ORGANIC LETTERS

2003
Vol. 5, No. 22
4017−4020

A New Method for the Stereoselective Synthesis of α-Substituted Serine Amino Acid Analogues

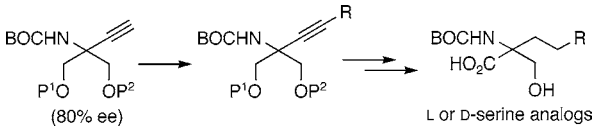
Jonathan W. Lane and Randall L. Halcomb*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

halcomb@colorado.edu

Received June 2, 2003

ABSTRACT



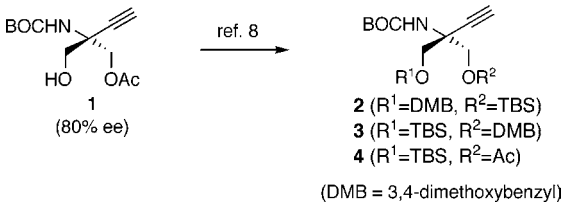
A new method was developed for the stereoselective synthesis of α-substituted serine amino acids. The strategy utilizes a common enantiomerically enriched intermediate obtained through an enzymatic desymmetrization. A variety of amino acids were synthesized in good ee's through nucleophilic acetylide addition reactions and palladium-catalyzed Sonogashira couplings.

The stereoselective construction of α,α-disubstituted α-amino acids has attracted a great deal of attention in the synthesis community for some time, and numerous elegant methods have been developed.[1] This attention is undoubtedly due to inherent structural challenges of these compounds as well as their notable effects on biological activity.[2] The α-substituted serine unit has been investigated in the design of peptides[1b] and is contained within natural products such as myriocin, (+)-lactacystin, (+)-conagenin, and sphingofungin E.[3] Traditionally, α-substituted serines are prepared through a number of standard methods including rearrangements of chiral trichloroacetimidates,[3b,4] alkylation of chiral enolates,[5] and the ring-opening of chiral aziridines.[6] However, to our knowledge, only one type of enzyme-catalyzed desymmetrization method for constructing these compounds is published.[3a,7] This method, based on the hydrolytic enzymatic desymmetrization of α-alkyl α-aminomalonate derivatives, was first utilized by Fukuyama and co-workers in their total synthesis of (−)-tantazole B.[7]

Fukuyama's method was subsequently employed in a recent effort by Nagao and co-workers.[3a] The latter study detailed a synthesis of α-substituted serines based on the enantioselective enzymatic hydrolysis of a short series of diethyl α-alkyl-α-(benzyloxycarbonylamino)malonates using pig liver esterase (PLE) or rabbit liver esterase (RLE).[3a] Although the results of this study were promising, findings suggested that the method could be somewhat limited by the identity of the desymmetrization substrate.

A more general enzymatic desymmetrization strategy for the enantioselective synthesis of α-substituted serine amino acids would be useful. Monoacetate **1** (Scheme 1), afforded

Scheme 1

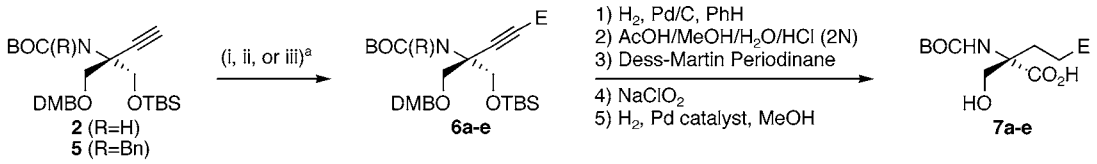


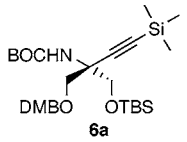
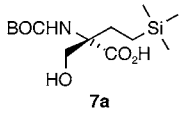
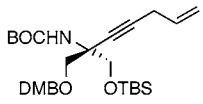
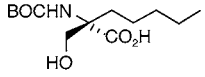
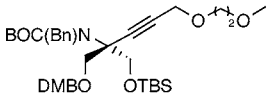
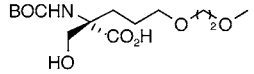
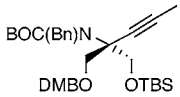
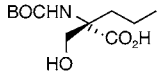
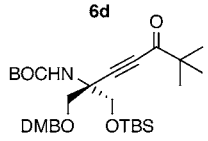
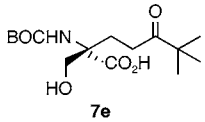
(1) For reviews on the synthesis of quaternary α-alkylated α-amino acids, see: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (c) Cativiela, C.; Dias-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (d) Cativiela, C.; Dias-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.

(2) (a) Barrett, G. C. *Amino Acids, Peptides and Proteins*; The Chemical Society: London, 1980; Vol. 13, p 1. (b) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 55. (c) Coppala, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules using Amino Acids*; Wiley: New York, 1987.

10.1021/ol034984j CCC: $25.00
Published on Web 10/09/2003

Table 1. Acetylide Addition Route to L-Serine Amino Acid Analogs



Entry	E^+	Addition Product	% Yield (Addition)	Amino Acid
1	TMS-Cl	 **6a**	91[i]	 **7a**
2	Allyl-Br	 **6b**	75[i]	 **7b**
3	MEM-Cl	 **6c**	85[ii]	 **7c**
4	MeI	 **6d**	98[ii]	 **7d**
5	$(CH_3)_3COCl$	 **6e**	60[iii]	 **7e**

[a] Key: (i) LDA (4 equiv), THF, DMPU, −50 °C, then E^+ (4 equiv); (ii) LDA (3 equiv), THF, DMPU, −50 °C, then E^+ (4 equiv) and warm to rt; (iii) CuI, toluene, NEt_3, 65 °C.

in 80% ee through a PLE-catalyzed enzymatic desymmetrization of the corresponding diacetate, was recently developed in this laboratory and utilized in the synthesis of constrained analogues of the α-*N*-acetylgalactosaminyl serine glycopeptide substructure.[8] Our goal was to recruit **1** as an intermediate for the stereoselective preparation of a variety of novel α-substituted serine analogues. Unfortunately, neither compound **1** nor any other intermediates were crystalline, so the ee could not be enhanced further.

The method bears notable advantages over previous ones. First, the divergent method is flexible. The terminal alkyne functional group in **1** is amenable to a variety of synthetic transformations, which facilitates the propagation of diversity at Cα. Specifically, compounds **2** and **3**, enantiomers available from **1** by a benzylation−deacylation−silylation or silylation−deacylation−benzylation sequence, respectively (Scheme 1),[8] can undergo acetylide additions to a variety of electrophiles. Compound **4**, also available from **1**,[8] is amenable to palladium-catalyzed Sonogashira couplings[9] with a variety of aryl halides. The orthogonal protecting groups in **2**−**4** provide selective access to both D- and L-amino acid configurations. Second, enantioselectivities are consistent. Compounds **2**−**4** were previously shown to maintain the enantiomeric ratio established in intermediate **1**. Therefore, all amino acid products arising from these intermediates would possess this ratio as well. This is advantageous since the enantioselectivity of a desymmetrization process is highly dependent on substrate structure.[10] Finally, the strategy avoids problems associated with substrate compatibility in the desymmetrization process. The method provides access to compounds that may not be directly available through an enzymatic desymmetrization.

(3) (a) Sano, S.; Hayashi, K.; Miwa, T.; Ishii, T.; Fujii, M.; Mima, H.; Nagao, Y. *Tetrahedron Lett.* **1998**, *39*, 5571 and references therein. (b) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Org. Lett.* **2002**, *4*, 151.

(4) Hatakeyama, S.; Matsumoto, H.; Fukuyama, H.; Mukugi, Y.; Irie, H. *J. Org. Chem.* **1997**, *62*, 2275.

(5) (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545. (b) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799.

(6) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345.

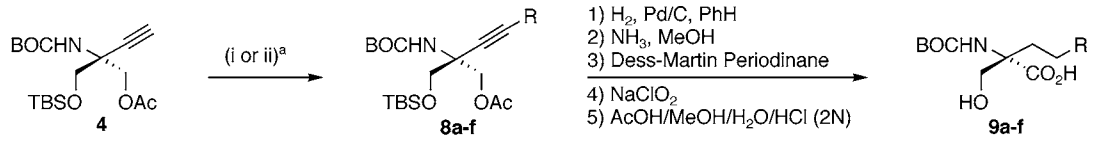
(7) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449.

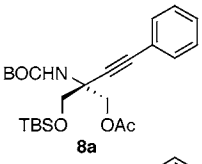
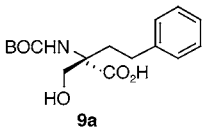
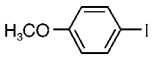
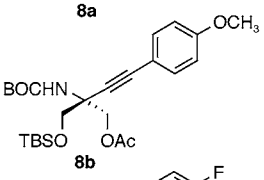
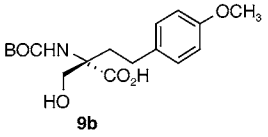
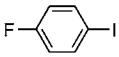
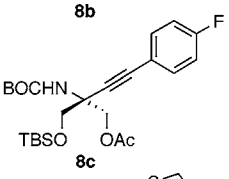
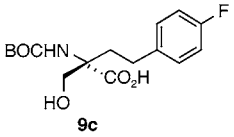
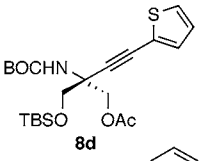
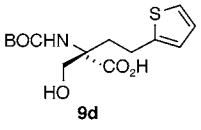
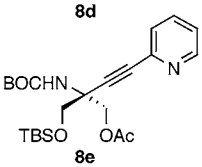
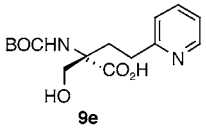
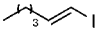
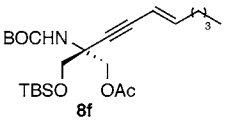
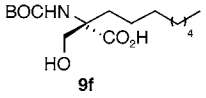
(8) Lane, J. W.; Halcomb, R. L. *J. Org. Chem.* **2003**, *68*, 1348.

(9) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729 and references therein.

(10) (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier: New York, 1994. (b) Ohno, M.; Otsuka, M. In *Organic Reactions: Chiral Synthons by Ester Hydrolysis Catalyzed by Pig Liver Esterase*; New York, 1989; pp 1−55.

Table 2. Sonogashira Coupling Route to L-Serine Amino Acid Analogues



Entry	RX	Sonogashira Product	% Yield (Coupling)	Amino Acid
1		 **8a**	95[i]	 **9a**
2		 **8b**	91[i]	 **9b**
3		 **8c**	87[i]	 **9c**
4		 **8d**	86[i]	 **9d**
5		 **8e**	73[ii]	 **9e**
6		 **8f**	82[i]	 **9f**

[a] Key: (i) RX (2 equiv), $Pd(PPh_3)_4$ 10%, CuI 20%, NEt_3, DMF, rt; (ii) RX (3 equiv), $PdCl_2(PPh_3)_2$ 10%, CuI 20%, NEt_3, CH_3CN, rt.

In an effort to synthesize a variety of α-substituted L-serine amino acids, compound **2** was utilized in a series of addition reactions to simple electrophiles (E^+). Acetylide additions of the dianion of **2** to chlorotrimethylsilane and allyl bromide (entries 1 and 2, Table 1) afforded **6a** and **6b**, respectively. Initial reduction of the internal alkyne functional group in these products[11] was followed by removal of the TBS protecting group under acidic conditions. The free primary hydroxyl group resulting from the deprotection was then oxidized in two steps to the necessary carboxylic acid. A final removal of the DMB protecting group through more forceful hydrogenation conditions provided the target *N*-protected amino acids **7a** and **7b**. Unfortunately, addition of the dianion of **2** to more reactive electrophiles such as 2-methoxyethoxymethyl chloride (MEM-Cl) and methyl iodide led to substantial quantities of *N*-alkylated products, even under carefully controlled reaction conditions. Therefore, to prevent alkylation at this position, an additional benzyl protecting group was installed on the nitrogen in compound **2**, producing compound **5**.[12] Acetylide additions of **5** to MEM-Cl and methyl iodide (entries 3 and 4) proceeded smoothly to provide **6c** and **6d**. Manipulations to these intermediates as before afforded the target amino acids **7c** and **7d**.[13] Finally, a copper-mediated addition of **2** to trimethylacetyl chloride (entry 5) provided **6e**.[14] Intermediate **6e** was then readily transformed as before to protected amino

(11) Benzene was utilized as the solvent in this hydrogenation reaction in an effort to prevent premature removal of the DMB protecting group (**6a**−**e**) and the TBS group (**8a**−**f**).

(12) Compound **5** was prepared by treating compound **2** with 1 equiv of potassium bis(trimethylsilyl)amide in THF at −55 °C followed by addition of benzyl bromide and tetrabutylammonium iodide and subsequent warming to room temperature.

(13) The DMB and benzyl protecting groups were simultaneously removed in the final hydrogenation sequence.

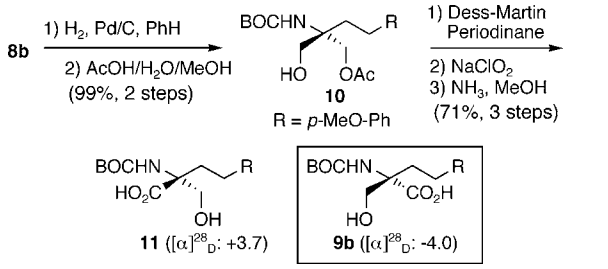
(14) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379.

acid **7e**. Importantly, the alkylation route could also provide the corresponding α-substituted D-serine amino acids through intermediate **3** using the aforementioned methods.

Studies by Crisp and co-workers resulted in the synthesis of a series of monosubstituted amino acids through palladium-catalyzed cross-couplings of aryl halides and aryl triflates with an ethynyloxazolidine substrate.[15] The second component of our strategy would expand upon this method by employing **4** as a substrate for palladium-catalyzed cross-couplings to various aryl halides (RX). Coupling of **4** to iodobenzene (entry 1, Table 2) afforded **8a**. Initial reduction of the internal alkyne functional group in this product[11] was followed by removal of the acetate group. The free primary hydroxyl group resulting from acetate removal was then oxidized in two steps to the necessary carboxylic acid. Removal of the TBS protecting group under acidic conditions provided the target *N*-protected L-serine amino acid **9a**. Phenyl groups containing an electron-donating substituent and an electron-withdrawing substituent (entries 2 and 3) were successfully incorporated to provide **8b** and **8c**, respectively. The successful incorporation of heteroaromatic groups (entries 4 and 5) provided intermediates **8d** and **8e**.[16] Finally, in addition to aryl halides, an iodoalkene[17] was successfully coupled to **4** (entry 6), affording intermediate **8f**. Straightforward manipulations to intermediates **8b**−**f**, as before, provided the desired *N*-protected amino acids **9b**−**f**. Importantly, a compound similar to **9f** was unavailable through methods reported earlier.[3a]

The corresponding α-substituted D-serine amino acids are also available through the coupling route. Synthesis of these targets bearing the opposite configuration at Cα is accomplished through modifications to the order of manipulations performed on intermediates **8a**−**f**.[18] This principle was demonstrated in the synthesis of the enantiomer of **9b**, compound **11** (Scheme 2). Initial reduction of the internal alkyne functional group in **8b** followed by TBS group removal gave **10**. Oxidation of the primary hydroxyl group in **10**, as before, and subsequent removal of the acetate group afforded the target compound **11** bearing the D-serine configuration.

Scheme 2



In summary, a new method was developed for the stereoselective synthesis of α-substituted serine amino acids. The method is based on a common enantiomerically enriched intermediate obtained through an enzymatic desymmetrization.[8] A variety of amino acids were synthesized selectively in good ee's through nucleophilic acetylide addition reactions and palladium-catalyzed Sonogashira couplings. This strategy is relatively general as well as flexible and, therefore, has advantages over previous desymmetrization-based methods for the synthesis of α-substituted serine amino acids.

Acknowledgment. This research was supported by an NSF Career Award (CHE-9733765). R.L.H. also thanks the Camille and Henry Dreyfus Foundation (Camille Dreyfus Teacher−Scholar Award), Pfizer (Junior Faculty Award), and Novartis (Young Investigator Award) for support. This work was facilitated by a 400 MHz NMR spectrometer that was purchased partly with funds from an NSF Shared Instrumentation Grant (CHE-0131003). Rich Shoemaker (University of Colorado) is thanked for his assistance in performing NMR characterizations.

Supporting Information Available: Experimental details and full characterization of all new compounds; ^{1}H and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034984J

(15) Crisp, G. T.; Jiang, Y.-L.; Pullman, P. J.; De Savi, C. *Tetrahedron* **1997**, *53*, 17489.

(16) The more reactive $PdCl_2(PPh_3)_2$ catalyst was necessary to circumvent the low reactivity of 2-bromopyridine (entry 5, Table 2).

(17) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138.

(18) No attempts were made to implement a similar strategy for the synthesis of D-serine amino acids from intermediates **6a**−**e**. Selective removal of the DMB protecting group over the acid-sensitive TBS protecting group was problematic in similar compounds.