

Preparation of 2-deoxy-2-*C-p*-tolylsulfonyl- β -D-glucopyranosyl *p*-tolyl sulfones having non-chair conformation and their elimination reactions†

Tohru Sakakibara,* Tomomi Suganuma and Yasuhiro Kajihara

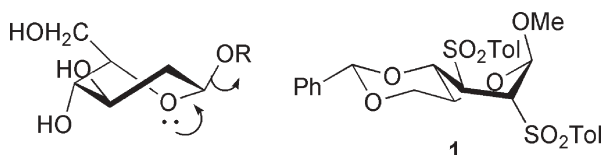
Received (in Bloomington, IN, USA) 23rd May 2007, Accepted 16th July 2007

First published as an Advance Article on the web 6th August 2007

DOI: 10.1039/b707802a

When the title sulfones, which have non-chair conformations, were stirred with silica gel, elimination of sulfinic acid occurred to give a 1-enitol derivative, if the hydroxyl group at C-6 was protected, whereas such an elimination did not proceed if the hydroxy group was free.

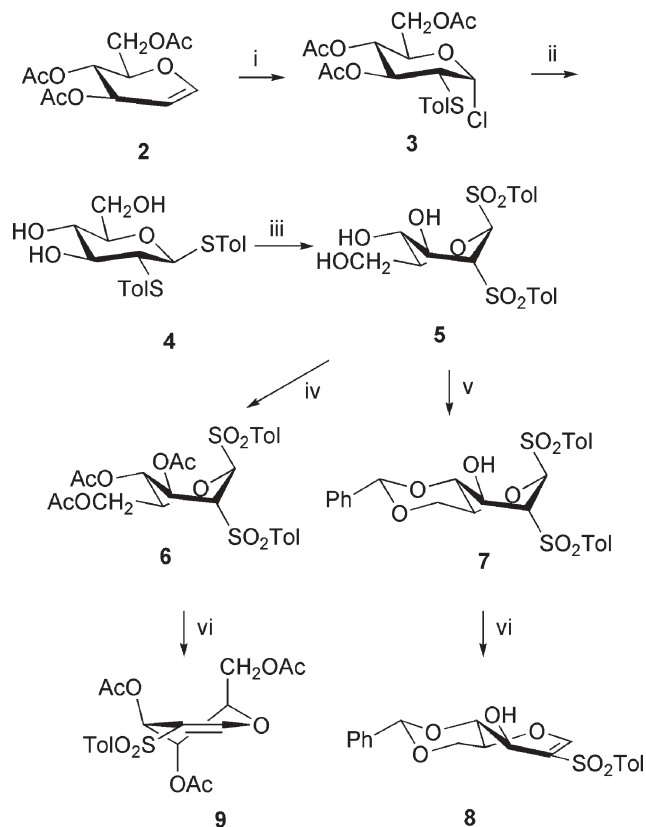
Replacement reactions at an anomeric center (C-1) are important in biological and chemical processes and hence they have been investigated extensively.¹ The theory of stereoelectronic effects predicts that in a β -D-glucopyranoside departure of a leaving group from C-1 should proceed through a non-chair conformation such as a boat or sofa form in which a lone pair on the ring oxygen atom can be antiperiplanar to the leaving group.² However, direct experimental evidence seems not to be presented, because a β -D-glucopyranoside inevitably occupies a chair conformation in solution. In fact, to our best knowledge, there is no report that describes a β -D-glucopyranosyl derivative which has a leaving group at C-1 taking up a non-chair conformation in solution.³



A sulfonyl group at C-1 behaves as a leaving group;⁴ therefore, we have synthesized 2-*C-p*-tolylsulfonyl- β -D-glucopyranosyl *p*-tolyl sulfone, expecting that such a compound exceptionally occupies a non-chair conformation, because we found that methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-*C*-di-*p*-tolylsulfonyl- β -D-glucopyranoside (**1**) adopts a non-chair conformation in solution.⁵

The intended ditosyl derivative **5** was prepared by addition of *p*-tolylsulfonyl chloride to tri-*O*-acetyl-D-glucal (**2**),⁶ followed by addition of sodium *p*-tolylthiolate in methanol, and then oxidation with *m*-chloroperbenzoic acid (Scheme 1). Compound **5**, as expected, occupies a non-chair conformation as judged from the coupling constants, $J_{1,2}$ 3.3, $J_{2,3}$ 5.4, $J_{3,4}$ 8.6, and $J_{4,5}$ 10.3 Hz. It is noteworthy that compound **5** occupies the non-chair conformation instead of a ¹C₄ conformation. The latter conformation is observed, for example, in phenyl 1-seleno-2,3,4,6-tetrakis-*O*-triisopropylsilyl- β -D-glucopyranoside.⁷ A non-chair conformation for **5** should be

caused by steric hindrance due to the two vicinal equatorial tosyl groups⁸ and a by strong bias for the hydroxymethyl group at C-5 to occupy the equatorial position.⁹ Acetylation of **5** with acetic anhydride in the presence of catalytic amounts of boron trifluoride etherate gave the tri-*O*-acetate **6**.¹⁰ Conventional benzylideneation of **5** gave the 4,6-*O*-benzylidene derivative **7** (Scheme 1). These derivatives again occupy a non-chair conformation. During column chromatography on silica gel (Merck silica gel 60, mesh), elimination of sulfinic acid partially occurred from the benzylidene derivative **7** to afford the 1-enitol derivative **8**, the structure of which was determined from ¹H NMR (δ , 7.87, d, $J_{1,3}$ 0.7 Hz, H-1), ¹³C NMR (δ , 155.28, C-1; 119.53, C-2) and elemental analyses. When a neutral silica gel (Kanto, silica gel 60N, 40–50 μ m) was



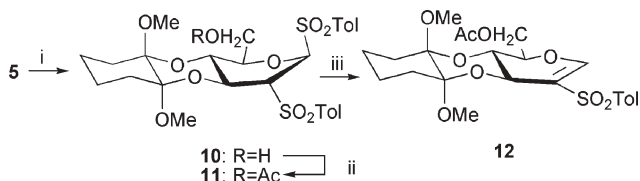
Scheme 1 Reagents and conditions: (i) TolS-Cl, CH₂Cl₂, room temp., 59 h, 63%; (ii) NaSTol, MeOH, Ar atmosphere, room temp., 8 h, 72%; (iii) *m*CPBA, CH₂Cl₂, Ar atmosphere, 1 h, 63%; (iv) Ac₂O, BF₃OEt₂, room temp., 20 h, 97%; (v) PhCH(OMe)₂, CSA, MeCN, room temp., 1 h, 91%; (vi) silica gel 60N, DMF, room temp., 24 h, 70% from **7** and 82% from **6**.

Graduate School of Integrated Science, Yokohama City University, 22-2, Seto, Kanazawa-ku, Yokohama 236-0027, Japan.
E-mail: baratoru@yokohama-cu.ac.jp; Fax: +81-45-787-2413;
Tel: +81-45-787-2183

† Electronic supplementary information (ESI) available: NMR data of **3–12** and NMR spectra of **6** and **7**. See DOI: 10.1039/b707802a

used, the decomposition was suppressed to give the benzylidene derivative **7** in 91% yield. When acetate **6** or benzylidene derivative **7** in DMF was stirred with silica gel (Merck) at room temperature for 24 h, elimination of sulfinic acid completely occurred to give the 1-enitols **9** and **8**, respectively, in high yields (Scheme 1). Similar treatment of the nonprotected **5**, however, resulted in the recovery of **5**. Thus, elimination of sulfinic acid was affected by the hydroxyl group at C-6; that is, if the hydroxyl group was free, the elimination reaction was suppressed, whereas it occurred smoothly, if the hydroxyl group was protected. Different from the 4,6-*O*-benzylidene derivative **8**, tri-*O*-acetyl-1-enitol **9** occupies a 5H_4 conformation, as judged from small coupling constants: $J_{3,4}$ 3.2 and $J_{4,5}$ 2.3 Hz. This is in good agreement with the case of 3,4,6-tri-*O*-acetyl-2-deoxy-2-nitro-D-glucal.¹¹

To confirm the generality of the phenomenon, we have synthesized the cyclohexane-1,2-diacetal **10** and its 6-*O*-acetate **11** (Scheme 2).¹² These compounds again did not take up the 4C_1 conformation, but a 4S_0 or ${}_{4,0}B$ -like conformation: $J_{1,2}$ 4.5, $J_{2,3}$ 9.7, $J_{3,4}$ 10.7, $J_{4,5}$ 10.5 Hz for **10** and $J_{1,2}$ 3.7, $J_{2,3}$ 9.2, $J_{3,4}$ 11.0, $J_{4,5}$ 10.3 Hz for **11**. The same treatment of the acetate **11** with silica gel (Merck), as described above, gave the 1-enitol **12** in 80% yield (Scheme 2), whereas even after 48 h the starting material was recovered in the case of the 6-*O* free **10**.



Scheme 2 Reagents and conditions: (i) 1,1,2,2-tetramethoxycyclohexane, CH(OMe)₃, CSA, MeOH, reflux for 18 h, 46%; (ii) Ac₂O, BF₃OEt₂, room temp., 99%; (iii) silica gel 60N in DMF, room temp., 24 h, 80%.

Although experimental evidence is not obtained at the present stage, hydrogen bonding between the hydroxyl group at C-6 and the ring oxygen atom (O-5) probably suppressed the elimination of the anomeric sulfonyl group.

Ab initio calculations (B3LYP/6-31+G*)¹³ of model **13** (Fig. 1) for the benzylidene derivative **7** were in good agreement with experimental results; the non-chair conformer (C-3 and C-4 are slightly lower and upper, respectively, from the ideal $B_{2,5}$ conformation) was more stable than the 4C_1 conformer by 2.0 kcal mol⁻¹. STO-3G level calculations of model compound **14** (Fig. 1) for the cyclohexane-1,2-diacetal **10** indicated that a non-chair conformer (the pyranose ring occupies a $B_{0,3}$ -like conformation, but its C-4 and C-5 take up fairly upper and slightly lower positions, respectively) is more stable than a chair conformer by 2.3 kcal mol⁻¹. During optimization at the 6-31G* level calculation, however, the chair and non-chair conformers gave the same non-chair conformer, which is in good agreement with the coupling constants observed.

This work is partially supported by a Grant-in-Aid for Scientific Research (No. 63540407) from the Ministry of Education, Science and Culture in Japan and The Grants in Support of the Promotion of Research at Yokohama City University.

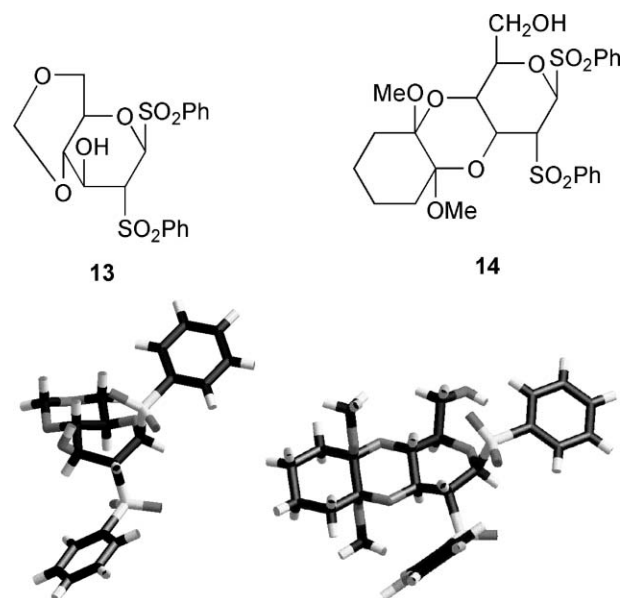


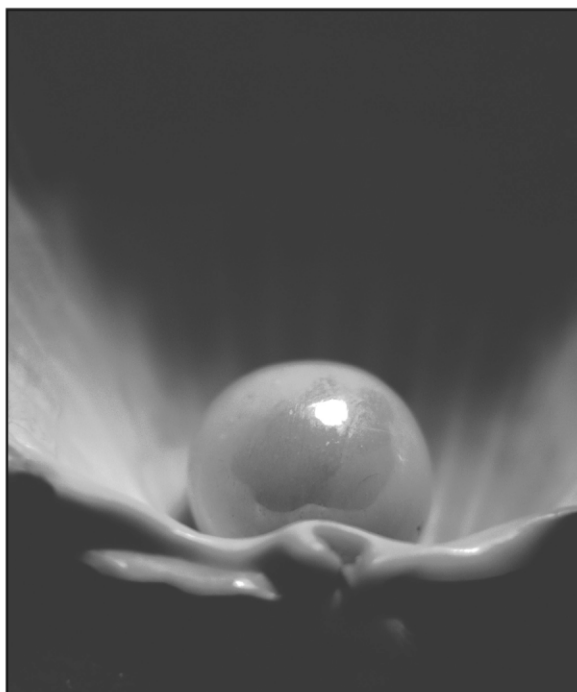
Fig. 1 Fully optimized structures of **13** (left) and **14** (right).

Notes and references

- For example: *Carbohydrate Chemistry*, ed. G.-J. Boons, Blackie Academic & Professional, London, 1998, ch. 4 and 5; A. F. Bochkov and G. E. Zaikov, *Chemistry of the O-glycosidic Bond*, Pergamon Press, Oxford, 1979.
- D. G. Gorenstein, J. B. Findlay, B. A. Luxon and D. Kar, *J. Am. Chem. Soc.*, 1977, **99**, 3473; A. J. Kirby, *Acc. Chem. Res.*, 1984, **17**, 305; C. W. Andrews, J. P. Bowen and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1989, 1913; C. W. Andrews, B. Fraser-Reid and J. B. Bowen, *J. Am. Chem. Soc.*, 1991, **113**, 8293; M. L. Sinnott, The Anomeric Effect and Associated Stereoelectronic Effects, in *ACS Symp. Ser. 539*, ed. G. R. J. Thatcher, ACS, Washington, DC, 1992, ch. 6, pp. 97–113; P. Deslongchamps, *Organic Chemistry Series, Vol. 1: Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983.
- The crystal structure of methyl 2-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-phenylsulfonyl-β-D-glucopyranoside occupies a 1A_B conformation: C. G. Suresh, B. Ravindran, K. N. Rao and T. Pathak, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2000, **C56**, 1030. The crystal structure of a puckered pyranoside (*N*-acetyl/muramic acid) at an active site of the enzyme lysozyme has a sofa conformation: R. Kuroki, L. H. Weaver and B. W. Matthews, *Science*, 1993, **262**, 2030.
- For example: D. S. Brown, S. V. Ley, S. Vile and M. Thompson, *Tetrahedron*, 1991, **47**, 1329.
- T. Sakakibara, K. Suzuki, A. Sakai, M. Shindo, C. Nagano, S. Narumi, Y. Kajihara and K. Mochizuki, *Tetrahedron Lett.*, 2003, **44**, 5711.
- The same reaction was performed to give a mixture which was used in the next reaction without separation: I. P. Smoliakova, R. Caple and D. Gregory, *J. Org. Chem.*, 1995, **60**, 1221.
- H. Abe, M. Terauchi, A. Matsuda and S. Shuto, *J. Org. Chem.*, 2003, **68**, 7439 and references cited therein.
- E. J. Corey, G. Sarakinos and A. Fischer, *Tetrahedron Lett.*, 1999, **40**, 7745.
- S. J. Angyal, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 157.
- 4**, $J_{1,2}$ 10.5, $J_{2,3}$ 10.2, $J_{3,4}$ 8.7, $J_{4,5}$ 9.4; **6**, $J_{1,2}$ 2.7, $J_{2,3}$ 2.9, $J_{3,4}$ 6.2, $J_{4,5}$ 9.7; **7**, $J_{1,2}$ 1.6, $J_{2,3}$ 2.9, $J_{3,4}$ 8.3, $J_{4,5}$ 10.2, $J_{5,6a}$ 10.2, $J_{5,6e}$ 5.3; **8**, $J_{1,3}$ 0.7, $J_{3,4}$ 7.3, $J_{4,5}$ 10.3, $J_{5,6a}$ 10.3, $J_{5,6e}$ 5.1; **12**, $J_{1,3}$ 1.4, $J_{3,4}$ 9.2, $J_{4,5}$ 10.8 Hz. In general, correlation between H-1 and H-5 is stronger than that of H-1 and H-3 or H-3 and H-5 because the distance between H-1 and H-5 is shorter than that of H-1 and H-3 or H-3 and H-5. In NOESY spectra, weak correlation between H-1 and H-5 was often observed in these non-chair conformers, suggesting that a small amount of 1C_4 conformer was also present in an equilibrium.
- R. U. Lemieux, T. L. Nagabhushan and S. W. Gunner, *Can. J. Chem.*, 1968, **46**, 405.

- 12 Cyclohexane-1,2-diacetal is prepared according to the literature; *e.g.* S. V. Ley, H. W. M. Priepe and S. L. Warriner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2290.
- 13 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala,

Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *GAUSSIAN 98 (Revision A.9)*, Gaussian, Inc., Pittsburgh, PA, 1998.



Looking for that **special** chemical biology research paper?

TRY this free news service:

Chemical Biology

- highlights of newsworthy and significant advances in chemical biology from across RSC journals
- free online access
- updated daily
- free access to the original research paper from every online article
- also available as a free print supplement in selected RSC journals.*

*A separately issued print subscription is also available.

Registered Charity Number: 207890

22030681

RSC Publishing

www.rsc.org/chembiology