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Radical homologation of D-gluconic acid: highly diastereoselective synthesis of D-*gluco*-KDO derivatives

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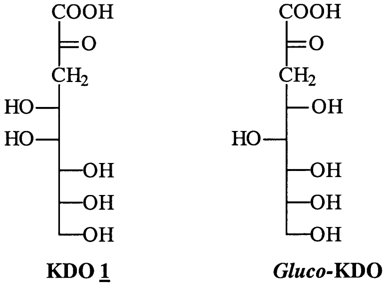
Abstract—D-glucono 1,5-lactone was converted to *O*-protected D-gluconic acids. The latter were transformed to *gluco*-KDO derivatives using Barton ester-based radical chemistry with high diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

3-Deoxy-D-*manno*-2-octulosonic acid (KDO) **1** (Fig. 1) is known as a vital sugar component of lipopolysaccharides (LPS) of the outer membrane of Gram-negative bacteria.[1–3] The rate-limiting enzyme for the incorporation of KDO into these LPS is CMP-KDO synthetase (3-deoxy-D-*manno*-octulosonate cytidylyl transferase).[4] Chemical synthesis of KDO and analogs has been intensively studied[5] in view to obtain effective inhibitors of this enzyme and potential anti-infective agents specific against Gram-negative bacteria.

The common strategies for the synthesis of KDO and its analogs involve homologation of lower monosaccharides D-mannose or D-arabinose with two and three carbons atoms, respectively. These also include radical carbon–carbon bond formation reactions, and the latter have proven to be an important tool in carbohydrate chemistry.[6] We previously reported the successful application of *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone (Barton ester) to the synthesis of KDO derivatives starting from penta-acetyl-D-gluconic acid.[7] As another part of this work, we found that using different protecting groups on the D-gluconic acid, addition of the arabinosyl radical to an olefin, namely ethyl α-(trifluoroacetoxy)acrylate,[8] resulted in the formation of the products with very high diastereoselectivity. Herein we wish to report the results of this highly diastereoselective radical reaction in the synthesis of phenylhydrazone and oxime derivatives of D-*gluco*-KDO starting from inexpensive commercial D-glucono-1,5-lactone.



KDO 1 *Gluco*-**KDO**

Figure 1.

By a literature procedure,[9] D-glucono-1,5-lactone **2** was converted to the D-gluconate ester **3** in 70% yield through reaction with 2,2-dimethoxypropane in acetone/methanol in the presence of a catalytic amount of *p*-toluenesulphonic acid (Scheme 1). In a similar manner, the ester **4** was also prepared in 70% yield by reaction with 1,1-dimethoxy-cyclohexane in cyclohexanone/methanol.

Protection of **3** and **4** with *tert*-butyldiphenylchlorosilane and imidazole in *N*,*N*-dimethylformamide led to **5** (95% yield) and **6** (92% yield), respectively. Treatment of **5** and **6** with 0.1 M of lithium hydroxide solution in tetrahydrofuran gave acids **7** and **8** in 70% yields. Acid **7** and **8** reacted with *N*-hydroxy-2-thiopyridone in the presence of dicyclohexylcarbodiimide (DCC) in anhydrous dichloromethane in the absence of light to give the corresponding Barton esters (Scheme 2). Irradiation of the Barton esters in situ with a tungsten lamp in the presence of ethyl α-(trifluoroacetoxy)acrylate, followed by work up with aqueous K_2CO_3, afforded the protected D-*gluco*-KDO ester derivatives **9** and **10** (both in 53% yield) as single isomers, verified by NMR of the crude product (Scheme 1). This modest yield could be explained by cleavage of the acetal groups of the compounds involved in the three steps reactions. The

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Keywords: KDO; radicalar reaction; diastereoselectivity.

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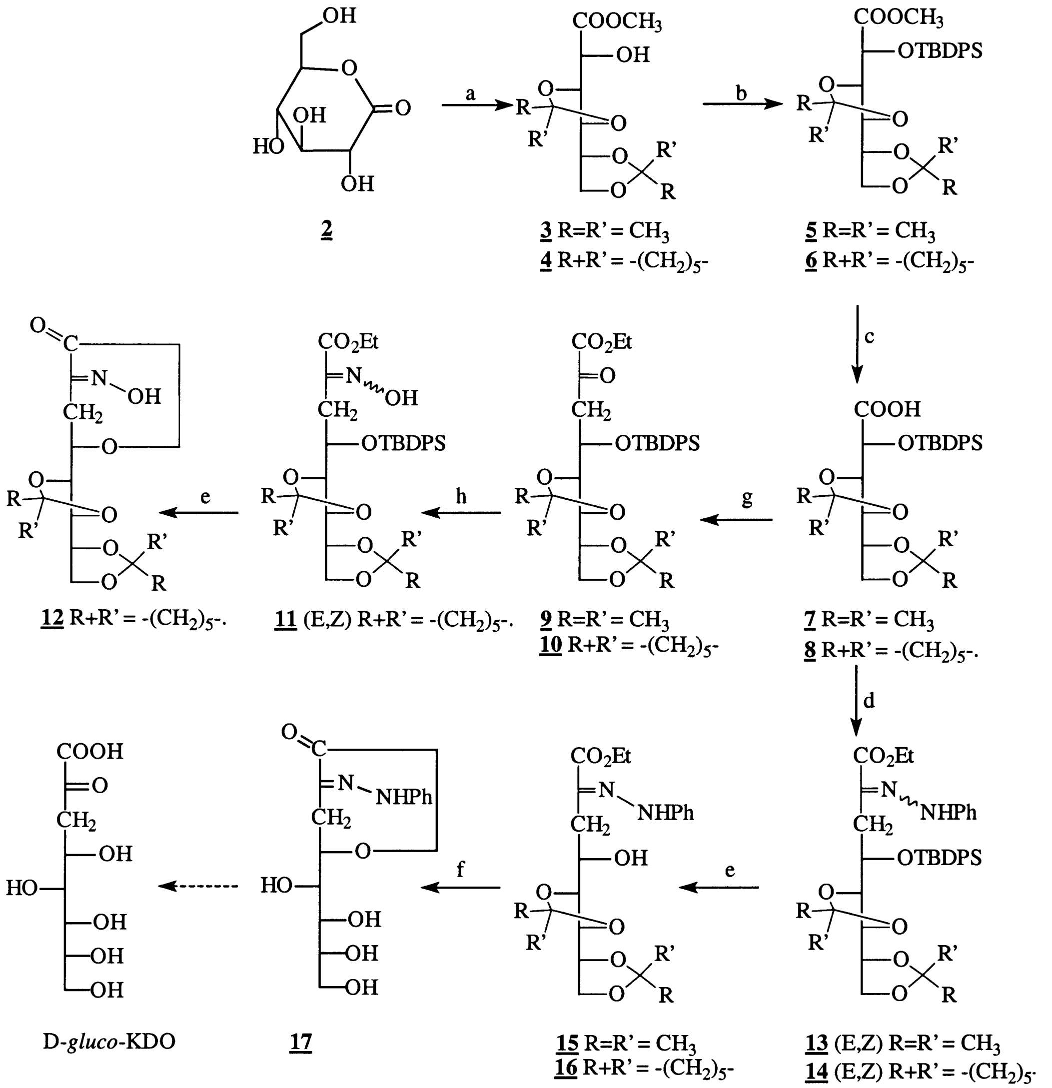
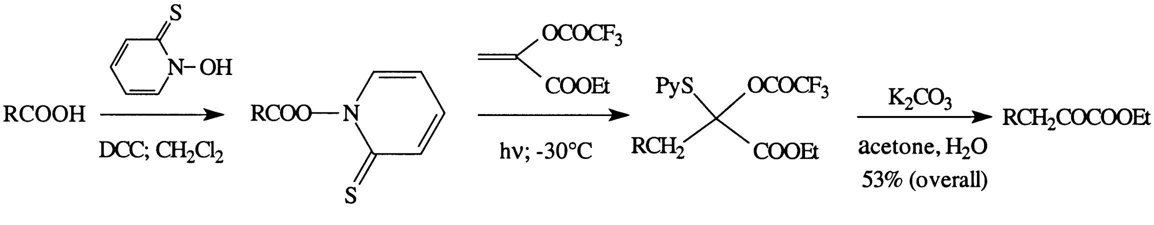


Scheme 1. (a) 2,2-dimethoxypropane (or 1,1-dimethoxycyclohexane), acetone (or cyclohexanone), MeOH, TsOH, rt, 18 h; (b) TBDPSCl, imidazole, DMF, 60°C, 12 h; (c) LiOH 0.1 M, THF, rt, 40 h; (d) i. *N*-hydroxy-2-thiopyridone, DCC, CH_2Cl_2, 0°C, 1 h; ii. $H_2C{=}C(OCOCF_3)(COOEt)$, *hν*, −30°C, 1 h; iii. $PhNHNH_2{\cdot}HCl$, Py, −20°C–rt, 12 h; (e) TBAF, THF, rt, 12 h; (f) HCl, EtOH, rt, 12 h; (g) i. *N*-hydroxy-2-thiopyridone, DCC, CH_2Cl_2, 0°C, 1 h; ii. $H_2C{=}C(OCOCF_3)(COOEt)$, *hν*, −30°C, 1 h; iii. saturated aqueous K_2CO_3/acetone 1:1, −20°C–rt, 12 h; (h) $HONH_2{\cdot}HCl$, Py, 0°C, rt, 12 h.

corresponding 4-epimers were not obtained from the above reactions.

The oxime **11** (proportion *E*/*Z*=6:1) was then obtained in 90% yield by treatment of **10** with hydroxylamine hydrochloride in pyridine. Removal of TBDPS group was achieved by reaction with tetra(*n*-butyl)ammonium fluoride (TBAF) in tetrahydrofuran to give the γ-lactone **12** in 90% yield.

Starting from acid **7** or **8**, work-up of the radical reaction intermediates with phenylhydrazine in pyridine gave phenylhydrazone derivatives **13** and **14**, both in 55% yields (proportion *E*/*Z*=6:1). Removal of the C-4 protecting group of these compounds with TBAF in tetrahydrofuran yielded **15** and **16** in 90 and 92% yields, respectively. *gluco*-KDO lactone **17** was obtained in 85% yield by the treatment of **15** or **16** with hydrochloric acid in ethanol.



Scheme 2.

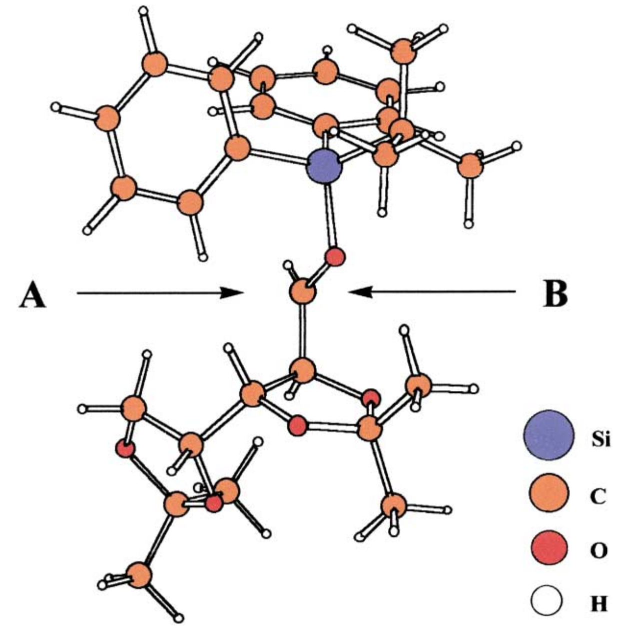


Figure 2.

In summary, the *O*-protected D-*gluco*-KDO was synthesized as the only diastereoisomer in good yields from D-glucono-1,5-lactone through the Barton ester mediated radical carbon–carbon bond formation reaction and the corresponding oxime and phenylhydrazone derivatives were also readily synthesized in good overall yields. The high diastereoselectivity of this radical reaction should help for a better understanding of the stereochemistry of other related radical reactions.

Aiming to understand the diastereoselectivity at molecular level, the reaction step involving the conversion of **7** to **9** was investigated theoretically using the semiempirical method PM3 (Parametric Method 3)[10]. The radical intermediate and the *gluco* and *manno* epimers were analyzed. From the thermodynamic data calculated in gas phase at 298 K and 1.0 atm, both products are equally probable with the *gluco* isomer being less stable by only 3.8 Kcal/mol. This energy difference is within the confidence limit of the calculation method used. It suggests that the stereoselectivities of the process g (Scheme 1) might be kinetically controlled. The fully optimized geometry for the radical intermediate is depicted in Fig. 2, where it can be seen that the attack through the side A, leading to the *manno* epimer, should be more difficult due the steric hindrance. A more detailed theoretical study is in progress and should be reported in a near future paper.

1. Experimental

1.1. General methods and starting materials

Melting points were determined with a Kofler hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 881 infrared spectrophotometer. Specific rotations were determined on a Jasco DIP–360 digital polarimeter. ^{1}H- and ^{13}C NMR spectra were determined with TMS internal reference on Varian Gemini 200 or Varian UNITY NMR spectrometers. Chemical shifts are reported (δ) relative to TMS. Column chromatography was carried out on silica gel 60 (0.040–0.063). Elemental analyses were performed by Atlantic Microlab Inc. *N*-hydroxy-2-thiopyridone was isolated from its sodium salt (Omadine), which was a gift of the Olin Corporation, Cheshire, CT. All reagents were purchased from the Aldrich Co. Inc. or Fluka Chemika-BioChemica and were used without further purification. Compound **3** was synthesized according to the literature method.[9]

1.1.1. Methyl 3,4:5,6-di-*O*-cyclohexylidene-D-gluconate 4. A mixture of D-gluconolactone **2** (17.8 g, 0.1 mol), methanol (5 mL), 1.1 dimethoxycyclohexane (50 mL), cyclohexanone (20 mL) and *p*-toluenesulphonic acid (300 mg) was stirred at room temperature for 48 h. The mixture was then neutralized by addition of sodium hydrogen carbonate, filtered and the filtrate concentrated. The resulting syrup was dissolved in dichloromethane (100 mL) and the solution was washed with water (2×50 mL). Concentration of the extract, followed by flash chromatography of the residue gave the ester **4** (25.5 g, 70%). mp 99–100°C; $[\alpha]_D=+6°$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.80 (m, 20H, cyclohex.); 3.00 (d, 1H, OH); 3.80 (s, 3H, OCH_3); 4.00 (m, 4H, H3, H5, H6, H6′); 4.20 (dd, 1H, H4); 4.30 (dd, 1H, H2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.1–37.2 (cyclohex.); 53.0 (OCH_3); 68.0; 70.0; 76.6; 77.6; 81.1 (C2, C3, C4, C5, C6); 110.8 [*C*(OR)$_2$]; 173.4 (CO); Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.16. Found: C, 61.75; H, 8.20.

1.1.2. Methyl 3,4:5,6-di-*O*-isopropylidene-2-*O*-*tert*-butyldiphenylsilyl-D-gluconate 5 and methyl 3,4:5,6-di-*O*-cyclohexylidene-2-*O*-*tert*-butyldiphenylsilyl-D-gluconate 6. A mixture of **3** (14.5 g, 0.05 mol) or **4** (18.5 g, 0.05 mol), *tert*-butyldiphenylsilyl chloride (15.6 g, 0.06 mol) and imidazole (8.12 g, 0.12 mol) in DMF (20 mL) was stirred at 60°C for 12 h. The mixture was cooled, diluted with dichloromethane (100 mL) and washed with water (2×50 mL). Concentration of the dried extract followed by flash chromatography gave the desired compounds **5** (25.08 g, 95% from **3**) and **6** (27.9 g, 92% from **4**). **5**: Mp 73–75°C; $[\alpha]_D=+64°$(*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (s, 9H, tButyl); 1.35–1.48 (3s, 12H, isoprop.); 3.37 (s, 3H, OCH_3); 3.85 (m, 1H, H6); 4.00–4.44 (m, 4H, H3, H4, H5, H6′); 4.45 (d, 1H, H2); 7.30–7.80 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7–27.5 [tButyl, C(CH_3)$_2$]; 51.5 (OCH_3); 67.6 (C6); 73.1; 77.0; 81.6 (C2, C3, C4, C5); 109.6; 110.4 [*C*(CH_3)$_2$]; 127.0–136.0 (ph); 171.0 (CO); Anal. Calcd for $C_{29}H_{40}O_7Si$: C, 65.88; H, 7.63. Found: C, 65.78; H, 7.68. **6**: Mp 86–87°C; $[\alpha]_D=+55$ (*c* 1, $CHCl_3$);^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H, tButyl); 1.50 (m, 20H, cyclohex.); 3.30 (s, 3H, OCH_3); 3.80–4.30 (m, 4H, H3, H5, H6, H6′); 4.35 (dd, 1H, H4); 4.45 (d, 1H, H2); 7.30–7.80 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.2–37.7 (tButyl, cyclohex.); 51.9 (OCH_3); 67.9 (C6); 73.9; 77.3; 77.5; 81.9 (C2, C3, C4, C5); 110.6; 111.4 [*C*(OR)$_2$]; 127.7–136.6 (ph); 171.5 (CO); Anal. Calcd for $C_{35}H_{48}O_7Si$: C, 69.05; H, 7.95 Found: C, 69.22; H, 8.01.

1.1.3. 3,4:5,6-Di-*O*-isopropylidene-2-*O*-*tert*-butyldiphenylsilyl-D-gluconic acid 7 and 3,4:5,6-di-*O*-cyclohexylidene-2-*O*-*tert*-butyldiphenylsilyl-D-gluconic acid 8. A solution of the ester **5** (2.11 g, 4 mmol) or **6** (2.43 g, 4 mmol) in THF (100 mL) was treated with 0.1 M lithium hydroxide solution (50 mL) and then stirred at room temperature for 40 h. The mixture was cooled to 0°C, adjusted to pH 2 with ice-cold 0.5 M hydrochloric acid and extracted immediately with dichloromethane (3×50 mL). The combined extracts were dried, concentrated in vacuum and the residue was submitted to flash chromatography to furnish the acids **7** (1.44 g, 70% from **5**) and **8** (1.66 g, 70% from **6**). **7**: Mp 141–143°C; $[\alpha]_D=+63°$(*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H, tButyl); 1.24–1.45 (4s, 12H, isoprop.); 3.70 (dd, 1H, H6); 4.00 (m, 3H, H3, H5, H6′); 4.20 (dd, 1H, H4); 4.40 (d, 1H, H2); 7.30–7.70 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7–27.4 [tButyl, $C(CH_3)_2$]; 67.6; 72.6; 76.8; 81.3 (C2, C3, C4, C5, C6); 109.7; 110.5 [$C(CH_3)_2$]; 127.0–136.0 (ph); 173.8 (CO); Anal. Calcd for $C_{28}H_{38}O_7Si$: C, 65.34; H, 7.44. Found: C, 65.40; H, 7.46. **8**: Mp 113–115°C; $[\alpha]_D=+30°$ (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H, tButyl); 1.50 (m, 20H, cyclohex.); 3.80 (m, 1H, H5); 4.10 (m, 3H, H3, H6, H6′); 4.30 (dd, 1H, H4); 4.40 (d, 1H, H2); 7.30–7.80 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.2–37.5 (tButyl, cyclohex.); 67.9 (C6); 73.4; 77.3; 77.4; 81.6 (C2, C3, C4, C5); 110.7; 111.6 [$C(OR)_2$]; 127.9–136.5 (ph); 174.5 (CO); Anal. Calcd for $C_{34}H_{46}O_7Si$: C, 68.65; H, 7.80. Found: C, 68.76; H, 7.86.

1.1.4. General procedure to obtain compounds ethyl 3-deoxy-5,6:7,8-di-*O*-isopropylidene-4-*O*-*tert*-butyldiphenylsilyl-D-*gluco*-oct-2-ulosonate 9, ethyl 3-deoxy-5,6:7,8-di-*O*-cyclohexylidene-4-*O*-*tert*-butyldiphenylsilyl-D-*gluco*-oct-2-ulosonate 10, ethyl 3-deoxy-5,6:7,8-di-*O*-isopropylidene-4-*O*-*tert*-butyldiphenylsilyl-D-*gluco*-oct-2-ulosonate (*EZ*)-phenylhydrazone 13 and ethyl 3-deoxy-5,6:7,8-di-*O*-cyclohexylidene-4-*O*-*tert*-butyldiphenylsilyl-D-*gluco*-oct-2-ulosonate (*EZ*)-phenylhydrazone 14. To a mixture of *N*-hydroxy-2-thiopyridone (127 mg, 1 mmol), DCC (216 mg, 1.05 mmol), and anhydrous dichloromethane in a round flask covered with aluminum foil was added acids **7** (514 mg, 1 mmol) or **8** (594 mg, 1 mmol) at 0°C under argon with stirring. After 1 h, the solution was cooled at −60°C and transferred dropwise into the olefin [$CH_2{=}C(OCOCF_3)(COOEt)$] (1.06 g, 5 mmol) which was placed in a flask under argon at −30°C and irradiated with a Q-Beam lamp. After the transfer, the photoreaction was continued for 1 h at −30°C. A solution of aqueous satured K_2CO_3–acetone (10 mL, 1:1) or pyridine (10 mL)/phenylhydrazine hydrochloride (2.2 g, 15 mmol) was added and the solution was stirred at −20°C to room temperature overnight. The mixture was diluted with CH_2Cl_2, washed with water, dried, concentrated in vacuum and purified by silica gel chromatography (hexane/EtOAc) to give ketones **9** and **10** (53%) or phenylhydrazone **13** and **14** (55%).

9: Oil; ^1H NMR (200 MHz, $CDCl_3$): δ 1.05 (m, 12H, CH_3CH_2, tButyl); 1.20–1.40 (3s, 12H, isoprop.); 3.10 (m, 2H, H3, H3’); 3.75 (m, 1H, H8); 4.00 (m, 3H, H5, H7, H8’); 4.15 (q, 2H, CH_2CH_3); 4.30 (dd, 1H, H6); 4.50 (d, 1H, H4); 7.40–7.70 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (CH_3CH_2), 19.4–27.1 [tButyl, $C(CH_3)_2$]; 43.5 (C3); 62.2 (CH_2CH_3); 67.3; 69.0; 77.0; 77.4; 82.1 (C4, C5, C6, C7, C8); 109.5; 109.6 [$C(CH_3)_2$]; 127.0–136.0 (ph); 160.0 (COOEt); 191.0 ($COCH_2$); Anal. Calcd for $C_{32}H_{44}O_8Si$: C, 65.72; H, 7.58. Found: C, 65.68; H, 7.63. **10**: oil; ^1H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9H, tButyl); 1.25 (t, 3H, CH_3CH_2); 1.30–1.70 (m, 20H, cyclohex); 3.10 (m, 2H, H3, H3′); 3.80 (m, 1H, H8); 3.90–4.10 (m, 4H, H4, H5, H7, H8′); 4.20 (q, 2H, CH_2CH_3); 4.50 (m, 1H, H6); 7.40–7.70 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (CH_3CH_2), 19.4–36.7 (tButyl, cyclohex.); 43.5 (C3); 62.2 (CH_2CH_3); 67.4; 69.4; 77.1; 77.4; 82.1 (C4, C5, C6, C7, C8); 110.1; 110.3 [$C(OR)_2$]; 127.5–135.9 (ph); 160.2 (COOEt); 191.1 ($COCH_2$); Anal. Calcd for $C_{38}H_{52}O_8Si$: C, 68.64; H, 7.88. Found: C, 68.68; H, 7.73. **13E**: oil; $[\alpha]_D=-133°$ (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (m, 12H, CH_3CH_2, tButyl); 1.15–1.40 (4s, 12H, isoprop.); 2.80 (m, 2H, H3, H3′); 3.70 (m, 2H, H8, H8′); 3.80–4.40 (m, 6H, CH_2CH_3, H4, H5, H6, H7); 6.90–7.50 (m, 11H, ph); 7.80 (m, 4H, ph); 9.10 (sl, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 (CH_3CH_2); 19.5–27.5 (tButyl, isoprop.); 31.6 (C3); 60.6 (CH_2CH_3); 67.7; 69.2; 76.8; 77.2; 81.4 (C4, C5, C6, C7, C8); 109.5; 110.0 [$C(CH_3)_2$]; 113.0–136.0 (ph); 143.3 (C=N); 164.5 (C=O); Anal. Calcd for $C_{38}H_{50}N_2O_7Si.H_2O$: C, 65.87; H, 7.56; N, 4.04. Found: C, 66.06; H, 7.55; N, 3.78. **14E**: Oil; ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H, tButyl); 1.20 (t, 3H, CH_3CH_2); 1.25–2.00 (m, 20H, cyclohex.); 2.90 (m, 2H, H3, H3′); 3.70–4.40 (m, 8H, CH_2CH_3, H4, H5, H6, H7, H8, H8′); 6.90–7.50 (m, 11H, ph); 7.80 (m, 4H, ph); 9.00 (sl, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3CH_2); 19.5–37.2 (C3, tButyl, cyclohex.); 60.7 (CH_2CH_3); 67.7; 69.6; 76.3; 77.0; 81.3 (C4, C5, C6, C7, C8); 110.0; 110.9 [$C(OR)_2$]; 113.9–136.0 (ph); 143.4 (C=N); 164.5 (C=O).

1.1.5. Preparation of ethyl 3-deoxy-5,6:7,8-di-*O*-cyclohexylidene-4-*O*-*tert*-butyldiphenylsilyl-D-*gluco*-oct-2-ulosonate (*EZ*)-oxime 11. To a solution of ketone **10** (664 mg, 1 mmol) in pyridine (10 mL) at 0°C was added hydroxylamine hydrochloride (105 mg, 1.5 mmol). The mixture was stirred at room temperature for 4 h and diluted with CH_2Cl_2 (50 mL). The solution was washed with water, dried, concentrated in vacuum and the residue was purified by silicagel chromatography (hexane/EtOAc) to afforded the desired compounds **11E** and **11Z** (611 mg, 90%; proportion *E*/*Z*=6:1).

11E: Oil; ^1H NMR (200 MHz, $CDCl_3$): δ 1.00 (s, 9H, tButyl); 1.25 (t, 3H, CH_3CH_2); 1.25–1.70 (m, 20H, cyclohex.); 2.70 (dd, 1H, H3); 3.20 (dd, 1H, H3′); 3.75–4.30 (m, 7H, CH_2CH_3, H4, H5, H7, H8, H8′); 4.50 (m, 1H, H6); 7.10–7.50 (m, 6H, ph); 7.75 (m, 4H, ph); 8.60 (sl, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3CH_2); 19.5–36.4 (C3, tButyl, cyclohex.); 61.4 (CH_2CH_3); 67.2; 69.7; 76.3; 77.0; 81.4 (C4, C5, C6, C7, C8); 110.0 [$C(OR)_2$]; 124.0–136.8 (ph); 149.5 (C=N); 163.3 (C=O).

1.1.6. Cleavage of TBDPS protective group: synthesis of ethyl 3-deoxy-5,6:7,8-di-*O*-cyclohexylidene-D-*gluco*-oct-2-ulosonate (*E*)-oxime 12, ethyl 3-deoxy-5,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-ulosonate (*E*)-phenylhydrazone 15 and Ethyl 3-deoxy-5,6:7,8-di-*O*-cyclohexylidene-D-*gluco*-oct-2-ulosonate (*E*)-phenylhydrazone 16. To a solution of oxime **11E** or hydrazone **13E** or **14E**

(1 mmol) in THF (10 mL) was added TBAF (523 mg, 2 mmol). The mixture was stirred at room temperature for 6–12 h and was then diluted with CH_2Cl_2 (50 mL). The solution was washed with water, dried, concentrated in vacuum and the residue was purified by silicagel chromatography (hexane/EtOAc) to give the desired compounds **12**, **15** or **16** in 90–92% yield.

12: Mp 157–159°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.70 (m, 20H, cyclohex.); 3.10 (m, 2H, H3, H3′); 3.90–4.20 (m, 5H, H5, H6, H7, H8, H8′); 4.90 (dd. 1H, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0–39.0 (C3, cyclohex.); 67.6; 74.8; 76.0; 77.0; 81.6 (C4, C5, C6, C7, C8); 110.6–110.9 [$\mathit{C}(OR)_2$]; 148.0 (C=N); 166.2 (CO); **15**: Mp 104–105°C; $[\alpha]_D=+40°$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.50 (m, 15H, $C\mathit{H}_3CH_2$, isoprop.); 2.90 (ddd, 2H, H3, H3′); 4.00 (m, 6H, H4, H5, H6, H7, H8, H8′); 4.30 (q, 2H, $C\mathit{H}_2CH_3$); 6.90–7.40 (m, 5H, Ph); 9.30 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5 ($CH_2\mathit{C}H_3$); 22.0–31.0 (tButyl, C3); 61.5 ($\mathit{C}H_2CH_3$); 68.2; 70.0; 77.3; 82.7 (C4, C5, C6, C7, C8); 110.4–110.5 [$\mathit{C}(CH_3)_2$]; 114.4; 122.4; 129.8; 133.3 (Ph); 144.2 (C=N); 166.0 (CO); Anal. Calcd for $C_{22}H_{32}N_2O_7$: C, 60.53; H, 7.39; N, 6.42. Found: C, 60.62; H, 7.37; N, 6.42. 16: oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, $C\mathit{H}_3CH_2$); 1.30–1.70 (m, 20H, cyclohex.); 2.90 (m, 2H, H3, H3′); 3.80–4.20 (m, 6H, H4, H5, H6, H7, H8, H8′); 4.30 (q, 2H, $C\mathit{H}_2CH_3$); 6.90–7.40 (m, 5H, Ph); 9.35 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($CH_2\mathit{C}H_3$); 23.7–37.0 (C3, cyclohex.); 61.1 ($\mathit{C}H_2CH_3$); 67.5; 70.0; 76.8; 77.5; 82.1 (C4, C5, C6, C7, C8); 110.5–110.6 [$\mathit{C}(OR)_2$]; 114.0; 121.7; 129.2; 133.2 (Ph); 143.6 (C=N); 165.4 (CO).

1.1.7. Synthesis of 3-deoxy-D-*gluco*-oct-2-ulosono-1,4-lactone (*E*)-phenylhydrazone 17. A solution of hydrazone **15** (218 mg, 0.5 mmol) in ethanol (5 mL) was treated with 1 M hydrochloric acid solution (5 mL) and stirred at room temperature for 12 h. The solution was concentrated in vacuum to give the lactone **17** (130 mg, 85%) which was recrystallized in ethanol. **17** was also prepared from **16** by this same procedure in 80% yield. **17**: Mp 225–227°C; $[\alpha]_D=+110°$ (*c* 0.5, DMSO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.90 (ddd, 2H, H3, H3′); 3.50 (m, 5H, 4OH, H5); 4.40 (t, 1H, H7); 4.55 (m, 2H, H8, H8′); 4.80 (m, 1H, H6); 5.00 (d, 1H, H4); ^{13}C NMR (50 MHz, DMSO *d6*): δ 27.9 (C3); 63.1; 70.2; 71.2; 71.8; 77.4 (C4, C5, C6, C7, C8); 113.5; 121.1; 129.0; 131.2 (Ph); 144.1 (C=N); 167.1 (CO); Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.13; H, 5.81; N, 9.07.

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