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Exploring Skeletal Diversity via Ring Contraction of Glycal-Derived Scaffolds

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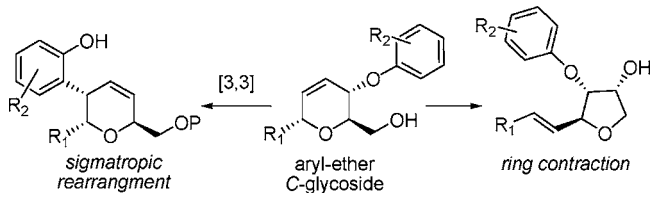
ABSTRACT



Aryl ether *C*-glycoside scaffolds have been prepared from tri-*O*-acetyl-D-glucal by *C*-glycosylation followed by allylic substitution with phenols mediated by Pd(0). The aryl ethers were subjected to either [3,3]-sigmatropic rearrangement to produce 3-pyranyl-phenols or Au(III)-mediated ring contraction to create highly substituted tetrahydrofurans.

The synthesis of focused, chemical libraries provides incentive and inspiration for the discovery of novel chemical reactions. Glycals are excellent starting scaffolds for library development due to their rigid structures and inherent stereochemical diversity. These attributes have previously been exploited in the synthesis of carbohydrate-based scaffolds.[1] Recently, diversity-oriented synthesis (DOS)[2] has increasingly emphasized skeletal diversity[3] involving the structural manipulation of scaffolds and synthesis of molecules with distinct skeletal frameworks.[4] However, sequences involving rearrangement or fragmentation processes are highly underdeveloped[5] and should continue to receive attention. Herein, we present a synthetic sequence for the creation of novel cyclic ethers featuring an unexpected skeletal modification of a glycal-derived scaffold discovered during library development.

Our initial plan entailed addition of various carbon nucleophiles to commercially available tri-*O*-acetyl-D-glucal (**1**) to afford a series of *C*-glycoside scaffolds **2a**−**c** (Scheme 1). Nucleophilic addition of phenols mediated by Pd(0) to the resulting allylic alcohol[6] would provide allylic ethers **3a**−**c** in a second diversification step. We anticipated that **3a**−**c** would be novel frameworks for skeletal diversification. For example, [3,3]-sigmatropic rearrangement of the allyl phenyl ethers may be used to effect positional diversification of the scaffolds (compounds **4a**−**c**) while unveiling a phenol for further diversification. Additionally, we serendipitously

(1) For recent examples, see: (a) Kubota, H.; Lim, J.; Depew, K. M.; Schreiber, S. L. *Chem. Biol*. **2002**, *9*, 265. (b) Jain, R.; Kamau, M.; Wang, C.; Ippolito, R.; Wang, H.; Dulina, R.; Anderson, J.; Gange, D.; Sofia, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2185. (c) Hunger, U.; Ohnsmann, J.; Kunz, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1104. (d) Hotha, S.; Tripathi, A. *J. Comb. Chem.* **2005**, *7*, 968. (e) Moilanen, S. B.; Tan, D. S. *Org. Biomol. Chem.* **2005**, *3*, 798.

(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Hirschmann, R.; Ducry, L.; Smith, A. B. *J. Org. Chem.* **2000**, *65*, 8307. (c) Krueger, E. B.; Hopkine, T. P.; Keaney, M. T.; Walters, M. A.; Boldi, A. M. *J. Comb. Chem.* **2002**, *4*, 229. (d) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (e) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095. (f) Kim, Y.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F., III.; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc*. **2004**, *126*, 14740. (g) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163.

(3) (a) Couladouros, E. A.; Sronglios, A. T. *Angew. Chem., Int. Ed*. **2002**, *41*, 3677. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613. (c) Oguri, H.; Schreiber, S. L. *Org. Lett*. **2005**, *7*, 47.

(4) For recent reviews, see: (a) Abel, U.; Koch, C.; Speitling, M.; Hansske, F. G. *Curr. Opin. Chem. Biol.* **2002**, *6*, 453. (b) Ortholand, J. Y.; Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271. (c) Boldi, A. M. *Curr. Opin. Chem. Biol*. **2004**, *8*, 281. (d) Tan, D. S. *Comb. Chem. High Throughput Screening* **2004**, *7*, 631.

(5) For a recent example, see: Kumar, N.; Kiuchi, M.; Tallarico, J. A.; Schreiber, S. L. *Org. Lett*. **2005**, *7*, 2535.

(6) (a) For palladium-mediated phenol addition to allylic carbonates, see: Toste, F. D.; Trost, B. M. *J. Am. Chem. Soc*. **1998**, *120*, 815. (b) For phenol addition to an *O*-pseudoglycal system, see: Sinou, D.; Bedjeguelal, K. *Eur. J. Org. Chem.* **2000**, 4071.

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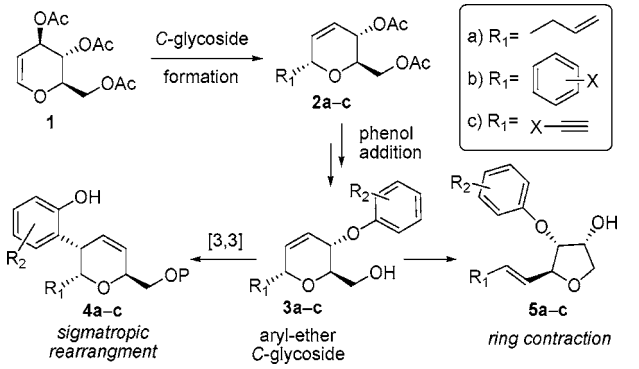
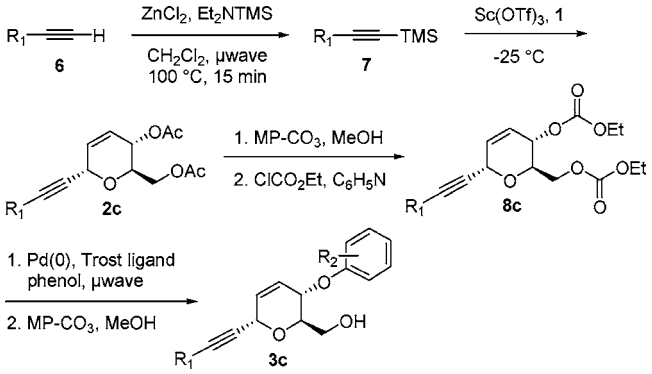
Scheme 1. Synthetic Plan for Diversification of Glycals



discovered conditions that rearrange scaffolds **3a**−**c** to the corresponding trisubstituted tetrahydrofurans **5a**−**c**.

In our initial studies, various carbon nucleophiles (allyl, aryl, and alkynyl) were used to create a diverse set of *C*-glycoside scaffolds (**2a**−**c**).[1a] Allyl *C*-glycoside **2a**[7] was formed using $Sc(OTf)_3$-catalyzed addition of allyl trimethylsilane to glycal **1**.[8] Pd(II)-mediated addition of arylboronic acids to glycals provided convenient access to aryl *C*-glycosides (**2b**).[9] A series of α-alkynyl *C*-glycosides (**2c**) were synthesized via $Sc(OTf)_3$-catalyzed addition of trimethylsilyl (TMS) alkynes **7** (generated in situ via terminal alkynes **6**)[10] to glycal **1** (Scheme 2).[11,12]

Scheme 2



We next pursued modification of the resulting allylic alcohol by palladium-mediated nucleophilic addition of phenols to produce aryl ethers **3a**−**c**.[6] Because the allylic acetates of **2a**−**c** were unreactive to Pd(0) activation, the bisacetates were converted to the corresponding biscarbonates (Scheme 2). Acetate hydrolysis was achieved using a solid-supported macroporous carbonate resin,[13] and the resulting diols were reprotected as bisethyl carbonates (cf. **8c**). We found that the catalyst system employed by Trost and coworkers ($Pd_2(dba)_3$·$CHCl_3$ and the Trost ligands)[14] provided optimal yields of the desired aryl ethers. Microwave irradiation (100 °C, 150−300 W) was employed to reduce reaction times from 12 h (required for thermal reactions) to 15 min.[15]

Phenols were found to add to the pyran ring both regio- and stereoselectively, with a net overall retention of configuration. The same regio- and stereochemistry was obtained when either enantiomeric ligand ((*R*,*R*)- or (*S*,*S*)-Trost ligands) was employed.[16] Interestingly, reactions were unsuccessful when achiral ligands such as diphenylphosphinobutane (dppb) or diphenylphosphinopentane (dppp) were employed. The regio- and stereochemistry of aryl ether additions were determined by examination of an X-ray crystal structure of the *p*-bromobenzoyl carbonate ester derived from an allyl *C*-glycoside.[17,18]

A selection of 12 phenols were evaluated for addition to a phenyl *C*-glycoside (**8a**, R_1 = phenyl) as part of a preliminary rehearsal screen.[19] On the basis of the successful addition of all the phenols, we next evaluated their addition to various *C*-glycosides **8a**−**c** (Figure 1). Diverse phenol

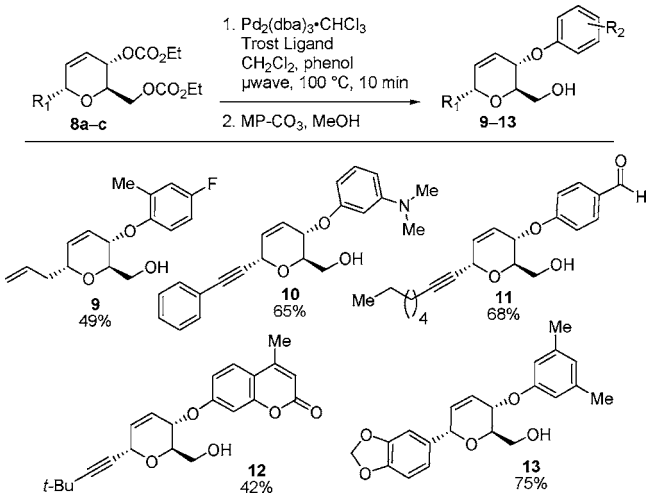


Figure 1. Representative *C*-glycosides prepared via the Pd-mediated aryl etherification.

functionality, including halogens (**9**), ortho substituents (**9**), aldehydes (**11**), nitrogen-containing phenols (**10**), as well as

(7) Lewis acid-catalyzed addition of allyltrimethylsilane to glycals: (a) Danishefsky, S. J.; De Ninno, S.; Lartey, P. *J. Am. Chem. Soc*. **1987**, *109*, 2082. (b) Yadav, J. S.; Reddy, B. V. S.; Chand, P. K. *Tetrahedron Lett*. **2001**, *42*, 4057. (c) Swamy, N. R.; Srinivasulu, M.; Reddy, T. S.; Goud, T. V.; Venkateswarlu, Y. *J. Carbohydr. Chem*. **2004**, *23*, 435.

(8) $Sc(OTf)_3$-catalyzed Ferrier addition to glycals, see ref 9b and: Ben, A.; Yamauchi, T.; Matsumoto, T.; Suzuki, K. *Synlett* **2004**, *2*, 225.

(9) (a) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett*. **2001**, *3*, 2013. (b) Figuera, N.; Forns, P.; Fernandez, J. C.; Fiol, S.; Fernandez-Forner, D.; Albericia, F. *Tetrahedron Lett*. **2005**, *46*, 7271.

(10) Andreev, A. A.; Konshin, V. V.; Komarov, N. V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett*. **2004**, *6*, 421.

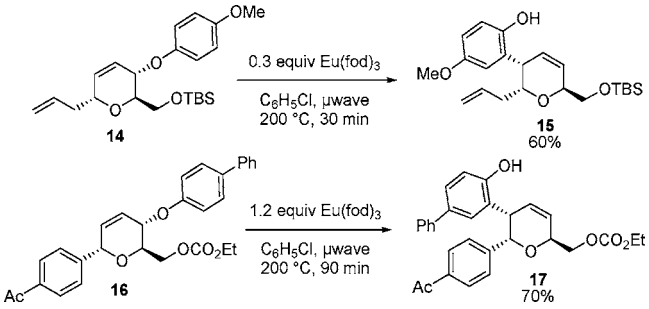
(11) I_2-catalyzed addition of TMS−alkynes to glycals: (a) Yaday, J. S.; Reddy, B. V. S.; Rao, C. V.; Reddy, M. S. *Synthesis* **2003**, 247. (b) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett*. **2003**, *44*, 6211.

(12) For Lewis acids that promote the addition of TMS−alkynes to glycals, see: (a) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett*. **1992**, *33*, 7911. (b) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun*. **1998**, 2665. (c) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett*. **2002**, *43*, 5437. (d) Isobe, M.; Phoosaha, W.; Saeeng, R.; Kira, K.; Yenjai, C. *Org. Lett*. **2003**, *5*, 4883. (e) Smitha, G.; Reddy, C. S. *Synthesis* **2004**, 834.

coumarins (**12**), successfully added to aryl, alkynyl, and allylic *C*-glycosides.

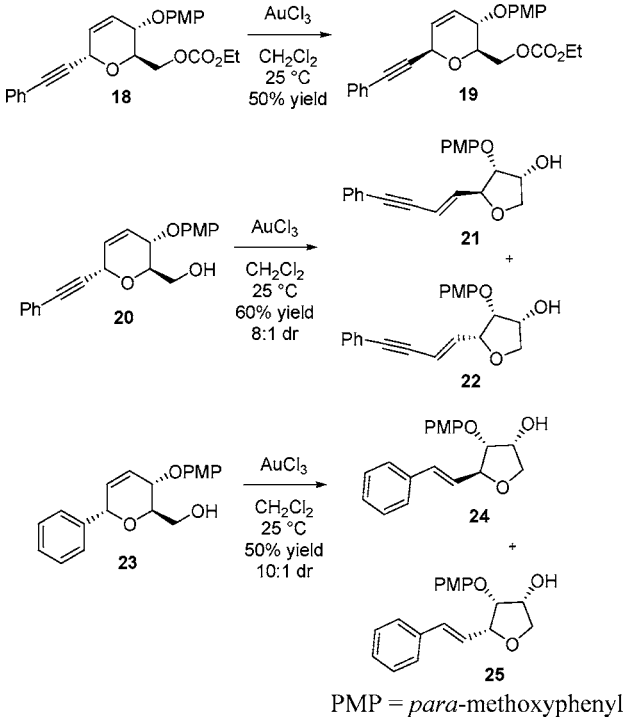
Methods for skeletal diversification were next examined using *C*-glycosides **4a**−**c** (Scheme 3). We first evaluated Eu-

Scheme 3. Europium-Catalyzed Sigmatropic Rearrangement



(III)-catalyzed Claisen rearrangements of allylic *C*-glycosides **4a**−**c**.[6a] The reaction required microwave heating at high temperatures (200−225 °C). Representative allyl (**14**) and aryl (**16**) *C*-glycosides underwent [3,3]-sigmatropic rearrangement to provide the desired phenols. However, preliminary studies demonstrated that alkynyl *C*-glycosides such as **18** (cf. Scheme 4) did not readily undergo rearrangement,

Scheme 4. Reactions of Alkynyl *C*-Glycosides with $AuCl_3$



PMP = *para*-methoxyphenyl

even after prolonged heating with excess $Eu(fod)_3$.

Alternate modifications of the alkynyl *C*-glycosides with alkynophilic Lewis acids were thus considered (Scheme 4).[20] On the basis of reports of gold-catalyzed hydration of alkynes,[21] we evaluated a number of alkynophilic catalysts and conditions to attempt hydration of alkyne **18**. Suprisingly, gold(III) chloride ($AuCl_3$) promoted partial epimerization to the corresponding β-*C*-glycosides (**19**) rather than alkyne hydration. Further experimentation revealed that in the presence of the primary alcohol alkynyl *C*-glycoside **20** was transformed into two new, more polar compounds which were identified as the ring-contracted tetrahydrofurans **21** and **22** (dr = 8:1, based on isolated yields).

The ring contraction was not limited to alkynyl glycosides, as aryl *C*-glycosides (Scheme 4, compound **23**) reacted similarly to provide tetrahydrofurans **24** and **25** (dr = 10:1). The structures of the *p*-bromobenzoyl ester-protected alkyne **22** (minor product) and aryl **24** (major product) were confirmed through X-ray crystallographic analysis.[18]

Other Lewis acids ($AuBr_3$, TfOH, $BF_3{\cdot}OEt_2$, TMSOTf, and $Sc(OTf)_3$) also promoted the ring contraction, albeit in lower conversion and selectivity. Time-dependent ^{1}H NMR studies of the ring contraction with substrate **23** indicate that the ratios of tetrahydrofuran diastereomers did not vary appreciably with time.[18] In addition, small amounts of the α-anomer of **23** (cf. **19**, Scheme 4) were also observed by ^{1}H NMR. The relative amounts of the α-pyran anomer did not change over time indicating that it does not participate in ring contraction.

A proposed mechanism for the ring contraction is illustrated in Scheme 5. We propose that $AuCl_3$ promotes ionization of the doubly activated carbon−oxygen bond of **32** to provide intermediate **33a**.[22] Ring closure then proceeds through allylic carbonium ion intermediates **33b** or **33c**. Tetrahydrofuran **34**, the major product of the reaction, would be afforded via conformer **33b** minimizing $A^{(1,3)}$-strain[23] between the aryl ether and the allylic cation and diaxial interactions with the pseudodiaxial hydrogen relative to conformer **33c**.

(13) Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett*. **1997**, *38*, 7959.

(14) See ref 6a. Trost ligand = (1*R*,2*R*)-(+)- or (1*S*,2*S*)-(−)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl).

(15) (a) Microwave-accelerated asymmetric allylic alkylations: Trost, B. M.; Anderson, N. G. *J. Am. Chem. Soc*. **2002**, *124*, 14320. (b) Reviews of microwave-accelerated organic synthesis: Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Kappe, C. O. *Angew. Chem., Int. Ed*. **2004**, *43*, 6250. (d) Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

(16) For preliminary studies, see: Su, S.; Acquilano, D. E.; Arumugasamy, J.; Beeler, A. B.; Eastwood, E. L.; Giguere, J. R.; Lan, P.; Lei, X.; Min, G. K.; Yeager, A. R.; Zhou, Y.; Panek, J. S.; Snyder, J. K.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett*. **2005**, *7*, 2751.

(17) This product may be predicted by the Trost mnemonic using the (*R*,*R*)-(+)-Trost ligand. See ref 6a and: Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc*. **1992**, *114*, 9327.

(18) See Supporting Information for details.

(19) For a recent example of rehearsal screening for library synthesis, see: Beeler, A. B.; Acquilano, D. E.; Su, Q.; Yan, F.; Roth, B. L.; Panek, J. S.; Porco, J. A., Jr. *J. Comb. Chem*. **2005**, *7*, *673*.

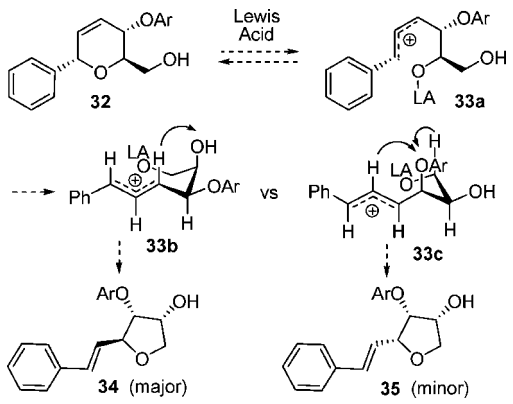
(20) Recent reviews on gold catalysis: (a) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem*. **2004**, *8*, 795. (b) Hoffmann-Roder, A.; Krause, N. *Org. Biomol. Chem*. **2005**, *3*, 387.

(21) Au-catalyzed hydration of alkynes: (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed*. **2002**, *41*, 4563. (b) Vasudevan, A.; Verzal, M. K. *Synlett* **2004**, *4*, 631.

(22) Acid-catalyzed ionization of alkynyl *C*-glycosides complexed with $Co_2(CO)_8$ has been shown to afford ring-opened products: Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett*. **1993**, *34*, 5757.

(23) Johnson, F. *Chem. Rev*. **1968**, *68*, 375.

Scheme 5. Proposed Mechanism for the Lewis Acid-Catalyzed Ring Contraction



A series of the *C*-glycosides **4a**−**c** were subjected to $AuCl_3$-mediated ring contraction to evaluate the scope of the reaction. Examples of successful contractions are shown in Figure 2 with substitutions on both the *C*-glycoside append-

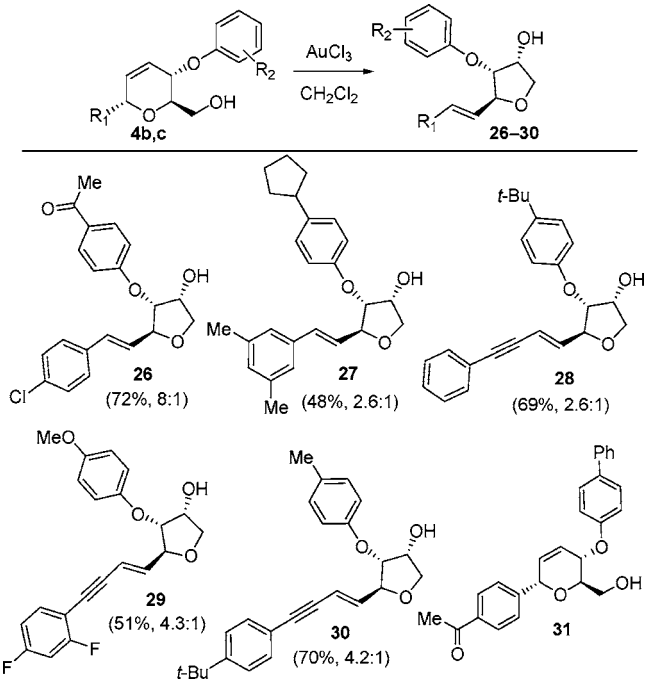


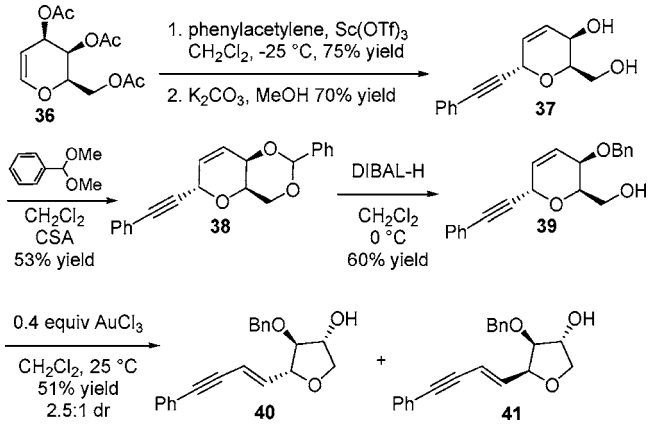
Figure 2. Au(III)-catalyzed ring contraction of aryl ether *C*-glycosides (yield, dr).

age and the aryl ether. Although aryl (**26**, **27**) and alkynyl (**28**−**30**) glycosides underwent ring contraction, the allyl *C*-glycosides (cf. **9**) were found to be unreactive.

In some cases, significant amounts (26% for **26**, 13% for **28**) of the tetrahydrofuran (**4b**,**c**) β-anomer were recovered. Incompatible functional groups such as aldehydes (**11**) and tertiary anilines (**10**) resulted in decomposition. Electron-deficient aryl *C*-glycosides (**31**) did not undergo ring contraction, likely due to their inability to support the proposed allylic carbonium ion intermediate (cf. Scheme 5, **33a**). In addition, electron-rich aryl glycoside substrates (cf. Figure 1, **13**) did not undergo clean ring contraction and led to a variety of other products.

The stereochemical diversity of tetrahydrofurans produced by the ring contraction was addressed using tri-*O*-acetyl-D-galactal (Scheme 6). TMS−phenylacetylene added to galactal

Scheme 6. Synthesis of Galactal-Derived Tetrahydrofurans **40** and **41**



36 in 75% yield under standard conditions.[24] The biscarbonate of **37** was found to be unreactive under the previous Pd(0) conditions that were successful for the glycal system and was therefore converted to a benzyl ether **39** (via aryl acetonide **38**) for ring contraction. The resulting tetrahydrofurans **40** and **41** were obtained in 51% overall yield (dr = 2.5:1).[18] The diastereoselectivity of this reaction is most likely controlled by minimization of strain between the benzyl ether and the newly formed enyne.

In summary, we have demonstrated the utility of aryl ether *C*-glycosides for rapid conversion to novel skeletal frameworks via either [3,3]-sigmatropic rearrangment or Au(III)-mediated ring contraction to highly substituted tetrahydrofurans. Further efforts are currently underway to expand the ring contraction methodology to related reaction types as well as to evaluate the biological activity of these novel compounds.

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Supporting Information Available: General information, selected spectral data, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For a previous example of TMS−alkyne addition to tri-*O*-acetal-D-galactal, see ref 12c.