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Synthesis of *C*-aryl-$\Delta^{2,3}$-glycopyranosides via uncatalyzed addition of triarylindium reagents to glycals ☆

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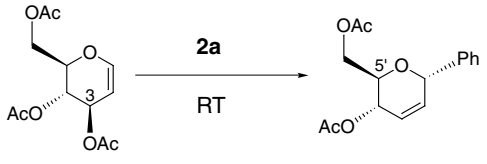
Abstract—2,3-Unsaturated-*C*-aryl glycopyranosides are important intermediates in the synthesis of medicinally important *C*-aryl glycosides. Treatment of glycal acetates with triarylindiums in ether at room temperature gives good yields of *C*-aryl-$\Delta^{2,3}$-glycosides of predominantly α-configuration. The mechanism of this reaction likely involves the formation of an oxocarbenium ion intermediate via indium(III) Lewis acid-assisted ionization of the glycal C.3 acetate. Coupling of trivinyl- and tris(alkynyl)indiums with glycals similarly led to *C*-vinyl- and *C*-alkynyl-$\Delta^{2,3}$-glycosides in good yield.

The great current interest in *C*-aryl glycosides stems from their occurrence in natural products, which possess important medicinal and therapeutic properties.[1] *C*-aryl glycopyranosides with a double bond in the 2,3-position are useful synthetic intermediates, since this unsaturation can be further functionalized to produce an array of complex carbohydrates.[2] Several synthetic methods allow access to such compounds, many relying on the addition of organometallic reagents to hex-2-enopyranosides.[3–5] Although these approaches give good yields of the desired glycosides, air- or moisture-sensitive, toxic, and/or pyrophoric reagents are frequently employed, and expensive transition metal catalysts are often required. Furthermore, strongly basic or acidic reaction conditions limit the functionality that can be employed in either the aryl or carbohydrate coupling partner. As an alternative, we sought to use easily prepared arylindiums as nucleophiles for the construction of *C*-aryl glycosides. These reagents are attractive because of their low toxicity, air- and moisture stability, wide functional group tolerance, and atom efficiency.[6,7]

The uncatalyzed addition of arylzinc species to glycal acetates has recently been reported.[8] Although triarylindiums are expected to be less reactive than organozincs, we hoped that the Lewis-acidic character of the organoindium reagent[6] might assist the reaction through an S_N1 manifold. Indeed, stirring tri-*O*-acetyl-D-glucal **1** in ether with 1 equiv of triphenylindium **2a** at room temperature for 24 h furnished the desired glycoside **3a** in 95% yield with 5:1 α/β selectivity (Table 1).

Table 1. Uncatalyzed addition of Ph_3In **2a** to tri-*O*-acetyl-D-glucal **1**[a]



1 **3a**

Entry	Eq. **2a**	Solvent	Time	Yield **3a**	α:β
1	1.0	Et_2O	24 h	95	5:1
2	0.50	Et_2O	48 h	90	5:1
3	0.33	Et_2O	48 h	40	5:1
4[b]	1.0	CH_2Cl_2	24 h	90	6:1
5[b]	0.50	CH_2Cl_2	24 h	93	6:1
6[b]	0.33	CH_2Cl_2	24 h	86	6:1
7[b]	1.0	Toluene	24 h	92	6:1
8	1.0	THF	24 h	<5	—
9[b]	1.0	CH_3CN	48 h	20	—

[a] Reactions were run at a concentration of 0.1 M glycal in the solvent listed.

[b] Reactions in CH_2Cl_2, toluene, and CH_3CN were performed by evaporating ether or THF from the indium reagent and redissolving the residue in the appropriate solvent, followed by addition of the carbohydrate.

Keywords: Glycals; Triorganoindiums; C-glycosidation.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.05.046

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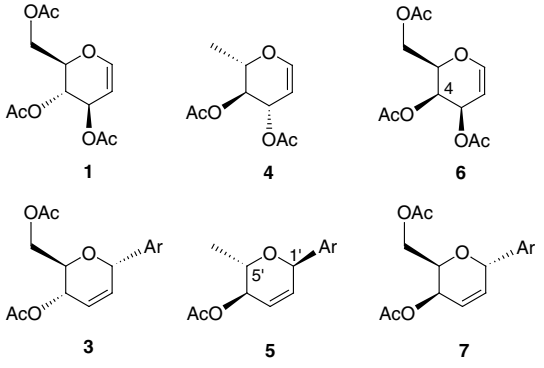
Nonpolar solvents such as ether, dichloromethane, and toluene proved to be the media of choice, with reactions performed in dichloromethane and toluene giving slightly better stereoselectivities than those run in ether (Table 1, entries 1, 4 and 7). Reactions performed in either THF or acetonitrile gave negligible quantities of glycoside **3a**, even after 48 stirring at room temperature (entries 8 and 9).

Since the atom efficiency of organoindium reagents in cross-coupling reactions has been well documented,[9] we attempted the coupling reaction described above with substoichiometric amounts of arylindium reagent (Table 1, entries 1–3 and 4–6). High yields were obtained after 24 h for reactions performed in dichloromethane employing either 0.50 or 0.33 equiv of **2a**; in ether, a longer reaction time (48 h) was required to obtain moderate to high yields of **3a** employing 0.33 or 0.50 equiv of **2a**, respectively.[10] These data suggest that all three aryl groups on indium are indeed capable of participating in the carbon–carbon bond-forming process.

The scope of the reaction was assessed by coupling a variety of arylindiums with glucal (**1**), rhamnal (**4**) and galactal (**6**) acetates (Table 2). Yields were good in the majority of cases, and even sterically hindered glycosides could be prepared efficiently (entries 5, 10, and 12). The α-configured[11] *C*-aryl-$\Delta^{2,3}$-glycoside is obtained predominantly in most instances, with electron poor arylindiums (entries 2, 3, and 8) generally giving better α-selectivities than electron rich (entries 6 and 11), an observation not unprecedented in Lewis-acid mediated C-glycosidation chemistry.[12] Furthermore, the solvent effect on stereoselectivity is more pronounced when electron-rich arylindiums are employed in the glycosylation (Table 2, compare entries 3 and 6 and Table footnotes c and d), implying the possible intermediacy of a carbohydrate-derived carbocation (vide infra).[13] The consistently high α-selectivity observed for products **7a**, **7c**, **7d** derived from glycosidation of **6** (entries 13–16) reflects the steric influence of the galactal axial C.4 acetate on the course of the addition reaction.[14] Product stereochemistries were confirmed by direct comparison with literature data and spectra[2] and also by ^{13}C NMR spectroscopy (as has been noted previously, the carbon chemical shift of *C5′* is diagnostic of the stereochemistry at the anomeric position[15]).

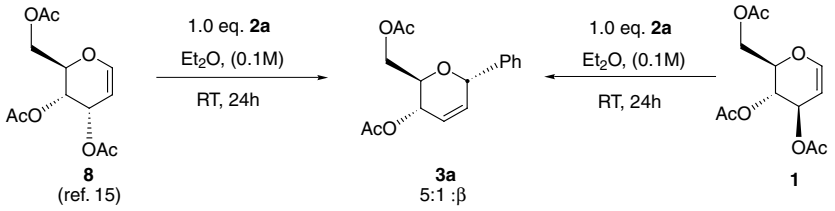
To further probe the mechanism of this reaction, we prepared tri-*O*-acetyl-D-allal **8**, the C.3 epimer of glucal, according to the protocol of Danishefsky.[16] This compound was subjected to 1 equiv of triphenylindium **2a** in ether at room temperature for 24 h (Scheme 1).

Table 2. Triarylindium additions to glycals **1**, **4**, and **6** in ether[a]

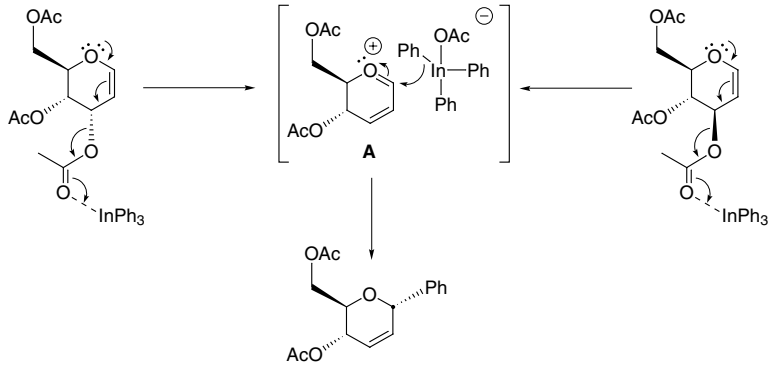


Entry	Glycal	**2** Ar_3In	**Ar**	Product	α:β	Yield
1	**1**	**2a**	Ph	**3a**	5:1	95
2	**1**	**2b**	3-F-Ph	**3b**	6:1	45
3[c]	**1**	**2c**	4-Cl-Ph	**3c**	6:1	89
4[b]	**1**	**2d**	4-Me-Ph	**3d**	6:1	68
5[b]	**1**	**2e**	2-Me-Ph	**3e**	4:1	55
6[d]	**1**	**2f**	4-OMePh	**3f**	1:1.5	75
7	**4**	**2a**	Ph	**5a**	5:1	60
8	**4**	**2c**	4-Cl-Ph	**5c**	5:1	70
9	**4**	**2d**	4-Me-Ph	**5d**	3:1	95
10[b]	**4**	**2e**	2-Me-Ph	**5e**	4.5:1	70
11	**4**	**2f**	4-OMePh	**5f**	1:1	55
12[b]	**4**	**2g**	2-Napththyl	**5g**	3:1	67
13	**6**	**2a**	Ph	**7a**	10:1	50
14	**6**	**2c**	4-Cl-Ph	**7c**	10:1	50
16	**6**	**2d**	4-Me-Ph	**7d**	10:1	80

[a] All reactions were run at a concentration of 0.1 M glycal and organo-indium in ether at room temperature for 24 or 48 h.
[b] The reaction took 48 h to reach completion.
[c] The reaction in CH_2Cl_2 gave 6:1 α:β **3c** in 92% yield.
[d] The reaction in CH_2Cl_2 gave 4:1 α:β **3f** in 90% yield.



Scheme 1. Reactions of allal **8** and glucal **1** with Ph_3In.



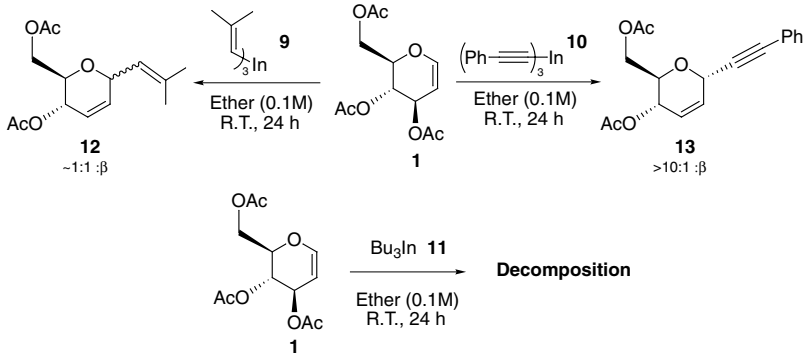
Scheme 2. Mechanistic proposal.

The coupling reaction gave the same stereoisomeric ratio of products (5:1 α:β) and approximately the same yield (95%) of **3a** as the analogous reaction of glucal **1** with **2a**. This result lends support to the proposal that the reaction proceeds through a common cationic intermediate, such as that represented by structure **A** (Scheme 2).

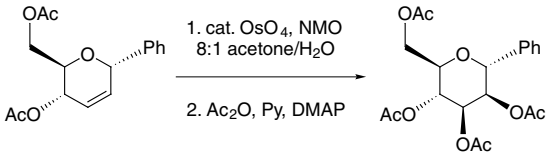
The triarylindium reagent acts as a Lewis acid in coordinating a lone pair on the C.3 acetate ester, thus facilitating an S_N1 ionization process (assisted by lone-pair donation from the pyranyl oxygen) that leads to **A**. The nucleophilic indate species[17] formed transfers a phenyl ligand preferentially to the more electrophilic C.1 carbon of the carbohydrate, furnishing the observed products. The resulting diorganoindium species can enter another reaction cycle with **1** (or **8**) in which it can again act as a Lewis acid and transfer another phenyl ligand to **A**.[18] Kinetically preferred axial addition of the carbon nucleophile is observed in most cases,[12c] except for very electron-rich nucleophiles, which can effectively compete with the counterion/solvent to occupy the sterically less-demanding β-face of the oxocarbenium ion.[13]

Finally, we studied the coupling reactions of alkenyl, alkynyl, and alkylindiums with glucal (Scheme 3). Reaction of 1 molar equivalent of tris(2-methylpropenyl)indium **9** with **1** in ether for 24 h gave a ~1:1 mixture of α:β *C*-vinyl-$\Delta^{2,3}$-glycosides **12** in 75% yield. In contrast, reaction of tris(phenylethynyl)indium **10** with **1** gave an 11:1 mixture of α:β *C*-alkynyl-$\Delta^{2,3}$-glycosides **13**[19] in 55% yield. Tributylindium **11** gave no addition products when combined with **1** in ether for 24–48 h, instead producing polar compounds likely resulting from acetate cleavage/hydrolysis.

The 2,3-unsaturated C-glycoside products of these reactions can be stereoselectively transformed into *C*-aryl glycosides[20] by dihydroxylation with OsO_4. For example, applying the UpJohn protocol[21] for catalytic



Scheme 3. Reaction of organoindiums **9**, **10**, and **11** with **1**.



Scheme 4. Preparation of *C*-aryl glycoside **14** via dihydroxylation.

osmylation to α-*C*-phenyl-$\Delta^{2,3}$–glycoside **3a**, followed by acylation (Ac_2O, pyridine, cat. DMAP) gives exclusively α-phenyl-mannoside **14**[22] in 85% overall yield, in which the hydroxyl groups have been introduced from the face of the carbohydrate opposite the aromatic moiety (Scheme 4). Although numerous *C*-glycosyl flavonoids that have been isolated possess a β-*C*-glycosidic linkage,[23] there are notable and important exceptions.[24] Since only a few procedures currently exist that provide access to α-*C*-aryl glycosides,[25] this mild, stereoselective sequence should prove of great utility in the synthesis of this class of compounds.

In summary, triorganoindiums are mild, atom-efficient and environmentally friendly reagents that can be employed in the preparation of a diverse array of 2,3-unsaturated C-glycosides.

Supplementary material

Complete experimental details and spectroscopic data for all compounds prepared in Table 2 and Schemes 4 and 6.

Acknowledgements

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References and notes

1. (a) Baycroft, B. W. *Dictionary of Antibiotics and Related Substances*; Chapman and Hall: London, 1988; (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2473; (c) Faulknew, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7–55; (d) Hacksell, U.; Davies, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1–65; (e) Franz, G.; Grun, M. *Planta Med.* **1983**, *47*, 131–140; (f) Suzuki, K.; Matsumoto, T. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, pp 352–403.
2. Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013–2015.
3. (a) Kwok, D.-I.; Farr, R. N.; Daves, G. D. *J. Org. Chem.* **1991**, *56*, 3711–3716; (b) Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533–538; (c) Daves, G. D. *Acc. Chem. Res.* **1990**, *23*, 201–220.
4. (a) Moineau, C.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1998**, *63*, 582–597; (b) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890–1896.
5. (a) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812–2815; (b) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89–91.
6. Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160.
7. Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267–1269.
8. Steinhuebel, D. P.; Fleming, J. F.; DuBois, J. *Org. Lett.* **2002**, *4*, 293–295.
9. For the initial report, see: Nomura, R.; Miyazaki, S.-I.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2738–2741.
10. Interestingly, whereas reactions carried out in CH_2Cl_2 were completely homogenous, reactions performed in ether or toluene had visible white precipitates that did not dissolve throughout the course of the reaction.
11. For C-glycosides **5** derived from di-*O*-acetyl-L-rhamnal **4**, the 'α-configuration' corresponds to a *trans* relationship between the substituents at C1′ and C5′ (Table 2).
12. (a) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289–4296; (b) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815–6818; (c) Nicotra, F. *Topics Curr. Chem.* **1997**, *187*, 55–83.
13. In ether, a 'cation-solvating' solvent, only electron-rich arylindiums can effectively compete with the solvent for addition to both sides of the oxonium ion; in the less polar CH_2Cl_2, a tight ion pair (with AcO^- or Cl^-) prevents the addition of nucleophiles to the less-hindered β-face of the oxonium ion. See Ref. 12a for a discussion of solvent effects on the stereochemistry of glycosidation.
14. Ferrier, R. J. *Topics Curr. Chem.* **2001**, *215*, 153–175.
15. The *gauche* effect predicts that C1′ and C5′ of α-glycopyranoside anomers will be shielded with respect to the corresponding carbons of the β-anomers: (a) Brakta, M.; Farr, R. N.; Chaguir, B.; Massiot, G.; Lavaud, C.; Anderson, W. R.; Sinou, D.; Daves, G. D. *J. Org. Chem.* **1993**, *58*, 2992–2998; (b) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1973; Chapter 3; (c) Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1988; Chapter 3.
16. Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J.; Golik, J.; Vyas, D. *J. Org. Chem.* **1990**, *55*, 1979–1981.
17. (a) Lee, P. H.; Lee, S. W.; Saemoon, D. *Org. Lett.* **2003**, *5*, 4963–4966; (b) Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *Chem. Commun.* **1991**, 824–825.
18. The weakness of the indium-carbon bond (~40 kcal/mol) has been cited as a possible reason for the atom efficiency of indium reagents in transferring their organic ligands (replacing them preferentially with more electronegative substitutents, such as halides); see Refs. 9 and 6.
19. (a) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett.* **2002**, *43*, 5437–5440; (b) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211–6215; (c) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Reddy, M. *Synthesis* **2003**, *2*, 247–250.
20. For previous literature on *C*-aryl glycoside synthesis, see: (a) Jaramillo, C.; Knapp, S. *Synthesis* **1993**, 1–20; (b) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913–9959; (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC: Boca Raton, 1995; (d) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995.
21. (a) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976; (b) Van Rheenen, V.; Cha, D. Y.; Hartley, W. M. *Org Synth. Coll.* **1988**, *6*, 342–347.
22. (a) Cettour, P.; Descotes, G.; Praly, J.-P. *J. Carbohydr. Chem.* **1995**, *14*, 445; (b) El Bahij, S.; Abbes, O.; Neuman, A.; Gillier-Pandraud, H. *Carbohydr. Res.* **1993**, *244*, 197–

204; (c) Bellosta, V.; Chassagnard, C.; Czernecki, S. *Carbohydr. Res.* **1991**, *219*, 1–7.
23. Wagner, H. *Fortschr. Chem. Organ. Naturst.* **1974**, *31*, 153–216.
24. Angucyclines: Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103–137; Epiorientin: Bhatia, V. K.; Seshadri, T. R. *Phytochemistry* **1967**, *6*, 1033–1034; Parkinsonin B: Bhatia, V. K.; Gupta, S. R.; Seshadri, T. R. *Tetrahedron* **1966**, *22*, 1147–1152; (a) There appears to be dispute over the structures of Epiorientin and Parkinsonin B; see Besson, E.; Chopin, J.; Gunasegaran, R.; Nair, A. G. R. *Phytochemistry* **1980**, *19*, 2787–2788; (b) Kumazawa, T.; Kimura, T.; Matsuba, S.; Sato, S.; Onodera, J. *Carbohydr. Res.* **2001**, *334*, 183–193.
25. See Refs. 8, 12a, and the following: (a) Schmidt, R. R.; Effenberger, G. *Liebigs Ann. Chem.* **1987**, 825–831; (b) Cai, M. S.; Qui, D.-X. *Carbohydr. Res.* **1989**, *191*, 125–129; (c) Verlhac, P.; Letreux, C.; Toupet, L.; Verrieres, A. *Carbohydr. Res.* **1996**, *291*, 11–20; (d) Rousseau, C.; Martin, O. R. *Org. Lett.* **2003**, *5*, 3763–3766.