ChemComm

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

Woo Song Lee, Ki Chang Jang, Jin Hyo Kim and Ki Hun Park*

Department of Agricultural Chemistry, Gyeongsang National University, Chinju 660-701, Korea.
E-mail: khpark@gshp.gsnu.ac.kr

Received (in Cambridge, UK) 20th November 1998, Accepted 23rd December 1998

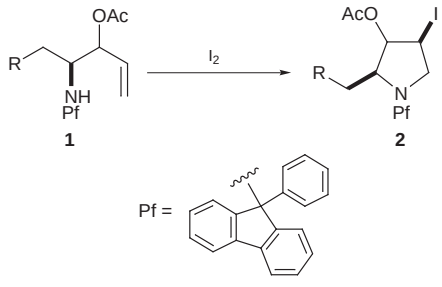
3-Acetyloxybut-1-enylamines 3–9 were easily transformed using iodine to pyrrolidine derivatives 3a–9a, precursors for aza sugars, *via* a diastereoselective iodoamidation.

Since the discovery that polyhydroxylated pyrrolidines are potent glycosidase inhibitors with potential therapeutic utility in the treatment of various diseases such as diabetes,[1] cancer[2] and viral infections,[3] 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,[4] starting from carbohydrates or non-carbohydrates. Here we report the highly diastereoselective iodoamidation of 3-acetlyoxybut-1-enylamines **1** for the preparation of pyrrolidine derivatives **2** (*e.g.* anisomycine,[5] 3,4-dihydroxyprolinol,[6] swainsonine[7] and lentiginosine[8]) (Scheme 1).

The requisite substrates **3**–**9** were prepared easily by the usual method from commercially available L-tyrosin, L-phenylalanine and L-serine.[9]† 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 α-position of α-amino aldehydes.[10] α-Amino aldehydes having the Pf group are very stable to Grignard reaction conditions.[11]

Compound **3** was treated with I_2 under biphasic conditions (aq. $NaHCO_3$–THF–Et_2O = 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_2Cl_2 and MeCN have been found to be acceptable solvents for iodoamidation, these solvents required much longer reaction times and resuted 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**,‡ this solvent mixture was not suitable. Thus, compounds **8** and **9** were treated with I_2 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.§



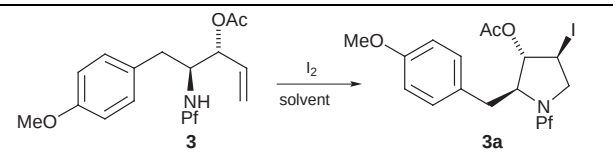
Scheme 1

The relative stereochemistries of the products **3a** and **4a** were determined from their ^{1}H NMR spectra based on the coupling constant values and 2D NOE experiments. For *trans*-**3a**, proton H_3 (t like, $J_{2,3}$, $J_{3,4}$ = 5.1 Hz) adjacent to the acetyloxy group gave weak correlation with protons (H_2 and H_4) adjacent to the *p*-tolylmethyl and iodine groups, but strong NOE cross peaks were observed between H_2–H_4 and H_2–H_{5b}, thereby allowing one to assign its relative stereochemistry. In pyrrolidine *cis*-**4a**, proton H_3 (t like, $J_{2,3}$, $J_{3,4}$ = 6.9 Hz) adjacent to the acetyloxy group displayed strong mutual correlation with the protons (H_2 and H_4) 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 ^{1}H NMR spectra of *trans*-**3a** and *cis*-**4a**, the stereochemistries of *trans*-**5a** (H_3, t like, $J_{2,3}$, $J_{3,4}$ = 5.1 Hz) and *cis* **6a** (H3, t like, $J_{2,3}$, $J_{3,4}$ = 6.9 Hz) could be determined from each coupling constant value. The stereochemistries of *trans*-**8a** (H3, dd, $J_{2,3}$ = 4.8, $J_{3,4}$ = 3.4 Hz) and *cis* **9a** (H3, 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,[12] the closest literature precedent to this haloamidation has been independently studied by the groups of Takahata[13] and Yoshida.[14] Takahata has shown that iodine-induced lactamization of γ,δ-unsaturated thioimidates proceeds regioselectively to provide γ-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

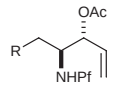
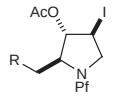
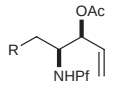
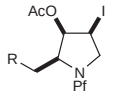
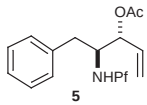
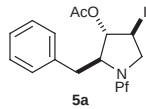
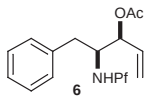
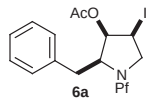
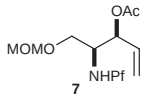
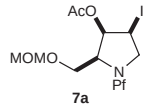
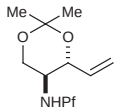
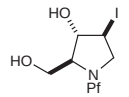
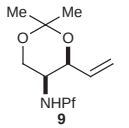
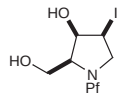
Table 1 Solvent effects in stereoselective iodoamidation[a]



Solvent	I_2/equiv.	*t*/h	Yield (%)[b]
THF	3.0	15	48[c]
MeOH	3.0	18	45[d]
CH_2Cl_2	3.0	6	50[e]
MeCN	3.0	6	60[f]
Biphase[g]	3.0	3	92

[a] All reactions were carried out under room temperature. [b] Isolated yield. [c] 48% Recovery of starting material. [d] 40% Recovery of starting material. [e] *50% Recovery of starting material.* [f] 35% Recovery of starting material. [g] $NaHCO_3$–THF–Et_2O = 2 : 1 : 1.

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

Substrates[a]	Conditions	Products[b]	Yield[c]
 **3** R = *p*-tolyl	I_2,biphase,[d] room temp. 3 h	 **3a**	92% (sole)
 **4** R = *p*-tolyl	I_2,biphase, room temp. 3.5 h	 **4a**	90% (25 : 1)
 **5**	I_2,biphase, room temp. 3 h	 **5a**	90% (62 : 1)
 **6**	I_2,biphase, room temp. 3 h	 **6a**	90% (5 : 1)
 **7**	I_2,biphase, room temp. 10 h	 **7a**	66% (21 : 1)
 **8**	I_2,THF, room temp. 10 h	 **8a**	92%[e] (20 : 1)
 **9**	I_2,THF, room temp. 10 h	 **9a**	88%[f] (sole)

[a] All allylic alcohols are enantiomeric pure. [b] The stereochemistry was signed by ^{1}H NMR and 2D NOE experiments. [c] Isolated yields. [d] 3 equiv. of I_2, aq. $NaHCO_3$–THF–Et_2O = 2 : 1 : 1. [e] Based on 65% conversion of starting material and 35% cleavage of the isopropylidene group of **8**. [f] Based on 80% conversion of starting material and 20% cleavage of the isopropylidene group of **9**.

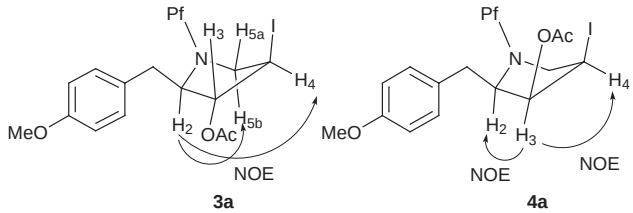


Fig. 1 NOE interactions derived from NOESY experiments.

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_3, amines, alcohols, thiols and Grignard compounds), giving novel aza sugar derivatives. Thus, we are currently investigating the preparation of all six diasteromers of anisomycin and other 3,4-dihydroxyprolinols.

This work was supported by a grant from the High-technology Development Project for Agriculture, Forestry and Fisheries. We thank the Korea Science and Engineering Foundation for a fellowship supporting the Postdoctoral research of Dr Woo Song Lee.

Notes and references

† Starting materials **3**–**9** were prepared by a sequential reaction, namely, free animo acids were treated with TMSCl in MeOH to give methyl esters, the amino groups of which were protected with PfBr in CH_2Cl_2. 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, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 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, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 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).

1 S. Horri, H. Fukase, T. Matsuo, Y. Kameda, N. Asano and K. Matsui, *J. Med. Chem*., 1986, **29**, 1038.
2 M. A. Spearman, J. C. Jamieson and J. A. Wright, *Exp. Cell Res*., 1987, **168**, 116; K. Tsukamoto, A. Uno, S. Shimada and G. Imokaw, *Clin. Res*., 1989, **37A**, 722.
3 A. Karpas, G. W. J. Fleet, R. A. Dwek, S. Petursson, S. K. Mamgoong, N. G. Ramsden, G. S. Jacob and T. W. Rademacher, *Proc. Natl. Acad. Sci. U.S.A.*, 1988, **85**, 9229; G. W. J. Fleet, *FEBS Lett*., 1988, **237**, 128.
4 G. Kinast and M. Schedel, *Angew. Chem. Int. Ed. Engl*., 1981, **20**, 805; A. Vasella and R. Voeffray, *Helv. Chim. Acta*, 1982, **65**, 1134; H. Iida, N. Yamazaki and C. Kibayashi, *J. Org. Chem*., 1987, **52**, 3337; D. Beaupere, B. Stasik, R. Uzan and G. Demailly, *Carbohydr. Res*., 1989, **191**, 163; C. H. von der Osten, A. J. Sinskey, C. F. Barbas, R. L. Pederson, Y.-F. Wang and C.-H. Wong, *J. Am. Chem. Soc*., 1989, **111**, 3924; G. W. J. Fleet, N. M. Carpenter, S. Petursson and N. J. Ramsden, *Tetrahedron Lett*., 1990, **31**, 409; A. Straub, F. Effenberger and P. Fischer, *J. Org. Chem*., 1990, **55**, 3926.
5 D. P. Schumacher and S. S. Hall, *J. Am. Chem. Soc*., 1982, **104**, 6076; H. H. Baer and M. Zamkanei, *J. Org. Chem*., 1988, **53**, 4786; R. Ballini, E. Marcantoni and M. Petrini, *J. Org. Chem*., 1992, **57**, 1316.
6 G. W. J. Fleet, S. J. Nicolas, P. W. Smith, S. V. Evans, L. E. Fellows and R. J. Nash, *Tetrahedron Lett*., 1985, **26**, 3127; N. Asano, K. Oseki and K. Matsui, *J. Med. Chem*., 1994, **37**, 3710.
7 H. Setoi, H. Takeno and M. Hashimoto, *J. Org. Chem*., 1985, **50**, 3948; R. B. B. III, J.-R. Choi, W. D. Montgomery and J. K. Cha, *J. Am. Chem. Soc*., 1989, **111**, 2580.
8 S. Nukui, M. Sodeoka, H. Sasaki and Shibasaki, *J. Org. Chem*., 1995, **60**, 398.
9 F. J. Sardina and H. Rapoport, *Chem. Rev*., 1996, **96**, 1825.
10 W. D. Lubell and H. Rapoport, *J. Am. Chem. Soc*., 1987, **109**, 236.
11 M. Gerspacher and H. Rapoport, *J. Org. Chem*., 1991. **56**, 3700.
12 S. Robin and G. Rousseau, *Tetrahedron*, 1998, **54**, 13681.
13 H. Takahata, T. Tamotsu and Y. Takao, *J. Org. Chem*., 1989, **54**, 4812; H. Takahata, K. Yamazaki, T. Takamatsu, T. Yamazaki and T. Momose, *J. Org. Chem*., 1990, **55**, 3947.
14 Y. Tamaru, S. Kawamura, K. Tanaka and Z. Yoshida, *Tetrahedron Lett*., 1984, **25**, 1063; Y. Tamaru, S.-i. Kawamura, T. Bando, K. Tanaka, M. Hojo and Z.-i. Yoshida, *J. Org. Chem*., 1988, **53**, 5491.

Communication 8/09083A