Formation of *C*-Glycosides by a Palladium-catalysed Coupling Reaction of Tributylstannyl Glycals with Organic Halides

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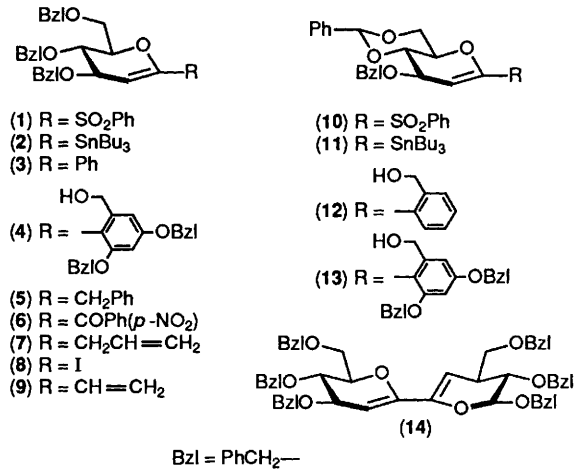
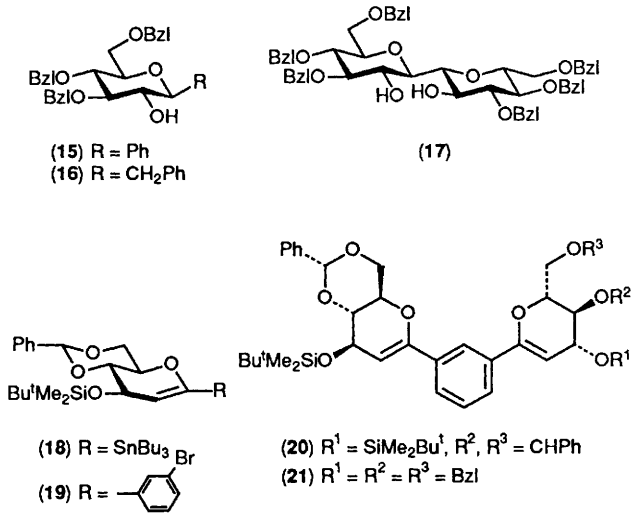
The palladium-catalysed coupling reaction of 1-(tributylstannyl)-D-glucals with unsaturated halides furnishes the corresponding 1-*C*-alkylated glucals, an efficient procedure for a symmetric or dis-symmetric di-*C*-glycosidation of 1,3-dibromobenzene.

We recently reported,[1] along with others,[2] the preparation of 1-substituted glycals by tin–lithium exchange on the corresponding 1-tributylstannyl glycals followed by alkylation with various electrophiles.[3] Although practical, this route to *C*-glycosides presents the inconvenience of having to use strongly basic carbanionic conditions which requires suitable protecting groups on such polyfunctional substrates. A more versatile process would, therefore, entail using a milder coupling reaction capable of tolerating a variety of functional groups. We now describe a procedure that uses the 1-tributylstannyl glycals that undergo a cross-coupling reaction with various electrophiles under palladium(0) catalysis,[4] a procedure well-documented by the in-depth studies of Stille.[5]

3,4,6-Tri-*O*-benzyl- or 3-*O*-benzyl-4,6-*O*-benzylidene-1-tributylstannyl-D-glucals (**2**) and (**11**), prepared by stannylation of the corresponding unsaturated sulphones (**1**) and (**10**),[1] were chosen as model substances for the glycosidation studies. A refluxing toluene solution of (**2**) in the presence of





bromobenzene (1.5 equiv.) and $Pd(Ph_3P)_4$ (0.1 equiv., 3 h) furnished the desired 1-*C*-arylated glycal (**3**)† m.p. 65—66 °C, $[\alpha]_D^{20}$ −7° ($CHCl_3$) in 88% yield.

The coupling of (**2**) with unprotected 2-bromo-3,5-dibenzyloxybenzyl alcohol also produced the 1-*C*-arylated glucal (**4**), $[\alpha]_D^{20}$ +4° ($CHCl_3$) in good yield (82%). Similarly, the application of these standard coupling conditions between the 1-stannyl-glucal (**11**) and the 2-bromobenzyl or 2-bromo-3,5-dibenzyloxybenzyl alcohols gave the corresponding arylated glycals (**12**) (75%), m.p. 163—164 °C, $[\alpha]_D^{19}$ −29° ($CHCl_3$) and (**13**) (73%), m.p. 100—101 °C, $[\alpha]_D^{20}$ +2° ($CHCl_3$).

This palladium-catalysed carbon–carbon bond formation at the C-1 of glycals is not limited to aromatic bromides. Thus, the 1-*C*-benzylated glycal (**5**) (74%), $[\alpha]_D^{20}$ −1° ($CHCl_3$) was also obtained under the same conditions ($PhCH_2Br$, 1.5 equiv., reflux in toluene). Omission of the electrophilic partner led to the dimeric glucal (**14**), m.p. 109 °C, $[\alpha]_D^{20}$ −35° ($CHCl_3$), with the best yield (85%) being obtained using $PdCl_2(MeCN)_2$ as the catalyst (0.1 equiv.) at 60 °C in dimethylformamide (DMF) (3 h).

Acylation [4-nitrobenzoyl chloride, 2 equiv., $PdCl_2(MeCN)_2$, 0.05 equiv., dichloroethane, reflux, 15 min] and allylation [allylbromide, 2 equiv., $Pd(dba)_2$ (dba = dibenzylidene acetone), 0.05 equiv., PPh_3, 0.1 equiv., tetrahydrofuran (THF), reflux, overnight] furnished the corresponding 1-substituted glycals (**6**) (71%), $[\alpha]_D^{20}$ −6° ($CHCl_3$) and (**7**) (74%), $[\alpha]_D^{22}$ +0.5 ($CHCl_3$). This method was unfortunately not synthetically useful with acetylenic or alkenyl iodides or bromides. Tin–halogen exchange was the major reaction pathway as in the reaction of (**2**) with 3-iodo-2-propyn-1-ol [$PdCl_2(MeCN)_2$ in DMF] which gave 75% of iodinated glycal (**8**), $[\alpha]_D^{20}$ −10° ($CHCl_3$). Vinylated compound (**9**) was obtained in a low yield (22%) by reacting (**2**) with vinyl bromide.

The remaining carbon–carbon double bond in the coupling products can be further functionalized. Thus, regio- and stereo-selective hydroboration–oxidation of compounds (**3**), (**5**), and (**14**) ($BH_3{\cdot}Me_2S$, then H_2O_2, NaOH) provided the corresponding 1-*C*-aryl-anhydro-D-glucitol derivatives (**15**) (82%), $[\alpha]_D^{20}$ +35° ($CHCl_3$), (**16**) (72%), $[\alpha]_D^{20}$ +24° ($CHCl_3$), and (**17**) (63%), $[\alpha]_D^{20}$ +18° ($CHCl_3$). Compound (**16**) represents an interesting *C*-analogue of β-phenyl-D-glucosides.

This method has been extended to 1,3-dibromobenzene. Coupling with 2.0 equiv. of the tin reagent (**18**) [$Pd(PPh_3)_4$, 0.1 equiv., PhMe, reflux, 5 h] gave the symmetrical 1,3-di-*C*-glycoside (**20**), $[\alpha]_D^{20}$ −30.5° ($CHCl_3$) in good yield (85%). However, the reaction of (**18**) with 2.5 equivalents of 1,3-dibromobenzene gave the mono-coupled product (**19**) (82%). Further coupling of (**19**) with tin reagent (**2**) yielded the dis-symmetrical product (**21**), $[\alpha]_D^{20}$ −16.5° ($CHCl_3$) in 79% yield.

This efficient sequential *C*-glycosidation of *meta*-substituted aromatic dibromides represents a promising strategic choice for the synthesis of di-*C*-glycosylated antitumour antibiotics such as hedamycin,[6] kidamycin[7] or pluramycins[8] and this work is currently being investigated further by our group.‡

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References

1 P. Lesimple, J.-M. Beau, G. Jaurand, and P. Sinaÿ, *Tetrahedron Lett.*, 1986, **27**, 6201.
2 K. C. Nicolaou, C.-K. Hwang, and M. E. Duggan, *J. Chem. Soc., Chem. Commun.*, 1986, 925; S. Hanessian, M. Martin, and R. C. Desai, *J. Chem. Soc., Chem. Commun.*, 1986, 926.
3 For the 1-*C*-lithiation of 2-phenylsulphinyl-D-glucals see: R. Preuss and R. R. Schmidt, *Liebigs Ann. Chem.*, 1989, 429.
4 For other palladium-mediated *C*-glycosidations see: R. A. Outten and G. D. Daves, Jr., *J. Org. Chem.*, 1989, **54**, 29 and previous work; M. Brakta, P. Lhoste, and D. Sinou, *J. Org. Chem.*, 1989, **54**, 1890; L. V. Dunkerton, J. M. Enske, and A. J. Serino, *Carbohydr. Res.*, 1987, **171**, 89; S. Youkai and T. J. Miwa, *J. Chem. Soc., Chem. Commun.*, 1983, 68; S. Czernecki and F. Gray, *Tetrahedron Lett.*, 1981, **22**, 437.
5 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508 and references cited therein.
6 M. Ceroni and U. Sequin, *Helv. Chim. Acta*, 1982, **65**, 302; I. Takahashi, K.-I. Takahashi, K. Asano, I. Kawamoto, T. Yasuzawa, T. Ashizawa, F. Tomita, and H. Nakano, *J. Antibiot.*, 1988, **41**, 1151.
7 M. Furukawa, I. Hayakawa, G. Ohta, and Y. Iitaka, *Tetrahedron*, 1975, **31**, 2989.
8 U. Hacksell and G. D. Davies, Jr., *Prog. Med. Chem.*, 1985, **22**, 1 and references cited therein.
9 R. W. Friesen and C. F. Sturino, *J. Org. Chem.*, 1990, **55**, 2572.

† All new compounds gave satisfactory analytical and spectroscopic data.

‡ Part of this work was previously presented (E. Dubois and J.-M. Beau, Seventh IUPAC Conference on Organic Synthesis, Nancy, France, July, 1988, Abstract 7-R9). While this article was being written, 1-*C*-arylation by various substituted bromobenzenes of 3,4,6-tri-*O*-(t-butyldimethylsilyl)-1-(tributylstannyl)-D-glucal appeared in print,[9] using mostly $Pd(Ph_3P)Cl_2$ as a catalyst.