Published in final edited form as:

Tetrahedron Lett. 2013 December 11; 54(50): 6889–6891. doi:10.1016/j.tetlet.2013.10.031.

Preparation of C-arylglycals via Suzuki-Miyaura cross-coupling of dihydropyranylphosphates

Michelle R. Leidy, J. Mason Hoffman, and Rongson Pongdee*

Department of Chemistry, Sewanee: The University of the South, 735 University Avenue, Sewanee, TN 37383-1000, USA

Abstract

The preparation of C-arylglycals has been accomplished employing the Suzuki-Miyaura cross-coupling reaction of dihydropyranylphosphates with arylboronate esters. The reaction is tolerant of both electron-donating (EDG) and electron-withdrawing (EWG) groups on the aromatic ring and affords the corresponding C-arylglycals in good to excellent yields (68-97%). Additionally, the ketene acetal phosphate derived from 6-deoxy-3,4-di-O-benzyl-L-rhamnal also couples efficiently to yield C-arylglycals in excellent yields.

Keywords

carbohydrates; deoxysugars; glycosides; natural products; Suzuki-Miyaura

C-Glycosides are prevalent structural features among glycosylated secondary metabolites, many of which possess intriguing and potent biological activities that may find clinical use for the treatment of a number of infectious diseases.¹ Some representative examples include aquayamycin (**1**), galtamycin (**2**), and medermycin (**3**) to mention only a few.² This general class of compounds has attracted considerable attention from medicinal chemists as biological probes or enzyme inhibitors due to their increased resistance to chemical or biological degradation. In addition, investigations by Kishi and others have found that C- and O-glycosides exhibit similar three-dimensional conformations in solution making C-glycosides ideally suited to serve as substrate mimics to investigate various biological phenomena.³

Over the years, numerous synthetic approaches have been reported for the construction of C-arylglycals.⁴ The development of these methods has primarily been fueled by the pivotal role that C-arylglycals perform as synthetic precursors for the establishment of 2-deoxy-β-C-aryl glycosidic linkages. While aspects of these processes are attractive, potential drawbacks relating to the strong acidity or basicity of the reaction conditions, the required

© 2013 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: +1-931-598-1846; fax: +1-931-598-1145; rpongdee@sewanee.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

stereochemical assembly of the glycosyl donors, the extremely fragile nature of the necessary starting materials, or difficulties associated with controlling the regiochemical incorporation of the sugar unit may hinder their applicability for the rapid development of C-arylglycosides as potential medicinal compounds.

To circumvent these obstacles toward the efficient synthesis of C-arylglycals, we envisioned the functionalization of sugar lactones as an ideal method for the construction of this important architectural motif. More specifically, we desired to explore the feasibility of utilizing carbohydrate-derived ketene acetal phosphates within the context of a Suzuki-Miyaura cross coupling reaction with arylboronate esters. Over the years, transition-metal mediated approaches toward the construction of complex structural frameworks have undergone exponential growth.⁵ While the use of phosphate electrophiles has been previously documented, we were surprised by the relatively few examples utilizing this functional group, compared to halogens or sulfonates, despite their ready availability and ease of preparation.⁶

Our initial efforts focused on identifying the optimal reaction conditions for our proposed reaction and are shown in Table 1. We were pleased to observe that all of the conditions we attempted resulted in the formation of **6a**, establishing the feasibility of our proposed coupling process. Additionally, palladium catalysis utilizing either Cl₂Pd(dppf) or (Ph₃P)₄Pd, proved substantially more efficient than NiCl₂(PCy₃)₂, which had been shown to work well for the coupling of arylphosphates with arylboronic acids.⁷ Furthermore, the difference in yield was negligible when triethylamine (Et₃N) was employed as an additive (entry 5 versus entry 4). However, previous reports from our laboratory had detailed the beneficial effects of incorporating Et₃N in the reaction mixture and we elected to continue its use in the development of our method.⁸

With the results of our initial feasibility and optimization study in-hand, we turned our attention toward exploring the substrate scope for our newfound process. We envisioned exploring both substituted electron-poor and electron-rich arylboronate esters to determine the overall robustness of our method. As depicted in Table 2, a wide-range of substrates coupled efficiently under our optimized conditions to provide the corresponding C-arylglycals. Yields were excellent, across the board, and varied marginally among *ortho*- (entries 1-3), *meta*- (entries 4-7), and *para*- (entries 8-15) substituted arylboronate esters.⁹ Additionally, the cross-coupling of electron-rich arylboronate esters, substrates that sometimes prove difficult, almost universally afforded C-arylglycals in excellent yields. We believe it is worth mentioning that unlike other palladium-catalyzed syntheses of C-arylglycals employing either pyranilindium or glycal tin reagents, the use of ketene acetal phosphate electrophiles did not result in the formation of any dimerized by-products derived from **4**.^{4g,4t} Furthermore, while structurally similar ketene acetal triflates have been utilized in cross-coupling events, these intermediates suffer from instability as well as poor conversions in both their formation and subsequent bond-forming reactions.¹⁰ On the other hand, cyclic ketene acetal phosphates enjoy significantly higher stabilities as well as dramatically improved coupling efficiencies, as witnessed not only in our method, but in related systems as well.¹¹

With our survey of substrate scope complete, we next focused on extrapolating our model system to actual sugar substrates. Since numerous biologically-active secondary metabolites possess 2,6-dideoxy- β -C-aryl glycosidic linkages, we elected to investigate the coupling of the ketene acetal phosphate derived from L-rhamnal as illustrated in Scheme 1.¹² Our synthesis originated with 3,4-di-*O*-acetyl-L-rhamnal (**7**), which is readily available from L-rhamnose via a Fischer-Zach reaction sequence.¹³ As such, Zémlen deacetylation of **7** using catalytic sodium methoxide (NaOCH₃) followed by benzylation of the resulting diol under standard conditions (BnBr, NaH) furnished 3,4-di-*O*-benzyl-L-rhamnal (**8**) in excellent overall yield for the two-step process.^{4x} Next, subjection of glycal **8** to an oxymercuration/demercurization sequence, as described by Piancatelli, afforded the C(1)-OH as a mixture of anomers that was immediately treated with buffered pyridinium chlorochromate (PCC) to afford the necessary lactone intermediate **9** in good yield.¹³⁻¹⁵ Employing similar conditions for the formation of model phosphate **4**, lactone **9** was smoothly converted to ketene acetal phosphate **10** employing lithium bis(trimethylsilyl)amide (LHMDS) and diphenylphosphoryl chloride.¹⁶ At this juncture, we were now poised to examine the applicability of our method to a real sugar substrate. Disappointingly, our initial attempts at the conversion of phosphate **10** to C-aryl glycal **11** proved unsuccessful. After careful consideration, we postulated that chelation of the palladium catalyst to the electron-rich oxygen atoms present in **10** was inhibiting the progress of the reaction.^{4i,17} With this in mind, we were gratified to observe the formation of C-aryl glycal **11** in excellent yield (88%) upon increasing the catalyst loading to twenty mole percent.

In summary, we have developed an efficient and robust method for the construction of C-aryl glycols from dihydropyranolphosphates with arylboronate esters under Suzuki-Miyaura conditions. Our method is flexible and is tolerant of various electron-donating and electron-withdrawing groups at the *ortho*-, *meta*-, and *para*- positions on the aromatic ring. Additionally, carbohydrate-derived ketene acetal phosphates work equally well to produce more complex C-aryl glycols as exemplified by the synthesis of **11**. Furthermore, the endocyclic olefin of **11** can be readily reduced to afford the corresponding 2-deoxy- β -C-aryl glycosidic linkage, prevalent among angucycline antitumor antibiotics, employing either catalytic hydrogenation over Adam's catalyst (H₂/PtO₂) or sodium cyanoborohydride (NaBH₃CN) in ethanolic hydrochloric acid.^{4i,4t,18} Our application of this method within the context of natural products synthesis will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This Letter is dedicated to Professor Carmelo J. Rizzo of Vanderbilt University on the occasion of his 51st birthday. We gratefully acknowledge financial support from the National Institute of Allergy and Infectious Diseases (R15, AI084075-02). Additionally, we thank the National Science Foundation, as part of its Major Research Instrumentation (MRI) Program (CHE-1126231), for the acquisition of a JEOL ECS-400 Nuclear Magnetic Resonance Spectrometer. Accurate mass measurements were performed by Dr. William Boggess of the Mass Spectrometry and Proteomics Facility at the University of Notre Dame.

References

- (1). (a) Cragg GM, Newman DJ, Snader KM. *J. Nat. Prod.* 1997; 60:52. [PubMed: 9014353] (b) Newman DJ, Cragg GM, Snader KM. *J. Nat. Prod.* 2003; 66:1022. [PubMed: 12880330] (c) Butler MS. *J. Nat. Prod.* 2004; 67:2141. [PubMed: 15620274] (d) Hultin PG. *Curr. Top. Med. Chem.* 2005; 5:1269. (e) Newman DJ, Cragg GM. *J. Nat. Prod.* 2012; 75:311. [PubMed: 22316239]
- (2). (a) Sezaki M, Kondo S, Maeda K, Umezawa H, Ohno M. *Tetrahedron.* 1970; 26:5171. [PubMed: 5499897] (b) Qian-Cutrone J, Kolb JM, McBrien K, Hunag S, Gustavson D, Lowe SE, Manly SP. *J. Nat. Prod.* 1998; 61:1379. [PubMed: 9834156] (c) Murenets NV, Smirnova OB. *Antibiot. Khimioter.* 1990; 35:20. [PubMed: 2383139] (d) Takano S, Hasuda K, Ito A, Koide Y, Ishii F, Haneda I, Chihara S, Koyama YJ. *Antibiotics.* 1976; 29:765. (e) Abe N, Enoki N, Nakakita Y, Uchida H, Sato R, Watanabe NJ. *Antibiotics.* 1991; 44:908. (f) Abe N, Nakakita Y, Nakamura T, Enoki N, Uchida H, Munekata MJ. *Antibiotics.* 1993; 46:1530. (g) Abe N, Enoki N, Nakakita Y, Uchida H, Nakamura T, Munekata MJ. *Antibiotics.* 1993; 46:1536. (h) Krohn K, Rohr J. *Top. Curr. Chem.* 1997; 188:127. (i) Antal N, Fiedler H-P, Stackebrandt E, Beil W, Ströck K, Zeeck AJ. *Antibiot.* 2005; 58:95.
- (3). (a) Wei A, Haudrechy A, Audin C, Jun H-S, Haudrechy-Bretel N, Kishi Y. *J. Org. Chem.* 1995; 60:2160. (b) Asensio JL, Espinosa JF, Dietrich H, Cañada FJ, Schmidt RR, Martín-Lomas M, André S, Gabius H-J, Jiménez-Barbero J. *J. Am. Chem. Soc.* 1999; 121:8995. (c) Rubinstenn G, Sinaÿ P, Berthault P. *J. Phys. Chem. A.* 1997; 101:2536. (d) Zhao Z, Hong L, Liu H.-w. *J. Am. Chem. Soc.* 2005; 127:7692. [PubMed: 15913355] (e) Choi, S.-h.; Mansoorabadi, SO.; Liu, Y.-n.; Chien, T.-C.; Liu, H.-w. *J. Am. Chem. Soc.* 2012; 134:13946. [PubMed: 22830643]
- (4). For selected references on C-glycoside synthesis: Matsumoto T, Katsuki M, Suzuki K. *Tetrahedron Lett.* 1988; 29:6935. Friesen RW, Sturino CF. *J. Org. Chem.* 1990; 55:5808. Friesen RW, Loo RW. *J. Org. Chem.* 1991; 56:4821. Boyd VA, Drake BE, Sulikowski GA. *J. Org. Chem.* 1993; 58:3191. Hosoya T, Takashiro E, Matsumoto T, Suzuki K. *J. Am. Chem. Soc.* 1994; 116:1004. Parker KA, Koh YH. *J. Am. Chem. Soc.* 1994; 116:11149. Friesen RW, Loo RW, Sturino CF. *Can. J. Chem.* 1994; 72:1262. Toshima K, Matsuo G, Ishizuka T, Ushiki Y, Nakata M, Matsumura S. *J. Org. Chem.* 1998; 63:2307. Calimente D, Postema MHD. *J. Org. Chem.* 1999; 64:1770. [PubMed: 11674258] Fuganti C, Serra S. *Synlett.* 1999; 1241. Futagami S, Ohashi Y, Imura K, Hosoya T, Ohmori K, Matsumoto T, Suzuki K. *Tetrahedron Lett.* 2000; 41:1063. Schmidt B. *Org. Lett.* 2000; 2:791. [PubMed: 10754682] Parker KA, Ding Q. *Tetrahedron.* 2000; 56:10255. Liu L, Postema MHD. *J. Am. Chem. Soc.* 2001; 123:8602. [PubMed: 11525671] Kaelin DE Jr, Lopez OD, Martin SF. *J. Am. Chem. Soc.* 2001; 123:6937. [PubMed: 11448205] Rammnauth J, Poulin O, Rakhit S, Maddaford SP. *Org. Lett.* 2001; 3:2013. [PubMed: 11418037] Brimble MA, Brenstrum TJ. *J. Chem. Soc., Perkin Trans.* 2001; 1:1624. Hauser FM, Hu X. *Org. Lett.* 2002; 4:977. [PubMed: 11893200] Kaelin DE Jr, Sparks SM, Plake HR, Martin SF. *J. Am. Chem. Soc.* 2003; 125:12994. [PubMed: 14570450] Lehmann U, Awasthi S, Minehan T. *Org. Lett.* 2003; 5:2405. [PubMed: 12841741] Apsel B, Bender JA, Escobar M, Kaelin DE Jr, Lopez OD, Martin SF. *Tetrahedron Lett.* 2003; 44:1075. Kim H, Men H, Lee C. *J. Am. Chem. Soc.* 2004; 126:1336. [PubMed: 14759180] Sherry BD, Loy RN, Toste FD. *J. Am. Chem. Soc.* 2004; 126:4510. [PubMed: 15070356] Li H, Procko K, Martin SF. *Tetrahedron Lett.* 2006; 47:3485. Kikuchi T, Takagi J, Isou H, Ishiyama T, Miyaura N. *Chem-Asian J.* 2008; 3:2082. [PubMed: 18844313] Sakamaki S, Kawanishi E, Nomura S, Ishikawa T. *Tetrahedron.* 2012; 68:5744.
- (5). (a) Suzuki A. *J. Organomet. Chem.* 1999; 576:147. (b) Diederich, F.; Meijere, A., editors. *Metal-Catalyzed Cross-Coupling Reactions.* Wiley-VCH; Weinheim: 2004. (c) Hassan J, Sévignon M, Gozzi C, Schulz E, Lemaire M. *Chem. Rev.* 2002; 102:1359. [PubMed: 11996540] (d) Miyaura, N., editor. *Topics in Current Chemistry.* Vol. 219. Springer-Verlag; New York: 2002. (e) Corbet J, Mignani G. *Chem. Rev.* 2007; 80:233. (f) Miyaura N, Suzuki A. *Chem. Rev.* 1995; 95:2457. (g) Suzuki A. *Chem. Commun.* 2005; 4759. (h) Doucet H. *Eur. J. Org. Chem.* 2008. 2013. (i) Han F-S. *Chem. Soc. Rev.* 2013; 42:5270. [PubMed: 23460083]
- (6). Sellars JD, Steel PG. *Chem. Soc. Rev.* 2011; 40:5170. [PubMed: 21731959]
- (7). Chen H, Huang Z, Hu X, Tang G, Xu P, Zhao Y, Cheng C-H. *J. Org. Chem.* 2011; 76:2338. [PubMed: 21388215]

- (8). (a) Pedzisa L, Vaughn IW, Pongdee R. *Tetrahedron Lett.* 2008; 49:4142. (b) Smith AB III, Ott GR. A similar effect, using Hünig's base, has been reported in Stille cross-coupling reactions. *J. Am. Chem. Soc.* 1998; 120:3935.
- (9). The involvement of arylboronate esters rather than arylboronic acids (Ref.a) as the coupling partner resulted in substantially improved yields in a number of cases. Additionally, the current method has also allowed for an expansion of substrate scope as C-aryl glycols that were previously inaccessible using arylboronic acids (**5c**, **5e**, **5f**, **5k**, **5m**) are efficiently produced employing arylboronate esters. Most importantly, the use of arylboronic acids failed to produce any C-aryl glycols when carbohydrate-derived ketene acetal phosphate **7** was employed under a variety of reaction conditions.
- (10). (a) Tsushima K, Araki K, Murai A. *Chem. Lett.* 1989:1313. (b) Tsushima K, Murai A. *Chem. Lett.* 1990:761. (c) Barber C, Jarowicki K, Kocienski P. *Synlett.* 1991:197. (d) Tsushima K, Murai A. *Tetrahedron Lett.* 1992; 33:4345. (e) Nicolaou KC, Theodorakis EA, Rutjes FPJT, Tiebes J, Sato M, Unterstell E, Xiao X-Y. *J. Am. Chem. Soc.* 1995; 117:1171. (f) Nicolaou KC, Rutjes FPJT, Theodorakis EA, Tiebes J, Sato M, Unterstell E. *J. Am. Chem. Soc.* 1995; 117:1173. (g) Fujiwara K, Tsunashima M, Awakura D, Murai A. *Tetrahedron Lett.* 1995; 36:8263. (h) Nicolaou KC, Sato M, Miller ND, Gunzner JL, Renaud J, Unterstell E. *Angew. Chem. Int. Ed. Engl.* 1996; 35:889.
- (11). (a) Nicolaou KC, Shi G-Q, Gunzner JL, Gärtner P, Yang Z. *J. Am. Chem. Soc.* 1997; 119:5467. (b) Nicolaou KC, Wallace PA, Shi S, Ouellette MA, Bunnage ME, Gunzner JL, Agrios KA, Shi G-q, Gärtner P, Yang Z. *Chem. Eur. J.* 1999; 5:618. (c) Sasaki M, Fuwa H, Ishikawa M, Tachibana K. *Org. Lett.* 1999; 1:1075. (d) Sasaki M, Ishikawa M, Fuwa H, Tachibana K. *Tetrahedron.* 2002; 58:1889.
- (12). (a) Skarbek, JD.; Speedie, MK. Antitumor Antibiotics of the Aureolic Acid Group: Chromomycin A3, Mithramycin A, and Olivomycin A. In: Aszalos, A., editor. *Antitumor Compounds of Natural Origin. Vol. 1.* CRC Press; Boca Raton, FL: 1981. p. 191 (b) Kharel MK, Pahari P, Shepherd MD, Tibrewal N, Nybo SE, Shaaban KA, Rohr J. *Nat. Prod. Rep.* 2012; 29:264
- (13). Zhao J, Wei S, Ma X, Shao H. *Carbohydr. Res.* 2010; 345:168. [PubMed: 19892323]
- (14). Bettelli E, Cherubini P, D'Andrea P, Passacantilli P, Piancatelli G. *Tetrahedron.* 1998; 54:6011.
- (15). Koviach JL, Chappell MD, Halcomb RL. *J. Org. Chem.* 2001; 66:2318. [PubMed: 11281772]
- (16). Occhiato EG, Prandi C, Ferrali A, Guarna A, Venturello P. *J. Org. Chem.* 2003; 68:9728. [PubMed: 14656100]
- (17). Ranier JD, Allwein SP. A similar hypothesis was made in the application of the Takai olefination procedure for the preparation of acyclic enol ethers. *J. Org. Chem.* 1998; 63:5310.
- (18). Tius MA, Gomez-Galeno J, Gu X.-q, Zaidi JH. *J. Am. Chem. Soc.* 1991; 113:5775.

Figure 1.
Structures of Natural Products Containing C-Glycosides

Scheme 1.

Reaction Conditions a) (a) NaOCH₃, MeOH (90%) (b) BnBr, NaH, DMF (89%); (c) Hg(OAc)₂, THF/H₂O; then NaBH₄ (76%); (d) PCC, NaOAc, 4 Å MS, CH₂Cl₂ (87%) (e) CIP(O)(OPh)₂, THF/HMPA, -78 °C; then LHMD (61%); (f) 61, 20 mol % (Ph₃P)₄Pd, 2 M Na₂CO₃, Et₃I THF, reflux (88%)

Table 1
Optimization of Suzuki-Myaura Cross-Coupling of Dihydroxyranylphosphate 1

Entry	Catalyst	Base	Solvent	Additive	Yield (%)
1	Cl ₂ Pd(dppf)	Na ₂ CO ₃	THF		51
2	CL ₂ Pd(dppf)	K ₃ PO ₄	THF		23
3	NiCl ₂ (PCy ₃) ₂	K ₃ PO ₄	Dioxane		10
4	(Ph ₃ P) ₄ Pd	Na ₂ CO ₃	THF		94
5	(Ph ₃ P) ₄ Pd	Na ₂ CO ₃	THF	Et ₃ N	91

Table 2
Substrate Scope for Suzuki-Miyaura Cross-Coupling of Dihydropyranylphosphate 1

Entry	Boronate Ester	Product	Yield (%)
1	5b , R=2-OCH ₃	6b	85
2	5c , R=2-N(CH ₃) ₂	6c	68
3	5d , R=2-CHO	6d	95
4	5e , R=3-OCH ₃	6e	95
5	5f , R=3,5-OCH ₃	6f	90
6	5g , R=3-NO ₂	6g	96
7	5h , R=3-CN	6h	77
8	5i , R=4-OCH ₃	6i	95
9	5j , R=4-SCH ₃	6j	95
10	5k , R=4-C(CH ₃) ₃	6k	81
11	5l , R=4-NHBoc	6l	89
12	5a , R=4-NO ₂	6a	97
13	5m , R=4-CON(CH ₃)(OCH ₃)	6m	97
14	5n , R=4-CO ₂ CH ₃	6n	92
15	5o , R=4-COCH ₃	6o	91