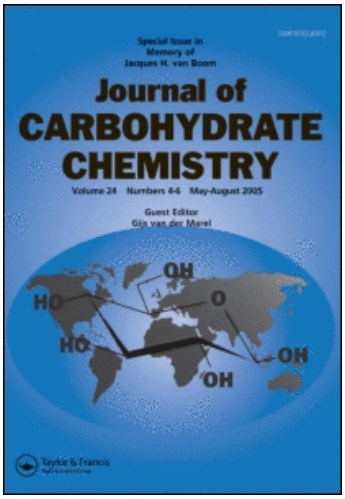


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Efficient Synthesis of 2'-Deoxy-β-D-furanosyl C-Glycosides. Palladium-Mediated Glycal-Aglycone Coupling and Stereocontrolled β- and α-Face Reductions of 3-Keto-furanosyl Moieties

Roger N. Farr; G. Doyle Daves Jr

To cite this Article Farr, Roger N. and Daves Jr, G. Doyle(1990) 'Efficient Synthesis of 2'-Deoxy-β-D-furanosyl C-Glycosides. Palladium-Mediated Glycal-Aglycone Coupling and Stereocontrolled β- and α-Face Reductions of 3-Keto-furanosyl Moieties', Journal of Carbohydrate Chemistry, 9: 5, 653 — 660
To link to this Article: DOI: 10.1080/07328309008543860
URL: http://dx.doi.org/10.1080/07328309008543860

J. CARBOHYDRATE CHEMISTRY, 9(5), 653-660 (1990)

Efficient Synthesis of 2'-Deoxy- β-D-furanosyl C-Glycosides. Palladium-Mediated Glycal-Aglycone Coupling and Stereocontrolled β- and α-Face Reductions of 3-Keto-furanosyl Moieties

Roger N. Farr† and G. Doyle Daves, Jr.*

†Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015 and Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180

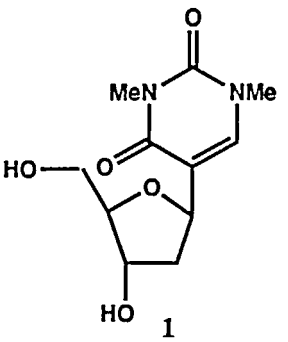
Received January 31, 1990 - Final form April 25, 1990

ABSTRACT

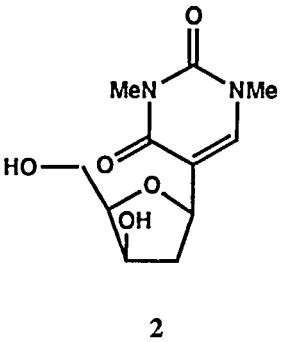
Efficient routes for selective syntheses of 2'-deoxy-β-D-furanosyl *C*-glycosides have been developed and demonstrated by preparation of the isomers 5-[2'-deoxy-β-D-*ribo*-(=*arabino*)furanosyl]-1,3-dimethyl-2,4(*1H,3H*)-pyrimidinedione and 5-[2'-deoxy-β-D-*xylo*-(=*lyxo*)furanosyl]-1,3-dimethyl-2,4(*1H,3H*)-pyrimidinedione. The syntheses involved regio- and stereospecific palladium-mediated coupling of a new glycal, 1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol with an appropriate aglycone derivative to form a single 2'-deoxy-3'-keto-β-D-furanosyl *C*-glycoside (as the corresponding silyl enol ether). Following desilylation, the ketone group of the furanosyl ring was reduced stereoselectively in either of two ways: by delivery of hydride from (a) the most hindered face of the carbonyl carbon using sodium (triacetoxy)borohydride or (b) the least hindered face using potassium tri-(*sec*-butyl)borohydride.

INTRODUCTION

In previous reports, we have described the synthesis of 2'-deoxyfuranosyl *C*-glycosides[1-4] by regio- and stereospecific palladium-mediated coupling[5,6] of furanoid glycals[7] with aglycone-mercuric acetates to yield intermediate 2'-deoxy-3'-keto-*C*-glycosides (as the corresponding enol ethers) followed by hydride reduction of the 3'-keto function.[1,2] We now report two significant improvements which are exemplified by direct, high yield syntheses of 5-[2'-deoxy- β-D-*ribo*(=*arabino*)furanosyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**1**) and 5-[2'-deoxy- β-D-*xylo*(=*lyxo*)furanosyl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**2**).[1,8,9]



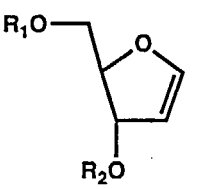
1



2

The key improvements we have made which lead to an excellent procedure for synthesis of 2'-deoxy- β-furanosyl *C*-glycosides are (a) design and synthesis of an optimized hydroxyl-substituted glycal for the palladium-mediated coupling reaction[1,3,5,6] and (b) achievement of stereospecific ketone reduction for conversion of intermediate 3'-keto *C*-glycosides to products.

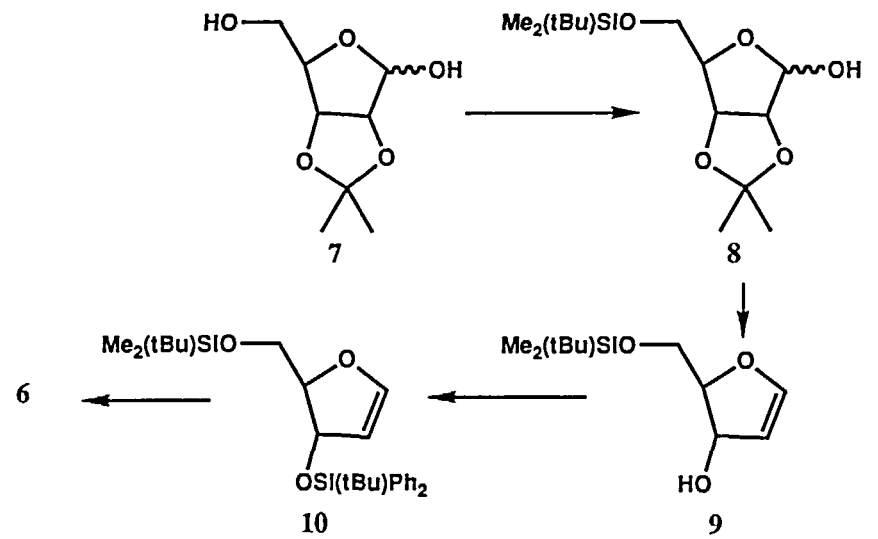
Glycal Hydroxyl Substitution. In palladium-mediated coupling reactions of furanoid glycals, substituted hydroxyl groups exert a directing effect on the attack of the organopalladium reagent on the glycal (enol ether) double bond and, thereby, determine the stereochemistry of the resulting *C*-glycoside product.[5,6] Thus, 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol[7] (3) which has both C-3 and C-5 hydroxyls free, undergoes palladium-mediated coupling with an aglycone to yield a mixture of α- and β-*C*-glycosides owing to competitive attack of the intermediate organopalladium reagent on both faces of the glycal ring.[1] The failure of **3** to exhibit stereospecific coupling is unique for furanoid glycals;[10] all other furanoid glycals studied, in which one or both of the hydroxyls of **3**[7] are substituted, exhibit stereospecific coupling to form either an α- or a β-*C*-glycoside.[1,11-14] When only one of the hydroxyls of a *ribo*-furanoid glycal is substituted (either the C-3 or C-5 hydroxyl);[7] palladium-mediated coupling occurs from the face of the glycal ring opposite the substituted (directing) hydroxyl to form a single *C*-glycosidic product.[1,2,5,6,11-14]



3, R_1, R_2 = H
4, R_1 = H, R_2 = CH_2OCH_3
5, R_1, R_2 = $Si(iPr)_3$
6, R_1 = H, R_2 = $Si(tBu)Ph_2$

5-Hydroxy-3-*O*-substituted furanoid glycals (e. g. **4**[1,7]) yield β-*C*-glycosides stereospecifically upon palladium-mediated coupling with a suitable aglycone derivative in good to high yield (65-95%).[1,2,11-14] Prior to the present report, all such derivatives of **3** which were available[7] have had C-3-*O*-alkyl groups (as in **4**) which we have been unable to remove from product *C*-glycosides without partial epimerization of the carbohydrate anomeric carbon. To circumvent this problem, we resorted to use of readily deprotected[1,2,11-14] 3,5-disilylated glycals (e. g. **5**)[1,2,7] for palladium-mediated coupling with aglycone derivatives to produce β-*C*-glycosides. Unfortunately, a bulky group on the face of the glycal experiencing organopalladium reagent attack leads to significantly depressed yields (25-50%)[1,2]

Now, we have succeeded in the preparation of 1,4-anhydro-2-deoxy-3-*O*-(t-butyldiphenylsilyl)-D-*erythro*-pent-1-enitol (**6**), a glycal which has the C-5 hydroxyl free and a readily removed stereodirecting group attached to the C-3 oxygen. This synthesis, which is a significant extension of previous glycal manipulation chemistry,[7] was accomplished by the judicious selection of silyl protecting groups. Thus, 2,3-*O*-(1-methylethylidene)-D-ribofuranose[15] (**7**) was selectively *t*-butyldimethylsilylated at the C-5 hydroxyl and the resulting intermediate **8**[16] was converted to glycal **9** by the Ireland procedure.[7,17] The C-3 hydroxyl of **9** was then derivatized using *t*-butyldiphenylsilyl chloride and the resulting differentially bis-silylated glycal **10** was selectively mono-desilylated using tetrabutylammonium fluoride to form **6**.

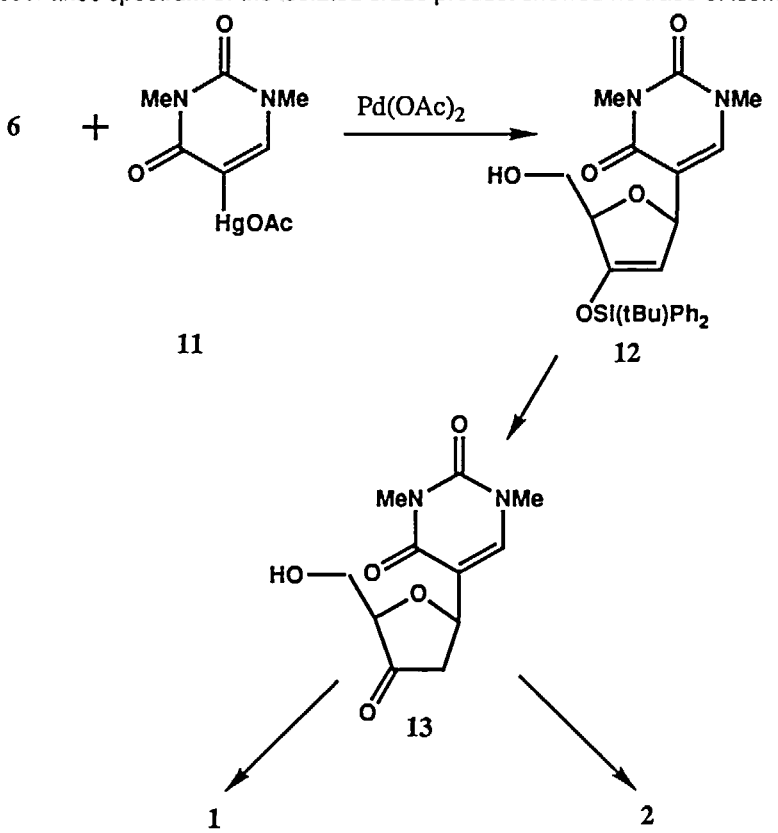


Palladium-mediated coupling of glycal **6** with(1,3-dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl)mercuric acetate[18] (**11**) in acetonitrile in the presence of one equivalent of

palladium acetate resulted in an 84 percent yield of the corresponding β-furanosyl *C*-glycoside **12** from which the silyl stereodirecting group was readily removed by tetrabutylammonium fluoride to produce the 2'-deoxy-3'-keto *C*-glycoside[1] (**13**).

Stereoselective Ketone Reduction. We have reported[1] that reduction of the ketone group of **13** using sodium or lithium borohydride leads to mixtures of 2'-deoxy *C*-glycosides **1** and **2**. We have now defined conditions for two complementary stereocontrolled reductions of the keto group of **13** which yield, respectively, *C*-glycoside **1** or *C*-glycoside **2** exclusively.

To achieve reduction of the 3'-keto group of **13** with hydride delivery from the hindered β-face of the carbohydrate ring, we employed sodium tri(acetoxy)borohydride in acetic acid at room temperature. Ketone reductions using this reagent, which apparently involves initial coordination of the borohydride reagent with the hydroxyl at *C*-5',[19,20] are rapid and stereospecific. Under these conditions, **13** was converted to **1** quantitatively. A 500 MHz ^{1}H nuclear magnetic resonance spectrum of the isolated crude product showed no trace of isomer **2**.



Equally effective reduction of the keto group of **13** to form the 2'-deoxy *C*-glycoside **2**, which is isomeric with **1** at C-3', by hydride delivery from the relatively unhindered α-face of

the carbohydrate was achieved using potassium tri-(*sec*-butyl)borohydride (K Selectride) at -80 °C. As in the previous case, this reduction was essentially quantitative and no trace of **1** was detected by nuclear magnetic resonance spectrometry.

The availability of furanoid glycal **6**, in which the hydroxyl at C-5 is free and that at C-3 is silylated, provides a direct, high yield route to β-furanosyl *C*-glycosides via palladium-mediated glycal-aglycone coupling. Use of this coupling reaction in combination with quantitative, essentially stereospecific reduction of the intermediate 3'-keto function from either the most hindered or least hindered face of the carbohydrate ring constitutes an extremely efficient synthetic route to 2'-deoxy-furanosyl *C*-glycosides.

EXPERIMENTAL

General Comments. Thin-layer chromatography (TLC) was carried out on prescored silica gel GF plates (Analtech). Preparative TLC was carried out on 1mm thick, 20 x 20 cm, silica gel GF plates (Analtech). For flash chromatography, silica gel 60 (230-400 mesh ASTM, E. Merck) was used. Columns were eluted with a positive nitrogen pressure. Nuclear magnetic resonance spectra were obtained on a Bruker AM 500 spectrometer and are referenced to tetramethylsilane. Melting points were measured with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were carried out by Quantitative Technologies, Bound Brook, N.J.

1,4 -Anhydro-2-deoxy-5 -O-[(1,1-dimethylethyl)dimethylsilyl]-3-O-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol(10). A mixture of **9**[7] (5.8 g, 25.2 mmol), imidazole (4.29 g, 63.0 mmol), and *t*-butyldiphenylsilyl chloride (7.6 g, 27.7 mmol) in 20 mL of dimethylformamide was stirred at room temperature for 18 h. The reaction mixture was then poured into 300 mL of ether and the resulting solution was washed with distilled water and brine and then dried over sodium sulfate. After evaporation of the volatiles *in vacuo*, purification was accomplished by flash chromatography on silica gel (ether-petroleum ether 1:10) to afford 11.33 g (96%) of **10** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 6H, Si-CH_3), 0.89 (s, 9H, t-butyl), 1.10 (s, 9H, t-butyl), 3.38 (ddd, 2H, $J_{4,5}$ = 5.0 Hz, $J_{4,5'}$ = 6.2 Hz, $J_{5,5'}$ = 10.9 Hz, H-5,5'), 4.49 (ddd, 1H, $J_{3,4}$ = 2.6 Hz, $J_{4,5'}$ = 6.2 Hz, $J_{4,5}$ = 5.0 Hz, H-4), 4.87 (m, 2H, H-2, H-3), 6.46 (dd, $J_{1,2}$ = 2.2 Hz, $J_{1,3}$ = 0.7 Hz, H-1), 7.46 (m, phenyl), 7.74 (m, phenyl). ^{13}C NMR ($CDCl_3$) δ 5.44, 18.28, 19.05, 25.83, 26.88, 62.97 (C-5), 76.81 (C-3), 89.20 (C-4), 103.30 (C-2), 127.55, 127.68, 129.60, 129.69, 133.93, 134.19, 135.78, 149.08 (C-1).[21]

Anal. Calcd for $C_{27}H_{40}O_3Si_2$: C, 69.2; H, 8.60. Found: C, 69.5; H 8.77.

1,4-Anhydro-2-deoxy-3-O-[(1,1, dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol(6). To a stirred solution of **10** (5.6 g, 12.0 mmol) in 25 mL of tetrahydrofuran at -22 °C, was added a 1M solution of tetra-n-butylammonium flouride in tetrahydrofuran (14.4 mL, 14.4 mmol). The resulting mixture was stirred for 2 h at room temperature during which time the reaction was complete based on TLC (ether:petroleum ether 1:1). 1,2-Dichloroethane (100 mL) was then added to the reaction mixture and the volatiles were removed *in vacuo*. The crude product was purified by flash chromatograghy to give 3.56 g (84%) of **6** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H, t-butyl), 3.25 (ddd, 2H, $J_{4,5}$ = 7.2 Hz, $J_{4,5'}$ = 3.4 Hz, $J_{5,5'}$ = 11.8 Hz, H-5,5'), 4.47 (ddd,1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 7.1 Hz, $J_{4,5'}$ = 3.4 Hz, H-4), 4.77 (dd, 1H, $J_{2,3}$ 2.8Hz, $J_{3,4}$ 3.4Hz, H-3), 4.97 (dd,1H, $J_{1,2}$ 2.6Hz, $J_{2,3}$ 2.7Hz, H-2), 6.47 (d, 1H, $J_{1,2}$ =2.6 Hz, H-1), 7.45 (m, phenyl), 7.72 (m, phenyl). ^{13}C NMR δ 18.93, 26.79, 62.69 (C-5), 76.39 (C-3), 89.23 (C-4), 103.93 (C-2), 127.60, 127.62, 127.75, 129.73, 129.85, 133.68, 133.69, 135.68, 135.69,148.67 (C-1).[21]

Anal. Calcd for $C_{21}H_{26}O_3Si$: C, 71.1; H, 7.39. Found: C, 70.8; H, 7.57.

1,3,-Dimethyl-5-(β-D-*glycero*-pentofuran-3' ulos-1'-yl)-2,4(*1H,3H*)-pyrimidinedione (13). To a solution of (1,3-dimethyl-2,4-dioxo-1,3-dihydropyrimidin-5-yl) mercuric acetate[18] (**11**) (460 mg, 11.56 mmol) in acetonitrile (25 mL) at room temperature was added palladium acetate (260 mg, 11.56 mmol). The mixture was stirred for five min, in which time the solution turned black, and then a solution of 1,4-anhydro-2-deoxy-3-0-[(1,1 dimethylethyl) diphenylsilyl]-D-*erythro*-pent-1-enitol (6) (491 mg, 13.87 mmol) in acetonitrile (5 mL) was added. After two h, sodium bicarbonate (243 mg, 28.9 mmol) was added and the resulting mixture was stirred for an additional 18 h. The mixture was then filtered through celite, and volatiles were removed *in vacuo*. Column chromatography of the residue using ether-petroleum ether (2:1) yielded 478 mg (84%) of **12** as a colorless oil.

To a solution of **12** (200 mg, 0.41 mmol) and acetic acid (48.8 mg, 0.82 mmol) in tetrahydrofuran (25 mL) at -78 °C was added a 1M solution of tetra-n-butylammonium fluoride (0.82 mL, 0.82 mmol) in tetrahydrofuran. The reaction was complete in 15 minutes based on TLC. One drop of acetic acid was added to the reaction mixture and cooling was discontinued. Volatiles were removed *in vacuo* and the resulting residue was purified by column chromatography using EtOAc-MeOH (9:1) to yield 100 mg (97%) of **13** as a colorless oil. Compound **13** exhibited spectrometric properties indistinguishable from those previously reported.[1]

5-[2'-Deoxy-β-D-*ribo*(=*arabino*)furanosyl]-1,3 dimethyl- 2,4-(*1H,3H*)-pyrimidinedione[1,3](1). To a solution of (**13**) (80 mg, .31 mmol) in acetic acid (10 mL) and acetonitrile (10 mL) at room temperature was added sodium triacetoxyborohydride (168 mg, O.79 mmol). The reaction was complete in 10 min based on TLC. Volatiles were removed *in vacuo* . A 500 MHz NMR spectrum of the residue showed that **1** was the sole product of the reaction; no trace of isomer **2** was observed. The residue was purified by column chromatography using EtOAc/MeOH (5:1) to give 80 mg (99%)of **1** as a white solid which exhibited spectrometric properties indistinguishable from those previously reported.[1,3]

5-[2'-Deoxy-β-D-*xylo*(=*lyxo*)furanosyl]-1,3-dimethyl-2,4-(*1H,3H*)-pyrimidinedione[1,3] (2). To a solution of **13** (120 mg, 0.47 mmol) in tetrahydrofuran (25 mL) at -78 °C was added a 1M solution of K selectride in tetrahydrofuran (0.95 ml, 0.95 mmol). After the reaction mixture was stirred for two h, the reaction was complete based on TLC. Several drops of acetic acid were then added and cooling was discontinued. After removing the volatiles from the reaction mixture *in vacuo,* a 500 MHz NMR of the residue showed that **2** was the sole product. The residue was purified by column chromatography using EtOAc/MeOH (5:1) to give 104 mg (86%) of **2** as a white solid which exhibited spectrometric properties indistinguishable from those previously reported.[1,3]

ACKNOWLEDGMENT

We thank the American Cancer Society and the National Institutes of Health (AI26261) for financial support.

REFERENCES AND FOOTNOTES

1. J. C.-Y. Cheng, U. Hacksell and G. D. Daves, Jr., *J. Org. Chem.*, **51**, 3093 (1986).

2. R. A. Outten and G. D. Daves, Jr., *J. Org. Chem.*, **52**, 5064 (1987).

3. U. Hacksell, J. C.-Y. Cheng and G. D. Daves, Jr., *J. Carbohydr. Chem.*, **5**, 287 (1986).

4. For a recent review of the chemistry and biology of C-glycosides see: U. Hacksell and G. D. Daves, Jr., *Prog. Med. Chem.*, **22**, 1 (1985).

5. G. D. Daves, Jr. in "Advances in Metal-Organic Chemistry"; L. S. Liebeskind, ed.; JAI Press: Greenwich, CT, in press.

6. G. D. Daves, Jr. and A. Hallberg, *Chem. Rev.*, **89**, 1433 (1989).

7. J. C.-Y. Cheng, U. Hacksell and G. D. Daves, Jr., *J. Org. Chem.*, **50**, 2778 (1985).

8. A. Matsuda, C. K. Chu, U. Reichman, K. Pankiewicz, K. A. Watanabe and J. J. Fox, *J. Org. Chem.*, **46**, 3603 (1981).

9. Chemical Abstracts names for these compounds are 2S-*trans*-and 2R-*cis*-5-[2,5-dihydro-5-(dihydroxymethyl)-2-furanyl]-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione (**1** and **2** respectively).

10. The only other failure to observe stereospecific C-glycoside formation occurred in the coupling of a 3-deoxypyranoid glycal (unpublished results).

11. U. Hacksell and G. D. Daves, Jr., *J. Org. Chem.*, **48**, 2870 (1983).

12. J. C.-Y. Cheng and G. D. Daves, Jr., *Organometallics*, **5**, 1753 (1986).

13. R. A. Outten and G. D. Daves, Jr., *J. Org. Chem.*, **54**, 29 (1989).

14. U. Hacksell and G. D. Daves, Jr., *Organometallics*, **2**, 772 (1983).

15. P. A. Levene and E.T. Stiller, J. Biol. Chem., **102**, 187 (1933).

16. It is significant that **8** was prepared directly from **D**-ribose rather than from **D**-ribonolactone as has been customary (see references 7 and 17).

17. R. E. Ireland, S. Thaisrivongs, N. Vanier and C. S. Wilcox, *J. Org. Chem.*, **45**, 48 (1980).

18. I. Arai and G. D. Daves, Jr., *J. Org. Chem.*, **43**, 4110 (1978).

19. D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, **110**, 3560 (1988).

20. T. E. A. Nieminen and T. A. Hase, *Tetrahedron Lett.*, **28**, 4725 (1987).

21. On the basis of the "alkylation shift", Dax *et al.* (K. Dax, B. I. Glanzer, G. Schultz and H. Vyplel, *Carbohydr. Res.* **162**, 13 (1987).) assigned ^{13}C resonances for glycals differently than assignments we reported earlier;[7] we have confirmed the assignments made be Dax *et al.*, and those reported here by ^{1}H-^{1}H and ^{1}H ^{13}C NMR correlation spectrometry.