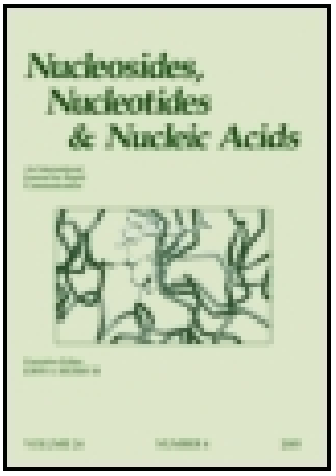

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A Reinvestigation of the Synthesis of 4-Thio-Pentofuranosides for Further Nucleosidic Synthesis

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A REINVESTIGATION OF THE SYNTHESIS OF 4-THIO-PENTOFURANOSIDES FOR FURTHER NUCLEOSIDIC SYNTHESIS.

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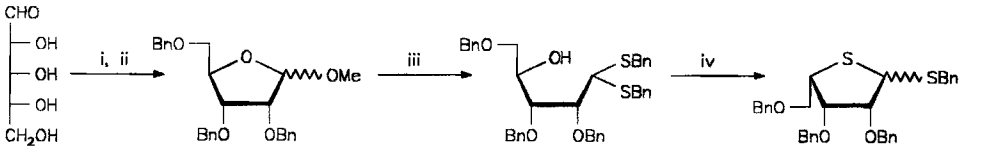
Abstract:

We demonstrate that the procedure of Huang and Hui[4], applied to the D-ribose and involving Ph_3P/I_2/Imidazole reagent system do not lead to the desired 4-thio-D-ribofuranoside derivative but gives its diastereoisomer 4-thio-L-lyxofuranoside derivative **4**.

Our research team has developped for several years a new series of sugar-modified oligonucleotides: the 4'-thio-ß-D-oligoribonucleotides **(4'-S-RNA)** in which the annular oxygen atom of the furanose moiety has been replaced with a sulfur atom, the base keeping the natural ß configuration [1,2]. 4'-S-RNA assembling requires suitable preparation of the corresponding 4'-thio-ß-D-ribonucleosides synthesized from 1-O-acetyl-2,3,5-tri-O-benzyl-4-thio-D-ribofuranoside[3]. Looking for improvements of 4-thio-D-ribofuranose synthesis, which is the limiting step of **4'-S-RNA** synthesis, we have been interested on a recent strategy described by Huang and Hui to achieve 2-deoxy-4-thio-D-ribose synthesis from 2-deoxy-D-ribose as starting material [4] involving a one pot reaction through Ph_3P / I_2 / Imidazole reagent system.

This procedure, making use of two consecutive SN_2 reactions seemed surprising because of the role of iodide anion in the ring closure reaction of dithioacetal derivatives [5-7]. To check this result, we applied the same experimental conditions to D-ribose **1** with the expectation of obtaining 4-thio-D-ribofuranoside (Scheme1).

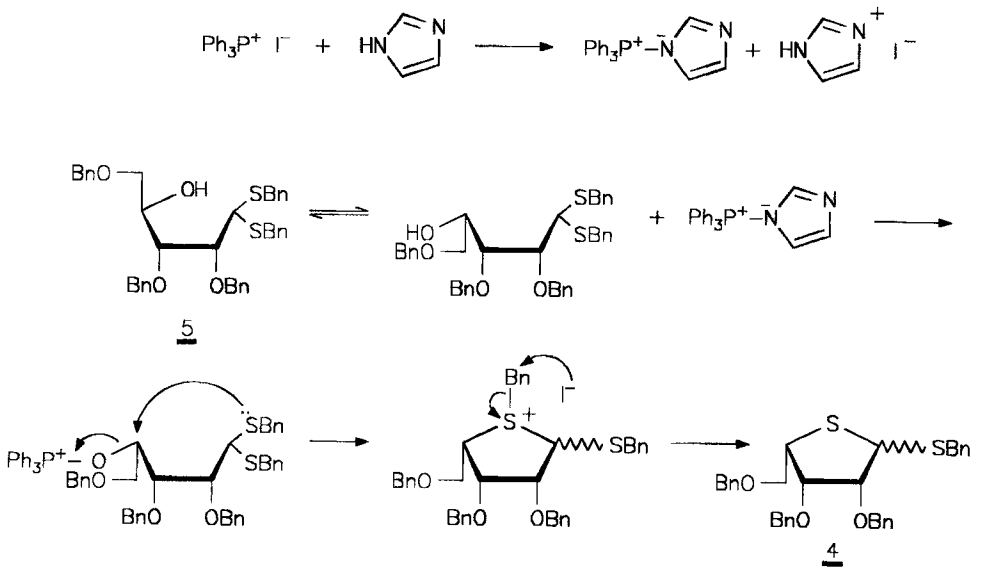
Methyl-2,3,5-tri-O-benzyl-D-ribofuranoside **2**, previously synthesized [8], was treated with benzyl mercaptan and BF_3 / Et_2O [9, 10] to give the dithiobenzylacetal **3** in 75 % yield. **3** was then reacted with Ph_3P / I_2 / Imidazole to afford **4** in 71 % yield.



1 2 3 4

(i = MeOH, HCl; ii = BnBr, KOH, THF; iii = BnSH, BF_3 / Et_2O; iv = Ph_3P / I_2 / Imidazole, THF)

Scheme 1

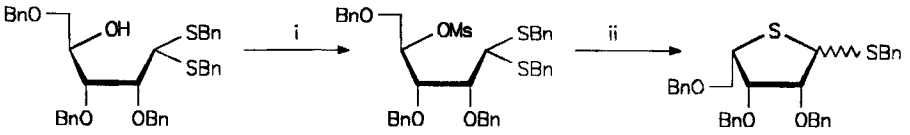


Scheme 2

Since we previously synthesized benzyl-2,3,5-tri-O-benzyl-1,4-dithio-D-ribofuranoside [3] and proved unambigously its configuration through NOE experiments [11], it was easily shown according to the mechanism of the alkylphosphonium reaction [12] that this compound **4** was a 4-thio-L-lyxofuranoside derivative (scheme 2).

To further confirm this structure, we decided to synthesize univocally benzyl-2,3,5-tri-O-benzyl-1,4-dithio-L-lyxofuranoside **4** starting from D-ribose according to our described synthetic pathway [3] (Scheme 3).

In this procedure, the key intermediate **3** was reacted with mesyl chloride to give the expected mesylated intermediate **5** as shown by NMR and mass spectral data. The nucleophilic substitution could be then directly achieved by warming the mesylated



3 5 4

(i = MsCl, Pyr.; ii = NBu_4I, $BaCO_3$, Pyr.)

Scheme 3

product with *tetra*-butylammonium iodide and barium carbonate as cyclisation agent in dry pyridine [6]. Under these conditions, 5 cyclised smoothly to give the benzyl-2,3,5-tri-O-benzyl-1,4-dithio-L-lyxofuranoside 4 in 71 % overall yield from 3.

The compound 4 obtained according to these differents routes exhibit the same physico-chemical properties which corroborate the 4-thio-L-lyxofuranoside structure. These results show unambigously that the use of Ph_3P/I_2/Imidazole is inappropriate to synthesize 4-thio-D-ribofuranose starting from D-ribose. However, the use of this reagent system instead of MesCl, NBu_4I, $BaCO_3$ reagents[3] was successful to achieve the intramolecular cyclisation of 2,3,5-tri-O-benzyl-L-lyxose dithiobenzylacetal, yielding 71% of the corresponding 4-thio-D-ribofuranoside derivative[3].

EXPERIMENTAL SECTION.

GENERAL METHODS.

^1H NMR and ^{13}C NMR spectra were determined with a BRUCKER AM 300 MHz or a BRUKER AC 250 MHz with tetramethylsilane as internal standard and chemical shift are quoted in ppm (s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, br = broad signal). Electron mass spectra (70 eV) were recorded on a JEOL JMS DX 300 mass spectrometer. Precoated MERCK Silica gel F_{254} plates were used for TLC. Column Chromatography was performed on MERCK silica gel (0.040-0.063 mm). All the solvants were distilled anhydrous according to the procedure given by D. D. PERRIN, and W. L. F. ARMAREGO, Purification of Laboratory Chemicals. Pergamon Press, London (1988). Methyl-2,3,5-tri-O-benzyl-D-ribofuranose, 2, was synthesized from D-ribose according to BARKER and FLETCHER Jr. procedure [8] in 80 % yield.

2,3,5-tri-O-benzyl-D-ribose dithiobenzylacetal **3**.

2 (4.34 g, 1 mmol) was stirred at 0° C with benzyl mercaptan (4.8 ml, 4.5 mmol) and boron trifluoride etherate (0.22 ml, 0.2 mmol). After 48 hrs continuous stirring, dithioacetal **3** (Rf = 0.46 in CH_2Cl_2 / MeOH : 99 / 1) was obtained. The reaction mixture was neutralized with a 5 % aqueous $NaHCO_3$ solution, diluted in methylene chloride, and extracted. The organic layer was dried over sodium sulfate and concentrated. The crude product applied on a silica gel column chromatography was eluted with CH_2Cl_2 / MeOH : 99 / 1. The appropriate fractions were combined and evaporated to give 0.487 g of **5** (yield = 75 %). MS: FAB>0 NBA m/z = 651 $[M+H]^+$. ^1H NMR (250MHz $CDCl_3$) δ = 3.61, (m, 3H, H_4, H_5, $H_{5'}$), 3.7, (m, 6H, -O-CH_2-Ph), 4.05, (m, 3H, H_1, H_2, H_3), 4.42-4.93, (m, 4H, -S-CH_2-Ph), 5.19, (d, 1H, OH), 7.11-7.72, (m, 25H, -O-CH_2-Ph).

Benzyl-2,3,5-tri-O-benzyl-1,4-dithio-L-lyxofuranose **4**.

A solution of the dithioacetal **3** (0.65 g, 1.0 mmol) in anhydrous tetrahydrofuran (13 ml) was treated at room temperature for 1 hr with triphenylphosphine (0.787 g, 3.0 mmol), iodine (0.634 g, 2.5 mmol) and imidazole (0.272 g, 4.0 mmol). The solution was finally filtered, then evaporated under reduced pressure. The crude product was applied on a silica gel (0.015-0.040 mm) column chromatography with hexane / dichloromethane : 70 / 30 as the eluant system to afford finally 0.385 g of pure **4** (Rf = 0.71 in CH_2Cl_2, yield 71 %). MS: FAB>0 NBA m/z = 543 $[M+H]^+$; 435 $[M+H-Ph-CH_2OH]^+$; 419 $[M+H-Ph-CH_2SH]^+$. ^1H NMR (250MHz $DMSOd_6$) δ = 3.51, (m, 1H, H_4), 3.75, (m, 2H, H_5, $H_{5'}$), 3.85, (s, 2H, -S-CH_2-Ph), 4.02, (dd, 1H, H_2, $J_{2,1}$ = 6.6, $J_{2,3}$ = 2.9), 4.32, (d, 1H, H_1, $J_{1,2}$ = 6.6), 4.38, (dd, 1H, H_3, $J_{3,4}$ = 3.2, $J_{3,2}$ = 3.0), 4.61, (m, 6H, -O-CH_2-Ph), 7.35, (m, 20H, -O-CH_2-Ph, -S-CH_2-Ph). ^{13}C NMR Decoupling ^1H (250MHz, $CDCl_3$) δ = 36.46, (s, 1C, C_5), 46.28, (s, 1C, C_4), 51.37, (s, C, C_1), 70.39-73.54, (m, 4C, CH_2), 79.07, (s, 1C, C_3), 86.92, (s, C, C_2), 127.07-129.32, (m, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$ aromatic), 137.82-138.24, (q, $C_{1'}$ aromatic).

2,3,5-tri-O-benzyl-4-O-mesyl-D-ribose dithiobenzylacetal **5** and Benzyl-2,3,5-tri-O-benzyl-1,4-dithio-L-lyxofuranoside **4**.

A solution of the dithioacetal **3** (0.836 g, 1.28 mmol) in anhydrous pyridine (20 ml) was treated slowly at 0°C with mesyl chloride (0.191 g, 1.67 mmol). The solution was stirred for 4 hrs until **3** had consumed to give **5** (Rf = 0.52 in CH_2Cl_2, MeOH - 995 : 5). To this reaction mixture was added barium carbonate (0.253 g, 1.28 mmol) and *tetra-*

butylammonium iodide (0.475 g, 1.28 mmol) and the dark yellow heterogenous solution was heated under reflux for 0.75 hr to give **4** (Rf = 0.71 in CH_2Cl_2). The reaction mixture was evaporated under reduced pressure, diluted with dichloromethane, washed with a 5 % aqueous $NaHCO_3$ solution and extracted. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was applied on a silica gel (0.015-0.040 mm) column chromatography with hexane / dichloromethane : 1 / 1 as the eluant system to afford finally 0.495 g of pure **4** (yield 71 %).

2,3,5-tri-O-benzyl-4-O-mesyl-D-ribose dithiobenzylacetal **5**.
MS: FAB>0 NBA m/z = 729 $[M+H]^+$; 633 $[M+H-CH_3SO_3H]^+$; 605 $[M+H-Ph-CH_2SH]^+$. ^1H NMR (250MHz $DMSOd_6$) δ = 3.12, (s, 3H, CH_3), 3.42, (m, 2H, H_5, $H_{5'}$), 3.71, (m, 3H, H_4, H_3 and H_2), 3.81, (m, 4H, -S-CH_2-Ph), 3.95, (m, 1H, H_1), 4.35-4.99, (m, 6H, -O-CH_2-Ph), 7.25, (m, 25H, -O-CH_2-Ph and -S-CH_2-Ph).

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(11) Benzyl-2, 3, 5-tri-O-benzyl-1, 4-dithio-D-ribofuranoside exhibited a wide NOE on the H_2, H_5 and $H_{5'}$ signals on irradiation of H_3 of the sugar ring but no enhancement of H_4. This result clearly shows that H_2, H_5, $H_{5'}$ and H_3 are on the same side of the sugar plane establishing thereby D-ribose structure.

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