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$PdCl_2/CuCl_2$-catalysed chlorocyclisation of sugar-derived aminoalkenitols in the synthesis of new iminohexitols

Peter Szolcsányi* and Tibor Gracza

Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia

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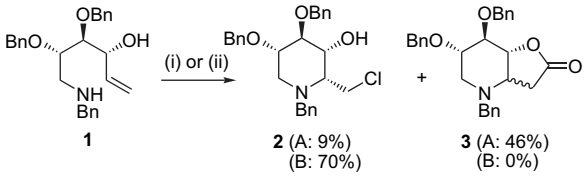
Abstract—The total synthesis of two novel L-*ido* and L-*altro* configured 6-chloro-1,5,6-trideoxyiminohexitols featuring a highly diastereoselective Pd(II)/$CuCl_2$-catalysed chlorocyclisation of sugar-derived aminoalkenitols has been accomplished. The requisite substrates were, in turn, prepared from chiral pool materials starting from the cheap and commercially available methyl-α-D-gluco- and methyl-α-D-galactopyranoside.

1. Introduction

Polyhydroxylated piperidines (azasugars and iminohexitols) are naturally occurring alkaloids with a wide range of unique biological properties,[1] which have led to synthetic and medicinal interest in their research producing an impressive array of functional analogues.[2] Thus, D-*galacto*,[3] L-*galacto*,[4] D-*gluco*[5] and L-*gulo*[6] configured 6-chloro-1,5,6-trideoxyiminohexitols are known. Recently, we described[7] the unexpected formation of partially protected L-*ido*-azasugar **2** along with desired lactones **3** during a Pd(II)-catalysed cyclocarbonylation of methyl-α-D-glucopyranoside derived aminoalkenitol **1** (conditions (i), Scheme 1). Clearly, $CuCl_2$ (used in excess as reoxidant for $Pd^0 \rightarrow Pd^{II}$) promoted the competitive chlorocyclisation of **1** at a comparable rate, even in the presence of carbon monoxide. This was proven by the 'blind' experiment with exclusion of CO from the reaction mixture with **2** being formed exclusively (conditions (ii), Scheme 1). To the best of our knowledge, there is only one more report[8] describing such a transformation, while the analogous iodocyclisation[9] on similar substrates is well documented. Thus, we decided to explore the Pd(II)/$CuCl_2$-catalysed chlorocyclisation of sugar-derived aminoalkenitols in more detail and herein we present its utility in the synthesis of two new C-6 chlorinated 1,5,6-trideoxyazasugars **12** and **13**.

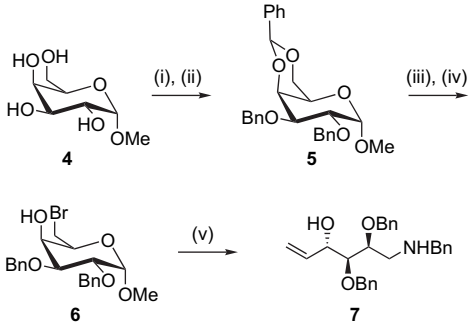


Scheme 1. Reagents and conditions: (i) CO, cat. Pd(II), $CuCl_2$, AcONa, AcOH; (ii) cat. Pd(II), $CuCl_2$, AcONa, AcOH.

2. Results and discussion

2.1. Preparation of substrates

In addition to the aminoalkenitol **1**,[7] we have chosen its diastereoisomer **7**[10] as a second substrate, the latter being prepared via a five-step sequence starting from commercially available methyl-α-D-galactopyranoside **4** (Scheme 2). Thus, 4,6-*O*-benzylidenation,[11] followed by 2,3-di-*O*-benzylation[12] afforded fully protected sugar **5**,[13] which was



Scheme 2. Reagents and conditions: (i) $PhCH(OEt)_2$, CSA, $CHCl_3$, reflux, 2 h, 88%; (ii) BnBr, NaH, DMF, rt, 3 h, 59%; (iii) 2% H_2SO_4, MeOH, rt, 4 h, 71%; (iv) Ph_3P, CBr_4, pyridine, 0–60 °C, 3 h, 61%; (v) Zn dust, $BnNH_2$, $NaBH_3CN$, ^{n}PrOH/H_2O, reflux, 3 h, 88%.

Keywords: Palladium catalysis; Copper(II) chloride; Aminoalkenitols; Azasugars; Chlorocyclisation; Total synthesis.
* Corresponding author. Tel.: +421 2 59325 166; fax: +421 2 52968 560; e-mail: peter.szolcsanyi@stuba.sk

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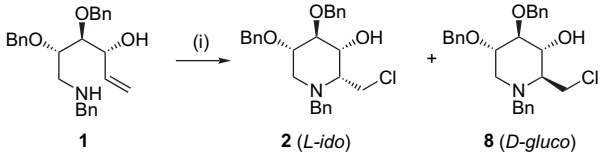
hydrolysed and subsequently halogenated to furnish primary bromide **6**.[14] The last transformation involved a one-pot three-step sequence (reductive elimination, ring opening and reductive amination) providing the desired aminoalkenitol **7** in 23% overall yield (Scheme 2).

2.2. $PdCl_2/CuCl_2$-catalysed chlorocyclisations

With both substrates **1** and **7** on hand, we subjected them to the $PdCl_2/CuCl_2$-catalysed chlorocyclisation under various reaction conditions. First, the influence of solvent on the chemoselectivity and/or diastereoselectivity (noticed[7] during aminocarbonylation of **1**) of the transformation was evaluated with aminoalkenitol **1** (Scheme 3).



1 **2** (*L-ido*) **8** (*D-gluco*)

Scheme 3. Reagents and conditions: (i) 0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa, see Table 1.

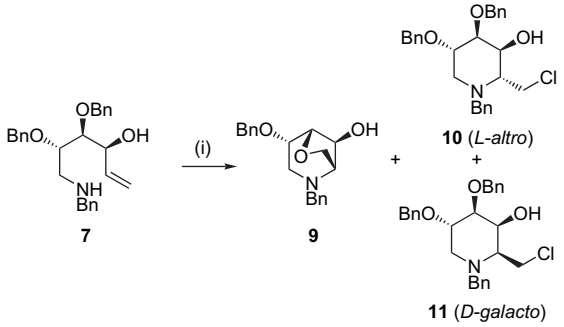
In all cases, L-*ido* configured C-6 chlorinated azasugar **2** was obtained (with full conversion of **1**) as a major product (resulting from the intramolecular Si-attack of nucleophilic amine to the Pd^{II}-activated double bond) along with its minor D-*gluco* diastereomer **8** (Table 1). The solvent of choice turned out to be glacial AcOH (Entry 1), which gave results superior to other solvents in terms of both yield (70%) and diastereoselectivity (90% de). Only slightly lower combined yields of products were obtained in CH_2Cl_2 (65%), THF (60%) and MeOH (59%), however, with considerably diminished des (71% and/or 67%, Entries 3–5). Chlorocyclisation of **1** in DMF (Entry 2) furnished a substantial amount of unidentified side products resulting in an unacceptably low yield (21%) of desired azasugars **2** and **8**. It is important to note that our best conditions (Entry 1) are far superior in terms of diastereoselectivity to those already reported[9b] for the iodocyclisation (5–26% de) of the perbenzylated analogue of **1**.

Table 1. $PdCl_2/CuCl_2$-catalysed chlorocyclisation of aminoalkenitol **1**

Entry	Solvent	Conditions	Yield (%)[a]	Ratio of **2/8** (de, %)[b]
1	AcOH	23 °C, 48 h	70	19/1 (90)
2	DMF	30 °C, 24 h	21	8/1 (82)
3	DCM	30 °C, 24 h	65	6/1 (71)
4	THF	30 °C, 24 h	60	6/1 (71)
5	MeOH	23 °C, 24 h	59	5/1 (67)
6	Toluene	30 °C, 48 h	56	3/1 (33)

[a] Isolated combined yield of **2**+**8** after FLC.
[b] Diastereomeric ratio determined by HPLC analysis of crude reaction mixture.

The same catalytic conditions were applied to the aminoalkenitol **7** and in this case we observed a significant solvent effect on the chemoselectivity and diastereoselectivity of the transformation (Table 2). In all of the solvents tested (Entries 1–6), we noticed the unexpected and rather surprising formation of bicyclic derivative **9** resulting in a lower combined yields of desired C-6 chlorinated azasugars L-*altro* **10** and D-*galacto* **11** in comparison to combined yields of **2**+**8** obtained from substrate **1** (Scheme 4).



7 **9** **10** (*L-altro*) **11** (*D-galacto*)

Scheme 4. Reagents and conditions: (i) see Table 2.

Considering the products distribution first, the best combined yields of **10** and **11** (53% and 54%) were obtained in DMF (Entry 2) and THF (Entry 4). On the other hand, the reaction was more selective towards the formation of **9** when conducted in glacial AcOH (48–52%, Entries 1, 7 and 8). Evaluating the diastereoselectivity second, the highest ratio of **10**/**11** (90% de) was obtained again in glacial AcOH (Entry 1), regardless of the amount of $CuCl_2$ used (Entries 7–9). DMF as a solvent performed comparably well (88% de). Due to its much higher chemoselectivity the latter is a solvent of choice for the preparation of L-*altro* **10** (Entry 2), which is again formed via Si-attack analogous

Table 2. Pd(II)/$CuCl_2$-catalysed chlorocyclisation and bicyclisation of aminoalkenitol **7**

Entry	Solvent	Catalyst and additive(s)	Conditions	Yield of **10**+**11**/**9** (%)[a]	Ratio of **10**/**11** (de, %)[b]
1	AcOH	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa	25 °C, 24 h	28/49	19/1 (90)
2	DMF	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa	25 °C, 19 h	53/11	15/1 (88)
3	DCM	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa	29 °C, 24 h	36/8	5/1 (67)
4	THF	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa	25 °C, 24 h	54/10	2/1 (33)
5	Toluene	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa	29 °C, 24 h	43/9	1/2 (33)
6	MeOH	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$, 3 equiv AcONa	25 °C, 24 h	32/7	1/3 (50)
7	AcOH	0.1 equiv $PdCl_2$, 2 equiv $CuCl_2$, 2 equiv AcONa	30 °C, 48 h	35/52	19/1 (90)
8	AcOH	0.1 equiv $PdCl_2$, 1 equiv $CuCl_2$, 1 equiv AcONa	28 °C, 48 h	25/48	19/1 (90)
9	AcOH	0.1 equiv $PdCl_2$, 3 equiv $CuCl_2$	30 °C, 24 h	27/50	19/1 (90)
10[c]	AcOH	0.1 equiv $PdCl_2$, 3 equiv AcONa	28 °C, 96 h	0/0	—
11[c]	AcOH	0.1 equiv $Pd(OAc)_2$, 2 equiv benzoquinone, 3 equiv AcONa	30 °C, 24 h	—/0	—

[a] Isolated combined yields of **10**+**11** and **9** after FLC.
[b] Diastereomeric ratio determined by HPLC analysis of crude reaction mixture.
[c] Full conversion of **7** with concomitant formation of complex mixture of unidentified products.

to **1**. Interestingly, the use of either toluene (Entry 5) or methanol (Entry 6) as solvents caused reversal of the diastereoselectivity in favour of D-*galacto* **11**, albeit with poor des (33% and 50%). In addition, AcONa was not an essential component (originally used as a basic trap to quench HCl eliminated during the catalytic cycle) of the reaction mixture (Entry 9). More importantly, $CuCl_2$ turned out to be an indispensable reagent for this particular transformation, as either its exclusion (Entry 10) or its replacement for benzoquinone provides neither the bicycle **9** nor the chlorinated azasugars **10/11**. Instead, complex reaction mixtures of unidentified products were formed while the substrate **7** was fully consumed (Table 2).

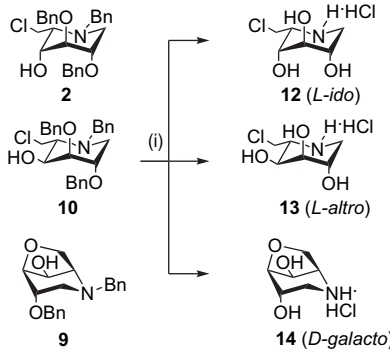
The unexpected formation of bicycle **9** from aminoalkenitol **7** under the applied reaction conditions might be explained as follows: the initial bis-coordination of $PdCl_2$ with both (C-3)OBn group and C=C moiety of **7** followed by the intramolecular Re-attack of *N*-nucleophile promotes the formation of a σ-Pd-complex I in a geometrically favourable $^1C_4$ chair conformation. As the presence of $CuCl_2$ is essential for the course of the transformation (Entries 1–9), we envisaged the subsequent formation of a heterobimetallic[15] σ-Pd/Cu-complex I. Its final reductive elimination releases both the bicycle **9** and the catalyst, which consequently re-enters the catalytic cycle (Scheme 5). Such $PdCl_2$/$CuCl_2$-catalysed *N*,*O*-bicyclisation of unsaturated 1,3-aminoalcohol constitutes a novel synthetic route for the preparation of 6-oxa-2-aza-bicyclo[3.2.1]octane skeleton.[16] On the other hand, the formation of chloroderivative **10** can be reasoned in a following way: Pd^{2+}-promoted activation of double bond of **7** followed by nucleophilic addition from its Si-face leads to σ-Pd-complex II with concomitant elimination of HCl. Subsequent formation of σ-Pd/Cu-complex II in the presence of $CuCl_2$ and the final reductive elimination furnishes desired **10** and regenerates $PdCl_2$ at the same time (Scheme 5).

The global deprotection of advanced intermediates **2** and **10** (isolated by careful flash chromatography of corresponding pure diastereomeric mixtures) using catalytic hydrogenolysis completed the total synthesis of two new azasugars, namely hydrochlorides of 6-chloro-1,5,6-trideoxy-1,5-imino-L-iditol **12** and 6-chloro-1,5,6-trideoxy-1,5-imino-L-altritol **13**. It is noteworthy that compounds **2**, **10**, **12** and **13** all exist in a $^1C_4$ conformation in $CDCl_3$ solution as evidenced by vicinal coupling constants in the ^1H NMR spectra (Table 3).

Table 3. Determination of $^1C_4$ conformation of **2**, **10**, **12** and **13**

Compound	Vicinal coupling (J) constants in ^1H NMR (Hz)
2	$J_{4,5}$=3, $J_{2,3}$=$J_{3,4}$=4.8
10	$J_{3,4}$=2.3, $J_{4,5}$=6.7
12	$J_{4,5}$=1.5, $J_{2,3}$=$J_{3,4}$=3.5
13	$J_{2,3}$=$J_{3,4}$=3.5, $J_{4,5}$=10.4

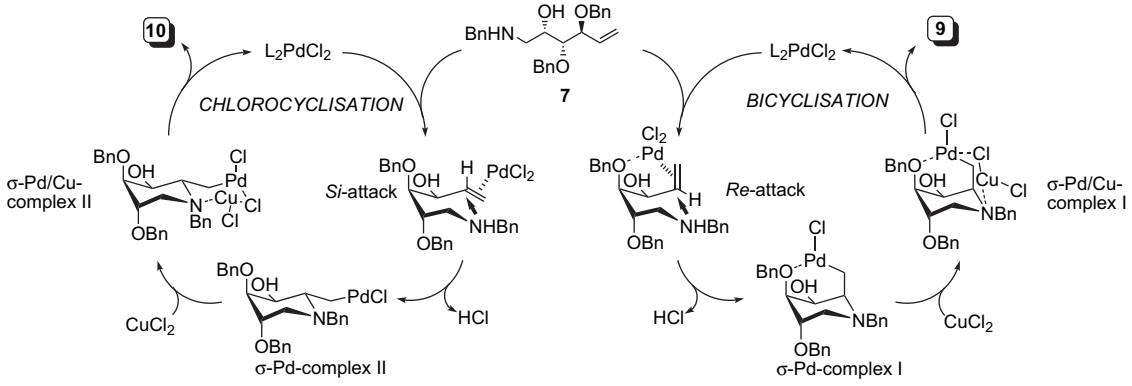
In addition, final total debenzylation of bicycle **9** afforded the hydrochloride of known[17] conformationally locked analogue of a strong glycosidase inhibitor 1-deoxy-D-galactonojirimycin, namely 1,5-dideoxy-3,6-anhydro-1,5-imino-D-galactitol **14** (Scheme 6).



Scheme 6. Reagents and conditions: (i) H_2/Pd–C, HCl, EtOH, rt, 24 h, 100%.

3. Conclusion

In conclusion, we have performed the total synthesis of two new C-6 chlorinated iminohexitols L-*ido* **12** and L-*altro* **13** featuring a $PdCl_2$/$CuCl_2$-catalysed chlorocyclisation of sugar-derived aminoalkenitols **2** and **7**. In addition, the $PdCl_2$/$CuCl_2$-catalysed *N*,*O*-bicyclisation of the aminoalkenitol **7** afforded a known bicyclic compound D-*galacto* **14**. This compound represents a conformationally locked analogue of the strong glycosidase inhibitor 1-deoxy-D-galactonojirimycin.



Scheme 5. Tentative mechanism of Pd(II)/$CuCl_2$-catalysed chlorocyclisation and bicyclisation of aminoalkenitol **7**.

4. Experimental

4.1. General

All reagents were used as received without further purification unless otherwise specified. All solvents were distilled before use: THF and toluene from Na, MeCN from P_2O_5, DMF from KOH, MeOH from MeONa, CH_2Cl_2 from activated 4 Å molecular sieves. Flash column liquid chromatography (FLC) was performed on Kieselgel 60 (40–63 μm). HPLC was performed on Separon SGX column (4×125 mm, 5 μm) using MeOH/H_2O as an eluent (80/20 v/v) and UV (254 nm) detection (flow rate 0.5 ml min^{-1}, injection volume 20 μl, column temperature 20 °C). Optical rotations were measured with a PolarL-μP polarimeter with a 10,000 cm cell at λ=589 nm. Elemental analyses were performed by the Microanalytical Service of Slovak University of Technology. Infrared (IR) spectra were recorded on a Nicolet Magna 750 FTIR spectrometer. NMR spectra were recorded on Varian VXR-300 (300 MHz) and Inova 600 (600 MHz) spectrometers. Chemical shifts (δ) are quoted in parts per million and the residual protic solvent was used as internal reference. The following abbreviations were used to characterise signal multiplicities: singlet (s), doublet (d), triplet (t), multiplet (m), broad (b). The COSY and NOESY techniques were used in assignment of ^1H–^1H relationships and the determination of relative configuration. The multiplicities of carbons were assigned from a broad-band decoupled analysis used in conjunction with APT. The HETCOR and HMQC techniques were used throughout for the assignment of the ^1H–^{13}C relationships.

4.1.1. (2*S*,3*S*,4*S*)-1-Benzylamino-2,3-di-*O*-benzyl-hex-5-ene-2,3,4-triol (7). Acid treated zinc dust [(17.95 g, 274.54 mmol, 60 equiv) prepared by gradual washing with 3% HCl (100 ml), H_2O (3×80 ml), EtOH (30 ml), acetone (30 ml), dry Et_2O (30 ml) and finally dried in vacuo] was added to the solution of bromoalcohol **6** (2.0 g, 4.576 mmol) in ^{n}PrOH/H_2O (19/1, 80 ml) mixture with vigorous stirring. Then $BnNH_2$ (7.38 g, 7.5 ml, 68.63 mmol, 15 equiv) and $NaBH_3CN$ (575 mg, 9.151 mmol, 2 equiv) were added and the resulting mixture was stirred at reflux for 3 h. After cooling to room temperature the suspension was filtered through Celite pad and washed with EtOH (20 ml). The filtrate was evaporated in vacuo and the residue was dissolved in Et_2O (200 ml) and treated with 20% aq HCl solution (20 ml). After 30 min the mixture was basified with 15% aq NaOH solution (pH 9), the organic phase was separated and the water layer was extracted with $CHCl_3$ (2×200 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo giving the crude product, which was purified by FLC (silicagel, hexanes/AcOEt/NH_4OH=6/4/0.03) to afford pure aminoalkenitol **7** (1.68 g, 88%) as a pale-yellow oil. R_f=0.18 (hexanes/AcOEt=1/1); $[\alpha]_D^{20}$ −13.1 (*c* 1.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.90 (m, 2H, H-1), 3.22–3.50 (br s, 2H, exchange with D_2O, OH, NH), 3.59 (dd, 1H, $J_{3,2}$=5.1, $J_{3,4}$=5.9 Hz, H-3); 3.69 (d, 1H, J=12.9 Hz, NCH_2Ph), 3.73 (m, 1H, H-2), 3.78 (d, 1H, J=12.9 Hz, NCH_2Ph), 4.29 (ddt, 1H, $J_{4,6E}$=$J_{4,6Z}$=1.6, $J_{4,3}$=$J_{4,5}$=5.9 Hz, H-4), 4.48 (d, 1H, J=11.4 Hz, OCH_2Ph), 4.58 (d, 1H, J=11.4 Hz, OCH_2Ph), 4.59 (d, 1H, J=11.4 Hz, OCH_2Ph), 4.66 (d, 1H, J=11.4 Hz, OCH_2Ph), 5.15 (dt, 1H, $J_{6E,4}$=$J_{6E,6Z}$=1.6, $J_{6E,5}$=10.5 Hz, H-6*E*), 5.33 (dt, 1H, $J_{6Z,4}$=$J_{6Z,6E}$=1.6, $J_{6Z,5}$=17.2 Hz, H-6*Z*), 6.00 (ddd, 1H, $J_{5,4}$=5.9, $J_{5,6E}$=10.5, $J_{5,6Z}$=17.2 Hz, H-5); δ_C (75 MHz, $CDCl_3$) 47.5 (t, C-1), 53.8 (t, N*C*H_2Ph), 72.2 (d, C-4), 72.4 (t, O*C*H_2Ph), 73.2 (t, O*C*H_2Ph), 79.6 (d, C-2), 81.4 (d, C-3), 115.3 (t, C-6), 127.3, 127.8, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5 (all d, all *C*H-Ph), 138.0, 138.2 (2×s, 2×*C*q-Ph), 138.5 (d, C-5), 139.2 (s, *C*q-Ph); ν_{max} (film on KBr)/cm^{-1} 698, 737, 1028, 1071, 1090, 1454, 1496, 2864, 3030, 3031, 3063, 3310; *m*/*z* (APCI$^+$) 418 $[M+1]^+$, 440 $[M+Na]^+$; found C 77.65, H 7.61, N 3.53%; $C_{27}H_{31}NO_3$ requires C 77.67, H 7.48, N 3.35%.

4.1.2. Typical procedure for $PdCl_2$/$CuCl_2$-catalysed chloroaminocyclisation of 7. Aminoalkenitol **7** (670 mg, 1.61 mmol), $PdCl_2$ (28 mg, 0.161 mmol, 0.1 equiv), $CuCl_2$ (648 mg, 4.82 mmol, 3 equiv) and AcONa (395 mg, 4.82 mmol, 3 equiv) were suspended in a glacial AcOH (16 ml) and the resulting deep-green heterogeneous mixture was stirred under Ar at 25 °C over 24 h. The light-green suspension was filtered over Celite pad (3×2 cm), solids were washed with AcOH (20 ml) and the filtrate was co-evaporated with toluene (20 ml) in vacuo. The resulting yellow-green-brown oil (932 mg) was taken up to AcOEt (100 ml), washed with 10% aq $NaHCO_3$ solution (2× 50 ml) and the combined water layers were extracted with AcOEt (50 ml). The combined organic extracts were washed with brine (50 ml), dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield a brown oil (622 mg), which was purified by FLC (20 g of silicagel, column 2.5× 19.5 cm, gradient elution: hexanes/AcOEt/Et_3N=460/40/3→250/250/3) to afford two fractions: first eluted the pure diastereomeric mixture of **10**/**11** (203 mg, 28%, 19/1) as a pale-yellow oil, second eluted the pure bicycle **9** (256 mg, 49%) as a pale-yellow waxy solid.

Data for *N*-benzyl-2,3-di-*O*-benzyl-6-chloro-1,5,6-trideoxy-1,5-imino-L-altritol **10**: R_f=0.58 (hexanes/AcOEt=3/1); $[\alpha]_D^{24}$ +38 (*c* 1.38, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 2.45 (br s, 1H, exchange with D_2O, OH), 2.58 (dd, 1H, $J_{1,2}$=2.6, $J_{1,1'}$=13.5 Hz, H-1), 2.71 (dd, 1H, $J_{1',2}$=6.1, $J_{1',1}$=12.9 Hz, H-1′), 2.93 (m, 1H, $J_{5,6}$=5.6, $J_{5,4}$=6.3 Hz, H-5), 3.42 (d, 1H, J=12.3 Hz, NCH_2Ph), 3.71 (m, 2H, H-2, H-3), 3.80 (dd, 1H, $J_{6,5}$=5.6, $J_{6,6'}$=12.0 Hz, H-6), 3.95 (dd, 1H, $J_{6',5}$=3.4, $J_{6',6}$=12.0 Hz, H-6′), 4.08 (d, 1H, J=12.6 Hz, NCH_2Ph), 4.18 (dd, 1H, $J_{4,3}$=2.3, $J_{4,5}$=6.7 Hz, H-4), 4.38 (d, 1H, J=12.0 Hz, OCH_2Ph), 4.47 (d, 1H, J=12.0 Hz, OCH_2Ph), 4.58 (d, 1H, J=11.5 Hz, OCH_2Ph), 4.66 (d, 1H, J=11.5 Hz, OCH_2Ph), 7.24–7.37 (m, 15H, 3×Ph); δ_C (75 MHz, $CDCl_3$) 41.2 (t, C-6), 48.4 (t, C-1), 57.3 (t, N*C*H_2Ph), 63.6 (d, C-5), 66.8 (d, C-4), 71.2 (t, O*C*H_2Ph), 72.4 (t, O*C*H_2Ph), 72.8 (d, C-2), 78.2 (d, C-3), 127.1, 127.5, 127.8, 127.9, 128.3, 128.5, 128.7 (all d, all *C*H-Ph), 137.8, 138.3, 138.7 (all s, all *C*q-Ph); ν_{max} (film on KBr)/cm^{-1} 699, 738, 1028, 1076, 1103, 1454, 1495, 2808, 2872, 3029, 3062, 3448, 3547; *m*/*z* (MALDI) 513 $[M+Na+K]^+$; found C 71.63, H 6.52, Cl 7.92, N 3.15%; $C_{27}H_{30}ClNO_3$ requires C 71.75, H 6.69, Cl 7.84, N 3.10%.

Data for *N*-benzyl-2-*O*-benzyl-3,6-anhydro-1,5-dideoxy-1,5-imino-D-galactitol **9**: R_f=0.08 (hexanes/AcOEt=3/1); $[\alpha]_D^{24}$ +18 (*c* 0.9, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 2.28 (br s, 1H, exchange with D_2O, OH), 2.43 (dd, 1H, $J_{1,2}$=3.5, $J_{1,1'}$=13.0 Hz, H-1), 2.79 (d, 1H, $J_{1',1}$=13.0 Hz, H-1′),

3.25 (br d, 1H, $J_{5,6}$=3.0 Hz, H-5), 3.55 (d, 1H, J=13.5 Hz, NCH_2Ph), 3.62 (d, 1H, J=13.5 Hz, NCH_2Ph), 3.65 (t, 1H, $J_{2,3}$=5.1 Hz, H-2), 3.78 (dd, 1H, $J_{6,5}$=3.6, $J_{6,6'}$=9.3 Hz, H-6), 4.02 (d, 1H, $J_{6',6}$=9.0 Hz, H-6′), 4.18 (d, 1H, $J_{3,2}$= 5.1 Hz, H-3), 4.44 (d, 1H, J=12.3 Hz, OCH_2Ph), 4.51 (d, 1H, $J_{4,5}$=1.2 Hz, H-4), 4.55 (d, 1H, J=12.3 Hz, OCH_2Ph), 7.25–7.36 (m, 10H, 2×Ph); δ_C (75 MHz, $CDCl_3$) 48.3 (t, C-1), 59.3 (t, NCH_2Ph), 63.9 (t, C-6), 64.0 (d, C-5), 71.5 (t, OCH_2Ph), 73.1 (d, C-4), 76.4 (d, C-2), 80.3 (d, C-3), 127.3, 127.6, 127.7, 128.0, 128.4, 128.9 (all d, all *C*H-Ph), 137.9, 138.2 (2×s, 2×*C*q-Ph); IR: ν_{max} (KBr)/cm^{-1} 697, 739, 746, 891, 1029, 1049, 1057, 1114, 1133, 1454, 2804, 2883, 2951, 3395; *m/z* (MALDI) 323 [M−H-1]$^+$; found C 73.79, H 7.14, N 4.32%; $C_{20}H_{23}NO_3$ requires C 73.62, H 7.22, N 4.30%.

4.1.3. Typical procedure for the catalytic debenzylation of 2 or 10. Protected piperidine **2** or **10** (87 mg, 0.193 mmol) was dissolved in EtOH (8 ml), 10% Pd–C (55 mg) was added followed by 35% aq HCl (10 drops) and the resulting black suspension was stirred under hydrogen atmosphere (balloon) at 23 °C over 12 h. The reaction mixture was filtered, solids were washed with EtOH (2×5 ml) and the clear filtrate was co-evaporated with AcOEt (5 ml) in vacuo yielding **12** or **13** (42 mg, 100%) as a pale-yellow hygroscopic foam.

Data for 6-chloro-1,5,6-trideoxy-1,5-imino-L-iditol hydrochloride **12**: $[\alpha]_D^{24}$ +18 (*c* 0.26, EtOH); δ_H (600 MHz, CD_3OD) 3.31 (ddd, 1H, $J_{1,3}$=1.1, $J_{1,2}$=2.2, $J_{1,1'}$=13.2 Hz, H-1), 3.48 (dd, 1H, $J_{1',2}$=1.9, $J_{1',1}$=13.2 Hz, H-1′), 3.70 (dtd, 1H, $J_{5,4}$=1.5, $J_{5,6'}$=5.8, $J_{5,6}$=8.5 Hz, H-5), 3.90 (ddd, 1H, $J_{6,4}$=0.6, $J_{6,5}$=8.7, $J_{6,6'}$=12.0 Hz, H-6), 3.97 (dd, 1H, $J_{6',5}$=5.7, $J_{6',6}$=12.0 Hz, H-6′), 3.99 (m, 1H, $J_{2,1'}$=1.9, $J_{2,1}$= 2.1, $J_{2,3}$=3.1 Hz, H-2), 4.00 (dd, 1H, $J_{4,5}$=1.1, $J_{4,3}$=3.5 Hz, H-4), 4.01 (m, 1H, $J_{3,2}$=3.2, $J_{3,4}$=3.7 Hz, H-3); δ_C (125 MHz, CD_3OD) 42.3 (t, C-6), 47.5 (t, C-1), 58.1 (d, C-5), 67.7 (d, C-4), 67.9 (d, C-2), 69.5 (d, C-3); ν_{max} (film on KBr)/cm^{-1} 756, 1002, 1054, 1131, 1560, 2437, 2534, 3014, 3273, 3421; found C 33.21, H 5.88, Cl 32.45, N 6.33%; $C_6H_{13}Cl_2NO_3$ requires C 33.05, H 6.01, Cl 32.51, N 6.42%.

Data for 6-chloro-1,5,6-trideoxy-1,5-imino-L-altritol hydrochloride **13**: $[\alpha]_D^{24}$ −19 (*c* 0.27, EtOH); δ_H (600 MHz, CD_3OD) 3.18 (dd, 1H, $J_{1,2}$=2.5, $J_{1,1'}$=12.9 Hz, H-1), 3.42 (dd, 1H, $J_{1',2}$=1.4, $J_{1',1}$=13.0 Hz, H-1′), 3.57 (dtd, 1H, $J_{5,6'}$= 2.9, $J_{5,6}$=7.6, $J_{5,4}$=10.4 Hz, H-5), 3.95 (dd, 1H, $J_{6,5}$=7.6, $J_{6,6'}$=12.6 Hz, H-6), 3.96 (t, 1H, $J_{3,4}$=3.2, $J_{3,2}$=3.8 Hz, H-3), 4.00 (dd, 1H, $J_{4,3}$=2.9, $J_{4,5}$=10.4 Hz, H-4), 4.05 (m, 1H, $J_{2,1}$=2.2, $J_{2,3}$=4.2 Hz, H-2), 4.12 (dd, 1H, $J_{6',5}$=2.9, $J_{6',6}$=12.6 Hz, H-6′); δ_C (125 MHz, CD_3OD) 43.4 (t, C-6), 46.4 (t, C-1), 57.5 (d, C-5), 66.1 (d, C-4), 67.7 (d, C-2), 70.4 (d, C-3); ν_{max} (film on KBr)/cm^{-1} 756, 881, 1071, 1434, 2517, 3346; found C 32.88, H 6.05, Cl 32.60, N 6.40%; $C_6H_{13}Cl_2NO_3$ requires C 33.05, H 6.01, Cl 32.51, N 6.42%.

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