Synthesis of 2′,3′-Dithiouridine

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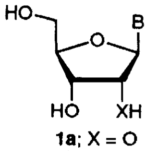
The synthesis of 2′,3′-dithiouridine **2**, starting from uridine, is described.

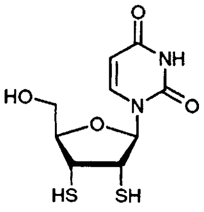
A particularly fundamental and interesting nucleoside modification is the replacement of the secondary 2′-hydroxy function of a ribonucleoside **1a** by a thiol group (as in **1b**). We have recently developed procedures[1,2] for the synthesis of the latter 2′-thioribonucleosides **1b** which take into account their tendency to undergo oxidative dimerization.[1] To the best of our knowledge, there is no previous report in the literature relating to the synthesis of a 2′,3′-dithioribonucleoside[3] (such as **2**), that is a ribonucleoside analogue in which both of the secondary hydroxy functions have been replaced by thiol groups. We now report the synthesis of 2′,3′-dithiouridine **2** starting from uridine **3**.

Uridine **3** was first converted (Scheme 1) *via* its 2′,3′-di-*O*-mesyl-5′-*O*-trityl derivative **4** into the corresponding 2′,3′-*lyxo*-epoxide **5** in 87% overall yield for the three steps (reactions i–iii). The latter compound **5** was then allowed to react with an excess of the sodium salt of 4-methoxybenzyl mercaptan in *N*,*N*-dimethylacetamide (DMA) solution at 100 °C to give a *ca.* 1 : 2 mixture of the isomeric thioethers **6** and **7** in 79% combined yield. No attempt was made to separate the thioethers **6** and **7** which were then subjected to a three-step process (mesylation, further reaction with the sodium salt of 4-methoxybenzyl mercaptan, followed by detritylation; reactions v, iv and vi, respectively) to give the bis(thioether) **8** as a crystalline solid, mp 126–127 °C, in 39% overall yield.† No isomeric bis(thioether) was detected in the products. In the course of this work, we have found that the acid-catalysed reaction between 4-methoxybenzyl thioethers and 2-nitrobenzenesulfenyl chloride proceeds with much greater facility than the corresponding reaction with *tert*-butyl thioethers.[1,4] Thus when the 5′-*O*-benzoyl derivative of the bis(thioether) **8** was treated (reaction viii) with 5.0 mol. equiv. of 2-nitrobenzenesulfenyl chloride in acetic acid—dichloromethane at 0 °C for 4 h, the bis(disulfide) **9** was obtained in 92.5% isolated yield. Treatment of the latter compound **9** with *ca.* 3.5 mol equiv. each of triphenylphosphine[2,5] and 9-phenylxanthen-9-ol (PxOH) in acetic acid–water (99 : 1 v/v) at 60 °C (reaction ix) followed by debenzoylation (reaction x) gave the bis(9-phenylxanthen-9-yl) derivative **10** of 2′,3′-dithiouridine **2** as a crystalline solid, mp 195–198 °C in *ca.* 85% overall yield for the two steps. When compound **10** was heated with pyrrole in glacial acetic acid solution[1] at 75 °C (reaction xi), 2′,3′-dithiouridine **2** was obtained and isolated as colourless needles, mp 131–132 °C, in 68% yield.

2′,3′-Dithiouridine **2** reacted readily with 2,2-dimethoxypropane in the presence of a catalytic quantity of toluene-4-sulfonic acid monohydrate in dry acetonitrile to give its 2′,3′-*S*-isopropylidene derivative **11** which was isolated as a colourless crystalline solid, mp 158–160 °C, in 79% yield. 2′,3′-Dithiouridine **2** also reacted readily both with methyl iodide and allyl bromide in the presence of *N*,*N*-(diisopropyl)ethylamine in THF solution to give the 2′,3′-di-*S*-methyl and -allyl derivatives **12a** and **12b**, respectively. The latter com-



1a; X = O
b; X = S



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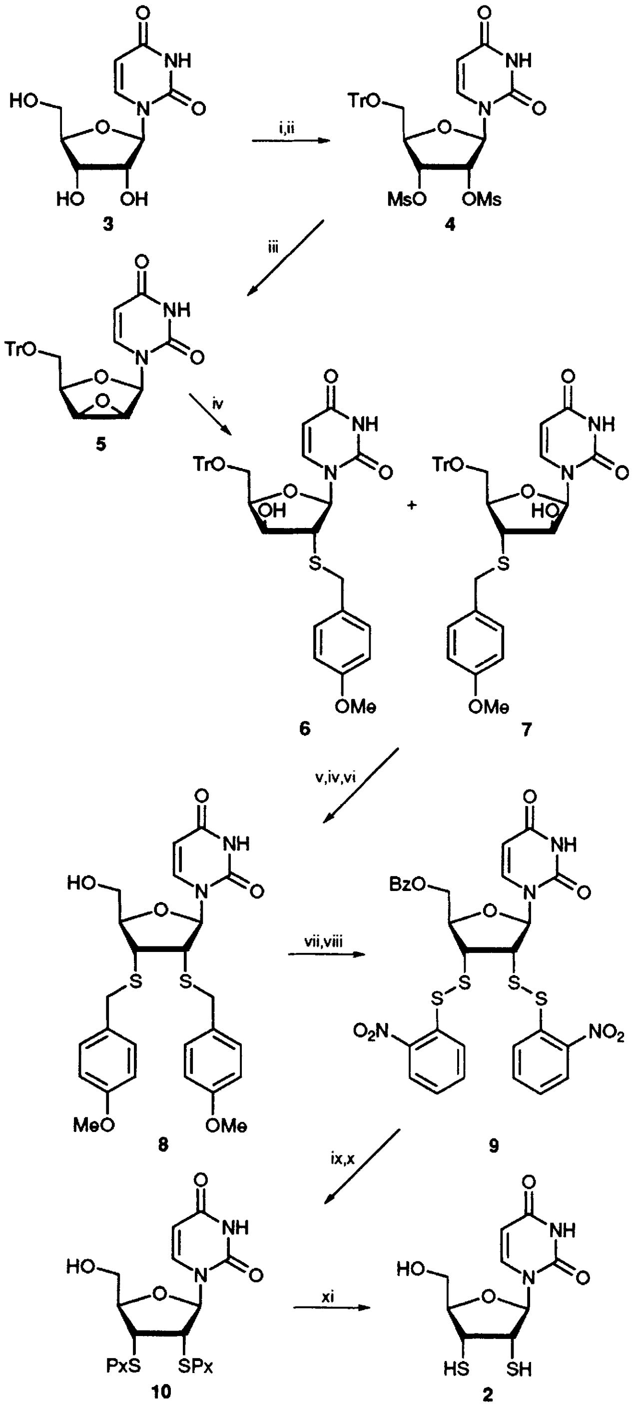
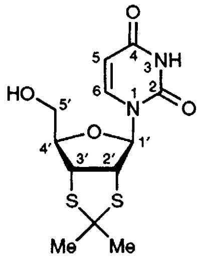


Scheme 1 *Reagents and conditions*: i, TrCl, C_5H_5N, 100 °C, 2 h; ii, MsCl, C_5H_5N, <5 °C, 4 h; iii, 1.0 mol dm^{-3} aq. NaOH–dioxane (1 : 9 v/v), reflux, 2 h; iv, 4-$(MeO)C_6H_4{\cdot}CH_2SH$, NaH, DMA (stirred together at 0 °C before addition of substrate), 100 °C, 1 h; v, MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min; vi, CF_3CO_2H, pyrrole, CH_2Cl_2, room temp., 10 min; vii, BzCl, C_5H_5N, 0 °C, 30 min; viii, 2-$(O_2N)C_6H_4SCl$, AcOH–CH_2Cl_2 (1 : 1 v/v), 0 °C, 4 h; ix, Ph_3P, PxOH, AcOH–H_2O (99 : 1 v/v), 60 °C, 30 min; x, NaOMe, MeOH, CH_2Cl_2, room temp., 10 min; xi, pyrrole, AcOH, 75 °C, 2 h. Tr = Ph_3C; Ms = CH_2SO_2; Px = 9-phenylxanthen-9-yl.



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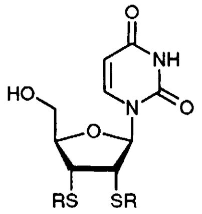

12a; R = Me
b; R = CH_2–CH=CH_2

pounds were isolated as colourless crystalline solids (mps 159–160 and 93 °C, respectively) in 91 and 92% yield. The structure of 2′,3′-dithiouridine **2** is based firmly on microanalytical data, NMR (^{1}H and ^{13}C) spectroscopic data,‡ and on its method of preparation. As compound **8** was the only bis(thioether) obtained when a mixture of the monothioethers **6** and **7** was subjected to the reaction sequence indicated (Scheme 1, reactions v, iv and vi), it would seem to be reasonable to assign the *ribo*-configuration to it. Finally, it is clear from an examination of molecular models that only *cis*-2′,3′-dithiols can give rise to cyclic *S*-isopropylidene derivatives. The possibility that compound **11** belongs to the *lyxo*-series can be excluded on the basis of NOE experiments carried out with a $(CD_3)_2SO$ solution of substrate: irradiation at δ 7.95 (H-6) led to a medium positive NOE effect at δ 4.64 (H-2′) and a small positive NOE effect at δ 4.41 (H-3′).

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Footnotes

† The bis(thioether) **8** was also obtained, albeit in only 8.5% yield, when 2′,3′-di-*O*-mesyl-5′-*O*-trityluridine **4** was allowed to react with the sodium salt of 4-methoxybenzyl mercaptan in DMA solution at 100 °C and the products were then treated wih trifluoroacetic acid and pyrrole in dichloromethane solutions at room temp. (Scheme 1, reaction vi). However, an overall yield of 8.5% for a four-step process would appear to compare unfavourably with an overall yield of 27% for a seven-step process (Scheme 1).

‡ 2′,3′-Dithiouridine **2**: A satisfactory elemental analysis was obtained; $\delta_H[(CD_3)_2SO$, 360 MHz] 3.02 (2 H, br.s), 3.64 (2 H, m), 3.76 (1 H, m), 3.83 (1 H, dd, *J* 4.4 and 6.7 Hz), 3.98 (1 H, m), 5.28 (1 H, t, *J* 5.3 Hz), 5.62 (1 H, d, *J* 8.1 Hz), 5.88 (1 H, d, *J* 4.3 Hz), 8.00 (1 H, d, *J* 8.1 Hz), 11.36 (1 H, br.s); $\delta_C[(CD_3)_2SO$, 90.6 MHz] 40.0, 47.4, 59.7, 86.6, 90.3, 101.4, 140.1, 150.6, 163.2.

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