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Chemoenzymatic Synthesis of *C*-4′-Spiro-oxetanoribonucleosides

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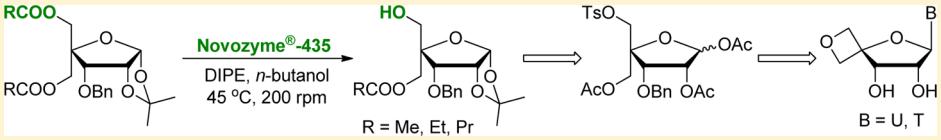
Supporting Information



ABSTRACT: Novozyme-435-mediated diastereoselective deacylation of one of the two diastereotopic acyloxymethyl groups in 5-*O*-acyl-4-*C*-acyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose has been achieved in quantitative yield. The exclusive selectivity of the lipase for the 5-*O*-acyl over the 4-*C*-acyloxymethyl group in the substrate was confirmed by chemical transformation of enzymatically monodeacetylated compound to 1,2-*O*-isopropylidene-*C*-4-spiro-oxetanoribofuranose. Further, the selective biocatalytic deacylation methodology has been utilized for the efficient synthesis of *C*-4′-spiro-oxetanoribonucleosides of uracil (U) and thymine (T) in 37 and 45% overall yields, respectively.

In the recent past, there has been an upsurge in the synthesis of conformationally constrained nucleoside analogues by modifying the sugar moiety in various ways.[1] Paquette[2] introduced the concept of spirocyclic restriction in nucleosides through insertion of a carbocyclic ring at *C*-4′ position of furanose ring. It has been envisaged that the presence of spiro-carbon in nucleoside restricts the conformational flipping of the furanose ring and thus enhances the selectivity and biological activity.[2−9] This has led to the synthesis of different classes of spironucleosides, such as *C*-1′-spiro-,[3,4] *C*-2′-spiro-,[5,6] *C*-3′-spiro-,[7,8] and *C*-4′-spironucleoside;[9−11] many of them have shown excellent antiviral activities.

Recently, it has been demonstrated that Novozyme-435 mediates diastereoselective transfer of an acetyl group from vinyl acetate to one of the two primary hydroxyl groups in 3-*O*-benzyl-4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (**1**), which has been efficiently used for the synthesis of bicyclic nucleosides (LNA monomers) in high yields.[12] This biocatalytic reaction has revealed exclusive preference of Novozyme-435 for the *C*-5 hydroxyl group over the *C*-4-(hydroxymethyl) group in the compound. We anticipated from the reaction that Novozyme-435 should also exhibit a similar preference for the deacylation of *C*-5-*O*-acyl over *C*-4-acyloxymethyl groups in its corresponding diacylated compounds **2** and thus can be utilized for the synthesis of *C*-4′-spiro-oxetanoribonucleosides, which have otherwise not been synthesized by classical chemical approaches.[11]

The diacylated compounds, i.e., 5-*O*-acyl-4-*C*-[(acyloxy)-methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose **2a−c**, were synthesized in quantitative yields by peracylation of dihydroxy sugar **1**[12] using the corresponding acid anhydrides in the presence of DMAP (Scheme 1). In a typical biocatalytic reaction, *n*-butanol was added as an acyl trapper to a solution of compound **2a−c** in DIPE and incubated with Novozyme-435 (50% w/w) at 45 °C and at 200 rpm in an incubator shaker. The lipase-mediated reaction led to the formation of a single product with slightly lower R_f value than the starting material as indicated by TLC examination. On completion, the reaction was quenched by filtering off the enzyme, and solvent was removed under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to afford monodeacylated compound in 90−96% yield, which was identified as 4-*C*-[(acyloxy)methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose **3a−c** on the basis of their spectral (IR, ^{1}H, ^{13}C NMR, ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, and HRMS) data analysis (Scheme 1). Although the length of acyl chain in acylated compounds **2a−c** does not affect selectivity of the lipase, the rate of reaction increases with increase in the lipophilicity and bulk of the acyl group in compound **2**, which was found in accordance with the "Kazlauskas rule".[13] That is, the rate of lipase-mediated debutanoylation reaction was 1.25 times faster than depropanoylation reaction, which in turn was 1.2 times faster than deacetylation. The biocatalytic deacylation reaction carried out under identical conditions, but without Novozyme-435, did not yield any product.

The structure of the monodeacetylated compound **3a** was further confirmed by its chemical transformation to 1,2-*O*-isopropylidene-*C*-4-spiro-oxetanoribofuranose (**6**) (Scheme 2). Thus, the debenzylation of **3a** afforded the dihydroxy compound **4**, which on selective mesylation of the primary hydroxyl group resulted in monomesylated derivative **5**. Subsequent deacetylation under alkaline conditions concomitantly led to intramolecular cyclization to form the spiro sugar derivative **6**, which confirms the structure of enzymatically

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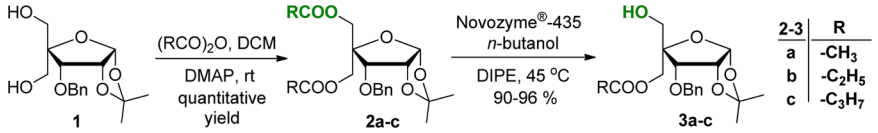
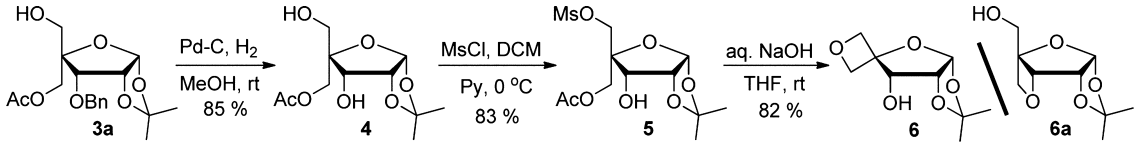
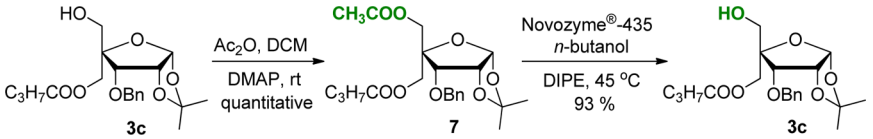
Scheme 1. Synthesis and Biocatalytic Deacylation Studies on 5-*O*-Acyl-4-*C*-acyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose 2a−c



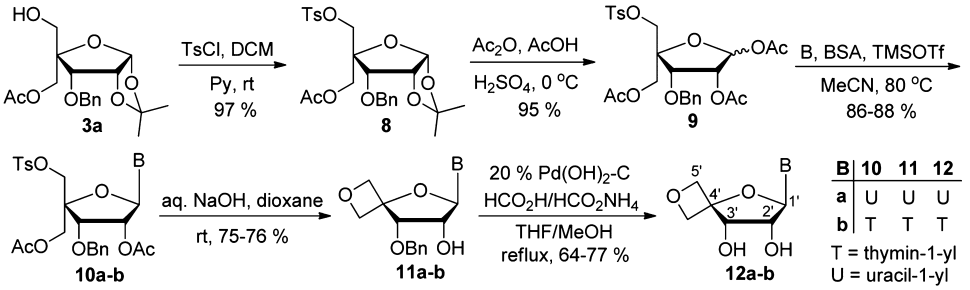
Scheme 2. Conversion of Novozyme-435-Catalyzed Monodeacetyled Compound 3a to Spiro-sugar Derivatine 6



Scheme 3. Novozyme-435-Mediated Deacylation Studies on Mixed Ester 7



Scheme 4. Chemoenzymatic Convergent Synthesis of *C*-4′-Spiro-oxetanoribonucleosides 12a,b



monodeacylated product as 4-*C*-(acetoxymethyl)-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose (**3a**). The alternative regioisomeric hydroxyl product, if formed during the lipase-mediated deacylation reaction, would have led to the bicyclic sugar derivative, 1,2-*O*-isopropylidene-3-*O*,4-*C*-methylene-α-D-ribofuranose (**6a**), under identical series of transformation (Scheme 2).[12] This result also confirms the structure of monodeacylated compounds **3b** and **3c** obtained from dipropanoate **2b** and dibutanoate **2c**, respectively.

The problem of acyl migration has been encountered in 1,3-diols and partially acylated polyhydroxy compounds.[14] Thus, there is a possibility of formation of 5-*O*-acyl-3-*O*-benzyl-4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose due to Novozyme-435-mediated deacylation of *C*-4-[(acyloxy)methyl] and subsequent migration of acyl group from *C*-5 to *C*-4 position. This problem was addressed by carrying out lipase-mediated deacylation reaction on mixed ester, i.e. 5-*O*-acetyl-3-*O*-benzyl-4-*C*-[(butanoyloxy)methyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (**7**). The mixed ester **7** was synthesized by acetylation of monodebutanoylated compound **3c** in quantitative yield (Scheme 3). It was observed that biocatalytic deacylation reaction on mixed ester **7** under standardized condition led to the formation of same compound, i.e. 3-*O*-benzyl-4-*C*-[(butanoyloxy)methyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (**3c**), which was also obtained from debutanoylation of dibutanoylated sugar derivative **2c**. If it would have been a case of acyl migration, a diastereomeric mixture of monodeacetylated compounds would have been obtained. The formation of only compound **3c** on lipase-mediated deacylation reaction on mixed ester **7** proved that Novozyme-435 has exclusive preference for the deacylation of acyloxy group at C-5 position of diacylated sugar derivatives **2a−c**.

The synthesis of *C*-4′-spiro-oxetanoribonucleosides **12a,b** was successfully achieved from monotosylated compound **8** obtained by tosylation of enzymatically deacetylated compound **3a** using *p*-toluenesulfonyl chloride in pyridine−DCM in 40 and 48% overall yields, respectively. Further, acetolysis of tosylated compound **8** led to the formation of triacetylated glycosyl donor **9** in 95% yield. The Vorbrüggen nucleoside coupling reaction of glycosyl donor **9** with nucleobases uracil and thymine in acetonitrile in the presence of *N*,*O*-bis-(trimethylsilyl)acetamide and trimethylsilyl trifluoromethanesulfonate afforded 4′-*C*-(acetoxymethyl)-2′-*O*-acetyl-3′-*O*-benzyl-5′-*O*-(*p*-toluenesulfonyl)uridine (**10a**) and 4′-*C*-(acetoxymethyl)-2′-*O*-acetyl-3′-*O*-benzyl-5′-*O*-(*p*-toluenesulfonyl)-thymidine (**10b**) in 86 and 88% yield. Nucleosides **10a,b** on deacetylation with aq NaOH in dioxane simultaneously led to the intramolecular cyclization leading to formation of benzylated spironucleosides **11a,b** in 76 and 75% yields, respectively. The debenzylation of nucleosides **11a,b** with 20% $Pd(OH)_2$−C led to the formation of *C*-4′-spiro-oxetanouridine (**12a**) and *C*-4′-spiro-oxetanoribothymidine (**12b**) in 64 and 77% yields, respectively (Scheme 4). It is worth mentioning that a previous attempt to synthesize *C*-4′-spiro-oxetanonucleosides failed due to susceptibility of the oxetane ring toward Lewis acid catalysts.[11] In the present paper, the synthesis of

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desired C-4′-spironucleosides has been easily achieved from suitably heterofunctionalized nucleosides obtained from a chemoenzymatic route.

The structures of all the synthesized compounds, i.e., **1**, **2a−c**, **3a−c**, **4−9**, **10a,b**, **11a,b**, and **12a,b** were established on the basis of their spectral (IR, ^{1}H, ^{13}C NMR, ^{1}H−^{1}H COSY, ^{1}H−^{1}H NOESY, ^{1}H−^{13}C HMQC, and HRMS) data analysis. The structure of the known compound **1** was further confirmed by the comparison of its physical and spectral data with those reported in the literature.[15]

In summary, Novozyme-435-catalyzed diastereoselective deacylation of one of the two diastereotopic acyloxymethyl functions of 5-*O*-acyl-4-*C*-[(acyloxy)methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose has been optimized for the first time. The developed biocatalytic methodology has been utilized for the synthesis of novel C-4′-spiro-oxetanoribonucleoside of uracil (U) and thymine (T), allowing an easy access to conformationally restricted C-4′-spiro-oxetanoribonucleosides.

EXPERIMENTAL SECTION

Materials. The *Candida antarctica* lipase-B (CAL-B or Novozyme-435) immobilized on polyacrylate was purchased from a commercial supplier. The enzyme was dried over P_2O_5 under vacuum for 24 h prior to use. For all the lipase-mediated reactions, AR-grade organic solvents were used, which were purchased from a commercial supplier.

General Procedure for the Synthesis of Diacylated Ribofuranose 2a−c. To a solution of 3-*O*-benzyl-4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (**1**) (0.64 g, 2.0 mmol) in DCM, acid anhydride (acetic, propanoic, or butanoic anhydride; 4.2 mmol) and a catalytic amount of DMAP (0.2 mmol) were added. The reaction mixture was stirred at rt for 2−4 h and then was poured into ice−water. The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic extract was washed with saturated aq bicarbonate solution (2 × 25 mL) and water (1 × 25 mL) and dried over anhydrous sodium sulfate. The excess solvent was evaporated under reduced pressure, and the residue thus obtained was purified by silica gel column chromatography using ethyl acetate in hexane as eluent to afford the diacylated compounds **2a−c** in quantitative yields.

*4-C-(Acetoxymethyl)-5-O-acetyl-3-O-benzyl-1,2-O-isopropylidene-α-D-ribofuranose (**2a**).* Compound **2a** was obtained as a colorless viscous oil (0.78 g, 99%): R_f = 0.5 (40% ethyl acetate in hexane); $[\alpha]^{31}_D$ = +56.8 (*c* 0.1, MeOH); IR (thin film) ν_{max} 2986, 2942, 1743, 1455, 1383, 1167, 1104, 1047, 1023, 872, 742, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 and 1.64 (6H, 2s), 1.97 and 2.08 (6H, 2s), 4.01 (1H, d, *J* = 11.6 Hz), 4.05 (1H, d, *J* = 5.2 Hz), 4.24 (1H, d, *J* = 11.6 Hz), 4.35 (1H, d, *J* = 12.8 Hz), 4.53 (1H, d, *J* = 12.4 Hz), 4.65−4.70 (2H, m), 4.78 (1H, d, *J* = 12.4 Hz), 5.76 (1H, d, *J* = 3.6 Hz), 7.31−7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7, 20.9, 26.0, 26.4, 64.0, 64.5, 72.4, 78.2, 78.5, 83.5, 104.2, 113.8, 127.8, 128.1, 128.4, 137.1, 170.4, 170.7; HR-ESI-TOF-MS *m*/*z* 417.1516 ([M + Na]$^+$), calcd for $[C_{20}H_{26}O_8 + Na]^+$ 417.1520.

*3-O-Benzyl-1,2-O-isopropylidene-5-O-propanoyl-4-C-[(propanoyloxy)methyl]-α-D-ribofuranose (**2b**).* Compound **2b** was obtained as a yellow oil (0.82 g, 98%): R_f = 0.5 (40% ethyl acetate in hexane); IR (thin film) ν_{max}: 1744, 1420, 1381, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07, 1.12 (6H, 2t, *J* = 7.5 Hz), 1.34 and 1.65 (6H, 2s), 2.23 and 2.35 (4H, 2 doublet of quartet, *J* = 2.1, 7.5 Hz), 4.03, 4.25, 4.38, and 4.68 (4H, 4d, *J* = 12 Hz, 2H each), 4.05 (1H, d, *J* = 5.1 Hz), 4.54 and 4.78 (2H, 2d, *J* = 12 Hz), 4.67 (1H, d, *J* = 4.8 Hz), 5.75 (1H, d, *J* = 3.9 Hz), 7.36−7.31 (5H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.0, 9.1, 26.0, 26.5, 27.4, 27.5, 63.9, 64.5, 72.4, 78.4, 78.6, 83.7, 104.21, 113.9, 127.8, 128.1, 128.5, 137.2, 173.8, 174.1; HR-ESI-TOF-MS *m*/*z* 445.1831 ([M + Na]$^+$), calcd for $[C_{22}H_{30}O_8 + Na^+]$ 445.1833.

*3-O-Benzyl-5-O-butanoyl-4-C-[(butanoyloxy)methyl]-1,2-O-isopropylidene-α-D-ribofuranose (**2c**).* Compound **2c** was obtained a yellow oil (0.9 g, 98%): R_f = 0.6 (40% ethyl acetate in hexane); IR (thin film) ν_{max} 1741, 1450, 1381, 1227, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87−0.95 (6H, m), 1.34 (3H, s), 1.51−1.67 (7H, m), 2.20 (2H, t, *J* = 7.6 Hz), 2.30 (2H, doublet of a triplet, *J* = 1.8, 7.5 Hz), 4.00, 4.26, 4.37, and 4.68 (4H, 4d, *J* = 12 Hz), 4.05 (1H, d, *J* = 5.4 Hz), 4.65 (1H, d, *J* = 5.4 Hz), 4.54 and 4.78 (2H, 2d, *J* = 12 Hz), 5.75 (1H, d, *J* = 3.6 Hz), 7.34−7.26 (5H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 18.3, 18.4, 26.1, 26.5, 36.0, 36.1, 64.8, 64.4, 72.4, 78.4, 78.6, 83.7, 104.2, 113.9, 127.8, 128.1, 128.5, 137.2, 173.0, 173.3; HR-ESI-TOF-MS *m*/*z* 473.2141 ([M + Na]$^+$), calcd for $[C_{24}H_{34}O_8 + Na^+]$ 473.2146.

General Procedure for Selective Biocatalytic Monodeacylation: Synthesis of Monoesters 3a−c. To a solution of diacylated compound **2a−c** (1.0 mmol) in DIPE (10 mL) was added *n*-butanol (0.09 mL, 1.0 mmol) followed by the addition of Novozyme-435 (50% w/w). The reaction mixture was stirred at 45 °C in an incubator shaker at 200 rpm. After 30−38 h, the reaction was quenched by filtering off Novozyme-435, the solvent was removed under reduced pressure, and the residue thus obtained was purified by silica gel column chromatography using ethyl acetate in hexane as gradient solvent system to afford monodecylated compound **3a−c** in 90−96% yield.

*4-C-(Acetoxymethyl)-3-O-benzyl-1,2-O-isopropylidene-α-D-ribofuranose (**3a**).* Compound **3a** was obtained as a colorless viscous oil (1.71 g, 96%): R_f = 0.3 (40% ethyl acetate in hexane); $[\alpha]^{30}_D$ = +48.7 (*c* 0.1, MeOH); IR (thin film) ν_{max} 3473, 2985, 2940, 1739, 1456, 1383, 1239, 1213, 1166, 1103, 1047, 1021, 874, 741, 699 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.27 and 1.47 (6H, 2s), 1.99 (3H, s), 3.33−3.39 (1H, m), 3.50 (1H, dd, *J* = 4.4 and 11.6 Hz), 4.09 (1H, d, *J* = 12.4 Hz), 4.23 (1H, d, *J* = 5.2 Hz), 4.47 (1H, d, *J* = 12.0 Hz), 4.55 (1H, d, *J* = 12.4 Hz), 4.66 (1H, d, *J* = 11.6 Hz), 4.78 (1H, dd, *J* = 3.6 and 5.2 Hz), 4.89−4.92 (1H, m), 5.71 (1H, d, *J* = 4.0 Hz), 7.28−7.38 (5H, m); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 20.7, 26.0, 26.4, 61.9, 64.0, 71.5, 78.3, 78.3, 85.1, 103.7, 112.3, 127.3, 127.5, 128.2, 138.1, 170.2; HR-ESI-TOF-MS *m*/*z* 375.1405 ([M + Na]$^+$), calcd for $[C_{18}H_{24}O_7 + Na]^+$ 375.1414.

*3-O-Benzyl-1,2-O-isopropylidene-4-C-[(propanoyloxy)methyl]-α-D-ribofuranose (**3b**).* Compound **3b** was obtained as a yellow viscous oil (0.50 g, 91%): R_f = 0.5 (60% ethyl acetate in hexane); IR (thin film) ν_{max} 2943, 1740, 1370, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, t, *J* = 7.5 Hz, CH_3CH_2OCO), 1.33 and 1.64 (6H, 2s), 1.95 (1H, brs), 2.35 (2H, doublet of quatret, *J* = 2.1, *J* = 7.5 Hz), 3.42 and 3.74 (2H, 2d, *J* = 12 Hz), 4.23 (1H, d, *J* = 5.1 Hz), 4.40 and 4.66 (2H, 2d, *J* = 12.6 Hz), 4.60 and 4.78 (2H, 2 d, *J* = 12 Hz), 4.64 (1H, d, *J* = 4.8 Hz), 5.75 (1H, d, *J* = 3.9 Hz), 7.36−7.31 (5H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.1, 25.9, 26.5, 27.4, 63.0, 64.0, 72.6, 77.9, 78.6, 85.4, 104.2, 113.7, 127.8, 128.5, 128.0, 137.5, 174.5; HR-ESI-TOF-MS *m*/*z* 389.1574 ([M + Na]$^+$), calcd for $[C_{19}H_{26}O_7 + Na^+]$ 389.1571.

*3-O-Benzyl-4-C-[(butanoyloxy)methyl]-1,2-O-isopropylidene-α-D-ribofuranose (**3c**).* Compound **3c** was obtained light yellow viscous oil (0.51 g, 90%): R_f = 0.6 (50% ethyl acetate in hexane); IR (thin film) ν_{max} 2985, 1740, 1381, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.5 Hz), 1.33 (3H, s), 1.58−1.67 (5H, m), 1.97 (1H, brs), 2.31 (2H, doublet of a triplet, *J* = 1.8 and 7.5 Hz), 3.41 and 3.73 (2H, 2d, *J* = 12 Hz), 4.23 (1H, d, *J* = 5.1 Hz), 4.38 and 4.67 (2H, 2d, *J* = 12.3 Hz), 4.64 (1H, d, *J* = 5.1 Hz), 4.60 and 4.78 (2H, 2d, *J* = 12 Hz), 5.75 (1H, d, *J* = 3.9 Hz), 7.37−7.26 (5H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 18.5, 25.9, 26.5, 36.1, 62.9, 63.9, 72.6, 77.9, 78.6, 85.4, 104.2, 113.7, 127.8, 128.0, 128.5, 137.4, 173.8; HR-ESI-TOF-MS *m*/*z* 403.1722 ([M + Na]$^+$), calcd for $[C_{20}H_{28}O_7 + Na^+]$ 403.1727.

*4-C-(Acetoxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose (**4**).* To a stirred solution of compound **3a** (0.50 g, 1.42 mmol) in dry methanol (10 mL), Pd−C (0.25 g) was added. The reaction mixture was stirred for 4 h under H_2 atmosphere at rt. The catalyst was filtered off and washed with methanol. The excess of solvent was removed under reduced pressure, the crude product thus obtained was purified by silica gel column chromatography using methanol in chloroform as gradient solvent system to afford compound **4** as white solid (0.31 g, 85%): R_f = 0.3 (5% methanol in chloroform); mp 110−112 °C; $[\alpha]^{32}_D$ = +8.85 (*c* 0.05, MeOH); IR (thin film) ν_{max} 3448, 2987, 2942, 1735, 1385, 1246, 1214, 1166, 1134, 1046, 1018, 874 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 and 1.64 (6H, 2s), 2.10 (3H, s), 2.15 (1H,

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brs), 2.79 (1H, dd, J = 3.6 and 8.4 Hz), 3.59 (1H, dd, J = 5.6 and 11.6 Hz), 3.73 (1H, d, J = 11.6 Hz), 4.34−4.40 (2H, m), 4.51 (1H, d, J = 11.6 Hz), 4.70 (1H, dd, J = 4.4 and 6.0 Hz), 5.84 (1H, d, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 20.9, 26.1, 26.4, 63.5, 63.7, 72.2, 79.5, 86.1, 104.4, 113.5, 171.3; HR-ESI-TOF-MS m/z 285.0945 ([M + Na]$^+$), calcd for [$C_{11}H_{18}O_7$ + Na]$^+$ 285.0945.

*4-C-(Acetoxymethyl)-1,2-O-isopropylidene-5-O-(methanesulfonyl)-α-D-ribofuranose (**5**).* A solution of compound **4** (0.30 g, 1.14 mmol) and methanesulfonyl chloride (0.10 mL, 1.26 mmol) in anhydrous dichloromethane:pyridine (10 mL, 4:1) was stirred at 0 °C for 4 h. On completion, the reaction mixture was poured over 10% ice-cold hydrochloric acid solution and extracted with chloroform (3 × 100 mL). The combined organic extract was washed with saturated aq sodium bicarbonate solution (2 × 100 mL), dried over anhydrous sodium sulfate, and excess of solvent was removed under reduced pressure. The residue thus obtained was purified by silica gel column chromatography using ethyl acetate in hexane as eluent to afford the mesylated compound **5** as colorless viscous oil (0.32 g, 83%): R_f = 0.5 (5% methanol in chloroform); $[\alpha]^{30}_D$ = +12.32 (c 0.1, MeOH); IR (thin film) ν_{max} 3482, 2988, 2940, 1736, 1376, 1354, 1240, 1175, 1094, 1047, 1019, 970, 874 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.25 and 1.47 (6H, 2s), 2.03 (3H, s), 3.20 (3H, s), 4.11 (1H, d, J = 12.4 Hz), 4.17 (1H, d, J = 10.8 Hz), 4.24−4.27 (2H, m), 4.51 (1H, d, J = 12.4 Hz), 4.61 (1H, t, J = 4.0 Hz), 5.65 (1H, d, J = 6.0 Hz), 5.69 (1H, d, J = 2.8 Hz); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 20.7, 25.7, 26.3, 36.8, 63.6, 69.5, 71.3, 79.9, 82.9, 103.4, 112.4, 170.2; HR-ESI-TOF-MS m/z 363.0716 ([M + Na]$^+$), calcd for [$C_{12}H_{20}O_9S$ + Na]$^+$ 363.0720.

*1,2-O-Isopropylidene-C-4-spiro-oxetanoribofuranose (**6**).* To a stirred solution of compound **5** (0.25 g, 0.73 mmol) in water/THF (2 mL, 1:1), 2 M NaOH (1.5 mL) was added, and reaction mixture was stirred at rt for 1 h. The reaction mixture was extracted with ethyl acetate (3 × 100 mL), washed with saturated aq sodium bicarbonate solution (2 × 100 mL) and brine solution (2 × 100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography using ethyl acetate in hexane as gradient solvent system to give **6** as white solid in (0.12 g, 82%): R_f = 0.5 (5% methanol in chloroform); mp 104−106 °C; $[\alpha]^{32}_D$ = −5.21 (c 0.05, MeOH); IR (thin film) ν_{max} 3402, 2924, 2852, 1722, 1458, 1376, 1314, 1253, 1215, 1186, 1165, 1136, 1096, 1015, 975, 873 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.20 and 1.33 (6H, 2s), 3.82 (1H, dd, J = 3.6 and 6.0 Hz), 4.43−4.46 (2H, m), 4.56 (2H, t, J = 8.0 Hz), 4.92 (1H, d, J = 6.8 Hz), 5.60 (1H, d, J = 2.8 Hz), 5.79 (1H, d, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 25.6, 26.6, 72.6, 77.7, 77.9, 78.8, 82.6, 102.8, 111.3; HR-ESI-TOF-MS m/z 225.0727 ([M + Na]$^+$), calcd for [$C_9H_{14}O_5$ + Na]$^+$ 225.0733.

*5-O-Acetyl-3-O-benzyl-4-C-[(butanoyloxy)methyl]-1,2-O-isopropylidene-α-D-ribofuranose (**7**).* It was synthesized from compound **3c** by following the general procedure used for the synthesis of **2a−c** as colorless viscous oil in 98% yield. R_f = 0.5 (30% ethyl acetate in hexane): IR (thin film) ν_{max} 1740, 1381, 1227, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.5 Hz), 1.34 (3H, s), 1.57−1.70 (5H, m), 1.97 (3H, s), 2.30 (2H, doublet of a triplet, J = 2.4, 7.5 Hz), 4.02, 4.24, 4.36, and 4.53 (4H, 4d, J = 12 Hz), 4.05 (1H, d, J = 5.7 Hz), 4.65 (1H, d, J = 5.4 Hz), 4.69 and 4.78 (2H, 2d, J = 12 Hz), 5.76 (1H, d, J = 3.6 Hz), 7.26−7.35 (5H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 18.4, 20.8, 26.0, 26.5, 36.1, 63.8, 64.7, 72.4, 78.3, 78.5, 83.6, 104.2, 113.9, 127.8, 128.1, 128.5, 137.2, 170.42, 173.4; HR-ESI-TOF-MS m/z 445.1836 ([M + Na]$^+$), calcd for [$C_{22}H_{30}O_8$ + Na$^+$] 445.1833.

*4-C-(Acetoxymethyl)-3-O-benzyl-1,2-O-isopropylidene-5-O-(p-toluenesulfonyl)-α-D-ribofuranose (**8**).* A solution of compound **3a** (2.0 g, 5.68 mmol) and p-toluenesulfonyl chloride (1.29 g, 6.82 mmol) in anhydrous dichloromethane:pyridine (40 mL, 4:1) was stirred at rt for 6 h. On completion, the reaction mixture was poured over 10% ice-cold hydrochloric acid solution and extracted with chloroform (3 × 100 mL). The combined organic extract was washed with saturated aq sodium bicarbonate solution (2 × 100 mL) and dried over anhydrous sodium sulfate, and the excess of solvent was removed under reduced pressure. The residue thus obtained was coevaporated with toluene (2 × 50 mL) and dried in vacuo to afford the tosylated compound **8** as colorless viscous oil (2.80 g, 97%): R_f = 0.3 (40% ethyl acetate in hexane); $[\alpha]^{32}_D$ = −2.77 (c 0.05, MeOH); IR (thin film) ν_{max} 3061, 3029, 2988, 1744, 1597, 1498, 1456, 1356, 1312, 1292, 1232, 1189, 1171, 1095, 1024, 874, 839, 816, 753, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 and 1.57 (6H, 2s), 1.94 (3H, s), 2.41 (3H, s), 4.03 (2H, dd, J = 10.0 and 10.4 Hz), 4.13 (1H, d, J = 4.8 Hz), 4.19 (1H, d, J = 12.4 Hz), 4.51 (1H, d, J = 12.4 Hz), 4.55 (1H, t, J = 4.4 Hz), 4.61 (1H, d, J = 12.4 Hz), 4.70 (1H, d, J = 11.6 Hz), 5.61 (1H, d, J = 3.6 Hz), 7.29−7.34 (7H, m), 7.73 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7, 21.6, 25.9, 26.5, 64.0, 69.4, 72.7, 78.4, 83.4, 104.1, 114.0, 127.8, 127.9, 128.1, 128.5, 129.9, 132.5, 137.0, 145.1, 170.4; HR-ESI-TOF-MS m/z 529.1492 ([M + Na]$^+$), calcd for [$C_{25}H_{30}O_9S$ + Na]$^+$ 529.1503.

*4-C-(Acetoxymethyl)-1,2-di-O-acetyl-3-O-benzyl-5-O-(p-toluenesulfonyl)-α,β-D-ribofuranose (**9**).* Acetic anhydride (1.9 mL, 19.8 mmol) and concentrated sulfuric acid (0.01 mL, 0.19 mmol) were added to a stirred solution of compound **8** (1.0 g, 1.98 mmol) in acetic acid (11.3 mL, 198 mmol) at 0 °C, and the resulting reaction mixture was stirred for 6 h at rt. The reaction was quenched by the addition of cold water (100 mL) and stirred for 30 min at rt and was extracted with ethyl acetate (3 × 200 mL). The organic layer was washed with saturated aq sodium bicarbonate solution (3 × 100 mL) and brine solution (2 × 100 mL) and then dried over anhydrous sodium sulfate. The excess of solvent was removed under reduced pressure, and the residue thus obtained was purified by silica gel column chromatography using ethyl acetate in petroleum ether as gradient solvent system to afford an anomeric mixture (α:β = ca. ∼1:10, based on comparison of integration of anomeric proton) of **9** (1.03 g, 95%) as colorless viscous oil: R_f = 0.3 (40% ethyl acetate in hexane); $[\alpha]^{32}_D$ = −9.87 (c 0.1, MeOH); IR (thin film) ν_{max} 3065, 3032, 2955, 1746, 1455, 1368, 1234, 1190, 1177, 1096, 1047, 983, 835, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.17 (s, C-1H$_\alpha$), 6.09 (s, C-1H$_\beta$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.5, 20.7, 20.7, 20.9, 21.6, 62.2, 63.7, 68.9, 73.6, 73.8, 78.6, 83.0, 91.2, 127.8, 128.0, 128.1, 128.5, 129.8, 129.9, 132.3, 136.7, 145.2, 169.0, 169.5, 170.3; HR-ESI-TOF-MS m/z 573.1390 ([M + Na]$^+$), calcd for [$C_{26}H_{30}O_{11}S$ + Na]$^+$ 573.1401.

General Procedure for the Synthesis of 4′-*C*-(Acetoxymethyl)-2′-*O*-acetyl-3′-*O*-benzyl-5′-*O*-(*p*-toluenesulfonyl)-ribonucleosides 10a,b. To the stirred solution of tri-*O*-acetylated sugar derivative **9** (0.50 g, 0.91 mmol) and uracil/thymine (1.36 mmol) in anhydrous acetonitrile (20 mL), *N*,*O*-bis(trimethylsilyl)-acetamide (0.91 mL, 3.64 mmol) was added dropwise. The reaction mixture was stirred at reflux for 1 h and then cooled to 0 °C. In the cooled reaction mixture, trimethylsilyl trifluoromethanesulfonate (0.28 mL, 1.55 mmol) was added dropwise under stirring, and the solution was heated at 70−80 °C for 6−10 h. The reaction was quenched with cold saturated aq solution of sodium bicarbonate (100 mL), and extraction was performed with dichloromethane (3 × 100 mL). The combined organic phase was washed with saturated aq sodium bicarbonate solution (2 × 100 mL) and brine solution (2 × 100 mL) and was dried over anhydrous sodium sulfate. The excess of solvent was removed under reduced pressure, and the residue thus obtained was purified by silica gel column chromatography using methanol in chloroform as eluent to afford nucleosides **10a−b** in 86 and 88% yield, respectively.

*4′-C-(Acetoxymethyl)-2′-O-acetyl-3′-O-benzyl-5′-O-(p-toluenesulfonyl)uridine (**10a**).* Compound **10a** was obtained as white solid (0.47 g, 86%): R_f = 0.3 (5% methanol in chloroform); mp 89−91 °C; $[\alpha]^{30}_D$ = +25.8 (c 0.1, MeOH); IR (thin film) ν_{max} 3198, 3032, 1736, 1696, 1458, 1369, 1232, 1190, 1177, 1110, 1048, 996, 814, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99 and 2.08 (6H, 2s), 2.45 (3H, s), 4.03 (1H, d, J = 12.4 Hz), 4.13 (1H, d, J = 10.4 Hz), 4.22 (1H, d, J = 10.8 Hz), 4.42−4.46 (2H, m), 4.51−4.54 (2H, m), 5.41 (1H, dd, J = 4.0 and 6.0 Hz), 5.68 (1H, dd, J = 2.4 and 8.0 Hz), 5.83 (1H, d, J = 3.6 Hz), 7.24−7.37 (8H, m), 7.78 (2H, d, J = 8.4 Hz), 9.11 (1H, brs); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.0, 23.0, 24.0, 64.4, 70.8, 76.1, 77.0, 79.8, 86.6, 92.5, 105.3, 130.3, 130.6, 130.8, 132.4, 134.6, 139.0, 143.3, 147.9, 152.1, 165.3, 172.2, 172.7; HR-ESI-TOF-MS m/z 625.1483 ([M + Na]$^+$), calcd for [$C_{28}H_{30}N_2O_{11}S$ + Na]$^+$ 625.1463.

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*4′-C-(Acetoxymethyl)-2′-O-acetyl-3′-O-benzyl-5′-O-(p-toluenesulfonyl)thymidine (**10b**).* Compound **10b** was obtained as a white solid (0.49 g, 88%): R_f = 0.3 (5% methanol in chloroform); mp 73−74 °C; $[\alpha]^{33}_D$ = +17.22 (*c* 0.05, MeOH); IR (thin film) ν_{max} 3189, 3033, 1744, 1718, 1695, 1458, 1369, 1231, 1190, 1177, 1119, 1046, 998, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.89 (3H, s), 1.97 and 2.05 (6H, 2s), 2.42 (3H, s), 3.99 (1H, d, *J* = 12.4 Hz), 4.08 (1H, d, *J* = 11.2 Hz), 4.21 (1H, d, *J* = 10.8 Hz), 4.39−4.44 (2H, m), 4.47−4.52 (2H, m), 5.38 (1H, dd, *J* = 3.6 and 6.4 Hz), 5.87 (1H, d, *J* = 3.6 Hz), 7.14 (1H, s) 7.19−7.21 (2H, m), 7.27−7.35 (5H, m), 7.76 (2H, d, *J* = 8.0 Hz), 8.86 (1H, brs); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.6, 23.0, 23.9, 64.5, 71.1, 76.1, 77.0, 79.8, 86.4, 91.7, 114.0, 130.2, 130.5, 130.8, 132.3, 134.5, 138.8, 139.0, 147.8, 152.2, 165.8, 172.2, 172.6; HR-ESI-TOF-MS *m*/*z* 639.1644 ([M + Na]$^+$), calcd for $[C_{29}H_{32}N_2O_{11}S + Na]^+$ 639.1619.

General Procedure for the Synthesis of 3′-*O*-Benzyl-*C*-4′-spiro-ribonucleosides 11a,b. To a stirred solution of compound **10a,b** (0.67 mmol) in dioxane/water (2 mL, 1:1) was added 2 M NaOH (1.5 mL), and the reaction mixture was stirred at rt for 30−35 h. The reaction mixture was neutralized with acetic acid and coevaporated with toluene under reduced pressure. The residue thus obtained was purified by silica gel column chromatography using methanol in chloroform as gradient solvent system to give **11a,b** in 76 and 75% yields, respectively.

*3′-O-Benzyl-C-4′-spiro-oxetanouridine (**11a**).* Compound **11a** was obtained as a white solid (0.17 g, 76%): R_f = 0.4 (10% MeOH in $CHCl_3$); mp 131−133 °C; $[\alpha]^{32}_D$ = +54.4 (*c* 0.05, MeOH); IR (KBr) ν_{max} 3538, 1689, 1465, 1413, 1389, 1263, 1110, 1054, 976, 878, 741, 732, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93 (1H, brs), 4.26 (1H, d, *J* = 5.2 Hz), 4.42−4.44 (1H, m), 4.62 (2H, d, *J* = 7.2 Hz), 4.77 (1H, d, *J* = 7.2 Hz), 4.82 (2H, dd, *J* = 11.6 and 17.6 Hz), 4.94 (1H, d, *J* = 7.2 Hz), 5.47 (1H, d, *J* = 2.8 Hz), 5.69 (1H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 7.31−7.40 (5H, m), 9.55 (1H, brs); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 73.4, 74.2, 78.5, 79.7, 80.4, 85.5, 94.3, 102.6, 128.1, 128.5, 128.7, 136.8, 141.3, 150.3, 163.2; HR-ESI-TOF-MS *m*/*z* 369.1062 ([M + Na]$^+$), calcd for $[C_{17}H_{18}N_2O_6 + Na]^+$ 369.1057.

*3′-O-Benzyl-C-4′-spiro-oxetanoribothymidine (**11b**).* Compound **11b** was obtained as a white solid (0.18 g, 75%): R_f = 0.4 (10% MeOH in $CHCl_3$); mp 65−67 °C; $[\alpha]^{29}_D$ = +31.0 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3421, 3197, 3058, 2927, 1690, 1466, 1458, 1269, 1248, 1127, 1101, 969, 740 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.79 (3H, s), 4.25 (1H, d, *J* = 4.4 Hz), 4.44 (1H, d, *J* = 7.2 Hz), 4.50 (1H, dd, *J* = 4.4 and 9.6 Hz), 4.60 (2H, dd, *J* = 7.2 and 11.6 Hz), 4.70 (1H, d, *J* = 12.0 Hz), 4.75 (1H, d, *J* = 6.4 Hz), 4.94 (1H, d, *J* = 11.2 Hz), 5.71 (2H, d, *J* = 5.6 Hz), 7.31−7.43 (6H, m), 11.37 (1H, brs); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 11.9, 71.6, 72.6, 77.5, 80.0, 80.2, 83.6, 89.6, 109.5, 127.4, 127.6, 128.1, 137.0, 138.4, 150.5, 163.6; HR-ESI-TOF-MS *m*/*z* 361.1390 ([M + H]$^+$), calcd for $[C_{18}H_{20}N_2O_6 + H]^+$ 361.1394.

*C-4′-Spiro-oxetanouridine (**12a**).* To a solution of nucleoside **11a** (0.10 g, 0.29 mmol) in anhydrous THF:MeOH (6 mL, 9:1, v/v) was added $Pd(OH)_2$−C (20 wt %, 0.02 g) and 88% formic acid (0.09 mL, 2.31 mmol). The reaction mixture was refluxed for 30 min whereupon it was cooled to rt. The catalyst was carefully filtered off and washed with excess MeOH, and the combined filtrate was concentrated. The crude product thus obtained was purified by silica gel column chromatography using methanol in chloroform as gradient solvent system to afford spironucleoside **12a** as a white solid (0.05 g, 64%): R_f = 0.2 (10% MeOH in $CHCl_3$); mp 222−224 °C; $[\alpha]^{31}_D$ = −0.71 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3372, 3186, 1691, 1676, 1474, 1394, 1318, 1283, 1237, 1157, 1097, 1038, 959, 844, 821 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 4.18 (1H, t, *J* = 4.4 Hz), 4.26−4.30 (1H, m), 4.42 (1H, d, *J* = 7.2 Hz), 4.53 (2H, s), 4.75 (1H, d, *J* = 7.2 Hz), 5.52 (1H, d, *J* = 6.0 Hz), 5.62−5.69 (3H, m), 7.58 (1H, d, *J* = 8.4 Hz), 11.36 (1H, brs); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 72.4, 73.6, 77.8, 81.0, 84.9, 90.0, 102.5, 142.4, 151.2, 163.6; HR-ESI-TOF-MS *m*/*z* 257.0769 ([M + H]$^+$), calcd for $[C_{10}H_{12}N_2O_6 + H]^+$ 257.0768.

*C-4′-Spiro-oxetanoribothymidine (**12b**).* To a solution of nucleoside **11b** (0.10 g, 0.29 mmol) in anhydrous MeOH (5 mL) was added 20% $Pd(OH)_2$−C (0.03 g) and ammonium formate (0.09 g, 1.36 mmol). The reaction mixture was refluxed for 4 h whereupon it was cooled to rt. The catalyst was carefully filtered off and washed with excess MeOH, and the combined filtrate was concentrated. The crude product thus obtained was purified by silica gel column chromatography using methanol in chloroform as gradient solvent system to afford spironucleoside **12b** as sticky solid (0.06 g, 77%): R_f = 0.2 (10% MeOH in $CHCl_3$); ^1H NMR (DMSO-d_6, 400 MHz): δ 1.77 (3H, s), 4.19 (1H, d, *J* = 4.4 Hz), 4.27−4.30 (1H, m), 4.38−4.43 (1H, m), 4.53 (2H, dd, *J* = 7.2 and 9.6 Hz), 4.75 (1H, d, *J* = 7.2 Hz), 5.67−5.70 (3H, brs), 7.40 (1H, s); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 12.1, 71.7, 73.3, 77.4, 80.7, 84.3, 89.1, 109.8, 137.3, 150.3, 163.9; HR-ESI-TOF-MS *m*/*z* 293.0751 ([M + Na]$^+$), calcd for $[C_{11}H_{14}N_2O_6 + Na]^+$ 293.0744.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of compounds **2a−c**, **3a−c**, **4−9**, **10a,b**, **11a−b**, and **12a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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