Single diastereomers of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes from intramolecular 1,3-dipolar cycloaddition of ω-unsaturated nitrones

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Supporting Information. Part 1 - Experimental procedures and spectral data

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General procedures

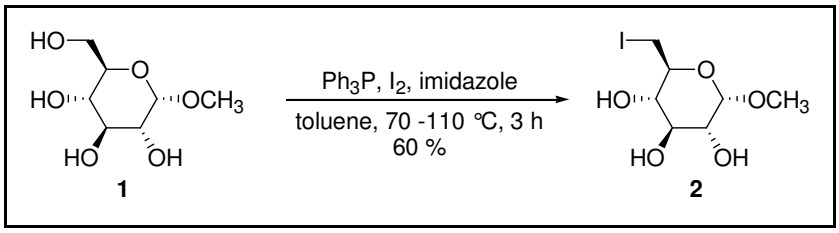
Abbreviations: equiv. (equivalent), LRMS (low resolution mass spectrometry); OPLC (overpressurised layer chromatography).

(*S*)-3-Ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate **18** was prepared as described.[1] Hexanes refer to a mixture of hexanes containing min. 55 % *n*-hexane. Anhydrous solvents were prepared as described.[2] Organic solutions were dried using anhydrous $MgSO_4$ and evaporated in rotary evaporators. TLC: Kieselgel 60 F_{254}, visualization: UV light, iodine and/or charring with H_2SO_4/ethanol. Optical rotation: 589 nm, quartz cell (100 mm), 25 °C. pH-measurement: microprocessor pH meter combined with pH glass electrode for organic solutions. IR spectra: CaF_2, ν_{max}/cm^{-1}, s, strong; m, medium; w, weak; br, broad. NMR: 400.13 MHz and 500.13 MHz (^1H); 125.76 MHz (^{13}C), respectively, $CDCl_3$ and C_6D_6 solutions, δ (ppm), *J* (Hz). The superscripts *, # denote interchangeable assignments. For the 2D experiments (HSQC, HMBC, NOESY) the standard software packages (INV4GSSW, INV4GSLRNDSW) were applied. LRMS: ESI technique. HRMS: high resolution sector instrument using FAB ion source. Samples were dissolved in glycerol, the resolution of the instrument was 10,000. TLC-MS: the analyte solution has been applied onto a 5 cm wide silica gel TLC plate as a band to obtain sufficient material. After developing in a solvent system the appropriate band was removed, the silica gel was suspended in MeOH (100 µL), sonicated, centrifuged and the supernatant was used for MS analysis. OPLC: OPLC-50 (Bionisis, France), 0.2 mm thick HTSorb™ 5 µm silica gel layers (OPLC-Nit Ltd., Hungary), hexane/EtOAc solvent mixtures, 50 bar, eluent flow: 500 µL/min. HPLC: UV/VIS detector, column: LiChrospher 6.1, RP select B (5 µm). Eluent system: gradient: 70-90% MeCN within 25 min, flow rate: 1 mL/min.

Activation of zinc: zinc powder (2.65 g, 40.60 mmol) was subsequently washed with 1 M HCl (3 × 50 mL), water (50 mL), ethanol (50 mL) and Et_2O (2 × 50 mL). Sonication: in an ultrasonic bath (37 kHz, 275 W).

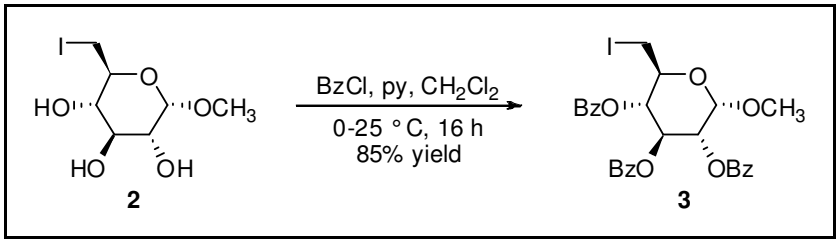
2-(Benzyloxy)acetaldehyde was freshly prepared using the procedure developed by Shiao *et al.*[3] and modified as follows. (±)-3-Benzyloxy-1,2-propanediol (3.32 g, 18.20 mmol) was dissolved in CH_2Cl_2 (120 mL) and treated with sodium metaperiodate (9.73 g, 45.5 mmol, 5 equiv.) in water (240 mL). This solution was stirred for overnight at rt, the phases were then separated, the organic layer was dried ($MgSO_4$), evaporated and the resulting oily 2-(benzyloxy)acetaldehyde was used without any further purification for the cycloaddition reactions.

Methyl 6-deoxy-6-iodo-α-D-glucopyranoside (2)[4, 5]



A three-necked, 1 L flask was equipped with a condenser, a mechanical shaker and a stopper. The solution of methyl α-D-glucopyranoside (10.00 g, 51.50 mmol) in toluene (300 mL) was agitated mechanically at room temperature while triphenylphosphine (20.24 g, 77.20 mmol, 1.50 equiv.) and imidazole (10.51 g, 154.92 mmol, 3.00 equiv.) were added portionwise. The mixture was heated to reflux then, after 1 h, cooled to 70 °C. Iodine (18.30 g, 72.10 mmol, 1.40 equiv.) was added portionwise under vigorous shaking and the initially brown mixture was vigorously agitated at 70 °C until the brown colour of iodine disappeared and then the mixture was heated at reflux for 3 h. The mixture was cooled in an ice-bath and extracted with water (5 × 200 mL), the aq. phase was backwashed with toluene (100 mL). The combined organic phases were dried ($MgSO_4$), evaporated and coevaporated with acetonitrile. The crude product (containing four spots according to TLC in toluene : *i*-PrOH 7 : 3, detection: UV, iodine vapor, and charring) was dissolved in hot etanol (100 mL) and hot EtOAc (500 mL) was added. The resulting precipitate (imidazolium iodide) was removed by filtration and the filtrate was concentrated and subjected to column chromatography (adsorbent: 250 g silica gel, eluent: toluene : *i*-PrOH 9 : 1). The product was obtained as a semisolid which was then crystallized from a toluene-*i*-PrOH mixture. 9.396 g (60 %), mp. 145.8-146.2 °C (lit.[6] value: 146-147 °C), R_f : 0.30, toluene : *i*-PrOH 7 : 3. The ^1H and ^{13}C NMR spectra of the above product were in full agreement with the published ones.[5]

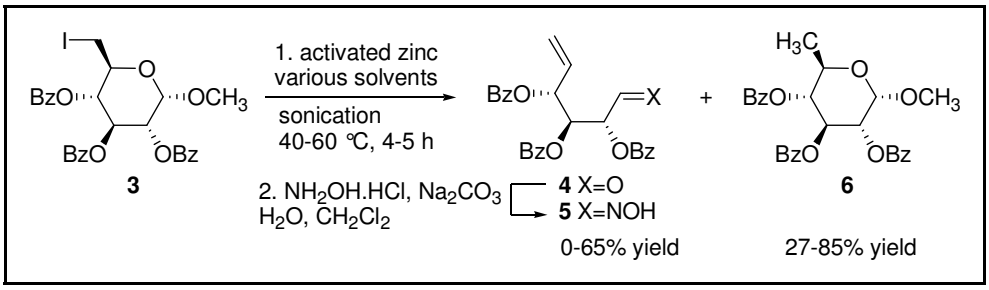
Methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (3).[7, 8]



Methyl 6-deoxy-6-iodo-α-D-glucopyranoside (**2**, 10.00 g, 32.89 mmol) dissolved in anhydr. pyridine (65 mL) and anhydr. CH_2Cl_2 (65 mL) was treated with benzoyl chloride (17.0 mL, 146.58 mmol, 4.46 equiv.) at 0 °C with stirring. After adding benzoyl chloride the mixture was allowed to warm to ambient temperature and stirring was continued at this

temperature for 16 h. The reaction mixture was evaporated and the residue was dissolved in EtOAc (500 mL), subsequently extracted with water (2 × 100 mL), aq. citric acid solution (2 × 100 mL), satd. aq. sodium carbonate solution (2 × 100 mL), the organic phase was dried ($MgSO_4$), evaporated and chromatographed (adsorbent: 250 g silica gel, eluent: hexanes : EtOAc 9 : 1). The title tribenzoate was crystallized from hexanes, 17.22 g (85 %). R_f : 0.30, hexanes : EtOAc 7 : 3, R_f : 0.75, toluene : *i*-PrOH 7 : 3. Mp. 104.6-106.1 °C (lit.[7, 8] value: 103-106 °C). The ^{1}H and ^{13}C NMR spectra of the above product were in full agreement with the published ones.[8]

(*E/Z*)-5,6-Dideoxy-2,3,4-tri-*O*-benzoyl-D-*xylo*-hex-5-enose oxime (5)[9] and methyl 6-deoxy-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (6)[10]



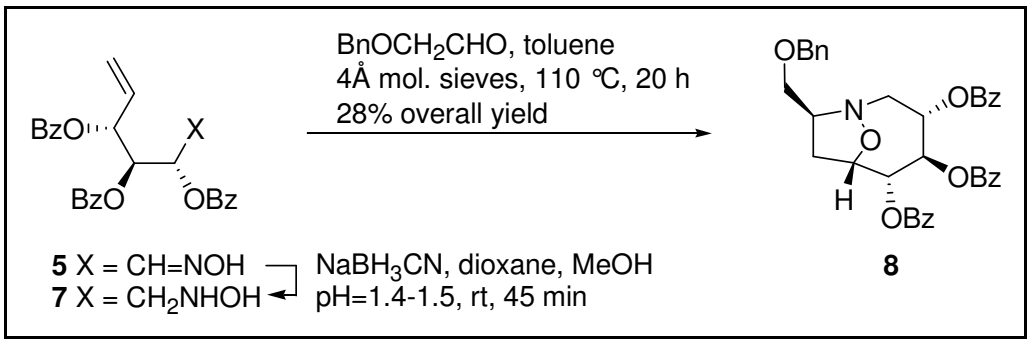
NH_4Cl (2.17 g, 40.60 mmol, 10 equiv.) $CeCl_3$[11] (0.050 g, 0.20 mmol, 0.05 equiv.) and activated zinc (2.65 g, 40.60 mmol, 10 equiv.) in THF (10 mL) was allowed to react in an ultrasonic bath at 40 °C for 15 min. Methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **3** (2.50 g, 4.06 mmol) was dissolved in THF (60 mL) and poured into the zinc slurry and sonication was continued. This solution was often mixed with a spatula at the beginning of the reaction to prevent the coagulation of zinc dust. After 2 h MeOH (10 mL) and after an additional 1 h water (1 mL) were added to the reaction mixture to dissolve the zinc salts from the zinc surface. After 4 h sonication the mixture was chilled in an ice-bath, filtered, washed with EtOAc (150 mL), dried ($CaCl_2$), evaporated *in vacuo* and the resulting aldehyde **4** (R_f : 0.30, hexanes : EtOAc 7 : 3) was used without purification directly for the next step. The crude aldehyde **4** was dissolved in CH_2Cl_2 (200 mL), satd. aq. Na_2CO_3 (100 mL) and $NH_2OH{\cdot}HCl$ (1.50 g, 21.59 mmol, 5.32 equiv.) were added and the resulting heterogeneous mixture was vigorously stirred for 16 h at rt. The layers were separated, the organic layer was dried ($CaCl_2$), evaporated and chromatographed (adsorbent: 30 g silica gel, eluent: hexanes : EtOAc 9 : 1) to give the title oily oximes (1 : 1 mixture of *E/Z* isomers, 1.057 g, 55 %, R_f : 0.53, 0.60, hexanes : EtOAc 1 : 1). The application of $HgCl_2$ in lieu of $CeCl_3$ in MeCN gave a slightly higher yield (65 %, see *Table 1*). The IR, ^{1}H and ^{13}C NMR spectra of the above product were in full agreement with the published ones.[9]

Along with the oxime the 6-deoxy derivative (**6**)[10] could also be isolated (R_f : 0.30, hexanes : EtOAc 7 : 3, R_f : 0.65, toluene : *i*-PrOH 7 : 3, mp 145.5-146.5 °C, lit.[10] value 139-140 °C) in variable amounts in different solvents (see *Table 1*).

*Table 1. Yields of compounds **5** and **6** in the zinc-mediated reaction of 6-deoxy-6-iodo derivative **3***

Solvent(s) and reaction conditions	*Yield of oxime **5**, %*	*Yield of 6-deoxy derivative **6**, %*
THF : MeOH : H_2O 70 : 10 : 1, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	55	32
neat THF, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	60	30
MeCN : MeOH : H_2O 50 : 2.5 : 2.5, 10 equiv. Zn, 0.05 equiv. $HgCl_2$, 10 equiv. NH_4Cl, sonication at 40 °C for 30 min then reflux for 30 min and this cycle was repeated for 5 h	65	27
neat dioxane, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	12	75
neat DMF, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	0	85
neat MeCN, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	0	85
neat acetone, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	0	85
neat di-*i*-propyl ether, 10 equiv. Zn, 0.05 equiv. $CeCl_3$, 10 equiv. NH_4Cl, sonication at 40 °C, 4 h	0	85

(3*S*,4*R*,5*S*,6*S*,8*S*)-8-(Benzyloxymethyl)-9-oxa-1-azabicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (8)



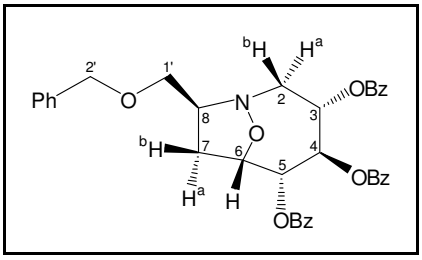
To a stirred solution of oxime **5** (3.44 g, 7.27 mmol) in dioxane (300 mL) and MeOH (300 mL) was added $NaBH_3CN$ (2.74 g, 43.60 mmol, 6 equiv.) while the solution was carefully treated with HCl/dioxane (1.7 M, ~30 mL) to maintain the pH between 1.4-1.5 using a combined pH glass electrode for organic solutions. After approximately 45 min, when the reduction stopped (the pH of the reaction solution did not alter further), the solution was evaporated *in vacuo,* co-evaporated with MeCN (100 mL), the residue was dissolved in a mixture of EtOAc (400 mL) and satd. aq. Na_2CO_3 solution (300 mL), the organic phase was washed with additional Na_2CO_3 solution (300 mL), water (300 mL) and brine (300 mL), dried ($MgSO_4$) and evaporated *in vacuo*. If the reaction solution still contains some starting material **5** (TLC), subsequent $NaBH_3CN$ (2.74 g, 43.60 mmol, 6 equiv.) has to be added and the pH must be maintained for a repeated 30 min period. The unstable hydroxylamine **7** was used immediately without any further purification to avoid its decomposition. R_f : 0.60, hexanes : EtOAc 1 : 1; TLC-MS (*m/z)*: 476 (100%, $[M+H]^+$), 498 (12, $[M+Na]^+$).

The above hydroxylamine **7** was dissolved in dry toluene (250 mL) and treated with freshly prepared 2-(benzyloxy)acetaldehyde (2 equiv.) in the presence of 4 Å molecular sieves and a Dean-Stark water trap. After stirring at 110 °C for 20 h, the solution was filtered, evaporated *in vacuo* and co-evaporated with MeCN (3 × 50 mL). The residue was purified by silica gel column chromatography [eluent: 0-5% (v/v) Et_2O in CH_2Cl_2] to give the title cycloaddition product **8** as a pale yellow oil (1.22 g, 28% overall yield).

R_f : 0.33, CH_2Cl_2 : Et_2O 95 : 5.

$[\alpha]_D$: -26 (c=0.5, MeOH).

IR (CaF_2, thin film): 990 (w), 1026 (m), 1069 (m), 1096 (s), 1177 (w), 1261 (s), 1278 (s), 1315 (m), 1451 (m), 1493 (w), 1584 (w), 1601 (w), 1724 (s), 2859 (w), 2942 (w), 3030 (w), 3057 (w) cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm) 2.25 (1H, ddd, $J_{6,7b\#}$ = 8.7 Hz, $J_{7a,7b}$ = 13.5 Hz, $J_{7b,8\#}$ = 4.6 Hz, H-7b); 2.96 (1H, ddd, $J_{6,7a^*}$ = 2.8 Hz, $J_{7a,7b}$ = 13.5 Hz, $J_{7a,8^*}$ = 8.6 Hz, H-7a); 3.14 (1H, dd, $J_{2a,2b}$ = 14.1 Hz, $J_{2a,3}$ = 7.7 Hz, H-2a); 3.41 (1H, dd, $J_{8,1'a}$ = 6.4 Hz, $J_{1'a,1'b}$ = 9.4 Hz, H-1'a); 3.60 (1H, dd, $J_{8,1'b}$ = 7.3 Hz, $J_{1'a,1'b}$ = 9.4 Hz, H-1'b); 3.75 (1H, m, H-8); 4.24 (1H, dd, $J_{2a,2b}$ = 14.1 Hz, $J_{2b,3}$ = 5.5 Hz, H-2b); 4.57 (1H, d, $J_{2'a,2'b}$ = 11.9 Hz, H-2'a); 4.66 (1H, d, $J_{2'a,2'b}$ = 11.9 Hz, H-2'b); 4.86 (1H, ddd, $J_{5,6}$ = 5.8 Hz, $J_{6,7b\#}$ = 8.7 Hz, $J_{6,7a^*}$ = 2.8 Hz, H-6); 5.66 (1H, dd, $J_{4,5}$ = 8.1 Hz, $J_{5,6}$ = 5.8 Hz, H-5); 5.84 (1H, ddd, $J_{2a,3}$ = 7.7 Hz, $J_{2b,3}$ = 5.5 Hz, $J_{3,4}$ = 9.4 Hz, H-3); 5.99 (1H, dd, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 8.1 Hz, H-4); 7.37 (14H, m, arom.); 7.90 (6H, m, arom.).

^{13}C NMR (126 MHz, $CDCl_3$, δ, ppm) 32.8 (C-7); 59.1 (C-2); 67.6 (C-8); 69.1 (C-3); 72.6 (C-4); 73.1 (C-1'); 73.2 (C-5); 73.4 (C-2'); 77.1 (C-6); 127.7-128.3 (arom.); 129.0 (arom. C_q);

129.1 (arom. C_q); 133.0 (arom.); 133.1 (arom.); 133.2 (arom.);138.0 (arom. C_q); 165.1 (CO); 165.1 (CO); 165.5 (CO).

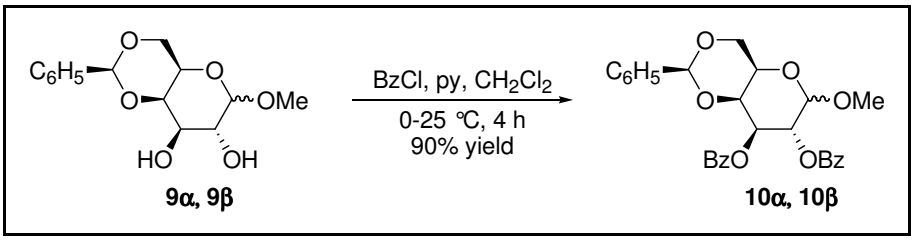
NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton)
top-face: H-3/H-2b; H-5/H-6; H-6/H-7b;
bottom-face: H-7a/H-8/H-4; H-8/H-2a/H-4.

LRMS (*m/z*): 608 (100%, $[M+H]^+$), 630 (25, $[M+Na]^+$).

HRMS (FAB, glycerol): calcd. for $C_{36}H_{34}NO_8^+$ $[M+H]^+$ *m/z* 608.22789, found *m/z* 608.2310.

Anal. calcd. for $C_{36}H_{33}NO_8$ (607.649) C, 71.16; H, 5.47; N, 2.31; found C, 71.03; H, 5.59; N, 2.48%.

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-α- and β-D-galactopyranoside (10α and 10β)



9α, 9β **10α, 10β**

Methyl 4,6-*O*-benzylidene-D-galactopyranoside (**9**, 5.00 g, 17.7 mmol)[12] was dissolved in a mixture of dry CH_2Cl_2 (40 mL) and pyridine (10 mL) then benzoyl chloride (5 mL) was added dropwise to the ice-cooled solution. The reaction mixture was stirred for 4 h at room temperature then ice was added. The cooled mixture was extracted with 0.1 M HCl, then successively washed with satd. $NaHCO_3$ solution and water, dried ($MgSO_4$) and evaporated to dryness. The crude product was dissolved in chloroform and precipitated with hexanes (amorphous foam, 7.80 g, 90%). A small amount was further purified by silica gel column chromatography (hexanes : EtOAc 85:15) and the mixture was separated into anomers.

α-anomer (**10α**): amorphous foam.

R_f : 0.10, hexanes : EtOAc 7 : 3.

$[\alpha]_D$: +182 (c=0.75, $CHCl_3$).

IR (CaF_2, thin film): 952 (w), 995 (m), 1028 (s), 1071 (m), 1099 (s), 1112 (s), 1181 (m), 1212 (w), 1275 (s), 1317 (m), 1399 (w), 1411 (w), 1452 (m), 1585 (w), 1602 (w), 1727 (s), 2864 (w), 3065 (br w) cm^{-1}.

^{1}H NMR ($CDCl_3$, δ, ppm): 3.35 (3H, s, OCH_3); 3.79 (1H, s, H-5); 4.03 (1H, d, $J_{6a,6b}$ = 12.8 Hz, H-6a); 4.24 (1H, d, $J_{6a,6b}$ = 12.8 Hz, H-6b); 4.55 (1H, s, H-4); 5.19 (1H, d, $J_{1,2}$ = 2.2 Hz, H-1); 5.48 (1H, s, CHPh); 5.70 (2H, m, H-2 and H-3); 7.14-7.92 (15H, m, arom.).

^{13}C NMR ($CDCl_3$, δ, ppm): 55.6 (OCH_3); 62.2 (C-5); 68.8 (C-2); 69.1 (C-6); 69.2 (C-3); 74.2 (C-4); 98.1 (C-1); 100.6 (CHPh); 126.1-133.1 (arom.); 165.9 and 168.1 (CO).

LRMS (*m/z*): 513.1 (100%, [M+Na$^+$]).

Anal. calcd. for $C_{28}H_{26}O_8$ (490.501) C, 68.56; H, 5.34; found C, 68.72; H, 5.25%.

β-anomer (**10β**): amorphous foam.

R_f : 0.17, hexanes : EtOAc 7 : 3.

$[\alpha]_D$: +165 (c=0.7, $CHCl_3$).

IR (CaF_2, thin film): 952 (w), 1013 (m), 1028 (m), 1071 (m), 1082 (m), 1107 (s), 1154 (m), 1176 (m), 1197 (w), 1278 (s), 1315 (m), 1415 (w), 1451 (m), 1601 (w), 1724 (s), 2855 (w), 3064 (br w) cm^{-1}.

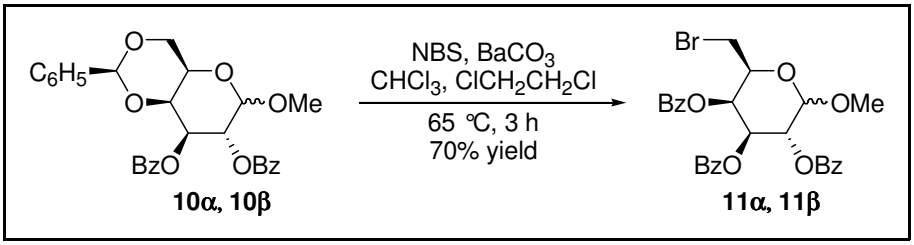
^{1}H NMR ($CDCl_3$, δ, ppm): 3.44 (3H, s, OCH_3); 3.56 (1H, s, H-5); 4.03 (1H, d, $J_{6a,6b}$=12.2 Hz, H-6a); 4.30 (1H, d, $J_{6a,6b}$=12.2 Hz, H-6b); 4.49 (1H, d, $J_{3,4}$ = 3.8 Hz, H-4); 4.58 (1H, d, $J_{1,2}$ = 8.1 Hz, H-1); 5.30 (1H, dd, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 3.8 Hz, H-3); 5.45 (1H, s, CHPh); 5.78 (1H, dd, $J_{1,2}$ = 8.1, $J_{2,3}$ = 10.8 Hz, H-2); 7.20-7.91 (15H, m, arom.).

^{13}C NMR ($CDCl_3$, δ, ppm): 56.5 (OCH_3); 66.4 (C-5); 68.9 (C-6); 69.0 (C-2); 72.7 (C-3); 73.5 (C-4); 100.7 (CHPh); 101.9 (C-1); 126.1-133.3 (arom.); 165.2 and 166.1 (CO).

LRMS (*m/z*): 513.1 (100%, [M+Na$^+$]).

Anal. calcd. for $C_{28}H_{26}O_8$ (490.501) C, 68.56; H, 5.34; found C, 68.43; H, 5.40%.

Methyl 6-bromo-6-deoxy-2,3,4-tri-*O*-benzoyl-α- and β-D-galactopyranoside (11α and 11β)



A suspension containing methyl 4,6-benzylidene-2,3-di-*O*-benzoyl-D-galactopyranoside (**10**, 6.60 g, 13.5 mmol), NBS (3.18 g, 17.8 mmol) and barium carbonate (2.80 g, 14.10 mmol) in a mixture of chloroform (165 mL) and 1,2-dichloroethane (25 mL) was stirred under reflux for 3 h. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in diethyl ether (50 mL), washed with water (3 × 10 mL), dried ($MgSO_4$) and evaporated to dryness. The syrup was dissolved in chloroform and precipitated with hexane (amorphous foam, 5.30 g, 70 %). A small amount was further purified by column chromatography (hexanes : EtOAc 9 : 1) and the mixture was separated into anomers.

α-anomer (**11α**): amorphous foam.

R_f : 0.16, hexanes : EtOAc 9 : 1.

$[\alpha]_D$: +195 (c=0.70, $CHCl_3$)

IR (CaF_2, thin film): 974 (w), 1000 (w), 1026 (m), 1068 (s), 1093 (s), 1106 (s), 1177 (w), 1207 (w), 1261 (s), 1283 (s), 1315 (w), 1451 (w), 1601 (w), 1724 (w), 2972 (w), 3059 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$, δ, ppm): 3.39-3.40 (2H, m, H-6a and H-6b); 3.44 (3H, s, OCH_3); 4.36 (1H, t, $J_{5,6a} = J_{5,6b} = 6.5$ Hz, H-5); 5.23 (1H, d, $J_{1,2} = 3.6$ Hz, H-1); 5.57 (1H, dd, $J_{2,3} = 10.8$, $J_{3,4} = 3.6$ Hz, H-3); 5.87 (1H, dd, $J_{1,2} = 3.6$ Hz, $J_{2,3} = 10.8$ H-2); 5.92 (1H, d, $J_{3,4} = 3.6$ Hz, H-4); 7.13-8.00 (15H, m, arom.).

^{13}C NMR ($CDCl_3$, δ, ppm): 29.3 (C-6); 55.8 (OCH_3); 68.4 (C-2); 69.1 (C-3); 69.4 (C-5); 69.8 (C-4); 97.6 (C-1); 128.2-133.6 (arom.); 165.4, 165.5 and 166.0 (CO).

LRMS (*m/z*): 590.9 (100%, [M(^{79}Br)+Na^+]), 592.9 (94, [M(^{81}Br)+Na^+]).

Anal. calcd. for $C_{28}H_{25}BrO_8$ (569.397) C, 59.06; H, 4.43; Br, 14.03, found C, 55.87; H, 4.59; Br, 14.35%.

β-anomer (**11β**): amorphous foam.

R_f : 0.23, hexanes : EtOAc 9 : 1.

$[\alpha]_D$: +79 (c=0.75, $CHCl_3$).

IR (CaF_2, thin film): 953 (w), 1027 (m), 1046 (m), 1069 (m), 1097 (s), 1105 (s), 1124 (m), 1177 (w), 1280 (s), 1270 (s), 1315 (w), 1451 (w), 1601 (w), 1724 (s), 2966 (br w), 3062 (br w) cm^{-1}.

^{1}H NMR ($CDCl_3$, δ, ppm): 3.42-3.49 (2H, m, H-6a and H-6b); 3.55 (3H, s, OCH_3); 4.10 (1H,

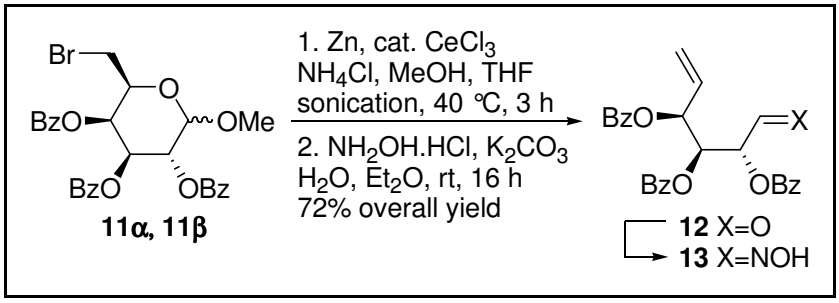
t, $J_{5,6a} = J_{5,6b} = 6.9$ Hz, H-5); 4.66 (1H, d, $J_{1,2} = 7.9$ Hz, H-1); 5.50 (1H, dd, $J_{2,3} = 10.3$ Hz, $J_{3,4} = 3.2$ Hz, H-3); 5.68 (1H, dd, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 10.3$ Hz, H-2); 5.94 (1H, d, $J_{3,4} = 3.2$ Hz, H-4); 7.15-8.0 (15H, m, arom.).

^{13}C NMR ($CDCl_3$, δ, ppm): 28.5 (C-6); 57.3 (OCH_3); 68.6 (C-4); 69.5 (C-2); 71.7 (C-3); 74.0 (C-5); 102.3 (C-1); 128.3-133.6 (arom.); 165.3 and 165.4 (CO).

LRMS (*m/z*): 590.9 (100%, [M(^{79}Br)+Na$^+$]), 593.0 (95, [M(^{81}Br)+Na$^+$]).

Anal. calcd. for $C_{28}H_{25}BrO_8$ (569.397) C, 59.06; H, 4.43; Br, 14.03, found C, 55.95; H, 4.64; Br, 14.24%.

2,3,4-Tri-*O*-benzoyl-5,6-dideoxy-L-*arabino*-hex-5-enose oxime (13)



A suspension of zinc dust (5.20 g, 93.2 mmol), NH_4Cl (8.80 g, 93.20 mmol) and a catalytical amount of $CeCl_3$ [11] were sonicated in a mixture of MeOH (50 mL) and THF (70 mL) for 15 min. After this pretreatment period methyl 6-bromo-6-deoxy-2,3,4-tri-*O*-benzoyl-D-galactopyranoside (**11**, 5.20 g, 9.3 mmol) was added to the reaction mixture. After 3 h sonication at 40 °C the reaction was complete, the suspension was filtered, and evaporated to dryness. The residue was dissolved in Et_2O (30 mL), extracted with water (3 × 10 mL) and dried ($MgSO_4$). The crude aldehyde **12** was used without further purification in the following reaction. The mixture of the above ethereal solution and water (30 mL) was cooled in an ice bath and $NH_2OH{\cdot}HCl$ (4.44 g, 93.00 mmol) was added. A solution of K_2CO_3 (10.20 g, 93.0 mmol) in water (20 mL) was added dropwise to the reaction mixture and stirred for 16 h. The organic layer was separated, washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (hexanes: EtOAc 85:15) to yield a sirupy product (3.20 g, 72 %, *E* : *Z* = 2 : 1, based on the integral intensities of proton H-6a in the ^{1}H NMR spectrum of the isomer mixture).

R_f : 0.18, 0.23 (*E/Z*), hexanes : EtOAc 8 : 2.

IR (CaF_2, thin film): 943 (w), 1026 (m), 1069 (m), 1096 (s), 1107 (m), 1263 (s), 1107 (s), 1177 (w), 1263 (s), 1316 (m), 1451 (m), 1584 (w), 1601 (w), 1724 (s), 2931 (w), 3063 (w), 3434 (br w) cm^{-1}.

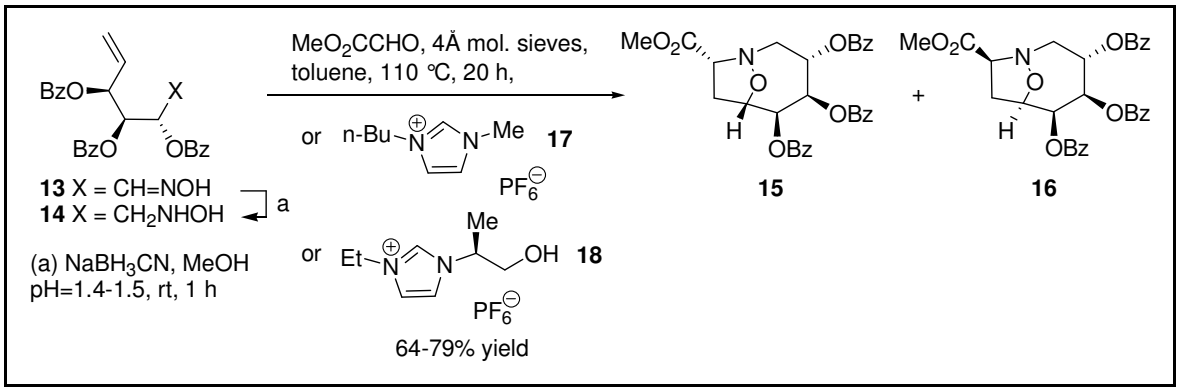
^{1}H NMR ($CDCl_3$, δ, ppm): 5.34 (0.33 H, d, $J_{5,6a}$ = 11.1 Hz, H-6a); 5.40 (0.67 H, d, $J_{5,6a}$ = 10.1 Hz, H-6a); (1H, d, $J_{6a,6b}$ = 17.1 Hz, H-6b) 6.00 (4H, m, H-2, H-3, H-4 and H-5); 7.46 (10 H, m, H-1, arom.); 8.03 (6 H, m, arom.).

^{13}C NMR ($CDCl_3$, δ, ppm): 66.1 (C-2_Z); 69.6 (C-2_E); 72.2 (C-4_Z); 72.9 (C-4_E); 73.1 (C-3_Z); 73.3 (C-3_E); 120.6 (C-6_Z); 121.1 (C-6_E); 128.3-133.4 (arom.); 131.2 (C-5_E); 131.7 (C-5_Z); 145.8 (C-1_E); 147.0 (C-1_Z); 165.1 and 165.5 (CO).

LRMS (*m/z*): 474.0 (50%, [M+H$^+$]), 496.1 (63, [M+Na$^+$]).

Anal. calcd. for $C_{27}H_{23}NO_7$ (473.474) C, 68.49; H, 4.90; N, 2.96; found C, 68.30; H, 5.18; N, 3.20%.

(3*S*,4*R*,5*R*,6*S*,8*R*)-8-(Methoxycarbonyl)-9-oxa-1-aza-bicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (15) and (3*S*,4*R*,5*R*,6*R*,8*S*)-8-(methoxy-carbonyl)-9-oxa-1-aza-bicyclo-[4.2.1]nonane-3,4,5-triyl tribenzoate (16)



To a stirred solution of oxime **13** (0.300 g, 0.63 mmol) in MeOH (100 mL) was added $NaBH_3CN$ (0.240 g, 3.79 mmol, 6 equiv.). The pH of the solution was maintained between 1.4-1.5 with 1 M HCl/MeOH and monitored either by a combined pH glass electrode for organic solutions or by the indicator bromocresol green. After 1 h the solution was evaporated *in vacuo* (the pH of the reaction mixture did not change further), co-evaporated to dryness with toluene (3 × 20 mL). The residue was dissolved in Et_2O (100 mL) and the ethereal solution was washed with aq. 0.1 M HCl (20 mL), satd. aq. Na_2CO_3 solution (2 × 50 mL) and distilled water (3 × 50 mL), dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The obtained hydroxylamine **14** was used without any further purification. R_f : 0.35, hexanes : EtOAc 1 : 1; TLC-MS (*m/z*): 476 (100%, [M+H]$^+$), 498 (12, [M+Na]$^+$).

The above crude product was dissolved in dry toluene (100 mL) and treated with freshly prepared methyl glyoxylate[13] (0.140 g, 1.57 mmol, 2.5 equiv.) in the presence of 4 Å molecular sieves. After stirring at 110 °C for 16 h, the solution was filtered, evaporated *in vacuo* and co-evaporated with toluene (3 × 50 mL). The residue was purified by column chromatography (hexanes : EtOAc 85 : 15). The diastereoisomers were separated in an

additional run of silica gel column chromatography (hexanes : *i*-PrOH 10 : 0.5) to give the cycloaddition product **15** (0.165 g) and **16** (0.055 g) in 64 % overall yield in a ratio of 3 : 1. In another experiment, starting from oxime **13** (0.120 g, 0.25 mmol), the cycloaddition step was carried out in achiral ionic solvent 1-*n*-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate **17** and the reaction yielded diastereoisomers **15** (0.088 g) and **16** (0.011 g) in 72 % overall yield in a ratio of 8 : 1.

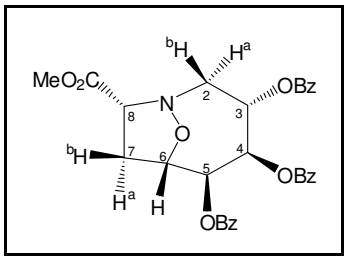
When the same reaction sequence was repeated with **13** (0.100 g, 0.21 mmol,) in chiral ionic solvent (*S*)-3-ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate **18**[1] diastereoisomer **15** (0.088 g) was obtained in 79 % overall yield. In the ^{1}H NMR spectrum of this sample there were only very small signals, beyond the signals of **15**, originating from unidentified impurities.

Compound 15:

R_f : 0.20, hexanes : EtOAc 7 : 3.

$[\alpha]_D$: +170 (c=0.55, $CHCl_3$).

IR (CaF_2, thin film): 985 (w), 1001 (w), 1027 (m), 1070 (m), 1095 (m), 1108 (m), 1120 (m), 1177 (w), 1263 (s), 1280 (s), 1451 (w), 1601 (w), 1725 (s), 2952 (w) 3062 (w) cm^{-1}.



^{1}H NMR ($CDCl_3$, δ, ppm): 2.69 (1H, ddd, $J_{6,7a}$ = 6.0 Hz, $J_{7a,8}$ = 10.1 Hz, $J_{7a,7b}$ = 13.3 Hz, H-7a); 2.84 (1H, ddd, $J_{6,7b}$ = 8.9 Hz, $J_{7b,8}$ = 8.9 Hz, $J_{7a,7b}$ = 13.3 Hz, H-7b); 3.22 (1H, dd, $J_{2a,3}$ = 8.99 Hz, $J_{2a,2b}$ = 13.3 Hz, H-2a); 3.75 (3H, s, OCH_3); 4.00 (1H, dd, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 13.3 Hz, H-2b); 4.76 (1H, m, H-6); 4.35 (1H, dd, $J_{7a,8}$ = 10.1 Hz, $J_{7b,8}$ = 8.9 Hz, H-8); 5.68 (1H, dd, $J_{4,5}$ = 4.0 Hz, $J_{5,6}$ = 1.85 Hz, H-5); 5.87 (1H, dd, $J_{3,4}$ = 9.48 Hz, $J_{4,5}$ = 4.0 Hz, H-4); 6.15 (1H, ddd, $J_{2a,3}$ = 8.99 Hz, $J_{2b,3}$ = 4.0 Hz, $J_{3,4}$ = 9.48 Hz, H-3); 7.17-8.10 (15H, m, arom. CH).

^{13}C NMR ($CDCl_3$, δ, ppm): 32.9 (C-7); 52.6 (OCH_3); 54.1 (C-2); 67.1 (C-3); 68.2 (C-8); 72.0 (C-5); 72.1 (C-4); 81.2 (C-6); 128.2-133.4 (arom.); 165.0, 165.4, 165.8 (3 × benzoyl CO); 168.1 (acetyl CO).

NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton)
top-face: H-2b/H-3; H-6/H-7b/H-8
bottom-face: H-2a/H-4/H-5/H-7a.

LRMS (*m/z*): 546.3 (100%, $[M+H^+]$), 568.2 (37, $[M+Na^+]$).

HRMS (FAB, glycerol): calcd. for $C_{30}H_{28}NO_9^+$ $[M+H]^+$ *m/z* 546.17586, found *m/z* 546.17794.

Anal. calcd. for $C_{30}H_{27}NO_9$ (545.537) C, 66.05; H, 4.99; N, 2.57; found C, 65.87; H, 5.18;

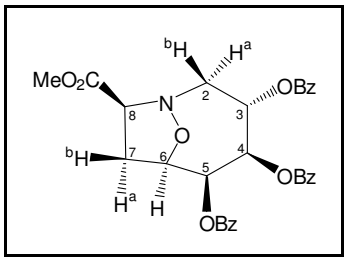
N, 2.73%.

Compound 16:

R_f : 0.26, hexanes : EtOAc 7 : 3.

$[\alpha]_D$: +7 (c=0.5, $CHCl_3$).

IR (CaF_2, thin film): 944 (w), 1026 (m), 1069 (m), 1096 (s), 1120 (s), 1178 (m), 1219 (m), 1265 (s), 1316 (m), 1451 (m), 1470 (m), 1585 (w), 1602 (w), 1730 (s), 2849 (s), 2916 (s), 3062 (w), 3259 (br w) cm^{-1}.



^{1}H NMR (500 MHz, C_6D_6, δ, ppm) 2.11 (1H, ddd, $J_{6,7a}$ = 9.6 Hz, $J_{7a,7b}$ = 13.7 Hz $J_{7a,8}$ = 9.3 Hz, H-7a); 3.21 (1H, ddd, $J_{6,7b}$ = 5.5 Hz, $J_{7b,7a}$ = 13.7 Hz, $J_{7b,8}$ = 10.1 Hz, H-7b); 3.34 (3H, s, Me); 3.64 (1H, dd, $J_{2a,2b}$ = 15.0 Hz, $J_{2b,3}$ = 3.7 Hz, H-2b); 3.72 (1H, dd, $J_{2a,2b}$ = 15.0 Hz, $J_{2a,3}$ = 10.0 Hz, H-2a); 4.09 (1H, dd, $J_{7a,8}$ = 9.3 Hz, $J_{7b,8}$ = 10.1 Hz, H-8); 4.71 (1H, ddd, $J_{5,6}$ = 7.9 Hz, $J_{6,7a}$ = 9.6 Hz, $J_{6,7b}$ = 5.5 Hz, H-6); 6.10 (1H, dd, $J_{4,5}$ = 4.9 Hz, $J_{5,6}$ = 7.9 Hz, H-5); 6.25 (1H, dd, $J_{3,4}$ = 10.2 Hz, $J_{4,5}$ = 4.9 Hz, H-4); 6.30 (1H, ddd, $J_{2b,3}$ = 3.7 Hz, $J_{2a,3}$ = 10.0 Hz, $J_{3,4}$ = 10.2 Hz, H-3); 6.92 (9H, m, arom.); 7.91 (4H, m, arom.); 8.24 (2H, m, arom.).

^{13}C NMR ($CDCl_3$, δ, ppm): 35.0 (C-7), 53.3 (OCH_3), 56.2 (C-2), 66.6 (C-8), 68.8 (C-3), 69.7 (C-5), 72.5 (C-4), 78.4 (C-6), 128.5-133.9 (arom.), 165.5, 168.6 (CO).

NOESY (connected protons, relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton)
top-face: H-2b/H-3; H-3/H-7b
bottom-face:H-2a/H-4; H-4/H-5/H-6; H-5/H-6/H-7a; H-7a/H-8.

LRMS (*m/z*): 546.1 (100%, $[M+H^+]$), 568.1 (39, $[M+Na^+]$).

HRMS (FAB, glycerol): calcd. for $C_{30}H_{28}NO_9^+$ $[M+H]^+$ *m/z* 546.17586, found *m/z* 546.17821.

Anal. calcd. for $C_{30}H_{27}NO_9$ (545.537) C, 66.05; H, 4.99; N, 2.57; found C, 66.19; H, 5.21; N, 2.78%.

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