Asymmetric synthesis of amino acids

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Introduction

Over the last several years, we have been interested in the development of new methods for the efficient asymmetric synthesis of nonproteinogenic amino acids. The synthesis of complex glycopeptides such as the potent antibiotic vancomycin [1] offers a variety of challenges in this area which are currently being pursued in this laboratory (Fig. 1). In addition to the unusual arylglycine synthons, vancomycin contains both syn and anti β-hydroxy tyrosine derivatives not readily amenable to synthesis by current reaction methodology.

Results and Discussion

Recent advances in amino acid synthesis have featured highly diastereoselective alkylation reactions of chiral glycine enolate synthons [2-4] (Scheme 1, Transform A). A complementary bond construction involves the diastereoselective electrophilic amination of chiral enolates (Scheme 1, Transform B). The advantages

Fig. 1. Vancomycin synthons.

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of electrophilic enolate amination are clear: The scope of the reaction is not constrained by the structure of the alkyl or aryl substituent in the amino acid target.

We have found that di-tert-butyl azodicarboxylate performs admirably as an electrophilic aminating agent [5]. This reagent reacts readily with lithium enolates derived from chiral N-acyl oxazolidinones 1 to provide the hydrazide adducts 2 in excellent yield with diastereoselectivities ranging from 97 to greater than 99% (Eqn. 1). The chiral auxiliary can be removed using either lithium hydroxide in THF/water, magnesium methoxide in methanol, or lithium naphthalenide in THF. The lithium hydroxide conditions proved to be uniquely effective for hydrolysis in base-sensitive cases such as $R = \text{aryl}$, providing the derived amino acid with less than 2% racemization. In this case, subsequent esterification with diazomethane followed by treatment with trifluoroacetic acid and hydrogenation with Raney nickel afforded the phenylglycine methyl ester 3 ($R = \text{Ph}$, $R' = \text{Me}$) in quantitative yield in 98% enantiomerically pure.

Several alternative enolate amination sequences which provide access to azido acids have also been developed (Scheme 2). Hydroxylation of the sodium enolates of N-acyl oxazolidinones using 3-phenyl-2-phenylsulfonyl oxaziridine provides the α-hydroxy compounds 4 with diastereoselectivities ranging from 90 ($R = \text{Ph}$) to greater than 99% ($R = \text{tert-butyl}$) [6]. In all cases, the minor diastereomeric product contaminants may be readily removed by column chromatography. Conversion of the hydroxy imide 4 to the corresponding azides 5 via the Mitsunobu reaction with HN$_3$ proceeds in excellent yield without racemization. Alternatively, N-acyl oxazolidinones as their derived boron enolates have been found to react with N-bromosuccinimide to give the α-bromo derivatives 6, which also provide α-azidocarboxamides when treated with tetramethylguanidinium azide [7]. The diastereoselectivity in these brominations is typically 95% for most cases. The α-azidocarboxamides 5 are readily converted to the enantiomerically pure amino acids by lithium hydroxide hydrolysis and azide reduction using stannous chloride in methanol or hydrogen and palladium on carbon. Racemization-prone phenylglycine derivatives are readily obtained from 5 ($R = \text{Ar}$) in 98% ee following this protocol.

The preceding two-step approaches to α-azidocarboxamides require Sa2 displacements by nucleophilic azide, which were found to be sluggish in hindered cases. Accordingly, a direct electrophilic azide transfer reaction has been developed which eliminates this problem [8]. Treatment of the potassium enolate derived from imide 1 with 2, 4, 6-trisopropylbenzenesulfonyl azide followed by an acetic acid quench provides the desired azide 7 in high yield with excellent stereoselectivity (Eqn. 2). Conversion to the amino acids proceeds as before.

In the sterically hindered case ($R = \text{tert-butyl}$), oxazolidinone hydrolysis occurs in poor yield, with attack at the oxazolidinone carbonyl to give a predominantly ring-opened product. In contrast, hydrolysis with lithium hydrogen peroxide in THF affords the desired azido acid in 98% yield.

Syn and anti β-hydroxy amino acids are readily available via asymmetric aldol reactions of the appropriate chiral glycine enolate synthon. The syn selective
The stannous triflate-derived enolate of isothiocyanatoacetyl oxazolidinone 9 undergoes a highly diastereoselective aldol reaction to afford the syn adducts as internally derived heterocycles 10 in 71-92% yields (Eqn. 5)[9]. In conjunction with the total synthesis of the antifungal agent echinocandin D [10], adduct 10 (R = p-BnOPhCH₂) was converted to N-Boc amino acid 13 in three steps (Eqn. 6)[11]. The oxazolidinone was removed by treatment with magnesium methoxide in methanol to provide methyl ester 11 in 95% yield. Following acylation with di-tert-butyl dicarbonate and desulfurization, the resultant N-Boc oxazolidinone 12 was hydroxylated to the desired amino acid derivative in 83% yield using aqueous lithium hydroxide.

α-Chloroacetyl oxazolidinone 14 has proven to be a useful anti β-hydroxy amino acid synthon [12]. The dibutyllithium triflate-mediated aldol reaction of 14 proceeds with 95-97% diastereoselection and in moderate yield, which can be increased by using excess enolate. Adduct 15 may be readily converted to allo-threonine (Eqn. 8). Displacement with sodium azide (DMF, 45°C) afforded azide 19 in 70% yield, along with 10-15% of the C-2 epimer. Hydrolysis with lithium hydroxide followed by catalytic hydrogenation provided an 82% yield of allo-threonine (20). The α-bromoacetyl carbamidom 16 (Eqn. 7) performs comparably in the aldol reaction; however, the azide displacement reaction of α-bromo aldol adduct 17, which proceeds smoothly at room temperature, affords the azide with no detectable epimerization. Therefore, the α-bromo adduct 21 was chosen for use in the synthesis of the unusual hydroxyproline derivative 23 found in echinocandin D (Eqn. 9)[11]. The intriguing aspect of this synthesis was associated with the conversion of 22 to 23, a formal cycloalkylation of an olefinic azide promoted by dicyclohexylborane. Treatment of 22 with dicyclohexylborane gave an intermediate azido trialkylborane, which reacted in situ in an intramolecular fashion to afford a 72% yield of the desired proline derivative 23. We are currently developing the scope of this reaction which should be generally useful for the synthesis of cyclic amino acids.

The asymmetric enolate amination reactions together with the glycine enolate aldol reaction methodology described herein are powerful tools for the synthesis of a wide variety of unusual amino acids. This methodology is currently being applied to the total synthesis of members of the vancomycin family of glycopeptides.
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References