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Efficient synthesis of 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose) from L-arabinose

Youhoon Chong, Chung K. Chu*

Department of Pharmaceutical and Biomedical Sciences, Center for Drug Discovery, College of Pharmacy, The University of Georgia, Athens, GA 30602, USA

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Abstract

An efficient and practical route for the large-scale synthesis of 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose) starting from L-arabinose was developed using Barton-type free-radical deoxygenation reaction as a key step. The radical precursor, a phenoxythiocarbonyl ester, was prepared in situ, and the most efficient deoxygenation was achieved by slow addition of tributyltin hydride to the reaction mixture. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: 2-Deoxy-L-*erythro*-pentose; 2-Deoxy-L-ribose; L-Nucleosides; L-Arabinose; Free-radical deoxygenation

1. Introduction

The use of L-carbohydrates and related nucleosides in medicinal application has greatly increased due to their potent biological activity and lower toxicity compared to their D-counterpart.[1–6] Among these, L-FMAU (clevudine),[2] L-thymidine (L-T),[3] L-3′-thiacytidine (3TC),[4] L-5-fluoro-3′-thiacytidine (FTC),[4a,5] L-2′,3′-dideoxycytidine (L-ddC),[6] and L-5-fluoro-2′,3′-dideoxycytidine (L-FddC)[6b,6c] showed potent antiviral activity with greatly reduced toxicity. For these reasons, modified nucleosides in the unnatural L configuration have become an important synthetic target, which requires ready access to L-carbohydrates, especially L-ribose and its derivatives. However, the high cost of L-ribose and 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose) has hampered their use as starting material for the synthesis of L-nucleosides in large quantities. We herein report a short, five-step synthesis of 2-deoxy-L-ribose (**6**) from an inexpensive and readily available starting material, L-arabinose (**1**).

2. Results and discussion

Even though several syntheses[7–10] of 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose) using L-arabinose[7], L-ribose[7c] or L-ascorbic acid[8] as the starting materials are known, none of these methods have proved to be an economical and efficient procedure for the preparation of 2-deoxy-L-ribose in large quantities. Our previous experience in the large-scale synthesis of L-FMAU from L-arabinose via L-ribose[11] showed the possibility of finding a very practical route to 2-deoxy-L-ribose since deoxygenation of the readily obtainable intermediate, benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**) (Scheme 1), would directly give rise to our target compound **6**. Because of the sterically hindered nature of the secondary hydroxyl group in carbohydrates, Barton-type radical deoxygenation conditions were tested first (Table 1).

The secondary alcohol **3** was reacted with several different types of reagents to give radical precursors **4a**–**4f**. The radical precursors **4a**–**4f** were treated with tri-*n*-butyltin hydride and AIBN under two different conditions. As was described in the literature,[7b,7e] normal free-radical deoxygenation conditions (Method A, Table 1) gave rise to the desired deoxygenated product **5** in a relatively low yield due to the hydrolysis of the starting material and formation of side products. Changing the reaction conditions circumvented this

* Corresponding author. Tel.: +1-706-5425379; fax: +1-706-5425381.

E-mail address: dchu@merc.rx.uga.edu (C.K. Chu).

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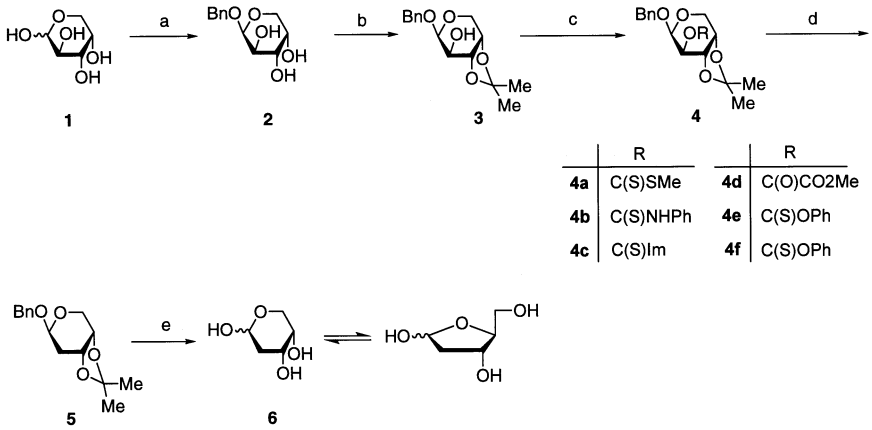


Scheme 1. Synthesis of 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose, **6**) from L-arabinose (**1**). Reagents and conditions: (a) BnOH, HCl(g); (b) 2,2-dimethoxypropane, *p*-TsOH, acetone; (c) (**4a**) NaH, CS_2, MeI, THF; (**4b**) NaH, PhNCS, THF; (**4c**) $C(S)Im_2$, THF, reflux; (**4d**) $ClC(O)CO_2Me$, pyr, CH_2Cl_2; (**4e**) PhOC(S)Cl, pyr, CH_2Cl_2; (**4f**) $CSCl_2$, PhOH, pyr, CH_2Cl_2, then **3**; (d) $n$$Bu_3SnH$, AIBN, toluene, reflux (Method A or Method B) ; (e) 4% TFA, 40 °C.

problem (Method B, Table 1). To a refluxing solution of radical precursor **4** in dry toluene, a solution of tri-*n*-butyltin hydride and AIBN in dry toluene was slowly added over 1 h. After stirring 1 h more under reflux, volatiles were evaporated under reduced pressure, and the remaining residue was filtered through a short silica gel pad to give a crude product **5** that was used for the next step without further purification. Method B proved to be better than method A under every reaction tested (Table 1). Even though the best yield was obtained through the *S*-methyl xanthate[7b,7e] (**4a**, Entry 1, Table 1), the high flammability of carbon disulfide restricted the use of this method for a large-scale synthesis. Other reagents such as phenyl isothiocyanate (**4b**, Entry 2, Table 1),[13] 1,1′-thiocarbonyldiimidazole (**4c**, Entry 3, Table 1),[12] methyl oxalyl chloride (**4d**, Entry 4, Table 1),[12] and phenoxythiocarbonyl chloride (**4e**, Entry 5, Table 1)[14] did not give promising results because either they were not reactive enough or the reagents used were too expensive. The most efficient deoxygenation was achieved by preparing the phenoxythiocarbonyl ester[14] in situ (**4f**, Table 1). Phenol and pyridine in anhydrous dichloromethane was treated with thiophosgene to give a phenoxythiocarbonyl chloride, which was directly reacted with the alcohol **3** to afford phenoxythiocarbonyl ester **4f**. To a refluxing solution of phenoxythiocarbonyl ester **4f** in dry toluene, a solution of tri-*n*-butyltin hydride and AIBN in toluene was slowly added over 1.5 h. The resulting dark-brown solution was stirred under reflux for an additional 1 h to give the deoxygenated compound **5**, which was treated with 4% trifluoroacetic acid in water at 40 °C for 10 h. The reaction mixture was washed several times with ethyl acetate to remove benzyl alcohol, and then the aqueous phase was filtered through Amberlite® IRA-400 (OH^-) ion-exchange resin. The water was thoroughly evaporated under reduced pressure and then coevaporated with ethanol and toluene several times to give the desired 2-deoxy-L-ribose (**6**) in 70% yield based on the starting alcohol **3**. These conditions were proved to be effective up to the 100-g (0.357-mol) scale, and the chemical yield became

Table 1
Free-radical deoxygenation of compound **3** (**3**→**5**)

Entry	Radical precursor	% yield	
		Method A [a]	Method B [b]
1	**4a**	54	85 84 [c]
2	**4b**	45	55
3	**4c**	0 [d]	36
4	**4d**		0 [e]
5	**4e**	55	59 [f]
6	**4f**		56 [g] 70 [g,h]

[a] To a stirred solution of compound **4** in dry toluene were added $n$$Bu_3SnH$ and AIBN. The resulting solution was stirred for 2 h under reflux.

[b] To a stirred solution of compound **4** in dry toluene was slowly added a solution of $n$$Bu_3SnH$ and AIBN in dry toluene over 1.5 h. After addition, the reaction mixture was stirred for additional 1 h under reflux.

[c] Scale: 50 g.

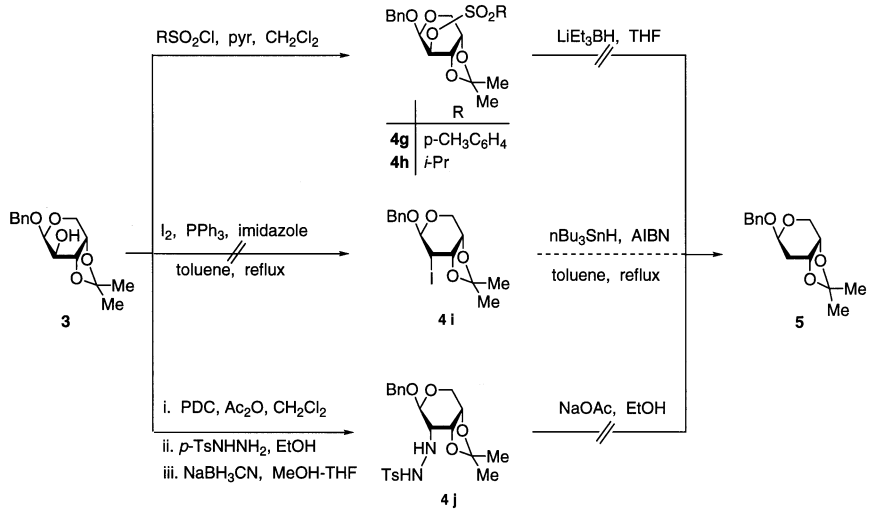
[d] Intermediate **4c** was converted to a side product whose structure remains to be determined.

[e] Intermediate **4d** was hydrolyzed to the starting material **3**.

[f] Intermediate **4e** was prepared by the reaction of **3** with the commercially available phenyl chlorothionoformate.

[g] Intermediate **4f** was prepared by the reaction of thiophosgene with phenol, followed by **3**.

[h] Scale: 100 g. The yield was obtained after hydrolysis to give 2-deoxy-L-ribose (**6**) because the separation of compound **5** was not practical.



Scheme 2. Attempted reductive deoxygenation of compound **3**.

even better (70%) as the scale of the reaction was increased (**4f**, Entry 6, Table 1).

Several reductive deoxygenation conditions were also tested (Scheme 2). Thus, the secondary alcohol **3** was converted into alkyl sulfonates (**4g** and **4h**) and treated with Super-Hydride® in refluxing THF. However, the sterically hindered nature of sulfonates (**4g** and **4h**) did not allow the reductive cleavage of the C–O bond. Instead, the sulfonates were converted into the starting alcohol **3** by hydrolysis. Attempted iodination, followed by a free-radical deoxygenation strategy, did not work at all because the initial iodination reaction under the Mitsunobu conditions was completely blocked (Scheme 2). Reductive deoxygenation of the corresponding ketone under the Wolff–Kishner conditions was tested (Scheme 2). Intermediate **3** was oxidized to the corresponding ketone, which was treated with *p*-toluenesulfonylhydrazide to give a cis- and trans-mixture of tosylhydrazone **4j**. However, sodium cyanoborohydride mediated reduction of the hydrazone **4j** did not go to completion, leaving one of the two double-bond isomers unreacted. The corresponding hydrazide obtained in a low yield (33%) was treated with sodium acetate trihydrate in refluxing ethanol, but it did not afford the desired deoxygenated compound **5**. Rather, the starting material decomposed under the reaction conditions.

In conclusion, after survey of available methods for free-radical deoxygenation, we have modified and improved a commonly used procedure to provide 2-deoxy-L-ribose (**6**) in higher yield from L-arabinose, which can be readily adapted to the large-scale synthesis.

3. Experimental

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR with tetramethylsilane as the internal standard. Chemical shifts (δ) are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC was performed on Uniplates (Silica Gel) purchased from the Analtech Co. Column chromatography was performed using Silica Gel G (TLC grade, >440 mesh) for vacuum-flash column chromatography. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

*(+)-Benzyl 3,4-*O*-isopropylidene-β-*L*-arabinopyranoside* (**3**).—Benzyl alcohol (1.0 L) was saturated with hydrogen chloride for 40 min at 0 °C, L-arabinose (200 g, 1.33 mol) was added, and the mixture was stirred at rt for 10 h, during which time benzyl β-L-arabinopyranoside (**2**) precipitated. To the mixture, EtOAc (1.5 L) was slowly added while stirring for additional precipitation. Filtration of the resulting solid, washing with EtOAc, and drying in air gave compound **2** as a white solid, which was used for the next step without further purification.

A mixture of benzyl β-L-arabinopyranoside (**2**), 2,2-dimethoxypropane (410 mL, 3.33 mol), and *p*-TsOH·H_2O (5.1 g, 0.027 mol) in acetone (2.5 L) was stirred at rt for 2 h. The reaction mixture was then neutralized with Et_3N and evaporated under reduced pressure to give (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**) as a yellow syrup, which was filtered through a short silica gel (2–20 micron) pad (20 cm height, 10 cm in diameter) washing with a 3:1 hexane–EtOAc. A yield of 343 g [1.22 mol, 92% yield based on L-arabinose (**1**)] of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**) was obtained as

a white solid: mp 52 °C; $[\alpha]_D^{23}$ 180.0° (*c* 20.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39–7.30 (m, 5 H), 4.94 (d, *J* 3.6 Hz, 1 H), 4.79 (d, *J* 11.7 Hz, 1 H), 4.55 (d, *J* 11.7 Hz, 1 H), 4.25–4.21 (m, 1 H), 4.21 (q, *J* 6.1 Hz, 1 H), 4.01 (dd, *J* 13.2, 2.4 Hz, 1 H), 3.94 (dd, *J* 13.1, 1.1 Hz, 1 H), 3.80 (d, *J* 3.2 Hz, 1 H), 2.28 (br s, 1 H), 1.53 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.0, 128.6, 128.1, 128.0, 109.2, 96.9, 75.9, 72.9, 70.0, 69.7, 59.8, 27.9, 25.8; HRFABMS (*m*/*z*) Found: 281.1415; Calcd for $C_{15}H_{21}O_5$: 281.1389 $[M+H]^+$. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.15.

Preparation of precursors (**4a**–**4f**) *for free-radical deoxygenation. Benzyl 3,4*-O-*isopropylidene-2*-O-*[(methylthio)thiocarbonyl]-β*-L-*arabinopyranoside* (**4a**).—To a stirred solution of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**) (42.7 g, 0.152 mol) in anhyd THF (500 mL), NaH (6.1 g, 0.152 mol) was slowly added at 0 °C. After the initial violent reaction subsided, the ice-bath was removed. After stirring for 30 min at rt, carbon disulfide (18.3 mL, 0.304 mol) was added at once. The resulting yellow suspension was stirred for 30 min, iodomethane (19.0 mL, 0.304 mol) was slowly added at rt, and the resulting yellow solution was stirred for an additional 30 min at rt. Water (50 mL) was added, and the volume of the reaction mixture was reduced to half by evaporation. The aqueous phase was extracted three times with EtOAc, and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give 57.7 g of the crude benzyl 3,4-*O*-isopropylidene-2-*O*-[(methylthio)thiocarbonyl]-β-L-arabinopyranoside (**4a**) as yellow syrup, which was used for the next step without further purification.

Benzyl 3,4-O-*isopropylidene-2*-O-*[*N*-phenylthioxocarbamoyl]-β*-L-*arabinopyranoside* (**4b**).—To a stirred solution of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**, 1.0 g, 3.57 mmol) and phenyl isothiocyanate (0.47 mL, 3.93 mmol) in anhyd THF (20 mL), NaH (157 mg, 3.93 mmol) was slowly added, and the reaction was monitored by TLC. After 2 h, the solvent was removed in vacuo, and the residue was partitioned between EtOAc and water. The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave benzyl 3,4-*O*-isopropylidene-2-*O*-[*N*-phenylthioxocarbamoyl]-β-L-arabinopyranoside (**4b**) as yellow syrup, which was used for the next step without further purification.

Benzyl 3,4-O-*isopropylidene-2*-O-*[1-imidazolyl(thiocarbobyl)]-β*-L-*arabinopyranoside (***4c**).—A solution of 1,1′-thiocarbonyldiimidazole (668 mg, 3.75 mmol) and (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**, 500 mg, 1.78 mmol) in dry THF (30 mL) was stirred under reflux overnight. After evaporation of the solvent, the remaining yellow residue was filtered through a short silica gel pad washing with a 3:1 hexane–EtOAc. The filtrate was concentrated to give benzyl 3,4-*O*-isopropylidene-2-*O*-[1-imidazolyl(thiocarbonyl)]-β-L-arabinopyranoside (**4c**), which was used for the next step without further purification.

Benzyl 3,4-O-*isopropylidene-2*-O-*[methyloxalyl]-β*-L-*arabinopyranoside* (**4d**).—To a stirred solution of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**, 0.5 g, 1.78 mmol) and pyridine (0.6 mL, 7.14 mmol) in anhyd CH_2Cl_2 (10 mL), methyl chlorooxalate (0.2 mL, 2.14 mmol) was added at rt. The colorless solution was stirred for 2 h at rt, and then diluted with 200 mL of CH_2Cl_2. The organic layer was washed with water, 2 N HCl, and brine, dried over $MgSO_4$, filtered, and evaporated to give benzyl 3,4-*O*-isopropylidene-2-*O*-[methyloxalyl]-β-L-arabinopyranoside (**4d**), which was used for the next step without further purification.

Benzyl 3,4-O-*isopropylidene-2*-O-*[phenoxythiocarbonyl]-β*-L-*arabinopyranoside* (**4e**).—To a stirred solution of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**, 0.5 g, 1.78 mmol) and pyridine (0.6 mL, 7.14 mmol) in anhyd CH_2Cl_2 (15 mL), phenyl chlorothionoformate (0.3 mL, 2.14 mmol) was added at rt. The resulting yellow solution was stirred for 2 h at rt until the color changed to green. After evaporation of the solvent, the residue was filtered through a short silica gel pad using a 10:1 hexane–EtOAc as the eluent. The filtrate was concentrated to give benzyl 3,4-*O*-isopropylidene-2-*O*-[phenoxythiocarbonyl]-β-L-arabinopyranoside (**4e**), which was used for the next step without further purification.

Benzyl 3,4-O-*isopropylidene-2*-O-*[phenoxythiocarbonyl]-β*-L-*arabinopyranoside* (**4f**).—To a stirred solution of thiophosgene (40.8 mL, 0.535 mol) in dry CH_2Cl_2 (500 mL), a solution of phenol (53.75 g, 0.571 mol) and pyridine (57.7 mL, 0.714 mol) in 250 mL of CH_2Cl_2 was slowly added (over 30 min) at 0 °C. The resulting dark wine–red solution was stirred for 30 min at rt. To this solution, a solution of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3,** 100 g, 0.357 mol) and pyridine (57.7 mL, 0.714 mol) in dry CH_2Cl_2 (500 mL) was added over 30 min. The resulting dark-green solution was stirred for 1 h at rt. The reaction mixture was diluted with 1 L of CH_2Cl_2 and washed with water (5 × 100 mL), satd $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude dark brown benzyl 3,4-*O*-isopropylidene-2-*O*-phenoxythiocarbonyl-β-L-arabinopyranoside (**4f**), which was used for the next step without further purification.

(+)-Benzyl 2-deoxy-β-L-erythro-*pentopyranoside* (**5**)

Method A. Conversion of **4a** *to* **5** *is representative.* A solution of crude benzyl 3,4-*O*-isopropylidene-2-*O*-[(methylthio)thiocarbonyl]-β-L-arabinopyranoside (**4a**, 2.0 g, 5.44 mmol), *n*-Bu_3SnH (2.19 mL, 8.15 mmol), and AIBN (90 mg, 0.54 mmol) in toluene was heated to reflux, and then a solution of AIBN (90 mg, 0.54 mmol) in 5 mL of toluene was slowly added over 30 min. The

resulting solution was refluxed for an additional 1 h. After solvent evaporation, the resulting residue was purified by column chromatography on silica gel (20:1 hexane–EtOAc) to give (+)-benzyl 2-deoxy-β-L-*erythro*-pentopyranoside (**5**, 768 mg, 2.93 mmol, 54% yield) as a colorless oil.

*(+)-Benzyl 2-deoxy-β-*L-erythro-*pentopyranoside* (**5**)

Method B. Conversion of **4f** *to* **5** *is representative*. To a refluxing solution of the crude benzyl 3,4-*O*-isopropylidene-2-*O*-phenoxythiocarbonyl-β-L-arabinopyranoside (**4f**) obtained above in anhyd toluene (1.5 L), a solution of nBu$_3$SnH (114.0 mL, 0.535 mol) and AIBN (11.8 g, 0.071 mol) in 500 mL of anhyd toluene was added over 1 h. After the addition, the brown solution was stirred for additional 30 min under reflux. The reaction mixture was concentrated under reduced pressure and filtered through a short silica gel (2–20 μm) pad (20 cm height, 10 cm in diameter) washing with a 6:1 hexane–EtOAc. The filtrate was washed with 5% NaOH solution, water, and brine, dried over $MgSO_4$, filtered, and evaporated to give 88.9 g of a mixture of (+)-benzyl 2-deoxy-β-L-*erythro*-pentopyranoside (**5**) and phenol as a colorless syrup. An analytical sample was obtained by column chromatography on silica gel (12:1 hexane–EtOAc): $[\alpha]_D^{23}$ 122.23° (*c* 8.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47–7.35 (m, 5 H), 5.08 (t, *J* 5.3 Hz, 1 H), 4.88 (d, *J* 11.9 Hz, 1 H), 4.60 (d, *J* 11.9 Hz, 1 H), 4.56 (q, *J* 5.7 Hz, 1 H), 4.25 (dt, *J* 6.5, 2.6 Hz, 1 H), 4.00 (dd, *J* 12.9, 2.8 Hz, 1 H), 3.87 (dd, *J* 12.9, 2.3 Hz, 1 H), 2.27 (dt, *J* 14.7, 4.6 Hz, 1 H), 1.96 (ddd, *J* 14.7, 6.0, 4.7 Hz, 1 H), 1.61 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.8, 128.3, 127.7, 127.5, 108.4, 95.6, 71.9, 69.8, 69.1, 61.1, 31.4, 27.2, 25.3; HRFABMS (*m*/*z*) Found: 265.1420, Calcd for $C_{15}H_{21}O_4$: 265.1440 $[M+H]^+$. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.93; H, 7.72.

*2-Deoxy-*L-erythro-*pentose (2-deoxy-*L-*ribose*, **6**).—A mixture of crude (+)-benzyl 2-deoxy-β-L-*erythro*-pentopyranoside (**5,** 73 g) in 4% aq trifluoroacetic acid was stirred for 10 h at 40 °C. The reaction mixture was poured into a separatory funnel and washed with EtOAc (3 × 500 mL). The aqueous layer was filtered through Amberlite® IRA 400 (OH^- form) ion-exchange resin and evaporated to dryness. The remaining syrup was coevaporated with EtOH and toluene twice and dried in vacuo to give 26 g (0.194 mol, 70% yield based on (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**)) of 2-deoxy-L-ribose (**6**) as a pale-yellow syrup. Anal. Calcd for $C_5H_{10}O_4 \cdot 0.1\ H_2O$: C, 44.18; H, 7.56 Found: C, 43.87; H, 7.26.

N-*(6-Benzyloxy-2,2-dimethyldihydro-[1,3]dioxolo-[4,5-*c*]pyran-7-yl)-*N′*-(4-toluenesulfonyl)hydrazine* (**4j**).—To a stirred solution of (+)-benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**3**, 3.0 g, 10.71 mmol) in dry CH_2Cl_2, pyridinium dichromate (PDC, 2.14 g, 5.68 mmol) and Ac_2O (2.93 mL, 31.05 mmol) were added at 0 °C. The resulting dark-brown mixture was stirred for 5 h under reflux, and then 0.5 equiv (2.14 g, 5.68 mmol) of PDC was added. The reaction mixture was stirred for 3 h under reflux. Solvent was evaporated to one third, and then EtOAc (100 mL) was added to the mixture. The mixture was filtered through a Celite pad, and the filtrate was purified by filtration through a silica gel pad washing with EtOAc. Evaporation under reduced pressure gave the corresponding ketone as a pale-yellow syrup, which was used for the next step without further purification.

A solution of the crude ketone obtained above (3.0 g, 10.8 mmol) and *p*-toluenesulfonhydrazide in abs EtOH was stirred for 2 h under reflux. The reaction mixture was cooled down and concentrated to give a yellow syrup which was purified by column chromatography on silica gel (4:1 hexane–EtOAc) to give a 2:1 cis- and trans-mixture of *N*-(6-benzyloxy-2,2-dimethyldihydro-[1,3]dioxolo[4,5-*c*]pyran-7-ylidene)-*N′*-(4-toluenesulfonyl)hydrazine (3.52 g, 7.89 mmol, 73% yield based on compound **3**) as a pale-yellow foam. The major isomer: ^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1 H), 7.74 (d, *J* 8.2 Hz, 2 H), 7.39–7.14 (m, 7 H), 5.07 (s, 1 H), 4.82 (d, *J* 5.5 Hz, 1 H), 4.59 (d, *J* 11.5 Hz, 1 H), 4.44 (d, *J* 11.5 Hz, 1 H), 4.16 (d, *J* 5.3 Hz, 1 H), 4.04 (m, 1 H), 3.90 (d, *J* 13.4 Hz, 1 H), 2.32 (s, 3 H), 1.26 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.17, 143.91, 136.45, 135.32, 129.33, 128.45, 128.21, 127.75, 127.48, 110.32, 97.93, 73.55, 71.11, 69.12, 57.28, 26.14, 25.69, 21.29. The minor isomer: ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 1 H), 7.58 (d, *J* 8.2 Hz, 2 H), 7.39–7.14 (m, 7 H), 5.35 (s, 1 H), 4.72 (d, *J* 11.4 Hz, 1 H), 4.61–4.52 (m, 2 H), 4.44 (d, *J* 11.5 Hz, 1 H), 3.63–3.55 (m, 2 H), 2.30 (s, 3 H), 1.41 (s, 3 H), 1.23 (s, 3 H).

To a stirred solution of *N*-(6-benzyloxy-2,2-dimethyldihydro-[1,3]dioxolo[4,5-*c*]pyran-7-ylidene)-*N′*-(4-toluenesulfonyl)hydrazine (770 mg, 1.72 mmol) in a 1:1 mixture of THF (10 mL) and MeOH (10 mL), a trace of methyl orange and sodium cyanoborohydride (108 mg, 1.72 mmol) were added, and then methanolic HCl (satd) was added dropwise keeping the color of the solution at the reddish–yellow transition-point. The mixture was stirred at rt for 1 h. A second portion of sodium cyanoborohydride (108 mg, 1.72 mmol) was added, followed by dropwise addition of methanolic HCl to maintain the pH at 3.8. The reaction mixture was stirred for another 1 h, and then neutralized with satd $NaHCO_3$. The mixture was evaporated to dryness, dissolved in water, and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to give yellow syrup, which was purified by column chromatography on silica gel (3:1 hexane–EtOAc) to give *N*-(6-benzyloxy-2,2-dimethyldihydro-[1,3]dioxolo[4,5-*c*]pyran-7-yl)-*N′*-(4-toluenesulfonyl)hydrazine (**4j**, 256 mg, 0.57 mmol, 33% yield) and unreacted starting

material (the major double-bond isomer, 356 mg, 0.80 mmol, 46% yield): For compound **4j** $[\alpha]_D^{25}$ 95.5° (*c* 3.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.99 (d, *J* 8.3 Hz, 2 H), 7.61–7.50 (m, 5 H), 7.45 (d, *J* 8.3 Hz, 2 H), 6.79 (s, 1 H), 5.00 (d, *J* 11.8 Hz, 1 H), 4.89 (d, *J* 6.9 Hz, 1 H), 4.72 (d, *J* 11.8 Hz, 1 H), 4.63 (dd, *J* 7.2, 3.3 Hz, 1 H), 4.37 (dt, *J* 7.2, 2.7 Hz, 1 H), 4.17 (br, 1 H), 3.89 (dd, *J* 12.8, 2.9 Hz, 1 H), 3.79 (dd, *J* 12.8, 2.6 Hz, 1 H), 3.03 (br, 1 H), 2.62 (s, 3 H), 1.63 (s, 3 H), 1.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.95, 137.08, 134.76, 129.49, 128.52, 128.23, 127.91, 109.70, 98.73, 72.80, 71.91, 69.33, 62.32, 58.27, 26.35, 24.94, 21.52; HRFABMS (*m*/*z*) Found: 449.1764, Calcd for $C_{22}H_{29}N_2O_6S$: 449.1746 $[M+H]^+$. Anal. Calcd for $C_{22}H_{28}N_2O_6S$: C, 58.91; H, 6.29; N, 6.25. Found: C, 59.17; H, 6.39; N, 6.22. For the recovered starting material: $[\alpha]_D^{26}$ 199.7° (*c* 4.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.87 (s, 1 H), 7.72 (d, *J* 8.3 Hz, 2 H), 7.29–7.19 (m, 7 H), 5.06 (s, 1 H), 4.83 (d, *J* 5.6 Hz, 1 H), 4.58 (d, *J* 11.5 Hz, 1 H), 4.46 (d, *J* 11.5 Hz, 1 H), 4.15 (d, *J* 5.5 Hz, 1 H), 4.05 (m, 1 H), 3.90 (d, *J* 13.4 Hz, 1 H), 2.33 (s, 3 H), 1.26 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.09, 144.03, 136.58, 135.49, 129.46, 128.38, 127.93, 127.89, 127.66, 110.51, 98.14, 73.72, 71.28, 69.35, 57.44, 26.30, 25.87, 21.47

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