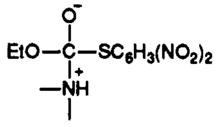
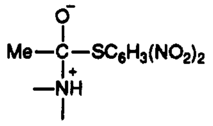
found in the pyridinolysis of DNPMC (pK_a° = 7.8)[12] compared to that of DNPA (pK_a° = 7.3).[13b] Assuming the same pK_a° increase in going from the aminolysis of DNPTA to that of DNPTC,[22] we can predict a pK_a° = 9.3 ± 0.1 for the reactions under study, which satisfactorily agrees with the previous prediction.

The fact that a concerted pathway occurs in the present reactions means that the putative intermediate 1 is too unstable to exist. This is in contrast to the relative stability of intermediate 2 found in the reactions of DNPTA with secondary alicyclic amines, where the mechanism is stepwise.[6,23] The higher instability of 1 relative to 2 could be due to the additional push exerted by EtO in 1 to expel either the amine or the thiolate anion. On the other hand, it is known that in the aminolysis of *O*-aryl acetates and carbonates substitution of MeO for Me on a tetrahedral carbon enhances the push provided by the aryloxy group attached to that carbon atom due to an inductive electron-withdrawing effect of the MeO group in $T^\pm$.[12,13,25] Therefore, it is possible that EtO in 1 also increases the push provided by the thio group in 1 to expel the amine compared with the same push from 2.[26] Either argument could explain why 1 is much more unstable than 2. The expulsion of the amine from 1 should be as fast as a C–N bond vibration; therefore, 1 would not have a significant lifetime and the concerted pathway is enforced.[27]



$\mathrm{EtO{-}\overset{O^-}{\underset{|+\atop -NH}{C}}{-}SC_6H_3(NO_2)_2}$

1



$\mathrm{Me{-}\overset{O^-}{\underset{|+\atop -NH}{C}}{-}SC_6H_3(NO_2)_2}$

2

Electron donation from the acyl group that destabilizes a zwitterionic tetrahedral intermediate and enforces a concerted mechanism has also been found in methoxycarbonyl group transfer from isoquinoline to pyridines.[14] (The acetyl transfer between pyridines is stepwise.[28]) Another example: In the aminolysis of benzoyl fluoride a concerted process was observed,[27] whereas a stepwise mechanism was found in the aminolysis of acetyl chloride.[29] The higher instability of the putative intermediate formed in the former reactions was attributed to electron donation from the benzene ring.[27]

It is known that aryl methyl carbonates are less reactive than aryl acetates toward amine nucleophiles.[12,13,25,30] Likewise, the aminolyses of methyl chlorocarbonate[30] and DNPTC (this work) are slower than the corresponding reactions of acetyl chloride[29] and DNPTA,[6] respectively. This must be due to the electron-releasing effect of the MeO or EtO group in the substrate, which results in resonance delocalization and, therefore, in stabilization of the carbonate relative to the acetate. This renders the CO carbon of the former substrate less positively charged and therefore less susceptible to amine attack. The $T^\pm$ formed in the carbonate reactions would be less stable in view of the great loss of resonance stabilization in going from reactants to $T^\pm$ (this resonance is very much inhibited in $T^\pm$).

Acknowledgment. The financial support by "Fondo Nacional de Desarrollo Científico y Tecnológico" (FONDECYT) is gratefully acknowledged.

Supplementary Material Available: Experimental details of the kinetic measurements and product studies and ^{1}H NMR and IR data for DNPTC (2 pages). Ordering information is given on any current masthead page.

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(23) The fact that a curved Brönsted-type plot was found in the aminolysis of DNPTA[6] does not prove per se that the reaction is stepwise. We have shown that the mechanism is stepwise in this and other reactions by fitting a semiempirical equation based on the existence of $T^\pm$ to the experimental points.[5,6,10-13,21] In similar reactions, an equation based on an extension of the Hammond postulate, which predicts a curved Brönsted plot for a concerted process, does not account satisfactorily for the experimental points.[24]

(24) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 828.

(25) Castro, E. A.; Bórquez, M. T.; Parada, P. M. *J. Org. Chem.* **1986**, *51*, 5072.

(26) A very large push from sulfur is not expected because of the difficulty of double bond formation from sulfur. We thank a referee for this comment.

(27) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 8479.

(28) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442.

(29) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869.

(30) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.

Preparation of *C*-Aryl Glucals via the Palladium-Catalyzed Coupling of Metalated Aromatics with 1-Iodo-3,4,6-tri-*O*-(triisopropylsilyl)-D-glucal

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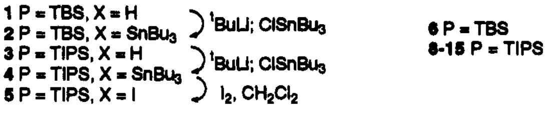
Summary: The preparation of the novel iodo glucal 5 from 3,4,6-tri-*O*-(triisopropylsilyl)-D-glucal (4), via a two-step procedure involving C1 stannylation and subsequent tin–iodine exchange, is described. The palladium-catalyzed coupling of 5 with a variety of metalated aromatics provides a facile and high yielding entry into *C*-aryl glucals, compounds that have been demonstrated to be useful precursors for the synthesis of *C*-aryl glycosides.

There is currently a great deal of interest in the synthesis of *C*-glycosides. We have previously reported that the palladium-catalyzed cross-coupling reaction of an aryl bromide and the C1-stannylated glucal 2 is a useful and simple method for the preparation of *C*-aryl glucals 6 (eq 1).[1] The glucal products of these reactions can be effi-



(1)

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(1) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572. See also refs 3a,b.

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ciently used for the synthesis of a variety of *C*-aryl glycosides by the stereoselective functionalization of the resulting enol ether double bond.[2–5] We, and others, have used this strategy for the synthesis of the *C*-aryl glycoside fragments of a number of biologically active natural products including the papulacandins,[2,3] chaetiacandin,[3,4] and vineomycinone B2 methyl ester.[5] In connection with several of our synthetic efforts, we required significant quantities of a variety of these *C*-aryl glucals. A severe limitation to this requirement was our inability to obtain useful quantities of the stannylated glucal **2** from **1** using a vinylic metalation strategy.[6a] The difficulties associated with this strategy arose due to competing α-silyl deprotonation of one or more of the methyls in the TBDMS protecting groups and, as a result, the stannylated glucal **2** was available in yields of only 12–30%. This chemistry has been described in a previous paper[6b] and a satisfying solution was found in the preparation of the stannylated glucal **4** containing TIPS protecting groups (eq 1).[7] Therefore, it was imperative that we demonstrate that this stannylated glucal could be utilized in the key palladium-catalyzed cross-coupling reaction with aryl bromides.

It soon became evident that the simple change from TBDMS to TIPS protecting groups was in fact a major modification. Whereas the *C*-aryl glucal **6** (R = 4-CN) was obtained in 81% yield by the coupling of **2** and 4-bromobenzonitrile,[1] under optimized reaction conditions, the best yield of **8** (R = 4-CN) in the coupling of **4** and 4-bromobenzonitrile was observed to be 67%. The results with bromobenzene and other aryl bromides were similarly discouraging.

The mechanism that has been proposed for the Stille reaction[8] involves a rapid oxidative addition of Pd(0) to the organic halide, followed by a slow transmetalation step to provide a diorgano-Pd(2^+) species. We attributed the disappointing results that were observed in the attempted coupling reactions of stannylated glucal **4** to a decrease in the rate of an already slow transmetalation step. We believe that a decrease in the rate of transmetalation is brought about by the increased steric bulk of the molecule, manifested at the C1 position, as a result of the protecting group change. Therefore, we reasoned that if we could reverse the sense of the coupling reaction, making the carbohydrate moiety the more reactive organic halide partner, better success might be achieved in the coupling reaction. Herein, we report the palladium-catalyzed couplings of the novel iodo glucal **5**,[9] obtained in high yield from the glucal **3**, can be accomplished under mild conditions with a variety of metalated aromatics in yields superior to those obtained in the originally described reaction.

The stannylated glucal **4** was converted into the iodo glucal **5** (89–100% yield) by treatment of a CH_2Cl_2 solution of **4** with I_2 in CH_2Cl_2 (eq 1). The two-step (stannylation, tin–iodine exchange) overall, isolated yield of **5** from glucal **3** is typically 85%. The isolable vinyl iodide **5**[10a] is stable for several weeks when stored under vacuum in the dark.[10b]

Table I. Palladium-Catalyzed Coupling of Iodo Glucal 5 and Metalated Aromatics 7

entry	substrates 7, ArM[a]	reaction conditions[b] (solvent/temp/time)	coupled product (yield, %)[c]
1	**7a** PhLi	THF/rt	N/R
2	**7b** $PhSnBu_3$	THF/reflux/24 h	**9** 20
3	**7c** PhMgBr	PhMe/reflux/10 h[d]	**9** 25
4	**7d** $PhB(OH)_2$	THF–aq Na_2CO_3/ 75 °C/1.5 h	**9** 81
5	**7e** PhZnCl	THF/rt/24 h[e]	N/R
6	**7e** PhZnCl	THF/rt/16 h[d]	**9** 74
7	**7e** PhZnCl	THF/rt/30 min	**9** 90
8	**7f** 4-$MeOC_6H_4B(OH)_2$	THF–aq Na_2CO_3/ 75 °C/40 min[f]	**10** 81
9	**7g** 4-$MeOC_6H_4ZnCl$	THF/rt/15 min[g]	**10** 73
10	**7h** 2-furylZnCl	THF/rt/30 min[g]	**11** 79
11	**7i** 2,5-$Cl_2C_6H_3B(OH)_2$	THF–aq Na_2CO_3/ 75 °C/15 min[f]	**12** 79
12	**7j** 1-naphthyl$B(OH)_2$	THF–aq Na_2CO_3/ 75 °C/90 min[f]	**13** 75
13	**7k** 2-MeC_6H_4ZnCl	THF/rt/15 min[g]	**14** 68
14	$(CH_2CH)_4Sn$	THF/reflux/8 h[f]	**15** 67

[a] The metalated aromatics **7** were commercially available or were prepared according to literature procedures[12,13] from the corresponding aryl bromides or unsubstituted aromatics by metal–halogen exchange or deprotonation, respectively. [b] $Pd(Ph_3P)_2Cl$ catalyst (10 mol %) and 4 equiv of ArM, unless stated otherwise. [c] Yield of chromatographically purified product. These materials were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy, and high resolution mass spectroscopy. [d] $Pd(Ph_3P)_4$ catalyst (10 mol %). [e] No Pd catalyst. [f] 2 equiv ArM. [g] $Pd(Ph_3P)_2Cl_2$ catalyst (5 mol %).

Although a variety of metalated aromatics[8,11–13] have been demonstrated to undergo palladium-catalyzed cross-coupling reactions with organic halides, the use of 1-alkoxy-1-iodoalkenes (the enol ethers of acyl iodides) as the organic halide partner in a Stille-type coupling reaction with organometallics has not been documented. In order to test the utility of the iodo glucal **5** in the coupling reaction, we treated **5** with a palladium catalyst and a metalated benzene under a variety of reaction conditions (eq 1; Table I, entries 1–7). Although tributylphenyltin (**7b**) and phenylmagnesium bromide (**7c**) underwent coupling with iodide **5**, the isolated yields of the *C*-phenyl glucal **9** were inferior to those obtained using phenylboronic acid (**7d**) and phenylzinc chloride (**7e**). The coupling reactions in these latter two cases were extremely clean, the only byproduct observed being biphenyl. The palladium catalyst is necessary in these reactions since, in its absence, no cross-coupling is observed (entry 5). While the reaction with arylzinc chloride **7e** proceeds quickly and cleanly at room temperature in THF with $Pd(Ph_3P)Cl_2$ as catalyst, the reaction occurs much more slowly and in lower yield using $Pd(Ph_3P)_4$ (compare entries 6 and 7). It ap-

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(2) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 5808.

(3) (a) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**, *31*, 5165. (b) Dubois, E.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1990**, 1191.

(4) Friesen, R. W.; Daljeet, A. K. *Tetrahedron Lett.* **1990**, *31*, 6133.

(5) Tius, M.; Gu, X.; Gomez-Galeno, J. *J. Am. Chem. Soc.* **1990**, *112*, 8188.

(6) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *23*, 3997. (b) Friesen, R. W.; Sturino, C. F.; Daljeet, A. K.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 1944.

(7) The yield in the stannylation of glucal **3** has been improved to 85–90% from the yield of 71%, as reported in ref 6, by the utilization of 4 equiv of t-BuLi.

(8) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(9) An iodo glucal analogous to **5** was obtained as an unexpected product (75%) in the attempted cross-coupling of a C-1 stannylated glucal with 3-iodo-2-propyn-1-ol.[3b]

(10) (a) The vinyl iodide **5** exhibited the following: ^1H NMR (200 MHz, $CDCl_3$) δ 1.03–1.05 (m, 63 H), 3.82–3.91 (m, 2 H), 4.06–4.15 (m, 2 H), 4.30–4.37 (m, 1 H), 5.38 (dd, 1 H, $J = 1.5, 5.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.2, 12.5, 12.6, 18.2, 61.9, 68.2, 69.7, 86.2, 107.8, 111.9. (b) We have only stored the iodide **5** for this length of time although it may be stable for longer storage periods since no decomposition was noted under these conditions. However, if **5** is stored in the presence of light, or even under argon in the dark, decomposition to unidentified materials is rapid.

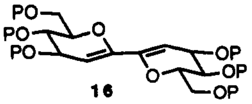
(11) Organolithiums and Grignard reagents: (a) Yamamura, M.; Moritani, I.; Murahashi, I. *J. Organomet. Chem.* **1975**, *91*, C39. (b) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191. (c) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408. (d) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.

(12) Zinc halides: (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

(13) Boronic acids: (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

pears that 4 equiv of the arylzinc, with respect to the iodo glucal **5**, is the ratio required for an optimum coupling reaction. When 1.3 or 2 equiv of **7e** was utilized, there was incomplete consumption of **5** after 24 h. It is also noteworthy that these reactions could be monitored visually since the initially pale yellow solution turns a dark red to black when all of the iodo glucal **5** is consumed.

We were pleased to find that the extension of the reaction to substituted arylboronic acids and arylzinc chlorides was also possible (entries 8–13). Especially interesting, in terms of the potential for preparing sialic acid conjugates, is the facile preparation of the *C*-furyl glucal **11** (entry 10).[14] Furthermore, the reaction is not limited to the coupling of metalated aromatics since the coupling of **5** and tetravinyltin provided the *C*-vinyl glucal **15** (entry 14).[15a] The isolated yields of the *C*-aryl glucals obtained under these mild reaction conditions were also superior to those that we had observed for every analogous example in our earlier work.[15b] Previously, the poorest substrates in the coupling reaction represented by **2** to **6** (eq 1) had been electron-rich aromatics.[1] Thus, the improved yield in the coupling of the anisole derivative (entries 8 and 9)[15b] was gratifying since many of the naturally occurring *C*-aryl glycosides are oxygen-substituted aromatics.[16] In addition, there was no evidence for the production of the glucal dimer **16** that previously had been the major byproduct (up to 15%) in all of our coupling reactions with stannyl glucal **2**.[1] Finally, purification of the glucals **9–15** is more easily accomplished than in the original procedure since the presence of this dimer had, in some cases, hampered chromatographic isolation.[17]



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As far as we are aware, this is the first example of the use of the enol ethers of acyl halides as the organic halide partner in a Stille-type coupling reaction with organometallics. We are continuing to explore the scope of this method in the synthesis of naturally occurring *C*-aryl glycosides as well as in the reactions of other non-carbohydrate derived 1-alkoxy-1-iodoalkenes.

Acknowledgment. We would like to thank Dr. Thomas Keller for a generous gift of the boronic acids **7d** and **7f** and the Natural Sciences and Engineering Research Council of Canada, the Canadian Foundation for AIDS Research, and the University of Toronto for financial support of this work.

Supplementary Material Available: Experimental procedure for the preparation of **5** and general procedures for the coupling of **5** and arylboronic acids and arylzinc chlorides, spectral data for **5** and **8–15**, and ^{1}H NMR spectra of **5** and **8–15** (23 pages). Ordering information is given on any current masthead page.

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(14) Danishefsky has demonstrated that the furan moiety of a C1-furyl glycal is a useful synthetic equivalent of a C1-carboxyl group. Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* 1988, *110*, 3929.

(15) (a) The yield of the *C*-vinyl glucal **15** (67%, entry 14) is contrasted to the yield of 22% observed by Beau[3b] in the coupling of a 1-stannyl glucal and vinyl bromide. (b) Compare, for example, the yields of compounds **9**, **10**, **13**, and **14** (entries 7, 9, 12, and 13, respectively) to the yields of **6** reported previously[1] that were obtained by using the stannylated glucal **2** and aryl bromides in which R = H (70%), R = 4-MeO (30%), Ar = 1-naphthyl (59%), and R = 2-Me (49%).

(16) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* 1985, *22*, 1.

(17) For example, the *C*-naphthyl glucal produced in the reaction of **2** and 1-bromonaphthalene (eq 1) had previously been obtained in pure form only in small amounts due to this purification problem.[1] This result is in contrast to the reaction shown in entry 12 in which glucal **13** was isolated in 75% yield.

Synthesis of the Monofluoro Ketone Peptide Isostere

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Summary: A synthetic method for the construction of monofluoro ketone peptide isosteres has been realized. The methodology has been employed in a synthesis of the fluoro ketone replacement for the natural substrate for D,D-carboxypeptidase-transpeptidase.

As part of an ongoing program designed to discover enzyme inhibitors that possess therapeutic potential we were interested in the synthesis of fluorinated ketone derivatives of bioactive peptides. The in vitro inhibition of serine proteases[1] by fluoro ketones that bear a structural resemblance to the natural substrates is well-documented. Fluoro ketone isosteres owe their inhibitory capacity to transition-state stabilization principles[2] that suggest that an enzyme binds the transition state much more strongly than the substrate itself. Similar to the hemiacetal formed by aldehyde inhibitors,[3] fluoro ketones are thought to form a stable hemiketal upon reaction with the active-site serine.[4] In theory, any serine protease can be targeted for inhibition by replacing the amide (Figure 1) located at the scissile bond site of the natural substrate with the ketofluoromethyl group [$C(O)CF_3$,[5] $C(O)CF_2$,$C(O)CFH$], while maintaining the appropriate amino acid residues at adja-

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(1) (a) Brady, K.; Abeles, R. H. *Biochemistry* 1990, *29*(33), 7608. (b) Govardhan, C. P.; Abeles, R. H. *Arch. Biochem. Biophys.* 1990, *280*(1), 137. (c) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* 1990, *33*(1), 394. (d) Ueda, T.; Kam, C.; Powers, J. C. *Biochem. J.* 1990, *265*(2), 539. (e) Allen, K. N.; Abeles, R. H. *Biochemistry* 1989, *28*(21) 8466. (f) Imperiali, B.; Abeles, R. H. *Biochemistry* 1987, *26*(14), 4474. (g) Stein, R. L.; Strimpler, A. L.; Edwards, P. D.; Lewis, J. J.; Mauger, R. C.; Schwartz, J. A.; Stein, M. M.; Trainor, D. A.; Wildonger, R. A.; Zottola, M. A. *Biochemistry* 1987, *26*(10), 2682. (h) Imperiali, B.; Abeles, R. H. *Biochemistry* 1986, *25*(13), 3760. (i) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry*, 1985, *24*(8), 813.

(2) (a) Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* 1976, *5*, 271. (b) Pauling, L. *Chem. Eng. News* 1946, *263*, 294.

(3) (a) Thompson, R. C. *Biochemistry* 1973, *12*, 47. (b) Westerik, J. O.; Wolfenden, R. *J. Biol. Chem.* 1972, *247*, 8195. (c) Evidence for a bound hemiacetal has been provided by X-ray crystallography: Delbaere, L. T. J.; Brayer, G. D. *J. Mol. Biol.* 1985, *183*, 89.

(4) Brady, K.; Anzhi, W.; Ringe, D.; Abeles, R. H. *Biochemistry* 1990, *29*(33), 7600.

(5) Although not shown in Figure 1 trifluoromethyl ketones have demonstrated significant potential as inhibitors of serine proteases.

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