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Syntheses of 1-thio-D-Xylose and D-Ribose Esters of Diorganoarsinous Acids and Their Anticancer Activity

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ABSTRACT: *Several thio-D-xylose and D-ribose esters of dialkylarsinous acids have been synthesized. The crystal structure of 1-S-dimethylarsino-β-D-xylopyranose,* **7a,** *has been obtained. Growth inhibition studies of about 60 strains of human cancer cells have been obtained in vitro for compounds* **6a, 7a, 13**, *and* **14**. *The results reveal that these compounds display a strong inhibition to subpanels of leukemia cells in vitro and high selectivity in inhibiting the growth of cancer cells.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:199–206, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20388

INTRODUCTION

In leukemia therapy, most adult patients with this disease die as a result of disease progression. The application of heavy metals such as platinum compounds in the treatment of some cancers is now well established. The use of arsenicals as therapeutic agents in medicine dates back more than 2400 years to ancient Greece and Rome [1]. The use of arsenic in treating leukemia was first described in the 19th century [2], and a report from Boston University in 1931 further suggested activity against chronic myelogenous leukemia [3]. Chinese investigation demonstrated the efficacy of arsenic trioxide in treating patients with relapsed acute promyelocytic leukemia (APL) [4]. This was further confirmed by studies conducted in the United States [5,6] and is currently being evaluated as therapy for other leukemia types. Although the precise mechanism of action of arsenic trioxide in APL is not clear, arsenical compounds could induce apoptosis in myeloid leukemia cell lines independent of the expression of PML and PML-RARα proteins. This has led to evaluation of this agent in other neoplasms [7]. Arsenic trioxide inhibits the growth and survival of multiple myeloma cell lines as well as patient cells in a dose and time-dependent manner [8–11]. However, the toxicity associated with inorganic arsenic oxides limits their use in therapy. Thus, organoarsenic compounds have received more attention because of their lower toxicity as compared with inorganic arsenicals [12,13]. Zingaro and coworkers have reported on the synthesis and application of organic arsenicals as antileukemic agents [14–19]. Herein, we report the synthesis of some new dimethylarsenic derivatives of D-ribose and D-xylose (**6a–c, 7a** and **13, 14**) and their anticancer activity in vitro.

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RESULTS AND DISCUSSION

Chemistry

The syntheses of 1-thioxylose and 1-thioribose derivatives are depicted in Scheme 1 and Scheme 2,

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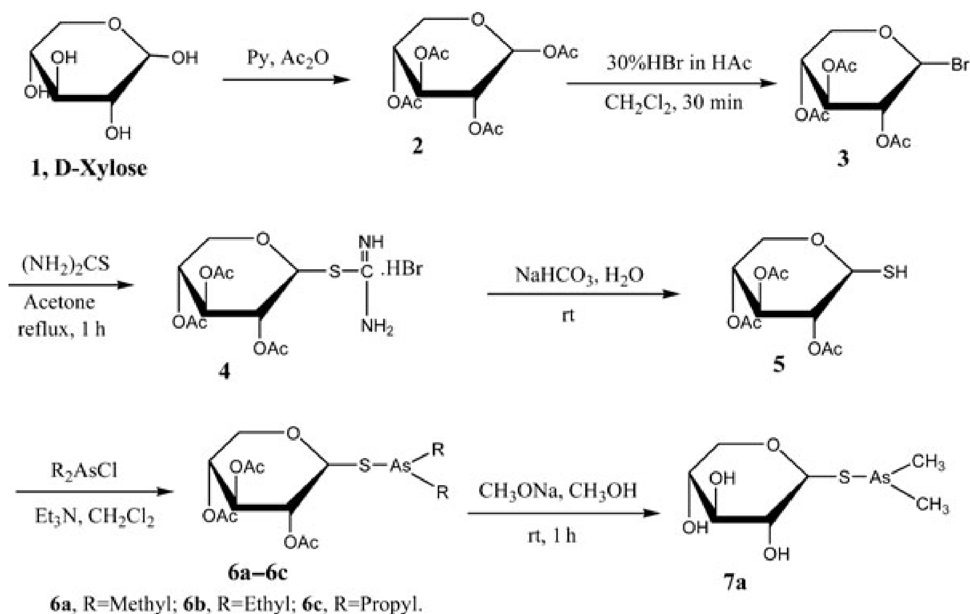
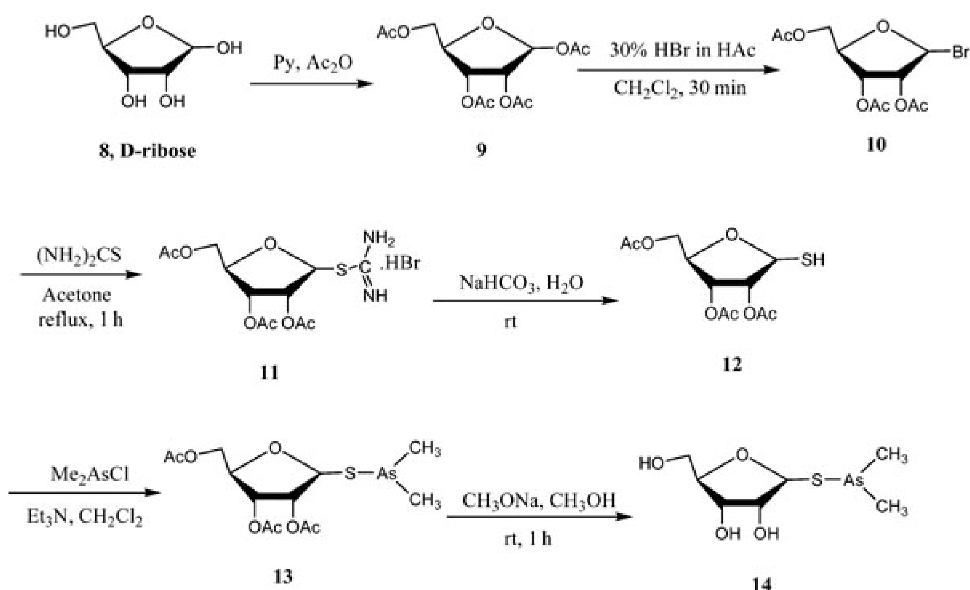


SCHEME 1

respectively. As is shown in Scheme 1, the treatment of D-xylose with acetic anhydride in pyridine at room temperature for 24 h afforded 1,2,3,4-tetra-*O*-acetyl-D-xylopyranose **2** in excellent yield. Treatment of 2 with 30% HBr/acetic acid in dichloromethane at 0°C for 30 min, followed by washing the solution with water three times, and then evaporation of solvent under reduced pressure, gives compound **3**, which was purified by recrystallization (80% yield). Steps **3** to **5** are straightforward. Compound **5** is relatively unstable. It must be kept in a freezer and cannot be purified by column chromatography. However, when the thiol proton was substituted by the dimethylarsenic group, a stable compound was obtained. Treatment of compound **5** with dialkylchloroarsine and triethylamine in dichloromethane at room temperature afforded compounds **6a,6b,6c**. Deacetylation of compound



SCHEME 2

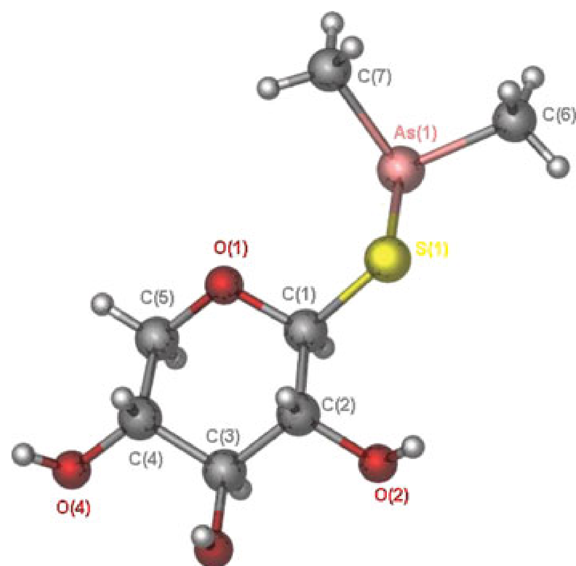


FIGURE 1 Crystal structure of **7a.**

6a with sodium hydroxide in methanol solution afforded **7a**.

In Scheme 2, the steps are similar to those in Scheme 1. The difference is that compound **10** is not stable compared with compound **5**, although they have similar structures. It was difficult to purify and must be treated as soon as possible. Compound **12** is more unstable than compound **5**. Treatment of **2** with dimethylchloroarsine in dichloromethane in the presence of triethylamine afforded compound **13**. Treatment of **13** with sodium methoxide in methanol solution at room temperature gave **14**.

To clearly gain the stereochemistry structure of the new compound **7a**, its single crystal structure was determined by X-ray crystallography. Compound **7a** was obtained in the form of air-stable, colorless crystals by slow evaporation from a solution of **7a** in methanol. A view of compound **7a** is shown in Fig. 1. X-ray analysis shows that it has a D-ß-pyranose structure.

Biology

The arsenic derivatives of sugars **6a, 7a, 13, 14** were selected by the National Cancer Institute for testing in the developmental therapeutics program against a panel of approximately 60 tumor cell lines. The in vitro test system and the information, encoded by the activity pattern over all cell lines, were obtained (see Experimental section) according to reported methods [20]. The antitumor activity of a test compound is given by three parameters for each cell line: pGI_{50} value (GI_{50} is the molar concentration of the compound that inhibits 50% net cell growth), pTGI value (TGI is the molar concentration of the compound leading to total inhibition of net cell growth), and pLC_{50} value (LC_{50} is the molar concentration of the compound that induces 50% net cell death). Moreover, a mean graph midpoint (MG-MID) is calculated for each of the mentioned parameters, giving an average activity parameter over all cell lines. For the calculation of the MG-MID, insensitive cell lines are included at the highest concentration tested. The discovery of compounds with new selectivity patterns is one of the targets of the screening program. Selectivity of a compound with respect to a certain cell line of the screen is characterized by a high deviation of the particular cell line parameter compared to the MG-MID value. The data from these in vitro screenings can be presented in different formats. In Table 1, the results in terms of number of cell lines investigated and activity range, together with the MG-MID values are presented.

TABLE 1 Overview of the Results of the In Vitro Antitumor Screening for Selected Compounds[a]

		pGI_{50}[b]			$pTGI$[c]			pLC_{50}[d]		
Compound	*No. Studied*[e]	*No. giving positive results*[e]	*Range*	*MG-MID*[f]	*No. high-activity results*	*Range*	*MG-MID*	*No. high-activity results*	*Range*	*MG_MID*
6a	54	54	6.64–8.00	6.55	28	5.53–7.61	5.78	28	5.13–7.03	5.08
7a	56	56	6.49–7.59	6.43	32	5.68–7.07	5.60	26	4.00–6.17	4.71
13	57	57	6.47–8.00	6.40	28	5.73–6.90	5.64	22	4.00–6.15	4.80
14	55	55	6.22–7.00	6.17	26	5.50–6.47	5.35	19	4.69–6.03	4.58

[a]Data obtained from the NCI's in vitro disease-oriented human tumor cells screen.
[b]pGI_{50} is the –log of the molar concentration that inhibits 50% net cell growth.
[c]pTGI is the –log of the molar concentration giving total growth inhibition.
[d]pLC_{50} is the –log of the molar concentration leading to 50% net cell death.
[e]Refers to the number of cell lines.
[f] MG-MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

TABLE 2 Inhibition of the In Vitro Cancer Cell Lines by Compounds **6a, 7a, 13, 14** (pLC_{50})

	pLC50			
Cell line	**6a**	**7a**	**13**	**14**
Leukemia				
CCRF-CEM	5.71	>4.00	>4.00	>4.00
HL-60(TB)	5.67	4.67	4.35	4.06
K-562	5.69	5.05	4.22	>4.00
MOLT-4	6.13	4.47	4.74	4.36
RPMI-8226	7.03	>4.00	4.61	>4.00
SR	nd	5.33	4.92	>4.00
Non-small cell lung cancer				
A549/ATCC	4.41	>4.00	4.41	>4.00
EKVX	4.43	4.12	4.26	4.40
HOP-62	4.44	4.50	4.46	4.46
HOP-92	4.91	5.06	4.76	4.75
NCI-H226	4.60	4.54	4.51	4.52
NCI-H23	5.29	5.46	4.67	4.48
NCI-H322M	4.39	4.30	4.37	4.31
NCI-H460	4.27	>4.00	4.20	>4.00
NCI-H522	6.14	5.20	5.48	6.03
Colon cancer				
COLO 205	5.13	>4.00	4.74	>4.00
HCT-116	nd	5.41	5.47	nd
HCT-15	5.48	5.48	5.39	4.74
HT29	>4.00	>4.00	>4.00	>4.00
KM12	4.64	>4.00	4.42	4.30
SW-620	5.27	5.15	5.30	5.02
CNS Cancer				
SF-268	4.39	4.34	4.41	4.30
SF-295	4.55	>4.00	4.48	4.40
SF-539	5.18	5.14	4.70	5.10
SNB-19	4.08	>4.00	4.01	>4.00
U251	5.27	5.23	4.94	4.51
Melanoma				
LOX IMVI	5.54	5.67	5.50	5.21
MALME-3M	5.58	>4.00	5.51	5.41
M14	5.49	5.28	5.79	5.68
SK-MEL-2	5.37	4.42	>4.00	4.58
SK-MEL-28	>4.00	>4.00	4.73	>4.00
SK-MEL-5	6.26	6.17	6.15	5.49
UACC-257	4.99	4.41	4.84	4.28
UACC-62	5.39	5.60	5.28	4.77
Ovarian cancer				
IGROV1	5.29	4.26	4.47	4.55
OVCAR-3	6.08	5.64	5.86	5.36
OVCAR-4	>4.00	>4.00	>4.00	>4.00
OVCAR-5	4.61	5.16	4.88	4.44
OVCAR-8	4.36	>4.00	4.56	>4.00
SK-OV-3	4.31	4.35	4.30	4.21
Renal cancer				
786-0	5.49	5.47	5.57	4.46
A498	4.87	4.86	4.95	4.59
ACHN	5.52	5.52	5.52	4.88
CAKI-1	5.64	5.11	5.35	5.14
RXF 393	5.07	4.01	5.00	4.22
SN12C	5.27	5.50	5.52	4.95
TK-10	5.51	5.43	5.46	5.27
UO-31	5.45	5.29	5.38	5.37

Continued

TABLE 2 Continued

Cell line	pLC50 6a	7a	13	14
		Prostate cancer		
PC-3	4.76	4.32	>4.00	4.48
DU-145	5.63	5.43	5.70	5.71
		Breast cancer		
MCF7	5.29	5.33	4.94	4.72
NCI/ADR-RES	4.10	4.21	4.24	>4.00
MDA-MB-231/ATCC	4.80	4.82	4.84	4.69
HS 578T	4.65	>4.00	>4.00	>4.00
MDA-MB-435	6.08	>4.00	4.86	4.50
T-47D	>4.00	>4.00	>4.00	>4.00
MG-MID	5.08	4.71	4.80	4.58

An evaluation of the data reported in Table 1 reveals that arsenic derivatives have good MG-MID values. It is obvious that **6a** has a little more effect than **7a** and **13** in inhibition of the cancer cell growth and **7a** and **13** also have a little more effect than **14**. Considering the pGI_{50}, the growth inhibition is 100% to the total selected human cancer cell, the average effective concentrations are very small. From the pTGI, it is to be noted that all of the four selected compounds have about 50% high-inhibition activities. Considering the pLC_{50}, these compounds display similar activities at active concentrations.

Evaluating the original data of pLC_{50} (see Table 2), these compounds show a high-inhibitory activity toward some cancer cells. And among selected eight kinds of tumors, 60 tumor cell lines, the value of LC_{50} against *Leukemia, Melanoma* and *Renal Cancer* reached average 10^{-6} M. Especially, the value of LC_{50} to *RPMI-8226*, *NCI-H522* and *SK-MEL-5* several kinds of tumor cell lines separately reached 10^{-8}, 10^{-7}, and 10^{-7} M. Consideration of the very low concentrations, 10^{-7} M, and examining the other data, it appears that these compounds have a high level of inhibitory activity as well as strong selectivity.

CONCLUSION

Several thio-D-xylose and D-ribose esters of dialkylarsinous acids have been synthesized. The crystal structure of 1-*S*-dimethylarsino-β-D-xylopyranose (**7a**) has been obtained. Growth inhibition studies of about 60 strains of human cancer cells have been obtained in vitro for compounds **6a, 7a, 13, 14**. The results reveal that these compounds display a strong inhibition toward subpanels of leukemia cells in vitro. The compound **6a** displays the best effect of inhibition. These compounds have high selectivity in inhibiting the growth of cancer cells. Because of this effectiveness at very low concentration, any toxicity would be greatly diminished.

EXPERIMENTAL

General

All commercial reagents and solvents purchased from the Aldrich and Sigma companies were used without further purification unless otherwise specified. ^1H NMR spectra were recorded on a Mercury 300 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (ppm, δ scale) relative to internal standard TMS (δ 0.0), and coupling constants (J) are reported in hertz (Hz). The high-resolution mass spectra (HRMS) measurements were obtained using a Kratos MS80 mass spectrometer. Chromatographic solvent proportions are expressed on a volume: volume basis. Thin layer chromatography was run using Analtech silica gel GF uniplates. Merck silica gel 60 F_{254} plates were used for analytical TLC. Plates were visualized by UV light. Normal phase flash chromatography was carried out on Merck silica gel 60 (70–230 mesh) with a forced flow of the indicated solvent system in the proportions described below. All moisture- and/or air-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Elemental analyses were performed by the Galbraith Laboratories (Knoxville, TN).

Synthesis of 1,2,3,4-Tetra-O-acetyl-β-D-xylopyranose (2)

D-xylose **1** (15 g, 0.1 mol) was dissolved in 100 mL of pyridine. Acetic anhydride (50 g, 0.49 mol) was

added dropwise with stirring at room temperature for 24 h. Pyridine and excess acetic anhydride were evaporated under reduced pressure, and the residue was poured into water. The mixture was extracted with chloroform three times (3 × 100 mL). The combined organic phases were washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solution was evaporated, and the purification was carried out on a silica gel column, using a solution of dichloromethane and methanol (100:3) to afford compound **2** (30.2 g, yield 95%). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.19 (1H, *d*, $J = 3.9$ Hz, H-1), 5.41 (1H, dd, $J_1 = 9.6$ Hz, $J_2 = 9.9$ Hz, H-2), 5.01–4.92 (2H, m, H-3, 4), 3.87 (1H, dd, $J_1 = 6.0$ Hz, $J_2 = 5.4$ Hz, H-5), 3.65 (1H, t, H-5, $J = 10.1$ Hz), 2.11 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.98 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 170.08, 169.74, 169.29, 168.97, 89.27, 69.52, 69.38, 68.68, 60.67, 20.84, 20.70, 20.64, 20.46. MS (ESI): 318 (M, 100%), 319 (M + 1, 15%). Anal. Calcd for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70; O, 45.24. Found: C, 48.94; H, 5.73.

*Synthesis of 1-Bromo-2,3,4-tri-O-acetyl-α-D-xylopyranose (**3**)*

1,2,3,4-Tetra-*O*-acetyl-ß-D-xylopyranose **2** (20 g, 0.06 mol) was dissolved in 100 mL of dichloromethane and cooled in an ice bath, 30% HBr/acetic acid (20 mL, 0.1 mol) solution was poured into mixture and kept stirring for 30 min. The solution was poured into 300 mL of ice water. The organic phase was separated and washed with a weak base solution to pH ∼7 and dried over anhydrous sodium sulfate. The solvent was evaporated at reduced pressure, and the residue was dissolved in acetone. The acetone was evaporated slowly in lower temperature to get the pure crystalline compound **3** (16.3 g, yield 80%). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.55 (1H, t, $J = 9.9$ Hz, H-1), 5.08–4.97 (2H, m, H-2, 3), 4.76 (1H, dd, $J_1 = 3.9$ Hz, $J_2 = 6.0$ Hz, H-4), 4.05 (1H, dd, $J_1 = 6.0$ Hz, $J_2 = 5.4$ Hz, H-5), 3.87 (1H, t, $J = 10.1$ Hz, H-5′), 2.12–2.03 (9H, m, 3×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 169.53, 169.44, 87.48, 70.69, 69.35, 67.92, 62.40, 20.64, 20.63, 20.60. HRMS (ESI): Calcd for $C_{11}H_{15}O_7Br$, 338.0001; found 338.0006.

*Synthesis of 1-Thiol-2,3,4-tri-O-acetyl-β-D-xylopyranose (**5**)*

1-Bromo-2,3,4-tri-*O*-acetyl-α-D-xylopyranose **3** (13.5 g, 0.04 mol) and thiourea (3.5 g, 0.046 mol) were dissolved in 50 mL of acetone, stirred at reflux for 1 h. After refluxing, evaporation of acetone, the residue was poured into 50 mL of saturated sodium bicarbonate solution, stirred at room temperature for 1 h, and the pH of solution was adjusted to 6 with dilute HCl. The mixture was extracted with dichloromethane three times (3 × 50 mL), and the organic solution was dried over anhydrous sodium sulfate, evaporation of the solvent to obtain the almost pure yellowish liquid product **5** (10.5 g) in about 93% yield. The compound **5** was used directly in the following steps because of its instability on silica gel column.

*Synthesis of 1-S-Dimethylarsino-2,3,4-tri-O-acetyl-β-D-xylopyranose (**6a**)*

1-Thiol-2,3, -tri-O-acetyl-β-D-xylopyranose **5** (5.0 g, 0.017 mol) and triethylamine (2.0 g) were dissolved in 30 mL of dichloromethane and placed into a 100-mL flask and immersed an ice-bath. Dimethylchloroarsine (2.5 g, 0.018 mol) was dissolved in 20 mL of dichloromethane and added to the flask while stirring vigorously. Stirring was continued for 2 h, and the temperature allowed rise to room temperature. The solution was poured into a separatory funnel, washed with water (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate. After removal of the dichloromethane, the residue was purified using flash column chromatography, diluted with solution of dichloromethane and methanol (100: 3 in volume), the product **6a** (5.0 g, yield 74.6%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.70–4.90 (3H, m, H-1,2,3), 4.58–4.63 (1H, m, H-4), 4.22–4.16 (1H, m, H-5), 3.38–3.43 (1H, m, H-5′), 2.05 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.03 (3H, s, CH_3), 1.37–1.34 (6H, m, $As(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 170.08, 169.82, 169.37, 83.70, 72.69, 71.98, 68.80, 66.17, 20.84, 20.74, 14.34, 13.76. MS (ESI): 396 (M, 100%), 397 (M + 1). Anal. Calcd for $C_{13}H_{21}AsO_7S$: C, 39.40; H, 5.34; As, 18.91; S, 8.09. Found: C, 38.98; H, 5.35; As, 19.22; S, 7.97.

*Synthesis of 1-S-Diethylarsino-2,3,4-tri-O-acetyl-β-D-xylopyranose (**6b**)*

Refer to the synthesis of 1-*S*-dimethylarsino-2,3,4-tri-O-acetyl-*β*-D-xylopyranose **6a**. ^{1}H (300 MHz, $CDCl_3$), δ: 5.20–4.85 (3H, m, H1,2,3), 4.58 (1H, d, $J = 5.7$ Hz, H-4), 4.16 (1H, dd, $J_1 = 5.1$ Hz, $J_2 = 6.3$ Hz, H-5), 3.33 (1H, dd, $J_1 = 9.6$ Hz, $J_2 = 1.5$ Hz, H-5′), 2.01 (3H, s, CH_3), 2.02 (3H, s, CH_3), 2.03 (3H, s, CH_3), 1.76 (4H, m), 1.20 (6H, dd, $J_1 = 7.5$ Hz, $J_2 = 6.9$ Hz, $As(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 170.15, 169.84, 169.40, 83.94, 72.85, 72.23, 68.88, 66.10, 20.97, 20.77, 20.64, 10.22. MS (ESI): 424 (M, 100%), 425 (M + 1). Anal. Calcd for $C_{15}H_{25}AsO_7S$: C,

42.46; H, 5.94; As, 17.66; S, 7.56. Found C, 42.55, H, 6.02, As, 17.52, S, 7.39.

*Synthesis of 1-S-Dipropylarsino-2,3,4-tri-O-acetyl-β-D-xylopyranose (**6c**)*

Refer to the synthesis of 1-*S*-dimethylarsino-2,3,4-tri-*O*-acetyl-*β*-D-xylopyranose **6a**. ^{1}H (300 MHz, $CDCl_3$), *δ*: 5.20–4.85 (3H, m, H1,2,3), 4.59 (1H, d, $J = 5.7$ Hz, H-4), 4.18 (1H, dd, $J_1 = 5.4$ Hz, $J_2 = 6.3$ Hz, H-5), 3.35 (1H, dd, $J_1 = 9.6$ Hz, $J_2 = 1.5$ Hz), 2.07–2.03 (9H, m, $3{\times}COCH_3$), 1.90–1.50 (10H, m, $2{\times}CH_2CH_3$, 1.12–0.95 (4H, m, $2{\times}CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 170.16, 169.84, 169.38, 84.20, 72.82, 72.17, 68.86, 66.03, 31.69, 31.36, 31.00, 20.76, 19.58, 16.12. MS (ESI): 452 (M, 100%), 453 (M + 1). Anal. Calcd for $C_{17}H_{29}AsO_7S$: C, 45.13; H, 6.46; As, 16.56; S, 7.09. Found C, 45.42, H, 6.38, As, 16.28, S, 7.19.

*Synthesis of 1-S-Dimethylarsino-β-D-xylopyranose (**7a**)*

1-*S*-Dimethylarsino-2,3,4-tri-*O*-acetyl-*β*-D-xylopyranose **6a** (2.0 g, xxx mol) and sodium methoxide (0.5 g) were dissolved in 40 mL of methanol, stirred for 1 h at room temperature. The solution was neutralized with acidic resin and filtrated. The methanol was evaporated slowly to yield the crystalline product **7a** (0.9 g, yield 66%). ^{1}H (300 MHz, $CDCl_3$), *δ*: 4.27–4.31 (1H, m, H-1), 3.79–3.83 (1H, m, H-2), 3.38–3.44 (1H, m, H-3), 3.26–3.10 (3H, m, H-4, 5, 5′), 1.27 (6H, d, $J = 1.5$ Hz As $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 87.10, 78.14, 75.12, 69.93, 69.80, 13.45, 12.90. MS (ESI): 270 (M, 100%), 271 (M + 1). Anal. Calcd for $C_7H_{15}AsO_4S$: C, 31.12; H, 5.60; As, 27.73; S, 11.87. Found C, 31.37; H, 5.72; As, 27.56; S, 11.68.

*Synthesis of 1,2,3,5-Tetra-O-acetyl-ß-D-ribofuranose (**9**)*

D-Ribofuranose (7.5 g, 0.05 mol) was dissolved in 100 mL of anhydrous pyridine, the solution was cooled to 0° C in an ice bath, stirred vigorously, and then 25 g (excess) acetic anhydride was added slowly, dropwise. The solution was allowed to come to ambient temperature, and the stirring was continued for 24 h. The mixture was evaporated at reduced pressure, the residue was put into water, extracted with ethyl acetate for two times, and washed with brine. The organic layer was dried over magnesium sulfate. The organic layer was evaporated to afford **9** (15.1 g, yield 95%). ^{1}H NMR (300 MHz, $CDCl_3$), *δ*: 6.26–5.70 (1H, m, H-1), 5.50–5.17 (1H, m, H-2), 5.07–4.93 (2H, m, H-3,4), 4.18–3.48 (2H, m, H-5,5′), 2.12 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.06 (3H, S, CH_3), 2.05 (3H, s, CH_3). ^{13}C NMR(75 MHz), *δ*: 170.08, 170.03, 169.58, 169.32, 92.24, 71.18, 69.67, 68.51, 63.01, 21.07, 20.98, 20.92, 20.87. HRMS (ESI): Calcd for $C_{13}H_{18}O_9$, 318.0951; found 318.0957.

*Synthesis of 2,3,5-tri-O-acetyl-1-S-dimethylarsino-ß-D-ribofuranose (**13**)*

1,2,3,5-Tetra-O-acetyl-ß-D-ribofuranose **9** (10 g, 0.03 mol) was dissolved in 90 mL of dichloromethane, stirred at 0°C, and dissolved in a solution containing 30% HBr/acetic acid (8.0 g, 0.1 mol) solution, after stirring for 30 min, the reaction was stopped. The reaction mixture was poured into 30 mL of ice water, and the organic layer was washed with water (2 × 20 mL), the organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain crude compound **10** (9.5 g). The compound **10** (9.5 g, 0.028 mol) was dissolved in 50 mL of acetone and thiourea (3 g, 0.04 mol), refluxed for 1 h with stirring under N_2, and then poured into a saturated sodium bicarbonate solution, and stirred at room temperature for another 2 h. The solution was adjusted pH to 6 with dilute HCl. Then the reaction mixture was extracted with dichloromethane (2 × 60 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude yellowish oil 1-thio-2,3,5-tri-*O*-acetyl-ß-D-ribofuranose **12** (6.5 g), which was not stable in column chromatography. This compound was stored in freezer for later use.

1-Thio-2,3,5-tri-*O*-acetyl-ß-D-ribofuranose **12** (5.0 g, 0.017 mol) and triethylamine (2.5 g, 0.025 mol) were dissolved in 50 mL of dichloromethane, cooled in an ice bath, and stirred under an atmosphere of nitrogen. Then, dimethylchloroarsine (3.0 g, 0.021 mol) diluted with dichloromethane (10 mL) was added dropwise, and allowed to come to room temperature. The stirring was continued for 1 h, water was poured into the solution, stirred. The two layers were separated and washed with water (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the crude product **13** (6.0 g), which was purified using flash column chromatography (diluted with the solution of dichloromethane and methanol (100:2)). ^{1}H NMR (300 MHz, $CDCl_3$), *δ*: 5.52 (1H, m, H-1), 5.13–5.07 (2H, m, H-5, 5′), 4.16 (1H, m, H-2), 3.80–3.72 (2H, m, H-3,4), 2.10 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.07 (3H, s, CH_3), 1.39–1.37 (6H, d, $J = 1.5$ Hz, As$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 169.78, 169.47, 81.71, 70.34,

67.00, 66.72, 63.13, 20.86, 20.81, 20.70, 14.30, 14.28. HRMS (ESI): Calcd for $C_{13}H_{21}AsO_7S$, 396.0224; found 396.0229.

*Synthesis of 1-S-Dimethylarsino-ß-D-ribofuranose (**14**)*

2,3,5-Tri-*O*-acetyl-1-*S*-dimethylarsino-ß-D-ribofuranose (1.0 g, xxx mol) was dissolved in methanol, and sodium methoxide (0.5 g) was added, and stirred for 1 h at room temperature. The solution was neutralized the solution with acidic resin. The acidic resin was filtrated, and the methanol filtrate was allowed to evaporate slowly. This yielded the crystalline product **14** (0.4 g). ^{1}H NMR (300 MHz, acetone-d_6), δ: 5.70–4.90 (1H, m, H-1), 3.80–3.40 (5H, m, H-2,3,4,5,5′), 1.27–1.20 (6H, d, $J = 1.5$ Hz, As $(CH_3)_2$). ^{13}C NMR (75 MHz), δ: 85.37, 73.56, 69.13, 67.86, 65.01, 25.75. HRMS (ESI): Calcd for $C_7H_{15}AsO_4S$, 270.1782; found 270.1776.

X-ray Crystallography

Crystallographic measurements were carried out on a Siemens P4 diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) and 12 kW rotating generator. The data were collected at 110 K. The structure was solved and refined using the programs SHELXS-97 [21] and SHELXL [21]. The program X-Seed [22] was used as an interface to the SHELX programs. Crystallographic.cif files (ccdc Nos. 644478) are freely available from www.ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk. These are available from there under the deposition number CCDC 644478 for **7a**.

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