Pergamon

Tetrahedron Letters 40 (1999) 5573–5576

TETRAHEDRON
LETTERS

STABLE AXIAL-RICH CONFORMATION OF PYRANOSES DERIVED FROM L-RHAMNOSE AND D-MANNOSE

Hidetoshi Yamada,* Mari Nakatani, Tomonari Ikeda, Yuzo Marumoto

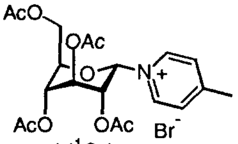
School of Science, Kwansei Gakuin University
Uegahara Nishinomiya 662-8501, Japan

Received 6 April 1999; revised 18 May 1999; accepted 28 May 1999

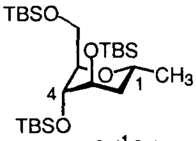
Abstract: Stable chair conformation with more axial substituents (axial-rich conformation) of pyranoses derived from L-rhamnose and D-mannose is described. The naturally stable ring conformation of L-rhamnose ($^1C_4$) and D-mannose ($^4C_1$) was flipped by introduction of a TBS group into a hydroxyl group at C-3 and a TPS group into a hydroxyl group at C-4 to give $^4C_1$ and $^1C_4$ conformers, respectively. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: carbohydrates; conformation

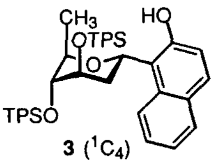
A chair conformation of pyranose with more equatorial substituents is generally predominant. However, chair conformation with more axial substituents (axial-rich conformation) sometimes results. Lemieux and Morgan reported pyridinium salt **1** with a positive charge on the C1-substituent is enforced to take $^1C_4$ conformation due to attraction between the charge and a lone pair of the ring oxygen.[1] Tius and coworker reported a tetrahydropyrane ring of **2** has $^1C_4$ when three hydroxyl groups at C3, 4, and 6 (sugar numbering) were protected by TBS groups.[2] Similar conformational flip was observed in **3** by Hosoya and Suzuki.[3] Both examples are based on the repulsion of the 1,2-*trans*-disilyl ethers of 2-deoxysugar. On the other hand, Kiss and Arnold reported that the C-5 aliphatic substituent has a strong tendency to assume an equatorial position. Thus, in a pyranose derivative **4** a smaller equatorially linked C-5 methyl group pushes the larger benzyloxy groups into the axial position.[4] We report herein the first example of pyranoses with axial-rich conformation by introduction of silyl groups into 3- and 4-OH groups of rhamnose and mannose.



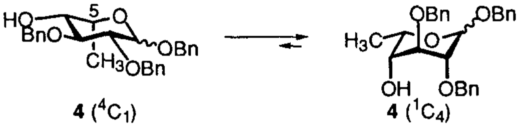
1 ($^1C_4$)



2 ($^1C_4$)



3 ($^1C_4$)



4 ($^4C_1$) **4** ($^1C_4$)

We preliminarily probed the actuality of a stable axial-rich conformer by disilylation of diol **5a** prepared from L-rhamnose. The value of $^3J_{H1-H2}$ on ^{1}H NMR was used as an approximate index of the conformational change. When the ring conformation is flipped, two hydrogen atoms on C1 and C2 would take axial conformation

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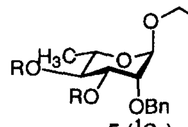
* email address: hidetosh@kwansei.ac.jp

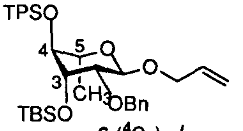
PII: S0040-4039(99)01077-1

to show coupling constant of 6-8 Hz. Disilylated compounds **5b-d**, however, showed a small value (0-3.2 Hz) on ^{1}H NMR. Because the coupling constant of the diol **5a** was 0 Hz, a small change in the ring conformation occurred in di-*O*-dimethyloctadecylsilylated **5c** and di-*O*-TBS **5d**. The changes were, however, insufficient to induce flipping. Treatment of **5a** with bigger TPSCl did not afford a disilylated product. On the other hand, NMR data of **6** that has a TBS ether at C-3 and TPS at C-4 suggested the pyranose ring was flipped to a 3,4,5-triaxial conformer. The coupling constant of **6** between H1 and H2 was 6.6 Hz (60 °C in C_6H_6).[5,11] The other coupling constants between the neighboring protons on the pyranoside ring were H2-H3: 2.7 Hz, H3-H4: 2.7 Hz, and H4-H5: 4.4 Hz. NOESY spectra showed correlations between H1 and H6, and also between H2 and methyl protons of the TPS group.



5 ($^1C_4$)

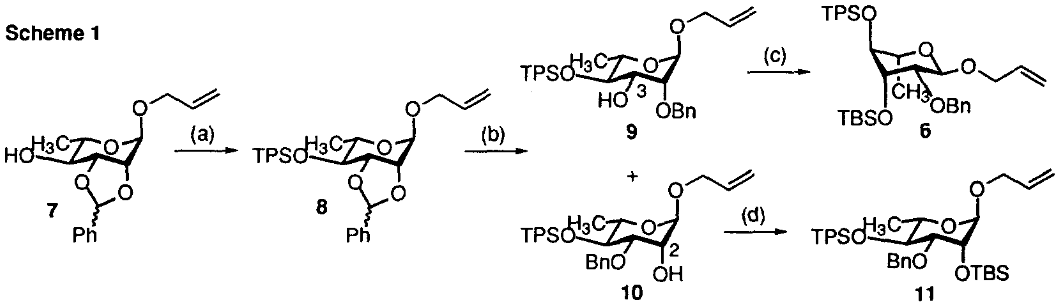
a: R = H, $J_{H1\text{-}H2}$ = 0 Hz
b: R = TES, $J_{H1\text{-}H2}$ = 0 Hz
c: R = $Si^{n}C_{18}H_{37}(CH_3)_2$, $J_{H1\text{-}H2}$ = 1.6 Hz
d: R = TBS, $J_{H1\text{-}H2}$ = 3.2 Hz



6 ($^4C_1$) $J_{H1\text{-}H2}$ = 6.6 Hz

The 'flipped' rhamnoside **6** was prepared as follows. TBS etherification of **7**,[6] followed by DIBALH reduction of benzylidene acetal **8** afforded 3-OH product **9** and 2-OH **10** in 30% and 60% yield, respectively. Introduction of a TBS group to the hydroxyl group of **9** did not proceed at room temperature. The reaction, however, was easily accomplished at 100 °C within 30 min to give **6** in 100% yield. Since the increased steric hindrance around the equatorial 3-OH of **9** ($^1C_4$) prevents the silylation, the reaction only took place via a minor 3,4,5-triaxial conformer ($^4C_1$) (Scheme 2) which has enough space for the introduction of TBS. The rate of equilibrium should be slow at room temperature, and thus 100 °C was required. Once the TBS group is introduced, the conformation is fixed based on the steric repulsion of TPS and TBS groups. In contrast, TBS etherification of **10** with axial 2-OH was achieved easily at room temperature to give **11** in 99% yield without forming any flipped product.

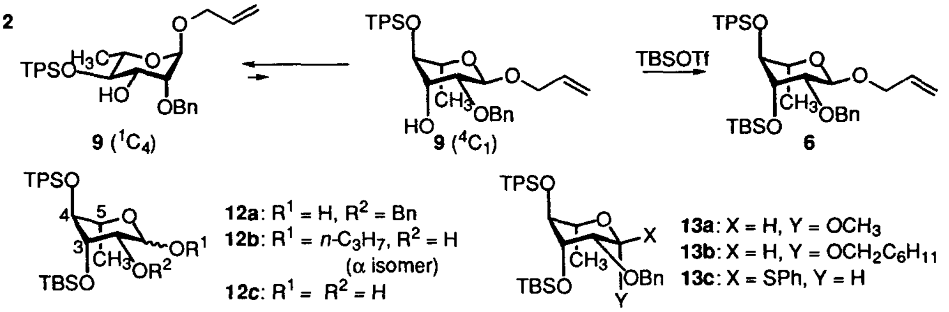
Scheme 1



Reagents and conditions: (a) TPSCl (1.5 equiv), imidazole (1.6 equiv), DMAP (0.5 equiv), 110 °C, 12 h, 87%; (b) DIBALH (3 equiv), CH_2Cl_2, 0 °C, 32 h, 90%; (c) TBSOTf (2 equiv), 2,6-lutidine (2.2 equiv), DMF, 100 °C, 30 min, 100%; (e) TBSOTf (2 equiv), 2,6-lutidine (2.2 equiv), DMF, rt, 5 min, 99%.

The ring flip is due to the two silyl protecting groups. Thus, deallylated compound **12a**, debenzylated **12b** (the allyl group was simultaneously reduced to a propyl group), and 1,2-dihydroxy compound **12c**[11] also maintaind the 3,4,5-triaxial conformation. Further, even the β isomers also kept the conformation. Methyl β-rhamnoside **13a** and cyclohexylmethyl β-rhamnoside **13b** which were prepared from phenylthiorhamnoside **13c** also had the $^4C_1$ conformation.[7] ^{1}H NMR coupling constants were H1-H2: 3.7 Hz, H2-H3: 3.4 Hz, H3-H4: 4.4 Hz, and H4-H5: 2.2 Hz for **13a**,[11] and 3.4, 3.4, 4.4, and 2.4 (Hz) for **13b**.[11] NOESY spectra of the compounds also assisted the conformation. In these cases, four of five substituents are axial.

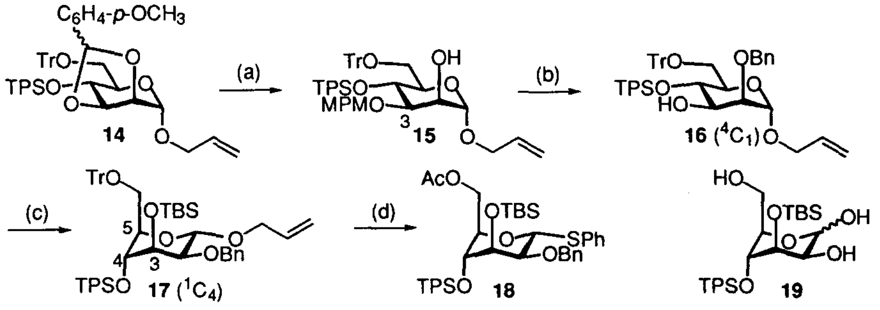
Scheme 2



Pyranose rings of D-mannose derivatives **17-19** were also enforced to take the axial-rich conformation ($^1C_4$) by the introduction of TBS and TPS groups. Since reductive cleavage of benzylidene acetal **8** gave an undesired 2-OH **10** as a major product, we chose anisilidene acetal **14** as the starting material in order to make good use of the selective reduction. Thus, **14**[8] was selectively cleaved to give 3-*O*-MPM product **15** in 69% yield along with 8% of 2-*O*-MPM compound. Benzylation of **15** followed by cleavage of the MPM group gave 3-OH product **16**. Introduction of a TBS group to the hydroxyl group at 110 °C provided 3,4,5-triaxial **17** with $^1C_4$ conformation.[9] Coupling constants between the neighboring protons on the pyranoside ring are H1-H2: 7.1 Hz, H2-H3: 2.4 Hz, H3-H4: 2.4 Hz, and H4-H5: 4.4 Hz.[11] NOESY spectra of **17** showed correlations at H-1 and H-6, H-2 and H-5, and also H1 and methyl protons of the TBS group. The conformation was also confirmed by X-ray diffraction study. Thioglycoside **18** prepared from **17** in three steps was easily crystallized from methanol to give single crystals (mp 125.5-126.0 °C).[11] ORTEP drawing of **18** clearly showed the $^1C_4$ conformation (see figure).[10] Similarly to the case of rhamnose, the axial-rich conformation was kept due to the two silyl protecting groups. Even triol **19** thus maintained the $^1C_4$ conformation.[11] It is significant that the 3,4,5-triaxial pyranoses, **12c** and **19**, are stable without ring-opening or re-flip to 3,4,5-triequatorial conformation.

In conclusion, the pyranose rings of L-rhamnose and D-mannose were flipped to $^4C_1$ and $^1C_4$, respectively, by the introduction of a TBS group into 3-OH and TPS into 4-OH group.

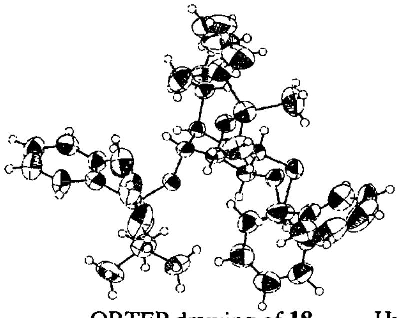
Scheme 3



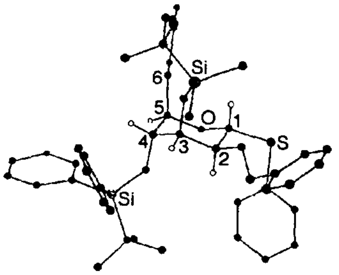
Reagents and conditions: (a) DIBALH (3.0 equiv), CH_2Cl_2, 0 °C, 2 h, 69%; (b) NaH (1.5 equiv), BnBr (2.0 equiv), DMF, 0 °C, 2 h, 89%; then DDQ (1.5 equiv), CH_2Cl_2, rt, 2 h, 88%; (c) TBSOTf (2.4 equiv), 2,6-lutidine, DMF, 110 °C, 92%; (d) (1) deallylation: $[Ir(cod)(MePh_2P)_2]PF_6$ (hydrogen activated), THF, rt, 50 min, then *m*-CPBA (3.0 equiv), THF-H_2O (10:1), rt, 1.5 h, 90% (2 steps), (2) introduction of SPh: PhSTMS (3.0 equiv), ZnI_2 (3.0 equiv), $(CH_2Cl)_2$, 60 °C, 6 h, 23% (detritylation took place simultaneously), (3) Ac_2O, pyridine, rt, 1 h, 96%.

Acknowledgment. We thank Miss Hiroko Takao and Prof. Mugio Nishizawa (Faculty of Pharmaceutical Sciences, Tokushima Bunri University) for the X-ray diffraction study of **18**. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (No. 10780359).

Figure



ORTEP drawing of **18**



Chem 3D drawing of **18**
Hydrogen atoms except on the pyranose ring are omitted.

References and notes

1. Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205-2213.
2. In this paper, following abbreviations are used; MPM: *p*-methoxyphenylmethyl, TBS: *tert*-butyldimethylsilyl, TES: triethylsilyl, TPS: *tert*-butyldiphenylsilyl. Others complied with a standard list of abbreviations (*J. Org. Chem.* **1999**, *64*, 21A).
3. Tius, M. A.; Bush-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181-5184. Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663-666.
4. Kiss, J.; Arnold, W. *Helv. Chim. Acta* **1975**, *58*, 297-301.
5. At 24 °C ^{1}H NMR spectra of **6** showed sharp signals due to H1, 2, 5, and 6; meanwhile, signals of H3 and 4 were observed as a broad peak without coupling in both $CDCl_3$ and C_6D_6 respectively. The observation suggests the existence of plural conformers that have subtle conformational differences around C3 and C4. At 60 °C all signals were averaged to be sharp.
6. Westerduin, P.; De Haan, P. E.; Dees, M. J.; Van Boom, J. H. *Carbohydr. Res.* **1988**, *180*, 195-205.
7. The β-isomers were prepared along with corresponding α-isomers. The glycosylation will be described in detail elsewhere.
8. The anisilidene acetal **14** was prepared from known allyl 6-*O*-trityl-α-D-mannopyranoside (Ogawa, T.; Yamamoto, H. *Carbohydr. Res.* **1985**, *137*, 79-88) by a formation of the anisilidene acetal [*p*-$CH_3OC_6H_4CH(OCH_3)_2$ (3 equiv), TsOH (0.1 equiv), DMF, 45 °C, 10 mmHg, 2 h, 74%] followed by *tert*-butyldiphenylsilylation [TPSCl (2.5 equiv), imidazole (2.6 equiv), 4-DMAP (0.5 equiv), DMF, 100 °C, 8 h, 62%].
9. Reaction at higher temperature effected deprotection of the trityl group, and 3,6-di-*O*-TBS-4-*O*-TPS compound was produced. This side product also had the $^1C_4$ conformation.
10. Colorless crystal; crystal system monoclinic; space group $P2_1$; a = 11.678000(0) Å, b = 11.559000(0) Å, c = 16.650999(0) Å, β = 103.959999(0)°, V = 2181.199951(0) Å^3, Z = 2; D (calc) 1.530 mg/cm^3; Mo, Kα radiation; θmax = 26.43°; 4908 reflections collected, of which 3998 were used in the solution of the structure; R index = 0.072; diffractometer Mac Science MXC18. Atomic coordinates, bond lengths and angles and thermal parameters are deposited in the Cambridge Crystallographic Data Centre.
11. Optical rotation and ^{1}H NMR data of ring flipped compounds. NMR data (400 MHz) were indicated by chemical shift with number of the proton, coupling pattern, coupling constants (Hz), and assignment when the proton is attached to a pyranose ring in parenthesis. **6**: $[\alpha]_D^{23}$ -58.6° (*c* 1.26, $CHCl_3$), ^{1}H NMR (60 °C in C_6D_6) δ -0.08 (3, s), 0.10 (3, s), 0.89 (9, s), 1.11 (9, s), 1.23 (3, d, 6.8; H6), 3.85 (1, dd, 4.4, 2.7; H4), 4.04 (1, dd, 6.6, 2.7; H2), 4.05 (1, dddd, 13.2, 5.9, 1.5, 1.5), 4.14 (1, qd, 6.6, 4.4; H5), 4.22 (1, dd, 2.7, 2.7; H3), 4.34 (1, dddd, 13.2, 5.1, 1.7, 1.5), 4.74 (1, d, 12.0), 4.86 (1, d, 12.0), 5.05 (1, ddd, 10.3, 3.2, 1.5), 5.15 (1, d, 6.6; H1), 5.29 (1, ddd, 17.3, 3.7, 1.7), 5.93 (1, dddd, 17.3, 10.3, 5.9, 5.1), 7.10 (1, tdd, 8.6, 2.2, 1.7), 7.18-7.23 (8H, m), 7.41 (2, br d, 7.6), 7.71-7.74 (4, m). **12c**: $[\alpha]_D^{23}$ -7.3° (*c* 0.75, $CHCl_3$ mixture of α and β isomers), ^{1}H NMR: (α isomer, $CDCl_3$) δ -0.09 (3, s), 0.08 (3, s), 0.86 (9, s), 1.15 (9, s), 1.19 (3, d, 7.2; H6), 1.99 (1, d, 4.4; O$\underline{\text{H}}$), 2.11 (1, d, 6.4; O$\underline{\text{H}}$), 3.84 (1, dd, 4.2, 2.9, H4), 3.97 (1, ddd, 6.4, 4.4, 3.4; H2), 4.22 (1, qd, 7.2, 4.2; H5), 4.25 (1, dd, 3.4, 2.9; H3), 5.03 (1, dd, 6.4, 6.4; H1), 7.16-7.22 (6, m), 7.69-7.80 (4, m). **13a**: $[\alpha]_D^{24}$ 8.4° (*c* 0.41, $CHCl_3$), ^{1}H NMR: ($CDCl_3$) δ -0.19 (3, s), -0.01 (3, s), 0.79 (9, s), 1.00 (9, s), 1.21 (3, d, 7.3; H6), 3.39 (3, s), 3.73 (1, dq, 7.3, 2.2; H5), 3.78 (1, dd, 4.4, 2.2; H4), 3.87 (1, dd, 3.7, 3.4; H2), 3.93 (1, dd, 4.4, 3.4; H3), 4.61 (1, d, 12.5), 4.66 (1, d, 12.5), 4.73 (1, d, 3.7; H1), 7.25-7.45 (11, m), 7.60-7.63 (4, m). **13b**: $[\alpha]_D^{24}$ 14.8° (*c* 1.56, $CHCl_3$), ^{1}H NMR: ($CDCl_3$) δ -0.19 (3, s), -0.03 (3, s), 0.76 (9, s), 1.02 (9, s), 0.86-1.27 (6, m), 1.22 (3, d, 7.3; H6), 1.55-1.79 (5, m), 3.04 (1, dd, 9.3, 6.3), 3.67 (1, dd, 8.8, 6.3), 3.76 (1, dq, 7.3, 2.4; H5), 3.80 (1, dd, 4.4, 2.4; H4), 3.86 (1, dd, 3.4, 3.4; H2), 3.91 (1, dd, 4.4, 3.4; H3), 4.55 (1, d, 12.2), 4.67 (1, d, 12.2), 4.83 (1, d, 3.4; H1), 7.23-7.42 (11, m), 7.62-7.66 (4, m). **17**: $[\alpha]_D^{23}$ 39.6° (*c* 1.01, $CHCl_3$), ^{1}H NMR: ($CDCl_3$) δ -0.46 (3, s), -0.24 (3,s), 0.56 (9, s), 0.90 (9, s), 2.93 (1, dd, 10.2, 2.9, H6), 3.24 (1, dd, 10.2, 8.3; H6), 3.53 (1, dd, 4.4, 2.4; H4), 3.74 (1, dd, 7.1, 2.4; H2), 3.81 (1, dd, 2.4, 2.4; H3), 4.11 (1, ddd, 8.3, 4.4, 2.9; H5), 4.16 (1, dddd, 13.2, 5.6, 1.5, 1.5), 4.49 (1, dddd, 13.2, 5.1, 1.5, 1.5), 4.63 (1, d, 12.0), 4.74 (1, d, 12.0), 4.84 (1, d, 7.1; H1), 5.21 (1, ddd, 10.3, 2.9, 1.5), 5.37 (1, ddd, 17.3, 3.4, 1.7), 6.03 (1, dddd, 17.3, 10.3, 5.6, 5.1), 7.18-7.48 (30, m). **18**: $[\alpha]_D^{22}$ 48.0° (*c* 0.75, $CHCl_3$), ^{1}H NMR: (60 °C in $CDCl_3$) δ -0.30 (3, s), -0.15 (3, s), 0.72 (9, s), 1.06 (9, s), 1.91 (3, s), 3.80 (1, dd, 3.2, 2.9; H4), 3.86 (1, dd, 9.0, 2.4; H2), 3.90 (1, dd, 11.7, 4.2; H6), 3.95 (1, dd, 2.9, 2.4; H3), 4.15 (1, ddd, 8.3, 4.2, 3.2; H5), 4.34 (1, dd, 11.7, 8.3; H6), 4.53 (1, d, 11.5), 4.62 (1, d, 11.5), 5.28 (1, d, 9.0; H1), 7.20-7.46 (14, m), 7.59-7.64 (6, m). **19**: $[\alpha]_D^{21}$ 12.5° (*c* 0.39, $CHCl_3$, mixture of α and β isomers), ^{1}H NMR: (α isomer, $CDCl_3$) δ -0.21 (3, s), -0.04 (3, s), 0.79 (9, s), 1.08 (9, s), 3.26 (1, dd, 12.0, 3.6; H6), 3.71 (1, dd, 4.9, 2.4; H4), 3.85 (1, dd, 12.0, 8.5; H6), 3.87 (1, dd, 6.8, 2.9; H2), 3.99 (1, ddd, 8.5, 4.9, 3.6; H5), 4.03 (1, dd, 2.9, 2.4; H3), 5.06 (1, d, 6.8; H1), 7.36-7.46 (6, m), 7.63-7.69 (4, H).