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Stereospecific Entry to [4.5]Spiroketal Glycosides Using Alkylidenecarbene C–H Insertion

Duncan J. Wardrop,* Wenming Zhang, and Joseph Fritz

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

wardropd@uic.edu

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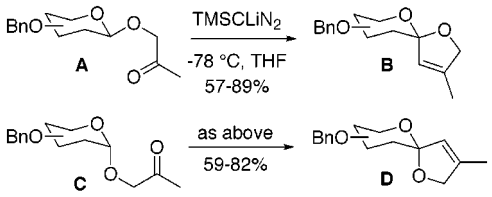
ABSTRACT



A novel method for the stereospecific preparation of [4.5]spiroketal glycosides utilizing the 1,5 C–H bond insertion of alkylidenecarbenes is described. Treatment of 2-oxopropyl β-pyranosides A with lithium (trimethylsilyl)diazomethane in THF at −78 °C afforded 1,6-dioxaspiro[4,5]-decenes B in good yield. Submission of the corresponding α-glycosides C to the same reagent gave the isomeric insertion products D in moderate to high yield.

The intramolecular C−H bond insertion reaction of alkylidenecarbenes is a powerful method for the preparation of five-membered carbocyclic[1] and heterocyclic rings.[2] Gilbert and co-workers have demonstrated that the ease with which this transformation occurs is dependent on, among other things, the dissociation energy of the C−H bond undergoing insertion.[3] Accordingly, insertion into C−H bonds flanked by one or more heteroatoms, such as those in acetals, is favored since these bonds are significantly weakened by the adjoining atoms.[4] Bearing this effect in mind, we reasoned that alkylidenecarbene **2**, generated from 2-oxopropyl pyranoside **1**, would readily undergo insertion at the adjoining activated anomeric C−H bond and thereby provide a convenient and stereospecific entry to [4.5]spiroketal glycosides **3**.[5] The 1,6-dioxaspiro[4,5]decane ring system thus formed constitutes the core structure of a wide range of biologically active natural products[6] including the phyllanthostatins,[7a] breynins,[7a] and attenols[7b] in addition to the spirophostins, a group of adenophostin A analogues recently prepared by van Boom.[7c] Although the intramolecular insertion of alkylidenecarbenes into acetal C−H bonds has been reported by Wills[8a] and others,[8b−e] to the best of our

(1) For reviews covering the 1,5-C−H insertion of alkylidenecarbenes, see: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383−405. (b) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274−285. (c) Taber, D. F. In *Methods of Organic Chemistry*, 4th ed.; Helmchen, G., Ed.; Georg Thieme Verlag: Stuttgart, New York, 1995; Vol. E21, pp 1127−1148. (d) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164−1170.

(2) For selected examples of the formation of 2,5-dihydrofurans, see: (a) Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086−1092. (b) Buxton, S. R.; Holm, K. H.; Skattebøl, L. *Tetrahedron Lett.* **1987**, *27*, 2167−2168. (c) Baird, M. S.; Baxter, A. G. W.; Hoorfar, A.; Jefferies, I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2575−2581. (d) Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927−4930. (e) Ohira, S.; Kitamura, T.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, *39*, 5375−5376. (f) Singh, G.; Vankayalapati, H. *Tetrahedron: Asymmetry* **2000**, *11*, 125−138.

(3) Gilbert J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251−5256.

(4) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609−614 and references therein.

(5) Despite the presence of numerous oxygen-activated C−H bonds in carbohydrates, reports of alkylidenecarbene insertion involving these substrates have been limited: (a) Hauske, J. R.; Guadliana, M.; Desai, K. *J. Org. Chem.* **1982**, *47*, 5019−5021. (b) Pérez-Pérez, M.-J.; Camarasa, M.-J. *Tetrahedron* **1994**, *50*, 7269−7282. (c) Ohira, S.; Sawamoto, T.; Yamoto, M. *Tetrahedron Lett.* **1995**, *36*, 1537−1538.

(6) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395−436.

(7) (a) Smith, A. B., III; Empfield, J. R. *Chem. Pharm. Bull.* **1999**, *47*, 1671−1678. (b) Takada, N.; Suenaga, K.; Yamada, K.; Zheng, S.-Z.; Chen, H.-S.; Uemura, D. *Chem. Lett.* **1999**, 1025−1026. (c) de Kort, M.; Regenbogen, A. D.; Valentijn, A. R. P. M., Challis, R. A. J.; Iwata, Y.; Miyamoto, S.; van der Marel, G. A.; van Boom, J. H. *Chem. Eur J.* **2000**, *6*, 2696−2704.

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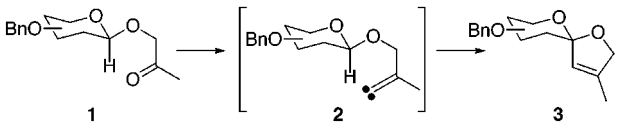
knowledge there have been no reports of insertion into the anomeric C−H bond of a carbohydrate.[9] Herein we therefore report the first examples of this transformation and demonstrate its potential as a method for the preparation of [4.5]-spiroketal glycosides.

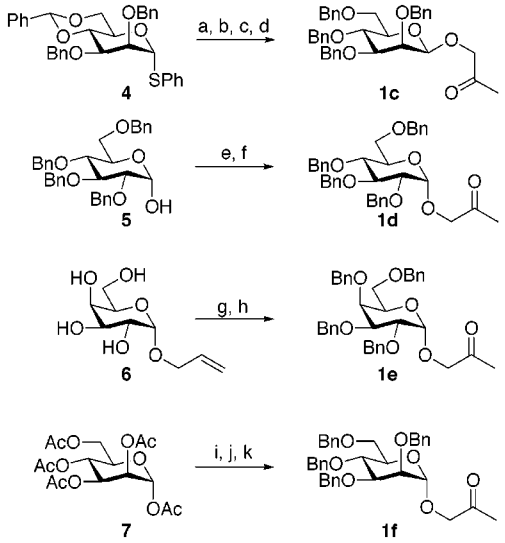
Scheme 1. C−H Bond Insertion Strategy for the Preparation of [4.5]Spiroketal Glycosides



An initial review of the literature revealed two practical methods for accessing the 2-oxopropyl pyranosides **1** required for our study: (i) Wacker oxidation of allyl pyranosides[10] and (ii) oxymercuration of propargyl pyranosides, as recently reported by Mereyala.[11] Known β-glycosides **1a** and **1b** (Table 1) were therefore prepared from D-glucose pentaacetate and D-galactose pentaacetate, respectively, following this later procedure. α-Mannopyranoside **1f** (Scheme 2), while not reported by Mereyala, was also prepared using this protocol. Thus, reaction of α-D-mannose pentaacetate (**7**) with propargyl alcohol and $BF_3{\cdot}Et_2O$ (1.5 equiv) in refluxing CH_2Cl_2 furnished the corresponding propargyl mannopyranoside as a single anomer in 77% yield. Zemplén de-O-acetylation, per-O-benzylation, and oxymercuration then gave **1f** in 76% yield. The stereochemistry at the anomeric center was determined by a gated decoupled ^{13}C NMR experiment, which revealed a J_{C1H1} value of 175 Hz consistent with the α-anomer.[12]

The corresponding β-mannoside **1c** was prepared from thioglycoside **4**[13] using Crich's method.[14] Thus, activation of **4** with 1-benzenesulfinyl-piperidine (BSP)/trifluoromethanesulfonic anhydride (Tf_2O), in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) and addition of propargyl alcohol, furnished the desired β-mannoside in high yield. Hydrolysis of the 4,6-benzylidene acetal, di-O-benzylation, and oxymercuration now gave **1c**. Glycosylation of 2,3,4,6-tetra-*O*-benzyl α-D-glucopyranose (**5**) with methallyl alcohol using

Scheme 2. Preparation of 2-Oxopropyl Pyranosides **1**[a]



[a] Reagents and conditions: (a) (i) BSP, TTBP, Tf_2O, CH_2Cl_2, 3 Å ms, −60 °C, 5 min; (ii) HC≡CCH_2OH, −60 °C → rt, 30 min, 79%; (b) AcOH, H_2O, 70 °C, 5 h, 70%; (c) NaH, BnBr, THF, 0 °C → rt, 8 h, 88%; (d) $Hg(O_2CCF_3)_2$ (0.2 equiv), acetone, H_2O, rt, 18 h, 77%; (e) TsCl, Bu_3NEtBr, methallyl alcohol, CH_2Cl_2, NaOH, H_2O, rt, 34 h; (f) OsO_4, $NaIO_4$, py, THF, H_2O, rt, 2 h, 64% from **5**; (g) NaH, BnBr, Bu_4NI, DMF, rt, 6 h, 92%; (h) (1) O_2, $PdCl_2$ (0.3 equiv), CuCl (3 equiv), DMF−H_2O (6:1), 40 °C, 8 h, 94%, (2) $NaClO_2$, CH_3CN, 2-methyl-2-butene, 60% from **6**; (i) HC≡CCH_2OH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, reflux, 12 h, 77%; (j) (1) MeONa (0.1 equiv), MeOH, rt, 1 h; (2) NaH, BnBr, Bu_4NI, DMF, rt, 15 h, 84%; (k) $Hg(O_2CCF_3)_2$ (0.2 equiv), acetone, H_2O, rt, 18 h, 92%.

Szeja's method[15] gave a 4:1 mixture of anomers, which although spectroscopically distinguishable proved to be inseparable by flash chromatography. This mixture was therefore directly submitted to Lemieux−Johnson oxidation, which when buffered with 1 equiv of pyridine gave methyl ketones **1a** and **1d**. Separation of these components by flash chromatography afforded **1d** in 64% yield from **5**. Substrate **1e** was prepared from allyl α-D-galactopyranoside (**6**) via per-O-benzylation and Wacker oxidation, which proceeded to give a 3:1 mixture of **1e** and the aldehyde (3-oxopropyl glycoside) resulting from anti-Markovnikov hydration.[16,17] As this aldehyde could not be separated from **1e** chromatographically, the mixture was directly submitted to $NaClO_2$ oxidation and the resulting carboxylic acid was then removed by flash chromatography to provide **1e** in 60% yield from **6**. The configuration of the anomeric stereocenters of **1d** and

(8) (a) Walker, L. F.; Connolly, S.; Wills, M. *Tetrahedron Lett.* **1998**, *39*, 5273−5276. (b) Schildknegt, K.; Bohnstedt, A. C.; Feldman, K. S.; Sambandam, A. *J. Am. Chem. Soc.* **1995**, *117*, 7544−7545. (c) Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett.* **2000**, *2*, 1855−1857. (d) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2000**, *41*, 6859−6863. (e) Taber, D. F.; Yu, H.; Incarvito, C. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 13285−13290.

(9) The intramolecular insertion of cyclopropylidenecarbenes into acetal C−H bonds has been reported: (a) Slessor, K. N.; Oehlschlager, A. C.; Johnston, B. D.; Pierce, H. D.; Grewal, S. K.; Wickremesinghe, L. K. G. *J. Org. Chem.* **1980**, *45*, 2290−2297. (b) Brinker, U. H.; Haghani, A.; Gomann, K. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 230−231.

(10) Lüning, J.; Möller, U.; Debski, N.; Welzel, P. *Tetrahedron Lett.* **1993**, *34*, 5871−5874.

(11) (a) Mereyala, H. B.; Gurrala, S. R. *Chem. Lett.* **1998**, 863−864. (b) Mereyala, H. B.; Gurrala, S. R. *Carbohydr. Res.* **1998**, *307*, 351−354.

(12) (a) Bock, K.; Pederson, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297. (b) Singh, G.; Vankayalapati, H. *Tetrahedron: Asymmetry* **2000**, *11*, 125−138.

(13) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930.

(14) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020.

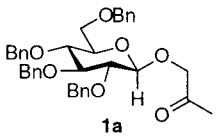
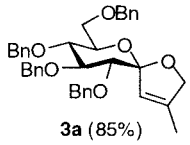
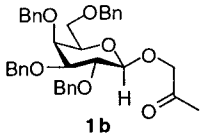
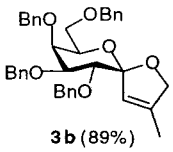
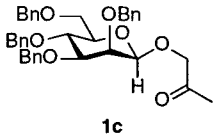
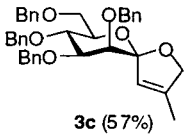
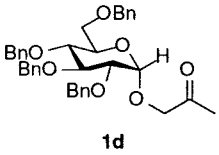
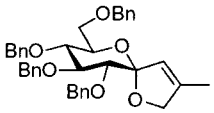
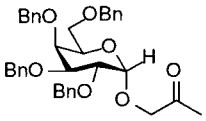
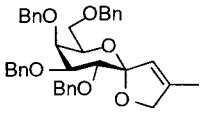
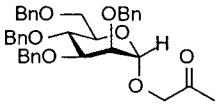
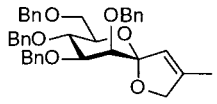
(15) Szeja, W. *Synthesis* **1988**, 223−224.

(16) For a discussion of the influence that heteroatoms have over the regiochemistry of the Wacker oxidation, see: (a) Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron Lett.* **1994**, *35*, 6481−6484. (b) Lüning, J.; Möller, U.; Debski, N.; Welzel, P. *Tetrahedron Lett.* **1993**, *34*, 5871−5874.

(17) In contrast to our finding, the Wacker oxidation of this substrate has previously been reported to lead to double bond isomerization and formation of a η^2-vinyl palladium complex of the resulting prop-1-enyl glycoside: Mereyala, H. B.; Lingannagaru, S. R. *Tetrahedron* **1997**, *53*, 17501−17512.

(18) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721−722.

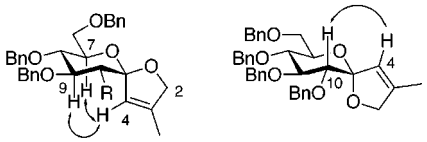
Table 1. Alkylidenecarbene Insertion at the Anomeric C−H Bond[23]

entry	substrate	product (yield)[a]
1	 **1a**	 **3a** (85%)
2	 **1b**	 **3b** (89%)
3	 **1c**	 **3c** (57%)
4	 **1d**	 **3d** (61%)[b]
5	 **1e**	 **3e** (59%)[c]
6	 **1f**	 **3f** (82%)

[a] Isolated yields after purification over Et_3N-deactivated silica gel. [b] 2,3,4,6-Tetra-*O*-benzyl D-glucopyranose (**10**) (14%) was also isolated. [c] 2,3,4,6-Tetra-*O*-benzyl D-galactopyranose (**11**) (20%) was also isolated.

1e was confirmed as being α by measurement of the H_1-H_2 (**1d**, J_{H1H2} = 3.6 Hz; **1e**, J_{H1H2} = 3.7 Hz) and C_1-H_1 (**1d**, J_{C1H1} = 169 Hz; **1e**, J_{C1H1} = 170 Hz) coupling constants.[14]

With the requisite collection of 2-oxopropyl glycosides **1** assembled, we now proceeded with our investigation of the insertion reaction. The results of this study are shown in Table 1. Gratifyingly, reaction of **1a** with lithium (trimethylsilyl)diazomethane (LTDM)[18] for 30 min cleanly furnished **3a** in 85% yield after purification by flash chromatography (entry 1).[19,20] As indicated in Figure 1, a NOESY experiment revealed correlations between H-4, H-7, and H-9 while no cross-peak was observed between H-4 and H-10. This



3a, R = OBn **3d**

Figure 1. Selected NOESY correlations for [4.5]spiroketal pyranosides **3a** and **3d**.

confirmed our expectation that the singlet carbene generated under these conditions would undergo insertion with retention of configuration.[21] β-Galactopyranoside **1b** and mannopyranoside **1c** (entries 2 and 3) also underwent insertion with retention of configuration to provide **3b** and **3c**, respectively.

Having established the viability of insertion into axial anomeric C−H bonds, we now examined the corresponding α-pyranosides. Thus, treatment of **1d** and **1e** (entries 4 and 5) with LTDM, at −78 °C, for 1.5 h gave spiroketals **3d** and **3e** in reasonable yield. The configuration of the acetal stereocenters, as shown for **3d** in Figure 1, was determined by a NOESY experiment, which revealed a correlation between H-4 and H-10. The formation of **3d** and **3e** was also accompanied by small amounts of a polar product, as indicated by thin-layer chromatography. These were isolated and, to our surprise, found to be D-glucopyranose (**10**)[22a] (14%) and D-galactopyranose **11**[22b] (20%), respectively. One possible rationale for the formation of these unexpected byproducts is outlined in Scheme 3. Reaction of **8** with lithium trimethylsilanoate, generated during the formation of **8**, and protonation of the resulting α-silanoxy vinyl anion would provide **9**.[23] Hydrolysis of this enol ether would then form the corresponding β-alkoxy aldehyde, which upon elimination of methacrolein[24] would lead to pyranoses **10** and **11**.

Because, compared to equatorial anomeric C−H bonds, axial C−H bonds have a decreased dissociation energy[4] and

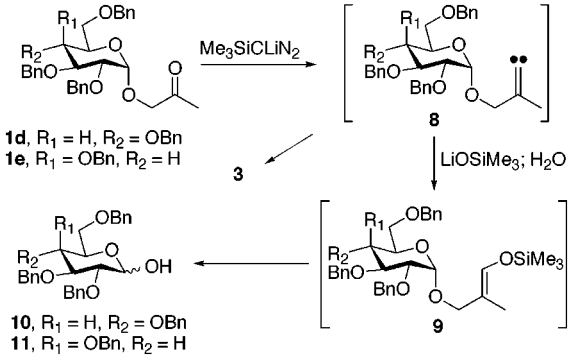
(19) **Typical Procedure for the Preparation of [4.5]Spiroketal Glycosides (3a).** To a solution of (trimethylsilyl)diazomethane (118 μL, 2.0 M in hexanes, 236 μmol) in THF (3 mL), at −78 °C, was added *n*-butyllithium (113 μL, 2.0 M in cyclohexane, 226 μmol). After 5 min of stirring, a solution of **1a** (70.7 mg, 119 μmol) in THF (1 mL) was added, and the resulting mixture was stirred for 30 min before saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. After warming to room temperature, this mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography over silica gel (EtOAc/hexanes/Et_3N, 38:212:1) to provide **3a** (60.1 mg, 85% yield). The insertion reaction of the α-pyranosides **1d**−**f** was carried out as described above, but the reaction time was extended to 1.5 h. In the case of substrates **1d**−**f**, shorter reaction times resulted in the formation of complex mixtures of products and significantly lower yields of **3d**−**f**.

(20) In agreement with observations made by Skattebøl[2b] and Wills,[8a] the 2-alkoxydihydrofuran moiety of **3** proved to be acid-sensitive. As a result, the purification of all insertion products was carried out over Et_3N-deactivated silica gel. Further details of this reactivity will be reported elsewhere.

(21) (a) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557−2563. (b) Ohira, S.; Ishi, S.; Shinohara, K.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1039−1040.

(22) (a) Liaigre, J.; Dubreuil, D.; Pradère; Bouhours, J.-H. *Carbohydr. Res.* **2000**, *325*, 265−277. (b) Desai, T.; Gigg, J.; Gigg, R. *Aust. J. Chem.* **1996**, *49*, 305−309.

Scheme 3. Rationale for the Formation of Pyranoses **10** and **11**



display increased reactivity in a number of reactions, including radical H-abstraction[4] and insertion of ozone,[25] it is tempting in our case to correlate the proclivity of C−H insertion with the configuration of the anomeric center. Indeed, **1a** and **1b** did give significantly higher yields of insertion than the corresponding α-anomers. However, α-mannoside **1f** (entry 6) underwent insertion to give **3f** in excellent yield with no mannopyranose byproduct being observed. Furthermore, the increased yield in this case is in contrast to α-mannoside **1c**, which undergoes insertion less efficiently than either **1a** or **1b**.[26] Whether the reversal in yields for the mannose series suggests a lack of correlation between anomeric stereochemistry and insertion efficiency or is a consequence of the axial C-2 benzyloxy substituent present in substrates **1c** and **1f** remains to be established.

In summary, we report a new strategy for the preparation of [4.5]spiroketal glycosides **3** involving the C−H insertion of alkylidenecarbenes at the anomeric position of gluco-, galacto-, and mannopyranosides. In contrast to existing methods for the synthesis of spiroketals,[27,28] the approach reported here does not rely upon thermodynamic or kinetic control to set the configuration of the acetal stereocenter but rather capitalizes on the fact that alkylidenecarbene insertion proceeds with retention of configuration. As a result, both isomers of **3** are equally accessible by starting from the appropriate anomer of **1**. Work to extend this methodology to other carbohydrate substrates and the preparation of spiroketal natural products is underway; our progress will be reported in due course.

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Supporting Information Available: Full experimental procedures and spectral data for compounds **1a**−**f** and **3a**−**f** and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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