

Efficient Synthesis of 2-Deoxy L-Ribose from L-Arabinose: Mechanistic Information on the 1,2-Acyloxy Shift in Alkyl Radicals

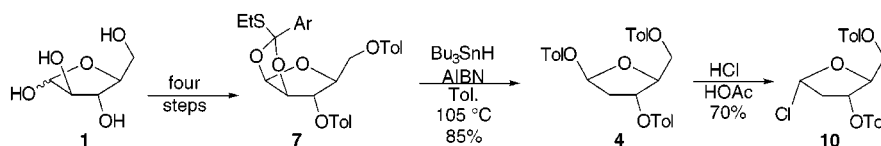
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ABSTRACT



Conversion of the inexpensive L-arabinose **1** into the ethylthio ortho ester **7** followed by generation of the dialkoxyalkyl radical **III** produces the desired 2-deoxy-L-ribose triester **4** in excellent overall yield. It has been shown that the similar dialkoxyalkyl radical **IV** is not an intermediate in the 1,2-acyloxy shift of anomeric radical **I**.

L-Nucleosides and their analogues have become useful agents for the treatment of viral diseases due in part to their good antiviral activity and generally low toxicity.¹ Either normal (L-RNA) or 2'-deoxy (L-DNA) L-nucleosides may also be of value in antisense oligonucleotide therapy as materials to bind pieces of D-m-RNA.² For these reasons, new methods for the preparation of L-nucleoside analogues and the carbohydrates from which they are derived are an important synthetic goal. We recently reported an efficient synthesis of L-ribose and 2-deoxy L-ribose from D-ribose and a fast preparation of the latter from L-arabinose³ as well as a

conceptually different approach to prepare 2-deoxy L-ribose from penta-1,4-dien-3-ol.⁴ We have reexamined the first approach and report herein a very efficient synthesis of 2-deoxy L-ribose which uses a radical rearrangement of an unusual cyclic monothio ortho ester.^{5,6} We also offer experimental evidence that the 1,2-acyloxy shift in alkyl radicals, first reported by Surzur⁷ and Tanner,⁸ and used extensively in carbohydrates by Giese,⁹ does not proceed via a cyclic dialkoxyalkyl radical.

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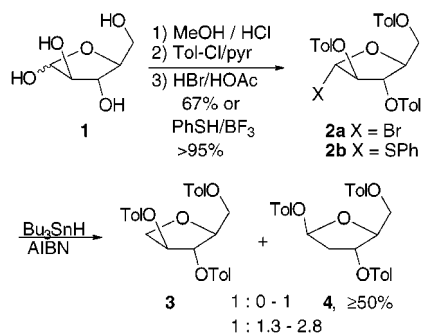
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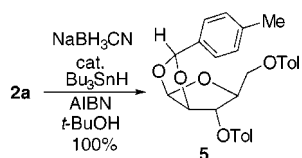
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To improve our earlier synthesis,⁴ we first prepared methyl L-arabinofuranoside. After esterification with toluoyl chloride to facilitate the later preparation of the desired α -chloride, we converted it to the anomeric bromide **2a** and thioether **2b** in 67% and 95% yields, respectively. However, radical-



promoted rearrangement—reduction of either **2a** or **2b** with tributyltin hydride and AIBN gave a mixture of the undesired “direct reduction” 1-deoxy product **3** and the desired 2-deoxy sugar **4**. This ratio varied widely depending on conditions, but was never better than 2.8:1 in favor of the rearranged product **4**, which was isolated in about 50% yield at best.¹⁰ Presumably the 1,2-acyloxy shift of the initially formed radical I to give II is slower in the arabino than in the ribo series (perhaps due to steric acceleration of the ribo case). Thus the radical I is reduced competitively with its rearrangement to II (and reduction to **4**). Hence we used the Stork catalytic hydride conditions,¹¹ e.g., catalytic Bu_3SnH with stoichiometric sodium cyanoborohydride, with, however, an unusual result, namely the complete formation of the 1,2-acetal **5** (the same product was formed without the tin reagent present indicating an ionic mechanism). This

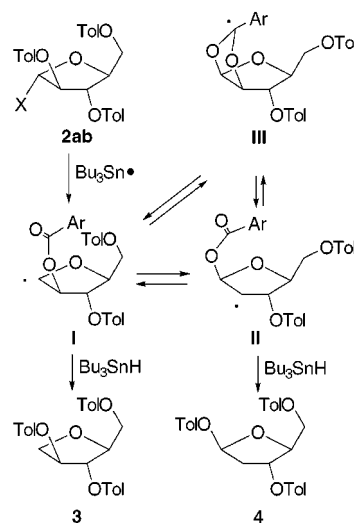


selective formation of a 1,2-acetal in carbohydrates, while a very useful synthetic transformation in itself, provided a possible solution to the problem of radical reduction due to a sluggish rearrangement. We hypothesized that if one prepared the dialkoxyalkyl radical III, it would open to the more stable ester radicals. Molecular mechanics calculations (PM3) indicated that II was ~ 3 kcal/mol more stable than I (the extensive results of Giese⁹ also supported this energy difference). If one generated III from a readily available precursor, it should open selectively to give II which would be reduced to **4**. It is also possible that the mechanism for the rearrangement of I to II proceeds via III. However,

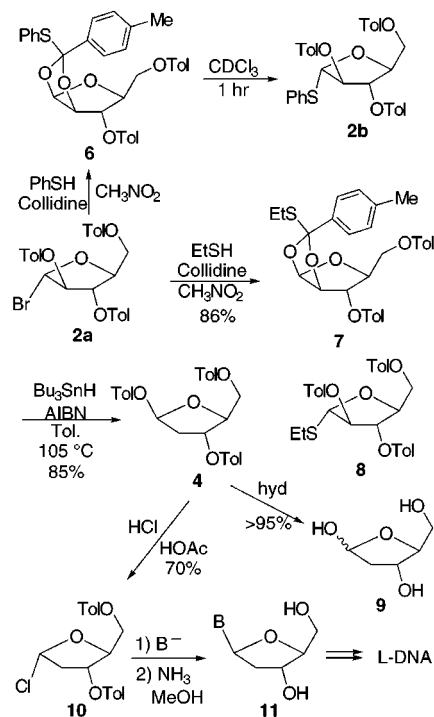
(10) Recently there have been reports of the use of Lewis acids to accelerate these rearrangements, for example: Lacôte, E.; Renaud, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2259. Also there has been a theoretical study on the effectiveness of protic acids for this acceleration: Zipse, H. *J. Am. Chem. Soc.* **1997**, *119*, 1087.

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irrespective of the mechanism of the rearrangement, generation of III should produce the desired product **4**.

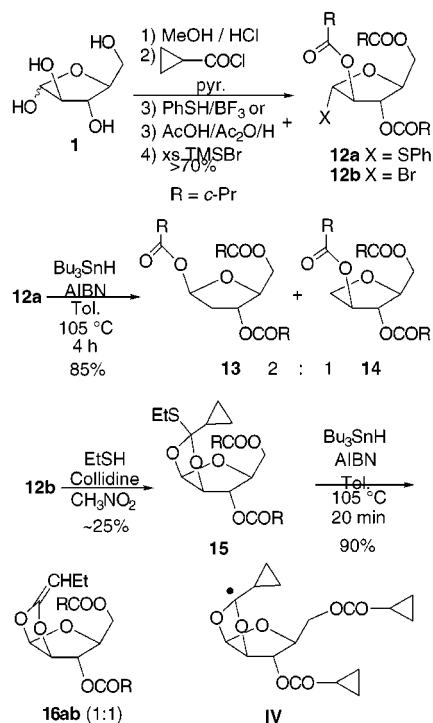


Solvolysis of the bromide **2a** in nitromethane in the presence of thiophenol and a hindered base gave the phenylthio ortho ester **6**, which proved unstable for use in our system as it readily rearranged to the α -thiophenyl arabinoside **2b**.¹² However, the ethylthio analogue **7**, prepared in 86% yield from **2a** and ethanethiol, was more stable. It was treated with tributyltin hydride in hot toluene to give the desired 2-deoxy L-ribose derivative **4** in 85% yield, along with small amounts (2–5%) each of the 1-deoxy compound **3**, the acetal **5**, and the product of solvolysis with internal trapping **8**. Thus generation of the dialkoxyalkyl radical III from the ethylthio compound **7** produced the desired radical II, in a much greater amount as compared to I as predicted, and from it the 2-deoxy L-ribose **4**. Hydrolysis of **4** furnished



2-deoxy L-ribose **9** in nearly quantitative yield, thereby ending a short six-step synthesis of **9** from **1** in 49% overall yield. Treatment of **4** with HCl in acetic acid gave the desired crystalline α -chloride **10** in 70% yield,¹³ from which the various L-nucleosides **11** were prepared in two simple steps and then their 5'-DMTr-protected phosphoramidites for use in solid-phase synthesis of L-DNA.

Finally we decided to test one possible mechanism for the rearrangement of I to give II, the intermediacy of the dialkoxyalkyl radical III. Ingold and others have proposed seven possible transition states for this rearrangement but exclude the dialkoxyalkyl radical, based mainly on ESR evidence.¹⁴ Yet this system allowed us to provide strong experimental evidence for whether the dialkoxyalkyl radical III might be an intermediate (or transition state) in this rearrangement. Hence we prepared the two substrates, the thioether **12a** and the bromide **12b** bearing cyclopropyl-carboxylates from L-arabinose **1**, in good yield. Treatment of **12a** under normal radical rearrangement conditions gave the expected 2:1 mixture of the 2-deoxy and 1-deoxy products, **13** and **14**, also in good yield. Solvolysis of the bromide **12b** with trapping with ethanethiol gave the second substrate **15**. Treatment of **15** under conditions identical to those for **12a** gave a very fast formation of a 1:1 mixture of the two stereoisomeric alkenes **16ab** resulting from rapid opening of the cyclopropylcarbinyl radical IV. We can now say unequivocally that the rearrangement of **12a** to give the deoxy products **13** and **14** does not proceed via the dialkoxyalkyl radical IV since when it is generated separately



by a different route, the same products are not formed. Thus the 1,2-acyloxy shift does not proceed via the intermediacy of the dialkoxyalkyl radical IV (III in the earlier discussion of **3** and **4**).¹⁵

Application of this chemistry to the synthesis of modified L-nucleosides and oligomers of L-DNA is currently underway in our laboratories.

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Supporting Information Available: Proton and carbon NMR spectra for all new compounds and procedures for the preparation of the thio ortho ester **7** and its conversion into **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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