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Molar-Scale Synthesis of 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose: DMSO Oxidation of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose and Subsequent Sodium Borohydride Reduction

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Abstract:

Two variants of oxidation with DMSO followed by sodium borohydride reduction have been investigated to make the synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4) suitable for large-scale manufacturing.

Introduction

The synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose has received renewed interest due to its role as the starting material for LNA (**1**) (locked nucleic acid, see Figure 1 below).[1] The synthesis of the LNA monomers employing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) was first reported by Wengel et al.[1−7] LNA has been shown to be the single nucleic acid modification that contributes to the highest affinity ever obtained by regular Watson−Crick hydrogen bonding to nucleic acids.[4] The increasing demand on supply of LNA for antisense,[8−15] prompted us to look for cost-efficient synthesis of **4** by a method that was suitable for scale-up.

The present work describes the investigation of two different methods for the oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) and subsequent stereospecific borohydride reduction of the intermediate 1,2:5,6-di-*O*-isopropylidene-α-D-ribofuranosid-3-ulose (**3**) to afford **4** (Scheme 1).

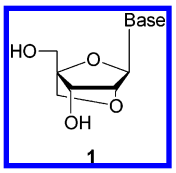

Figure 1. **LNA-nucleoside.**

Results and Discussion

A variety of oxidation procedures exist for the oxidation of **2**; however, in addition to expensive reagents, most have scale-up issues including waste concerns and tedious isolation procedures (pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC);[16−18] RuO_2 or $RuCl_3$, $NaIO_4$).[19,20] Oxidation procedures using activated DMSO or other oxidized forms of dimethyl sulfide[21,22] all suffer the same problem of emission of the malodorous volatile dimethyl sulfide. A solution to this was addressed by Crinch and Neelamkavil who, on a millimolar scale, oxidized **2** to **3** in 83% yield using fluorous sulfoxide, which was readily recovered and recycled.[23] Another ingenious solution reported in the literature is to substitute DMSO for dodecyl-methyl sulfoxide to avoid the emission of dimethyl sulfide during Corey−Kim and Swern oxidations.[24,25] On a larger scale the emission of dimethyl sulfide from the reaction can be trapped efficiently in a scrubber containing a 15% aqueous solution of sodium hypochlorite.

We first turned our attention to the known DMSO−acetic anhydride oxidation followed by sodium borohydride reduction.[26,27] The oxidation is likely to be initiated by formation

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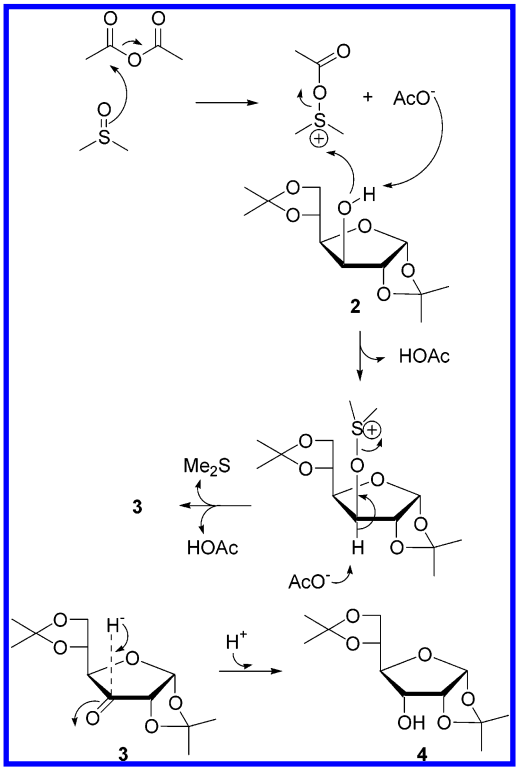
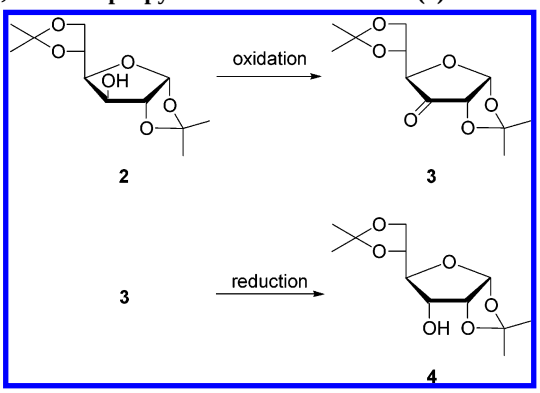


Figure 2. **Mechanism of oxidation with DMSO/Ac_2O followed by reduction.**

Scheme 1. **Synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4)**



of an oxysulfonium salt intermediate via the nucleophilic attack of the electronegative oxygen of DMSO on the electrophilic carbon in acetic anhydride.[28] (Figure 2) The secondary alcohol reacts by nucleophilic attack on the positively charged sulphur of the oxysulfonium salt with subsequent backside displacement of the acetate ion to give the alkoxysulfonium salt. The ketone group is formed by elimination of dimethyl sulfide. The nucleophilic attack of the hydride ion (or BH_4^- ion) can for steric reasons only happen from the *exo* face of the tricyclic 1,2:5,6-di-*O*-isopropylidene-α-D-ribofuranosid-3-ulose (**3**), yielding the stereoselectivity during the reduction.[29]

We explored the possibility of combining the oxidation and the reduction in one pot. As observed by J. D. Albright and L. Goldman[28] the molar ratio of alcohol to acetic

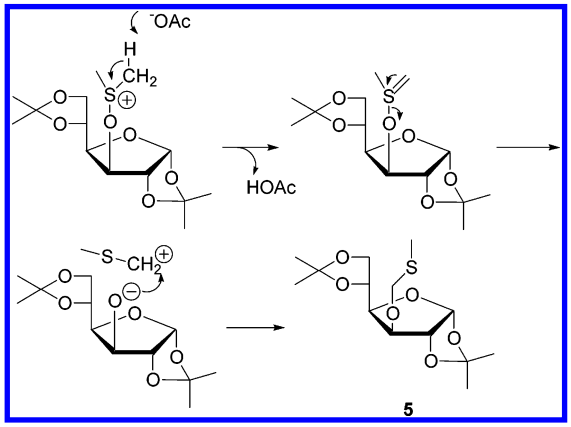


Figure 3. **Formation of major by-product during oxidation with DMSO/Ac_2O.**

anhydride could be reduced to 1:5 without any reduction in the yield. When the complete oxidation of **2** was confirmed by TLC, portionwise addition of sodium borohydride was effected, with stirring and cooling to keep the slightly exothermic reaction below 25 °C. The minimum amount of sodium borohydride that was needed to reduce **3** was determined to 0.42 equiv. We carefully followed the oxidation and reduction by TLC and noticed formation of by-products during the one-pot reaction. The major by-product (formed in 20% yield) was isolated and identified by NMR as the 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylthio)methyl-α-D-glucofuranose (**5**).[30,31] Formation of this by-product can be explained by a Pummerer rearrangement (Figure 3), and the formation is known from the Swern oxidation (DMSO/TFAA) to be temperature dependent, i.e. formation increases with increasing temperature. We have seen, however, that increasing the reaction temperature on a 20-g scale resulted in a faster oxidation without increasing formation of by-product **5**.

This finding was noted by Pojer et al.,[30] who also found that only a small quantity of acetic acid was required in the reaction mixture for the efficient production of the methylthiomethyl ether at room temperature. We assumed that the other by-products were acetylated carbohydrates. This was indirectly confirmed by TLC analysis. Samples of **2** and **4** were acetylated and proved to comigrate with the by-products. The by-products were hydrolysed by concentrated NH_4OH to afford products, which comigrated with **2** and **4**. To remove the acetylated by-products, the subsequent extraction procedure was improved to afford pure **4**. The extraction procedure takes advantage of the fact that **4** is soluble in water in addition to being soluble in many organic solvents. Extraction of **4** from the concentrated MTBE layer into an aqueous layer and then extracting the aqueous layer with dichloromethane affords pure **4**, leaving all impurities in the MTBE layer. Omitting this extraction procedure results in an impure product which will not crystallize from cyclohexane. In our hands this procedure has proven to be robust, affording yields ranging from 50 to 60%. Despite the fact that the DMSO/Ac_2O oxidation is slow, the

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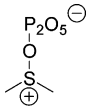

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Figure 4. **Proposed oxidative species during oxidation with DMSO/P_2O_5.**

combination with the fast reduction process turns this one-pot reaction into a robust, good yielding, cheap, and easy process.

Looking for a similar procedure with less formation of by-products, we then turned our attention to the use of phosphorus pentoxide in DMSO as the oxidant. Phosphorus pentoxide was used in preference to chromium trioxide, oxalyl chloride, chromic acid, and PCC in a few examples.[32−34] Onodera et al. reported a thorough investigation of the reaction conditions.[35−38] They recommended that with the use of dimethyl sulfoxide as solvent, oxidations are best performed at room temperature, since decomposition of the sugar is observed at higher temperatures. They also observed that the use of too large an excess of phosphorus pentoxide decreases the yield of the product and that a catalytic amount of phophorus pentoxide is also ineffective. On the basis of these results, they suggest that one equivalent of phosphorus pentoxide participate in the oxidation per alcohol moiety. The oxidation mechanism is believed to proceed by a mechanism similar to that described for the Ac_2O/DMSO oxidation, by which the oxidative species is the sulfoxonium derivative **6** (Figure 4).

Oxidation of **2** with one equivalent of phosphorus pentoxide in dimethyl sulfoxide for 3 h at 50 °C afforded **3** (>65%). The oxidation proceeds with less formation of by-product as compared to that from the DMSO/Ac_2O procedure, but the work-up was difficult since aqueous washes of the DMSO/P_2O_5 mixture affords H_3PO_4 (aqueous layer becomes pH 1), which catalyses the hydrolysis of the isopropylidene protection. In small scale this is not a problem, but in large scale, where the separation of layers is more time-demanding, this causes a decreased yield of isolated product. Taking advantage of the fact the MTBE and DMSO are not mixable enabled us to extract the intermediate ulose **3** from the DMSO/P_2O_5 mixture, leaving the polar by-products in the DMSO layer (i.e. loss of isopropylidene protection). The MTBE layer was added slowly to a cold, stirred, aqueous solution of sodium borohydride, thereby neutralising the formed H_3PO_4 in situ. The presence of MTBE during reduction diminishes the excessive foaming. Subsequent addition of dichloromethane, separation of the layers, and work-up as described above affords crystalline and analytically pure **4** in total yield from **2** between 65 and 75%. As reported by Onodera, we observed that higher reaction temperature during oxidation (60−65 °C) decreases the isolated yield of **4** (to ∼45%), but the purity and ease of isolation of product was not affected. We recommend that the reaction temperature does not exceed 55 °C. Attempts to combine the oxidation and reduction steps in a one-pot fashion resulted in a decrease of isolated yield of **4** to approximately 58%. In summary, this procedure is fast, good yielding, and uses cheap chemicals; however it is dependent on good temperature control during addition of phosphorus pentoxide and during oxidation of **2**. It is our experience that the addition of the phosphorus pentoxide to the dimethyl sulfoxide was best executed while the temperature of the solution was kept below 20 °C.

Conclusions

We have developed two procedures for the large-scale synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**). Both reactions afford crystalline and analytically pure product without employing chromatography. To our knowledge, this is the largest-scale synthesis of **4** reported to date.

Experimental Section

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (98+%) was purchased from Pliva Pharmaceutical Industry Inc. and used without further purification. P_2O_5 (min 99%) was purchased from ACROS, and $NaBH_4$ powder (98+%) was purchased from Aldrich. Solvents were HPLC grade, of which DMSO was dried over molecular sieves (4 Å). If the water content by KF is >0.2%, the yield of the two-pot, two-step procedure will decrease, and sometimes the reaction does not go to completion. TLC analysis was performed on Merck silica 60 F_{254} aluminum sheets and developed with 2 M aqueous sulphuric acid followed by charring. The intermediate **3** can be developed with a solution of 2,4-dinitrophenylhydrazine (100 mg) in ethanol (90 mL) and concentrated hydrochloric acid (10 mL). ^{1}H and ^{13}C NMR spectra were recorded respectively at 400 and 100 MHz with the solvent as internal standard (δ_H: $CDCl_3$ 7.26 ppm; δ_C: $CDCl_3$ 77.0 ppm). *J* values are given in Hz. Elemental analyses were obtained from the University of Copenhagen, Microanalytical Department. Measurements of optical rotation were obtained from The Technical University of Denmark.

One Pot, Two-Step Procedure Using DMSO/Ac_2O/$NaBH_4$. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**) (260 g, 1.0 mol) was dissolved in a mixture of anhydrous DMSO (2 L) and Ac_2O (500 mL, 5.0 mol) and stirred at 20−25 °C for 24 h in a 5-L glass flask under a nitrogen blanket. By this time TLC (eluent: DCM/MeOH, 95:5) indicated complete conversion of **2**. The solution was cooled on an ice−water bath, and sodium borohydride (16 g, 0.42 mol) was added portionwise during 15 min to keep reaction temperature in the range of 20−25 °C. After complete addition of sodium borohydride, the reaction mixture was stirred for 1 h at 20−25 °C. By then TLC (eluent: DCM/

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MeOH, 95:5) indicated complete formation of target compound (**4**), and water (2.5 L) was added. The resulting mixture was extracted with DCM (3 × 1 L). The combined organic layer was washed with water (2 × 1 L) and brine (1 L), dried ($MgSO_4$) to diminish residual salts (which interfere with the subsequent extraction method), filtered, and concentrated in vacuo to afford an oil. The oil was dissolved in MTBE (300 mL) and extracted with water (2 × 750 mL). The combined aqueous layer was extracted with DCM (2 × 400 mL). The combined DCM layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give an oil. Two crystallizations from cyclohexane (500 mL and 300 mL, respectively) afforded analytically pure 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) (151 g, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (1H, d, $J_{1,2} = 3.8$ Hz, H-1), 4.59 (1H, dd, $J_{2,1} = 4.0$ Hz, $J_{2,3} = 5.1$ Hz, H-2), 4.29 (1H, ddd, $J_{5,6b} = 4.9$ Hz, $J_{5,6a} = 6.6$ Hz, $J_{5,4} = 6.6$ Hz, H-5), 4.08−3.97 (3H, m, H-3, H-4, H-6a), 3.80 (1H, dd, $J_{6b,5} = 4.8$ Hz, $J_{6b,6a} = 8.5$ Hz, H-6b), 2.55 (1H, d, $J_{OH,3} = 8.4$ Hz, 3-OH), 1.56, 1.45, 1.36, 1.35 (4 × 3H, 4 × s, 2 × isopropylidene).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.6, 109.6, 103.7, 79.6, 78.8, 75.5, 72.4, 65.7, 26.5, 26.4, 26.2, 25.2.

Anal. Calcd for $C_{12}H_{20}O_6 \cdot 1/2H_2O$: C, 53.52; H, 7.86. Found: C, 53.77; H, 7.72.

Melting point: 75−76 °C (lit. 77−78 °C).[27]

Optical rotation $[\alpha]^{25}_D$ +37.6° (*c* 1, chloroform); lit. $[\alpha]^{25}_D$ +38° (*c* 1, chloroform).[39]

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(methylthio)methyl-α-D-glucofuranose (**5**)[26,31] was isolated by dry column vacuum chromatography[40] of the MTBE layer. Analytical data: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 4.78, 4.69 (2 × 1H, 2 × d, $J = 11.5$ Hz, O−CH_2−S), 4.55 (1H, d, $J_{2,1} = 3.8$ Hz, H-2), 4.31 (1H, d, $J_{3,4} = 3.0$ Hz, H-3), 4.25 (1H, dt, $J_{5,4} = 8.0$ Hz, $J_{5,6} = 5.9$, H-5), 4.12 (1H, dd, $J_{4,5} = 8.0$ Hz, $J_{4,3} = 3.0$ Hz, H-4), 4.09 (1H, dd, $J_{6a,6b} = 8.5$ Hz, $J_{6a,5} = 6.1$ Hz, H-6a), 3.97 (1H, dd, $J_{6b,6a} = 8.5$ Hz, $J_{6b,5} = 5.7$ Hz, H-6b), 2.17 (3H, s, S−CH_3), 1.49, 1.41, 1.32, 1.31 (4 × 3H, 4 × s, 2 × isopropylidene).

^{13}C NMR ($CDCl_3$, 100 MHz): 111.7, 108.9 (2 × isopropylidene), 105.1 (C-1), 82.7 (O−CH_2−S), 81.0, 78.9, 74.6, 72.2, 67.4, 26.7, 26.7, 26.2, 25.3, 13.8.

Anal. Calcd for $C_{14}H_{24}O_6S$: C, 52.48; H, 7.55. Found: C, 52.52; H, 7.51.

Two-Pot, Two-Step Procedure Using DMSO/P_2O_5/$NaBH_4$. Anhydrous DMSO (650 mL) was cooled to 18−20 °C under nitrogen in a 3-L round-bottom glass flask. DMSO will be solidified at 18 °C, so it is important to keep it just above freezing point. To this cold solution was added P_2O_5 (142 g, 1.0 mol, 1 equiv) in three portions under N_2 atmosphere. The addition of P_2O_5 to DMSO is exothermic, and if the mass temperature exceeds 28 °C, the colour darkens, and the product will be of inferior quality. The mixture was cooled to 18−20 °C between each addition. After addition of P_2O_5 was completed, the mixture was stirred at 18−25 °C for 10−15 min. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**) (260 g, 1.0 mol) was dissolved in anhydrous DMSO (1.3 L) and added during 30 min (to keep temperature between 18 and 25 °C) to the stirred solution of P_2O_5 in DMSO under N_2 atmosphere. The resulting solution was heated to 50−55 °C for 3 h. TLC (eluent: DCM/MeOH, 95:5) shows complete conversion of **2** (R_f = 0.68) to ulose (**3**) (R_f = 0.81). The reaction mixture was allowed to reach 25−30 °C and was extracted twice with MTBE (1.5 and 1 L) in a 6-L separation funnel. The combined MTBE layer (∼4 L) was concentrated in vacuo (water-bath temperature set to 40 °C) to approximately 2 L and allowed to reach 25−30 °C. $NaBH_4$ (24 g, 0.63 mol) was dissolved in water (1 L, 55.6 mol) at 0−10 °C, and the concentrated MTBE layer was added to the aqueous layer during 30 min to keep the temperature between 0 and 10 °C. TLC (eluent: EtOAc/heptane, 6:4) after 30 min shows full conversion of **3** (R_f = 0.53) to 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) (R_f = 0.39). The reaction mixture was allowed to reach 25−30 °C. DCM (1 L) and water (500 mL) were added, and the layers were separated. The aqueous layer was extracted once more with DCM (500 mL). The combined organic layers were concentrated in vacuo to an oil which was subsequently dissolved in MTBE (300 mL) and extracted with water (3 × 500 mL). The combined aqueous layer was extracted with DCM (3 × 500 mL). The combined DCM layer was dried (Na_2SO_4, 100 g), filtered, and concentrated in vacuo to an oil. Crystallization from cyclohexane (500 mL), washing of crystals with cold *n*-pentane, and drying hereof in vacuo afforded analytically pure 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) 191 g (73% yield). NMR data were in accordance with the above.

Melting point: 74−75 °C (lit. 77−78 °C).[27]

Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.31; H, 7.71.

Optical rotation$[\alpha]^{25}_D$ +37.8° (*c* 1, chloroform); lit. $[\alpha]^{25}_D$ +38° (*c* 1, chloroform).[40]

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