chromatography. During this study, no differences in the reactivity of the two isomers were detected.

The yields and stereoselectivity arising from the eight conditions listed in Table I were compared. Thermolyses provided the alkoxycyclopentene annulated products in 50–75% yields with the endo isomers predominating because of the endo effect.[10] Fluoride-initiated rearrangements were studied in detail to yield the optimum conditions listed in Table I,[11] which gave the highest exo/endo ratio of products when tetra-*tert*-butylammonium fluoride (TBAF)[7,12] was used. Whereas the nature of the intermediate in this rearrangement is not yet known, there may be conceptual similarities with the process recently described by Larsen[8d] in which thioenol ether terminated vinylcyclopropanes have been postulated during a low-temperature rearrangement to cyclopentenes. Trimethylsilyl iodide in the presence of hexamethyldisilazane provided the highest yields of the siloxycyclopentenes. Somewhat surprisingly, both exo and endo vinylcyclopropanes gave the siloxycyclopentenes, although our studies on vinylcyclopropanes not containing the enol ether showed that endo isomers furnished the products of divinylcyclopropane rearrangement.[6a,b] Lewis acid catalysis led predominantly to endo somers and to aldehyde **15**, which was shown *not* to be an intermediate in the reaction.

The stereochemistry of the resulting hydroxycyclopentenes was determined by protection with *tert*-butyldimethylsilyl chloride and comparison of GC and ^{1}H NMR data of their *tert*-butyldimethylsilyl ethers with those of the siloxy derivatives obtained by pyrolysis of the corresponding siloxy vinylcyclopropanes.[13] The relative percentages of exo and endo isomers were determined by integration of the ring-junction protons in ^{1}H NMR spectroscopy.[13] The endo isomers were equilibrated with TBAF at room temperature to yield a 80:20 ratio of isomers. Thus control of the stereochemistry at the oxygenated center may be available through the different conditions of this rearrangement: endo configuration from a $FeCl_3$-catalyzed reaction, exo from the fluoride-initiated rearrangement. The generality of such control is under investigation.[11]

In summary, we have described an efficient method for the annulation of oxygenated cyclopentenes that proceeds under extremely mild conditions at temperatures as low as −90 °C. At the present time, the optimum conditions (in terms of yield) for rearrangement are treatment of the vinylcyclopropane with 1.1 equiv of HMDS and TMSI at −20 °C (Table I, entry 3). This affords a 90% yield of the oxycyclopentenes with a 1.2:1.0 exo:endo ratio. The conditions leading to the most stereochemically pure product involved the use of 5 equiv of TBAF·H_2O over 12 h (Table I, entry 5, 5.7:1.0 exo:endo). The stereochemistry at the oxygenated center can be somewhat controlled by equilibration of the free alcohols with fluoride. Detailed investigations of the mechanistic course of these rearrangements, the optimization of conditions, and the conversion of intermediate **2** to (−)-specionin are in progress.[13,14]

Acknowledgment. We express our gratitude to the following agencies for their generous financial support: the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (AI-00564, AI-19749, GM-40648), and the Jeffress Trust Fund.

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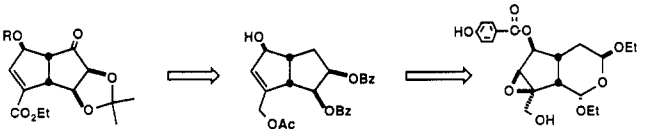
(13) All compounds were characterized by IR and ^{1}H and ^{13}C NMR spectroscopy, elemental analyses, or high-resolution mass spectrometry.

(14) The reduction of the ketone and ester functionalities in **2a** to **i** has been accomplished in three steps as of this writing.



i Specionin

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The Preparation of *C*-Arylglycals. The Palladium-Catalyzed Coupling of 3,4,6-Tri-*O*-(*tert*-butyldimethylsilyl)-1-(tributylstannyl)-D-glucal and Aryl Bromides

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Summary: The palladium-catalyzed couplings of the protected 1-(tributylstannyl)-D-glucal **1** and substituted aryl bromides provide the corresponding *C*-arylglucals **4–15** and a dimer **16** resulting from the homocoupling of **1**.

Many of the *C*-aryl glycosides that have been isolated from natural sources, such as the gilvocarcins,[1] nogalamycin,[1,2] arugomycin,[1,3] and the papulacandins,[1,4] exhibit antibiotic and/or antitumor activity. As a result, there has been a considerable effort directed toward the formation of the unique C–C bond that directly links the carbohy-

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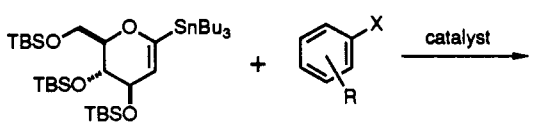
Table I. Palladium-Catalyzed Coupling of the Stannylglucal 1 and Aryl Bromides in Refluxing Solvent[a]

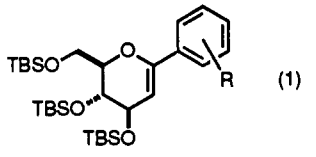
entry	ArX (1.1–2 equiv)	catalyst (5 mol %)	solvent[b]	coupled product	yield, % (dimer)[c]
1	PhBr	$Pd(Ph_3P)_4$	PhH	4	50[d]
2	PhBr	$Pd(Ph_3P)_2Cl_2$	PhH	4	52[d]
3	PhBr	$Pd(Ph_3P)_4$	DMF[e]	4	34[d]
4	PhBr	$Pd(Ph_3P)_4$	THF	4	70[d]
5	4-$NO_2C_6H_4Br$	$Pd(Ph_3P)_2Cl_2$	PhMe	5	78 (4)
6	4-CNC_6H_4Br	$Pd(Ph_3P)_2Cl_2$	PhMe	6	81 (8)
7	1-bromonaphthalene	$Pd(Ph_3P)_2Cl_2$	PhMe[e]	7	59 (15)[f]
8	4-$MeO_2CC_6H_4Br$	$Pd(Ph_3P)_2Cl_2$	PhMe	8	56 (8)
9	4-ClC_6H_4Br	$Pd(Ph_3P)_2Cl_2$	PhMe	9	49 (8)
10	2-MeC_6H_4Br	$Pd(Ph_3P)_2Cl_2$	PhMe	10	49 (11)
11	2-$AcOCH_2C_6H_4Br$	$Pd(Ph_3P)_2Cl_2$	PhMe	11	46 (15)
12	PhBr	$Pd(Ph_3P)_2Cl_2$	PhMe	4	41 (12)
13	2-$AcOC_6H_4Br$	$Pd(Ph_3P)_2Cl_2$	PhMe	12	40 (11)
14	2-$BnOC_6H_4Br$	$Pd(Ph_3P)_2Cl_2$	PhMe	13	44 (4)
15	4-$MeOC_6H_4Br$	$Pd(Ph_3P)_2Cl_2$	PhMe[e]	14	30 (13)
16	2,5-$(MeO)_2C_6H_3Br$	$Pd(Ph_3P)_2Cl_2$	PhMe[e]	15	65 (9)

[a] A general procedure for the coupling reaction and physical constants ($[\alpha]_D$; IR, ^1H NMR and/or ^{13}C NMR, and high-resolution mass spectroscopy; and/or elemental analysis) for **4–15** are available in the supplemental material. [b] Approximate concentration of 1: 0.05 M for entries 1–4 and 0.2–1 M for entries 5–16. [c] Yields of isolated, chromatographically pure products. Note that a 10% yield of dimer **16** involves the consumption of 20% of **1**. [d] Dimer yield not measured. [e] Reaction done at 100 °C. [f] The yield is based on a ^1H NMR integrated ratio of a chromatographically pure mixture of **7** and **16**. A small amount of pure **7** was isolated and characterized.

drate residue and the aromatic moiety of the *C*-aryl glycosides.[5]

We are interested in developing a rapid and facile route to *C*-aryl glycosides that is relatively flexible with respect to aromatic substitution pattern and type. The fundamental difference between our anticipated route and previous results is that the functionalization of C1 and C2, and the determination of the anomeric carbon stereogenicity, would occur subsequent to the key C–C bond forming reaction. The strategy that we envisaged was the palladium-catalyzed coupling of a 1-stannylglycal such as **1** and an aryl halide **2** (eq 1). The resulting *C*-arylglycal **3** would





(1)

then be suited for further synthetic manipulation about the activated glycal double bond. Although the palladium-catalyzed coupling of vinylstannanes and aryl halides is a well-documented process,[6] at the time we began this work there were no examples in which enol ethers such as **3** had been isolated from coupling reactions that employed 1-alkoxy-1-stannylalkenes as substrates.[7] Herein, we describe our results for the preparation and isolation of *C*-arylglycals **3**[8] according to this protocol.

We set out to determine the optimum reaction conditions (solvent, catalyst, temperature) for the coupling of the protected 1-(tributylstannyl)-D-glucal **1**[9] and bromobenzene according to eq 1. Thus, hot solutions of **1** and bromobenzene were treated with various palladium catalysts (Table I, entries 1–4), producing the phenylglucal **4** (R = H in **3**) in the yields indicated. The optimum yield of **4** (70%) was realized in refluxing THF (0.06 M in **1**), using $Pd(Ph_3P)_4$ as catalyst (entry 4). Employing these conditions, **4** was produced very cleanly along with a small amount (ca. 10%) of a single byproduct (vide infra).

Although the coupling of bromobenzene proceeded readily under the "standard" conditions, the extension to substituted bromobenzenes (1-bromo-4-nitrobenzene and 4-bromoanisole) was not straightforward. The reaction in these cases was quite capricious in nature, sometimes proceeding to completion while at other times, under apparently identical conditions, failing completely. A great deal of effort was expended in attempting to clarify these observations by careful notation of the particular batch of palladium catalyst that was employed and consistent prehandling of **1** and the aryl bromides. These considerations, as well as attempts at varying the catalyst and/or the concentration of the reactants in THF, proved fruitless. However, in refluxing toluene and at concentrations of approximately 0.2–1 M in **1**, the coupling proceeded reproducibly without incident using $Pd(Ph_3P)_2Cl_2$ as catalyst (entries 5 and 15).

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(8) Previous reports for the preparation of this class of compound, although elegant, have relied on multistep reaction sequences and were directed toward specific intermediates in total synthetic efforts.[5a]

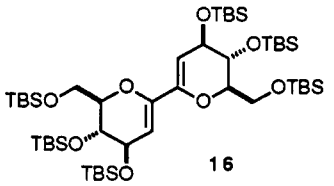
(9) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 359.

Utilizing these revised "standard" conditions, a wide variety of substituted aryl bromides (entries 5–16) were coupled successfully. A number of points regarding these latter entries deserve mention.

The crude reaction mixtures were quite clean, providing the expected *C*-arylglucals **4–15**[10] in moderate to good yields. Especially satisfying is the observation that oxygenated aromatics, such as are found in many *C*-aryl glycoside antibiotics, can be easily introduced (entries 13–16). It should also be noted that the conditions of choice for the coupling of bromobenzene itself are the original "standard" reaction conditions (compare entries 4 and 12).

Secondly, the isolated yields of the *C*-arylglucals reflect, at least qualitatively, an ordering based on the electron-withdrawing capabilities of the aromatic substituent ortho or para to the bromide.[11]

Finally, a single byproduct (accounting for up to 30% of the starting material **1**; entries 7 and 11) was observed in all cases and was identified as the dimer **16** resulting from the homocoupling of **1**.[12] Various attempts at decreasing the production of **16** by modification of the reaction conditions, including the use of nickel catalysis or the zinc glucal derived from **1**,[13] were not successful. We are investigating the mechanism by which **16** is formed in an effort to reduce the loss of material via this reaction pathway.[14]



16

We feel that the wide range of substituted aromatic moieties that can be appended onto the sugar nucleus, in a single synthetic step, make this an attractive method for the synthesis of *C*-arylglycals. In order to be generally useful as a method for the preparation of *C*-aryl glycosides, the synthetic capabilities of the remaining enol ether double bond of these materials must be addressed. Preliminary work along these lines is very encouraging and will be reported in due course.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council of Canada and the University of Toronto is gratefully acknowledged.

Supplementary Material Available: A general procedure for the coupling of **1** and aryl bromides and physical constants for **1** and **4–16** (4 pages). Ordering information is given on any current masthead page.

(10) The purification of these materials was effected by silica gel chromatography of the crude reaction mixtures after evaporation of the reaction solvent. The arylglucals are relatively stable at −5 °C but decompose when stored at room temperature.

(11) A similar ordering, based on electron-withdrawing properties, has been observed in the palladium-catalyzed rate (not yield) of reaction of substituted aryl bromides with vinylstannanes[6a] and terminal acetylenes. (a) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453. (b) Fitton, P.; Rick, A. E. *J. Organomet. Chem.* **1971**, *28*, 287.

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Asymmetric Synthesis of 2-Alkyl(Aryl)-2,3-dihydro-4-pyridones by Addition of Grignard Reagents to Chiral 1-Acyl-4-methoxypyridinium Salts

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Summary: Grignard addition to a chiral 1-acyl-4-methoxypyridinium salt provides synthetically useful 2-alkyl(aryl)-2,3-dihydro-4-pyridones in high diastereomeric excess.

The reaction of nucleophiles with 1-acylpyridinium salts has proven to be a valuable method for the synthesis of substituted dihydropyridines and pyridines.[2,3] The addition of Grignard reagents to 1-acylpyridinium salts of 4-methoxypyridine is particularly interesting, for synthetically useful 1-acyl-2,3-dihydro-4-pyridones result. These dihydropyridones have been utilized as synthetic intermediates for the synthesis of quinolizidinones.[4,5] For example, we recently reported highly stereocontrolled syntheses of the Lythraceae alkaloid (±)-lasubine II[5a] and the quinolizidine alkaloid (±)-myrtine[5b] from 4-methoxypyridine in four and five steps, respectively. The synthetic potential of 1-acyldihydropyridones prompted us to pursue an enantioselective synthesis of these heterocycles via Grignard addition to chiral 1-acyl-4-methoxypyridinium salts.

Our strategy for developing the desired asymmetric synthesis followed the route depicted in Scheme I.

The chiral 1-acylpyridinium salts **2** were prepared in situ from a 4-methoxypyridine **1** and an optically active chlo-

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