Phosphine-Free Suzuki−Miyaura Cross-Coupling in Aqueous Media Enables Access to 2-C-Aryl-Glycosides

Isidro Cobo,[†,‡] M. Isabel Matheu,[‡] Sergio Castillón,[‡] Omar Boutureira,*[,†,‡] and Benjamin G. Davis*[,†]

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, U.K., and Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain

omar.boutureira@urv.cat; ben.davis@chem.ox.ac.uk

ABSTRACT
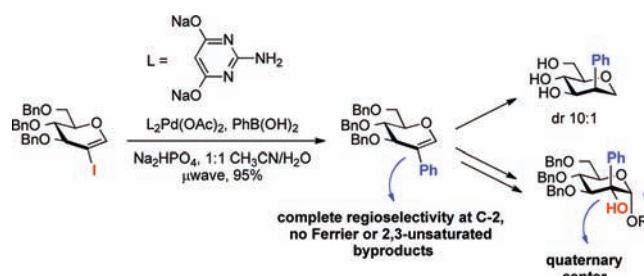
A general strategy for the synthesis of 2-aryl-glycals and their elaboration to 2-C-aryl-α-glycosides and 1,5-anhydro-2-C-aryl-2-deoxy alditols are described. The use of reliable, efficient phosphine-free Suzuki−Miyaura cross-coupling of 2-iodoglycals in aqueous media as a key step proceeds with complete regioselectivity at C-2 and enables access to 2-aryl-glycals with different configurations in excellent yields.

C-Arylglycosides are members of the C-glycosides[1] family of carbohydrate mimetics, and their synthesis has attracted considerable interest due to the presence of such motifs in several naturally occurring bioactive products.[2] Many methods have been developed for the synthesis of 1-C-arylglycosides where a carbon atom substitutes the anomeric glycosidic oxygen.[3] The most common method for 1-C-arylglycosides synthesis involves the use of transition-metal-catalyzed reactions, in particular, the addition of organometallic species to the sp²-hybridized anomeric center of glycals.[4] Regioselectivity may be efficiently controlled using a directing halogen atom at the anomeric position[5] (e.g., 1-haloglycals). However, and when this regiocontrol element is missing, reactions often lead to the formation of Ferrier and other 2,3-unsaturated products due to β-elimination processes.[4−7] Although the high demand for functionalized 1-C-arylglycosides has stimulated

---

† University of Oxford.
‡ Universitat Rovira i Virgili.
(1) (a) Štambaský, J.; Hocek, M.; Kočovský, P. *Chem. Rev.* **2009**, *109*, 6729. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier: Oxford, 1995. (c) Yuan, X.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393. (d) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913. (e) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1. (f) Sinaÿ, P. *Pure Appl. Chem.* **1997**, *69*, 459. (g) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545.
(2) (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742. (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (c) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363. (d) Moose, E. V.; Ben, R. N. *Curr. Top. Med. Chem.* **2005**, *5*, 1351. (e) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (f) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55.
(3) (a) Subrahmanyam, A. V.; Palanichamy, K.; Kaliappan, K. P. *Chem.—Eur. J.* **2010**, *16*, 8545 and references therein. (b) Lee, D. Y. W.; He, M. *Curr. Top. Med. Chem.* **2005**, *5*, 1333. (c) Martin, S. F. *Pure Appl. Chem.* **2003**, *75*, 63.

(4) (a) Xiang, S.; Cai, S.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 4608. (b) Bai, Y.; Leow, M.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 5648. (c) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709. (d) Li, H.-H.; Ye, X.-S. *Org. Biomol. Chem.* **2009**, *7*, 3855. (e) de la Figuera, N.; Forns, P.; Fernández, J.-C.; Fiol, S.; Fernández-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2005**, *46*, 7271. (f) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013.
(5) (a) Koester, D. C.; Liebeling, M.; Neufeld, R.; Werz, D. B. *Org. Lett.* **2010**, *12*, 3934. (b) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797. (c) Somsák, L. *Chem. Rev.* **2001**, *101*, 81. (d) Jeanneret, V.; Meerpoel, L.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 543.
(6) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201.

extensive studies on metal-catalyzed C−C bond-forming reactions,[8] the development of more efficient methods that involve arylation at other positions is highly desirable. C-Functionalizations at other positions of the sugar ring leading to C-branched sugars are by far less explored because they usually require many steps,[9] the use of strongly basic organolithium and Grignard reagents,[10] or the use of toxic reagents such as tin or mercury.[11] Particularly, the synthesis of 2-C-aryl-modified-carbohydrates[12] is rare, even though they are of potential interest for the development of new biologically active carbohydrate mimetics.

We envisaged a general strategy for accessing 2-arylglycals (Scheme 1) as key intermediates for synthesizing 2-C-arylglycosides. We anticipated that this could be achieved through the use of 2-haloglycals as privileged starting materials for this transformation featuring a regiocontrol element at the desired C-2 position.[13−15] Herein we report a general and efficient method for the synthesis of 2-arylglycals **9** with different configurations under relatively mild conditions by an aqueous, phosphine-free Suzuki−Miyaura cross-coupling of 2-iodoglycals **5−8** with aryl boronic acids in the presence of an inexpensive Pd complex[16] (Scheme 1).

Although iodo-derivates are preferable over chlorine or bromine for these reactions[17] they are less used, probably due to the lack of a general method for their preparation.[18] Thus, starting 2-iodoglycals **5−8** were prepared by treating alkenyl sulfanyl derivatives **1** or commercially available glycals **2** with iodonium reagents in aqueous media to

Scheme 1. General Strategy towards the Preparation of 2-Arylglycals **9**
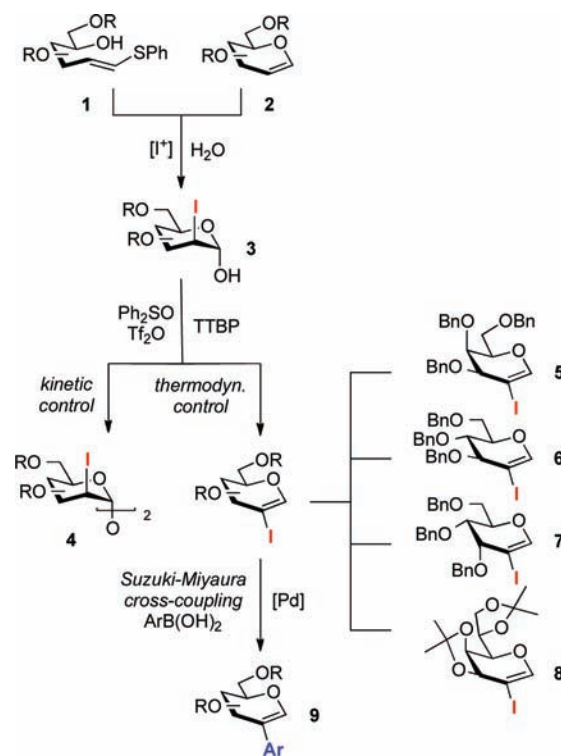
provide the corresponding 2-deoxy-2-iodopyranoses **3** which were then eliminated with Ph_2SO/Tf_2O and TTBP. Importantly, the optimization of original reaction conditions by driving the reaction under thermodynamic control allowed the selective preparation of otherwise elusive 2-iodoglycals **5** and **6** (see Supporting Information (SI) for details). Under kinetic control, 2-deoxy-2-iodo-trehaloses **4** were principally obtained.[18,19]
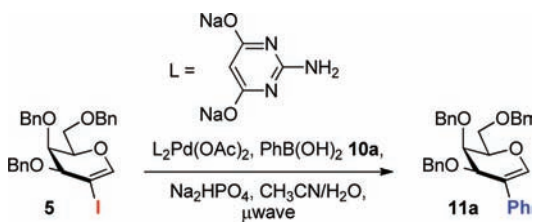
The feasibility of the Suzuki−Miyaura cross-coupling reaction was initially examined by using our recently developed Pd catalyst[16] (Table 1). Treatment of 2-iodogalactal **5** and phenylboronic acid **10a** with 2 mol % catalyst and Na_2HPO_4 in 1:3 CH_3CN/H_2O afforded 2-phenylgalactal **11a** in 82% yield with complete selectivity at C-2 after 300 min at 100 °C (entry 1). Attempts to decrease the catalyst loading proved ineffective (entry 2). Changing the solvent ratio from 1:3 to 1:1 CH_3CN/H_2O to increase the solubility of **5** improved the yield of **11a** to 90% after only 30 min at 100 °C (entry 3). Next, the effect of reaction temperature was evaluated (entries 4−6), 125 °C being optimal. The best yield for **11a** (95%) was finally obtained with 2 mol % catalyst in 1:1 CH_3CN/H_2O at 125 °C for only 5 min (entry 6). Globally, the use of this cheap and environmentally friendly catalyst provides several advantages; carrying out the reaction under aqueous conditions is key since the use of *nonpolar* solvents accelerates

(7) Bai, Y.; Zeng, J.; Cai, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 4394.

(8) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177.

(9) (a) Koester, D. C.; Holkenbrink, A.; Werz, D. B. *Synthesis* **2010**, 3217. (b) Yin, J.; Linker, T. *Org. Biomol. Chem.* **2009**, *7*, 4829. (c) Sridhar, P. R.; Kumar, P. V.; Seshadri, K.; Satyavathi, R. *Chem.—Eur. J.* **2009**, *15*, 7526. (d) Elamparuthi, E.; Kim, B. G.; Yin, J.; Maurer, M.; Linker, T. *Tetrahedron* **2008**, *64*, 11925. (e) Bouisset, T.; Gosselin, G.; Griffe, L.; Meillon, J.-C.; Storer, R. *Tetrahedron* **2008**, *64*, 6657. (f) Xavier, N. M.; Rauter, A. P. *Carbohydr. Res.* **2008**, *343*, 1523.

(10) Cleator, E.; McCusker, C. F.; Steltzer, F.; Ley, S. V. *Tetrahedron Lett.* **2004**, *45*, 3077.

(11) Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69.

(12) (a) Robinson, T. V.; Pedersen, D. S.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2009**, *74*, 5093. (b) Maurya, S. K.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 3307. (c) Willson, M.; Perie, J. *Spectrochim. Acta Part A* **1999**, *55*, 911. (d) Sugimura, H.; Osumi, K.; Koyama, T. *Chem. Lett.* **1991**, *20*, 1379. (e) Augé, C.; Gautheron, C.; David, S.; Malleron, A.; Cavayé, B.; Bouxom, B. *Tetrahedron* **1990**, *46*, 201. (f) Lee, J. B.; Scalon, B. *J. Chem. Soc. D* **1969**, *17*, 955.

(13) (a) Hayashi, M.; Tsukada, K.; Kawabata, H.; Lamberth, C. *Tetrahedron* **1999**, *55*, 12287. (b) Hayashi, M.; Amano, K.; Tsukada, K.; Lamberth, C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 239. (c) Lamberth, C.; Bednarski, M. *Carbohydr. Lett.* **1995**, *1*, 369.

(14) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949.

(15) (a) Leibeling, M.; Milde, B.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem.—Eur. J.* **2011**, *17*, 9888. (b) Leibeling, M.; Koester, D. C.; Pawliczek, M.; Schild, S. C.; Werz, D. B. *Nat. Chem. Biol.* **2010**, *6*, 199. (c) Leibeling, M.; Koester, D. C.; Pawliczek, M.; Kratzert, D; Dittrich, B.; Werz, D. B. *Bioorg. Med. Chem.* **2010**, *18*, 3656.

(16) (a) Spicer, C. D.; Davis, B. G. *Chem. Commun.* **2011**, *47*, 1698. (b) Chalker, J. M.; Wood, C. S. C.; Davis, B. G. *J. Am. Chem. Soc.* **2009**, *131*, 16346.

(17) (a) Gómez, A. M.; Pedregosa, A.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2003**, *44*, 6111. (b) Gómez, A. M.; Danelón, G. O.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun.* **2002**, 2024.

(18) Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S.; Seeberger, P. H. *J. Org. Chem.* **2007**, *72*, 8998.

(19) Backus, K. M.; Boshoff, H. I.; Barry, C. S.; Boutureira, O.; Patel, M. K.; D'Hooge, F.; Lee, S. S.; Via, L. E.; Tahlan, K.; Barry, C. E.; Davis, B. G. *Nat. Chem. Biol.* **2011**, *7*, 228.

competing elimination reactions[20] and also avoids the use of degassed solvents combined with expensive, easily oxidized phosphines that are particularly detrimental for the success of this reaction. For example, we observed 40% hydrodehalogenation of 2-iodogalactal **5** when reacted with PBu$_3$ (see SI for details).

Table 1. Optimization of Reaction Conditions for the Suzuki–Miyaura Cross-Coupling of 2-Iodogalactal **5** with Phenylboronic Acid **10a**[a]

entry	[Pd] (mol %)	CH$_3$CN/H$_2$O (v/v)	temp (°C)	t (min)	yield[b] (%)
1	2	1:3	100	300	82
2	0.1	1:3	100	30	NR[c]
3	2	1:1	100	30	90
4	2	1:1	40	720	NR[c]
5	5	1:1	80	190	84
6[d]	2	1:1	125	5	95

[a] Reactions were performed in a sealed vessel under single-mode microwave irradiation (65 W) with 2-I-galactal **5** (1 equiv), PhB(OH)$_2$ **10a** (1.5 equiv), L$_2$Pd(OAc)$_2$ (up to 5 mol %), and Na$_2$HPO$_4$ (5 equiv) in solvent (0.02 M) unless otherwise indicated. [b] Isolated yield. [c] NR = no reaction (>98% starting material was recovered). [d] Microwave power (300 W).

Encouraged by these results, a variety of arylboronic acids **10b–h** containing representative groups with potential in different imaging modalities[21] (e.g., PET, MRI, and fluorescence) were examined to expand the scope of the Suzuki–Miyaura cross-coupling of 2-iodogalactal **5** (Table 2). Phenylboronic acids with electron-withdrawing groups (entries 1, 3, and 7) or electron-donating groups (entry 2) afforded excellent results. Similarly, the use of sterically hindered boronic acids (entries 4 and 6), or heterocyclic derivatives (entry 5), also afforded excellent results although longer reaction times were required. Next, 2-iodoglycals **6–8** were reacted with phenylboronic acid **10a** under the optimized reaction conditions (Table 1, entry 6) and 2-phenylglycals **12–14** were efficiently obtained in excellent yields (up to 95%) confirming that different configurations are compatible with this procedure (Table 3).

Having demonstrated the success of the Suzuki–Miyaura cross-coupling reaction with 2-iodoglycals, the potential of the resulting 2-arylglycals as intermediates for the preparation of 2-*C*-arylglycoconjugates was

(20) Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908.

(21) Spicer, C. D.; Triemer, T.; Davis, B. G. *J. Am. Chem. Soc.* **2012**, *134*, 800.
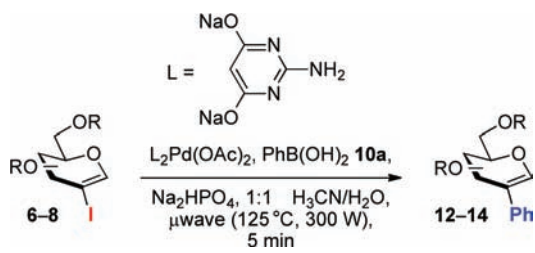
Table 2. Scope of Suzuki–Miyaura Cross-Coupling of 2-Iodogalactal **5** with Arylboronic Acids **10b–h**[a]

entry	boronic acid	Ar	product	t (min)	yield[b] (%)
1	**10b**	4-CN	**11b**	5	95
2	**10c**	4-OMe	**11c**	5	95
3	**10d**	4-F	**11d**	5	90[c]
4	**10e**	2-Me	**11e**	40	90
5	**10f**	3-Py	**11f**	40	89
6	**10g**	1-Naph	**11g**	5	94
7	**10h**	3,5-(CF$_3$)$_2$	**11h**	5	95

[a] *Conditions*: a mixture of 2-I-galactal **5** (1 equiv), ArB(OH)$_2$ **10b–h** (1.5 equiv), L$_2$Pd(OAc)$_2$ (2 mol %), and Na$_2$HPO$_4$ (5 equiv) in 1:1 CH$_3$CN/H$_2$O (0.02 M) was microwave irradiated (125 °C, 300 W) unless otherwise indicated. [b] Isolated yield. [c] Traces of 3,4,6-tri-*O*-benzyl-D-galactal were also detected (see Supporting Information for a mechanistic investigation).

Table 3. Scope of Suzuki–Miyaura Cross-Coupling of 2-Iodoglycals **6–8** with Phenylboronic Acid[a]

entry	2-I-glycal	product	yield[b] (%)
1	**6**	**12**	95[c]
2	**7**	**13**	95
3	**8**	**14**	96

[a] *Conditions*: a mixture of 2-I-glycal **6–8** (1 equiv), PhB(OH)$_2$ **10a** (1.5 equiv), L$_2$Pd(OAc)$_2$ (2 mol %), and Na$_2$HPO$_4$ (5 equiv) in 1:1 CH$_3$CN/H$_2$O (0.02 M) was microwave irradiated (125 °C, 300 W) for 5 min unless otherwise indicated. [b] Isolated yield. [c] Traces of 3,4,6-tri-*O*-benzyl-D-glucal were also detected (see Supporting Information for full details).

investigated. Thus, 2-phenylglucal **12** was efficiently hydrogenated with Pd/C in methanol to afford 1,5-anhydro-2-*C*-aryl-2-deoxy alditols **15** and **16** in 95% yield and *dr* 10:1 as indicated by the analysis of diagnostic coupling constants and key NOE signals in **15** and **16** both present in their $^4C_1$ conformation (Scheme 2).

Scheme 2. Synthesis and Conformational Analysis of 1,5-Anhydro-2-*C*-aryl-2-deoxy Alditols **15** and **16**
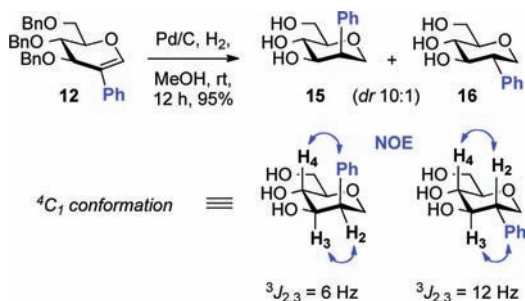
The preparation of challenging quaternary 2-*C*-aryl moieties was next studied using our two-step approach, which involves the epoxidation of starting 2-arylglycals followed by ring opening of resulting 2-*C*-aryl branched 1,2-anhydropyranosides.[22] Thus, treatment of 2-phenylglucal **12** with Oxone and acetone afforded epoxide **17** in quantitative yield[23,24] (Scheme 3). Next, 2-*C*-phenyloxirane **17** was subjected to an acid-promoted glycosylation with EtOH or BnOH. Under such conditions, 2-*C*-phenylglycosides **18** and **19** were obtained in good yields (85−90%) with exclusive α-selectivity (Scheme 3). The stereochemistry of compounds **18** and **19** was initially deduced by analysis of diagnostic $^3J_{3,4} = 9.5$ Hz coupling constants that account for a $^4C_1$ conformation. Moreover, the anomeric $^1J_{C1-H1} = 174.8$ Hz coupling constant is indicative of an α-configuration.[25] Finally, selective NOE irradiation of the aromatic Ph protons at C-2 caused an enhancement of signals corresponding to H-1 and H-4, which confirmed the axial disposition of the Ph group at C-2 in both **18** and **19**.

In conclusion, we have developed a general catalytic strategy for the efficient synthesis of 2-arylglycals by phosphine-free Suzuki−Miyaura cross-coupling of 2-iodoglycals in aqueous media using an inexpensive Pd catalyst.

To the best of our knowledge this transformation represents the first transition-metal-catalyzed 2-*C*-arylation of 2-haloglycals. The simplicity and relative mildness of this method allow the regioselective preparation of various 2-arylglycals with different configurations in excellent yields with no Ferrier or 2,3-unsaturated byproduct detected. Notably, the 2-iodoglycal substrates proved unstable in the presence of phosphines, necessitating systems that avoid their use. The elaboration of the 2-*C*-arylglycal moiety gives access to both 1,5-anhydro-2-*C*-aryl-2-deoxy alditols and challenging quaternary 2-*C*-aryl-α-glycosides which will broaden the plethora of 2-*C*-aryl branched glycosides at positions different than C-1. Further application of this methodology to the synthesis of more complex 2-*C*-aryl branched glycosides is currently under investigation.

Scheme 3. Synthesis and Conformational Analysis of Branched 2-*C*-Phenylglycosides **18** and **19**

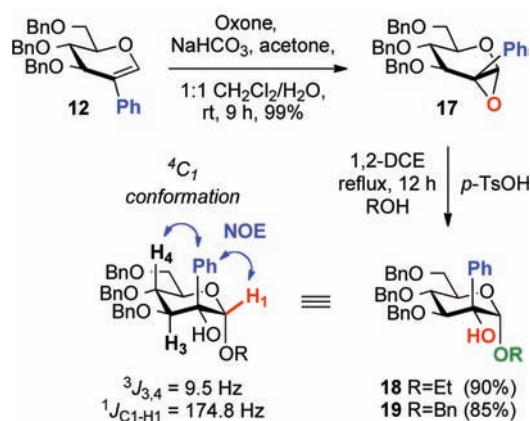(22) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(23) Initial attempts using Gin's epoxidation conditions were unsuccessful, see: (a) Honda, E.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 7343 and references therein. (b) Kim, J.-Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303.

(24) Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydr. Res.* **2006**, *341*, 2714.

(25) Tvaroska, I.; Taravel, F. R. *Adv. Carbohydr. Chem. Biochem.* **1995**, *51*, 15.