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

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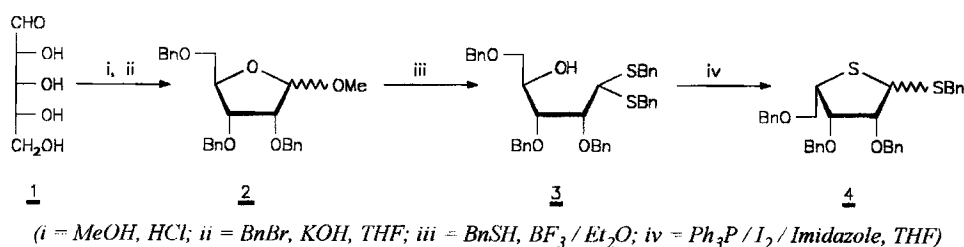
Abstract:

We demonstrate that the procedure of Huang and Hui⁽⁴⁾, applied to the D-ribose and involving $\text{Ph}_3\text{P}/\text{I}_2$ /Imidazole reagent system do not lead to the desired 4-thio-D-ribofuranoside derivative but gives its diastereoisomer 4-thio-L-lyxofuranoside derivative **4**.

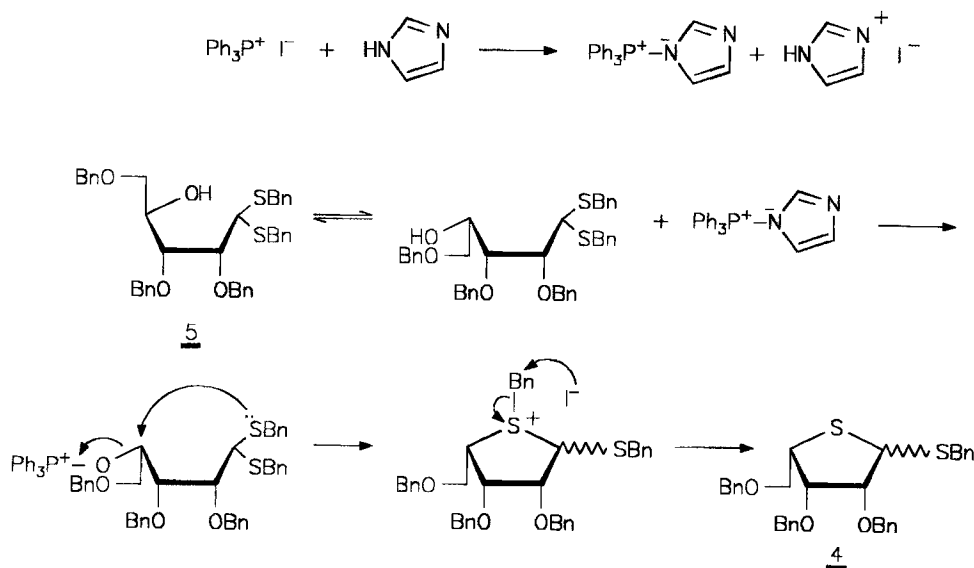
Our research team has developed for several years a new series of sugar-modified oligonucleotides: the 4'-thio- β -D-oligoribonucleotides (**4'-S-RNA**) in which the annular oxygen atom of the furanose moiety has been replaced with a sulfur atom, the base keeping the natural β configuration (1,2). 4'-S-RNA assembling requires suitable preparation of the corresponding 4'-thio- β -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 $\text{Ph}_3\text{P} / \text{I}_2 / \text{Imidazole}$ reagent system.

This procedure, making use of two consecutive $\text{S}_\text{N}2$ 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 $\text{BF}_3 / \text{Et}_2\text{O}$ (9, 10) to give the dithiobenzylacetal **3** in 75 % yield. **3** was then reacted with $\text{Ph}_3\text{P} / \text{I}_2 / \text{Imidazole}$ to afford **4** in 71 % yield.



Scheme 1

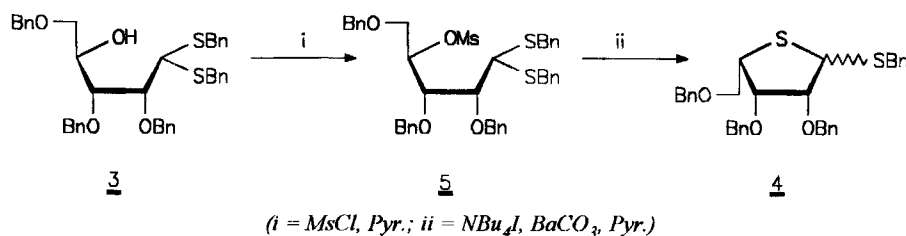


Scheme 2

Since we previously synthesized benzyl-2,3,5-tri-O-benzyl-1,4-dithio-D-ribofuranoside (**3**) and proved unambiguously 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



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 different routes exhibit the same physico-chemical properties which corroborate the 4-thio-*L*-lyxofuranoside structure. These results show unambiguously that the use of $\text{Ph}_3\text{P/I}_2/\text{Imidazole}$ 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 solvents 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 CH₂Cl₂ / MeOH : 99 / 1) was obtained. The reaction mixture was neutralized with a 5 % aqueous NaHCO₃ 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 CH₂Cl₂ / 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 CDCl₃) δ = 3.61, (m, 3H, H₄, H₅, H_{5'}), 3.7, (m, 6H, -O-CH₂-Ph), 4.05, (m, 3H, H₁, H₂, H₃), 4.42-4.93, (m, 4H, -S-CH₂-Ph), 5.19, (d, 1H, OH), 7.11-7.72, (m, 25H, -O-CH₂-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 CH₂Cl₂, yield 71 %). MS: FAB>0 NBA m/z = 543 [M+H]⁺; 435 [M+H-Ph-CH₂OH]⁺; 419 [M+H-Ph-CH₂SH]⁺. ¹H NMR (250MHz DMSO-d₆) δ = 3.51, (m, 1H, H₄), 3.75, (m, 2H, H₅, H_{5'}), 3.85, (s, 2H, -S-CH₂-Ph), 4.02, (dd, 1H, H₂, J_{2,1} = 6.6, J_{2,3} = 2.9), 4.32, (d, 1H, H₁, J_{1,2} = 6.6), 4.38, (dd, 1H, H₃, J_{3,4} = 3.2, J_{3,2} = 3.0), 4.61, (m, 6H, -O-CH₂-Ph), 7.35, (m, 20H, -O-CH₂-Ph, -S-CH₂-Ph). ¹³C NMR Decoupling ¹H (250MHz, CDCl₃) δ = 36.46, (s, 1C, C₅), 46.28, (s, 1C, C₄), 51.37, (s, C, C₁), 70.39-73.54, (m, 4C, CH₂), 79.07, (s, 1C, C₃), 86.92, (s, C, C₂), 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 CH₂Cl₂, 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** ($R_f = 0.71$ 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 $^+$ NBA $m/z = 729$ $[\text{M}+\text{H}]^+$; 633 $[\text{M}+\text{H}-\text{CH}_3\text{SO}_3\text{H}]^+$; 605 $[\text{M}+\text{H}-\text{Ph}-\text{CH}_2\text{SH}]^+$. ^1H NMR (250MHz DMSO-d_6) $\delta = 3.12$, (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, $-\text{S}-\underline{\text{CH}_2}-\text{Ph}$), 3.95, (m, 1H, H_1), 4.35-4.99, (m, 6H, $-\text{O}-\underline{\text{CH}_2}-\text{Ph}$), 7.25, (m, 25H, $-\text{O}-\text{CH}_2-\underline{\text{Ph}}$ and $-\text{S}-\text{CH}_2-\underline{\text{Ph}}$).

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