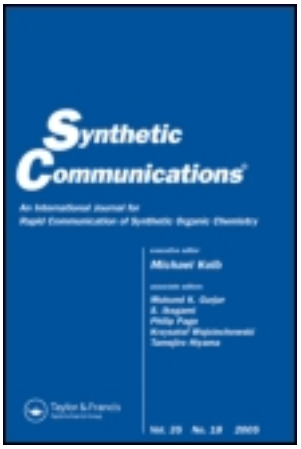

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IMPROVED AND PRACTICAL SYNTHESIS OF 2-DEOXY-L-RIBOSE BY HYPOPHOSPHITE-MEDIATED DEOXYGENATION

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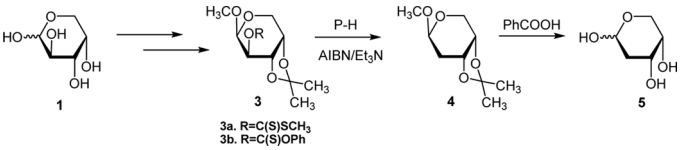
GRAPHICAL ABSTRACT



Abstract *An improved and practical route for a large-scale synthesis of 2-deoxy-L-ribose starting from L-arabinose has been developed. This is the first reported synthesis of 2-deoxy-L-ribose in which deoxygenation has been mediated by hypophosphite reagents instead of by organotin reagents.*

Keywords 2-Deoxy-L-ribose; hypophosphite-mediated deoxygenation; hypophosphorous acid; *N*-ethylpiperidine hypophosphite; synthesis

INTRODUCTION

Recently, nucleosides with unnatural L-configurations as antiviral agents have drawn considerable attention because of their unique potency, mechanism, and toxicity profile,[1–7] which include β-L-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]cytosine (3TC),[2] β-L-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]-5-fluorocytosine (FTC),[2a,3] L-2′,3′-dideoxycytidine (L-ddC),[4] L-5-fluoro-2′,3′-dideoxycytidine (L-FddC),[4] L-thymidine (L-dT),[5] and 2′-fluoro-5-methyl-β-L-arabinofuranosyl-uracil (L-FMAU).[6] Furthermore, L-nucleosides with 2-deoxy-L-ribose or L-ribose backbones are attractive building blocks for the corresponding oligonucleotides in "antisense" therapy.[7]

RESULTS AND DISCUSSION

A great deal of effort, therefore, has been devoted to the synthesis of 2-deoxy-L-ribose. Several methods are known in the literature.[8,9] Most of them use L-arabinose,[8]

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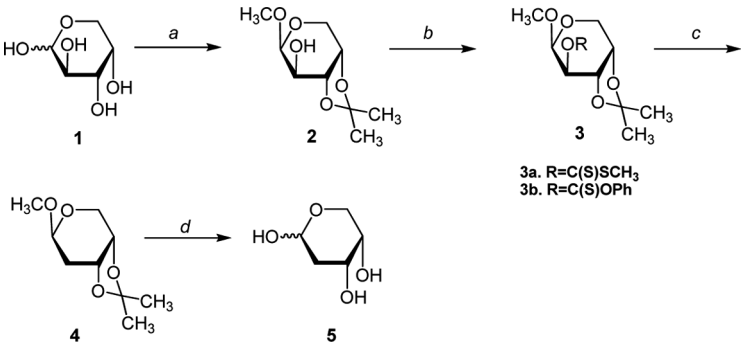
L-ribose,[8b] or L-ascorbic acid[9] as the starting materials, but none of these have been proved to be an efficient and practical procedure for preparation of 2-deoxy-L-ribose in large quantities. Herein, we improved a reported method (Scheme 1)[8] starting from L-arabinose in general and introduced hypophosphite-mediated reagents into this method to make this synthetic route suitable for a large scale.

Of all the steps involved in the synthesis of 2-deoxy-L-ribose (Scheme 1), deoxygenation of the intermediate **3** is the key step. First, Barton–McCombie radical deoxygenation[10] conditions were tested (entries 1 and 2, Table 1). The secondary alcohol **2** was treated with several different types of reagents to give radical precursors **3a** and **3b**. These radical precursors were treated respectively with tri-*n*-butyltin hydride and 2,2-azobisisobutyronitrile (AIBN). As described in the literature,[8a] normal free-radical deoxygenation conditions gave the desired deoxygenated product **4** in a relatively poor yield because of the hydrolysis of the precursor **3**. Also, the problems associated with the price, toxicity, and removal of tin residues prompted a search for other hydrogen sources.

In a search for a hydrogen source for the deoxygenation of compound **3**, we found hypophosphorous acid and its salt, *N*-ethylpiperidine hypophosphite (EPHP), introduced by Barton and Jang,[11] to be very efficient substitutes for tri-*n*-butyltin hydride for typical substrates.

The reaction of thiocarbonates **3a** and **3b** with hypophosphorous acid and triethylamine in refluxing dioxane in the presence of AIBN afforded the deoxy product **4** (entries 3 and 4, Table 1). Triethylamine protected the thiocarbonyl moiety as well as acid-labile protecting groups from acidic hydrolysis during the reaction. Heating a mixture of **3** and EPHP in the presence of AIBN in dry dioxane at reflux under a nitrogen atmosphere gave exclusively **4**. Compound **4** was readily deprotected by benzoic acid to give the target product **5** in good yield with good optical purity.

Under such modified procedure, the formation of tri-*n*-butyltin methylmercaptide complex by-product in the tri-*n*-butyltin hybride method was avoided, thus making the improved procedure environmentally acceptable. Furthermore, the expected product **4** was formed cleanly because the water solubility of hypophosphite residue



Scheme 1. Synthesis of 2-deoxy-L-ribose. Reagents and conditions: (a) (i) HCl/CH_3OH (81.4%); (ii) 2,2-dimethoxypropane, *p*-TsOH, DMF (95%); (b) for **3a**: NaH, CS_2, CH_3I, THF (90%); for **3b**: PhOC(S)Cl, py., CH_2Cl_2(95%); (c) different conditions; see Table 1; (d) PhCOOH, H_2O, reflux (different yields; see Table 1).

Table 1. Free radical–mediated deoxygenation of compound **3**

Entry	Radical precursor	Reagents	Solvent	Time (h)	Yield of **5**[a] (%)
1	**3a**	*n*-Bu_3SnH/AIBN	Toluene	6	54
2	**3b**	*n*-Bu_3SnH/AIBN	Toluene	6	55
3	**3a**	H_3PO_2/Et_3N/AIBN	Dioxane	4	75
4	**3b**	H_3PO_2/Et_3N/AIBN	Dioxane	4	79
5	**3a**	EPHP/AIBN	Dioxane	2.5	81
6	**3b**	EPHP/AIBN	Dioxane	2.5	85

[a]Yield obtained after deprotection of **4** to give 2-deoxy-L-*erythro*-pentopyranoside (**5**) because the separation of compound **5** was neither practical nor necessary.

and hypophosphite salt–derived side products allowed easy and efficient purification without chromatographic techniques. Consequently, the reaction can be scaled up to kilogram quantities without any complications.

CONCLUSION

In summary, we have reported an improved synthesis of 2-deoxy-L-ribose with hypophosphite-mediated deoxygenation. Compared to previously reported procedures, this method can be utilized as a practical and economical procedure for a large scale and can be performed without the use of either expensive reagents or column chromatographic purification of any intermediates.

EXPERIMENTAL

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. All melting points are uncorrected. ^{1}H NMR data were recorded on an Inova-400 spectrometer in $CDCl_3$, dimethylsulfoxide (DMSO-d_6), or D_2O using tetramethylsilane (TMS) as an internal standard. Mass spectra were performed on Micro Mass Q-Tof Micro MS. Optical rotations were measured with a WZZ-2A automatic polarimeter equipped with a sodium (589 nm) lamp at 20 °C.

Methyl 3,4-*O*-Isopropylidene-β-L-arabinopyranoside (3)

Acetyl chloride (8.1 ml, 117 mmol) was added to a suspension of L-arabinose (100 g, 667 mol) in anhydrous MeOH (480 ml) at room temperature, and the mixture was refluxed for 6 h and cooled to 0 °C. The precipitated solid was filtered and washed with cold MeOH (20 ml) to give the first crop as a crystalline powder **2** (53.1 g). The filtrate was concentrated to about half of its volume to give a suspension, which was refluxed for 2 h and cooled to 0 °C. The solid was filtered, washed, and dried as before to give the second crop (20.2 g) as a crystalline powder. The concentration and filtration were repeated to afford an additional 15.7 g product (totally 89.0 g, 81.4%). Mp 160–162 °C (lit.[8c] mp 162–164 °C); ^{1}H NMR (400 MHz, D_2O): δ 3.31 (s, 3H, OCH_3), 3.56 (dd, 1H, H_5), 3.73 (m, 1H, H_4), 3.75 (d, 1H, H_3), 3.78 (d, 1H, H_5), 3.89 (bs, 1H, H_2), 4.73 (d, 1H, H_1); MS: m/z 187.14 $[M + Na]^+$, 203.11 $[M + K]^+$.

p-Toluenesulfonic acid (0.5 g, 2.9 mmol) was added to the mixture of methyl β-L-arabinopyranoside (46.7 g, 284.5 mmol) and 2,2-dimethoxypropane (100 ml, 814.6 mmol) in dry DMF (300 ml), and the suspension was stirred at room temperature for 48 h. The mixture was adjusted to pH 8 by addition of aqueous ammonia and evaporated to give a syrup, which was diluted with EtOAc (300 ml). The solution was washed with brine, saturated $NaHCO_3$ solution, and brine. The aqueous washings were combined and extracted with EtOAc (50 ml), which was washed with brine and combined with the organic solution. The extract was dried over $MgSO_4$ and evaporated to dryness to give a syrup **3** (55.2 g, 95.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 and 1.53 (2 s, 6H, isopropylidene-CH_3), 2.27 (d, 1H, 2-O*H*), 3.45 (s, 3H, OCH_3), 3.78 (m, 1H, H_2), 3.93 (s 2H, H_5), 4.16–4.23 (m, 2H, $H_{3,4}$), 4.71 (d, 1H, H_1); MS: m/z 227.14 $[M + Na]^+$, 431.30 $[2M + Na]^+$.

Methyl 3,4-*O*-Isopropylidene-2-*O*-[(methylthio)thiocarbonyl]-β-L-arabinopyranoside (3a)

The syrup **2** (24.5 g, 0.12 mol) and imidazole (0.41 g, 6 mmol) were dissolved in anhydrous tetrahydrofuran (THF) (150 ml) and cooled to 0 °C. NaH (60%, 9.6 g, 0.2 mol) was added to the solution under a nitrogen atmosphere. The suspension was stirred for 2 h and cooled to 0 °C. Carbon disulfide (21.6 ml, 0.36 mol) was added to the mixture and stirred at room temperature for 12 h. Methyl iodide (11.2 ml, 0.18 mol) was added at 0 °C and stirred for another 2 h at room temperature. The batch was quenched with ice water (300 ml) and extracted with EtOAc (3 × 50 ml), and the combined organic phase was washed with brine, dried over MgSO, and evaporated in vacuo to give 37.76 g (quant.) of crude **3a** as yellow solid. Recystallization from EtOAc afforded 31.8 g of pure **3a** (90%). Mp 122–124 °C (lit.[7b] mp 127–130 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 and 1.42 (2s, 6H, isopropylidene-CH_3), 2.59 (s, 3H, SCH_3), 3.32 (s, 3H, OCH_3), 3.90 (m, 2H, H_5, $H_{5'}$), 4.38 (m, 2H, H_3, H_4), 4.89 (d, 1H, H_1), 5.61 (dd, 1H, H_2); MS: m/z 294.99 $[M + H]^+$.

Methyl 3,4-*O*-Isopropylidene-2-*O*-phenoxythiocarbonyl-β-L-arabinopyranoside (3b)

Phenyl chlorothionoformate (20.2 ml, 0.144 mol) was added to a stirred solution of **2** (24.5 g, 0.12 mol) and pyridine (30 ml, 0.36 mol) in dry CH_2Cl_2 (400 ml), at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (150 ml) and washed with 1 M HCl solution, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a crude dark brown syrup **3b** (38.8 g, 95%), which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 and 1.60 (2s, 6H, isopropylidene-CH_3), 3.45 (s, 3H, OCH_3), 4.00 (m, 2H, H_5, $H_{5'}$), 4.31 (m, 1H, H_4), 4.51 (m, 1H, H_3), 5.06 (d, 1H, H_1), 5.47 (dd, 1H, H_2), 7.14–7.43 (m, 5H, -C$_6H_5$); MS: m/z 341.20 $[M + H]^+$.

Methyl 3,4-*O*-Isopropylidene-2-deoxy-β-L-arabinopyranoside (4)

Method A. A solution of a thionocarbonate (**3**, 0.12 mol), hypophosphorous acid (79.5 g, 0.6 mol, 50% in H_2O), and triethylamine (180 ml, 1.32 mol) in dioxane

(400 ml) under a nitrogen atmosphere was treated at 30-min intervals with small portions of a solution of azobisisobutyronitrile (AIBN, 2 g) in dioxane (30 ml) during reflux. When the reaction was complete, the solution was concentrated in vacuo and diluted with EtOAc (400 ml). The organic solution was washed successively with saturated $NaHCO_3$ solution, 1 M HCl solution, saturated $NaHCO_3$ solution, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo to give **4** as a yellowish syrup (18.9 g from Entry 3, quant.; 19.4 g from entry 4, quant.). The product **4** was used for the next step without further purification.

Method B. The solution of a thionocarbonate (**3**, 0.12 mol) and the EPHP (107.4 g, 0.6 mmol) in dioxane (400 ml) under nitrogen was treated at 30-min intervals with small portions of a solution of AIBN (2 g) in dioxane (30 ml) during reflux. When the reaction was complete, the solution was concentrated in vacuo and diluted with EtOAc (400 ml). The organic solution was washed successively with saturated $NaHCO_3$ solution, 1 M HCl solution, saturated $NaHCO_3$ solution, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo to give **4** as a yellowish syrup (22.3 g from entry 5, quant.; 24.2 g from entry 6, quant.). The product **4** was used for the next step without further purification.

2-Deoxy-L-ribose (5)

The syrup **4** (22 g, 0.12 mol) obtained previously was heated at reflux in a saturated aqueous solution of benzoic acid (200 ml) for 1 h. After cooling to room temperature, chloroform (50 ml) as added, and the aqueous layer was separated and washed again with chloroform (30 ml). When the aqueous phase was evaporated to half of its original volume, activated carbon was added, and the mixture was stirred for 1 h. Then the water phase was filtered and concentrated in vacuo to give **5** as a pale yellowish syrup (12.1 g from entry 3, 75% two steps from **3a**; 12.7 g from entry 4, 79% two steps from **3b**; 13.0 g from entry 5, 81% two steps from **3a**; 13.7 g from entry 6, 85% two steps from **3b**). $[\alpha]_D^{20} = +50^\circ$ (c = 1.0, H_2O) [lit.[7a] $[\alpha]_D^{20} = +52^\circ$ (c = 1.0, H_2O)]; ^1H NMR (400 MHz, DMSO-d_6): δ 1.47 and 1.78 (m, 2H, H_2, $H_{2'}$), 3.46–3.53 (m, 2H, H_5, $H_{5'}$), 3.63 (m, 1H, H_4), 3.83 (m, 1H, H_3), 4.32–4.35 (m, 2H, -OH_3, -OH_5), 4.97 (m, 1H, H_1), 6.00 (d, 1H, -OH_1); MS: m/z 157.07 $[M + Na]^+$, 173.04 $[M + K]^+$.

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