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Total Synthesis Without Protecting Groups: Pyrrolidines and Cyclic Carbamates†

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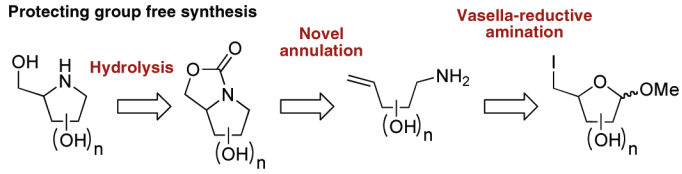
ABSTRACT



A protecting group free synthesis of 2,3-*cis* substituted hydroxypyrrolidines is reported. Two novel reaction methodologies allow for the stereoselective formation of cyclic carbamates from olefinic amines, and the formation of primary amines via a Vasella/reductive amination reaction, both performed in aqueous media.

As noted inhibitors of glycosidases, imino-sugars have enormous therapeutic potential in diseases such as viral infection, bacterial infection, lysosomal storage disorders, cancer and diabetes.[1] Although the nature of the glycosidases that will be inhibited by certain imino-sugars can, to some extent, be predicted from the number, position and configuration of the substituents, there can be marked differences in the inhibition of isoenzymes of a given glycosidase in different species and even within the same cell.[1a] Many tumor cells display aberrant glycosylation due to an altered expression of glycosyltransferases[2] and levels of glycosidases are elevated in the sera of many patients with tumors.[3] However, largely due to the limited availability of the imino-sugars, only few [principally 1-deoxynojirimycin (DNJ), 1-deoxymannojirimycin (DMJ), Castanospermine, and Swainsonine (Figure 1)] have been widely studied for their therapeutic potential.[1b]

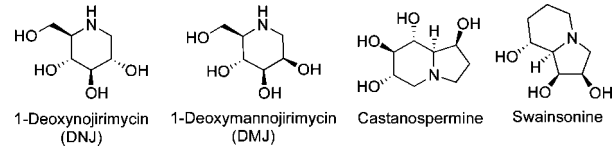


Figure 1. Imino-sugars widely studied for their therapeutic potential.

Five-membered imino-sugars are also known as hydroxypyrrolidines and include the α-galactosidase inhibitor 1,4-dideoxy-1,4-imino-D-lyxitol (**1**),[4] the mannosidase inhibitors 1,4-dideoxy-1,4-imino-D-mannitol (**2**)[5] and its 6-deoxy analogue (**3**),[6] 1,4-dideoxy-1,4-imino-D-xylitol (**4**),[7] and 1,4-

† Dedicated to Professor Brian Halton on the occasion of his 40th year at Victoria University of Wellington.

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dideoxy-1,4-imino-L-lyxitol (**5**)[8] (Figure 2). More elaborate members include Swainsonine[9] (Figure 1) (whose properties include the inhibition of both lysosomal α-mannosidase[10] and mannosidase II[11]), the antibiotic Anisomycin (**6**),[12] Broussonetinine A (**7**),[13] and the potent inhibitor of *β*-galactosidase and α-mannosidase, Gualamycin (**8**)[14] (Figure 2).

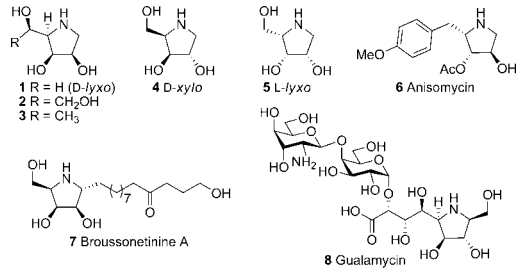
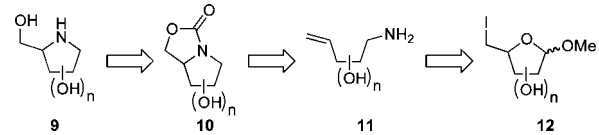


Figure 2. Compounds containing the 2,3-*cis*-disubstituted hydroxypyrrolidine core.

Many strategies for the synthesis of *cis*-2-substituted-3-hydroxypyrrolidines (such as **1**, **4**, and **5**) have been reported.[15,16] Though elegant and creative, many of these strategies are lengthy, some show poor diastereoselectivity, and all employ standard protecting group manipulations. The use of protecting groups has the disadvantage of requiring organic solvents for reaction, workup, and purification, which is environmentally deleterious. In addition, extensive protecting group manipulations lead to lengthy syntheses requiring both a protection and deprotection step per protecting group, resulting in reduced atom economy, and hence reaction efficiency. In view of this, we investigated a protecting-group free synthesis of polyhydroxylated pyrrolidine alkaloids.

It has previously been reported that cyclic carbamates can be prepared, in modest yield, from the reaction of acylic amines equipped with a halogen-leaving group and either tetraethylammonium bicarbonate[17] or sodium carbonate.[18] In view of this, we postulated that the imino-sugars **9** could be prepared via an iodine-promoted halocyclization/*in situ* carbonylation reaction to give carbamates **10**, which could be subsequently hydrolyzed (Scheme 1). The linear amino-

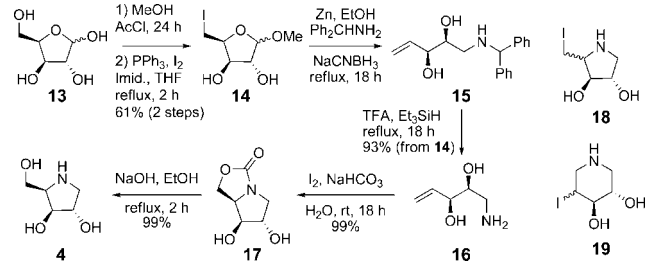
Scheme 1. Retrosynthesis for the Formation of Polyhydroxylated Pyrrolidines via Cyclic Carbamates



alcohols **11** are in turn accessible via reductive amination of hydroxyaldehydes, themselves obtained following Vasella reaction of methyl iodofuranosides **12**,[19] prepared in two steps from pentose monosaccharides. Thus, the chiral information embedded within the pentose carbohydrate precursors would be translated into the final products and, without the use of protecting groups, the complete synthesis will be amenable to chemistry in aqueous media.

The synthesis of the hydroxypyrrolidines starts with the conversion of D-xylose (**13**, Scheme 2) into its methyl

Scheme 2. Synthesis of *cis*-2,3-Disubstituted Hydroxypyrrolidines Using Novel Annulation Methodology



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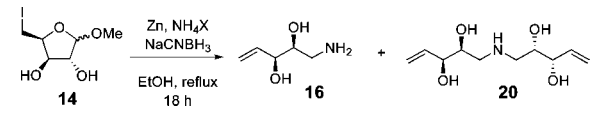
the methyl 5-iodofuranoside **14**.[20] Vasella reaction of iodoglycoside **14** with zinc in ethanol in the presence of catalytic acetic acid showed complete conversion of the starting material to a less mobile product, as gauged by TLC, but isolation of pure aldehyde proved problematic. In contrast, *in situ* imine formation using (diphenylmethyl)-amine and subsequent reduction with sodium cyanoborohydride led to the smooth formation of amine **15** in a three-step, one-pot procedure. Deprotection of crude amine **15**, using TFA and Et_3SiH, gave linear amine **16** as the TFA salt in 93% over the two steps. With the olefinic amine in hand, we set out to produce the pyrrolidine ring system via halocyclization. As anticipated, subjecting amine **16** to iodine and $NaHCO_3$ in water led to the formation of a single product with a mass of 160.0605 [M + H^+] and a carbonyl group, as evidenced by a carbonyl peak at 1680 cm^{-1} in the IR and δ164.4 in the ^{13}C NMR spectra. Extensive 2D NMR analysis (COSY, HMBC, HSQC) confirmed the compound to be cyclic carbamate **17** {[M + H^+] required:160.0604}, isolated as a single diastereoisomer in near quantitative yield.

The formation of the cyclic carbamate can be rationalized by the *in situ* reaction of the initial haloamine **18** in a tandem carbonylation reaction, similar to that described for addition of CO_2 to 1,2-hydroxyhalides.[21] In our case, the generated haloamine is believed to react with CO_2 formed *in situ*. Interestingly, sodium bicarbonate and iodine have been used in the halocyclization of preformed olefinic carbamates (methoxycarbonyl amides), but cyclization of these substrates led to mixtures of five- and six-membered cyclic amides.[22] The reactions were slow (two weeks) and poor yielding.[22] The halocyclization/ carbonylation reaction however, proceeds with complete diastereo- and regioselectively to give the five-membered *cis*-2,3-product exclusively. The *cis*-2,3-configuaration is in agreement with observations that iodine-promoted intramolecular cyclizations are often directed by the allylic hydroxyl to give preferentially the *cis*-product.[23] The stereochemistry of carbamate **17** was unequivocally proved by hydrolysis of the carbamate to form known D-*xylo* pyrrolidine **4**[16b] in excellent yield (99%). Interestingly, subjection of unprotected amine **16** to iodine in the presence of DBU did not lead to product, while prolonged reaction times or the use of a stronger base (NaOH) gave a complex mixture resembling both isomers of iodomethylpyrrolidine **18** and iodopiperidine **19** products, as previously observed.[24] Altering the source of iodine to *N*-iodosuccinimide (NIS), without $NaHCO_3$ as a base, gave a similar result. These observations demonstrate the critical importance of both $NaHCO_3$ and I_2 in this annulation.

Given the potential of this annulation methodology, we set out to develop a method to synthesize precursor olefinic amine **16** without any need for protecting groups. It is a well-known fact that the use of ammonia or ammonium salts in reductive amination reactions typically results in the formation of amine dimers (cf. **20**, Table 1) due to the lower nucleophilicity of ammonia compared to the primary amine product of the reductive amination. However, given that our initial experiments using ammonium chloride in the reductive amination lead to mixtures of monomer and dimer, we optimized the reaction conditions to achieve preferential formation of monomer **16** and present the results in Table 1.

Table 1. Vasella Reductive Aminations of Furan **14**



entry	conditions[a,b]	ratio **16:20**[c]	yield (**16**)[d]
1	$(NH_4)_2CO_3$ (10 equiv)	3:7	30%
2	NH_4Cl (10 equiv)	2:3	40%
3	NH_4HCO_3 (10 equiv)	2:3	40%
4	NH_4OAc (10 equiv)	2:3	40%
5	NH_4OAc (100 equiv)	1:1	50%
6	NH_4OAc (sat.)	3:2	60%
7	NH_4OAc (sat.), AcOH (10 equiv)	4.5:5.5	45%
8	NH_3 (30% solution in H_2O)	—	degradation
9	NH_3 (60 equiv), TFA (2 equiv)	5.5:4.5	55%
10	NH_3 (60 equiv), AcOH (7 equiv)	3:2	60%
11	NH_4OAc (sat.), NH_3 (10 equiv)	4:1	80%
12	NH_4OAc (sat.), NH_3 (60 equiv)	20:1	96% (95%)[e]

[a] All reactions were performed by the addition of activated Zn (5 equiv), amine (as indicated) and $NaCNBH_4$ (2 equiv) to a solution of the iodofuranoside in ethanol (20 mL/mmol). [b] NH_3 was added as a 30% solution in H_2O. [c] Ratios calculated from the integral values of the corresponding ^1H NMR signals (**16**:**20**). [d] Molar yields. [e] Isolated yield.

In optimizing the yield and selective formation of the monomer, our efforts first focused on the effects of the anion in the ammonium salt [NH_4Cl, $(NH_4)_2CO_3$, NH_4HCO_3 and NH_4OAc; Table 1, Entries 1−4]. With the exception of the less soluble carbonate, the addition of 10 equivalents of salt gave very similar results with monomer being formed in reasonable yield (40%), but mediocre selectivity (2:3, monomer:dimer, w/w). Next, taking advantage of the greater solubility of NH_4OAc in EtOH, we increased the concentration of NH_4OAc in an attempt to drive monomer formation. An increase from 10 to 100 equiv NH_4OAc proved beneficial with the monomer being formed in a 1:1 ratio (Entry 5). Increasing the ammonia concentration through use of a saturated solution of NH_4OAc in EtOH again showed a marked improvement in the formation of the monomer, both in yield (60%) and selectivity (3:2) (Entry 6).

The nucleophilicity of amination product **16** is higher than ammonia and causes the problems associated with the formation of dimer **20**. Likewise, amine **16** is more basic

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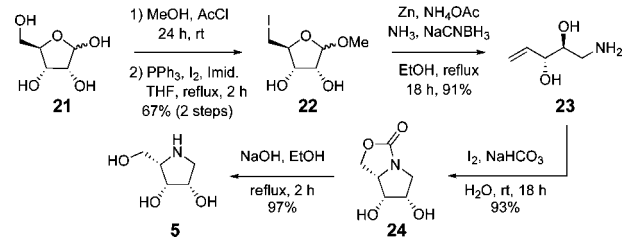
than ammonia. The correct balance between free and protonated ammonia was thought, therefore, to be critical in the optimization. To test this, a series of experiments were performed in which the ammonium salt to ammonia ratio was altered. First, the addition of AcOH to a saturated solution of NH_4OAc (Entry 7) led to a reduction in both yield and selectivity compared to NH_4OAc alone (cf. Entry 6); thus, a more basic reaction medium is needed. Use of 30% aqueous ammonia as the amine source with various concentrations of added acids were assessed. Without acid (Entry 8), degradation of starting material occurred and no product could be detected. The use of trifluoroacetic acid (TFA) or acetic acid (Entries 9 and 10) led to product formation, albeit without significant improvements in monomer yield. In contrast, adding ammonia (10 equiv) to a saturated NH_4OAc solution in EtOH provided a marked improvement in both selectivity and monomer yield (80%), (Entry 11). Further optimization via addition of 60 equiv of ammonia (Entry 12), resulted in almost exclusive formation of amine **16**, in excellent yield (95%).

Due to the absence of protecting groups and the associated water solubility of monomer **16**, removal of excess ammonium acetate was achieved only after adding HCl in isopropanol to the reaction mixture; the much less soluble NH_4Cl was removed by filtration through Celite. Following normal phase SiO_2 column chromatography, monomer **16** was isolated in 95% yield (as its HCl salt) and subsequently cyclized to carbamate **17**, again quantitatively. To the best of our knowledge, this provides the first efficient synthesis of a primary amine via reductive amination methodology without any need for functional group protection. The usefulness of this remarkably efficient transformation is ably demonstrated by the five-step synthesis of imino-sugar **4**, in 57% overall yield; this is the best reported to date. The reductive amination with tandem halocyclization/carbonylation reaction shows promise, as cyclic carbamates themselves exhibit interesting biological activities,[25] and are useful synthetic intermediates for a wide range of imino-sugars, including (−)-8-*epi*-swainsonine,[26] pyrrolizidine alkaloids such as (−)-7-epiaustraline, (−)-1,7-diepiaustraline,[27] and pyrrolam A.[28]

To illustrate the versatility of the protecting group-free synthesis of *cis*-2-substituted-3-hydroxypyrrolidines, we set out to synthesize 1,4-dideoxy-1,4-imino-L-lyxitol (**5**) (Scheme 3). D-Ribose (**21**) was converted into methyl iodoglycoside

Scheme 3. Synthesis of the *cis*-2,3-Disubstituted Hydroxypyrrolidine **5** from D-Ribose



22 (67%), following literature proceedures.[20] Again, Vasella reductive amination proceeded smoothly to the olefinic amine **23** (91%). Halocyclization/carbonylation using our iodine-promoted annulation methodology gave carabamate **24** in 93% yield, which was hydrolyzed (97%) to the *cis*-2,3-disubstituted 1,4-dideoxy-1,4-imino-L-lyxitol **5**, with data in full agreement with those published.[16b]

As illustrated, the entire synthetic route can be accomplished without need of group protection and with most reactions being performed in nontoxic solvents (EtOH or water). It is effected in a mere five steps, with an overall yield of 55%, again the highest yet reported.

Herein we have reported a novel, stereoselective, five-step strategy for the synthesis of *cis*-2,3-disubstituted hydroxypyrrolidines. This strategy is not merely competitive in yield and the number of linear-steps, but employs many of the principles of Green Chemistry. Few alternative total syntheses proceed without the need for functional group protection. Furthermore, we have identified two novel reaction methodologies: the first for the stereoselective formation of cyclic carbamates from olefinic amines, and the second, for the formation of primary amines without the need for protecting groups. Given the growing importance of environmentally benign chemistry, our two new synthetic methodologies are important additions to the Green Chemist's toolbox. We believe that both methodologies will find wide application in the synthesis of a range of imino-sugars. Further investigations into the scope and limitations of this annulation reaction are underway in our laboratories.

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

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