

## ASYMMETRIC SYNTHESIS OF $\omega$ -BROMO-2(S)-AZIDO ACIDS AS PRECURSORS FOR THE SYNTHESIS OF NOVEL AMINO ACIDS<sup>1</sup>

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**Abstract:** A series of  $\omega$ -bromo-2(S)-azido acids with side-chain lengths ranging from 3-5 methylene units has been synthesized. These intermediates enable the facile synthesis of chiral non-natural amino acids containing virtually any nucleophile capable of substituting the  $\omega$ -bromo group.  
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With a surge of interest focused on small peptides and peptidomimetics, new methods are needed to prepare an array of non-natural amino acids designed to improve binding potency, chemical and biological stability, and pharmacokinetic characteristics when substituted into peptide-based lead compounds. In particular, we are interested in preparing optically pure amino acids in which the side-chains may be charged or difficult to protect. A possible strategy is to produce  $\omega$ -halo- $\alpha$ -amino acids, in which the  $\omega$ -halogen can be displaced by a nucleophile late in the synthesis to provide the desired side-chain functionality. Previous methods which produce  $\omega$ -halo amino acids are not adequate, in that they provide racemic products which may be difficult or costly to purify.<sup>2,3</sup> These methods are also incompatible with an  $\alpha$ -amino 9-fluorenylmethoxycarbonyl (Fmoc) protected peptide synthetic approach, in that the  $\alpha$ -amino group must be protected by a nucleophile-stable benzyloxycarbonyl (Z) or *tert*-butyloxycarbonyl (*t*-Boc) group so that it will not react with  $\omega$ -halo groups. This paper focuses on an asymmetric strategy; the synthesis of three  $\omega$ -bromo-2(S)-azido acid intermediates (Figure 1).

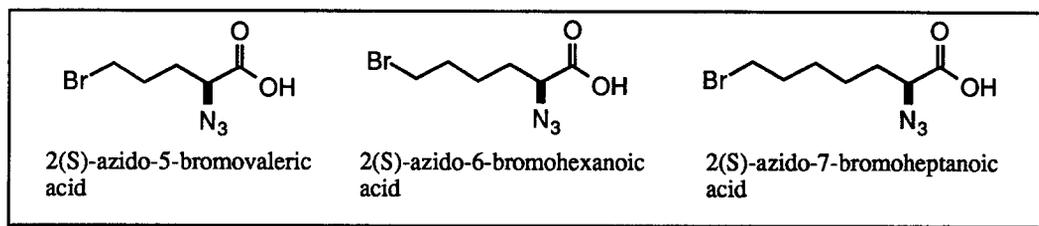
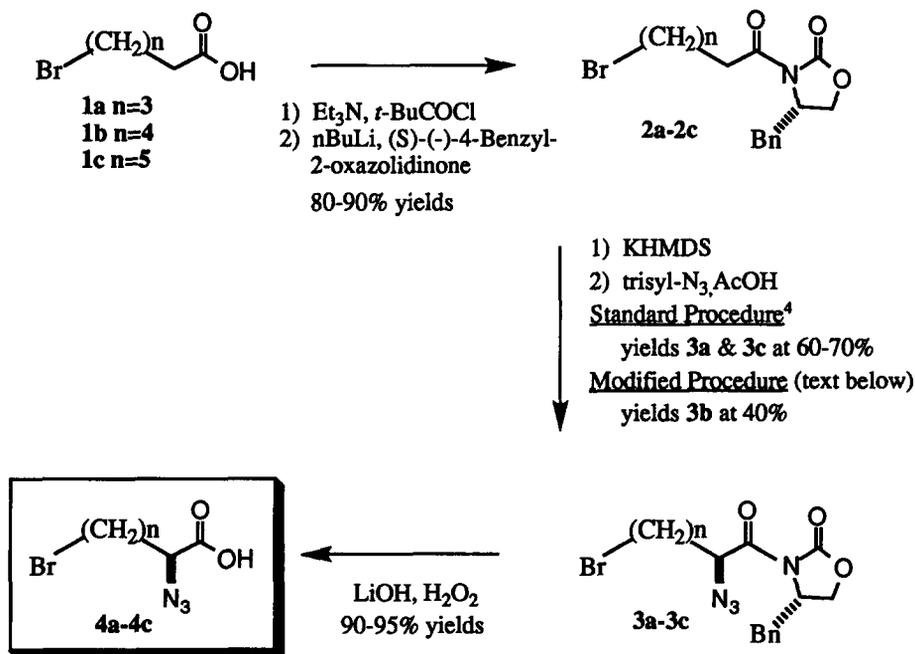


Figure 1:  $\omega$ -Bromo-2(S)-Azido Acids

Charged side-chain functionalities can lead to solubility incompatibilities if incorporated early in an asymmetric synthesis requiring the use of anhydrous THF. Our strategy is to perform anhydrous operations early to define  $\alpha$ -carbon chirality by using the (S)-(-)-4-benzyl-2-oxazolidinone chiral auxiliary of Evans *et. al.*<sup>4</sup> in the synthesis of common  $\omega$ -bromo-2(S)-azido acid intermediates (Figure 1). This methodology hinges on the fact that the 2(S)-azido group acts as a protected form of the  $\alpha$ -amino group and the organic-soluble  $\omega$ -bromo group “saves a place” for the desired nucleophile towards the end of the synthesis.

Starting materials, displayed in Scheme 1, were chosen to produce amino acid analogs with side-chain lengths as follows: 5-bromovaleric acid (**1a**) for amino acids possessing three methylene groups in side-chain length, 6-bromohexanoic acid (**1b**) for analogues containing a four carbon side-chain, and 7-bromoheptanoic acid (**1c**) which will produce amino acids reaching five methylene units from the  $\alpha$ -carbon. We utilize the enantioselective synthetic rationale of Evans *et. al.*<sup>4</sup> which involves attaching a chiral auxiliary at the acid functionality of the molecule forming the carboximides (**2a-2c**). Next, the enolate is formed with KHMDS to allow the electrophilic addition of the azide in a 95% diastereomeric excess for **3a-3c** as determined by <sup>1</sup>H-NMR. The minor diastereomer was removed by flash chromatography.



Scheme 1: Synthesis of  $\omega$ -Bromo-2(S)-Azido Acids **4a-4c**

It is important to note that product **3b** could not be produced with the 30 min. enolization time recommended by Evans *et. al.*<sup>4</sup> We determined by NMR and mass spectrometry that the enolate efficiently attacks to displace the  $\omega$ -bromo group to form the five-membered cyclopentane carboximide. A modified procedure serves as a partial solution to this problem. This procedure utilizes excess trisyl azide added early in the enolization process to compete with the intramolecular cyclization reaction, providing **3b** in 40% yield. Removal of the Evans auxiliary with H<sub>2</sub>O<sub>2</sub> and LiOH<sup>4</sup> gives the respective 2(S)-azido- $\omega$ -bromo acids (**4a-4c**).

With the lack of a series of available and inexpensive chiral building blocks available from commercial suppliers, we designed the homologous series of  $\omega$ -bromo-2(S)-azido acids. The intermediates 2(S)-azido-5-bromovaleric acid (**4a**), 2(S)-azido-7-bromoheptanoic acid (**4c**), and 2(S)-azido-6-bromohexanoic acid (**4b**) have been characterized and prepared in 60%, 60%, and 34% overall yields, respectively. Recently, N- $\phi$ -methyl homolysine was synthesized in our laboratory starting with methylamine and 7-bromoheptanoic acid.<sup>5</sup> This nucleophilic substitution reaction was quantitative, and after *t*-Boc protection of the alkyl-amine, the product was obtained by following the chiral synthetic route of Evans *et. al.*<sup>4</sup> With the bromo group easily reacting at ambient temperature and pressure, and the reaction being driven to completion by excess amine,<sup>6</sup> we realized the possibility and advantages of side chain differentiation toward the end of a synthetic process. The methodology is efficient in that there are less synthetic steps since common intermediates are used. Further, charged functionalities are easily incorporated after formation of the chiral center in anhydrous conditions. With the wide array of nucleophiles available, it is envisioned that the homologous series would be useful in combinatorial organic or synthetic peptide strategies. Preliminary reactions with a variety of nucleophiles have shown that this methodology works.<sup>7</sup> Catalytic hydrogenation of the 2(S)-azido group produces enantiomerically pure non-natural L-amino acids.

The azido intermediates are not amenable to low or high resolution mass spectrometry, therefore, analytical NMR data are provided below for comparison of each azido intermediate **3a-4c**.<sup>8</sup>

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8. **(3(2S),4S)-3-(2-Azido-1-oxo-5-bromovaleryl)-4-(phenylmethyl)-2-oxazolidinone(3a)**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.22 (m, 5 H, aromatics), 4.98 (dd,  $J = 4.9, 8.5$  Hz, 1 H, 2-H), 4.74-4.67 (m, 1 H, 4-H), 4.33-4.25 (m, 2 H,  $\text{OCH}_2$ ), 3.51-3.45 (m, 2 H,  $\text{BrCH}_2$ ), 3.35 (dd,  $J = 3.3, 13.4$  Hz, 1 H,  $\text{CHHC}_6\text{H}_5$ ), 2.85 (dd,  $J = 9.5, 13.4$  Hz, 1 H,  $\text{CHHC}_6\text{H}_5$ ), 2.15-1.98 (m, 4 H,  $\text{Br-CH}_2\text{-CH}_2\text{-CH}_2$ );  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.48, 152.91, 134.67, 129.43, 129.12, 127.62, 66.74, 59.96, 55.47, 37.63, 32.40, 30.01, 29.21.  
**2(S)-Azido-5-bromovaleric Acid (4a)**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.00 (dd,  $J = 4.2, 8.0$  Hz, 1 H,  $\text{C}_2\text{-H}$ ), 3.46 (t,  $J = 6.1$  Hz, 2 H,  $\text{BrCH}_2$ ), 2.15-1.90 (m, 4 H,  $\text{C}_3\text{-H}_2$   $\text{C}_4\text{-H}_2$ );  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  175.32, 61.07, 32.29, 29.92, 28.68.  
**(3(2S),4S)-3-(2-Azido-1-oxo-6-bromohexanoyl)-4-(phenylmethyl)-2-oxazolidinone (3b)**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.20 (m, 5 H, aromatics), 4.98 (dd,  $J = 5.0, 8.2$  Hz, 1 H, 2-H), 4.72-4.63 (m, 1 H, 4-H), 4.34-4.22 (m, 2 H,  $\text{OCH}_2$ ), 3.46 (t,  $J = 6.6$  Hz, 2 H,  $\text{BrCH}_2$ ), 3.34 (dd,  $J = 3.2, 13.4$  Hz, 1 H,  $\text{CHHC}_6\text{H}_5$ ), 2.85 (dd,  $J = 9.6, 13.2$  Hz, 1 H,  $\text{CHHC}_6\text{H}_5$ ), 2.00-1.85 (m, 4 H,  $\text{Br-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$ ), 1.85-1.60 (m, 2 H,  $\text{Br-CH}_2\text{-CH}_2\text{-CH}_2$ );  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  170.59, 152.99, 134.71, 129.44, 129.11, 127.60, 66.71, 60.21, 55.46, 37.64, 33.02, 31.80, 30.29, 24.59.  
**2(S)-Azido-6-bromohexanoic Acid (4c)**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.94 (dd,  $J = 5.2, 8.2$  Hz, 1 H,  $\text{C}_2\text{-H}$ ), 3.42 (t,  $J = 6.6$  Hz, 2 H,  $\text{BrCH}_2$ ), 2.00-1.75 (m, 4 H,  $\text{C}_3\text{-H}_2$   $\text{C}_5\text{-H}_2$ ), 1.75-1.55 (m, 2 H,  $\text{C}_4\text{-H}_2$ );  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  175.34, 61.56, 32.87, 32.03, 30.47, 24.39.  
**(3(2S),4S)-3-(2-Azido-1-oxo-7-bromoheptanoyl)-4-(phenylmethyl)-2-oxazolidinone(3c)**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.20 (m, 5 H, aromatics), 4.97 (dd,  $J = 4.7, 8.7$  Hz, 1 H, 2-H), 4.74-4.65 (m, 1 H, 4-H), 4.33-4.20 (m, 2 H,  $\text{OCH}_2$ ), 3.44 (t,  $J = 6.9$  Hz, 2 H,  $\text{BrCH}_2$ ), 3.40 (dd,  $J = 3.1, 13.2$  Hz, 1 H,  $\text{CHHC}_6\text{H}_5$ ), 2.85 (dd,  $J = 9.6, 13.5$  Hz, 1 H,  $\text{CHHC}_6\text{H}_5$ ), 2.00-1.70 (m, 4 H,  $\text{Br-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$ ), 1.70-1.45 (m, 4 H,  $\text{Br-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$ );  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  171.02, 152.77, 134.74, 129.45, 129.11, 127.60, 66.68, 60.40, 55.45, 37.65, 33.47, 32.42, 31.04, 27.53, 25.28.  
**2(S)-Azido-7-bromoheptanoic Acid (4c)**:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.93 (dd,  $J = 5.2, 8.0$  Hz, 1 H,  $\text{C}_2\text{-H}$ ), 3.43 (t,  $J = 6.3$  Hz, 2 H,  $\text{BrCH}_2$ ), 2.00-1.80 (m, 4 H,  $\text{C}_3\text{-H}_2$   $\text{C}_6\text{-H}_2$ ), 1.60-1.45 (m, 4 H,  $\text{C}_4\text{-H}_2$   $\text{C}_5\text{-H}_2$ );  $^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  175.61, 61.61, 33.38, 32.37, 31.12, 27.57, 24.88.

Synthesis of the carboximides (**2a-2c**) is straightforward following Evans' procedure and typically yields 80-90%, therefore extensive analytical NMR data for these compounds has not been included.  $^1\text{H-NMR}$  spectra for these compounds is similar to **3a-3c**, the only major difference being  $\delta$  3.00 (m, 2 H) for **2a-2c** and  $\delta$  4.97-4.98 (dd, 1 H) for **3a-3c** on the  $\alpha$ -carbon, respectively.