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An efficient, enantioselective synthesis of branched polyhydroxylated pyrrolidines†

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Abstract

The enantioselective synthesis of branched polyhydroxylated pyrrolidines from a novel α-methylene bicyclic lactam (**4b**) is described.

Polyhydroxylated pyrrolidines have generated a great deal of synthetic interest in the past decade due to their structural resemblance to the sugar moiety of monosaccharides.[1] Because of their ability to mimic carbohydrates, they function as potent inhibitors of glycosidases; enzymes that are involved in a wide range of important biological processes.[2] The discovery that these sugar mimetics display considerable activity against cancer,[3] diabetes,[1] and viral infections (anti-HIV behavior)[4] has led to an enhanced interest in them as potential therapeutic agents. Recently, the syntheses of novel polyhydroxylated piperidines, **1**, and pyrrolidines, (+)-**2**, containing branched skeletons[5] (Scheme 1) have been reported in an attempt to develop more selective and potent glycosidase inhibitors. Due to our previous success in preparing azasugars from bicyclic lactams[6] and our continued effort in expanding the versatility of this chiral molecule, we anticipated that the synthesis of branched polyhydroxylated pyrrolidines, **2**, could be achieved in high enantiomeric purity from an appropriately functionalized 5,5-bicyclic lactam (**4b**).

It was envisioned that bicyclic lactam **4b**, possessing an α-methylene substituent, could be accessed from the known lactam **3b**.[6] The olefin, **4b**, would be subjected to dihydroxylation conditions to afford diol **5b**—hopefully with some degree of *exo–endo* selectivity. Reductive cleavage of **5b**, after diol protection, would complete an efficient synthesis of pyrrolidine **6**. The latter could be further elaborated to azasugars such as **2**, with the option of placing a variety of substituents (R^2) on the nitrogen atom.

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† This paper is dedicated with respect and admiration to Professor Harry Wasserman on his 80th birthday.

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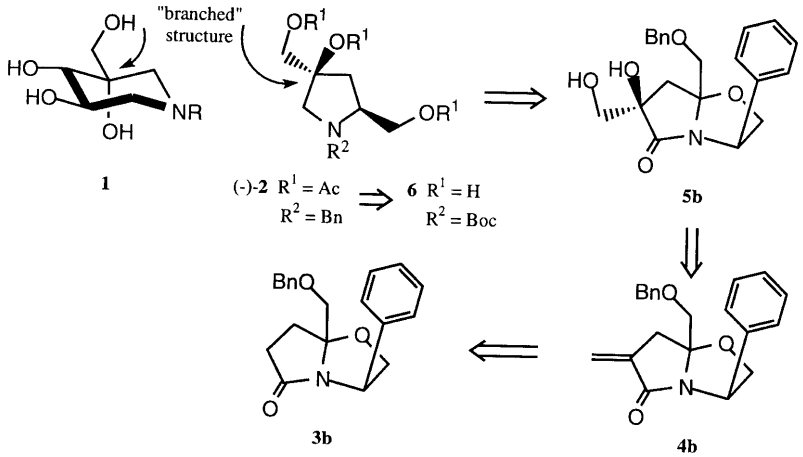
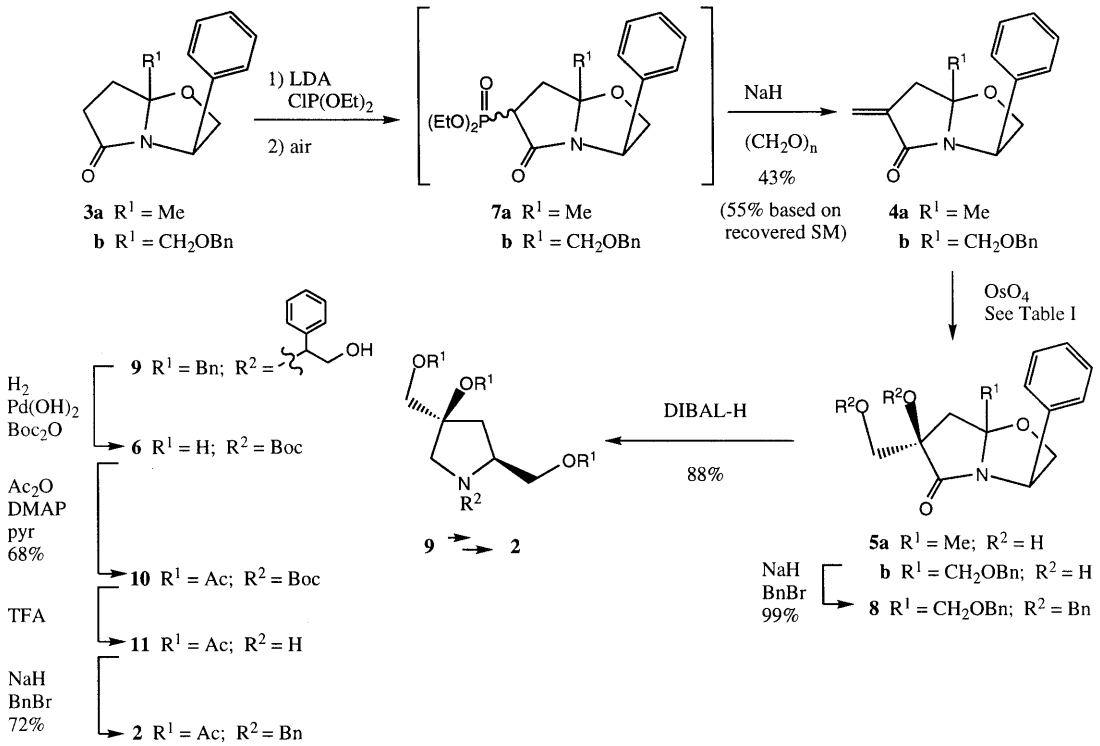


Scheme 1.

The route to **2** and **6** began with the preparation of known bicyclic lactam **3b**[6] from 2,3-dihydrofuran in 47% yield over three steps. Readily available lactam **3a**,[7] containing an angular methyl substituent, was also prepared and employed as a model. Attention was then turned toward the introduction of the α-methylene substituent. Although a variety of methods to prepare α-methylene lactones are known,[8] all attempts to use these met with failure or limited success. Diez and co-workers[9] reported similar difficulties in preparing chiral α-methylene 2-piperidones. In an effort to avoid these problems, the enolate anions of both lactams **3a** and **3b** were treated with diethyl phosphorochloridite[10] followed by immediate air oxidation of the resultant reaction products (Scheme 2). In both cases (lactams **7a** and **7b**), the ^{31}P NMR spectra of the crude reaction mixtures revealed a 2.5:1 ratio of C–P to O–P bond formation products—the C–P products being a mixture of *exo–endo* diastereomers (3:1). This crude mixture was treated with NaH followed by paraformaldehyde to provide a 43% yield (55% yield based on recovered starting material) of the desired α-methylene bicyclic lactams **4a** and **4b** over the two steps.

Initial experiments to introduce vicinal hydroxyls were performed on lactam **4a**, which was treated with OsO_4–NMO to furnish a disappointing 3:1 (NMR) mixture of diastereomers (Table 1). In order to increase the selectivity of the dihydroxylation, quinuclidine was added as a ligand since it was anticipated that the ligand–OsO_4 complex[11] would provide increased facial selectivity due to its greater steric bulk as compared to OsO_4 alone. The selectivity did increase, providing a 7:1 mixture of diastereomers at the newly formed tertiary alcohol center (diol **5a**). Attention was now turned to bicyclic lactam **4b**. Treatment of **4b** with OsO_4–quinuclidine, however, gave a poor mixture of diastereomers (3:1) as compared to the model system (7:1). This result suggested that the dihydroxylation might be occurring preferentially from the *exo*-face; the decrease in *exo*-facial selectivity with lactam **4b** perhaps arising from the larger angular benzyloxymethyl substituent shielding the β-face of the lactam. It was felt that the addition of a ligand bulkier than quinuclidine might improve the facial selectivity of the dihydroxylation. Lactam **4b** was subsequently treated with AD-mix-α and AD-mix-β, respectively[11] providing a greater than 15:1 (NMR) mixture of diastereomers. It is interesting to note that in the reactions using either AD-mix-α or AD-mix-β, the same ratio of diastereomers was observed (15:1) with the same sense of stereochemistry. This strongly suggests that the



Scheme 2.

Table 1

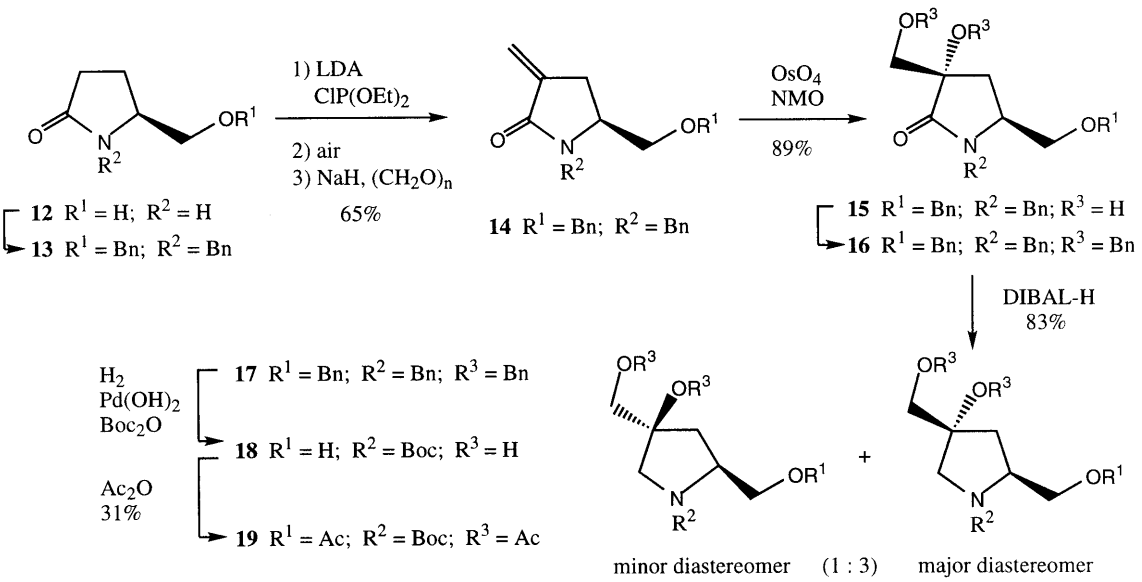
Lactam	Ligand	de	Yield (%)
4a	–	3:1	89
4a	Quinuclidine	7:1	96
4b	Quinuclidine	3:1	93
4b	AD-mix-α	15:1	98
4b	AD-mix-β	15:1	100

increase in the observed facial selectivity is not due to the chirality of these ligands, but is due solely to their steric bulk. The stereochemistry of the dihydroxylation products **5**, were tentatively assigned, at this point, as taking place from the *exo*-face.

The two hydroxyl groups were transformed to their benzyl ethers, **8**, and the C–O cleavage step was next addressed to prepare pyrrolidine **9**. From earlier results in our laboratory,[12] it was anticipated that this reaction would proceed with retention of configuration of the angular substituent. Thus, treatment of **8** with DIBAL-H furnished an 88% yield of pyrrolidine **9**; the reductive cleavage of the ring C–O bond occurring with very high diastereoselectivity (no trace of C-2 diastereomers being observed). The 15:1 mixture of diastereomers obtained from the dihydroxylation could also be separated by column chromatography at this point, providing compound **9** as a single diastereomer. The stereochemistry at C-2 was tentatively assigned as

having occurred with retention of configuration. Catalytic hydrogenation (H_2, 4 atm, $Pd(OH)_2$) in the presence of Boc_2O afforded branched pyrrolidine **6**, which was immediately acetylated to provide **10** in 68% yield. It is interesting to note that if Boc_2O is not added to the hydrogenation, only *N*-benzyl deprotection is observed and the *O*-benzyl groups remain intact.[13] Pyrrolidine **10** provides a convenient entry into branched pyrrolidines, because by simply treating **10** with TFA in CH_2Cl_2, the Boc protecting group can be removed (pyrrolidine **11**), leaving the nitrogen free to react with any number of electrophiles. The ease at which **10** is transformed into *N*-benzylated pyrrolidine **2** illustrates the usefulness of this intermediate.

With an efficient, enantioselective synthesis of pyrrolidine **10** in hand (ten steps from 2,3-dihydrofuran, 12% overall yield), it was necessary to confirm the absolute configuration. Commercially available (*S*)-(+)-5-(hydroxymethyl)-2-pyrrolidinone **12** was dibenzylated to afford pyrrolidinone **13** in 80% yield (Scheme 3). The latter was olefinated [LDA/$(EtO)_2PCl$, air, NaH/$(CH_2O)_n$) to the α-methylene lactam **14** in 65% yield. Dihydroxylation of **14** employing OsO_4–NMO gave a 2.5:1 (NMR) mixture of diastereomers (diol **15**). Similar results were obtained using quinuclidine. Surprisingly, addition of AD-mix-α or AD-mix-β decreases the diastereoselectivity, affording a 1:1 ratio of diastereomers. It was assumed that the major product in the OsO_4–NMO dihydroxylation arose from α-facial selectivity; the *trans* product being favored due to shielding of the β-face by the benzyloxymethyl C-5 substituent. Dibenzylation of the diol moiety followed by a DIBAL-H reduction furnished the tetrabenzyl pyrrolidine **17** in high yield. Hydrogenolyses of the *N*-benzyl and *O*-benzyl groups in the presence of Boc_2O afforded **18**, which was immediately acetylated to provide pyrrolidine **19** as a 3:1 mixture of diastereomers. When the ^1H NMR spectrum of pyrrolidine **19** was compared to the ^1H NMR spectrum of pyrrolidine **10** prepared via the bicyclic lactam route, it became apparent that the minor diastereomer of **19** was identical to **10**. With the absolute configuration of **19** known, this sequence proved the relative stereochemistry of **10**, with the acetoxymethyl substituents lying *anti* to each other. Since (+)-**2** had previously been prepared in the literature,[5b] to confirm the absolute configuration of **10**, it only became necessary to determine the stereochemistry of **2** prepared from **10** above ($[\alpha]_D$ lit.=



Scheme 3.

+30.0,[14] $[\alpha]_D$ of **2** = −44.2). The negative optical rotation observed for **2** proved that the stereochemical assignment was correct, with the dihydroxylation proceeding from the *exo*-face and the C–O ring reduction occurring with retention of configuration to afford (−)-**2**.

In conclusion, an efficient, enantioselective route to branched, *N*-substituted pyrrolidines has been accomplished using chiral bicyclic lactams. A convenient entry into branched pyrrolidines is now available using intermediate **10**, which may be elaborated in a variety of ways.

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14. The $[\alpha]_D$ value of our sample, −44.2, does not compare well to the literature value, +30.0, because their compound was contaminated with trace amounts of another undetermined isomer—see Ref. 5b.