Observation of a 1,5-Silyl-Migration on Fructose

Stefan Furegati, Andrew J. P. White, Andrew D. Miller*

Imperial College Genetic Therapies Centre, Department of Chemistry, Flowers Building, Armstrong Road, Imperial College London, London SW7 2AZ, UK
Fax +44(20)75945803; E-mail: a.miller@imperial.ac.uk

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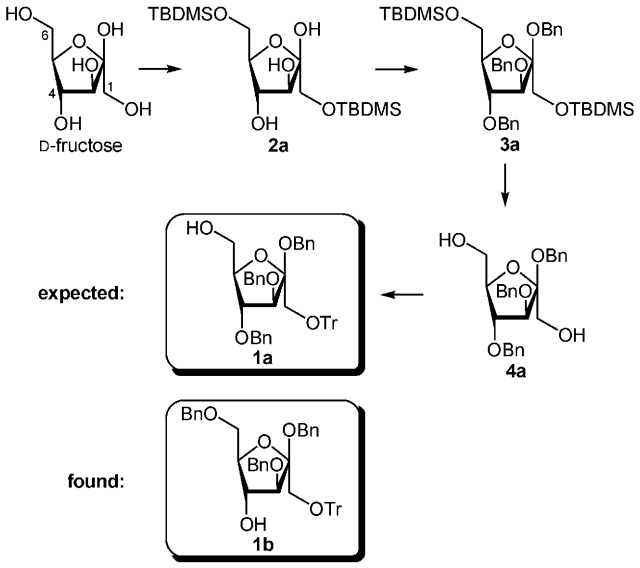
Abstract: During synthetic studies involving fructose, an unexpected silyl migration was observed – resulting in a sterically more crowded product. 1,4-Silyl migrations have been observed previously taking place in several different carbohydrate derivatives. However, here we report for the first time an apparent base-assisted 1,5-silyl migration in fructose, identified by evidence from X-ray crystallography and 2D-NMR spectroscopy. This novel migration is related to the Brook rearrangement, and appears to be mediated via an anionic, cyclic transition state involving pentavalent silicon.

Key words: carbohydrates, fructose, protecting groups, regioselectivity, silyl migration

In order to investigate the biological behavior of unsymmetrically substituted fructose-1,6-bisphosphates we realized the need to combine D-fructose with different substituents at O(1) and O(6), and hence the need for synthetic intermediates with differential protection. Whereas for many carbohydrates the protecting group chemistry is well elaborated, this is surprisingly not the case for fructose. As part of our chosen route to products, we intended to prepare **1a** (Scheme 1) by initial protection of both primary hydroxyl groups of D-fructose with TBDMS groups followed by benzylation to give **3a**, desilylation to yield **4a**, and mono-tritylation giving rise to **1a** ready for controlled functionalization.

Trityl chloride has been used typically to regioselectively protect O(1) – or both primary hydroxyl groups – of D-fructose.[1] However, we elected to use TBDMSCl instead owing to the formation of complex mixtures when 1-*O*-trityl-D-fructofuranose was subjected to benzylation. Initially, a di-*O*-(*tert*-butyldimethylsilyl)-β-D-fructofuranose product (85%)[2] was obtained as fine, colorless needles (thought to be **2a**) after recrystallization from hexane. This was then subjected to benzylation affording a colorless oil comprising tri-*O*-benzyl-di-*O*-(*tert*-butyldimethylsilyl)-β-fructofuranose (43%)[3] as the main intermediate product (thought to be **3a**). Thereafter we performed a desilylation reaction yielding a tri-*O*-benzyl-β-D-fructofuranose (84%)[4] intermediate product (assumed to be **4a**) that was then monotritylated after some optimization to give a wax-like tri-*O*-benzyl-*O*-trityl-β-D-fructofuranose intermediate product (74%).[5] This final intermediate product was thought to be **1a**, but exhaustive



Scheme 1 Expected route towards synthetic intermediate product **1a** using orthogonal protecting groups.

2D ^{1}H NMR and ^{13}C NMR spectroscopic analysis at 60° C revealed that in fact the product was **1b**, against all our reasonable expectations. This unexpected product immediately suggested to us the possibility of protecting group migration during the synthetic scheme leading to **1b**. We also recognized the possibility of furanose to pyranose transformation when D-fructose was silylated leading to alternative protection products.

In order to investigate these possibilities, a crystal structure of the first di-*O*-(*tert*-butyldimethylsilyl)-β-D-fructofuranose intermediate product[2] was obtained. The solid-state structure (Figure 1) revealed the presence of two independent molecules (**A** and **B**) with identical absolute configurations and very similar conformations; excluding the disordered *tert*-butyldimethylsilyl groups, the rms fit of the two molecules was ca. 0.018 Å. Despite the disorder in both silyl moieties, the crystallographic data were of sufficient quality to prove that the functionalization and absolute configuration of the first di-*O*-(*tert*-butyldimethylsilyl)-β-D-fructofuranose intermediate product was consistent with the expected structure **2a** (Figure 1).

Therefore, having excluded the possibility of pyranose forms, we considered that the only reasonable explanation for the formation of unexpected product **1b** starting from expected intermediate product **2a**, was protecting group

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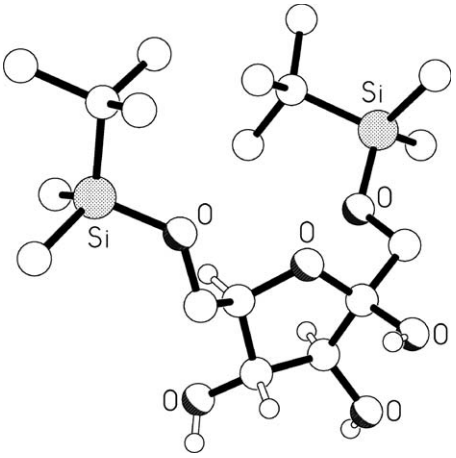
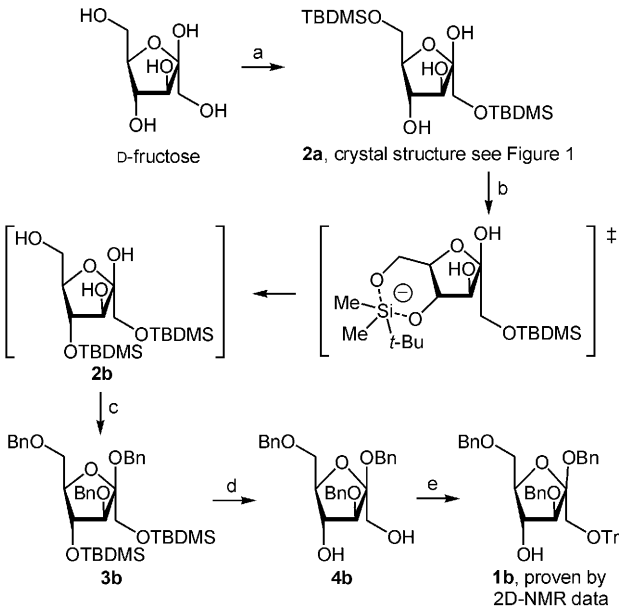


Figure 1 The molecular structure of one (**A**) of the two independent molecules present in the crystals of **2a**.

migration either through the formation of tri-benzylated intermediate product **4a** that transmutes into **4b**, or through the interconversion of intermediate **2a** into **2b** via a 1,5-silyl migration (Scheme 2), followed by tri-benzylation to give **3b** and desilylation to form **4b**.

While benzyl group migration is a possibility via some form of benzyl-cation migration, 1,5-silyl migration in **2a** leading to **2b** was considered to be a more logical explanation. Benzylation of **2a** requires NaH treatment to generate oxy-anions that are subsequently trapped by addition of benzyl bromide. The use of NaH clearly opens up the possibility of general base-assisted 1,5-silyl migration to give **2b** (Scheme 2). Proof of this possibility was obtained by the treatment of intermediate product **2a** with NaH, leading to the isolation of pure 1,4-di-*O*-(*tert*-butyldimethylsilyl)-β-D-fructofuranose (**2b**, 42%).[6]



Scheme 2 *Reagents and conditions*: (a) TBDMSCl (2.0 equiv), pyridine, r.t.; (b) NaH (3.3 equiv), DMF, 0 °C; (c) BnBr (3.3 equiv), Bu_4NI (0.3 equiv), r.t.; (d) TBAF (2.2 equiv), THF, r.t.; (e) trityl chloride (10 equiv), pyridine, 60 °C.

It would be desirable to explain why the observed migration takes place when **2b** appears more sterically crowded than **2a**, and therefore apparently less desirable. After some consideration, ab initio calculations of the ground states of the 20 possible configurations of the silyl groups on di-*O*-(*tert*-butyldimethylsilyl)-D-fructofuranose (10 β-anomers and 10 α-anomers) were not performed given the expectation that energies would be too similar to segregate one from the other. Transition state analyses were not expected to be of much value either given the uncertainty of sodium ion involvement in the transition state and the extra possibility of dimerization adding further computational complications.[7] A simple molecular mechanics[8] comparison was performed demonstrating that **2a** was indeed 15.4 kJ/mol more stable than **2b** taking into account only steric considerations. However, **2b** may be rendered more stable through the formation of more extensive intramolecular β-face hydrogen bonding interactions involving β-face hydroxyl functional groups, than are feasible in **2a**.

Analogous base-assisted silyl migrations have been reported within the last few years in various carbohydrate systems,[9] but not in fructose. Moreover, all these examples are 1,4-silyl migrations. In our case, we would suggest that for the first time we have amassed sufficient evidence to propose a novel base-assisted 1,5-silyl migration. All these migrations seem to be related to the base-catalyzed migration of silyl groups from carbon to oxygen in α-, β- and γ-silyl alcohols yielding silyl ethers. This type of rearrangement, known as the Brook rearrangement,[10] is clearly driven by Si–O bond formation.

In conclusion we have reported for the first time an unexpected 1,5-silyl migration in fructose resulting in the formation of a more sterically crowded product, stabilized through other means such as intramolecular hydrogen bonding.

Anhydrous solvents were used for the reactions, which were carried out under argon. The crude products were subjected to flash column chromatography (SiO_2) for purification/separation, except from **1**, which could be crystallized.

Acknowledgment

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References

(1) (a) Bredereck, H.; Henning, I.; Zinner, H. *Chem. Ber.* **1953**, *86*, 476. (b) Bredereck, H.; Protzer, W. *Chem. Ber.* **1954**, *87*, 1873.

(2) D-Fructose: $[\alpha]_D^{22}$ –90.9 (*c* 10.34, H_2O).
Analytical data of **2a**: $[\alpha]_D^{22}$ +5.4 (*c* 5.00, MeOH); mp = 91.5–93.5 °C; R_f = 0.62 (SiO_2, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03–0.01 (12 H, m, CH_3–Si), 0.78–0.82 (18 H, m, CH_3–C–Si), 3.72–4.34 (10 H, m, 2 CH_2, 3 CH, 3 OH). ^{13}C NMR (100.4 MHz, $CDCl_3$, two conformations): δ = –5.63, –5.62, –5.59, –5.53, –5.46, –5.39, –5.37, –5.30 (4 C, CH_3–Si), 18.4, 18.5 (2 C, C–Si), 25.81, 25.90, 25.94 (6 C,

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CH_3–C–Si), 63.6, 64.0 (CH_2), 64.6, 66.8 (CH_2), 77.5, 78.8 (CH), 78.9, 79.0 (CH), 85.7, 87.8 (CH), 104.2, 106.3 (C-2). MS (ESI): *m/z* (%) = 431 (100) $[M + Na]^+$. Crystal data: crystal derived from toluene, $C_{18}H_{40}O_6Si_2$, M = 408.68, trigonal, $P3_1$ (no. 144), a = 17.0933 (13) Å, c = 15.5690 (16) Å, V = 3939.5 (6) Å^3, Z = 6 (2 independent molecules), D_c = 1.034 g cm^{-3}, μ(Cu-K$_\alpha$) = 1.433 mm^{-1}, T = 293 K, colorless needles, Oxford Diffraction Xcalibur PX Ultra diffractometer; 8947 independent measured reflections, F^2 refinement, R_1 = 0.094, wR_2 = 0.252, 4167 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 143°], 592 parameters. The absolute structure of **2a** was determined by a combination of *R*-factor tests [R_1^+ = 0.0935, R_1^- = 0.0960] and by use of the Flack parameter [x^+ = +0.00(8)]. CCDC 270727.

(3) Analytical data of **3b**: $[\alpha]_D^{22}$ –12.9 (*c* 0.500, MeOH); R_f = 0.21 (SiO_2, hexane–Et_2O 19:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.10–0.00 (12 H, m, CH_3–Si), 0.77–0.85 (18 H, m, CH_3–C–Si), 3.46–4.80 (13 H, m, 5 CH_2, 3 CH), 7.12–7.31 (15 arom. H). ^{13}C NMR (100.4 MHz, $CDCl_3$, two conformations): δ = –5.31, –5.27, –5.24, –5.18, –4.92, –4.21 (4 C, CH_3–Si), 17.9, 18.3, 18.4 (2 C, C–Si), 25.7, 25.8, 25.83, 25.9, 26.0 (6 C, *C*H_3–C–Si), 63.0, 64.7, 64.8, 66.9, 67.6, 69.4, 72.2, 72.6, 72.9, 73.4 (5 C, CH_2), 76.5, 80.1, 80.2, 82.8, 84.5, 85.5 (3 C, CH), 104.7, 104.8 (C-2), 127.1, 127.2, 127.5, 127.52, 127.6, 127.67, 127.7, 127.8, 127.85, 127.9, 128.0, 128.1, 128.2, 128.23, 128.3, 128.4, 128.5 (15 arom. CH), 138.3, 138.4, 138.43, 138.5, 138.6 (3 arom. C). MS (ESI): *m/z* (%) = 701 (100) $[M + Na]^+$, 517 (35).

(4) Analytical data of **4b**: $[\alpha]_D^{22}$ –17.6 (*c* 1.07, MeOH); R_f = 0.21 (SiO_2, EtOAc–hexane 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38–4.84 (15 H, m, 5 CH_2, 3 CH, 2 OH), 7.18–7.39 (15 arom. H). ^{13}C NMR (100.4 MHz, $CDCl_3$, two conformations): δ = 63.5, 64.4, 64.7, 64.9, 65.2, 70.9, 72.8, 72.9, 73.0, 73.6 (5 C, CH_2), 76.5, 79.6, 80.5, 82.7, 84.8, 84.9 (3 C, CH), 104.8, 105.1 (C-2), 127.4, 127.45, 127.5, 127.6, 127.7, 127.8, 127.82, 127.86, 127.9, 128.0, 128.1, 128.16, 128.2, 128.3, 128.49, 128.50, 128.53, 128.7 (15 arom. CH), 137.8, 137.9, 138.0, 138.3, 138.7. 138.9 (3 arom. C). MS (ESI): *m/z* (%) = 473 (20) $[M + Na]^+$, 186 (100).

(5) Analytical data of **1b**: $[\alpha]_D^{22}$ –3.9 (*c* 1.07, MeOH); R_f = 0.17 (SiO_2, Et_2O–hexane 1:1). ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C): δ = 3.03, 3.26 (2 H, 2 d, J = 9.5 Hz, CH_2-1), 3.62 (1 H, dd, J = 11.1, 6.0 Hz, CH_2-6), 3.77 (1 H, dd, J = 11.1, 2.4 Hz, CH_2-6), 3.92–3.95 (1 H, m, CH-5), 4.12–4.23 (1 H, m, CH-4), 4.28 (1 H, d, J = 7.8 Hz, CH-3), 4.56 (6 H, s, 3 × CH_2–Ph), 5.50 (1 H, d, J = 5.6 Hz, O*H*–CH-4), 7.12–7.50 (30 H, m, arom. H). ^{13}C NMR (100.4 MHz, DMSO-d_6, 60 °C, the only fructose derivative found here displaying only one conformation): δ = 63.7 (CH_2–Ph), 66.2 (CH_2-1), 70.3 (CH_2-6), 71.7 (CH_2–Ph), 72.4 (CH_2–Ph), 74.7 (CH-4), 80.0 (CH-5), 85.0 (CH-3), 103.8 (C-2), 126.5, 126.9, 126.95, 127.0, 127.1, 127.2, 127.25, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.05, 128.1, 128.3, 128.4 (30 arom. CH), 138.5, 138.9, 143.5, 147.8 (6 arom. C). The assignment of the ^{1}H- and ^{13}C NMR spectra was based on COSY, HSQC and HMBC spectra (unsuccessful for *C*Ph_3 though). NOESY cross peaks between C*H*-3 and both CH_2-1 proved that the β-anomer was present. MS (ESI): *m/z* (%) = 715 (19) $[M + Na]^+$, 243 (26) $[Ph_3C]^+$, 186 (100).

(6) Analytical data of **2b**. Acid quenching or warming to r.t. lead to an exothermic reaction resulting in complex mixtures. Isolation of **2b** – the main product whereas no **2a** was found – was only successful when the cold mixture was subjected to column chromatography very quickly: $[\alpha]_D^{22}$ ca. 0 (*c* 1.05, MeOH); R_f = 0.13 (SiO_2, EtOAc–hexane 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03–0.19 (12 H, m, CH_3–Si), 0.86–0.95 (18 H, m, CH_3–C–Si), 3.49–4.25 (10 H, m, 2 CH_2, 3 CH, 3 OH). ^{13}C NMR (100.4 MHz, $CDCl_3$, two conformations): δ = –4.9, –4.8, –4.6, –4.5, –3.6 (4 C, CH_3–Si), 17.8, 17.9, 18.3, 18.4 (2 C, C–Si), 25.6, 25.6, 25.7, 25.8 (6 C, *C*H_3–C–Si), 63.2, 63.4 (CH_2), 64.5, 65.7 (CH_2), 77.2, 77.6 (CH), 79.1, 79.2 (CH), 84.4, 86.9 (CH), 103.3, 107.2 (2-C). MS (ESI): *m/z* (%) = 431 (100) $[M + Na]^+$.

(7) Oral communication by Henry Rzepa.

(8) Molecular mechanics (MM2) of Chem3D Ultra 9.0: for **2a** the X-ray data of the conformation yielding the lower energy were used whereas for **2b** several conformations were tried and again the one resulting in the lowest energy was chosen.

(9) (a) Yoon, S. *J. Korean Chem. Soc.* **2002**, *46*, 590. (b) Arias-Pérez, M. S.; López, M. S.; Santos, M. J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1549. (c) Li, Y.; Horton, D.; Barberousse, V.; Samreth, S.; Bellamy, F. *Carbohydr. Res.* **1999**, *316*, 104. (d) Akai, S.; Nishino, N.; Iwata, Y.; Hiyama, J.; Kawashima, E.; Sato, K.; Ishido, Y. *Tetrahedron Lett.* **1998**, *39*, 5583.

(10) (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

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