JOC Article
pubs.acs.org/joc

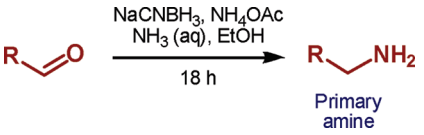
Protecting-Group-Free Synthesis of Amines: Synthesis of Primary Amines from Aldehydes via Reductive Amination

Emma M. Dangerfield,[†,‡] Catherine H. Plunkett,[†,‡] Anna L. Win-Mason,[†,‡] Bridget L. Stocker,*[,†] and Mattie S. M. Timmer*[,‡]

[†]*Malaghan Institute of Medical Research, PO Box 7060, Wellington, New Zealand, and* [‡]*School of Chemical and Physical Sciences, Victoria University of Wellington, PO Box 600, Wellington, New Zealand*

bstocker@malaghan.org.nz; mattie.timmer@vuw.ac.nz

Received January 4, 2010



New methodology for the protecting-group-free synthesis of primary amines is presented. By optimizing the metal hydride/ammonia mediated reductive amination of aldehydes and hemiacetals, primary amines were selectively prepared with no or minimal formation of the usual secondary and tertiary amine byproduct. The methodology was performed on a range of functionalized aldehyde substrates, including *in situ* formed aldehydes from a Vasella reaction. These reductive amination conditions provide a valuable synthetic tool for the selective production of primary amines in fewer steps, in good yields, and without the use of protecting groups.

Introduction

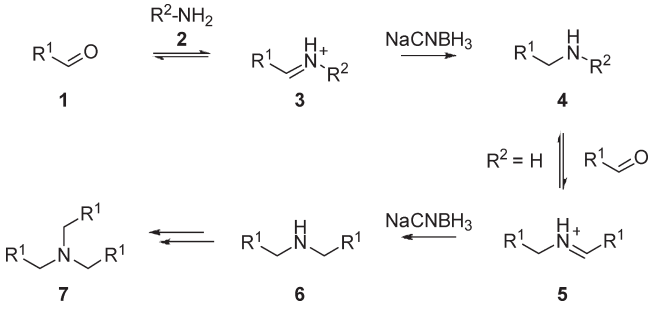
Amines are an important class of compounds found in many natural products, pharmaceuticals, and other valuable organic molecules including dyes and agrochemicals.[1,2] Although there are many synthetic transformations that can be used to prepare amines,[1] methodology for the selective synthesis of primary amines is more limited. Of these, reductive aminations are particularly important,[3−5] and reactions utilizing molecular hydrogen as the reducing agent[4] in the presence of a suitable catalyst have proven very effective.[5,6] The use of hydrogen gas under high pressure and temperature, however, shows significant functional group incompatibility for double bonds and aromatic groups are also hydrogenated. As an alternative, metal hydride reducing agents can be employed, though the selective formation of primary amines under these conditions is challenging.

Traditionally, protecting groups have been used when preparing primary amines via metal hydride reductive amination.[7−9] Protecting groups have an important role in organic synthesis,[10] yet their incorporation into a synthetic route has a number of disadvantages including an increase in the total number of steps in the sequence (protection and deprotection steps) and decreases in atom-economy.[11] Protecting groups also add functional groups and structural complexity to a molecule, which can have detrimental effects on orthogonality and reactivity. In metal hydride reductive aminations, the use of protecting groups is crucial to prevent overalkylation (Scheme 1). In this reaction a carbonyl, typically a ketone or an aldehyde (**1**), reacts with a protected amine (**2**, R^2 = alkyl, aryl) to form an imine (**3**) that is subsequently

(1) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2004.
(2) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.
(3) Baxter, E.; Reitz, A. *Organic Reactions*; Wiley: New York, 2002; Vol. 59.
(4) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037–1057.
(5) Bódis, J.; Lefferts, L.; Müller, T. E.; Pestman, R.; Lercher, J. A. *Catal. Lett.* **2005**, *104*, 23–28.
(6) Gomez, S.; Peters, J. A.; van der Waal, J. C.; van der Brink, P. J.; Maschmeyer, T. *Appl. Catal., A* **2004**, *261*, 119–125.
(7) Kagan, F.; Rebenstorf, M. A.; Heinzelman, R. V. *J. Am. Chem. Soc.* **1957**, *79*, 3541–3544.
(8) Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, *4*, 2898–2905.
(9) Sharma, S. K.; Songster, M. F.; Colpitts, T. L.; Hegyes, P.; Barany, G.; Castellino, F. J. *J. Org. Chem.* **1993**, *58*, 4993–4996.
(10) For examples of recently developed protecting groups, see: (a) Katayama, H.; Utsumi, T.; Ozawa, C.; Nakahara, Y.; Hojo, H.; Nakahara, Y. *Tetrahedron Lett.* **2009**, *50*, 818–821. (b) Kojima, M.; Nakamura, Y.; Nakamura, A.; Takeuchi, S. *Tetrahedron Lett.* **2009**, *50*, 939–942. (c) Ali, A.; Van den Berg, R. J. B. H. N.; Overkleeft, H. S.; Filippov, D. V.; Van der Marel, G. A.; Codee, J. D. C. *Tetrahedron Lett.* **2009**, *50*, 2185–2188. (d) Timmer, M. S. M.; Stocker, B. L.; Northcote, P. T.; Burkett, B. A. *Tetrahedron Lett.* **2009**, *50*, 7199–7204. (e) Fortin, M.; Kaplan, J.; Pham, K.; Kirk, S.; Andrade, R. B. *Org. Lett.* **2009**, *11*, 3594–3597. (f) Khaliullin, F. A.; Klen, E. E. *Russ. J. Org. Chem.* **2009**, *45*, 135–138.
(11) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

Published on Web 07/28/2010 DOI: 10.1021/jo100004c

SCHEME 1. Reductive Amination of Aldehydes



reduced (often with $NaCNBH_3$)[12] to give the desired amine product **4**. Without a protecting group (R^2 = H), multiple alkylation events typically occur, resulting in the formation of the undesired secondary (**6**) or tertiary (**7**) amine products.[3−5] This overalkylation is a consequence of the increased reactivity of the primary amine product **4** (R^2 = H) compared to ammonia (**2**, R^2 = H) in subsequent reductive amination events.[3,13,14] Though the formation of tertiary amines (**7**) can be significantly reduced by using an excess of amine (**2**) or by adjusting the pH,[3] it is difficult to prevent the formation of secondary amines (**6**). Generally, protected amines (**2**, R^2 = alkyl, aryl) are used as the amine source to avoid this problem.[7−9]

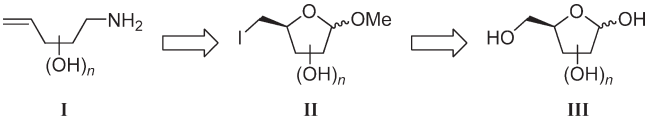
To provide alternative methodology for the synthesis of primary amines, Miriyala et al. established a more selective reductive amination protocol whereby primary amines were produced from ketones using ammonia and titanium(IV) isopropoxide-$NaBH_4$.[15] Unfortunately, the extension of this methodology to aldehydes was ineffective and predominantly resulted in secondary amine formation. This reduction in selectivity is a consequence of the reduced steric bulk and high reactivity of aldehydes when compared to ketones.[13] Accordingly, the selective formation of primary amines from aldehydes using reductive amination has continued to pose a significant challenge.

Given the importance of primary amines as synthetic products and intermediates, we were interested in developing new methodology for the preparation of amines from aldehydes without the need for protecting groups. Recently, we reported a procedure for the preparation of primary amines from methyl glycosides using a Vasella-reductive amination reaction that did not require the use of protecting groups.[16] In this work, methyl iodo-glycosides, derived from either D-ribose or D-xylose, were efficiently converted into primary amines in a single synthetic step using ammonia as the nitrogen source. For this methodology to have wider applicability, however, the scope and limitations of this novel reductive amination protocol needed to be determined. Herein, we report the results of our studies on the chemoselective reductive amination of aldehydes.

Results and Discussion

In our protecting-group-free synthesis, a Vasella reaction[17] and a reductive amination were used to prepare linear alkenylamines (**I**) in one step from an alkyl halo-glycoside precursor (**II**), itself readily available from the parent monosaccharide (**III**) in two steps[18] (Scheme 2). Here, the typical Vasella-reductive amination protocol[16] involved the overnight reflux of a suspension of Zn, NH_4OAc (excess), NH_3, $NaCNBH_3$, and the iodo-sugar in ethanol. Under these conditions the primary alkylamine was produced exclusively (> 20:1 primary:secondary). Excess NH_4OAc was crucial to selectively obtaining the primary amine, and Dowex-H^+ ion exchange chromatography proved most suitable for isolating the product from the reaction mixture. With greater affinity for the ion-exchange resin, the alkylamine was readily separated from the ammonium salts by first washing the column with water (to remove the salts), then eluting the amine product with aqueous ammonia. Using these conditions **9** and **11** (entries 1 and 2, Table 1) were synthesized from **8** and **10** in excellent yields (95% and 91%) and chemoselectivities.

SCHEME 2. Retrosynthesis of Primary Alkenylamines

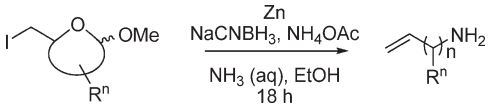


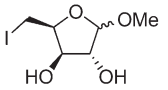
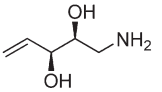
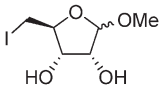
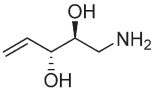
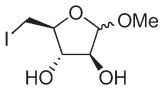
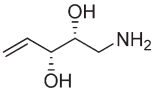
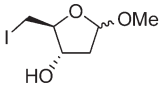
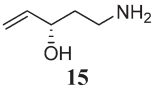
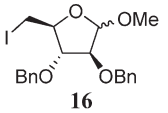
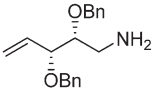
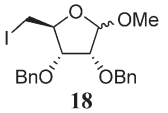
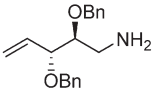
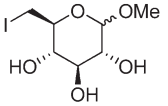
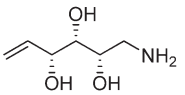
To gain insight into the factors responsible for the preferential formation of the primary amine, we investigated the influence that pH has on the chemoselectivity of the reaction. Using methyl iodo-glycoside **8** as a model substrate, the Vasella-reductive amination was conducted over a pH range from 7 to 12, and the resulting ratio of primary to secondary amine products was recorded (Table 2). A neutral solution, obtained by the addition of AcOH (10 equiv) to the reaction mixture, gave the secondary amine as the major product (4.5:5.5, **9**:**22**, entry 1, Table 2). At pH 8, obtained when a saturated solution of NH_4OAc was used without the addition of AcOH or NH_3, the formation of primary amine **9** was favored (entry 2). Increasing the pH of the reaction mixture to 10 using NH_3 (10 equiv) improved the selectivity even further with a 4:1 ratio of primary:secondary amine being observed (entry 3). Having noted the beneficial influence that increasing the pH has on chemoselectivity, 60 equiv of NH_3 was then added. Under these conditions the primary amine was the only product observed by ^1H NMR (> 20:1, **9**:**22**, entry 4). From these results it appears that the pH-dependent selectivity relates to the amount of free ammonia in solution. At neutral or acidic pH, a greater proportion of ammonia will be protonated to give the non-nucleophilic ammonium cation. As the pH increases, the availability of ammonia increases, thereby favoring nucleophilic attack at the carbonyl and the formation of the primary amine product. Interestingly, the use of ammonia only leads to decomposition, and the addition of NH_4OAc is required to stablilize the amine product.

Using our optimized conditions, we then investigated the applicability of the Vasella-reductive amination reaction conditions for the synthesis of primary amines from other methyl iodo-glycosides. Reaction of D-arabinoside **12** (entry 3, Table 1) proceeded uneventfully, giving the corresponding

(12) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
(13) Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607–2616.
(14) Pelter, A.; Rosser, R. M.; Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717–720.
(15) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463–1471.
(16) Dangerfield, E. M.; Timmer, M. S. M.; Stocker, B. L. *Org. Lett.* **2009**, *11*, 535–538.
(17) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016.
(18) Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jørgensen, M. R.; Madsen, R. *Synthesis* **2002**, *12*, 1721–1727.

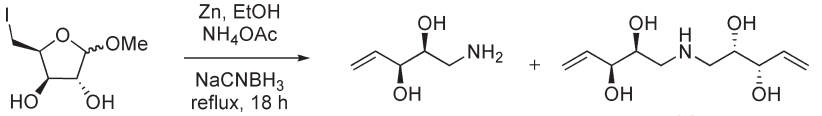
TABLE 1. Vasella-Reductive Amination of Methyl Iodo-glycosides



Entry	Substrate	Major Product	Ratio[a] (1°:2° amine)	Yield[b]
1	 **8**	 **9**	>20:1	95%
2	 **10**	 **11**	>20:1	91%
3	 **12**	 **13**	>20:1	93%
4	 **14**	 **15**	>20:1	81%
5	 **16**	 **17**	3:1	81%
6	 **18**	 **19**	2:1	98%
7[c]	 **20**	 **21**	9:1	93%

[a]Ratio obtained from ^{1}H NMR of the crude material. [b]Combined yield of primary and secondary amines following purification. [c]See Table 3.

TABLE 2. Vasella-Reductive Amination under Different pH Conditions



8 **9** **22**

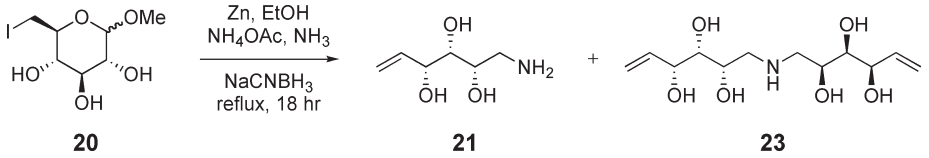
entry	additive[a]	pH[b]	ratio[c] (**9**:**22**)
1	AcOH (10 equiv)	7	4.5:5.5
2	none	8	3:2
3	aq NH_3 (10 equiv)	10	4:1
4	aq NH_3 (60 equiv)	12	> 20:1

[a]Conditions: Zn (5 equiv), $NaCNBH_3$ (3 equiv), sat. ethanolic NH_4OAc (20 mL/mmol). [b]pH of the solution at the start of the reaction after all reagents have been added. [c]Ratio obtained from ^{1}H NMR of the crude material.

alkenylamine **13** in an excellent yield (93%). As anticipated, the stereochemistry around the furanose ring had no significant effect on the yield or selectivity of the reaction. Although byproducts from Vasella reactions have been well documented, with reductive dehalogenation and the reduction of the aldehyde to the alcohol being the most common degradation products,[19] the Vasella-reductive amination

(19) Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem.* **1991**, *56*, 2213–2217.

TABLE 3. Vasella-Reductive Amination at Different Reaction Concentrations



20 **21** **23**

entry	concentration	ratio[a] (**21**:**23** amine)	yield (%)[b]
1	40 mL of sat. NH_4OAc in ethanol per mmol	> 20:1	50
2	20 mL of sat. NH_4OAc in ethanol per mmol	9:1	93
3	5 mL of sat. NH_4OAc in ethanol per mmol	1:1	99

[a]Ratio obtained from ^{1}H NMR of the crude material. [b]Combined yield of primary and secondary amines following purification.

occurred smoothly and with no other products observed. To further investigate the applicability of our reaction, 2-deoxyriboside **14** was subjected to the same reductive amination protocol (entry 4, Table 1). Again, exclusive formation of the primary amine was observed with alkenylamine **15** being isolated in good yield (81%). This result illustrated that the absence of an α-hydroxyl function in the aldehyde substrate did not adversely affect the efficiency or selectivity of the reaction. Here, it should also be noted that alkenylamines have a wide variety of applications, as in addition to their use as intermediates in the synthesis of iminosugars,[16,20] primary alkenylamines have wide application as synthetic intermediates in total synthesis[21] and in particular as substrates for ring-closing metathesis.[22]

Given the promise of our methodology, we then explored the role that the functional group pattern has on the chemoselectivity of the reaction. The fully protected methyl iodoglycosides of D-arabinose **16**[23] and D-ribose **18**[18] were subjected to the Vasella-reductive amination conditions (entries 5 and 6). In both instances, the primary amines were the major products, although the secondary amines were also observed. Following Dowex-H^+ ion exchange chromatography, the relative integrals of the corresponding ^{1}H NMR signals were used to determine the ratio of primary to secondary amine, and the assignments confirmed after separation of the two amine products via silica gel chromatography (DCM → DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v). HRMS allowed for the identification of each product, as did the HMBC correlations between the CH_2-1 and the CH_2-1′ for the secondary amine product. Here, it is interesting to note that the δ of C-1 of primary alkenylamines **17** (δ = 42.3 ppm) and **19** (δ = 42.5 ppm) was lower than the corresponding δ of C-1 for the secondary amine product by *ca.* 8 ppm. This observation was consistent for all primary and secondary amines formed and provided a convenient means by which to readily distinguish the two products. The reduced selectivity observed for **16** and **18** suggested that the functional group pattern of the substrate can affect the chemoselectivity, though not as adversely as decreasing the pH of the reaction solution.

Next, we turned our attention to the Vasella-reductive amination of methyl 6-iodo-glucoside **20** (entry 7, Table 1) to determine if the methodology was applicable to pyranosides. When the reaction was conducted in more dilute conditions (40 mL of sat. NH_4OAc in ethanol with 16 mL of 30% aqueous NH_3 per mmol), only the desired primary amine **21** was produced (entry 1, Table 3); however, the yield was poor because a significant amount of uncharacterizable degradation products was formed. Using the standard reaction concentration (20 mL of NH_4OAc in ethanol with 8 mL of 30% aqueous NH_3 per mmol), the selectivity for primary amine **21** was slightly reduced (**21**:**23** = 9:1, entry 2), though the overall yield was significantly improved (93%). To further study the effect that concentration had on the reaction outcome, more concentrated conditions (5 mL of sat. NH_4OAc in ethanol with 2 mL of 30% aqueous NH_3 per mmol) were used (entry 3). These conditions led to a reduction in chemoselectivity, producing a 1:1 ratio of **21**:**23**, though the overall yield was improved with no observed degradation. From these results, it is apparent that overdilution of the reaction mixture leads to increased degradation and poor yields, presumably as a consequence of a reduced rate in imine reduction, resulting in imine degradation.

Following our investigations into the Vasella-reductive amination methodology, we next explored the direct reductive amination of several aldehydes to determine whether the Vasella step was a requirement for good selectivity. To directly assess the effect of the initial Vasella reaction on the chemoselectivity, the benzyl protected aldehyde **24** was formed by subjecting methyl iodo-glycoside **18** to a Vasella reaction, followed by standard workup procedures. Aldehyde **24** was then subjected to the reductive amination conditions to give **19** in an equimolar ratio with the secondary amine (entry 1, Table 4). Though modest chemoselectivity was obtained, this result nevertheless paralleled that observed during the Vasella-reductive amination of riboside **18** (2:1, primary:secondary amine, entry 6, Table 1) and suggested that the Vasella reaction had little effect on the chemoselectivity of the reductive amination. Given this, we sought to investigate the reductive amination of unfunctionalized aldehydes. Here, nonanal (**25**) was subjected to the reductive amination conditions with primary amine **26** being formed exclusively and in excellent yield (98%) (entry 2,

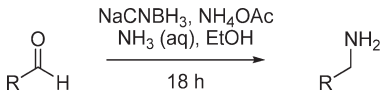
(20) (a) Dangerfield, E. M.; Plunkett, C. H.; Stocker, B. L.; Timmer, M. S. M. *Molecules* **2009**, *14*, 5298–5307. (b) Dangerfield, E. M.; Gulab, S. A.; Plunkett, C. H.; Timmer, M. S. M.; Stocker, B. L. *Carbohydr. Res.* **2010**, *345*, 1360−1365.

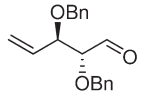
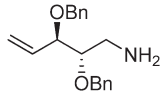
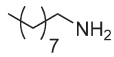
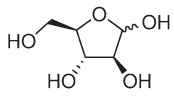
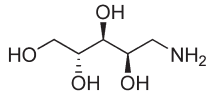
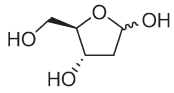
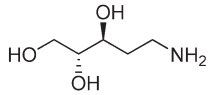
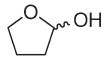
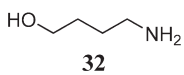
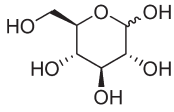
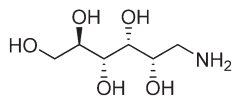
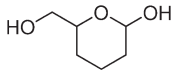
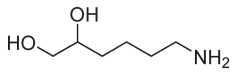
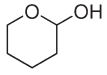
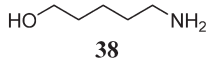
(21) (a) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Org. Lett.* **2009**, *11*, 1179–1181. (b) Paderes, M. C.; Chemler, S. R. *Org. Lett.* **2009**, *11*, 1915–1918. (c) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045–6047. (d) Fukumoto, H.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2731–2734.

(22) (a) Pavlyuk, O.; Teller, H.; McMills, M. C. *Tetrahedron Lett.* **2009**, *50*, 2716–2718. (b) Wang, H.; Matsuhashi, H.; Doan, B. D.; Goodman, S. N.; Ouyang, X.; Clark, W. M. *Tetrahedron* **2009**, *65*, 6291–6303. (c) Verhelst, S. H. L.; Martinez, B. P.; Timmer, M. S. M.; Lodder, G.; Van der Marel, G. A.; Overkleeft, H. S.; Van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598–9603.

(23) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2002**, *43*, 7577–7579.

TABLE 4. Reductive Amination of Masked Aldehyde (Hemiacetal) and Aldehyde Substrates



Entry	Substrate	Major Product	Ratio[a] (1°:2° amine)	Yield[b]
1	 **24**	 **19**	1:1	97%
2	 **25**	 **26**	>20:1	98%
3	 **27**	 **28**	>20:1	85%
4	 **29**	 **30**	>20:1	86%
5	 **31**	 **32**	11:1	60%
6	 **33**	 **34**	>20:1	87%
7	 **35**	 **36**	8:1	65%
8	 **37**	 **38**	7:1	81%

[a]Ratio obtained from ^{1}H NMR of the crude material. [b]Combined yield of primary and secondary amines following purification.

Table 4). This result was significant because it illustrated that hydroxyl substituents were not required for the selective reductive amination of aldehydes and therefore markedly increased the scope of the reductive amination methodology. These results also indicated that the addition of zinc (for the one-pot Vasella-reductive amination reaction) did not significantly alter the outcome of the reaction and negates the possibility of boron ester[24] or zinc chelate[25] formation having a decisive influence on the chemoselectivity of the reaction.

Unfortunately, the unprotected aldehyde products from the Vasella reaction of furanosides **8**, **10**, and **12** readily condensed into polymeric mixtures of acetals and could not be isolated for study in a reductive amination reaction that was independent of the Vasella reaction.

Next, we examined the furanose series of hemiacetals **27**, **29**, and **31** (entries 3−5, Table 4). Reductive amination of D-xylose (**27**) and 2-deoxy-D-ribose (**29**) gave the corresponding primary amines, **28** and **30**, in excellent selectivity and in good yield (> 85%). These results parallel those for the furanose Vasella-reductive amination series (cf. entries 1−4, Table 1) and expand the scope of the reaction to hemiacetals. To investigate the influence that the hydroxylation pattern has on the chemoselectivity, the unsubstituted furanoside **31** was then subjected to the reductive amination conditions (entry 5, Table 4). Here, the ratio of primary to secondary amine was also good (11:1), although the yield for the reaction was reduced (60%). Amine **32** and its dimer were the only products observed, suggesting that the reduced yield for this reaction was due to the formation of non-amine byproducts, which could not be extracted from the salts using a Dowex-H^+ column.

(24) (a) Garlaschelli, L.; Mellerio, G.; Vidari, G. *Tetrahedron* **1989**, *45*, 7379–7386. (b) Dubois, L.; Fiaud, J.-C.; Kagan, H. B. *Tetrahedron* **1995**, *51*, 3803–3812.

(25) (a) Nieuwpoort, G.; Brussee, J.; Reedijk, J. *Inorg. Chim. Acta* **1983**, *68*, 131–135. (b) Rustagi, S. C.; Rao, G. N. *J. Inorg. Nucl. Chem.* **1974**, *36*, 1161–1163.

Given our encouraging results, the reductive amination of a series of pyranoses was then explored. First, D-glucose (**33**) was treated with a saturated solution of NH_4OAc in ethanol, aqueous NH_3, and $NaCNBH_3$ to give 1-amino-1-deoxy-D-glucitol (**34**) in good yield (87%) and with excellent selectivity (> 20:1, primary:secondary amine) (entry 6, Table 4). Hemiacetals with decreasing hydroxylation were then subjected to the reductive amination reaction, with hydroxymethylpyranose **35** (entry 7) yielding the corresponding amine **36** with good selectivity (8:1), albeit in moderate overall yield (65%). The absence of the hydroxymethyl group (**37**, entry 8) did not significantly alter the monomer to dimer ratio (7:1), and primary amine **38** was produced in good yield. The mono- and dialkylated products could be easily separated by flash column chromatography on silica gel and through a comparison of the $\underline{C}H_2N$ chemical shifts of the two products, the primary and secondary amines could be easily identified by ^{13}C NMR [e.g., C-5 of 5-aminopentanol **38** has an upfield chemical shift (δ = 39.4 ppm) compared to the C-5 of the secondary amine (δ = 47.7 ppm)]. HMBC correlations and HRMS were also used to confirm the identity of the amines. Taken as a whole, these results demonstrate the applicability of our methodology to the synthesis of a variety of primary amines from different aldehyde precursors, and in almost all instances, good chemoselectivity was observed.

Conclusion

We have demonstrated that primary amines can be selectively produced from aldehydes via metal hydride reductive amination without the need for protecting groups. The most important influences on the chemoselectivity are pH, the number of amine equivalents, and reaction concentration, with ideal conditions being a pH of approximately 12, a large excess of ammonia, and an aldehyde concentration of 20 mL of sat. NH_4OAc in ethanol per mmol. Overall, the reductive amination methodology is applicable to a wide range of functionalized substrates, and the yields of the primary amines are typically good. Without requiring protecting groups, the methodology is fast and efficient (and thus atom-economic) and provides a valuable synthetic tool for the selective formation of primary amines. The application of this methodology in the protecting-group-free syntheses of further natural products is currently underway.

Experimental Section

Unless otherwise stated all reactions were performed under atmospheric air. Hemiacetals **31**, **35**, and **37** were synthesized according to the procedure by Tamaru and co-workers.[26] Methyl iodo-glycosides were synthesized according to the procedure by Madsen and co-workers.[18] The Zn dust was activated by the careful addition of conc H_2SO_4, followed by decantation and washing with EtOH (3×) and hexanes (3×), and storage under dry hexanes. All solvents were removed by evaporation under reduced pressure. Reactions were monitored by TLC analysis on silica gel coated plastic sheets (0.20 mm, Polygram SIL G/UV_{254}) with detection by spraying with 20% H_2SO_4 in EtOH followed by charring at ~150 °C, by dipping in I_2 in silica, or by spraying with a solution of ninhydrin in EtOH followed by charring at ~150 °C. Column chromatography was performed on silica gel (40−63 μm). Dowex W50-X8 acidic resin was used for ion exchange chromatography. NMR peak assignments are based on 2D NMR experiments (COSY, HSQC, and HMBC).

General Procedure for the Synthesis of Alkenylamines. To a solution of methyl iodo-glycoside (1 mmol) in a saturated solution of NH_4OAc in EtOH (20 mL) were added activated Zn (327 mg, 5 mmol), $NaCNBH_3$ (188 mg, 3 mmol), and 30% aqueous NH_3 (8 mL). The mixture was stirred at reflux for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was redissolved in H_2O, loaded onto a Dowex H^+ ion-exchange resin, and washed several times with H_2O to remove excess salt. The amine product was then eluted with 15% to 30% aqueous NH_3. Further purification was achieved using gradient flash chromatography (DCM/EtOH/MeOH/30% aqueous NH_3, 25/2/2/1 to 5/2/2/1, v/v/v/v). The alkenylamines were converted to the HCl salts for characterization.

(2*S*,3S)-1-Amino-pent-4-ene-2,3-diol Hydrochloride (9). By subjecting xyloside **8** (60.1 mg, 0.22 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **9** was obtained as the HCl salt (32 mg, 0.21 mmol, 95%). R_f = 0.37 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{20}_D = -40.0$ (c = 0.07, EtOH); IR (film) 3405, 3212, 2888, 1555, 1434, 1016 cm^{-1}. ^1H NMR (300 MHz, D_2O) δ 5.71 (ddd, $J_{3,4}$ = 6.4, $J_{4,5\text{-}cis}$ = 10.5 Hz, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-4), 5.34 (d, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-5-*trans*), 5.28 (d, $J_{4,5\text{-}cis}$ = 10.5 Hz, 1H, H-5-*cis*), 4.10 (dd, $J_{2,3}$ = 5.0 Hz, $J_{3,4}$ = 6.4 Hz, 1H, H-3), 4.05 (s, 1H, NH), 3.81 (ddd, $J_{1a,2}$ = 3.3 Hz, $J_{2,3}$ = 5.0 Hz, $J_{1b,2}$ = 9.7 Hz, 1H, H-2), 3.15 (dd, $J_{1a,2}$ = 3.3 Hz, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1a), 2.98 (dd, $J_{1b,2}$ = 9.7 Hz, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 135.8 (C4), 117.9 (C5), 73.9 (C3), 72.0 (C2), 42.0 (C1); HRMS(ESI) m/z calcd for $[C_5H_{11}O_2N + H]^+$ 118.0863, obsd 118.0871.

(2*S*,3*R*)-1-Amino-pent-4-ene-2,3-diol Hydrochloride (11). By subjecting riboside **10** (51.2 mg, 0.19 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **11** was obtained as the HCl salt (26 mg, 0.17 mmol, 91%). R_f = 0.41 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{18}_D = +8.2$ (c = 0.28, EtOH); IR (film) 3345, 2946, 2835, 1651, 1450, 1018 cm^{-1}. ^1H NMR (300 MHz, D_2O) δ 5.88 (ddd, $J_{3,4}$ = 6.6, $J_{4,5\text{-}cis}$ = 10.5, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-4), 5.35 (d, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-5-*trans*), 5.31 (d, $J_{4,5\text{-}cis}$ = 10.5 Hz, 1H, H-5-*cis*), 4.12 (dd, $J_{2,3}$ = 5.6, $J_{3,4}$ = 6.6 Hz, 1H, H-3), 3.81 (ddd, $J_{1a,2}$ = 3.0, $J_{2,3}$ = 5.6, $J_{1b,2}$ = 9.7 Hz, 1H, H-2), 3.23 (dd, $J_{1a,2}$ = 3.0, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1a), 2.95 (dd, $J_{1b,2}$ = 9.7, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1b); ^{13}C NMR (75 MHz, D_2O) δ 135.4 (C4), 118.3 (C5), 74.0 (C3), 69.8 (C2), 41.1 (C1); HRMS(ESI) m/z calcd for $[C_5H_{11}O_2N + H]^+$ 118.0863, obsd 118.0873.

(2*R*,3*R*)-1-Amino-pent-4-ene-2,3-diol Hydrochloride (13). By subjecting arabinoside **12** (274 mg, 1 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **13** was obtained as the HCl salt (143 mg, 93 mmol, 93%). R_f = 0.61 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{20}_D$ = +50.6 (c = 1.0, EtOH); IR (film) 3412, 3252, 3045, 1632, 1432, 1013 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 5.74 (ddd, $J_{3,4}$ = 5.3, $J_{4,5\text{-}cis}$ = 10.5, $J_{4,5\text{-}trans}$ = 17.3 Hz, 1H, H-4), 5.23 (d, $J_{4,5\text{-}trans}$ = 17.3 Hz, 1H, H-5-*trans*), 5.17 (d, $J_{4,5\text{-}cis}$ = 10.5 Hz, 1H, H-5-*cis*), 3.99 (t, $J_{3,4} = J_{2,3}$ = 5.3 Hz, 1H, H-3), 3.70 (ddd, $J_{1a,2}$ = 2.8, $J_{2,3}$ = 5.3, $J_{1b,2}$ = 9.9 Hz, 1H, H-2), 3.03 (dd, $J_{1a,2}$ = 9.9, $J_{1a,1b}$ = 13.1 Hz, 1H, H-1a), 2.87 (dd, $J_{1a,2}$ = 2.8, $J_{1a,1b}$ = 13.1 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, D_2O) δ 135.4 (C4), 118.2 (C5), 73.7 (C3), 69.7 (C2), 41.5 (C1); HRMS(ESI) m/z calcd for $[C_5H_{11}O_2N + H]^+$ 118.0868, obsd 118.0869.

(*S*)-5-Amino-pent-1-en-3-ol Hydrochloride (15). By subjecting deoxyriboside **14** (100 mg, 0.38 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **15** was obtained as the HCl salt (42 mg, 0.31 mmol, 81%). R_f = 0.4 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{17}_D = -3.2$

(26) Kojima, K.; Kimura, M.; Satoshi, U.; Tamaru, Y. *Tetrahedron* **2006**, *62*, 7512–7520.

(c = 0.1, EtOH); IR (film), 3359, 3047, 2955, 2927, 2854, 1635, 1428, 1134, 1056 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.35 (ddd, $J_{3,4}$ = 6.1, $J_{4,5b}$ = 10.5, $J_{4,5a}$ = 17.3 Hz, 1H, H-4), 5.06 (dd, $J_{5a,5b}$ = 1.3, $J_{4,5a}$ = 17.3 Hz, 1H, H-5a), 5.04 (dd, $J_{5a,5b}$ = 1.3, $J_{4,5b}$ = 10.5 Hz, 1H, H-5b), 4.04 (ddd, $J_{3,4}$ = 6.1, $J_{2a,3}$ = 5.2, $J_{2b,3}$ = 7.3 Hz, 1H, H-3), 2.96 (m, 2H, H-1), 1.38 (m, 2H, H-2); ^{13}C NMR (125 MHz, D_2O) δ 138.8 (C4), 115.8 (C5), 70.1 (C3), 36.3 (C1), 32.9 (C2); HRMS(ESI) m/z calcd for $[C_5H_{12}NO]^+$ 102.0919, obsd 102.0921.

(2*R*,3*R*)-2,3-Bis-benzyloxy-pent-4-enylamine Hydrochloride (17). To a solution of methyl arabinoside **16** (50.0 mg, 0.110 mmol) in a saturated solution of NH_4OAc in EtOH (2.2 mL) were added activated Zn (36 mg, 0.550 mmol), $NaCNBH_3$ (21 mg, 0.330 mmol), and 30% aq NH_3 (0.88 mL). The mixture was stirred at reflux for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was redissolved in 10 mL of EtOAc and made basic using 1 M NaOH. The layers were separated, and the aqueous layer extracted with EtOAc. Organic extracts were combined and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to obtain alkenylamine **17** together with the secondary amine product, in a 3:1 ratio (primary:secondary), as a colorless oil (29 mg, 0.096 mmol, 81%). Amine **17** was purified using gradient flash chromatography (DCM/EtOH/MeOH/30% aq NH_3, 475/2/2/1 to 95/2/2/1, v/v/v/v), then converted to the HCl salt. R_f = 0.31 (DCM/EtOH/MeOH/30% aq NH_3, 95/2/2/1, v/v/v/v); $[\alpha]^{20}_D$ = +6.0 (c = 0.3, $CHCl_3$); IR (film) 3371, 3087, 3064, 3030, 2924, 2866, 2054, 1955, 1641, 1586, 1496, 1454, 1390, 1352, 1307, 1207, 1088, 996, 927, 734, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 10H, CH Ph), 5.84 (ddd, $J_{3,4}$ = 7.5, $J_{4,5\text{-}cis}$ = 10.6, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-4), 5.34 (d, $J_{4,5\text{-}cis}$ = 10.6 Hz, 1H, H-5*cis*), 5.33 (d, $J_{4,5\text{-}trans}$ = 17.1 Hz, 1H, H-5*trans*), 4.81 (d, $J_{Ha,Hb}$ = 11.5 Hz, 1H, CH_aH_b Bn), 4.65 (d, $J_{Ha,Hb}$ = 11.9 Hz, 1H, CH_aH_b Bn), 4.62 (d, $J_{Ha,Hb}$ = 11.5 Hz, 1H, CH_aH_b Bn), 4.41 (d, $J_{Ha,Hb}$ = 11.5 Hz, 1H, CH_aH_b Bn), 3.96 (dd, $J_{2,3}$ = 5.7, $J_{3,4}$ = 7.5 Hz, 1H, H-3), 3.50 (ddd, $J_{1a,2}$ = 3.8, $J_{2,3}$ = 5.7, $J_{1b,2}$ = 7.7 Hz, 1H, H-2), 2.87 (dd, $J_{1a,2}$ = 3.8, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1a), 2.73 (dd, $J_{1b,2}$ = 7.7, $J_{1a,1b}$ = 13.2 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.4 (C_q Ph), 135.0 (C4), 128.4−127.6 (CH Ph), 119.0 (C5), 82.8 (C2), 81.5 (C3), 73.6 (CH_2 Bn on C2), 70.6 (CH_2 Bn on C3), 42.5 (C1); HRMS(ESI) m/z calcd for $[C_{19}H_{24}NO_2]^+$ 298.1807, obsd 298.1808.

(2*S*,3*R*)-2,3-Bis-benzyloxy-pent-4-enylamine Hydrochloride (19). To a solution of methyl riboside **18** (305 mg, 0.671 mmol) in a saturated solution of NH_4OAc in EtOH (13 mL) were added activated Zn (219 mg, 3.36 mmol), $NaCNBH_3$ (125 mg, 2.011 mmol), and 30% aq NH_3 (5.3 mL). The mixture was stirred at reflux for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was redissolved in 20 mL of EtOAc and made basic using 1 M NaOH. The layer were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to obtain alkenylamine **19** together with the secondary amine product in a 2:1 ratio (primary:secondary), as a colorless oil (218 mg, 0.655 mmol, 98%). Amine **19** was purified using gradient flash chromatography (DCM/EtOH/MeOH/30% aq NH_3, 475/2/2/1 to 95/2/2/1, v/v/v/v), then converted to the HCl salt. R_f = 0.23 (DCM/EtOH/MeOH/30% aq NH_3, 95/2/2/1, v/v/v/v); $[\alpha]^{21}_D$ = −40.4 (c = 1, $CHCl_3$); IR (film) 3379, 3064, 3030, 2865, 1952, 1675, 1586, 1454, 1349, 1206, 1089, 1066, 994, 927, 734, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 10H, CH Ph), 5.89 (ddd, $J_{3,4}$ = 7.7, $J_{4,5\text{-}cis}$ = 10.5, $J_{4,5\text{-}trans}$ = 17.2 Hz, 1H, H-4), 5.37 (d, $J_{4,5\text{-}cis}$ = 10.5 Hz, 1H, H-5-*cis*), 5.34 (d, $J_{4,5\text{-}trans}$ = 17.2 Hz, 1H, H-5-*trans*), 4.70 (d, $J_{Ha,Hb}$ = 11.4 Hz, 1H, CH_aH_b Bn), 4.65 (d, $J_{Ha,Hb}$ = 11.9 Hz, 1H, CH_aH_b Bn), 4.56 (d, $J_{Ha,Hb}$ = 11.4 Hz, 1H, CH_aH_b Bn), 4.38 (d, $J_{Ha,Hb}$ = 11.9 Hz, 1H, CH_aH_b Bn), 3.89 (dd, $J_{2,3}$ = 5.3, $J_{3,4}$ = 7.7 Hz, 1H, H-3), 3.47 (ddd, $J_{1b,2}$ = 4.1, $J_{2,3}$ = 5.3, $J_{1a,2}$ = 5.6 Hz, 1H, H-2), 5.89−5.82 (m, 2H, H-1a and H-1b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.3 (C_q Ph), 135.8 (C4), 128.4−127.6 (CH Ph), 119.2 (C5), 82.8 (C2), 80.5 (C3), 72.8 (CH_2 Bn on C2), 70.3 (CH_2 Bn on C3), 42.3 (C1); HRMS(ESI) m/z calcd for $[C_{19}H_{24}NO_2]^+$ 298.1807, obsd 298.1804. Dimer: R_f = 0.72 (DCM/EtOH/MeOH/30% aq NH_3, 95/2/2/1, v/v/v/v); HRMS-(ESI) m/z calcd for $[C_{38}H_{44}NO_4]^+$ 578.3270, obsd 578.3263.

(2*S*,3*S*,4*R*)-1-Amino-hex-5-ene-2,3,4-triol Hydrochloride (21). By subjecting glucoside **20** (890 mg, 2.93 mmol) to the general procedure for the synthesis of alkenylamines, alkenylamine **21** was obtained as the HCl salt (501 mg, 2.74 mmol, 93%). R_f = 0.20 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); $[\alpha]^{17}_D$ = +6.6 (c = 1.0, EtOH); IR (film) 3320, 3227, 3046, 2925, 1622, 1550, 1409, 1342, 1127, 1066, 1016, 935, 840, 737 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 5.71 (ddd, $J_{4,5}$ = 6.9, $J_{5,6\text{-}cis}$ = 10.6, $J_{5,6\text{-}trans}$ = 17.2 Hz, 1H, H-5), 5.21 (d, $J_{5,6\text{-}trans}$ = 17.2 Hz, 1H, H-6-*trans*), 5.14 (d, $J_{5,6\text{-}cis}$ = 10.6 Hz, 1H, H-6-*cis*), 4.05 (dd, $J_{3,4}$ = 6.7, $J_{4,5}$ = 6.9 Hz, 1H, H-4), 3.80 (ddd, $J_{2,3}$ = 2.9, $J_{1a,2}$ = 4.8, $J_{1b,2}$ = 7.6 Hz, 1H, H-2), 3.36 (dd, $J_{2,3}$ = 2.9, $J_{3,4}$ = 6.7 Hz, 1H, H-3), 2.98 (m, 2H, H-1a and H-1b); ^{13}C NMR (125 MHz, D_2O) δ 135.8 (C5), 118.4 (C6), 74.2 (C3), 73.2 (C4), 67.0 (C2), 42.3 (C1); HRMS(ESI) m/z calcd for $[C_6H_{14}NO_3]^+$ 148.0974, obsd 148.0977.

General Procedure for the Synthesis of Glycamines. To a solution of hemiacetal (1 mmol) in a saturated solution of NH_4OAc in EtOH (20 mL) were added $NaCNBH_3$ (188 mg, 3 mmol) and 30% aq NH_3 (8 mL). The mixture was stirred at reflux for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was redissolved in H_2O, loaded on to a Dowex H^+ ion-exchange resin, and washed several times with H_2O to remove excess salt. The amine product was then eluted with 15% to 30% aq NH_3. The eluent was concentrated under reduced pressure.

Nonylamine Hydrochloride (26). By subjecting aldehyde **25** (430 mg, 3.03 mmol) to the general procedure for the synthesis of glycamines, nonylamine **26** was obtained as the acetate salt, which was then converted into the HCl salt by the addition of 1 M HCl (534 mg, 2.97 mmol, 98%). All spectroscopic data was in full agreement with that of a commercial sample (Aldrich).

1-Amino-1-deoxy-D-arabinitol (28). By subjection of arabinose (**27**) (150 mg, 1 mmol) to the general procedure for the synthesis of glycamines, glycamine **28** was obtained as the acetate salt. Addition of HCl (1 M), followed by concentration, gave the HCl salt of **28** (128 mg, 0.85 mmol, 85%). R_f = 0.01 (DCM/EtOH/MeOH/NH_3 (aq) 5/2/2/1 v/v/v/v); $[\alpha]^{16}_D$ = +14.8 (c = 1.2, H_2O); IR (film), 3372, 3364, 2967, 2943, 1634, 1070, 1032 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 3.99 (ddd, $J_{2,3}$ = 1.8, $J_{1a,2}$ = 5.4, $J_{1b,2}$ = 7.4 Hz, 1H, H-2), 3.68, (dd, $J_{4,5a}$ = 2.9, $J_{5a.5b}$ = 11.8 Hz, 1H, H-5a), 3.57 (ddd, $J_{4,5a}$ = 2.9, $J_{4,5b}$ = 5.9, $J_{3,4}$ = 8.9 Hz, 1H, H-4), 3.51 (dd, $J_{4,5b}$ = 5.9, $J_{5a,5b}$ = 11.8 Hz, 1H, H-5b), 3.27 (dd, $J_{2,3}$ = 1.8, $J_{3,4}$ = 8.9 Hz, 1H, H-3), 3.01 (m, 2H, H-1); ^{13}C NMR (125 MHz, D_2O) δ 71.0 (C2), 70.3 (C3), 66.2 (C4), 62.6 (C5), 42.4 (C1); HRMS(ESI) m/z calcd for $[C_5H_{14}NO_4]^+$ 152.0923, obsd 152.0918.

1-Amino-1,2-dideoxy-D-ribitol (30). By subjecting 2-deoxyribose (**29**) (134 mg, 1 mmol) to the general procedure for the synthesis of glycamines, glycamine **30** was obtained as the acetate salt. Addition of HCl (1 M), followed by concentration, gave the HCl salt **25** (117 mg, 0.87 mmol, 87%). R_f = 0.02 (DCM/EtOH/MeOH/NH_3 (aq) 5/2/2/1 v/v/v/v); $[\alpha]^{16}_D$ = +16.3 (c = 1.0, H_2O); IR (film), 3375, 3342, 3297, 2948, 2917, 1471, 1014 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 3.57 (m, 2H, H-3, and H-5a), 3.48 (m, 2H, H-4, and H-5b), 3.04 (m, 2H, H-1), 1.83 (dddd, J = 2.9, J = 6.2, J = 8.8, $J_{2a,2b}$ = 14.5 Hz, 1H, H-2a), 1.64 (dddd, J = 6.6, J = 8.2, J = 9.8, $J_{2a,2b}$ = 14.5 Hz, 1H, H-2b); ^{13}C NMR (125 MHz, D_2O) δ 74.2 (C4), 69.5 (C3), 62.2 (C5), 37.1 (C1), 29.2 (C2); HRMS(ESI) m/z calcd for $[C_5H_{14}NO_3]^+$ 136.0974, obsd 136.0972.

4-Amino-butan-1-ol Hydrochloride (32). By subjecting furanol **31** (470 mg, 5.34 mmol) to the general procedure for the synthesis of glycamines, glycamine **32** was obtained as the acetate salt together with its secondary amine product in a 11:1 ratio (primary:secondary). Addition of HCl (1 M), followed by concentration, gave a mixture of the corresponding HCl salts (401 mg, 3.21 mmol, 60%). Primary and secondary amines were separated using gradient flash chromatography (DCM/EtOH/MeOH/30% aq NH_3, 95/2/2/1 to 10/2/2/1, v/v/v/v) and converted to the HCl salt for characterization. **27**: R_f = 0.24 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); IR (film) 3374, 3280, 3042, 2982, 2844, 1634, 1443, 1405, 1054, 1033, 1015, 907, 698 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 3.58 (t, $J_{1,2}$ = 6.5 Hz, 2H, H-1), 2.98 (t, $J_{3,4}$ = 7.4 Hz, 2H, H-4), 1.67 (tt, $J_{3,4}$ = 7.4 $J_{2,3}$ = 7.6 Hz, 2H, H-3), 1.57 (tt, $J_{1,2}$ = 6.5, $J_{2,3}$ = 7.6 Hz, 2H, H-2); ^{13}C NMR (125 MHz, D_2O) δ 60.9 (C1), 39.3 (C4), 28.2 (C2), 23.4 (C3); HRMS(ESI) m/z calcd for $[C_4H_{11}ON + H]^+$ 90.0913, obsd 90.0911. Bis(5-hydroxy-butyl)-amine hydrochloride: R_f = 0.45 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); HRMS(ESI) m/z calcd for $[C_8H_{19}O_2N + H]^+$ 162.1494, obsd 162.1492.

1-Amino-1-deoxy-D-glucitol Hydrochloride (34). By subjecting **33** (180 mg, 1 mmol) to the general procedure for the synthesis of glycamines, glycamine **34** was obtained as the acetate salt. Addition of HCl (1 M), followed by concentration, gave the HCl salt of **34** (156 mg, 0.86 mmol, 86%). R_f = 0.01 (DCM/EtOH/MeOH/NH_3 (aq) 5/2/2/1 v/v/v/v); $[\alpha]^{16}_D$ = −6.1 (c = 1.5, H_2O); IR (film), 3431, 3388, 2975, 2947, 1633, 1090, 1054, 1014 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 3.87 (ddd $J_{1a,2}$ = 3.2, $J_{2,3}$ = 5.2, $J_{1b,2}$ = 9.5 Hz, 1H, H-2), 3.65 (m, 2H, H-6a, H-3) 3.58 (m, 1H, H-5), 3.48 (m, 2H, H-6b and H-4), 3.06 (dd, $J_{1a,2}$ = 3.2, $J_{1a,1b}$ = 13.1 Hz, 1H, H-1a), 2.91 (dd, $J_{1b,2}$ = 9.5, $J_{1a,1b}$ = 13.1 Hz, 1H, H-1b); ^{13}C NMR (125 MHz, D_2O) δ 70.7 (C5), 70.6 (C4), 70.5 (C3), 69.9 (C2), 62.5 (C6), 41.8 (C1); HRMS(ESI) m/z calcd for $[C_6H_{16}NO_5]^+$ 182.1028, obsd 182.1028.

6-Amino-hexane-1,2-diol Hydrochloride (36). By subjecting pyranose **35** (100 mg, 0.763 mmol) to the general procedure for the synthesis of glycamines, glycamine **36** was obtained together with secondary amine product in a 8:1 ratio (primary: secondary) as the acetate salts, which were then converted into the HCl salt by the addition of 1 M HCl (83.7 mg, 0.495 mmol, 65%). **36**: R_f = 0.18 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); IR (film) 3353, 3204, 2928, 2856, 1710, 1662, 1393, 1267, 1125, 1073, 1046, 1013, 883, 740 cm^{-1}.^1H NMR (500 MHz, D_2O) δ 3.68 (ddd, $J_{1a,2}$ = 3.9, $J_{1b,2}$ = 6.8, $J_{2,3}$ = 10.9 Hz, 1H, H-2), 3.56 (dd, $J_{1a,2}$ = 3.9, $J_{1a,1b}$ = 11.7 Hz, 1H, H-1a), 3.45 (dd, $J_{1b,2}$ = 6.8, $J_{1a,1b}$ = 11.7 Hz, 1H, H-1b), 2.98 (t, $J_{5,6}$ = 7.7 Hz, 2H, H-6), 1.67 (m, 2H, H-5), 1.50 (m, 2H, H-3), 1.41 (m, 2H, H-4); ^{13}C NMR (125 MHz, D_2O) δ 71.3 (C2), 65.2 (C1), 39.3 (C6), 31.5 (C3), 26.6 (C5), 21.7 (C4); HRMS(ESI) m/z calcd for $[C_6H_{16}NO_2]^+$ 134.1176, obsd 134.1175. 6-(5,6-Dihydroxy-hexylamino)-hexane-1,2-diol hydrochloride: R_f = 0.34 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); ^1H NMR (500 MHz, D_2O) δ 3.68 (ddd, $J_{1a,2}$ = 3.9, $J_{1b,2}$ = 6.8, $J_{2,3}$ = 10.9 Hz, 2H, H-2), 3.56 (dd, $J_{1a,2}$ = 3.9, $J_{1a,1b}$ = 11.7 Hz, 2H, H-1a), 3.45 (dd, $J_{1b,2}$ = 6.8, $J_{1a,1b}$ = 11.7 Hz, 2H, H-1b), 3.02 (t, $J_{5,6}$ = 7.9 Hz, 4H, H-6), 1.67 (m, 4H, H-5), 1.50 (m, 4H, H-3), 1.41 (m, 4H, H4); ^{13}C NMR (125 MHz, D_2O) δ 71.3 (C2), 65.2 (C1), 47.3 (C6), 31.5 (C3), 25.4 (C5), 21.8 (C4); HRMS(ESI) m/z calcd for $[C_{12}H_{28}NO_4]^+$ 250.2018, obsd 250.2020.

5-Amino-pentan-1-ol Hydrochloride (38). By subjecting pyranose **37** (400 mg, 3.92 mmol) to the general procedure for the synthesis of glycamines, glycamine **38** was obtained as the acetate salt together with the secondary amine products in a 7:1 ratio (primary:secondary) and then converted to the HCl salt (515 mg, 3.18 mmol, 81%). Primary and secondary amine products were then separated using gradient flash chromatography (DCM/EtOH/MeOH/30% aq NH_3, 95/2/2/1 to 10/2/2/1, v/v/v/v) and converted to the HCl salts for characterization. **38**: R_f = 0.44 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); IR (film) 3425, 3294, 2935, 2868, 1623, 1517, 1472, 1208, 1130, 1022, 951, 736, 699 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 3.58 (t, $J_{1,2}$ = 6.7 Hz, 2H, H-1), 2.95 (t, $J_{5,4}$ = 7.6 Hz, 2H, H-5), 1.64 (tt, $J_{3,4}$ = 7.6, $J_{4,5}$ = 7.6 Hz, 2H, H-4), 1.55 (tt, $J_{1,2}$ = 6.7, $J_{2,3}$ = 7.5 Hz, 2H, H-2), 1.39 (tt, $J_{2,3}$ = 7.5, $J_{3,4}$ = 7.6 Hz, 2H, H-3); ^{13}C NMR (125 MHz, D_2O) δ 61.2 (C1), 39.4 (C5), 30.6 (C2), 26.7 (C4), 21.9 (C3); HRMS(ESI) m/z calcd for $[C_5H_{13}ON + H]^+$ 104.1075, obsd 104.1070. 5-(5-Hydroxy-pentylamino)-pentan-1-ol hydrochloride: R_f = 0.63 (DCM/EtOH/MeOH/30% aq NH_3, 5/2/2/1, v/v/v/v); IR (film) 3309, 3117, 2934, 2862, 1496, 1369, 1207, 1079, 1022, 734, 697 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 3.58 (t, $J_{1,2}$ = 6.5 Hz, 4H, H-1), 2.82 (t, $J_{4,5}$ = 7.3 Hz, 4H, H-5), 1.59 (tt, $J_{3,4}$ = 7.3, $J_{4,5}$ = 7.3 Hz, 4H, H-4), 1.55 (tt, $J_{1,2}$ = 6.5, $J_{2,3}$ = 7.6 Hz, 4H, H-2), 1.36 (tt, $J_{2,3}$ = 7.6, $J_{3,4}$ = 7.3 Hz, 4H, H-3); ^{13}C NMR (125 MHz, D_2O) δ 61.3 (C1), 47.7 (C5), 30.7 (C2), 26.4 (C4), 22.5 (C3); HRMS(ESI) m/z calcd for $[C_{10}H_{23}O_2N + H]^+$ 190.1807, obsd 190.1801.

Acknowledgment. The authors would like to acknowledge the financial contributions of the Wellington Medical Research Foundation, the Tertiary Education Commission (Top Achiever doctoral scholarship, E.M.D.), Victoria University of Wellington (postgraduate scholarship, Curtis-Gordon research scholarship, C.H.P.), and Lottery Health Research (B.L.S. and M.S.M.T.).

Supporting Information Available: Full experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.