## 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- $\beta$ -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,<sup>2</sup> the macrodilactones clavosolides B and C from Myristra clavosa,<sup>3</sup> a series of steroid derivatives from the starfish *Henricia leviuscula*,<sup>4</sup> and the aromatic antitumor compound cleistanthins A.<sup>5</sup> 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

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(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.

methodology is demonstrated in the first total synthesis of 4,8-dimethyl-6-O-(2',4'-di-O-methyl- $\beta$ -D-xylopyranosyl)hydroxyquinoline **3**, a natural product isolated from extracts of the cyanobacterium *Lyngbya majuscula*<sup>6</sup> thus confirming the structure and absolute configuration of the natural product.<sup>7</sup>



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

<sup>(5)</sup> Ramesh, C.; Ravindranath, N.; Ram, T. S.; Das, B. Chem. Pharm. Bull. 2003, 51, 1299.

<sup>(6)</sup> Orjala, J.; Gerwick, W. H. Phytochemistry 1997, 45, 1087.

<sup>(7)</sup> 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.

<sup>(8)</sup> Lopez, R.; Fernandez-Mayoralas, A. J. Org. Chem. 1994, 59, 737.

<sup>(9) (</sup>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.

steps and 70% overall yield, and then reaction of **4** with 2-methoxypropane gave a 4:1 mixture of acetals **5** and **6**.<sup>9</sup> The major product **5** could be isolated in 65% yield by careful SiO<sub>2</sub> 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 <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub> showed downfield shifts of the signals assigned to 2-H and 3-H from  $\delta$ 3.48 and  $\delta$ 3.62 respectively in diol **9** to  $\delta$ 4.85 and  $\delta$ 5.06 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<sup>10</sup> 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.<sup>11</sup> Interestingly, in our case, whilst

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 <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub> 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  $\delta 4.52$  (d, *J* 9.3 Hz) in 13 to  $\delta 5.16$  (d, *J* 5.2 Hz) in the silyl migrated product 1. The different conformations of dimethyl ethers 1 and 13 in CDCl<sub>3</sub> were confirmed by NOE studies (Figure 2). These changes in the spectral properties of 3- versus their 4-silyl ether counterparts in CDCl<sub>3</sub> 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 <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub>, 1-H of the major isomer 14 resonated at  $\delta 5.16$  (d, J 3.9 Hz)

<sup>(10)</sup> 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.

<sup>(11) (</sup>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 3. Proposed Mechanism of Silyl Migration



compared with the minor product **9**  $\delta$ 4.69 (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<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> 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**.<sup>9b,12</sup> 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.<sup>6</sup> 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 hydroxy-quinoline **20** were investigated (Scheme 6). The first approach was based on the method of Madugula and co-workers for the preparation of substituted quinolines.<sup>13</sup>





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

<sup>(12)</sup> The known benzyl ether 17 was prepared via benzylation of alcohol 5 followed by deprotection of the acetonide with TsOH in MeOH.<sup>9b</sup>

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

<sup>(14)</sup> 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.<sup>14</sup> 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.<sup>15</sup> The spectroscopic data of **20** were in accord with the aglycone isolated in very low yields from extracts of *L. majuscula*.<sup>6</sup>

Scheme 7. Model Glycosylations Using 2-Naphthol



To optimize the glycosylation conditions, model studies were conducted using 2-naphthol as the acceptor (Scheme 7).<sup>16</sup> Reaction of naphthol with **1**, NIS, TMSOTf in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN at -42 °C showed the most promise giving a 1:1 mixture of  $\alpha$ : $\beta$  anomers **23** in 51% yield. Interestingly when the same conditions were used with the 3-acetoxy analogue **24**,<sup>17</sup> the  $\alpha$ -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  $\alpha$ : $\beta$ -anomers 26 (Scheme 8). The products were inseparable by column chromatography, but on removal of the TIPS group with TBAF both the  $\beta$ - and  $\alpha$ -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<sup>6</sup> isolated from *Lyngbya majuscula* confirming the structure of the natural product.

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.

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

<sup>(17)</sup> 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.

The authors declare no competing financial interest.