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A Selective and Rapid Access to Six- or Seven-Membered Ring Iminosugars via 6,8-Diazabicyclo[3.2.1]oct-6-ene Intermediates

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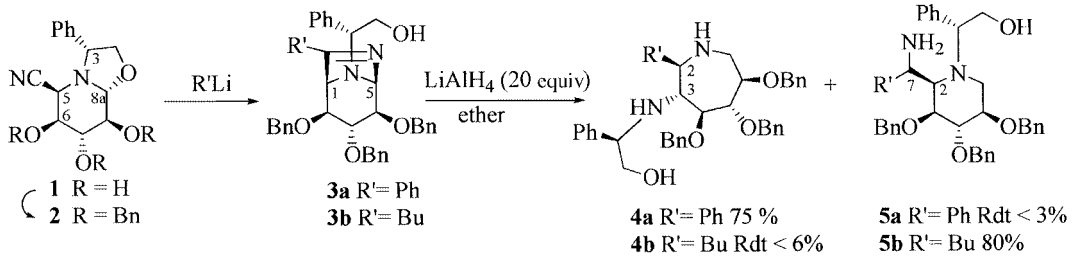
A selective and rapid access to six- or seven-membered ring iminosugars is reported. The key step of the strategy involves the highly regio- and stereoselective reduction of 6,8-diazabicyclo[3.2.1]oct-6-ene intermediates, depending on the nature of imine substituents.

Introduction

The iminosugars have been widely studied as inhibitors of oligosaccharide-processing enzymes such as glycosidases and glycosyltransferases.[1,2] Several glycosidases inhibitors have already been tested or approved in the treatment of diabetes,[3] Gaucher's disease,[4] HIV infection,[5] viral infections,[6] and cancer.[7] Much effort has been devoted toward the syntheses of five- and six-membered ring iminocyclitol families,[8] notably the 1-deoxy analogues. Relatively few preparations of the seven-membered ring homologues have been reported so far, despite data in the literature[9] indicating that many of these compounds have higher glycosidase-inhibition potencies than their five- or six-membered ring counterparts.

This enhancement may be due to the flexibility of the perhydroazepine ring system, which then allows the ring to adopt quasi-flattened conformations, which are much more favorable to binding within the active site of the enzyme.[10]

With the aim of researching new carbohydrates mimetics, we describe here a selective and rapid access to substituted six- or seven-membered ring iminosugars via a 6,8-diazabicyclo[3.2.1]oct-6-ene intermediate[11] from the trihydroxylated 5-cyano-8a-oxazolopiperidine **1** (Scheme 1).



Scheme 1. Syntheses of six- or seven-membered ring iminosugars.

Results and Discussion

After benzylation of the hydroxyl functions of compound **1**, obtained in a facile, three-step synthesis from commercially available starting materials,[12] the addition of a lithium derivative on the cyano group of **2** led to the 6,8-diaza-

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bicyclo[3.2.1]oct-6-ene imines **3**. In the ESI mass spectrum of the diazabicyclo compound **3a**, a peak for the protonated molecule was observed at m/z = 625, and in the ^{1}H NMR spectrum, two doublets were observed at δ = 4.06 (J = 3.5 Hz) and 5.46 ppm (J = 2.5 Hz), which are attributed to bridgehead 1-H and 5-H, respectively; a ^{1}H,^{13}C COSY analysis indicates an equatorial configuration.

The next step involved the one-pot reduction and ring-enlargement process of the 6,8-diazabicyclo[3.2.1]oct-6-ene imines **3** – this occurs in a regio- and diastereoselective manner. This key step permitted the selective synthesis of six- and seven-membered iminosugars, compounds **4a** and **5b**, respectively, according to the nature of the substitution pattern at the imine carbon atom (Scheme 1). In the phenyl series, treatment of imine **3a** with a large excess of $LiAlH_4$ (20 equiv.) afforded the polyhydroxyazepane compound **4a**, which was characterized by 1D- and 2D NMR experiments. The coupling constant $J_{2\text{-H/3-H}}$ = 8.5 Hz indicates that 2-H and 3-H are *trans* to each other. In the crude mixture, no trace of the six-membered ring derivative **5a** could be characterized by NMR spectroscopy. To confirm this selective synthesis of compound **4a**, an electrospray mass spectrum (ESI/MS)[13] of the crude reaction mixture recorded at 30 V of the skimmer was effected, and the products ions, obtained from ERMS experiments (Energy resolved mass spectrometry)[14] from collision of $[MH]^+$ ions, show the presence of **5a** with a very low relative abundance (1–3%).[15]

In contrast, in the butyl series, the piperidine derivative **5b** was formed from the aliphatic imine **3b** under the same experimental conditions; however, a trace of the seven-membered-ring compound **4b** was observed only by mass spectrometry – the relative abundances were from 4 to 6%.[16] The relative configuration of the newly created stereogenic center (C-7) of **5b** was determined directly from the NMR spectroscopic data and by comparison with the literature.[17] Indeed, the 2-H/7-H coupling constant of 4.5 Hz indicates a *R*/*R* configuration for the C-2/C-7 stereocenters.

These regioselective imine reductions proved to be highly dependent on their substitution patterns. In the butyl series, morpholine intermediates previously described[11] may be involved for the unique formation of compound **5b** (Figure 1).

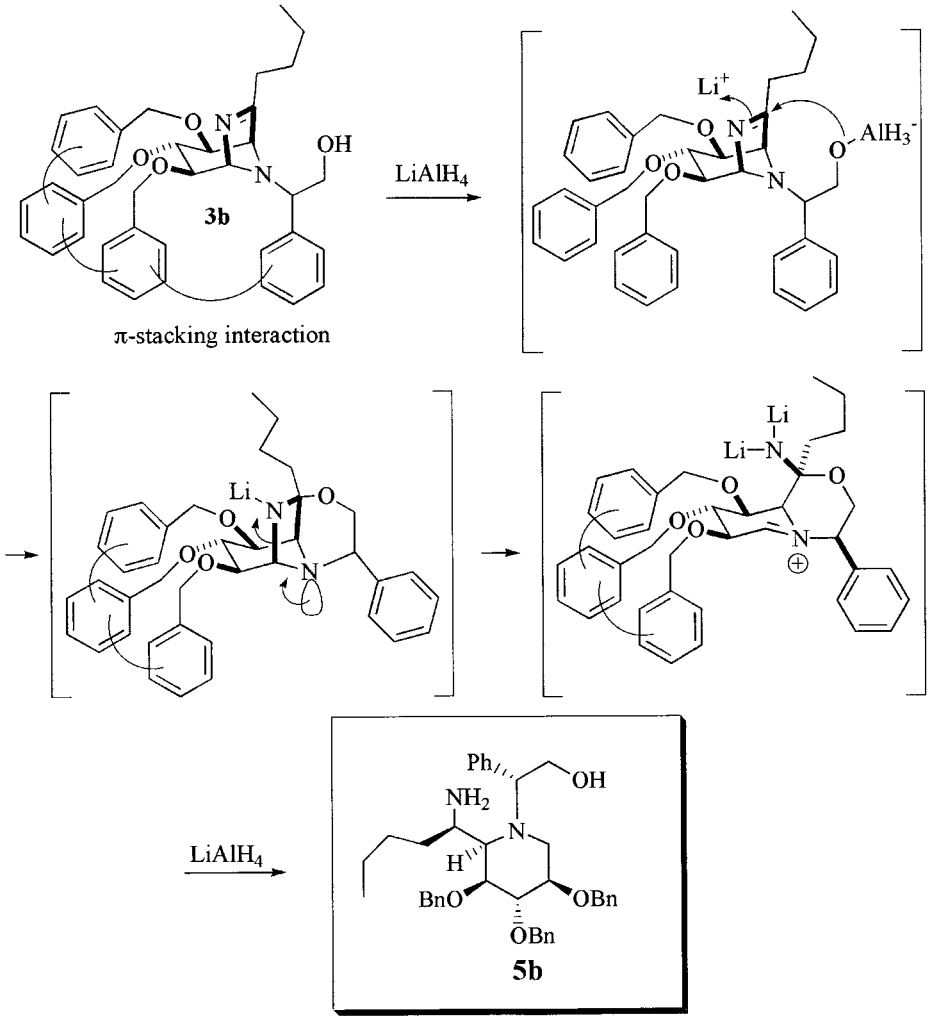


Figure 1. π-Stacking interaction favoring the piperidine system.

Indeed, these intermediates, which were obtained by a preferential attack of the alcohol function on the *si* face of imine **3b** and are favored by a π-stacking interaction between an adjacent benzyl group and the phenyl group of the oxazolidine ring, may be reduced to a piperidine system by $LiAlH_4$ (Figure 1). In the phenyl series, a π-stacking interaction between the aromatic groups could avoid the formation of the transient morpholine and permit only the access of the seven-membered ring derivative **4a** (Figure 2).

To confirm the π-stacking interaction during the formation of the azepan compound, we decided to extend this methodology by using an aromatic furan substituent (Scheme 2). Treatment of the imine **6** under the same experimental conditions ($LiAlH_4$ 20 equiv.) afforded the unprecedented bicyclic aminal **7** as a single diastereomer 7S.

The structure of **7** was ascertained by typical NMR chemical shifts; a signal at δ = 4.50 ppm and one at δ = 55.0 ppm, observed in the ^1H and ^{13}C NMR spectra, respectively, were attributed to that arising from the C-7 reduced position. The *erythro* configuration is indicated by the small coupling constant (J = 4.5 Hz) between 2-H and 7-H. It is interesting to mention that the electrospray spectrum of the reduction mixture exhibits peaks for two protonated molecules, one at m/z = 617 for compound **7** and the other at m/z = 619. The collision-induced dissociation (CID) of $[MH]^+$ (m/z = 619) produced the characteristic

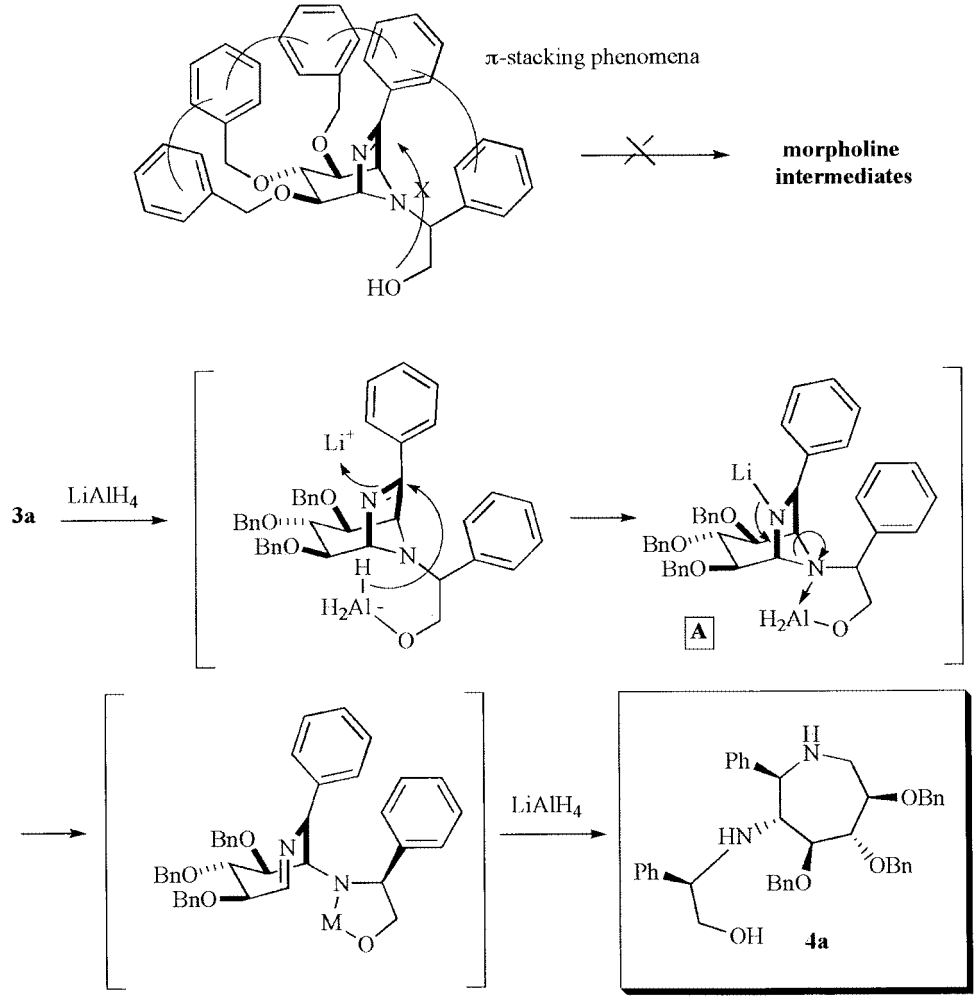
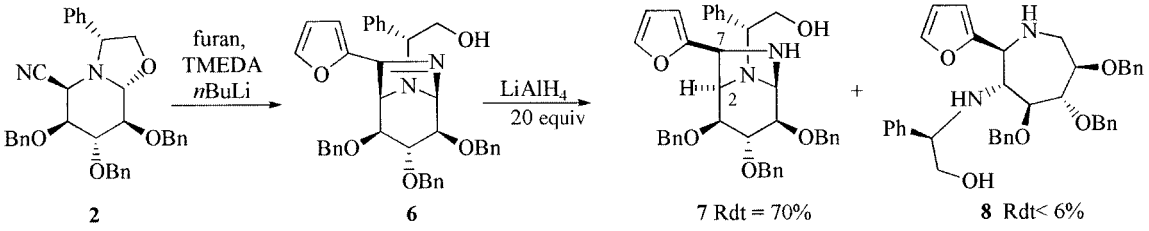


Figure 2. π-Stacking interaction favoring the azepane system.



Scheme 2. The use of furan as imine substituent.

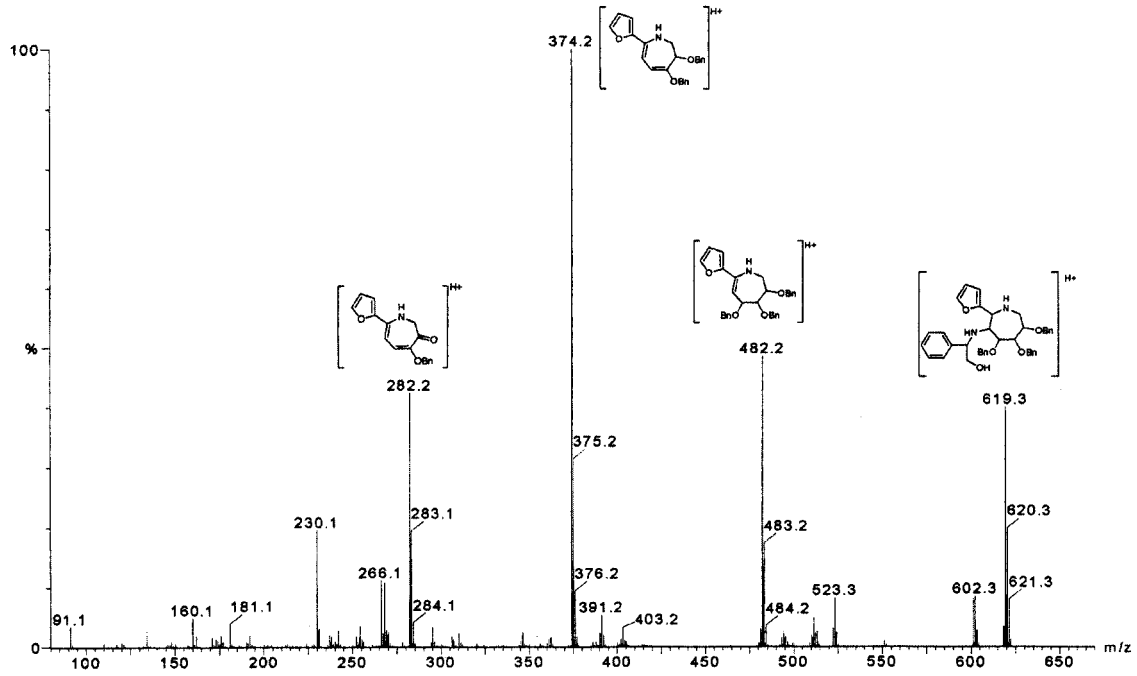


Figure 3. CID of $[MH]^+$ of compound **8**.

daughter ions of the seven-membered ring compound **8** with peaks at *m*/*z* = 482, 374, and 282 (Figure 3), which are analogues of the product ions observed for **4a** (492 and 384) and **4b** (472 and 364).

The isolation of compound **7** supports the formation of an intermediate of type **A** (Figure 2). Consequently, this methodology, applied with a heterocyclic aromatic substituent, avoids the formation of the transient morpholine and permits the quasi-exclusive access of the seven-membered ring compounds **8**.

In conclusion, we have demonstrated that trihydroxylated 2-cyano-6-oxazolopiperidine **1** is a useful building block for ring-expansion reactions. The choice of the precursor in the reduction reactions permitted a selective access for the construction of chiral 2,3-disubstituted-4,5,6-trihydroxyazepane or for the construction of chiral diamines containing a 2-substituted-4,5,6-trihydroxypiperidine skeleton. Considering the high potential of so-called "azasugars" for drug discovery, we now envision extending this methodology to the preparation of new carbohydrate mimics. This synthetic work and the biological evaluations are in progress, and the results will be reported in due course.

Experimental Section

(3*R*,5*R*,6*S*,7*R*,8*S*,8a*R*)-6,7,8-Tribenzyloxy-3-phenylhexahydro-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (2): Sodium hydride (865 mg, 36.2 mmol) was added to a solution of compound **1** (1 g, 3.62 mmol) in dry DMF (40 mL), under argon. The reaction mixture was stirred for 1 h at room temperature and cooled to 0 °C. A solution of freshly distilled benzyl bromide (9.5 mL, 79.64 mmol) was then added dropwise. Stirring was continued for 22 h at room temperature. After the addition of methanol (17 mL), the mixture was stirred continuously for one more hour. The reaction mixture was then quenched by adding a saturated aqueous sodium hydrogen carbonate solution (30 mL). The mixture was extracted with CH_2Cl_2 (120 mL × 4), the combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting yellow oil on silica gel (cyclohexane/ether, 9:1) yielded **2** (1.5 g, 75%) as an oil. R_f = 0.57 (cyclohexane/ether, 8:3). $[\alpha]_D$ –73 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2229 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.67 (dd, *J* = 8, 9 Hz, 1 H, 8-H), 3.7–3.8 (m, 2 H, 5-H and 6-H), 3.8–3.9 (m, 1 H, 7-H), 3.87 (t, *J* = 8 Hz, 1 H, 2-H), 4.00 (t, *J* = 8 Hz, 1 H, 3-H), 4.41 (t, *J* = 8 Hz, 1 H, 2-H), 4.44 (d, *J* = 8 Hz, 1 H, 8a-H), 4.6–4.7 (2d AB, *J* = 11.5 Hz, 2 H, O–CH_2-Ph), 4.8–5.0 (2d AB, *J* = 11.5 Hz, 2 H, O–CH_2-Ph), 4.9–5.0 (2d AB, *J* = 10.5 Hz, 2 H, O–CH_2-Ph), 7.2–7.4 (m, 20 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 48.8 (C-5), 62.9 (C-3), 73.8 (O–CH_2-Ph), 74.0 (O–CH_2-Ph), 74.8 (C-2), 76.6 (O–CH_2-Ph), 78.2 (C-6), 81.9 (C-8), 82.0 (C-7), 92.6 (C-8a), 113.1 (CN), 127–129 (CH arom.), 136.3–138.7 (C_q arom.) ppm. MS (ESI): *m*/*z* = 547 $[M + H]^+$. HRMS ($C_{35}H_{35}N_2O_4$): calcd. 547.2597; found 547.2590.

General Procedure for Compounds 3a and 3b: A lithium derivative (0.57 mmol) was added to a solution of compound **2** (250 mg, 0.45 mmol) in dry ether (1.7 mL), under argon at –78 °C. The reaction mixture was stirred for 1 h at –78 °C and 3 h at 0°C. The reaction mixture was then quenched by the addition of ice. The mixture was extracted with CH_2Cl_2 (120 mL × 4), the combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting yellow oil on silica gel (CH_2Cl_2/MeOH, 18:1) yielded **3a** (200 mg, 70%) or **3b** (207 mg, 75%) as oils.

(2*R*)-2-Phenyl-2-[(1*R*,2*S*,3*R*,4*R*,5*S*)-2,3,4-trisbenzyloxy-7-phenyl-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl]ethanol (3a): R_f = 0.35 (CH_2Cl_2/MeOH, 18:1). $[\alpha]_D$ –29 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3297 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.85 (s, 1 H, OH), 3.24 (t, *J* = 7.5 Hz, 1 H, 3-H), 3.45 (t, *J* = 5 Hz, 1 H, CH_2–OH), 3.56 (dd, *J* = 3.5, 7.5 Hz,

1 H, 2-H), 3.6–3.7 (m, 2 H, C*H*$_2$–OH and C*H*-Ph), 3.71 (dd, *J* = 2.5, 7.5 Hz, 1 H, 4-H), 4.06 (d, *J* = 3.5 Hz, 1 H, 1-H), 4.46 (s, 2 H, O–CH$_2$-Ph), 4.56 and 4.65 (2d AB, *J* = 11 Hz, 2 H, O–CH$_2$-Ph), 4.76 and 4.82 (2d AB, *J* = 12 Hz, 2 H, O–CH$_2$-Ph), 5.46 (d, *J* = 2.5 Hz, 1 H, 5-H), 7.0–7.7 (m, 25 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.0 (–CH$_2$–OH), 65.3 (–CH-Ph), 65.9 (C-1), 72.6 (O–CH$_2$-Ph), 72.7 (O–CH$_2$-Ph), 75.6 (O–CH$_2$-Ph), 79.4 (C-2), 81.0 (C-4), 83.9 (C-3), 85.4 (C-5), 127–129 (CH arom.), 131–139.5 (C$_q$ arom.), 174.3 (C-7) ppm. MS (ESI): *m*/*z* = 625 [M + H]$^+$. HRMS ($C_{41}H_{41}N_2O_4$): calcd. 625.3066; found 625.3078.

(2*R*)-2-Phenyl-2-[(1*R*,2*S*,3*R*,4*R*,5*S*)-2,3,4-trisbenzyloxy-7-butyl-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl]ethanol (3b): R_f = 0.35 (CH$_2$Cl$_2$/MeOH, 18:1). [*a*]$_D$ –17.5 (*c* = 0.95, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3277, 1945, 1878, 1809, 1631 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7 Hz, 3 H, CH$_3$ butyl), 1.2–1.4 (m, 4 H, CH$_2$ butyl), 2.1–2.2 (m, 1 H, CH$_2$ butyl), 2.4–2.5 (m, 1 H, CH$_2$ butyl), 3.25 (t, *J* = 7 Hz, 1 H, 3-H), 3.45 (t, *J* = 5 Hz, 1 H, C*H*$_2$–OH), 3.5–3.6 (m, 3 H, 1-H, C*H*-Ph and 2-H), 3.6–3.7 (m, 2 H, 4-H and C*H*$_2$–OH), 4.25 and 4.52 (2d AB, *J* = 12 Hz, 2 H, O–CH$_2$-Ph), 4.72 and 4.74 (2d AB, *J* = 11 Hz, 2 H, O–CH$_2$-Ph), 4.80 and 4.84 (2d AB, *J* = 12 Hz, 2 H, O–CH$_2$-Ph), 5.27 (d, *J* = 3 Hz, 1 H, 5-H), 7.1–7.4 (m, 20 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7 (CH$_3$), 22.5, 27.7, 32.2 (CH$_2$ butyl), 64.9 (–CH$_2$–OH), 65.1 (C-1), 66.6 (–CH-Ph), 72.5 (2× O–CH$_2$-Ph), 75.5 (O–CH$_2$-Ph), 79.3 (C-2), 80.9 (C-4), 83.9 (C-3), 84.7 (C-5), 126–129 (CH arom.), 138.8–139.5 (C$_q$ arom.), 179.7 (C-7) ppm. MS (ESI): *m*/*z* = 605 [M + H]$^+$. HMRS ($C_{39}H_{45}N_2O_4$): calcd. 605.3379; found 605.3391.

General Procedure for Compounds 4a, 5b, and 7: The imine derivative (0.2 mmol) dissolved in ether was added dropwise to a suspension of $LiAlH_4$ (145 mg, 3.9 mmol) in dry ether (2 mL) at –10 °C under argon. The reaction mixture was stirred for 12 h at room temperature. The mixture was then quenched by adding an aqueous sodium hydroxide solution (1 M, 0.3 mL) and washed with distilled water (0.6 mL). The resulting precipitate was filtered through Celite® and extracted with THF. The combined organic layers were evaporated under reduced pressure. Flash chromatography of the resulting oil on silica gel yielded **4a** (CH$_2$Cl$_2$/MeOH, 18:0.2; 94 mg; 75%), **5b** (CH$_2$Cl$_2$/MeOH, 18:1; 97 mg; 80%), or **7** (cyclohexane/ethyl acetate: 6:4; 86 mg; 70%).

(2*R*)-2-Phenyl-2-[[(2*R*,3*R*,4*S*,5*R*,6*R*)-4,5,6-tribenzyloxy-2-phenylhexahydro-1*H*-azepin-3-yl]amino]ethanol (4a): Oil. R_f = 0.15 (CH$_2$Cl$_2$/MeOH, 18:1). [*a*]$_D$ –23.5 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3452, 2929, 1601, 1452 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.00 (br. s, 3 H, NH and OH), 2.88 (dd, *J* = 4.5, 8 Hz, 1 H, –C*H*-Ph), 2.94 (dd, *J* = 3.5, 15 Hz, 1 H, 7-H), 2.98 (t, *J* = 8.5 Hz, 1 H, 3-H), 3.04 (dd, *J* = 8, 10.5 Hz, 1 H, –C*H*$_2$-OH), 320 (dd, *J* = 4.5, 10.5 Hz, 1 H,–C*H*$_2$-OH), 3.31 (dd, *J* = 3.5, 15 Hz, 1 H, 7-H), 3.55 (d, *J* = 8.5 Hz, 1 H, 2-H), 3.6–3.7 (m, 2 H, 4-H and 6-H), 3.93 (dd, *J* = 6.5, 8 Hz, 1 H, 5-H), 4.51 and 4.97 (2d AB, *J* = 11 Hz, 2 H, O–CH$_2$-Ph), 4.61 and 4.75 (2d AB, *J* = 11 Hz, 2 H, O–CH$_2$-Ph), 4.62 (s, 2 H, O–CH$_2$-Ph), 6.8–8.0 (m, 25 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 48.8 (C-7), 62.1 (–CH-Ph), 63.1 (C-3), 66.8 (–CH$_2$-OH), 71.1 (C-2), 72.0 (O–CH$_2$-Ph), 74.7 (O–CH$_2$-Ph), 75.5 (O–CH$_2$-Ph), 81.3 (C-6 or C-4), 81.9 (C-4 or C-6), 84.9 (C-5), 127–129 (CH arom.), 138.1, 138.5, 140.7, 144.3 (C$_q$ arom.) ppm. MS (ESI): *m*/*z* = 629 [M + H]$^+$. HRMS ($C_{41}H_{45}N_2O_4$): calcd. 629.3377; found 629.3379.

(2*R*)-2-[(2*R*,3*S*,4*S*,5*R*)-2-[(7*R*)-7-Aminopentyl]-3,4,5-trisbenzyloxypiperidin-1-yl]-2-phenylethanol (5b): Oil. R_f = 0.15 (CH$_2$Cl$_2$/MeOH, 18:1.5). [*a*]$_D$ –25 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3366, 3300, 3172, 1875, 1452, 1067 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7 Hz, 3 H, CH$_3$ butyl), 1.2–1.5 (m, 5 H, CH$_2$ butyl), 1.6–1.7 (m, 1 H, CH$_2$ butyl), 2.2–2.5 (br. s, 3 H, 2 NH and OH), 2.60 (dd, *J* = 11, 14 Hz, 1 H, 6-H), 2.86 (dd, *J* = 5, 14 Hz, 1 H, 6-H), 3.1–3.2 (m, 1 H, 5-H), 3.22 (dd, *J* = 4.5, 7 Hz, 1 H, 2-H), 3.3–3.4 (m, 1 H, 7-H), 3.68 (dd, *J* = 4, 10.5 Hz, 1 H, –C*H*$_2$–OH), 3.79 (t, *J* = 7.5 Hz, 1 H, 4-H), 3.8–3.9 (m, 2 H, –C*H*$_2$–OH and 3-H), 3.91 (dd, *J* = 4, 7.5 Hz, 1 H, –CH-Ph), 4.29 (s, 2 H, O–CH$_2$-Ph), 4.59 and 4.69 (2d AB, *J* = 11.5 Hz, 2 H, O–CH$_2$-Ph), 4.75 (s, 2 H, O–CH$_2$-Ph), 7.0–7.6 (m, 20 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH$_3$ butyl), 22.8, 28.6, 34.5 (CH$_2$ butyl), 44.3 (C-6), 51.0 (C-2), 61.2 (C-7), 63.7 (–CH$_2$–OH), 66.3 (–CH-Ph), 72.2 (O–CH$_2$-Ph), 72.9 (O–CH$_2$-Ph), 74.3 (O–CH$_2$-Ph), 77.5 (C-5), 79.5 (C-3), 81.8 (C-4), 127–129 (CH arom.), 138.0, 138.4, 138.7, 140.2 (C$_q$ arom.) ppm. MS (CI, NH_3): *m*/*z* = 609 [M + H]$^+$. HMRS ($C_{39}H_{49}N_2O_4$): calcd. 609.3692; found 609.3587.

(2*R*)-2-Phenyl-2-[(1*R*,2*S*,3*R*,4*R*,5*S*,7*S*)-2,3,4-trisbenzyloxy-7-(furan-2-yl)-6,8-diazabicyclo[3.2.1]oct-8-yl]ethanol (7): Oil. R_f = 0.44 (CH$_2$Cl$_2$/MeOH, 20:1). [*a*]$_D$ –197 (*c* = 0.9, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2922, 2868, 1602, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.54 (br. s, 2 H, OH and NH), 3.48 (t, *J* = 4.5 Hz, 1 H, 1-H), 3.64 (m, 4 H, 2-H, 4-H, and –C*H*$_2$-OH), 3.84 (t, *J* = 5 Hz, 1 H, –CH-Ph), 4.22 (m, 1 H, 3-H), 4,18–4,31 [dd AB, *J* = 12 Hz, 2 H, O–CH$_2$-Ph], 4.50 (d, *J* = 4.5 Hz, 1 H, 7-H), 4.56 (d, *J* = 2.5 Hz, 1 H, 5-H), 4.70 and 4.6 (2d AB, *J* = 11.5 Hz, 2 H, O–CH$_2$-Ph), 4.73 and 4.80 (2d AB, *J* = 12 Hz, 2 H, O–CH$_2$-Ph), 6.27 (dd, *J* = 2, 3 Hz, 1 H, furan), 6.30 (d, *J* = 3 Hz, 1 H, furan), 6.90 (d, *J* = 2 Hz, 1 H, furan), 7.0–7.5 (m, 20 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.0 (C-7), 61.2 (C-1), 65.4 (CH-Ph), 66.3 (CH$_2$–OH), 71.2 (O–CH$_2$-Ph), 72.6 (O–CH$_2$-Ph), 74.0 (C-5), 75.0 (O–CH$_2$-Ph), 81.5 (C-3), 82.7 (C-2), 83.9 (C-4), 106.5 (CH furan), 110.2 (CH furan), 127.3–129.0 (CH arom.), 138.4–139.9 (C$_q$ arom.), 141.1(CH furan), 152.9(C$_q$ furan) ppm. MS (CI, NH_3): *m*/*z* = 617 [M + H]$^+$. HMRS ($C_{39}H_{41}N_2O_5$): calcd.617.3015; found 617.3028.

(2*R*)-2-Phenyl-2-[(1*R*,2*S*,3*R*,4*R*,5*S*)-2,3,4-trisbenzyloxy-7-furan-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl]ethanol (6): A solution of *n*BuLi (2.5 M in hexane, 1.52 mL, 4.39 mmol) was added to a solution of TMEDA (0.57 mL, 4.39 mmol) in dry THF (3 mL) at –20 °C under argon. A solution of furan (0.363 mL, 4.94 mmol) was then added dropwise, and the mixture was cooled to – 30 °C. Thereafter compound **2** (412 mg, 0.76 mmol) was added, and the reaction mixture was warmed to –20 °C. Stirring was continued for 2 h at –20 °C. The reaction mixture was quenched by adding a saturated aqueous ammonium chloride solution and extracted with CH_2Cl_2 (10 mL × 5), the combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting crude on silica gel (cyclohexane/ethyl acetate, 6:4) yielded **6** (348 mg, 75%%) as an oil. R_f = 0.37 (cyclohexane/ethyl acetate, 6:4). [*a*]$_D$ –153 (*c* = 1, $CHCl_3$). IR (NaCl): $\tilde{\nu}$ = 3279, 2922, 2360, 1618 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.35 (t, *J* = 7.5 Hz, 1 H, 4-H), 3.54 (t, *J* = 5 Hz, 1 H, –C*H*$_2$–OH), 3.62 (dd, *J* = 4, 7.5 Hz, 1 H, 3-H), 3.71 (m, 2 H, –C*H*$_2$–OH and C*H*-Ph), 3.81 (dd, *J* = 3, 7 Hz, 1 H, 5-H), 4.1 (d, *J* = 4 Hz, 1 H, 2-H), 4.48 and 4.62 (2d AB, *J* = 12 Hz, 2 H, O–CH$_2$-Ph), 4.66 and 4.76 (2d AB, *J* = 11 Hz, 2 H, O–CH$_2$-Ph), 4.80 (dd, *J* = 12 Hz, 2 H, O–CH$_2$-Ph), 5.67 (d, *J* = 3 Hz, 1 H, 1-H), 6.44 (dd, *J* = 1.5, 3.5 Hz, 1 H, furan), 6.79 (d, *J* = 3.5 Hz, 1 H, furan), 7.10–7.40 (m, 20 H, arom.), 7.43 (d, *J* = 1.5 Hz, 1 H, furan) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.2 (CH$_2$–OH), 65.5 (CH-Ph), 66.6 (C-2), 72.3 (O–CH$_2$-Ph), 72.6 (O–CH$_2$-Ph), 75.8 (O–CH$_2$-Ph), 78.8 (C-3), 81.1 (C-5), 83.8 (C-4), 85.3 (C-6), 112.2, 115.8 (CH furan), 127.6–128.9 (arom.), 137.9–139.7 (C$_{aq}$ arom.), 145.5, 148.7, 164.2 ppm. MS (CI, NH_3): *m*/*z* = 615 [M + H]$^+$. HMRS ($C_{39}H_{39}N_2O_5$): calcd. 615.2859; found 615.2849.

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