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Silyl Migrations in D-Xylose Derivatives: Total Synthesis of a Marine Quinoline Alkaloid

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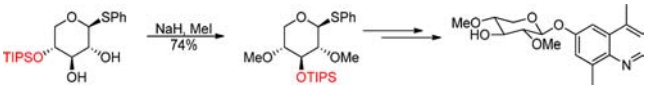
ABSTRACT



A versatile method for the synthesis of orthogonally protected D-xylose 1-thioethers is described using unusual silyl group migrations which were pivotal in the synthesis of 4,8-dimethyl-6-*O*-(2′,4′-di-*O*-methyl-β-D-xylopyranosyl)hydroxyquinoline confirming the structure and absolute configuration of the natural product.

Given the many biological events being uncovered in which carbohydrates play an integral part including the importance of glycosylated secondary metabolites as leads in the pharmaceutical industry, the development of strategies for the synthesis of carbohydrate building blocks remains an important goal. In nature, glycosylation with D-xylose dimethyl ethers occurs on a wide variety of structural frameworks including, for example, the cytotoxic macrolactones ankaraholides A and B from the cyanobacteria *Geitlerima* sp[1] and polycavernoside A from the red alga *Polycavernosa tsudai*,[2] the macrodilactones clavosolides B and C from *Myristra clavosa*,[3] a series of steroid derivatives from the starfish *Henricia leviuscula*,[4] and the aromatic antitumor compound cleistanthins A.[5] Herein we report a versatile method for the synthesis of orthogonally protected D-xylose thioethers **1** and **2** using unusual migrations of triisopropylsilyl (TIPS) groups (Figure 1). The value of the methodology is demonstrated in the first total synthesis of 4,8-dimethyl-6-*O*-(2′,4′-di-*O*-methyl-β-D-xylopyranosyl)-hydroxyquinoline **3**, a natural product isolated from extracts of the cyanobacterium *Lyngbya majuscula*[6] thus confirming the structure and absolute configuration of the natural product.[7]

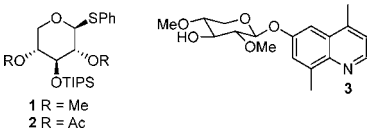


Figure 1. Target compounds.

The substrate diols **9** and **10** required for the pivotal silyl migrations were prepared as shown in Scheme 1. D-Xylose was readily converted to the known thioether **4**[8] in three

(1) Andrianasolo, E. H.; Goss, H.; Geoger, D.; Girt, M. M.; McPhail, K.; Leal, R. M.; Mooberry, S. L.; Gerwick, W. H. *Org. Lett.* **2005**, *7*, 1375.
(2) Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147.
(3) (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386. (b) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303.
(4) Ivanchina, N. V.; Kicha, A. A.; Kalinovsky, A. I.; Dmitrenok, P. S.; Dmitrenok, A. S.; Chaikina, E. L.; Stonik, V. A.; Gavagnin, M.; Cimino, G. *J. Nat. Prod.* **2006**, *69*, 224.
(5) Ramesh, C.; Ravindranath, N.; Ram, T. S.; Das, B. *Chem. Pharm. Bull.* **2003**, *51*, 1299.
(6) Orjala, J.; Gerwick, W. H. *Phytochemistry* **1997**, *45*, 1087.
(7) Previous methods for the synthesis of D-xylose 2,4-dimethyl ether derivatives include: (a) Ferrier, R. J.; Prasad, D.; Rudowski, A.; Sangster, I. *J. Chem. Soc.* **1964**, 3330. (b) Paquette, L. A.; Barriault, L.; Pissarnitski, D. *J. Am. Chem. Soc.* **2000**, *122*, 619. (c) Fujiwara, K.; Murai, A. *J. Am. Chem. Soc.* **1998**, *120*, 10770.
(8) Lopez, R.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1994**, *59*, 737.
(9) (a) Toyooka, N.; Nakazawa, A.; Hirniyama, T.; Nemoto, H. *Heterocycles* **2003**, *59*, 75. (b) Stick, R. V.; Stubbs, K. A.; Watts, A. G. *Aust. J. Chem.* **2004**, *57*, 779.

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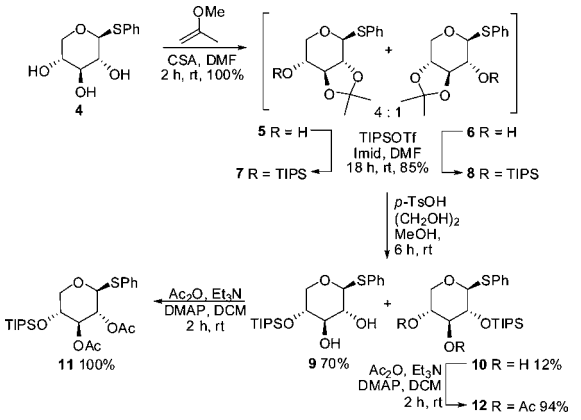
steps and 70% overall yield, and then reaction of **4** with 2-methoxypropane gave a 4:1 mixture of acetals **5** and **6**.[9] The major product **5** could be isolated in 65% yield by careful SiO_2 column chromatography. However it proved more efficient to convert the mixture to TIPS ethers **7** and **8** and then selectively deprotect the acetals with *p*TsOH giving diols **9** and **10** which were readily separated. The structure of the major product **9** was confirmed by HMBC studies as well as by conversion to diacetate **11**. The 400 MHz ^{1}H NMR spectrum in $CDCl_3$ showed downfield shifts of the signals assigned to 2-H and 3-H from δ3.48 and δ3.62 respectively in diol **9** to δ4.85 and δ5.06 in diacetate **11**. The structure of the minor product diol **10** was similarly confirmed by NMR studies and by conversion to diacetate **12**.

Scheme 1. Preparation of Protected D-Xylose Phenyl Thioether **9**



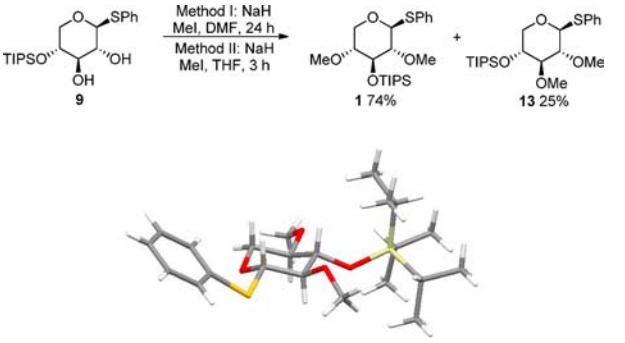
The pivotal step in the preparation of 2,4-dimethyl ether **1** was treatment of diol **9** with NaH, MeI in DMF for 24 h to give **1**, in which the TIPS group had migrated from the 4- to the 3-position, in 74% yield (Scheme 2). In addition a minor product **13** (25% yield) arising from simple methylation was isolated. The same mixture of products was formed using THF as the solvent, but the reaction was complete in just 3 h. Dimethyl ether **1** was recrystallized from dichloromethane, and X-ray crystallography confirmed the proposed structure.

Whilst silyl migrations are known in carbohydrate chemistry[10] to the best of our knowledge this is the first example of migration of a silyl group from the 4-position in a xylose derivative to the apparently more sterically constrained 3-position. During studies on the reactivity of glycosyl donors, Bols and co-workers reported that bulky silyl groups change the pyranoside conformation to a more "axial-rich" conformer.[11] Interestingly, in our case, whilst

(10) See for example: (a) Lassaletta, J. M.; Meichle, M.; Weiler, S.; Schmidt, R. R. *J. Carbohydr. Chem.* **1996**, *15*, 241. (b) Faghih, R.; Reid, B. F. *Carbohydr. Res.* **1987**, *169*, 247. (c) Teranishi, K.; Ueno, F. *Tetrahedron Lett.* **2003**, *44*, 4843. (d) Furegati, S.; White, A. J. P.; Miller, A. D. *Synlett* **2005**, 2385. (e) Lassaletta, J. M.; Schmidt, R. R. *Synlett* **1995**, 925.

(11) (a) Pedersen, C. M.; Marcinscu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465. (b) Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem.—Eur. J.* **2007**, *13*, 7576.

Scheme 2. Migration of the TIPS Group and X-ray Structure of Silyl Ether **1**



3-silyl ether **1** exists in the chair conformation in the solid state, the 400 MHz ^{1}H NMR spectrum in $CDCl_3$ indicated that a conformational change had occurred by comparison with 4-silyl ether **13**. All vicinal coupling constants in **1** were significantly smaller (*J ca.* 5 Hz) than in **13** (*J ca.* 9 Hz), and there was a downfield shift of 1-H from δ4.52 (d, *J* 9.3 Hz) in **13** to δ5.16 (d, *J* 5.2 Hz) in the silyl migrated product **1**. The different conformations of dimethyl ethers **1** and **13** in $CDCl_3$ were confirmed by NOE studies (Figure 2). These changes in the spectral properties of 3- versus their 4-silyl ether counterparts in $CDCl_3$ proved to be general and were empirically useful to analyze reaction mixtures prior to purification and full characterization of the products as discussed later.

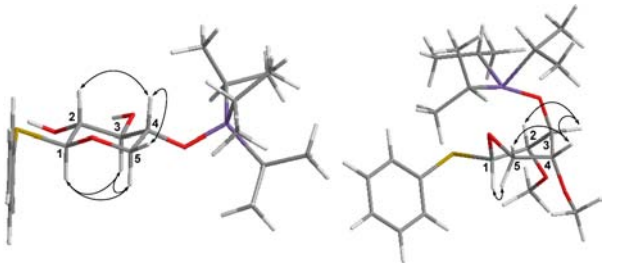
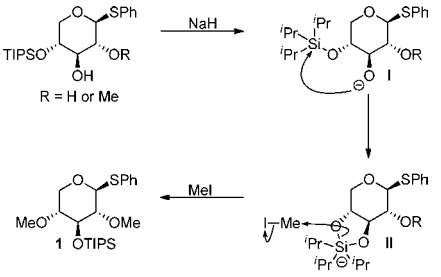


Figure 2. Conformations of diol **9** (left) and silyl ether **1** (right) showing important NOEs.

We propose that migration occurs via attack of alkoxide **I** on silicon to give the five-membered silyl intermediate **II** (Scheme 3). Subsequent reaction of **II** with an electrophile such as methyl iodide occurs preferentially from the less sterically hindered trajectory giving the migrated silyl ether **1** as the major product.

To explore the generality of this transformation for the preparation of orthogonally protected D-xylose derivatives, diol **9** was treated with NaH in DMF and the reaction was quenched with methanol rather than methyl iodide (Scheme 4). A 4:1 mixture of inseparable diols **14** and **9** was formed. In the 400 MHz ^{1}H NMR spectrum in $CDCl_3$, 1-H of the major isomer **14** resonated at δ5.16 (d, *J* 3.9 Hz)

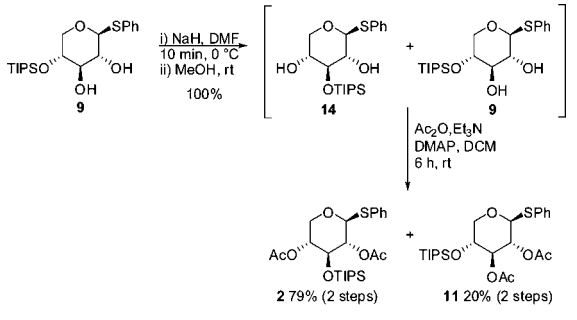
Scheme 3. Proposed Mechanism of Silyl Migration



compared with the minor product **9** δ4.69 (d, J 8.0 Hz) in accord with our earlier observations. The mixture of diols **14** and **9** was acetylated giving diacetates **2** and **11** which were readily purified by SiO_2 column chromatography. The major product diacetate **2** (79% yield over the two steps) was generated via migration of the TIPS group from the 4- to the 3-position in accord with protonation of intermediate **II** (R = H, Scheme 3) occurring preferentially from the less hindered trajectory.

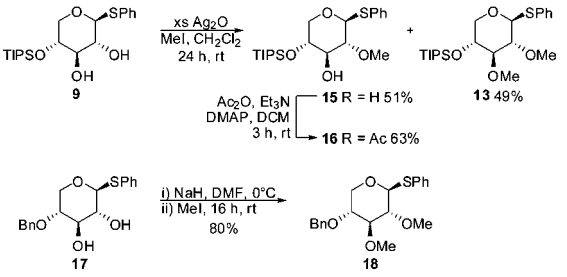
3-Silyl ether **14** was also obtained as the major product on treatment of 2-silyl ether **10** with NaH in DMF and the reaction quenched with methanol. Since the NMR data for **10** in $CDCl_3$ were in accord with a boat conformation with the silyl group axial, it is likely that migration occurs to the axial 4-hydroxyl prior to further migration to the 3-position. From these studies it is apparent that it is unnecessary to separate diols **9** and **10** (Scheme 1) prior to the silyl migration and quenching with an appropriate electrophile.

Scheme 4. Silyl Migrations Give 3-Silyl Ether **14** as the Major Product



Since silyl migration is dependent upon formation of alkoxide **I** and hence the pentacoordinate intermediate **II** (Scheme 3), the reaction conditions may be readily modified for the synthesis of 2,3- rather than 2,4-dimethyl ethers. For example, reaction of diol **9** with silver oxide, MeI in CH_2Cl_2 gave dimethyl ether **13** and 2-monomethyl ether **15** in 49% and 51% yield respectively confirming that no silyl migration occurred under these conditions (Scheme 5).

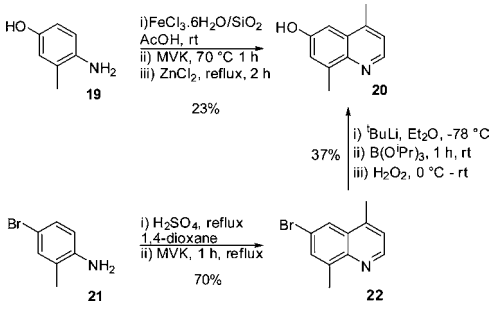
Scheme 5. Synthesis of 2,3-Dimethyl Ethers



Monomethyl ether **15** was readily acetylated to **16**. An alternative approach to a 3,4-dimethyl ether was via methylation of the known 4-benzyloxy diol **17**.[9b,12] Thus we have established a versatile approach for the synthesis of differentially protected D-xylose 1-thioethers including 2,4-dimethyl ether **1** and diacetate **2** as well as 2,3-dimethyl ethers **13** and **18** and 2,3-diacetate **11**.

Turning to glycosylated quinoline **3**, the structure of the natural product was elucidated by spectroscopic methods and the absolute configuration assumed on the basis of the more usual D-xylose.[6] To confirm the structure and absolute stereochemistry we embarked on the total synthesis using 2,4-dimethyl thioether **1** prepared as described above. Two different routes to the synthesis of hydroxyquinoline **20** were investigated (Scheme 6). The first approach was based on the method of Madugula and coworkers for the preparation of substituted quinolines.[13]

Scheme 6. Synthesis of Hydroxyquinoline **20**



Treatment of 4-hydroxy-2-methylaniline **19** with methylvinyl ketone (MVK) in the presence of activated iron(III) chloride followed by addition of zinc chloride gave **20** in 23% yield. However, the reaction was capricious and could not be reproduced reliably. Similar problems were

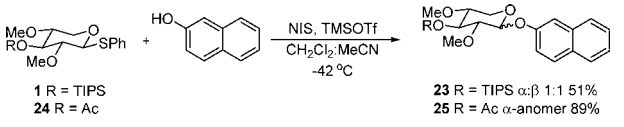
(12) The known benzyl ether **17** was prepared via benzylation of alcohol **5** followed by deprotection of the acetonide with TsOH in MeOH.[9b]

(13) Madugula, S. R. M.; Thallapelly, S.; Bandarupally, J.; Yadav, J. S. U.S. Patent 2007123708, May 2007.

(14) Beight, D. W.; Bonjouklian, R.; Liao, J.; Mcmillen, W. T.; Parkhurst, B. L.; Sawyer, J. S.; Yingling, J. M.; York, J. S. U.S. Patent WO2004026971, April 2004.

encountered using sulfuric acid rather than iron(III) chloride.[14] In contrast, with the less activated 4-bromo-2-methylaniline, **21**, reaction with MVK and sulfuric acid under reflux gave bromoquinoline **22** consistently in 70% yield. Bromide **22** was converted to the required hydroxy quinoline **20** via formation of a boronic ester followed by oxidation.[15] The spectroscopic data of **20** were in accord with the aglycone isolated in very low yields from extracts of *L. majuscula*.[6]

Scheme 7. Model Glycosylations Using 2-Naphthol



To optimize the glycosylation conditions, model studies were conducted using 2-naphthol as the acceptor (Scheme 7).[16] Reaction of naphthol with **1**, NIS, TMSOTf in CH_2Cl_2/CH_3CN at −42 °C showed the most promise giving a 1:1 mixture of α:*β* anomers **23** in 51% yield. Interestingly when the same conditions were used with the 3-acetoxy analogue **24**,[17] the α-anomer **25** was isolated as the sole product in 89% yield.

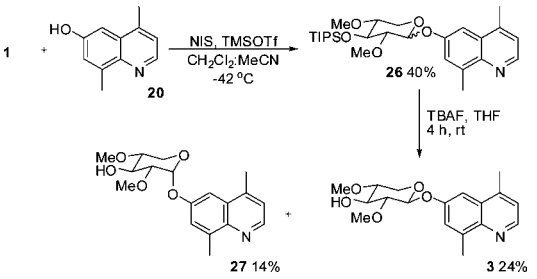
These reactions conditions were used for the coupling of thioether **1** with hydroxyquinoline **20** giving a 1.4:1 mixture of α:*β*-anomers **26** (Scheme 8). The products were inseparable by column chromatography, but on removal of the TIPS group with TBAF both the *β*- and α-anomers **3** and **27** were isolated. The spectroscopic data and optical rotation of synthetic **3** were in accord with those reported for the natural product[6] isolated from *Lyngbya majuscula* confirming the structure of the natural product.

(15) (a) McCubbin, J. A.; Tong, X.; Wang, R.; Zhao, Y.; Snieckus, V.; Lemieux, R. P. *J. Am. Chem. Soc.* **2004**, *126*, 1161. (b) Bunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3901.

(16) For previous studies on the synthesis of aryl glycosides, see: Paul, S.; Jayaraman, N. *Carbohydr. Res.* **2007**, *342*, 1305.

(17) Acetate **24** was prepared from silyl ether **1** by deprotection with TBAF and acetylation of the resultant 3-alcohol in 78% yield over the two steps.

Scheme 8. Completing the Synthesis of Natural Product **3**



In conclusion, migration of silyl ethers in xylose derivatives occurs readily giving the 3-silyl ether as the major product. Evidence is presented for a mechanism involving generation of a five-membered silyl intermediate preferentially followed by reaction with electrophiles from the less hindered trajectory. This rearrangement was pivotal in the preparation of 2,4-dimethyl-3-triisopropylsilyl-D-xylose thioether **1** used for the synthesis of glycosylated quinoline **3** confirming the structure and absolute configuration of the natural product.

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Supporting Information Available. Preparation and characterization of the compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.