Electronic Supplementary Information (ESI)

Synthesis of 4a-carba-α-D-lyxofuranose from isopropyloxy-2,3-O-isopropylidene-L-erythruronolactone via Tebbe mediated cascade reaction

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Experimental section

General information: All reactions are carried under nitrogen atmosphere in oven dried glassware equipped with a magnetic stirrer and a rubber septum unless otherwise indicated. All solvents are freshly distilled before use; THF over sodium and benzophenone; DCM over calcium hydride. All other commercial reagents were used without further purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) of aliquots using glass sheets coated (0.25 mm layered thickness) with silica gel F254 (Merck Kiesel gel 60). TLC plates are viewed under UV light and charred with phosphomolybdic acid. Column chromatographies were carried out with silica gel 60-120 mesh (Merck). 1H and 13C NMR spectra were recorded in deuterated solvents, on Bruker Avance 300 MHz Spectrometer. IR spectra were recorded with a Thermo Nicolet nexus 670 FT-IR spectrometer. HRMS were obtained on a Q STAR XL HYBRID (PE SEIEX) analytical instrument. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Melting points were recorded on a FISHER JOHNS melting point apparatus.

2,3-O-isopropylidene-D-ribo-γ-lactone (8).

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\text{H} \quad \text{C} \quad \text{O} \\
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To a solution of 2,3−O−isopropylidene−D−ribose (7) (2.0 g, 10.52 mmol) in water (25 mL) was added BaCO₃ (12.88 g, 65.26 mmol) at 0°C. To this reaction mixture, bromine (1.62 ml, 31.58 mmol) was added for a period of 30 min at 0°C, allowed to stir for 1 h at the same temperature. After completion of the reaction 10% hypo solution (10 mL) was added to quench the excess bromine at 0°C. Reaction mixture was filtered and passed through a pad of celite and extracted with CHCl₃ and the extract was washed with water, brine, dried over anhy. Na₂SO₄ and concentrated to give a residue. Purification of the residue on silica gel (elution with 50% ethyl acetate in hexanes) afforded 1.30 g (66%) of 8 as a white solid: Mp 177−180°C; [α]D²⁰ 62.4 (c 0.79, CHCl₃); IR (KBr) vmax 3468, 2991, 1775, 1389, 1201, 1079 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 1.38 (s, 3H), 1.5 (s, 3H), 2.92 (t, 1H, J = 4.84 Hz), 3.8 (m, 1H), 4.0 (m, 1H), 4.64 (s, 1H), 4.85 (d, 2H, J = 5.81 Hz); 13C NMR (75 MHz, CDCl₃) δ 25.4, 26.6, 61.8, 75.6, 78.2, 82.9, 113.1, 175.2; MS (EI): m/z 173 (M-15); MS (ESI): (188); HRMS (ESI) m/z calcd 211.0582, found 211.0577;

(3a,6aS)-6-hydroxy-2,2-dimethylperhydrofuro(3,4-d) (1,3) dioxol-4-one (9).

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\text{O} \quad \text{O} \\
\text{HO} \quad \text{C} \\
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To the solution of 2,3−O−isopropylidene−D−ribose (7) (2.0 g, 10.52 mmol) in water (25 mL) was added BaCO₃ (12.88 g, 65.26 mmol) at 0°C. To this reaction mixture, bromine (1.62 ml, 31.58 mmol) was added for a period of 30 min at 0°C, allowed to stir for 1 h at the same temperature. After completion of the reaction 10% hypo solution (10 mL) was added to quench the excess bromine at 0°C. Reaction mixture was filtered and passed through a pad of celite and extracted with CHCl₃ and the extract was washed with water, brine, dried over anhy. Na₂SO₄ and concentrated to give a residue. Purification of the residue on silica gel (elution with 50% ethyl acetate in hexanes) afforded 1.30 g (66%) of 8 as a white solid: Mp 177−180°C; [α]D²⁰ 62.4 (c 0.79, CHCl₃); IR (KBr) vmax 3468, 2991, 1775, 1389, 1201, 1079 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 1.38 (s, 3H), 1.5 (s, 3H), 2.92 (t, 1H, J = 4.84 Hz), 3.8 (m, 1H), 4.0 (m, 1H), 4.64 (s, 1H), 4.85 (d, 2H, J = 5.81 Hz); 13C NMR (75 MHz, CDCl₃) δ 25.4, 26.6, 61.8, 75.6, 78.2, 82.9, 113.1, 175.2; MS (EI): m/z 173 (M-15); MS (ESI): (188); HRMS (ESI) m/z calcd 211.0582, found 211.0577;
extracted with EtOAc. The extract was washed with water, brine, dried over anhy. Na₂SO₄ and concentrated in vacuo. The solid obtained was recrystallized in ethyl acetate to give (9) as a white solid (2.08 g, 72%) : Mp 100–102°C; [α]D²⁰ -21.341 (c 1.0, CHCl₃); IR (KBr) ν max 3412, 1756, 1383, 1080 cm⁻¹; ¹H NMR (200 MHz, CDCl₃), 1.41 (s, 3H), 1.53 (s, 3H), 4.68 (d, 1H, J = 5.63 Hz), 4.91 (d, 1H, J = 5.34 Hz), 5.87 (s, 1H); ¹³C NMR (50 MHz, CDCl₃ + DMSO) δ 24.0, 25.1, 73.3, 78.9, 98.3, 111.9, 172.4; MS (LCMS) m/z calcd for [M+H]+ 175, found 175;

(3aR,6aS)-6-isopropoxy-2,2-dimethylperhydrofuro(3,4-d)(1,3)dioxol-4-one (5).

To the solution of lactol 9 (0.75 g, 4.31 mmol) in anhydrous 2-propanol (20 mL), PPTS (0.11 g, 0.43 mmol) was added. Reaction mixture was refluxed at 80°C for a period of 1.5 h. After completion of the reaction, reaction mixture was concentrated to a syrup in vacuo, which was then dissolved in 50 mL of EtOAc, washed with water, brine, dried using anhy. Na₂SO₄ and concentrated in vacuo to give a residue. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexane) afforded 5 as a light yellow oil (0.63 g, 84%) : [α]D²⁰ +45.6 (c 0.42, CHCl₃); IR (KBr) ν max 2983, 1795, 1380, 1108, 929, 771 cm⁻¹; ¹H NMR (300 MHz, CDCl₃), δ 1.22 (d, 3H, J = 4.46 Hz), 1.24 (d, 3H, J = 4.46 Hz), 1.37 (s, 3H), 1.45 (s, 3H), 4.03 (septet, 1H, J = 5.94 Hz), 4.48 (d, 1H, J = 5.2 Hz), 4.76 (d, 1H, J = 5.2 Hz), 5.4 (s,1H); ¹³C NMR (75 MHz, CDCl₃), δ 21.2, 23.0, 25.6, 26.6, 72.3, 74.5, 79.7, 102.2, 114.1, 173.3; HRMS (ESI) m/z calcd for C₁₀H₁₇O₅ 217.1015, found 217.1078.

(3aS,4S,6aR)-4-isopropoxy-2,2-dimethyl-6-methylene-tetrahydrofuro[3,4-d][1,3]dioxole(4)

(Reaction with 1eq of Tebbe reagent)

To the solution of lactone 5 (0.15 g, 0.69 mmol) in dry THF (10 mL), Tebbe reagent (1.49 mL, 0.69 mmol, 0.5 M solution in toluene) was added at 0°C. (Stirring continued for a period of 1 h. at 0°C). After being stirred for 1 h. at 0°C the reaction mixture was quenched by adding 10% aq NaOH solution(1.2 mL) for a period of 10 min. Precipitate was filtered through a pad of celite, washed with EtOAc. Filtrate and washings were combined and washed with water, brine, dried (Na₂SO₄), concentrated in vacuo to give a residue. Purification of the residue on silica gel (elution with 2-3% ethyl acetate in hexane) afforded (0.027 g, 18.2%) compound 4 as a light yellow oil: [α]D²⁰ + 8 (c 0.1, CHCl₃); IR (KBr) ν max 761, 1216, 1463, 1232, 2855, 2924 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.18 (d, 6H, J = 6.04 Hz), 1.32 (s, 3H), 1.44 (s,
3H), 3.91 (multiplet, 1H), 4.41(d, 1H, J = 6.04 Hz), 4.48 (s, 1H), 4.97 (d, 1H, J = 6.04 Hz), 5.25 (s, 1H); 13C NMR (75 MHz,CDCl 3 ) δ 21.49, 23.28, 25.57, 26.7, 70.4, 78.84, 83.01, 88.18, 105.67, 113.0, 161.15; HRMS(ESI) m/z calcd for [C11H18O4+H]+ 215.1278, found 217.1281. Compound 1 (0.017 g, 13%) and starting material 5 (0.025 g, 17%) were also isolated.

(3aR,4S,6aS)-2,2-dimethyl-6-methyleneperhydrocyclopenta[d][1,3]dioxol-4-ol (1)

(Reaction with 2 eq of Tebbe reagent)

To the solution of lactone 5 (0.1 g, 0.48 mmol) in dry THF (10 mL), Tebbe reagent (2.2 mL, 1.06 mmol, 0.5 M solution in toluene) was added at 0° C. (Stirring continued for a period of 1 h. at 0°C). After being stirred for 1 h. at 0°C the reaction mixture was quenched by adding 10% aq NaOH solution(2 mL) for a period of 10 min. Precipitate was filtered through a pad of celite, washed with EtOAc. Filtrate and washings were combined and washed with water, brine, dried (Na2SO4), concentrated in vacuo to give a residue. Purification of the residue on silica gel (elution with 20−25% ethyl acetate in hexane) afforded (0.032 g, 40%) compound 1 as a light yellow oil: [α]D20 -125.24 (c 2.67, CHCl3); IR (KBr) νmax 2935, 1375, 1219, 772 cm−1; 1H NMR (300 MHz, CDCl3) δ 1.3 (s, 3H), 1.41 (s, 3H), 1.42−1.45 (brs, 1H), 2.17 (d, 1H, J = 15.11 Hz), 2.77−2.88 (m, 1H), 4.15 (d, 1H, J = 4.53 Hz), 4.38 (d, 1H, J = 5.29 Hz), 4.78 (d, 1H, J = 6.04 Hz), 5.17 (s, 1H), 5.28 (s, 1H); 13C NMR (50 MHz,CDCl3 ) δ 24.1, 26.3, 38.1, 74.3, 81.2, 86.0, 110.9, 114.3, 147.6; HRMS(ESI) m/z calcd for [(C9H14O3F)+ ] 189.0926, found 189.0928.

(3aR,4S,6aR,6aS)-6-(hydroxymethyl)-2,2-dimethylperhydrocyclopenta[d][1,3]dioxol-4-ol (11), and (3aR,4S,6S,6aS)-6-(hydroxymethyl)-2,2-dimethylperhydrocyclopenta[d][1,3]dioxol-4-ol (12)

To the solution of lactone 1 (0.1 g, 0.51 mmol) in THF (10 mL), BH3.Me2S (0.16 mL, 1.55 mmol) was added drop wise at −10° C. Stirring continued for 16 h at room temperature. After which time NaOH (3N, 1.3 mL) followed by (30%) H2O2 (2.2 mL) solution were added at 0°C and stirring continued for 30 min at the same temperature. The reaction mixture was diluted with EtOAc, washed with water, brine, dried using anhydrous Na2SO4 and concentrated in vacuo to give a residue. Purification of the residue on silica gel (elution with 50% ethyl acetate in hexane) afforded 11 (0.057 g, 53%) and 12 (0.028 g, 15%) as low melting solids. For compound 11; mp 41−43°C; [α]D30 +38 (c 0.97, CH2Cl2); IR (KBr) νmax 3418, 2933, 1617, 1379,1210, 1059, 1019, 866, 518 cm−1; 1H NMR (300 MHz, CDCl3) δ 1.38 (s, 3H), 1.42−1.45 (brs, 1H), 1.49 (bs, 1H), 1.61 (dd, 1H, J = 5.6 Hz, 13.3 Hz ), 1.95 (dt, 1H, J = 4.0 Hz, 13.3 Hz), 2.23 (bs,1H), 2.39 (m, 1H), 3.7 (dd, 1H, J = 6.3 Hz, 11.4 Hz), 3.9 (dd, 1H, J = 4.0 Hz,11.4 Hz), 4.16 (d, 1H, J = 4.0 Hz), 4.36 (dd, 1H, J = 1.5 Hz, J = 5.6 Hz), 4.75 (t, 1H, J = 5.6 Hz); 13C NMR (75 MHz,CDCl3 ) δ 23.7, 25.9, 32.9, 42.4,
61.8, 75.3, 81.4, 86.7, 110.3; HRMS(ESI) m/z calcd. for $\left[ (C_{9}H_{16}O_{4}Na)^{+} \right] 211.0946$, found 211.0953; For compound 12; $[\alpha]^{20}_{D} -3.2$ (c 0.625, CH$_2$Cl$_2$); (KBr) $\nu_{max}$ 3412, 2926, 2855, 1461, 1377, 1271, 1041, 864, 759 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.26 (S, 3H), 1.39 (S, 3H), 1.54 (d, 1H, $J = 13.67$ Hz), 2.38 (m, 2H), 3.62 (dd, 1H, $J = 10.55$ Hz), 3.8 (dd, 1H, $J = 5.47$ Hz); 13C NMR (50 MHz, CDCl$_3$); $\delta$ 23.9, 26.5, 35.55, 47.2, 64.5, 76.8, 83.9, 88.2, 109.7; HRMS(ESI) m/z cacd. for $\left[ (C_{9}H_{16}O_{4}Na)^{+} \right] 211.0949$, found 211.0946

1,2,3,5-tetra-O-acetlycarba-$\alpha$-D-lyxofuranose (14).

Diol 11 (0.05 g.) was treated with methanolic hydrochloric acid (MeOH/HCl, 5 mL) at 0$^\circ$C for 15 min. The reaction mixture was concentrated in vacuo to remove all the solvent. The crude residue was dissolved in DCM (7 mL) and treated with triethyl amine (0.35 mL, 3.5 mmoles), acetic anhydride (0.25 mL, 2.7 mmols), and a few crystals of DMAP for 6 h at room temperature. Then methanol (1ml) was added, and stirring was continued for 15 min. Then solution was diluted with 0.1N HCl, the layers are separated, and the organic layer was washed with saturated aqueous NaHCO$_3$. The aqueous layer was re-extracted twice using DCM (10 mL $\times$ 2). The total organic extracts are combined and dried using anhydrous Na$_2$SO$_4$ and concentrated in vacuo to give a residue. Purification of the residue on silica gel (elution with 22–25% ethyl acetate in hexanes) afforded 14 (0.098 g, 92%) as a yellow oil. $[\alpha]^{20}_{D} +32$ (c 0.123, CH$_2$Cl$_2$); IR (KBr) $\nu_{max}$ 3466, 2924, 2854, 1742, 1437, 1369, 1226, 1036, 893, 761, 603 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.77 (m, 1H), 2.02 (S, 6H), 2.06 (S, 3H), 2.08 (S, 3H), 2.17 (m, 1H), 2.68 (m, 1H), 4.04 (2 dd, AB system, 2H, $J = 6.6$ Hz, 10.9 Hz, 8.4Hz, 10.9 Hz), 5.21 (m, 2H), 5.45 (t, 1H, $J = 3.8$ Hz); 13C NMR (75 MHz, CDCl$_3$); $\delta$ 20.55 (2C), 20.69, 20.89, 31.88, 37.25, 62.39, 72.17, 75.33, 77.42, 169.84, 169.97, 170.47, 170.71; HRMS (ESI) m/z cacd. for $\left[ (C_{16}H_{20}O_{8}Na)^{+} \right] 339.1058$, found 339.1055.
$^1$H NMR OF COMPOUND 7 IN CDCl$_3$ (300 MHz)
$^{13}$CNMR OF COMPOUND 7 IN CDCl$_3$ (75 MHz)

$^{13}$C NMR OF COMPOUND 7 IN CDCl$_3$ (75 MHz)
$^{1}$H NMR OF COMPOUND 9 IN CDCl$_3$ (200 MHz)
$^{13}$C NMR of compound 9 in CDCl$_3$ + DMSO(D-6) in 50 MHz
$^1$H NMR OF COMPOUND 5 IN CDCl$_3$ (300 MHz)
$^{13}$C NMR OF COMPOUND 5 IN CDCl$_3$ (75 MHz)
$^1$H NMR OF COMPOUND 1 IN CDCl$_3$ (300 MHz)
$^{13}$C NMR OF COMPOUND 1 IN CDCl$_3$ (50 MHz)
NOE SPECTRUM OF COMPOUND 1

Pulse Sequence: NOE010
NOE OF 1

NOE SPECTRUM OF COMPOUND 1
$^1$H NMR OF COMPOUND 11 IN CDCl$_3$ (300 MHz)
$^{13}$C SPECTRUM OF COMPOUND 11 IN CDCl$_3$(75 MHz)
NOE SPECTRUM OF COMPOUND 11

[Diagram of a chemical structure with annotations]
1H NMR SPECTRUM OF COMPOUND 12 IN CDCl3 (200 MHz)
$^{13}$C NMR SPECTRUM OF COMPOUND 12 IN CDCl$_3$(50 MHz)
1H NMR SPECTRUM OF COMPOUND 14 IN CDCL3 (300 MHz)
$^{13}$C NMR SPECTRUM OF COMPOUND 14 IN CDCl$_3$ (75 MHz)
$^1$H NMR OF COMPOUND 4 IN 300 MHz
C13 NMR of compound 4 in CDCl₃ (75 MHz)