Dihydroxyacetone Variants in the Organocatalytic Construction of Carbohydrates: Mimicking Tagatose and Fuculose Aldolases

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General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H₂SO₄ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating; or with a solution of ninhydrin in EtOH followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ¹H NMR and ¹³C NMR spectra were referenced internally to the residual solvent peak. For characterization of other compounds refer to previous communication.¹

(*S*)-4-((*S*)-Hydroxy(4-bromophenyl)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, 2k):

Purification by silica gel column: 10-15-25% EtOAc in hexane. ¹H NMR (CDCl₃ 400MHz major product, anti-diastereomer): δ 7.47(d, J = 8.4Hz, 2H), 7.27(d, J = 8.4Hz, 2H), 4.85(d, J = 8.0Hz, 1H), 4.24(d, J = 17.6Hz, 1H), 4.24 (d, J = 8.0Hz, 1H), 4.05 (d, J = 17.6Hz, 1H), 3.67 (d, J = 2.0Hz, 1H), 1.37 (s, 3H), 1.25 (s, 3H) (syn-diastereomer): δ 5.17 (m, 1H), 4.42 (m, 1H), 2.88 (brd, 1H); ¹³C NMR (CDCl₃, 100 MHz anti-diastereomer): δ 210.9, 138.3, 131.1, 128.7, 121.9, 101.2, 75.9, 72.0, 66.6, 23.5, 23.2; syn-diastereomer: δ 207.4, 139.1, 131.3, 128.2, 121.8, 101.1, 77.7, 70.8, 67.1, 24.2, 23.5; HRMS: C₁₃H₁₅BrO₄Na (MNa⁺), calcd 337.0046, obsd 337.0040; HPLC (Daicel Chiralcel OJ-H hexane/isopropanol = 97:3, flow rate 1ml/min, λ = 254nm): t_r = 20.26 (anti, major), t_r = 24.59 (anti, minor), t_r = 41.63 (syn, major), t_r = 55.92 (syn, minor).

(*S*)-4-((*S*)-Hydroxy(4-cyanophenyl)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, 2l):

Purification by silica gel column: 10-15-25% EtOAc in hexane. ¹H NMR (CDCl₃ 300MHz major product, anti-diastereomer): δ 7.65 (d, J = 8.4Hz, 2H), 7.53 (d, J = 8.4Hz, 2H), 4.95 (d, J = 7.8Hz, 1H), 4.28 (d, J = 17.6Hz, 1H), 4.22 (d, J = 7.8Hz, 1H), 4.08 (d, J = 17.6Hz, 1H), 3.81(bs, 1H), 1.38 (s, 3H), 1.22 (s, 3H); (syn-diastereomer): δ 5.27 (brs, 1H), 4.45 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz anti-diastereomer):

δ 210.1 , 144.1 , 131.3 , 127.3 , 118.3 , 111.3 , 100.9 , 76.2 , 71.4 , 66.1 , 23.0 , 22.8 ; syn-diastereomer: δ 207.2 , 145.4 , 132.0 , 127.2 , 111.6 , 101.2 , 77.6 , 70.7 , 67.0 , 24.0 , 23.3; HRMS: $C_{14}H_{14}NO_4$ (M-H)-, calcd, 260.0928, obsd, 260.0924; HPLC (Daicel Chiralcel OJ-H hexane/isopropanol = 96:4, flow rate 1ml/min, λ = 254nm) : t_r = 49.95 (anti, major), t_r = 58.46 (anti, minor), t_r = 97.31 (syn, major), t_r = 129.36 (syn, minor).

(S)-4-((S)-Hydroxy-thiophen-3-yl-methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, 2m):

Purification by silica gel column: 10-15-25% EtOAc in hexane. 1H NMR ($CDCl_3$, 300MHz major product, anti-diastereomer): δ 7.32-7.28 (m, 2H), 7.16-7.12 (m, 1H), 5.05 (d, J = 7.1Hz, 1H), 4.37 (d, J = 7.1Hz, 1H), 4.23 (d, J = 17.4Hz, 1H), 4.03 (d, J = 17.4Hz, 2H), 1.42 (s, 3H), 1.36(s, 3H); syn-diastereomer: δ 5.28 (brs, 1H), 4.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz anti-diastereomer): δ 210.3, 140.5, 126.4, 125.3, 122.6, 101.2, 76.2, 69.0, 66.6, 23.6 , 23.3; HRMS: $C_{11}H_{14}O_4SNa$ (MNa+), calcd, 265.0505, obsd, 265.0500; HPLC (Daicel Chiralcel AS hexane/isopropanol = 99:1, flow rate 1ml/min, λ = 254nm): t_r = 18.82 (anti, major), t_r = 31.74 (anti, minor), t_r = 39.04 (syn, major), t_r = 129.36 (syn, minor).

(S)-4-((S)-Furan-3-yl-hydroxy-methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, 2n):

Purification by silica gel column: 10-15-25% EtOAc in hexane. 1H NMR ($CDCl_3$, 300MHz major product, anti-diastereomer): δ 7.46 (1H), 7.38 (1H), 6.47 (1H), 4.95 (d, J = 6.6Hz, 1H), 4.37 (d, J = 6.6Hz, 1H), 4.23 (d, J = 17.1Hz, 1H), 4.03 (d, J = 17.1Hz, 2H), 3.33, brs, 1H), 1.45 (s, 3H), 1.43 (s, 3H); syn-diastereomer: δ 5.17 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz anti-diastereomer): δ 210.1 , 142.9 , 140.3 , 124.2 , 109.3 , 101.2 , 76.2 , 66.6 , 65.8 , 23.7 , 23.4; HRMS: $C_{11}H_{14}O_5Na$ (MNa+): calcd, 249.0733, obsd, 249.0738; HPLC (Daicel Chiralcel AS hexane/isopropanol = 95:5, flow rate 1ml/min, λ = 254nm) : t_r = 11.31 (anti, major), t_r = 15.99 (anti, minor), t_r = 18.11 (syn).

(S)-4-((S)-cyclohexyl(hydroxy)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 3, 3d):

Purification by silica gel column: 2 – 5% EtOAc in hexane. 1H NMR ($CDCl_3$, 300MHz ,anti-diastereomer): δ 4.28 (dd, J_1 = 17.4Hz, J_2 = 1.5Hz, 1H), 4.20

(dd, $J_1 = 7.8\text{Hz}$, $J_2 = 1.5\text{Hz}$, 1H), 4.02 (d, $J = 17.4$, 1H), 3.72-3.68 (m, 1H), 3.02 (d, $J = 3.00\text{Hz}$, 1H), 1.82-1.10 (m, 11), 1.48 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, anti-diastereomer): δ 212.4, 100.9, 74.2, 73.3, 66.6, 38.4, 29.5, 26.4, 26.4, 26.2, 26.0, 23.8, 23.6; HRMS: $\text{C}_{13}\text{H}_{22}\text{O}_4\text{Na}$ (MNa^+), calcd 265.1401, obsd 265.1403; $[\alpha]_{\text{D}} = +99.8$ ($c = 1.00$, CHCl_3).

Purification by silica gel column: 5% EtOAc in hexane. ^1H NMR (CDCl_3 , 300MHz, anti-

diastereomer): δ 9.24 (t, $J = 2.1\text{Hz}$, 1H), 9.13 (d, $J = 2.1\text{Hz}$, 2H), 5.46 (t, $J = 5.7\text{Hz}$, 1H), 4.57 (dd, $J_1 = 5.7\text{Hz}$, $J_2 = 1.4\text{Hz}$, 1H), 4.30 (dd, $J_1 = 17.4\text{Hz}$, $J_2 = 1.4\text{Hz}$, 1H), 4.03 (d, $J = 17.4\text{Hz}$, 1H), 2.10 (m, 1H), 1.84-1.00 (m, 10H), 1.51 (s, 3H), 1.46 (s, 3H). HRMS: $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_9$ (M-H^-), calcd 435.1409, obsd 435.1413; HPLC (Daicel Chiralcel OD-H hexanes/isopropanol = 90:10, flow rate 1ml/min, $\lambda = 254\text{nm}$) : $t_{\text{r}} = 18.4\text{min}$. (anti, minor), $t_{\text{r}} = 24.3\text{min}$. (anti, major).

(4*R*,5*R*)-4-((*R*)-1-hydroxy-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one (3f):

^1H -NMR (500 MHz, CDCl_3): δ 1.49 (s, 3H), 1.56 (s, 3H), 2.41 (d, $J = 3.8\text{Hz}$, 1H), 3.41 (s, 3H), 3.46 (s, 3H), 4.01 (d, $J = 16.6\text{Hz}$, 1H), 4.10 (quin, $J = 3.4\text{Hz}$, 1H), 4.28 (dd, $J_1 = 1.5\text{Hz}$, $J_2 = 16.6\text{Hz}$, 1H), 4.47 (q, $J = 1.6\text{Hz}$, 1H), 4.68 (d, $J = 6.8\text{Hz}$, 1H); ^{13}C -NMR (120 MHz, CDCl_3): δ 22.9, 24.9, 54.3, 55.3, 67.0, 71.1, 75.87, 100.5, 103.1, 206.5; $[\alpha]_{25}^{\text{D}} = -64.95$ ($c = 0.97$, CHCl_3).

HPLC (Daicel Chiralcel AD hexanes/isopropanol = 90:10, flow rate 1ml/min, $\lambda = 254\text{nm}$) : $t_{\text{r}} =$

12.45 min. (anti, minor), $t_{\text{r}} = 14\text{min}$. (anti, major).

(4*R*,5*S*)-4-((*R*)-1-(tert-butyldimethylsilyloxy)-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-

ol: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.12 (s, 3H), 0.16 (s, 3H), 0.92 (s, 9H), 1.44 (s, 3H), 1.45 (s, 3H), 3.42 (s, 3H), 3.48 (s, 3H), 3.72 (m, 1H), 3.82 (dd, $J=2.4, 12.4\text{Hz}$, 1H), 3.89-4.00 (m, 3H), 4.36 (d, $J=8.8\text{ Hz}$, 1H).

13: Purification by silica gel column: 15 – 35% EtOAc in hexane. $^1\text{HNMR}$ (CDCl_3 , 300MHz): δ

5.63 (d, $J=5.1\text{Hz}$, 1H), 4.64 (dd, $J_1=2.40\text{Hz}$, $J_2=7.80\text{Hz}$, 1H), 4.41 (d, $J=6.3\text{Hz}$, 1H), 4.39-4.34 (m, 2H), 4.29 (d, $J=17.10\text{ Hz}$, 1H), 4.21, (dd, $J_1=3.6\text{Hz}$, $J_2=6.3\text{Hz}$, 1H), 4.11-4.09 (m, 1H), 4.06 (d, $J=17.10\text{Hz}$, 1H), 3.62 (brs, 1H), 1.56 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.34 (s, 6H); $^{13}\text{CNMR}$ (CDCl_3 , 75 MHz): δ 207.9, 109.7, 108.7, 101.3, 96.6, 73.3,

71.1, 70.6, 70.3, 67.2, 65.0, 26.0, 25.0, 24.1, 24.0, 23.6; HRMS $\text{C}_{18}\text{H}_{28}\text{O}_9(\text{M}+\text{H})$: Calcd, 389.1806, obsd 389.1796; $[\alpha]_D = +14.06$ ($c=1.00$, CHCl_3).

(*S*)-diethyl 2-(2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-2-hydroxymalonate (15):

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 1.31(t, $J=4.4\text{Hz}$, 3H), 1.33 (t, $J=4.0\text{Hz}$, 3H), 1.47 (s, 3H), 1.49 (s, 3H), 3.93-3.99 (m, 2H), 4.30 (q, $J=4.4\text{Hz}$, 2H), 4.35 (d, $J=4.0\text{ Hz}$, 2H), 4.74 (s, 1H), 5.25(d, $J=1.6\text{Hz}$, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 13.9, 14.0, 23.5, 23.6, 63.2, 63.5, 66.77, 78.6, 89.0, 101.6, 167.3, 167.7,

205.0; LRMS ($\text{M}+\text{H}$): 305; GC (varion capillary column, CP-chirasil-Dex CB, 150°C isothermal): 13.96 min, 14.90 min.

(*R*)-ethyl 2-((*S*)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate

(17): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.33(t, $J=7.2\text{Hz}$, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 4.06 (q, $J=17.2\text{ Hz}$, 1H), 4.30 (d, $J=1.6\text{Hz}$, 1H), 4.35 (q, $J=7.2\text{Hz}$, 2H), 4.41 (s, 1H), 4.70 (d, $J=1.6\text{Hz}$, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 13.8, 23.2, 23.7, 63.8, 67.1, 73.3, 101.7, 120.7, 123.5, 204.6; LRMS ($\text{M}+\text{H}$): 301; GC

(varion capillary column, CP-chirasil-Dex CB, 130°C isothermal): anti major (8.4 min), anti minor (8.6 min); syn major (9.0 min), syn minor (9.2 min).

X-ray structure of acetonide protected D-tagatose **11** (crystal prepared by slow of evaporation of a solution of **11** in CH₂Cl₂): Ortep diagram. The non-hydrogen atoms are drawn as 30 % probability Ellipsoids.

4a

4a

¹ . Suri, J. T.; Ramachary, D. B.; Barbas III, C. F. *Org. Lett.* **2005**, 1383-1385.