

# Diastereoselective iodoamidation of 3-acetyloxybut-1-enylamines: simple synthesis of a precursor of aza sugars involving a pyrrolidine ring

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**3-Acetyloxybut-1-enylamines 3–9 were easily transformed using iodine to pyrrolidine derivatives 3a–9a, precursors for aza sugars, via a diastereoselective iodoamidation.**

Since the discovery that polyhydroxylated pyrrolidines are potent glycosidase inhibitors with potential therapeutic utility in the treatment of various diseases such as diabetes,<sup>1</sup> cancer<sup>2</sup> and viral infections,<sup>3</sup> much attention has been concentrated on the development of convenient and efficient routes to these compounds. In general, synthetic routes to aza sugars require azide displacement/reduction and intramolecular N-alkylative cyclisation with protecting group manipulation,<sup>4</sup> starting from carbohydrates or non-carbohydrates. Here we report the highly diastereoselective iodoamidation of 3-acetyloxybut-1-enylamines **1** for the preparation of pyrrolidine derivatives **2** (e.g. anisomycine,<sup>5</sup> 3,4-dihydroxyprolinol,<sup>6</sup> swainsonine<sup>7</sup> and lenti-ginosine<sup>8</sup>) (Scheme 1).

The requisite substrates **3–9** were prepared easily by the usual method from commercially available L-tyrosin, L-phenylalanine and L-serine.<sup>9†</sup> Fortunately, each diastereomeric allylic alcohol given by the Grignard reaction could be isolated in pure form by column chromatography. We chose the 9-phenylfluoren-9-yl (Pf) group for protection of the amine since this protecting group has been shown to inhibit deprotonation at the  $\alpha$ -position of  $\alpha$ -amino aldehydes.<sup>10</sup>  $\alpha$ -Amino aldehydes having the Pf group are very stable to Grignard reaction conditions.<sup>11</sup>

Compound **3** was treated with I<sub>2</sub> under biphasic conditions (aq. NaHCO<sub>3</sub>–THF–Et<sub>2</sub>O = 2 : 1 : 1) at room temperature for 3 h to give the all *trans* pyrrolidine **3a** (*vide infra*) as the sole product in high yield *via* a diastereoselective iodoamidation. Although THF, MeOH, CH<sub>2</sub>Cl<sub>2</sub> and MeCN have been found to be acceptable solvents for iodoamidation, these solvents required much longer reaction times and resulted in 35–50% recovery of the starting material. As shown in Table 1, the optimum reaction conditions involved biphasic conditions to improve reactivity and affording pyrrolidine **3a**.

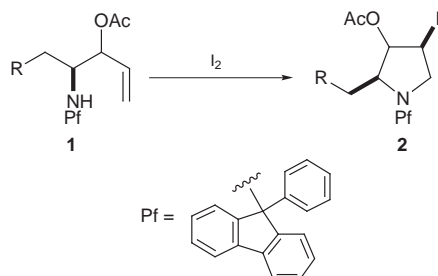
Treatment of **4** under the same conditions afforded a 25 : 1 ratio of the *cis* and *trans* isomers of pyrrolidine **4a**. Compounds **5** and **6** were cyclized according to these standard conditions to give the expected the corresponding pyrrolidines *trans*-**5a** and *cis*-**6a** in high yield, respectively. Compound **7** was also exposed to the same reaction conditions to give *cis*-**7a** in a ratio of 20 : 1 in 66% yield. In the case of starting materials *trans*-**8** and *cis*-**9**,<sup>‡</sup> this solvent mixture was not suitable. Thus,

compounds **8** and **9** were treated with I<sub>2</sub> in THF to give the corresponding *trans*-**8a** and *cis*-**9a** in 92% (based on 65% conversion) and 88% (based on 80% conversion) yields, respectively (Table 2). The structures of all pyrrolidines **3a–9a** were confirmed by their characteristic spectroscopic data.<sup>§</sup>

The relative stereochemistries of the products **3a** and **4a** were determined from their <sup>1</sup>H NMR spectra based on the coupling constant values and 2D NOE experiments. For *trans*-**3a**, proton H<sub>3</sub> (t like,  $J_{2,3}, J_{3,4} = 5.1$  Hz) adjacent to the acetyloxy group gave weak correlation with protons (H<sub>2</sub> and H<sub>4</sub>) adjacent to the *p*-tolylmethyl and iodine groups, but strong NOE cross peaks were observed between H<sub>2</sub>–H<sub>4</sub> and H<sub>2</sub>–H<sub>5b</sub>, thereby allowing one to assign its relative stereochemistry. In pyrrolidine *cis*-**4a**, proton H<sub>3</sub> (t like,  $J_{2,3}, J_{3,4} = 6.9$  Hz) adjacent to the acetyloxy group displayed strong mutual correlation with the protons (H<sub>2</sub> and H<sub>4</sub>) adjacent to the *p*-tolylmethyl and iodine groups, thereby verifying the structure of *cis*-**4a** as shown in Fig. 1.

Based on the coupling constant values in the high-field <sup>1</sup>H NMR spectra of *trans*-**3a** and *cis*-**4a**, the stereochemistries of *trans*-**5a** (H<sub>3</sub>, t like,  $J_{2,3}, J_{3,4} = 5.1$  Hz) and *cis*-**6a** (H<sub>3</sub>, t like,  $J_{2,3}, J_{3,4} = 6.9$  Hz) could be determined from each coupling constant value. The stereochemistries of *trans*-**8a** (H<sub>3</sub>, dd,  $J_{2,3} = 4.8, J_{3,4} = 3.4$  Hz) and *cis*-**9a** (H<sub>3</sub>, dd,  $J_{2,3} = 2.4, J_{3,4} = 4.2$  Hz) were also confirmed using coupling constant values.

Although numerous construction methods for the electrophilic cyclisation have been developed,<sup>12</sup> the closest literature precedent to this haloamidation has been independently studied by the groups of Takahata<sup>13</sup> and Yoshida.<sup>14</sup> Takahata has shown that iodine-induced lactamization of  $\gamma,\delta$ -unsaturated thioimides proceeds regioselectively to provide  $\gamma$ -lactams. Yoshida has reported that *N*-(*p*-tolylsulfonyl)pent-4-enylamines were subjected to stereoselective haloamidation to afford mainly *cis* substituted pyrrolidines. Although these methodologies have been proven to be useful protocols, they are of limited use for the direct synthesis of polyhydroxylated aza sugars because these reactions proceed *via* 5-*exo-trig* cyclisation. Thus, we are the first to observe chiral induction on the pyrrolidine ring through an diastereoselective iodoamidation and to succeed in



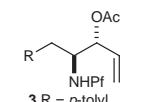
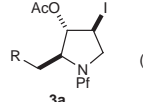
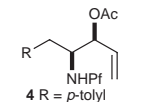
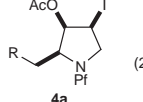
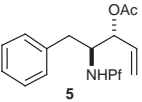
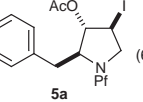
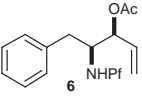
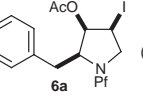
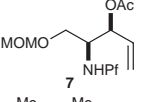
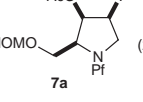
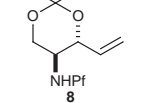
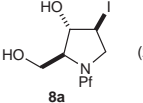
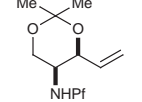
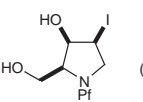
Scheme 1

Table 1 Solvent effects in stereoselective iodoamidation<sup>a</sup>

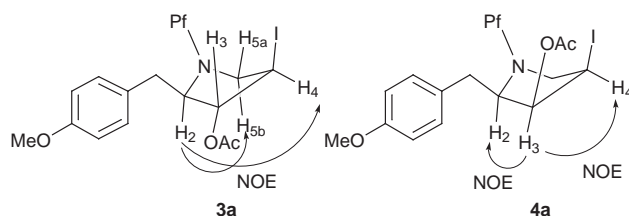
Solvent	I <sub>2</sub> /equiv.	t/h	Yield (%) <sup>b</sup>
THF	3.0	15	48 <sup>c</sup>
MeOH	3.0	18	45 <sup>d</sup>
CH <sub>2</sub> Cl <sub>2</sub>	3.0	6	50 <sup>e</sup>
MeCN	3.0	6	60 <sup>f</sup>
Biphase <sup>g</sup>	3.0	3	92

<sup>a</sup> All reactions were carried out under room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> 48% Recovery of starting material. <sup>d</sup> 40% Recovery of starting material. <sup>e</sup> 50% Recovery of starting material. <sup>f</sup> 35% Recovery of starting material. <sup>g</sup> NaHCO<sub>3</sub>–THF–Et<sub>2</sub>O = 2 : 1 : 1.

**Table 2** Diastereoselective iodoamidation of 3-acetoxybut-1-enylamines with iodine

Substrates <sup>a</sup>	Conditions	Products <sup>b</sup>	Yield <sup>c</sup>
	I <sub>2</sub> , biphase, <sup>d</sup> room temp. 3 h		92% (sole)
	I <sub>2</sub> , biphase, room temp. 3.5 h		90% (25 : 1)
	I <sub>2</sub> , biphase, room temp. 3 h		90% (62 : 1)
	I <sub>2</sub> , biphase, room temp. 3 h		90% (5 : 1)
	I <sub>2</sub> , biphase, room temp. 10 h		66% (21 : 1)
	I <sub>2</sub> , THF, room temp. 10 h		92% <sup>e</sup> (20 : 1)
	I <sub>2</sub> , THF, room temp. 10 h		88% <sup>f</sup> (sole)

<sup>a</sup> All allylic alcohols are enantiomeric pure. <sup>b</sup> The stereochemistry was signed by <sup>1</sup>H NMR and 2D NOE experiments. <sup>c</sup> Isolated yields. <sup>d</sup> 3 equiv. of I<sub>2</sub>, aq. NaHCO<sub>3</sub>-THF-Et<sub>2</sub>O = 2 : 1 : 1. <sup>e</sup> Based on 65% conversion of starting material and 35% cleavage of the isopropylidene group of **8**. <sup>f</sup> Based on 80% conversion of starting material and 20% cleavage of the isopropylidene group of **9**.



**Fig. 1** NOE interactions derived from NOESY experiments.

using a strong electron-donating group, 9-phenylfluoren-9-yl (Pf), on an amine moiety.

In conclusion, we found that optically active starting materials **1** as chiral building blocks are converted easily to pyrrolidine derivatives **2** via a diastereoselective iodoamidation. These species should be valuable for the total synthesis of polyhydroxylated aza sugars having a pyrrolidine ring and may be suitable for substitution with various nucleophiles (NaN<sub>3</sub>, amines, alcohols, thiols and Grignard compounds), giving novel aza sugar derivatives. Thus, we are currently investigating the preparation of all six diastereomers of anisomycin and other 3,4-dihydroxyprolinols.

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## Notes and references

† Starting materials **3–9** were prepared by a sequential reaction, namely, free amino acids were treated with TMSCl in MeOH to give methyl esters, the amino groups of which were protected with PBr in CH<sub>2</sub>Cl<sub>2</sub>. The methyl esters were then subjected to reduction and Swern oxidation to afford aldehydes, which were reacted with vinylmagnesium bromide to give separable allylic alcohols.

‡ The relative stereochemistries of the corresponding acetonides *trans*-**8** ( $J = 8.1$  Hz for the proton on oxygen) and *cis*-**9** ( $J = 1.0$  Hz for the a proton on oxygen) were confirmed by coupling constant analysis.

§ Selected data for **3a**: colorless prisms, mp 67–68 °C;  $[\alpha]_D^{22} +33.0$  ( $c$  1.3, CHCl<sub>3</sub>);  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 1.61 (3H, s), 2.37 (1H, dd,  $J$  4.0, 13.6), 2.44 (1H, dd,  $J$  6.7, 10.1), 2.67 (1H, dd,  $J$  9.7, 13.6), 2.73 (1H, m), 3.00 (1H, dd,  $J$  2.7, 10.2), 3.28 (1H, dt,  $J$  4.3, 5.1), 3.71 (3H, s), 4.56 (1H, t-like,  $J_{2,3}$ ,  $J_{3,4}$  5.1), 6.72 (2H, d,  $J$  8.7), 6.89 (2H, d,  $J$  8.7), 7.23–7.34 (13H, m). For **4a**: colorless prisms, mp 70–71 °C;  $[\alpha]_D^{20} -22.9$  ( $c$  1.2, CHCl<sub>3</sub>);  $\delta_H$  (500 MHz, CDCl<sub>3</sub>): 2.08 (3H, s), 2.19 (1H, dd,  $J$  3.4, 14.1), 2.65 (1H, dd,  $J$  3.7, 9.2), 2.86 (1H, dd,  $J$  10.9, 14.1), 3.17 (1H, dd,  $J$  9.2, 11.2), 3.43 (1H, ddd,  $J$  3.5, 7.2, 10.8), 3.55 (1H, ddd,  $J$  3.7, 7.2, 8.1), 5.17 (1H, t-like,  $J_{2,3}$ ,  $J_{3,4}$  6.9), 6.65 (2H, d,  $J$  8.7), 6.87 (2H, d,  $J$  8.7), 7.24–7.75 (13H, m).

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