Preparation of Chiral, *C*-Protected α-Amino Aldehydes of High Optical Purity and Their Use as Condensation Components in a Linear Synthesis Strategy

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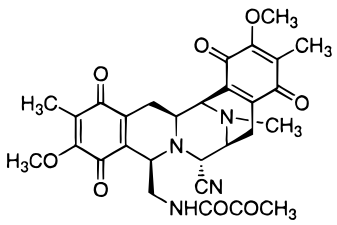
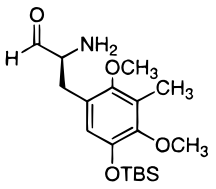
In connection with our interest in the development of an enantioselective synthetic route to the saframycin antibiotics,[1] we were led to consider the viability of chiral α-amino aldehydes as synthetic intermediates and their use as condensation components in a directed, linear assembly process. In this context, condensation refers to any transformation that involves imine formation as an initial step, such as the Strecker synthesis of α-amino nitriles, the Pictet−Spengler cyclization (forming a tetrahydroisoquinoline), or reductive amination reactions. The issue of protection of the amine and aldehyde groups arises naturally in the context of the proposed directed, linear assembly strategy, as it does in the synthesis of peptides from α-amino acids. There were several concerns attending the execution of the proposed strategy. A problem shared with peptide synthesis is the issue of epimerization of the α-center, both pre- and post-coupling. In the case at hand, this issue was of particular concern given the greater propensity of aldehydes to enolize versus carboxylic acids. And, while *N*-protected α-amino aldehydes are widely used synthetic building blocks,[2] their counterparts in this strategy, "*C*-protected α-amino aldehydes", in which the amino group is free and the aldehyde is protected (at the aldehyde level of oxidation), have been much less explored.[3] In this work we have developed a novel series of *C*-protective groups for α-amino aldehydes that is based upon the amino nitrile function,[4] a development that was inspired by consideration of the saframycin A structure. This series displays a greatly expanded range of lability of the aldehyde protective group compared to existing acetal-based protective groups.[3] We show that these *C*-protected α-amino aldehyde components can be prepared with high enantiomeric enrichment and can be coupled with *N*-protected α-amino aldehydes in directed condensation reactions and maintain a high degree of optical purity in the process.

We initiated our studies with the complex α-amino aldehyde **1**, which was imagined to be a synthetic precursor to saframycin



(−)-saframycin A



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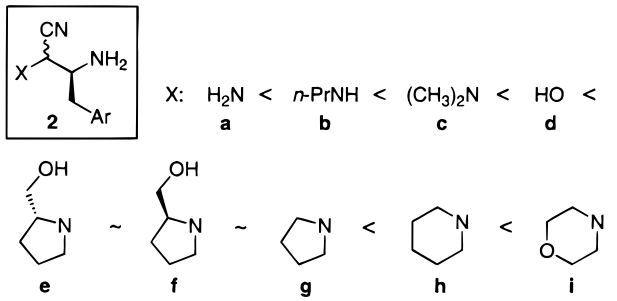
A. *N*-Cbz, *N*-Fmoc, and *N*-trifluoroacetyl derivatives of **1** were prepared in gram quantities and up to 96% ee by the diastereoselective alkylation of pseudoephedrine glycinamide hydrate,[5] amide reduction with LAB,[6] *N*-protection, and oxidation.[7] These products were then used to prepare *C*-protected derivatives of **1**. For example, treatment of *N*-Fmoc-**1** (96% ee) with hydrogen cyanide followed by cleavage of the Fmoc group afforded the corresponding cyanohydrins (**2d**) in 88% yield and 96% ee.[7] That compounds **2d** are formed without epimerization of the α-center and that they are sustainable both in solution and in neat form are noteworthy findings. Self-condensation occurs only slowly in protic media (e.g., >1 d, 0.04 M in methanol),[8] is much slower in aprotic solvents, and does not occur to a detectable extent in neat form. Sequential treatment of *N*-Fmoc-**1** with hydrogen cyanide and morpholine followed by cleavage of the Fmoc group afforded morpholino nitriles **2i** in 86% yield.[7] The diastereomers **2i** were readily separated by flash column chromatography and were shown to be 92 and 94% ee, respectively, thereby establishing that iminium ion formation and its trapping by cyanide are rapid relative to epimerization of the α-center, a surprising and highly useful finding. Eight different amino nitriles were prepared



Ar = 5-*tert*-butyldimethylsiloxy-2,4-dimethoxy-3-methylphenyl or 2,4-dimethoxy-5-hydroxy-3-methylphenyl (see structure **1**)

in this manner; cyclic aminal derivatives (e.g., from *N*,*N*′-dimethylethylenediamine), oxazolidines (from 2-(methylamino)-ethanol and from (*S*,*S*)- and (*R*,*R*)-pseudoephedrine), and *O*-methyl oxime derivatives were also prepared.[7] Of the 14 derivatives that were prepared, six were assayed for stereochemical purity at the α-carbon; each was formed with ≤2% epimerization.[7] Of the amino nitrile derivatives, those formed from cyclic secondary amines were the most stable, more stable than those derived from

(1) For leading references, see: Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1988; Vol. 2, Chapter 3.

(2) Reviews: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164. (b) Fisher, L. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399−484. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546. (d) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825−1872.

(3) For leading references to prior work describing the preparation of acetal-, thioacetal-, and aminal-protected α-amino aldehydes, see: (a) Bringmann, G.; Geisler, J.-P. *Synthesis* **1989**, 608−610. (b) Thiam, M.; Chastrette, F. *Tetrahedron Lett.* **1990**, *31*, 1429−1432. (c) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 418−421. (d) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359−361. (e) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489−7492. (f) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038−1049.

(4) The amino nitrile function has been widely used to enable a variety of synthetic transformations. For examples, see: (a) Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741−2744. (b) Ksander, G.; Bold, G.; Lattmann, R.; Lehmann, C.; Fruh, T.; Xiang, Y.-B.; Inomata, K.; Buser, H.-P.; Schreiber, J.; Zass, E.; Eschenmoser, A. *Helv. Chim. Acta* **1987**, *70*, 1115−1172. (c) Stork, G. S. *Pure Appl. Chem.* **1989**, *61*, 439−442. (d) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1992**, *70*, 54−59. (e) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202−9203.

(5) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322−3327.

(6) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623−3626. We have not previously reported the preparation of β-amino alcohols by reduction of pseudoephedrine glycinamide derivatives with LiH_2NBH_3 (LAB).

(7) See Supporting Information for preparation and for ee and de determinations.

(8) Two diastereomeric (six-membered ring) amino nitrile dimers were formed. α-(2-Pyridyl)amino cyanohydrins (Reynaud, P.; Tupin, T.; Delaby, R. *Bull. Soc. Chim. Fr.* **1957**, 718−721. Podhorez, D. E. *J. Heterocycl. Chem.* **1991**, *28*, 971−976) and hindered secondary α-amino cyanohydrins (Davidsen, S. K.; Chu-Moyer, M. Y. *J. Org. Chem.* **1989**, *54*, 5558−5567) have been reported.

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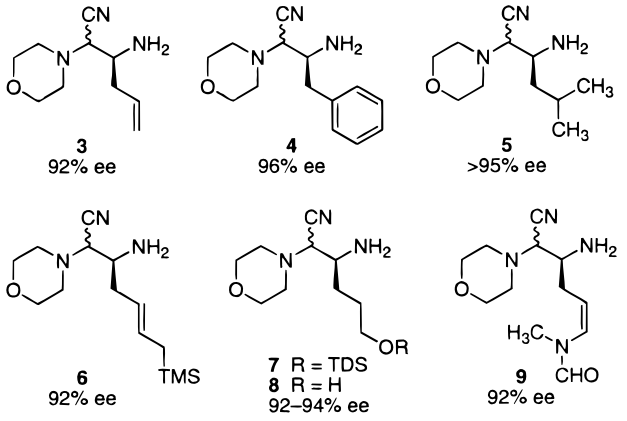
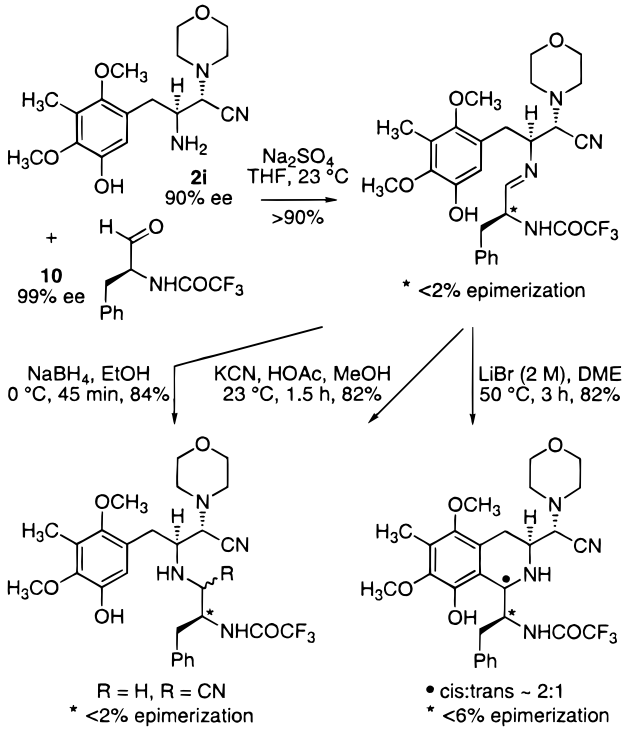
acyclic secondary amines which, in turn, were dramatically more stable than those from primary amines and from ammonia (ranked qualititatively above in order of their observed stability toward silica gel).[9,10] For example, while ammonia derivative **2a** did not withstand thin-layer chromatographic analysis (but was formed cleanly in solution, ^{1}H NMR analysis), the morpholino nitriles **2i** exhibited no apparent sensitivity to silica gel, nor to mild acids, and could be stored for months without decomposition.

We have begun to explore the scope of the chemistry to prepare highly enantiomerically enriched *C*-protected α-amino aldehydes using the morpholino nitrile function. Thus far, the data show the methodology to be of general utility; compounds **3**−**7** below were prepared in ≥92% ee and typically 70−85% yield (from the *N*-protected amino alcohol, 4 steps), in the same manner described above for **2i**. Compounds **8** and **9** (prepared from *N*-Fmoc **7** and *N*-Teoc **3**, respectively) show that polar, reactive functional groups may be incorporated within these *C*-protected α-amino aldehyde synthons.



For the directed, linear condensation strategy proposed, a critical issue was the possibility that epimerization might occur during condensation reactions. This was explored in the coupling of the *C*-protected derivative **2i** (90% ee)[11] with a 10% excess of (*S*)-*N*-trifluoroacetyl phenylalaninal (**10**, 99% ee) using anhydrous tetrahydrofuran with suspended sodium sulfate at 23 °C, leading to the clean formation (>90% yield) of just two imines, in a ratio of 95:5, a value equivalent to the enantiomeric purity of the component **2i**.[12] Although epimerization of the phenylalaninal-derived α-center was observed to occur upon standing, this could be avoided almost entirely by promptly conducting further transformations of the imine intermediate. Thus, reductive amination, amino nitrile synthesis, and Pictet−Spengler cyclization were all successfully conducted with ≤5% epimerization at the α-center in each case (Scheme 1).[13] The stability of the morpholino nitrile *C*-protective group to both the conditions of the Strecker reaction and the more vigorous conditions of Pictet−Spengler cyclization is noteworthy.[14] In this regard, lithium ion was found to be a particularly mild and effective means of selectively activating the imine group; other Lewis acids brought about decomposition, which we attributed to ionization of the amino nitrile group. That little epimerization occurred during the Pictet−Spengler cyclization was especially encouraging for the planned synthesis of the saframycins.

Scheme 1



In conclusion, we have synthesized a series of enantiomerically enriched, *C*-protected α-amino aldehydes using the amino nitrile function as a *C*-protective group. The lability of this group can be modulated over a wide range as a function of the amine that is incorporated. Among the findings of this work that we believe challenge conventional thinking are the following: the addition of hydrogen cyanide to chiral, *N*-protected α-amino aldehydes occurs reversibly and with little to no epimerization; the rate of trapping of iminium ions derived from chiral, *N*-protected α-amino aldehydes by cyanide greatly exceeds the rate of racemization of the aldehyde or the iminium ion; and, α-amino cyanohydrins can be prepared, chromatographed, and stored without racemization or self-condensation. Finally, we have shown that *N*- and *C*-protected α-amino aldehydes can undergo directed coupling (condensation by reductive amination, Strecker synthesis, or Pictet−Spengler cyclization) efficiently and with minimal epimerization. By analogy to peptide chemistry, the application of these findings to the preparation of higher order α-amino aldehyde oligomers and to solid-phase methodology is envisioned.

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Supporting Information Available: Detailed stereochemical determinations, listings of analytical data, and reaction conditions for representative transformations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The newly formed stereocenters, represented with a wavy line in structure **2**, were typically formed with little selectivity. See Supporting Information for details of stereochemical determinations.

(10) For earlier examples of structures of the type $H_2NCHRCH(CN)NR'R''$, see: (a) Cook, A. H.; Smith, E. *J. Chem. Soc.* **1949**, 3001−3007. (b) Herranz, R.; Suarez-Gea, M.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1993**, *58*, 5186−5191.

(11) For simplicity in the analysis, only a single diastereomer of **2i** was employed, tentatively assigned as the (*S*,*S*)-diastereomer.

(12) Imine formation and the subsequent transformations were also conducted with (*R*)-**10** to confirm that the source of isomerism was the α-center.

(13) Analogous condensation reactions with *N*-Fmoc alaninal (≥95% ee) led to significant epimerization of the α-center. The rate of epimerization of *N*-protected α-amino aldehydes is well-appreciated to vary with the side chain (see ref 2).

(14) In no event was scrambling of the amino nitrile center observed.