deposition of particles is the more important of the two depositional pathways.

Concluding Remarks

Let us review our operating hypothesis: A broad range of dioxins and furans, which are injected into the atmosphere by many combustion sources, form a uniform, ambient air mixture. As the air mass moves away from the (primarily) urban sources, it is diluted with cleaner air and starts to "age". Less chlorinated dioxins and furans partition into the vapor phase; this process is highly temperature dependent. The particles with their enhanced load of the more chlorinated dioxins and furans are deposited by both wet and dry processes. Although the dry process dominates, the efficiency of the wet process improves for the more chlorinated dioxins and furans. Every process that occurs favors a deposited profile enriched in the more chlorinated dioxins and furans. It is, therefore, not surprising that the sediment profiles are enriched in octachlorodioxin and that the next most abundant are the heptachlorodioxins and -furans. Our data suggest that only the most chlorinated dioxins and furans are persistent in the atmosphere. This finding may be of interest to policy makers because these dioxins and furans tend to be the least toxic.

The one part of our hypothesis that we have not yet addressed well is the issue of photochemical degradation in the atmosphere. We suspect that such a mechanism is operative; Orth and co-workers, for example, have shown that 2378-D in the vapor phase degrades photochemically with a half-life of about 2 min.[31] There are too few data, however, on which to generalize. Furthermore, there are no data at all on the degradation of dioxins and furans in the particle phase. We are busily correcting these lapses.

Dr. Jean M. Czuczwa, Dr. Brian D. Eitzer, and Carolyn J. Koester have done all the work on this project. It was not easy to quantitate a few picograms of material, but they did it routinely. They also made major contributions to the development of the concepts discussed above. The U.S. Department of Energy, the U.S. Environmental Protection Agency, and the Westinghouse Corporation supported this research.

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C-Glycoside Synthesis by Palladium-Mediated Glycal–Aglycon Coupling Reactions

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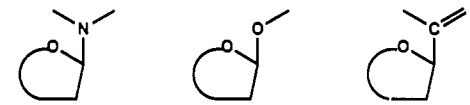
Living systems utilize numerous, structurally diverse *N*- and *O*-glycosides in metabolically functional roles. These glycosides possess reactive aminal (N) and acetal (O) glycosidic linkages between their glycon (carbohydrate) and aglycon (noncarbohydrate) structural units. Also present in nature are *C*-gylcosides (*C*-nucleosides)[1] in which a glycon (usually furanosyl or pyranosyl) and an aglycon (heterocyclic or anthracyclic) are linked via a hydrolytically stable carbon–carbon bond (C).[2] It is noteworthy that, with the single exception of pseudouridine, which is a constituent nucleoside of transfer RNA, and closely related naturally occurring derivatives,[3] all other naturally occurring C-glycosides appear to be antibiotics.[1] Many microbial[1] and plant species[4] elaborate and deploy *C*-glycosides; presumably they derive significant competitive advantage from this ability. It is interesting to speculate[5] that the impressive biological effects exhibited by "natural stable analogue" *C*-glycosides depend importantly on the resistance of the carbon–carbon glycosidic linkage to hydrolytic or enzymatic cleavage.[2]



The discovery of the antibiotic formycin[6] and the recognition[7] that it was a *C*-nucleoside isomer of adenosine created great interest in the mid 1960s and fo-

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(1) For reviews of the chemistry and biology of *C*-glycosides, see: (a) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1–65; (b) Buchanan, J. G. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 243–299. Goodchild, J. *Top. Antibiot. Chem.* **1982**, *6*, 99–227.

(2) Carbocyclic nucleosides, in which the carbohydrate ring oxygen is replaced by carbon, are a second class of naturally occurring, hydrolytically stable nucleoside analogues; see: Marquez, V. E.; Lim, M. I. *Med. Res. Rev.* **1986**, *6*, 1–40.

(3) Daves, G. D., Jr.; Cheng, C. C. *Prog. Med. Chem.* **1976**, *13*, 303–349.

(4) For reviews of plant *C*-glycosides, see: Franz, G.; Gruen, M. *Planta* **1983**, *47*, 131–140. Bandyukova, V. A.; Yugin, V. A. *Khim. Prir. Soedin.* **1981**, 5–24. Chopin, J.; Bouillant, M. L. In *The Flavonoids*; Harborne, J. B.; Mabry, T. J., Mabry, H., Eds.; Academic Press: New York, 1975; pp 631–691.

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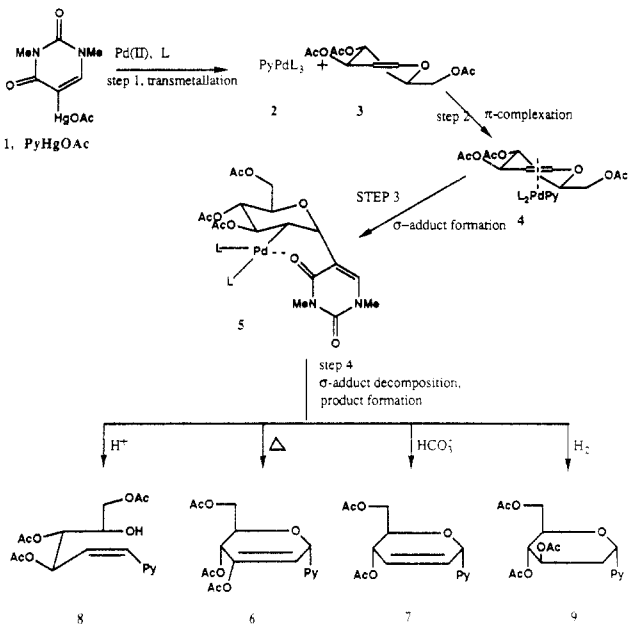
(6) Hori, M.; Ito, E.; Takita, T.; Koyama, Y.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1964**, *17A*, 96–99. Aizawa, S.; Hidaka, T.; Otake, N.; Yonehara, H.; Inose, K.; Igarashi, N.; Suzuki, S. *Agric. Biol. Chem.* **1965**, *29*, 375–376.

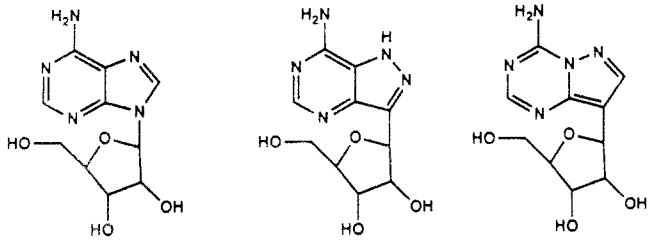
(7) Robins, R. K.; Townsend, L. B.; Cassidy, F.; Gerster, J. F.; Lewis, A. F.; Miller, R. L. *J. Heterocycl. Chem.* **1966**, *3*, 110–114. Koyama, G.; Maeda, K.; Umezawa, H.; *Tetrahedron Lett.* **1966**, 597–602.

0001-4842/90/0123-0201$02.50/0

Scheme I
Mechanism of *C*-Glycoside Formation by Coupling of a Glycal with an Organopalladium Reagent

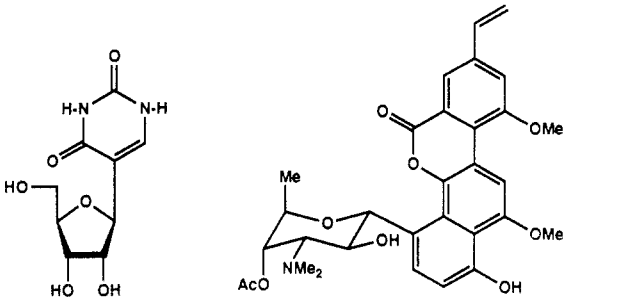


cused attention on *C*-nucleosides as potentially important agents for biological research and for therapeutic applications. Ward and Reich[8] carried out an elegant series of investigations that demonstrated that formycin can substitute for adenosine in numerous enzymatic reactions. These workers[8] determined that the antibiotic action of formycin derives, to an important degree, from its elongated *C*-glycosyl bond (1.55 Å as compared with 1.47 Å for the *N*-glycosyl bond of adenosine), which allows for significantly greater conformational mobility.[1] Several synthetic *C*-nucleoside analogues of nucleic acid constituent *N*-nucleosides, for example, APTR,[9] have exhibited important antitumor and antileukemic properties.[1,9]



Adenosine Formycin APTR

The biological importance and structural complexity of *C*-glycosides present a synthetic challenge, which has stimulated significant activity.[1] Three conceptually different strategies for *C*-glycoside synthesis have been developed.[1] An effective approach used primarily for preparation of nitrogen heterocyclic *C*-nucleosides involves construction of a heterocyclic aglycon beginning with a C-1 carbon substituent introduced onto a carbohydrate moiety.[1,9] Danishefsky[10] has synthesized an anthracycline *C*-glycoside, vineomycin B_2, by the inverse process, construction of a pyranosyl moiety from an aglycon aldehydo substituent. Because natural *C*-glycosides exhibit great structural diversity in both glycon and aglycon moieties (compare pseudouridine and ravidomycin[1]), an effective method for formation of a glycosidic linkage between preformed aglycon and carbohydrate derivatives would be broadly useful for the synthesis of various classes of *C*-glycosides. We undertook the development of such a method.[11] This goal has been achieved by the development of a palladium-mediated coupling reaction that links 1,2-unsaturated carbohydrates (glycals) with aryl or heteroaryl aglycons in a regio- and stereospecific manner.



Pseudouridine Ravidomycin

The development of organopalladium chemistry for the synthesis of *C*-glycosides was stimulated in our laboratory by a report by Bergstrom and Ruth[12] that reaction of a pyrimidinylmercuric salt with olefins in the presence of palladium(II) achieved pyrimidine C-5 alkylation in good yield. We reasoned that realization of a similar reaction involving an olefin derived from a carbohydrate, specifically a 1,2-unsaturated carbohydrate or glycal, would afford a conceptually new, remarkably direct and general *C*-glycoside synthesis. Research related to the development of this palladium-mediated *C*-glycoside synthesis is the subject of the present Account.

Mechanism of the Glycal–Aglycon Coupling Reaction

We and others have made a detailed study of the palladium-mediated reactions of many aryl and heterocyclic metallic and halo derivatives with cyclic enol ethers and glycals.[13-34] The overall reaction process,

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(9) Fox, J. J.; Watanabe, K. A.; Klein, R. S.; Chu, C. K.; Tam, S. Y. K.; Reichman, U.; Hirota, K.; Wempen, I.; Lopez, C.; Burchenal, J. H. *Colloq. INSERM* **1978**, *81*, 241–269.

(10) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285–1293.

(11) Lewis acid catalyzed formation of a C-glycosidic bond was reported as early as 1955 (Hurd, C. D.; Bonner, W. A. *J. Am. Chem. Soc.* **1955**, *77*, 1664, 1759); recently, interest in this route, which yields mixtures of α and β anomers, has been revived (see, e.g.: Kwok, D. I.; Daves, G. D., Jr. *J. Org. Chem.* **1989**, *54*, 4496–4497).

(12) Bergstrom, D. E.; Ruth, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 1587–1589.

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(18) Kalinoski, H. T.; Hacksell, U.; Barofsky, D. F.; Barofsky, E.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 6476–6482.

(19) Cheng, J. C.-Y; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3083–3090.

(20) Arai, I.; Daves, G. D., Jr. *J. Heterocycl. Chem.* **1978**, *15*, 351–352.

(21) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1979**, *44*, 21–23.

(22) Arai, I.; Hanna, R.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 7684–7685.

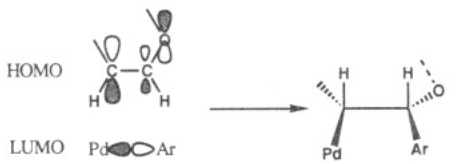
(23) Lee, T. D.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 399–402.

(24) Hacksell, U.; Daves, G. D., Jr. *Organometallics* **1983**, *2*, 772–775.

which is a version of the Heck arylation reaction,[35] is envisaged as involving four discrete organometallic reaction steps[36,37] (illustrated for the reaction[14-19] of aglycon mercurial derivative **1**[13] with 3,4,6-tri-*O*-acetyl-D-glucal[38] (**3**) in the presence of Pd(II), Scheme I): (1) organopalladium reagent formation via transmetalation (or oxidative addition when a halo–aglycon derivative is used, vide infra), (2) π-complex formation whereby the enol ether double bond of the glycal becomes a ligand on palladium, (3) collapse of this π-complex by syn insertion of the olefinic π-bond into the Pd–aglycon bond with σ-adduct formation, and (4) adduct decomposition with palladium elimination and product formation. It is obvious that, for effective use in *C*-glycoside synthesis, each of these four consecutive organometallic reaction steps must occur selectively and in a predictable manner.

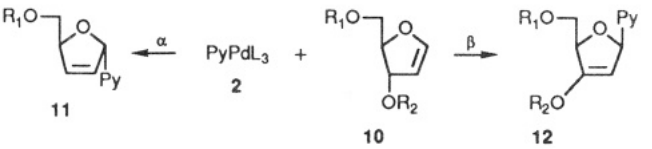
Reaction Control for Selective *C*-Glycoside Synthesis

Regiochemistry. The regiochemistry of *C*-glycosidic bond formation is determined by the manner in which a π-complex collapses to the corresponding σ-organopalladium adduct (Scheme I, step 3); for glycals and other cyclic enol ethers, this reaction is invariably regiospecific in the proper sense, with the newly formed bond linking the aglycon to the carbohydrate carbon α to the ring oxygen (the anomeric carbon).[29,36,37] This regiochemical outcome is readily rationalized. The dominant interaction is that of the highest occupied molecular orbital of the enol ether π-system with the antibonding (σ^*) Pd(II)–aglycon orbital. This interaction leads to σ-bond formation between the electron-deficient palladium(II) center and the enol ether β-carbon (which is the site of greatest electron density) with concomitant migration of the electron-rich (anionic) ipso carbon of the aglycon to the enol ether α-carbon in a syn stereochemical sense.[23,29]



This rationalization cannot be generalized to reactions of acyclic[21,29,36,37] or exocyclic[39,40] enol ethers, which usually yield regioisomeric mixtures upon palladium-mediated arylation. Significant efforts have been made to understand the reasons for the striking differences observed between reactions of cyclic and acyclic enol ethers and to develop strategies for regiochemical control of these latter reactions.[29,36]

Table I
Stereochemistry of *C*-Glycoside Formation by Palladium-Mediated Glycal Aglycon Coupling[a]



% yield of 11	substituents	% yield of 12
29	**a**: $R_1 = R_2 = H$	45
0	**b**: $R_1 = H$, $R_2 = CH_2OCH_3$	65
78	**c**: $R_1 = CH_2OCH_3$, $R_2 = H$	0
0	**d**: $R_1 = R_2 = CH_2OCH_3$	71
0	**e**: $R_1 = CH_2OCH_3$, $R_2 = Si(iPr)_3$	92
0	**f**: $R_1 = R_2 = Si(iPr)_3$	51
0	**g**: $R_1 = H$, $R_2 = Si(Ph)_2tBu$	84

[a] Data taken from refs 19, 20–22, and 37.

Stereochemistry. Using furanoid glycals,[41] which fortuitously have become readily available as a result of a new procedure developed by Ireland and co-workers,[42] we established[25,27,43] that the stereochemistry of the coupling reaction is determined by the relative accessibility of the two respective faces of the cyclic enol ether double bond to the organopalladium reagent for π-complex formation (Scheme I, step 2). Ribofuranoid glycals (**10**), with one or both of the carbohydrate hydroxyls substituted, undergo stereospecific palladium-mediated coupling to yield a single product (either an α-*C*-glycoside, **11**, or a β-*C*-glycoside, **12**, Table I). If only one of the two glycal hydroxyls is substituted (**10b**, **10c**, or **10g**), π-complex formation occurs exclusively from the face of the furanoid ring opposite the substituted hydroxyl. When both glycal hydroxyls are substituted (**10d**, **10e**, or **10f**), the organopalladium reagent attacks from the β-face of the glycal, indicating that the proximal C-3 substituent interferes with π-complex formation more effectively than the substituent at C-4, which is more remote from the enol ether double bond.

Only when both hydroxyls of the glycal remain unsubstituted (**10a**) is a mixture of stereoisomeric *C*-glycosides (**11a** and **12a**) produced; presumably in this case the two substituents (hydroxyl and hydroxymethyl, respectively) are too small to effectively direct the coupling reaction. We have found one other glycal in which palladium-mediated coupling with an aglycon derivative yields a stereoisomeric mixture of α- and β-*C*-glycosides. Thus, reaction of aglycon derivative **1** with the pyranoid glycal 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-(phenylmethylene)-D-*erythro*-hex-1-enitol[44] (**13**)

(25) Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 2870–2876.
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(37) Daves, G. D., Jr. In *Advances in Metal-Organic Chemistry*; Vol. 2; Liebeskind, L. S., Ed.; JAI Press: Greenwich, Ct, in press.
(38) Roth, W.; Pigman, W. In *Methods in Carbohydrate Chemistry*; Academic Press: New York, NY, 1963; Vol. II, p 405.
(39) Kwok, D.-I.; Daves, G. D., Jr., unpublished results.
(40) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458–5461.
(41) Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778–2780.
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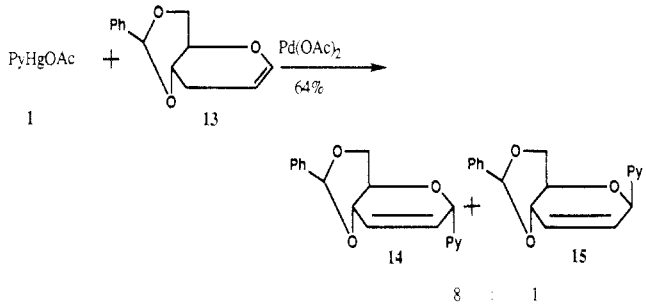
(43) Farr, R. N.; Daves, G. D., Jr., unpublished results.
(44) Richtmeyer, N. Methods *Carbohydr. Chem.* **1962**, *1*, 107. Lemieux. R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61–69. Fraser-Reid, B.; Tam, S. Y.-K.; Radatus, B. *Can. J. Chem.* **1975**, *53*, 2005–2016.

in the presence of palladium(II) acetate led to an 8:1 mixture of α- and β-*C*-glycosides **14** and **15**, respectively, in a combined yield of 64%.[39] This result is consistent with the concept that, while π-complex formation and subsequent coupling is exquisitely sensitive to the relative steric environments of the two faces of the cyclic enol ether, substituents that are quite small (e.g., OH) or farther from the reaction site than C-3 are not sufficient to effect stereospecific coupling.



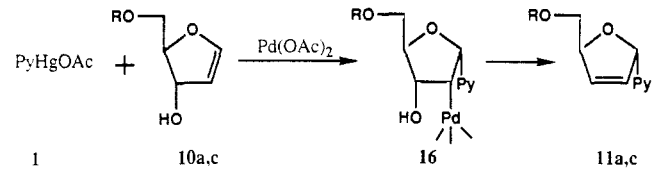
To date, glycal **13** is the only pyranoid glycal studied that lacks a substituted oxygen group at C-3; in all other cases, palladium-mediated coupling reactions involving pyranoid glycals have been stereospecific, yielding *C*-glycoside products resulting from organopalladium attack and π-complex formation on the face of the unsaturated carbohydrate ring opposite that of the C-3 (allylic) substituent.[14-17,19,28,32-34]

Thus, the stereospecific preparation of either α- or β-furanosyl or pyranosyl *C*-glycosides is readily accomplished through selection of the configuration of *C*-3 of the glycal and/or by use of stereodirecting substituents on the glycal oxygens.

Organopalladium Adduct Decomposition to *C*-Glycoside Product. The reaction of pyrimidine mercurial **1** with glycal **3**[13-18] produced a single intermediate σ-organopalladium adduct (**5**, Scheme I). In reaction mixtures containing only anions and ligands with a relatively low affinity for palladium (acetate and acetronitrile), adduct **5** decomposed essentially as it formed via several competing modes, forming a complex mixture of products.[14,17,19] When the coupling reaction was carried out with chloride ions present, adduct **5** accumulated in the reaction mixture and, following stabilization with triphenylphosphine[15,16] or triphenylarsine[16] ligands, was successfully isolated.[15,16] By the choice of appropriate reaction conditions, we were able to achieve selective decomposition of adduct **5** to yield any one of four *C*-glycoside products (**6–9**) essentially quantitatively.[15,19] In this case,[15,16,19] and others[24,25] where the intermediate organopalladium adduct is sufficiently stable to accumulate in the reaction mixture, the introduction of a hydrogen atmosphere results in replacement of palladium with hydrogen by a reductive elimination process (**5** → **9**, Scheme I).

Each of the organopalladium adduct decomposition modes, which give rise to *C*-glycoside products **6–8**, involves an elimination reaction in which palladium and a substituent on carbon β to palladium is lost via a process that has strict stereochemical requirements.[28,37] Formation of **6** by β-hydride elimination (which is perhaps the most common organometallic adduct decomposition process[35]) requires a syn-periplanar alignment of metal and β-hydrogen. *C*-Glycoside **7** is formed by elimination of palladium and β-acetate and involves an anti-periplanar alignment of these substituents; for organopalladium adduct **5**, this requirement is met by inversion of the carbohydrate ring from the more stable chair conformation with palladium in an equatorial position[14,17] to place palladium and 3′-acetate in trans-diaxial positions. Similarly, loss of palladium with rupture of the carbohydrate ring, **5** → **8** (probably after protonation or Lewis acid coordination of the ring oxygen[19]), involves an anti-periplanar transition state.

An additional, less common organopalladium adduct decomposition mode has been observed for glycal adducts that lack syn β-hydrogen and anti-periplanar β-oxygen substituents. Reaction of aglycon derivative **1** with furanoid glycals such as **10a** or **10c** in the presence of palladium acetate yields intermediate organopalladium adducts in which the β-elimination processes illustrated in Scheme I are precluded. In these cases, adduct decomposition occurred by syn elimination of palladium and β-hydroxyl (e.g., **16** → **11**$_{a,c}$).[24,27,45]



These reactions illustrate the richness of the decomposition chemistry available to highly functionalized σ-organopalladium carbohydrate adducts and the potential to select individual adduct decomposition modes for the synthesis of *C*-glycosides with specified carbohydrate substitution patterns. Selection of specific σ-organopalladium decomposition reactions is accomplished by (a) use of conformational constraints in the carbohydrate ring and (b) control of the leaving-group ability of oxygen substituents β to palladium.[19,28]

Under conditions wherein palladium-mediated reaction of aglycon derivative **1** with 3,4,6-tri-*O*-acetyl-D-glucal[38] (**3**) yields a mixture of *C*-glycoside products as a result of competing σ-adduct decomposition pathways,[19] reaction with 3-*O*-acetyl-4,6-di-*O*-benzylidene-D-glucal[46] (**17**) yields a single *C*-glycoside product, **18**.[19] Glycal **17** is an analogue of **3** in which the carbohydrate ring is conformationally restricted owing to incorporation of the C-4 and C-6 oxygen substituents into an annealated ring with the C-3 acetoxy group in a pseudoequatorial position.

C-Glycoside **18** is formed by syn elimination of palladium hydride from the intermediate σ-organopalladium adduct; elimination of palladium acetate is precluded by the significantly higher energy required for the σ-adduct to achieve the anti-periplanar (trans-diaxial) alignment of palladium and acetate necessary for this reaction.

Glycal **19**,[47] the C-3 epimer of **17**, in which the C-3 acetoxy group is pseudoaxial also undergoes palladium-mediated coupling with **1** to yield a single *C*-glycoside product **20**. In this case, the product (**20**) is formed by attack of the organopalladium reagent on the

(45) We have also observed a complex β-hydride elimination reaction involving migration of acetate to the palladium-bearing carbon (see ref 13).

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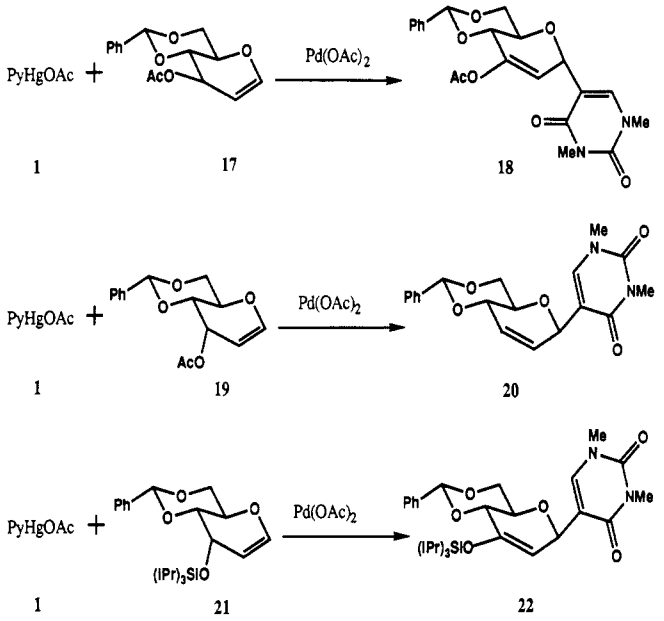


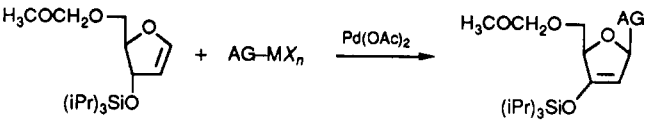
β-face of the glycal (opposite the allylic oxygen substituent) to form a σ-organopalladium adduct in which palladium and the C-3 acetoxy group are anti periplanar as required for elimination of palladium acetate. Similarly, coupling of **1** with glycal **21**[19] involves organopalladium reagent attack from the β-face of the glycal. However, in this case, the oxygen substituent ((triisopropylsilyl)oxy) anti to axial palladium in the intermediate σ-adduct is a poor leaving group; as a result, the adduct decomposes by syn β-hydride elimination to produce the silyl enol ether β-*C*-glycoside **22**.[19,28] These reactions illustrate a straightforward strategy for control of formation and decomposition of intermediate σ-organopalladium adducts that makes readily available either α- or β-*C*-glycosides with or without retention of the C-3 oxygen substituent.

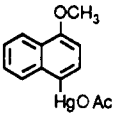
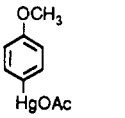
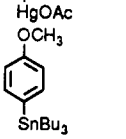
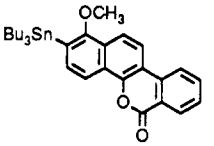
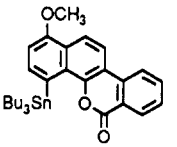
Organopalladium Reagent Formation

Transmetalation Using Tri-*n*-butylstannyl Derivatives of Aglycons. The formation of the reactive organopalladium reagent **2**, which undergoes coupling with glycals to form *C*-glycosides, involves a transmetalation reaction between pyrimidine mercurial **1** and (usually)[48] stoichiometric palladium(II) (Scheme I). The use of organomercurials as precursors to palladium–aglycon reagents is attractive[6-28,40] because direct electrophilic mercuration of many aromatic and heterocyclic aglycons is facile.[49] When mercuration is difficult[49] or the organomercurial of the aglycon is too insoluble in the reaction medium (usually acetonitrile) to permit reaction, we have found[30,31] that tri-*n*-butylstannyl derivatives[50] of aglycons are attractive alternatives. Representative reactions are shown in Table II.

These reactions indicate that there are no significant differences in the effectiveness of arylmercurials and arylstannanes in the palladium-mediated glycal–aglycon coupling reactions; both are excellent precursors to the reactive organopalladium reagent which undergoes coupling with glycals. The much greater solubility of tri-*n*-butylstannyl derivatives in organic solvents than corresponding mercuric acetate derivatives significantly extends the scope and utility of this organometallic route to *C*-glycosides.

Table II
Coupling Reactions of Aglycon–Mercuric Acetate and Tri-*n*-butylstannyl Derivatives with a Furanoid Glycal (10e) in the Presence of Stoichiometric Palladium(II) Acetate[a]



$AG–MX_n$	*C*-glycoside product: % yield
	96
	57
	70
	57
	66

[a] Data taken from ref 25.

Glycal–Aglycon Coupling Using Catalytic Palladium. We[13,21,29] and others[32-34,51-54] have demonstrated coupling reactions between enol ethers and aryl compounds using catalytic quantities of palladium. While these palladium-catalyzed coupling reactions were encouraging, in each case, achievement of an acceptable yield of coupled product required elevated reaction temperatures (80–120 °C) and several equivalents of either the enol ether or aglycon precursor. Study of factors that affect the palladium-mediated coupling of enol ethers with aryl halides has permitted development of a glycal–aglycon coupling reaction that is catalytic in palladium and is as effective as the corresponding reaction utilizing metallo derivatives of aglycons and stoichiometric palladium.

The sensitivity of palladium-mediated reactions to reaction conditions is well recognized; effects of reaction solvent, added salts and ligands for palladium, and catalyst nature and form have been noted.[17,19,23,55,56]

(48) It is possible, in some instances, to make this reaction catalytic by addition of a reoxidant for Pd(0) to the reaction mixture. See ref 26 and see, e.g.: Backvall, J.-E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892–6898.
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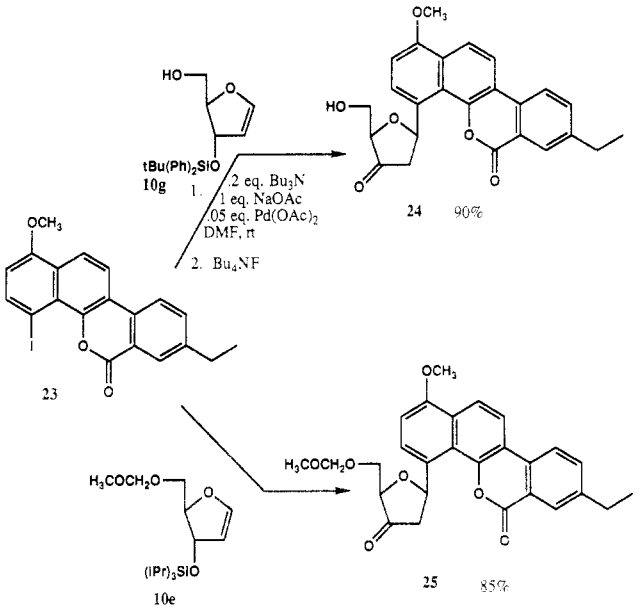
Addition of a quaternary ammonium salt remarkably accelerates certain palladium-mediated coupling reactions;[22,55] use of dimethylformamide as reaction solvent[55-57] with added salts and/or base further increases the rate of reaction. Thus, reaction of stoichiometric portions of 8-ethyl-4-iodo-1-methoxybenzo[*d*]naphtho-[1,2-*b*]pyran-6-one[43] (**23**) and glycals **10e** or **10g** in a



reaction medium consisting of 1 equiv of sodium acetate, 0.2 equiv of tri-*n*-butylamine, and 5 mol % of palladium acetate in dimethylformamide at room temperature led to essentially quantitative coupling. Following in situ desilylation of the intermediate silyl enol ethers, the corresponding 3′-keto *C*-glycosides **24** and **25**, related to the ravidomycin–gilvocarcin class of antibiotics,[1,11] were isolated in excellent yields.[43]

Summary and Conclusions

The palladium-mediated coupling of a glycal, either furanoid or pyranoid, with a suitable aglycon derivative is a powerful, direct method for *C*-glycoside synthesis. The coupling reaction forms the *C*-glycosidic bond both regio- and stereospecifically in good to excellent yields. The factors that determine the course of the reaction and the structure of the *C*-glycosidic product produced are well understood. Proper selection of glycal permits facile preparation of either α- or β-*C*-glycosides and allows retention of the 3′-oxygen to form 2′-deoxy *C*-glycosides or, alternatively, loss of the 3′-substituent to form 2′,3′-dideoxy *C*-glycosides. The coupling reaction is equally facile when heterocyclic, simple aryl, or complex anthracycline aglycons are used. The reaction utilizes either metallo–aglycon derivatives (stoichiometric palladium) or iodo–aglycon derivatives (catalytic palladium) with equal effectiveness.

The directness of the approach to *C*-glycosides, the generality of the palladium-mediated coupling reaction, which permits great flexibility in selection of aglycon and glycal reactants, and the versatility of the reaction, which provides for preselection of α- or β-*C*-glycoside products with preselected carbohydrate functionality, are impressive advantages that should facilitate the syntheses of many useful *C*-glycosides for biological and pharmacological study.

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