Carbohydrate Cyclic Ketene Acetals

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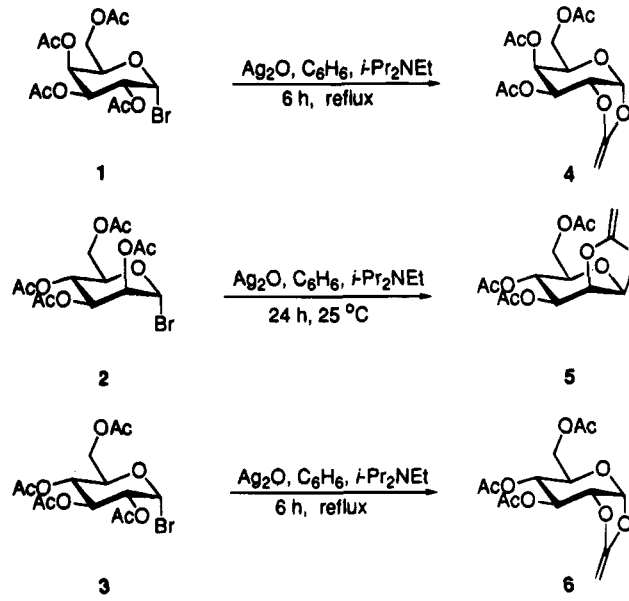
The stereoselective synthesis of *O*-glycosides using a number of glycosyl donors has been a topic of considerable interest over a period of decades.[1,2] Recent advances in understanding the roles of carbohydrates as elements of numerous biological systems have occasioned the need for synthetic oligosaccharides and other glycoconjugates, and thereby catalyzed renewed interest in novel approaches for effecting glycosylations and related transformations.

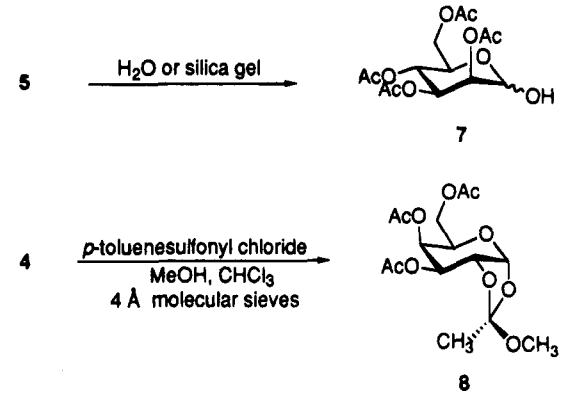
Cyclic ketene acetals (1,2-*O*-vinylidene acetals[3]) have long been used as versatile synthetic intermediates in organic synthesis.[4] Their traditional applications in the area of electrophilic addition reactions, as well as [2 + 2] cycloadditions, have received much attention. It is interesting that there is no example of the use of any carbohydrate cyclic ketene acetal as a synthetic intermediate in spite of reports over a period of more than 60 years that they can form as transient intermediates in transformations involving carbohydrates.[5] Herein, we report the first direct synthesis of these elusive species by a mild and convenient method and provide examples of their utility as synthetic intermediates in carbohydrate chemistry.

The 1,2-*O*-vinylidene acetals of interest (**4**, **5**, and **6**) were first observed (^{1}H NMR) as minor products when the respective tetra-*O*-acetyl-α-D-hexapyranosyl bromides (**1**, **2**, and **3**)[6] were treated with *N*-methylacetamide under the conditions described by Sinaÿ for the synthesis of

Scheme 1



Scheme 2



O-glycosyl imidates.[7] We subsequently found that **4**–**6** could be obtained in essentially quantitative yields by simple omission of *N*-methylacetamide (Scheme 1).[8] Mannose derivative **5** was formed under ambient conditions, while **4** and **6** required elevated temperatures, presumably reflecting the obligatory intermediacy of a 1,2-*trans*-hexapyranosyl bromide.[9]

Early studies of the mechanism of glycosylation established that the 1,2-cyclic acetoxonium ion of type **i**, typically derived by 1,2-*trans* liberation of bromide ion from the appropriate 2-*O*-acetylhexapyranosyl bromide,

(1) (a) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056. (b) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *34*, 155. (c) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189. (d) Ogawa, T.; Takahashi, Y. *Carbohydr. Res.* **1985**, *138*, C5. (e) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (f) Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1989**, *187*, 149. (g) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331. (h) Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860. (i) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927. (j) Raghaven, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. (k) Boons, G.-J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593. (l) Watanabe, Y.; Nakamoto, C.; Yamamoto, T.; Ozaki, S. *Tetrahedron* **1994**, *50*, 6523. (m) Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R. L.; Ritzen, H.; Wong, C.-H. *J. Org. Chem.* **1994**, *59*, 864. (n) For a recent review on the synthesis of *O*-glycosides, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(2) For recent examples of the use of glycals in glycosylations to give fully oxygenated products, see: (a) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 8473. (b) Liu, K. K.-C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1895. (c) Liu, K. K.-C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1892.

(3) IUPAC nomenclature as outlined in: IUPAC *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*; Pergamon: Elmsford, NY, 1979; Section A, p 14.

(4) Brassard, P. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; pp 487–519, and references cited therein.

(5) Freudenberg first postulated the formation of a transient cyclic ketene acetal to explain the formation of products derived from the base-catalyzed dehalogenation of a 1,2-*O*-(1-chloroethylidene)hexapyranoside (Freudenberg, K.; Scholz, H. *Chem. Ber.* **1930**, *63*, 1969). Additionally, Sinaÿ and co-workers have suggested the formation of a transient ketene acetal species to explain the elimination of a selenoxide to afford a spiro-ortholactone (Jaurand, G.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 572. Jaurand, G.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1982**, 701).

(6) The tetra-*O*-acetyl-α-D-hexapyranosyl bromides **1**–**3**, in turn, were obtained by treatment of the corresponding penta-*O*-acetyl-D-hexapyranosides with a solution of 33% HBr in HOAc (see, e.g., Hudson, C. S.; Dale, J. K. *J. Am. Chem. Soc.* **1918**, *40*, 992).

(7) Sinaÿ, P. *Pure Appl. Chem.* **1978**, *50*, 1437.

(8) Compounds **4**–**6** were characterized by ^{1}H NMR spectroscopy; especially diagnostic was a resonance in the range δ 3.37–3.55 (d, *J* = 3.6 Hz) for each compound, characteristic of the geminal protons of a vinylic system. The structures were further confirmed by high resolution (chemical ionization, methane) mass spectrometry *m/z* 330.096 (**4**), 330.093 (**5**), and 330.090 (**6**) ($C_{14}H_{18}O_9$ requires *m/z* 330.094). Optical rotation data for **4**: $[\alpha]^{20}_D$ +95.0° (*c* 1.0, $CHCl_3$); **5**: $[\alpha]^{20}_D$ −80.5° (*c* 1.0, $CHCl_3$), and **6**: $[\alpha]^{20}_D$ +79.9° (*c* 1.0, $CHCl_3$). Compounds **4**–**6** were each stored as a dry syrup for periods of six months at 4 °C with no apparent degradation, as judged by ^{1}H NMR spectroscopy.

(9) A 1,2-*trans* relationship of the halide and *O*-acetyl group is required for facile formation of the acetoxonium ion **i** whose deprotonation must lead to the ketene acetals. See ref 10 and Pacsu, E. In *Advances in Carbohydrate Chemistry*; Pigman, W. W., Wolfrom, M. L., Eds; Academic: New York, 1945; Vol. 1, pp 77–127.

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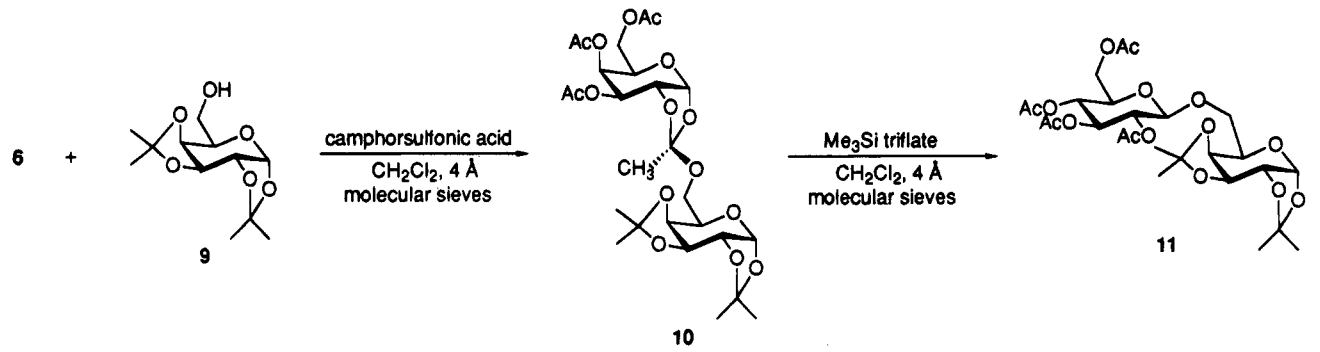
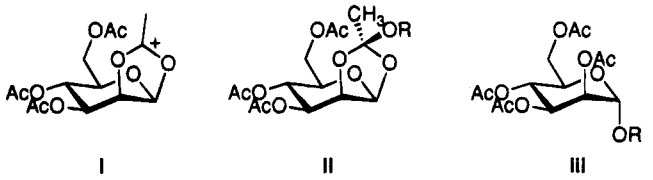
Scheme 3



was a key intermediate in the synthesis of 1,2-*O*-alkyl orthoesters **ii** and alkyl *O*-glycosides, **iii**.[10] The obvious structural relationship between acetoxonium ion and the cyclic ketene acetals described here suggested that the latter should be capable of serving as a convenient precursor for species of type **i**.



To characterize the actual chemical behavior of 1,2-*O*-vinylidene acetals, compounds **4**–**6** were used for the three most fundamental transformations noted previously for acetoxonium ions of type **i** (Scheme 2). These included ready conversion to the corresponding 2,3,4,6-tetra-*O*-acetyl-D-hexapyranose derivative (e.g. **5** → **7**) upon exposure of the compounds to aqueous media or silica gel. Treatment of **4**–**6** with methanol in the presence of *p*-toluenesulfonyl chloride provided the respective *exo*-methyl orthoesters in good yields, as exemplified by the conversion **4** → **8** in Scheme 2.[11]

The ability of carbohydrate cyclic ketene acetals to participate in glycosylation reactions was assessed using glucopyranose derivative **6** (Scheme 3). Treatment with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9**) in the presence of (1*S*)-(+)-10-camphorsulfonic acid in CH_2Cl_2[13] provided orthoester **10** in 85% yield;[12,14] this compares very favorably with the yields of orthoester obtained starting from 2-*O*-acetylglycopyranosyl bromides.[10b] Trimethylsilyl triflate-catalyzed rearrangement[15] of **10** in CH_2Cl_2 provided 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (**11**) in 61% overall yield from **6**. The structure of **11** was confirmed by comparison of its mp, optical rotation, and spectral data with literature values.[16]

The ability of carbohydrate cyclic ketene acetals to afford fully oxygenated disaccharides suggests that they may be comparable in scope to other recently described methods for glycosylation.[1,2] In common with other orthoester methodologies, one limitation of the use of carbohydrate cyclic ketene acetals is the need for a participating substituent at C-2. However, in addition to their structural simplicity the ketene acetals have several potential advantages relative to glycosyl halides or orthoesters as synthetic intermediates. These include the absence of byproducts formed concomitant with the production of acetoxonium ions (i.e., **i**) *in situ*, the absence of competing nucleophiles derived from alkyl orthoesters during glycosylation reactions,[16c] the ability to control reaction conditions more narrowly to facilitate the formation of hindered carbohydrate orthoesters,[17] and the use of the (intrinsically asymmetric) carbohydrate ketene acetal functionality for stereocontrolled synthetic modifications prior to orthoester rearrangements. Our studies of these parameters, as well as our finding of chemistry unique to the carbohydrate cyclic ketene acetals, will be reported in due course.

Acknowledgment. This study was supported by Research Grant CA53913 from the National Cancer Institute.

Supporting Information Available: Experimental procedures and physical data for the syntheses of compounds **4**–**6**, **8**, **10** and **11**, and for the syntheses of the *exo*-methyl orthoester derivatives of **5** and **6** (4 pages).

JO950801Y

(10) (a) Lemieux, R. U.; Cipera, J. D. T. *Can. J. Chem.* **1956**, *34*, 906. (b) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2199, and references therein.

(11) The structure of **8** and the analogous methyl orthoesters derived from **5** and **6** were established by ^1H NMR spectroscopy[12] and by comparison of physical properties with those reported for the authentic methyl orthoesters. See: (a) Alfredsson, G.; Borén, H. B.; Garegg, P. J. *Acta Chem. Scand.* **1972**, *26*, 3431. (b) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1975**, *44*, C14. (c) Reference 12.

(12) The ^1H NMR spectrum of each analogue included a singlet at δ 1.72, characteristic of the CCH_3 resonance of an *exo*-orthoester. See: Mazurek, M.; Perlin, A. S. *Can. J. Chem.* **1965**, *43*, 1918.

(13) For examples of the use of a camphorsulfonic acid in glycosylations, see: (a) Wakamatsu, T.; Nakamura, H.; Naka, E.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 3895. (b) Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975.

(14) The optical rotation of **10** ($[\alpha]^{23}_D$ −23.9° (*c* 0.90, $CHCl_3$)) compared favorably with that reported for an authentic sample ($[\alpha]_D$ −21.2° ($CHCl_3$): Ogawa, T.; Matsui, M. *Carbohydr. Res.* **1976**, *51*, C13).

(15) (a) Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6. (b) Gass, J.; Strobl, M.; Loibner, A.; Kosma, P.; Zähringer, U. *Carbohydr. Res.* **1993**, *244*, 69.

(16) (a) Freudenberg, K.; Noe, A.; Knopf, E. *Chem. Ber.* **1927**, *60*, 238. (b) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron* **1967**, *23*, 693. (c) Kochetkov, N. K.; Bochkov, A. F.; Sokolovskaya, T. A.; Snyatkova, V. J. *Carbohydr. Res.* **1971**, *16*, 17. (d) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13.

(17) Millar, A.; Kim, K. H.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1986**, *51*, 189.