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Chinese Chemical Letters 23 (2012) 996–998

CHINESE CHEMICAL LETTERS

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First total synthesis of a naturally occurring nucleoside disulfide: 9-(5′-Deoxy-5′-thio-β-D-xylofuranosyl)adenine disulfide

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Received 27 April 2012
Available online 18 July 2012

Abstract

A naturally occurring nucleoside disulfide, 9-(5′-deoxy-5′-thio-β-D-xylofuranosyl)adenine disulfide, was first synthesized from D-xylose over 7 steps in 20% overall yield. The key step involved Vorbrüggen glycosylation of silylated N^6-benzoyladenine with xylose diacetate moiety.

Keywords: Naturally occurring nucleoside; Total synthesis; Vorbrüggen glycosylation; Marine sponge; Nucleoside disulfide

9-(5′-Deoxy-5′-thio-β-D-xylofuranosyl)adenine disulfide **1** was first isolated from an Australian marine sponge, *Trachycladus laevispirulifer*, by Capon and coworkers in 2010 [1]. This compound is also the third natural xylo-nucleoside identified, while the other two are 9-(5′-deoxy-5′-thiomethyl-β-D-xylofuranosyl)adenine **2** [2] and 4-amino-7-(5′-deoxy-β-D-xylofuranosyl)-5-iodopyrrolo[2,3-*d*]pyrimidine **3** [3]. Though nucleoside disulfide **1** exhibits little cytotoxic effects against human breast and cervical cancer cell lines in biological assays, its chemical ecology role in enhancing survival of the producing organism remains undetermined [4]. Due to its unique chemical structure and our consistent interest in marine nucleosides [5], the first total synthesis of nucleoside disulfide **1** is reported in the present paper, Fig. 1.

From a synthetic point of view, the target molecule **1** could be synthesized from either adenosine or D-xylose. In our approach, D-xylose was employed as starting material, which is ideal for diversity-oriented synthesis of nucleoside disulfides containing different nucleobases for biological studies, Scheme 1.

To this end, crystalline 1,2-*O*-isopropylidene-α-D-xylofuranose **2** was prepared in 73% yield by acid-catalyzed acetylation of D-xylose, followed by partial hydrolysis with aqueous sodium carbonate in one pot with a modification of the reported method [6]. Then 5-OH was selectively converted into tosylate with triethylamine as base to afford **3** in 92% yield [7]. Protection of 3-OH as benzoate gave **4** in 91% yield. Substitution of the tosylate with thioacetate in anhydrous DMF at 80 °C afforded **5** in 97% yield [8]. The 1,2-*O*-isopropylidene group was removed in acetic acid/acetic anhydride with catalytic amount of sulfuric acid to give nucleoside acceptor **6** in 88% yield [9].

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1001-8417/$ – see front matter
http://dx.doi.org/10.1016/j.cclet.2012.06.011

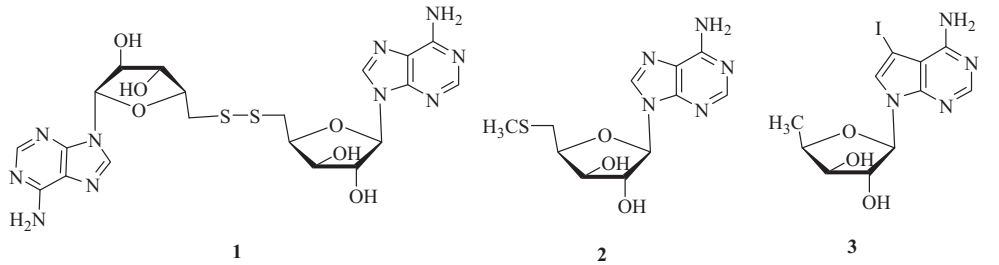
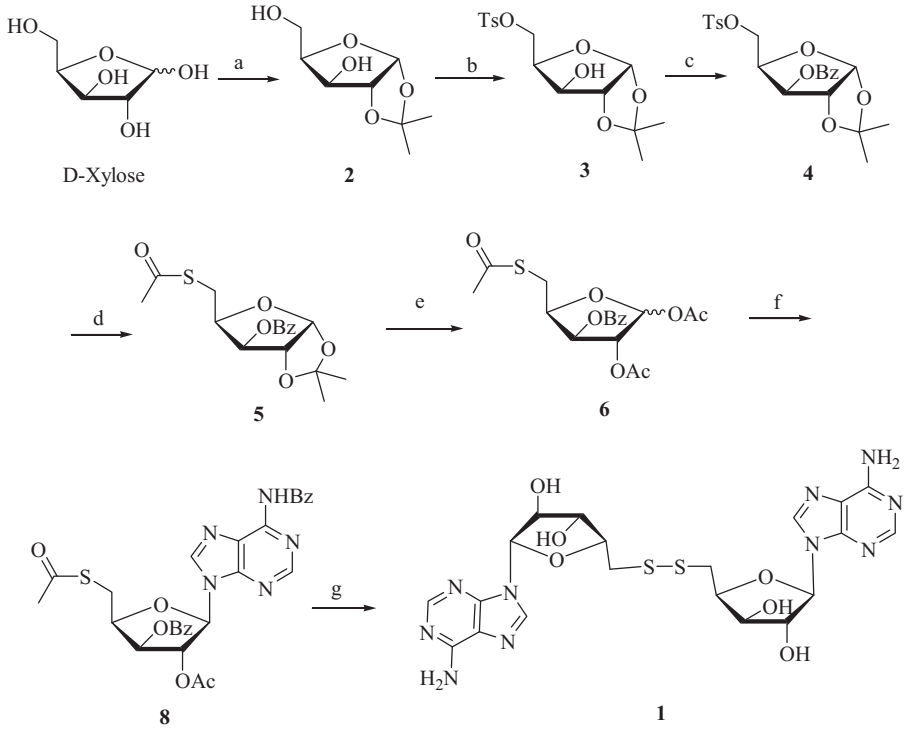


Fig. 1. Naturally occurring xylo-nucleosides.

In the key step of our synthetic route, Vorbrüggen glycosylation [10] was ultilized to attach adenine to xylose moiety. When CH_3CN/BSA/TMSOTf were used as solvent/silylating reagent/catalyst respectively, N^3-, N^7-, and N^9-glycosylated products were obtained in a 2:2:3 ratio (determined by HPLC). Due to the fact that 1,2-dichloroethane favors the formation of δ-complex of the persilyated purine **7** with TMSOTf [11], when it was used as the solvent instead of CH_3CN, desired nucleoside **8** was obtained in 87% yield [12]. Removal of all protecting groups with ammonia and *in situ* oxidation with air afforded the target nucleoside disulfide **1** in 88% yield. All spectra data are in accordance with those of the reported [13].

In conclusion, we developed the first efficient route for the synthesis of 9-(5′-deoxy-5′-thio-β-D-xylofuranosyl)adenine disulfide **1** from D-xylose. The D-xylose diacetates **6** were proved to be a valuable building block for preparation of related nucleoside disulfides. Our progress in synthesis of other nucleoside disulfides and investigation of their biological reactivity will be reported in due course.



Scheme 1. Reagents and conditions: (a) Acetone, H_2SO_4, Na_2CO_3, r.t., 3 h, 73.1%; (b) TsCl, Py, r.t., 4 h, 92.1%; (c) BzCl, Py, r.t., 5 h, 97%; (d) potassium thioacetate, DMF, 80 °C, 3 h, 97.5%; (e) AcOH, Ac_2O, H_2SO_4, 24 h, 88%; (f) N^6-benzoyladenine (**7**), BSA, TMSOTf, dichloroethane, 0 °C to 80 °C, 2 h, 87%; (g) aqueous ammonium hydroxide, methanolic ammonia, air, overnight, 88%.

Acknowledgments

We thank NSFC (Nos. 20962009 and 21062006), NCET (No. 11-1000), the Training Project of Jiangxi Youth Scientists, Education Department of Jiangxi Province (No. GJJ 11223), and Bureau of Science & Technology of Nanchang City for financial support.

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[12] Spectra data of **8**: R_f = 0.49 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 8.52 (s, 1H), 8.26 (s, 1H), 7.93 (d, 2H, J = 8.0 Hz), 7.88 (d, 2H, J = 8.0 Hz), 7.54–7.46 (m, 2H), 7.38 (q, 4H, J = 8.0 Hz), 6.19 (s, 1H), 5.78 (s, 1H), 5.61 (d, 1H, J = 4 Hz), 4.56–4.52 (m, 1H), 3.3–3.29 (m, 2H), 2.27 (s, 3H). 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 169.1, 165.0, 164.9, 152.7, 151.6, 149.8, 141.2, 134.1, 133.5, 132.7, 129.7, 128.9, 128.7, 128.3, 128.0, 123.4, 88.1, 80.5, 80.0, 75.6, 30.5, 27.3, 20.7; ESI-MS: m/z 576.2 $[M+H]^+$.
[13] Spectra data of 9-(5′-deoxy-5′-thio-β-D-xylofuranosyl)adenine disulfide **1**: R_f = 0.20 (DCM:MeOH, 5:1); $[\alpha]_D^{25}$ −16 (c 0.4, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.14 (s, 1H), 7.38 (br s, 2H), 6.16 (d, 1H, J = 5.4 Hz), 6.02 (d, 1H, J = 3.9 Hz), 5.88 (s, 1H), 4.43–4.39 (m, 1H), 4.34 (d, 1H, J = 2.5 Hz), 4.04 (br d, 1H, J = 2.7 Hz), 3.16–3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 152.9, 149.1, 140.3, 119.3, 90.2, 81.6, 81.3, 75.9, 37.6; ESI-MS: 587.1 $[M+Na]^+$; HRMS (ESI) m/z calcd. for $C_{20}H_{25}N_{10}O_6S_2$ $[M+H]^+$: 565.13945, found: 565.13826.