mmol), $W(CO)_6$ (53 mg, 0.15 mmol), DABCO (175 mg, 1.56 mmol, dried azeotropically), and THF (5 mL) was irradiated under N_2 for 5 h. The solvent was removed under reduced pressure to give crude reaction mixture, which was purified by careful column chromatography (pentane:Et_3N, 99:1) to give the desired disaccharide **27** (252 mg, 70%) as a colorless oil. $[\alpha]^{23}_D + 141$ ($CHCl_3$, *c* 0.50); IR (neat) 3064, 2931, 1642, 1472, 1254, 1087, 837, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (app. d, $J = 8.0$ Hz, 1H), 4.92 (dd, $J = 9.5$, 1.8 Hz, 1H), 4.77 (app. t, $J = 5.7$ Hz,1H), 4.21 (dd, $J = 5.7$, 3.6 Hz, 1H), 4.09 (dq, $J = 10.2$, 4.2 Hz, 1H), 3.98 (br dd, $J = 3.9$, 1.8 Hz, 1H), 3.83 (dq, $J = 7.6$, 6.3 Hz, 1H), 3.42 (dd, $J = 10.4$, 3.9 Hz, 1H), 3.17 (dd, $J = 9.2$, 2.4 Hz, 1H), 1.99 and 1.94 (ddd, $J = 13.4$, 4.2, 1.8 Hz, 1H), 1.68, 1.64, and 1.61 (ddd, $J = 13.2$, 3.8, 2.1 Hz), 1.27 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.60, 102.91, 99.52, 80.50, 75.42, 69.97, 69.25, 69.18, 64.19, 39.64, 26.12, 26.09, 25.89, 18.71, 18.46, 18.20, 18.17, 17.42, −3.36, −4.04, −4.20, −4.47, −4.52, −4.62; HRMS (FAB$^+$) Calcd for $C_{30}H_{62}O_6Si_3Li$ [$(M + Li)^+$], 609.4014, found 609.4025. Anal. Calcd for $C_{30}H_{62}O_6Si_3$: C, 59.75; H, 10.36. Found: C, 59.97; H, 10.33.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for compounds **2**−**7**, **8a**, **8b**, **9a**, **9b**, **10**, **12a**, **12b**, **13a**, **13b**, **16**, **23a**, **23b**, **25a**, **25b**, and **26** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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