Small-Scale One-Pot Reductive Alkylation of Unprotected Aminocyclitols with Supported Reagents

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Abstract: A protocol for the reductive alkylation of unprotected aminocyclitols with supported reagents and scavengers is described. The method is operatively simple and provides the corresponding secondary amines in high yields and purities.

Key words: alkylations, aldehydes, supported reagents, aminocyclitols

Aminocyclitols are a group of aminocycloalkane polyols found in a variety of natural products[2] and synthetic compounds. They have multiple applications in medicinal chemistry as antibiotics,[3] glycosidase inhibitors,[4–7] modulators of sphingolipid metabolism,[8,9] and are used as pharmacological tools for the study of inositol-related cellular processes.[10] In addition, some of them are advanced key synthetic intermediates in the total synthesis of several *Amarilladaceae* alkaloids.[11]

The use of combinatorial chemistry to generate libraries of compounds is a common approach in medicinal chemistry to explore the chemical space in search of new entities with defined biological profiles. Along this line, nitrogen functionalization of aminocyclitol systems offers the opportunity to explore the influence of side chain variations in structure–activity studies. A common structural modification is N-alkylation. Classical approaches to *N*-alkylaminocyclitols include, *inter alia*, the regio and stereoselective nucleophilic attack of suitable amines upon appropriate cyclitol epoxides,[12] sulfites[13] or sulfates,[14] and the reductive amination of polyhydroxy cyclohexanones.[15] Although reductive alkylation of amines with aldehydes or ketones is a common approach to secondary and, to a lesser extent, tertiary amines, this method has been scarcely used in the aminocyclitol arena. In some cases,[16] the method requires elaborated and cumbersome purification protocols that make the process unsuitable for combinatorial chemistry, where the simultaneous manipulation and workup of a large number of reactions, sometimes in a microtiter plate format, is required for library production. In this context, we recently reported on a combinatorial approach leading to N-substituted aminocyclitol libraries for its preliminary evaluation as glucocerebrosidase inhibitors.[17] An inherent limitation of the method was the need to carry out the N-alkylation step on a fully protected penta-*O*-benzylaminocyclitol scaffold. This required a subsequent 'on-bench' massive deprotection of the library members, since the required reaction conditions were not compatible with the technical restrictions imposed by the robotic automated system used. For this reason, the possibility to carry out the N-alkylation step from a fully unprotected aminocyclitol scaffold seemed attractive to us. As an additional value, the design of a simple and efficient workup and purification protocols would enable the construction and in situ screening of large aminocyclitol libraries.

Initial experiments were addressed at the direct reductive alkylation of unprotected 1-amino-1-deoxy-*scyllo*-inositol (**1**) and aldehyde **2a** (1.5:1 ratio) with $NaBH_3CN$ (2.8 equiv/mol) in MeOH–H_2O (5:1) in the presence of a catalytic amount of AcOH.[18] This afforded a mixture of amines (the expected secondary amine, together with minor amounts of the corresponding tertiary amine and some unreacted starting amine) after reaction workup.[19] The use of an alternative water-compatible reducing agent, such as α-picoline-borane[20] afforded complex reaction mixtures under otherwise similar reaction conditions. As an alternative strategy, we considered the use of polymer supported cyanoborohydride (PSCBH)[21] and the decrease of the water content of the system by using DMSO as a solvent, which would presumably drive the equilibrium towards imine formation. Interestingly, the choice of the solvent system was critical for the efficiency of the process, since only DMSO afforded a good balance between solubility of the starting aminocyclitol and reaction rates in the presence of excess PSCBH.[22] The molar ratio of aldehyde versus aminocyclitol was also important in this reaction system, since an excess aldehyde (3:1 ratio) led to a non-negligible percentage of overalkylation to the corresponding tertiary amine, whereas an excess aminocyclitol might avoid the above problem at the expense of the reaction yield.[23] In both scenarios, the presence of significant amounts of residual starting amine or tertiary amine would complicate the purification of the required secondary amine. After some experimentation, a molar ratio of 1.5:1 (aminocyclitol/aldehyde) was considered optimal and it was used in all experiments. Reductive alkylation of

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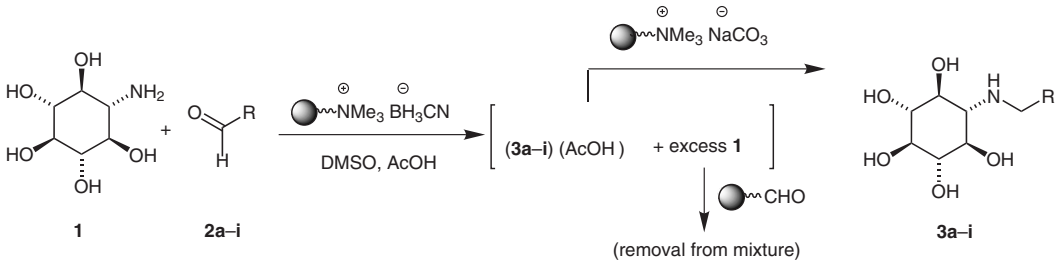
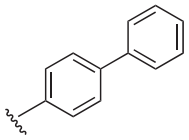
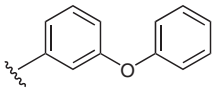
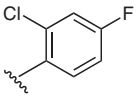
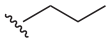
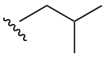
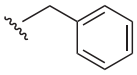
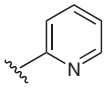
amines with cyanoborohydride requires the use of acidic conditions to ensure the protonation and activation of the intermediate imine for the subsequent borohydride reduction.[23] In our case, the use of excess AcOH afforded good results.[24] The resulting aminocyclitol acetates could be easily freed at the end of the process by treatment with the basic carbonate resin IRA900, as described in the experimental section. Finally, in order to design a methodology amenable to combinatorial protocols, the excess of starting aminocyclitol **1** was removed with PS-benzaldehyde resin (Wang resin), which played the role of reaction scavenger in this process.

The above optimized procedure was tested with a set of aromatic and aliphatic aldehydes **2a–i** with different steric and/or electronic demands (Table 1).[25] In all cases, purities and yields of the resulting aminocyclitols **3a–i** were good to excellent, as determined by HPLC(LS) and HPLC-MS of the crude material. No trace of the corresponding tertiary amine was detected in any of the above examples, which proves the versatility and reproducibility

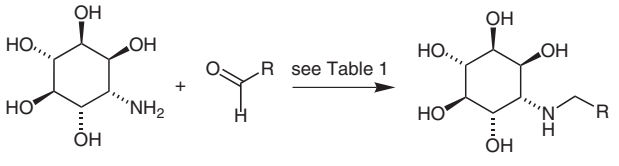
Table 1 One-Pot Reductive Alkylation of Aminocyclitols with Supported Reagents and Scavengers



Entry	Aldehyde R	Yield (%) (purity, %)[a]
1	 **2a**	96 (100)
2	 **2b**	95 (100)
3	 **2c**	90 (94)
4	 **2d**	77 (80)
5	 **2e**	73 (76)
6	 **2f**	90 (96)
7	 **2g**	83 (95)
8	 **2h**	85 (95)
9	 **2i**	84 (97)

[a] Yields based on purities estimated from HPLC using a light scattering detector.

of our protocol. Interestingly, this process has also been successfully applied to the reductive alkylation of the isomeric (±)-1-amino-1-deoxy-*chiro*-inositol (**4**) with aldehydes **2c** and **2j** with similar results (Scheme 1).



4

2c (see Table 1) **5c:** R = 2-Cl-5-FC_6H_3; 81% (88%)

2j R = 2-$MeOC_6H_4$ **5j:** R = 2-$MeOC_6H_4$; 85% (93%)

Scheme 1 Reaction of inositol **4** with aldehydes **2c** and **2j**; yields are based on isolated compounds and purities are shown in brackets

In summary, a solution-phase procedure for the reductive alkylation of unprotected aminocyclitols **1** and **4** with a set of aldehydes with different structural and electronic requirements has been developed with the aid of supported reagents and scavengers. The corresponding secondary amines are obtained in generally high yields and purities with no trace of the undesired tertiary amines. The method is operatively simple and easily adaptable to combinatorial protocols

All the materials were obtained commercially and used without further purification. Solvents were distilled prior to use and dried by standard methods.[26] Analytical samples were homogeneous as confirmed by TLC and afforded spectroscopic results consistent with the assigned structures. NMR spectra were recorded on a 500 MHz instrument. Chemical shifts are reported in delta units (δ), parts per million (ppm) relative to the central signal of the quintuplet centered at 3.31 ppm for MeOD. TLC was performed on silica gel (Alugram Sil G/UV). HPLC conditions for aminocyclitol analysis: RPC18 column (5 μ, 110 Å); solvent A (H_2O + 1% TFA); solvent B (MeCN + 1% TFA); conditions 1 (for compounds **3c**, **3f**, **3g**, **3h**, **3i**, **5c**): t = 0 min (80% A; 20% B); t = 9 min (56% A; 44% B); t = 14 min (56% A; 44% B); conditions 2 (compounds **3a**, **3b**, **3d**, **3e**, **5j**): t = 0 min (90% A; 10% B); t = 10 min (90% A; 10% B); t = 15 min (0% A; 100% B); t = 20 min (0% A; 100% B). The following resins were used in this study: IRA 900 ($NaCO_3^-$ form, Fluka, Cat. # 21850, 3.5 mmol/g loading), Wang resin (Aldrich, Cat. # 547409, 3.0 mmol/g loading), IRA 900 (BH_3CN^- form, Aldrich, Cat. # 526304, 2.0 mmol/g loading).

1-Amino-1-deoxy-*scyllo*-inositol (1)

A solution of 1-azido-1-deoxy-2,3,4,5-tetra-*O*-benzyl-*scyllo*-inositol[12] (1 g, 1.8 mmol) in a 1:1 mixture of THF–MeOH (30 mL) containing aq 35% HCl (0.5 mL) was treated with 10% Pd/C (100 mg) and stirred at r.t. for 24 h under H_2 (3 atm). The mixture was filtered and the solid residue washed with MeOH–H_2O mixture (5 mL). The combined filtrates were evaporated to dryness to give **1**·HCl as a solid in quantitative yield. The above hydrochloride was taken up in a 9:1 MeOH–H_2O mixture (50 mL) and stirred for 3 h at r.t. in the presence of IRA 900 resin ($NaCO_3^-$ form, 2 g, equivalent to 7 mmol). The resin was next filtered and washed with an additional 9:1 MeOH–H_2O mixture (10 mL) and the combined filtrates were evaporated to dryness to give **1**; yield: 315 mg (98%).

^{1}H NMR (500 MHz, D_2O): δ = 2.62 (t, J = J' = 10.0 Hz, 1 H), 3.18 (t, J = J' = 9.3 Hz, 2 H), 3.27–3.34 (m, 3 H).

HRMS: m/z calcd for $C_6H_{14}NO_5$: 180.0872; found: 180.0867.

(±)-1-Amino-1-deoxy-*chiro*-inositol (4)

Following the same protocol described for **1**, (±)-1-azido-1-deoxy-2,3,4,5-tetra-*O*-benzyl-*chiro*-inositol[12] afforded the aminocyclitol **4** in 97% isolated yield.

^{1}H NMR (500 MHz, D_2O): δ = 3.28 (t, J = J' = 4.0 Hz, 1 H), 3.50 (m, 2 H), 3.73 (dd, J = 9.6, 3.8 Hz, 1 H), 3.80 (dd, J = 9.6, 4.4 Hz, 1 H), 3.85 (t, J = J' = 3.3 Hz. 1 H).

HRMS: m/z calcd for $C_6H_{14}NO_5$: 180.0872; found: 180.0865.

Reductive Alkylation of 1 and 4 with Aldehydes 2a–j; General Procedure

To a screw cap glass vial was added a solution of **1** or **4** (15 mg, 83 μmol) in DMSO (3.5 mL), followed by AcOH (70 μL) and the appropriate aldehyde **2a**–**j** (55 μmol) at r.t. After shaking for 1 h, supported cyanoborohydride (150 mg, equiv to 300 μmol) was added portionwise and the mixture was shaken for additional 16 h. Wang resin (15 mg, equiv to 45 μmol) was added and the resulting slurry was shaken for 12 h. The resins were filtered and thoroughly washed with MeOH–H_2O (9:1). The combined filtrates were evaporated to dryness and the residue was taken up in 9:1 MeOH–H_2O (3 mL). This solution was treated with carbonate resin (500 mg, equiv to 1.75 mmol) and Wang resin (15 mg, equiv to 45 μmol) and stirred for 4 h. The resins were filtered, washed with MeOH–H_2O (9:1), and evaporated to dryness to give compounds **3a**–**i**, **5c**, and **5j** (Table 1).

1-(4-Phenylbenzyl)amino-1-deoxy-*scyllo*-inositol (3a)

^{1}H NMR (500 MHz, MeOD): δ = 2.60 (t, J = 10.0 Hz, 1 H), 3.25–3.41 (m, not integrated, overlapped with MeOD), 4.04 (s, 2 H), 7.36–7.41 (m, 1 H), 7.46–7.50 (m, 4 H), 7.63–7.67 (m, 4 H).

HRMS: m/z calcd for $C_{19}H_{23}NO_5$ (M + H^+): 346.1646; found: 346.1654.

1-(3-Benzyloxyphenyl)amino-1-deoxy-*scyllo*-inositol (3b)

^{1}H NMR (500 MHz, MeOD): δ = 2.47 (t, J = 9.5 Hz, 1 H), 3.12–3.30 (m, 5 H), 4.00 (s, 2 H), 6.87–6.91 (m, 1 H), 6.99 (s, 1 H), 7.00 (s, 1 H), 7.05 (s, 1 H), 7.09–7.16 (m, 2 H), 7.30–7.38 (m, 3 H).

HRMS: m/z calcd for $C_{19}H_{23}NO_6$ (M + H^+): 362.1598; found: 362.1604.

1-(2-Chloro-4-fluorobenzyl)amino-1-deoxy-*scyllo*-inositol (3c)

^{1}H NMR (500 MHz, MeOD): δ = 2.40–2.46 (m, 1 H), 3.12–3.39 (m, not integrated, overlapped with MeOD), 4.16 (s, 2 H), 7.05–7.10 (m, 1 H), 7.21–7.26 (m, 1 H), 7.52–7.57 (m, 1 H).

HRMS: m/z calcd for $C_{13}H_{17}ClFNO_5$ (M + H^+): 322.0858; found: 322.0862.

1-Butylamino-1-deoxy-*scyllo*-inositol (3d)

^{1}H NMR (500 MHz, MeOD): δ = 0.90–1.00 (m, 3 H), 1.29–1.56 (m, 4 H), 2.33–2.39 (m, 1 H), 2.85 (t, J = 7.5 Hz, 2 H), 3.14–3.28 (m, 5 H).

HRMS: m/z calcd for $C_{10}H_{21}NO_5$ (M + H^+): 236.1498; found: 236.1496.

1-(2,2-Dimethylpropyl)amino-1-deoxy-*scyllo*-inositol (3e)

^{1}H NMR (500 MHz, MeOD): δ = 0.96 (s, 9 H), 2.32 (t, J = 10.0 Hz, 1 H), 3.15–3.31 (m, not integrated, overlapped with MeOD).

HRMS: m/z calcd for $C_{11}H_{23}NO_5$ (M + H^+): 250.1654; found: 250.1660.

1-(2-Methylpropyl)amino-1-deoxy-*scyllo*-inositol (3f)

^{1}H NMR (500 MHz, MeOD): δ = 0.95 (d, J = 6.5 Hz, 6 H), 1.73–1.82 (m, 1 H), 2.31–2.37 (m, 1 H), 2.67 (d, J = 9.0 Hz, 2 H), 3.10–3.27 (m, 5 H).

HRMS: *m*/*z* calcd for $C_{10}H_{21}NO_5$ (M + H^+): 236.1498; found: 236.1498.

1-(3-Methylbutyl)amino-1-deoxy-*scyllo*-inositol (3g)
^{1}H NMR (500 MHz, MeOD): δ = 0.94 (d, *J* = 6 Hz, 6 H), 1.40–1.46 (m, 2 H), 1.57–1.73 (m, 1 H), 2.36–2.44 (m, 1 H), 2.89 (t, *J* = 8 Hz, 2 H), 3.13–3.28 (m, 5 H).

HRMS: *m*/*z* calcd for $C_{11}H_{23}NO_5$ (M + H^+): 250.1654; found: 250.1638.

1-Phenethylamino-1-deoxy-*scyllo*-inositol (3h)
^{1}H NMR (500 MHz, MeOD): δ = 2.58 (t, *J* = 10.5 Hz, 2 H), 2.79–2.84 (m, 1 H), 3.10–3.26 (m, 7 H), 7.15–7.68 (m, 5 H).

HRMS: *m*/*z* calcd for $C_{19}H_{23}NO_5$ (M + H^+): 284.1498; found: 284.1500.

1-(2-Pyridylmethyl)amino-1-deoxy-*scyllo*-inositol (3i)
^{1}H NMR (500 MHz, MeOD): δ = 2.57–2.65 (m, 1 H), 3.11–3.31 (m, not integrated, overlapped with MeOD), 4.18 (s, 2 H), 7.28–7.34 (m, 1 H), 7.44–7.52 (m, 1 H), 7.77–7.84 (m, 1 H), 8.49–8.55 (m, 1 H).

HRMS: *m*/*z* calcd for $C_{12}H_{18}N_2O_5$ (M + H^+): 271.1294; found: 271.1285.

1-(2-Chloro-4-fluorobenzyl)amino-1-deoxy-D-*chiro*-inositol (5c)
^{1}H NMR (500 MHz, MeOD): δ = 3.02–3.06 (m, 1 H), 3.53–3.60 (m, 2 H), 3.80–3.92 (m, 4 H), 4.07–4.11 (m, 1 H), 7.04–7.09 (m, 1 H), 7.19–7.24 (m, 1 H), 7.48–7.53 (m, 1 H).

HRMS: *m*/*z* calcd for $C_{13}H_{17}ClFNO_5$ (M + H^+): 322.0852; found: 322.0859.

1-(2-Methoxybenzyl)amino-1-deoxy-D-*chiro*-inositol (5j)
^{1}H NMR (500 MHz, MeOD): δ = 3.00 (t, *J* = 4.5 Hz, 1 H), 3.51–3.59 (m, 2 H), 3.68 (d, *J* = 13.5 Hz, 2 H), 3.80–3.88 (m, 3 H), 3.86 (s, 3 H), 4.13 (t, *J* = 3.0 Hz, 1 H), 6.90 (t, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 7.5 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 2 H).

HRMS: *m*/*z* calcd for $C_{14}H_{26}NO_6$ (M + H^+): 300.1447; found: 300.1436.

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(21) The use of supported reagents and scavengers in combinatorial chemistry protocols facilitates workup procedures, allows the use of excess reagents, the reduction of the reaction scale, and avoids the hazards associated to the handling of toxic reagents, such as $NaBH_3CN$.
(22) Several reaction systems were tried. Aminocyclitol **1** is only slightly soluble in MeOH, MeCN, THF, *i*-PrOH, and dioxane. In our reductive alkylation protocol with PSCBH, addition of H_2O increases the solubility of **1** at the expense of the reaction rate, which became too slow for practical purposes.
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(25) Aldehydes **2a–c** and **2j** are benzaldehyde derivatives with different electronic properties; **2e**,**f** are α-branched aliphatic aldehydes; **2g** and **2h** are β-branched (aliphatic or aromatic) aldehydes; and **2i** is an example of an heteroaromatic aldehyde.
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