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Synthesis of 1-Deoxy-4-thio-D-ribose starting from Thiophene-2-carboxylic acid

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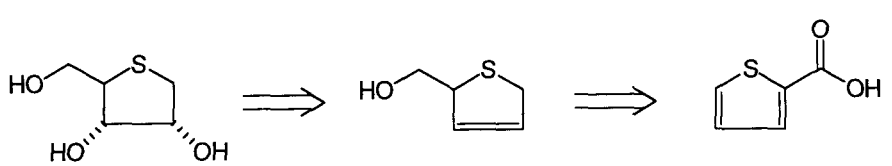
Abstract: The *de novo* synthesis of 1-deoxy-4-thio-D-ribose starting from thiophene-2-carboxylic acid is described. The key step is the cis-dihydroxylation of *S*-2-acetoxy-2,5-dihydrothiophene, which is obtained by enzymatic alcoholysis. © 1997 Elsevier Science Ltd.

The replacement of the ring oxygen of a pyranose or furanose system by sulfur[1] leads to sugar analogues, commonly called thiasugars,[2] which often exhibit interesting biological activities. Whereas numerous different synthetic routes to 5-thiopyranoses are well established,[3] easy and flexible approaches to 4-thiofuranose systems are still needed because such compounds could be used as sugar mimics, for instance, in nucleoside analogues. Most of the known routes to these compounds are starting from the chiral pool,[4,5,6] and to our knowledge de novo syntheses to 1-deoxy-4-thio-furanoses have not been reported in the literature.

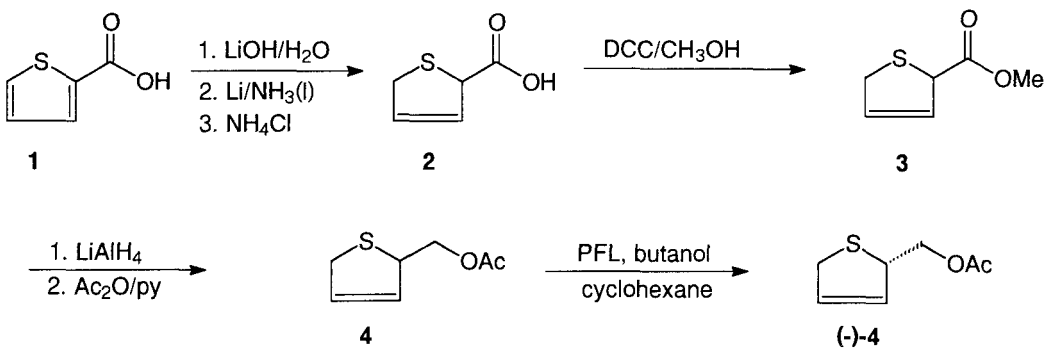
Following the retrosynthetic analysis shown in Scheme 1, a short route to 1-deoxy-4-thio-D-ribose starting from thiophene-2-carboxylic acid is presented in this paper. Until now, such an approach has not been used for the synthesis of 4-thiofuranoses although a high degree of diastereoselection is expected in the cis-dihydroxylation step[7] of the dihydrothiophene intermediate and other functionalisations of the double bond are feasible.



Scheme 1

Results and Discussion

2,5-Dihydrothiophene-2-carboxylic acid (**2**) was synthesised by Birch reduction of thiophene-2-carboxylic acid (**1**). Modification of the procedure from Joullie et. al.[8] gave 2,5-dihydrothiophene-2-carboxylic acid (**2**) in 75 % yield after recrystallisation from hexane. Instead of using diazomethane, as has been described,[9] the esterification of the carboxylic acid **2** was carried out with DCC in ether using methanol as the alcohol component. Reduction of the methyl ester **3** gave 2-acetoxymethyl-2,5-dihydrothiophene (**4**) after acetylation (Scheme 2).



Scheme 2

For the enzymatic resolution of **4** lipase-catalysed hydrolysis and alcoholysis as well as enzymatic acetylation of the corresponding alcohol have been investigated. As we have already reported in a preliminary communication,[10] the best results are being obtained in alcoholysis catalysed by lipase from *Pseudomonas fluorescens* [PFL] with butanol in cyclohexane to give **(-)-4** with 93 % ee in 31 % yield. Interestingly, with this kind of a primary alcohol enzymatic alcoholysis is much better than hydrolysis or acetylation for resolution.[11] The absolute configuration of the remaining (-)-2-acetoxymethyl-2,5-dihydrothiophene [**(-)-4**] could be unambiguously established by comparison with independently synthesised material. The preparation of **(-)-4** started by DCC-esterification of 2,5-dihydrothiophene-2-carboxylic acid (**2**) with *R*-pantholactone. The diastereomeric esters could be separated by HPLC, the one with the lower melting point was shown to possess the *S,R*-configuration **7** by X-ray crystallography.[10] A drawing of the structure is shown in Figure 1. The product obtained after reduction of *S,R*-**7** with $LiAlH_4$ and acetylation proved to be identical with **(-)-4** derived from the enzymatic alcoholysis, according to their spectra, their GC retention times and their specific rotation values.

Despite the fact that a lot of methods for the oxidation of double bonds are known, the functionalisation of the key intermediate **(-)-4** was problematical due to the thioether unit, which can be easily oxidised leading to a sulfoxide intermediate that is prone to aromatisation.[12]

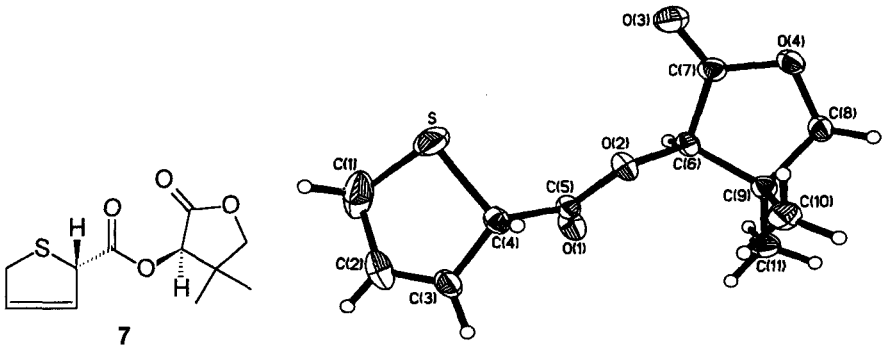


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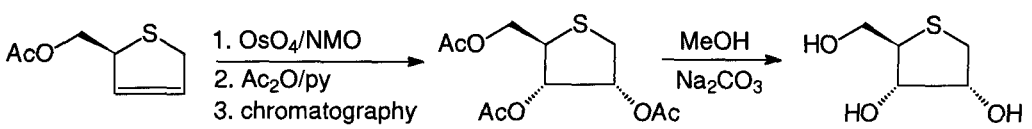
Figure 1

Treatment of the (-)-acetate **(-)-4** with OsO_4/NMO in water/acetone proved to be the best method for the cis-dihydroxylation; at room temperature even on the long reaction time necessary for the complete oxidation of the double bond generation of the sulfoxide could be reduced.[13] After acetylation the triacetate **5** was obtained in 90 % de. By chromatography on silica gel with hexane/ethyl acetate **(+)-5** could be isolated diastereomerically pure in 43 % yield (Scheme 3).



(-)-4 **(+)-5** **(+)-6**

Scheme 3

The use of $KMnO_4/H_2O$[14] led also to the cis-diol, but with a lower de-value whereas $KMnO_4/CH_2Cl_2$ at lower temperature[15] gave aromatisation. Use of $RuCl_3/NaIO_4$[16] resulted in unidentified oxidation and decomposition products. Several other attempts to functionalise only the double bond in **(-)-4** were not successful, for instance treatment with peroxy acids gave the corresponding sulfone and halo- or metallocyclisation[17] using NIS, $Pb(OAc)_4$ or PhSeCl led to decomposition or aromatisation.

Deprotection of **(+)-5** with $MeOH/Na_2CO_3$ led cleanly to (+)-1-deoxy-4-thio-D-ribose [**(+)-6**] in 90 % yield as an oil. The enantiomeric excess was determined to be 92 % ee by comparison with the specific rotation value of (-)-1-deoxy-4-thio-L-ribose, which has been recently synthesised by us starting from D-arabitol.[6]

Conclusion

As a result of our studies[6,10] both enantiomers of the formerly unknown 1-deoxy-4-thio-ribose are now readily available. Besides the importance of **(+)-6** as a sugar mimic, it should also be a precursor for the synthesis of 4'-thionucleosides[18] as the introduction of a base, after oxidation of the anomeric center, has been described in the literature.[19]

Experimental

General. Dicyclohexylcarbodiimide (DCC), D-(-)-2-hydroxymethyl-3,3-dimethyl-γ-butyrolactone, N-methyl-morpholine-N-oxide (NMO) and butanol were purchased from Fluka. Lithium thiophene-2-carboxylate was prepared according to literature.[20] Organic solvents were distilled before use or, if otherwise noted, dried according to typical procedures. Organic extracts were dried over Mg_2SO_4. All reactions were monitored by TLC prior to work-up. Solvents were removed with a rotary evaporator (T<40 °C). TLC was run on silica plates 60 F_{254} (Merck) and visualised with UV fluorescence (254 and 366 nm) and/or molybdatophosphoric acid.[21] ^1H and ^{13}C NMR were recorded on a Bruker ARX 400, specific rotation values on a Perkin-Elmer Polarimeter 241, melting points on a Büchi 510 and mass spectra on a Varian MAT 311. For gas chromatography Shimadzu GC-14A was used. Conversion was determined by GC analysis using SE-52 and enantiomeric excess using FS-CYCLODEX beta-I/P. RP-18 was used for the HPLC separation of **7** / **8**. Chromatography was performed on Merck Kieselgel 60 (40-63 μm).

2,5-Dihydrothiophene-2-carboxylic acid (2)

Reduction of lithium thiophene-2-carboxylate (35.0 g, 260 mmol) was carried out with lithium (4.4 g, 630 mmol), which was dissolved in liquid ammonia (700 mL) at -75 °C. After 6-7 min NH_4Cl (30 g) was added to the blue solution and the solvent was evaporated. The yellow solid was dissolved in conc. HCl

(300 mL), extracted with $CHCl_3$, the combined organic layer dried and evaporated. Recrystallisation from hexane afforded the title compound as a colorless solid (25.3 g, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71-3.85 (m,2H), 4.73-4.76 (m,1H), 5.77-5.80 (m,1H), 6.00-6.03 (m,1H), 11.57 (COOH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.8(t), 55.8(d), 127.1(d), 132.7(d), 178.3(s); mp: 69-71 °C.[8]

Methyl-2,5-dihydrothiophene-2-carboxylate (3)

2,5-Dihydrothiophene-2-carboxylic acid (2) (13.0 g, 100 mmol) was dissolved in dry ether (300 mL) under argon atmosphere and DCC (21.0 g, 100 mmol) was added. After 30 min dry methanol (10 mL) was added and the reaction mixture was stirred for 30 min. After the addition of hexane (250 mL), the precipitate was filtered off over Celite. The organic layer was dried and evaporated to give the title compound as a light yellow liquid (13.0 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s,3H), 3.73-3.83 (m,2H), 4.72-4.75 (m,1H), 5.77-5.79 (m,1H), 5.97-6.00 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.8(t), 53.0(q), 55.8(d), 127.5(d), 132.8(d), 172.7(s).[9]

2-Acetoxymethyl-2,5-dihydrothiophene (4)

A solution of methyl-2,5-dihydrothiophene-2-carboxylate (3) (14.4 g, 100 mmol) in dry ether (150 mL) was added dropwise to a suspension of $LiAlH_4$ (3.80 g, 100 mmol) in dry ether (300 mL) at 0 °C under argon atmosphere. After 1.5 h water was added and the mixture extracted with ether. The combined organic layer was dried and evaporated. The yellow liquid was treated with pyridine (150 mL) and acetic acid anhydride (100 mL) at 0 °C. After 2 h the reaction mixture was poured into precooled 6N HCl and ether. After extraction with ether, the combined organic extracts were sequentially washed with $NaHCO_3$ and brine, dried and evaporated. Kugelrohr distillation gave the title compound as a yellow liquid (12.0 g, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s,3H), 3.73-3.78 (m,2H), 4.11-4.18 (m,2H), 4.42-4.44 (m,1H), 5.78-5.81 (m,1H), 5.92-5.95 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2(q), 39.0(t), 54.1(d), 68.8(t), 129.9(d), 130.7(d), 171.0(s); bp: 95 °C ($3*10^{-2}$ mbar).

***S*-(-)-2-Acetoxymethyl-2,5-dihydrothiophene [(-)-4]**

A mixture of (±)-2-acetoxymethyl-2,5-dihydrothiophene (4) (500 mg, 3.16 mmol), cyclohexane (20 mL), butanol (2.33 g, 31.6 mmol) and 150 mg lipase from *Pseudomonas fluorescens* were stirred at room temperature until 63 % conversion (≈73 h, monitored by GC) was reached. After filtration over Celite and evaporation of the solvent, the crude product was chromatographed on silica gel using cyclohexane ethyl acetate 8:2 to give the title compound as a colorless liquid (133 mg, 31 %). The enantiomeric excess was determined by chiral GC to be 93 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s,3H), 3.73-3.78 (m,2H), 4.11-

4.18 (m,2H), 4.42-4.44 (m,1H), 5.78-5.81 (m,1H), 5.92-5.95 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2(q), 39.0(t), 54.1(d), 68.8(t), 129.9(d), 130.7(d), 171.0(s); $[\alpha]^{20}$ = -57.4 (c 1.75, $CHCl_3$); ms (70 eV): 158 [M^+]; $C_7H_{10}O_2S$ (158.21): calcd. C: 53.14, H: 6.37, found C: 52.47, H: 6.03.

(+)-Tri-*O*-acetyl-1-deoxy-4-thio-D-ribose [(+)-5]

A mixture of *S*-(-)-2-acetoxymethyl-2,5-dihydrothiophene **[(-)-4]** (474 mg, 3 mmol), NMO (704 mg, 6 mmol), acetone (8 mL) and OsO_4 (8 mL, 0.06 mmol, solution in water) was stirred for 20 d at room temperature. After addition of $Na_2S_2O_3$, the black reaction mixture was evaporated to dryness. To the crude product acetic acid anhydride (3 mL) and pyridine (5 mL) was added at 0 °C and stirred overnight. The reaction mixture was poured into precooled 6N HCl and ether. After extraction with ether, the combined organic extracts were sequentially washed with $NaHCO_3$ and brine, dried and evaporated. Chromatography on silica gel using cyclohexane ethyl acetate 85:15 gave the title compound as a colorless oil (356 mg, 43 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.98 (A<u>B</u>X, 1H, ^{2}J=11.4Hz ^{3}J=5.5Hz, CH_2S), 3.20 (A<u>B</u>X, 1H, ^{2}J=11.4Hz ^{3}J=5.1Hz, CH_2S), 3.69-3.72 (m, 1H, CHS), 4.18 (<u>A</u>BX, 1H, ^{2}J=11.6Hz ^{3}J=6.1Hz, CH_2O), 4.27 (A<u>B</u>X, 1H, ^{2}J=11.6Hz ^{3}J=6.4Hz, CH_2O), 5.27-5.29 (m, 1H, CH<u>CH</u>CHS), 5.49-5.53 (m, 1H, <u>CH</u>CHCHS); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6(q), 19.7(q), 19.8(q), 29.9(t), 44.7(d), 63.7(t), 72.4(d), 74.4(d), 168.9(s), 169.0(s), 169.5(s); $[\alpha]^{20}$ = +64.2 (c 0.75 $CHCl_3$); ms (70 eV): 276 [M^+]; $C_{11}H_{16}O_6S$ (276.30): calcd. C: 47.82, H: 5.84, found C: 48.13, H: 5.58.

(+)-1-Deoxy-4-thio-D-ribose [(+)-6]

A mixture of (+)-tri-*O*-acetyl-1-deoxy-4-thio-D-ribose **[(+)-5]** (138 mg, 0.5 mmol) and methanol / Na_2CO_3 (8 mL) was stirred for 16 h at room temperature. The solvent was removed under reduced pressure, and the crude product was filtered over silica gel using CH_3OH-CH_2Cl_2 9:1 to give the title compound as an colorless oil (67 mg, 90 %). ^{1}H NMR (400 MHz, D_2O): δ = 2.77 (<u>A</u>BX, 1H, ^{2}J=11.2 Hz ^{3}J=4.2 Hz, CH_2S), 3.05 (A<u>B</u>X, 1H, ^{2}J=11.2 Hz ^{3}J=4.9 Hz, CH_2S), 3.34-3.41 (m, 1H, CHS), 3.64 (<u>A</u>BX, 1H, ^{2}J=11.3 Hz ^{3}J=6.9 Hz, CH_2O), 3.83 (A<u>B</u>X, 1H, ^{2}J=11.3 Hz ^{3}J=5.2 Hz, CH_2O), 4.02-4.05 (m, 1H, CH<u>CH</u>CHS), 4.34-4.37 (m, 1H, <u>CH</u>CHCHS); ^{13}C NMR (100 MHz, D_2O): δ = 32.2(t), 50.4(d), 63.3(t), 74.3(d), 76.3(d); $[\alpha]^{20}$ = +67.4 (c 0.25 H_2O); ms (70 eV): 150 [M^+]; $C_5H_{10}O_3S$ (150.19): calcd. C: 39.99, H: 6.71, found C: 39.71, H: 6.59.

2,5-Dihydrothiophene-2-carboxylic acid pantholactone ester (7) / (8)

2,5-Dihydrothiophene-2-carboxylic acid **(2)** (130 mg, 1 mmol) was dissolved in dry ether (7 mL) under argon atmosphere and DCC (206 mg, 1 mmol) was added. After 15 min D-(-)-2-hydroxymethyl-3,3-

dimethyl-γ-butyrolactone (130 mg, 1 mmol) was added, and the reaction mixture was stirred for 30 min. The precipitate was filtered off over Celite. The organic layer was dried and evaporated to give a colorless solid. The diastereomeric esters **7** / **8** were separated by HPLC using H_2O-CH_3OH 1:1 to give the *S,R*-diastereomer **7** (61 mg, 25 %) and the *R,R*-diastereomer **8** (63 mg, 26 %). *S,R*-**7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s,3H), 1.26 (s,3H), 3.82-3.95 (m,2H), 4.04-4.10 (m,2H), 4.93-4.96 (m,1H), 5.38 (s,1H), 5.91-5.94 (m,1H), 6.11-6.14 (m,1H); ^{13}C NMR (100 MHz $CDCl_3$): δ = 19.9(q), 23.3(q), 39.6(t), 40.6(s), 55.8(d), 75.8(d), 76.3(t), 126.8(d), 132.6(d), 170.8(s), 171.9(s); ms (70 eV): 242 [M^+]; mp: 110-112 °C; $C_{11}H_{14}O_4S$ (242.29): calcd. C: 54.53, H: 5.82, found C: 54.37, H: 5.80. The sample for the X-ray analysis was crystallised from diethyl ether. Crystallographic data $C_{11}H_{14}O_4S$, M = 242, orthorhombic, space group $P2_12_12_1$ (No.19), a = 6.4553(6), b = 10.510(1), c = 17.901(2) Å, V = 1214.5(2) Å^3, Z = 4, d_c = 1.325 g/cm; CuK_α radiation (24 °C); reflections collected 5050, unique reflections 2252, observed reflections 2018 [$I > 2\sigma(I)$], R1-index 0.0415 [all data].[22] *R,R*-**8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s,3H), 1.26 (s,3H), 3.83-3.97 (m,2H), 4.00-4.11 (m,2H), 4.94-4.97 (m,1H), 5.40 (s,1H), 5.91-5.94 (m,1H), 6.13-6.17 (m,1H); ^{13}C NMR (100 MHz $CDCl_3$): δ = 20.0(q), 23.2(q), 39.6(t), 40.7(s), 54.8(d), 75.7(d), 75.8(t), 126.8(d), 132.7(d), 171.3(s), 172.2(s); ms (70 eV): 242 [M^+]; mp: 135-137 °C; $C_{11}H_{14}O_4S$ (242.29): calcd. C: 54.53, H: 5.82, found C: 54.41, H: 5.76.

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sulfur or a nitrogen atom. See also Lehmann, J. *Kohlenhydrate: Chemie und Biologie*; 2.ed. Thieme: Stuttgart, New York, 1996, 130.

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