ORGANIC LETTERS

2003
Vol. 5, No. 12
2107−2109

Efficient Synthesis of Enantiopure β-Amino-γ-Keto Acids from L-Homoserine

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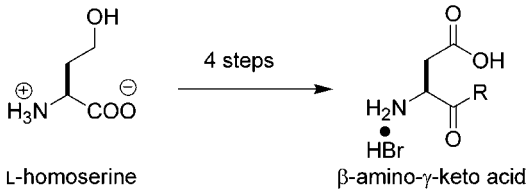
Received March 26, 2003

ABSTRACT



A variety of β-amino-γ-keto acids were prepared in four steps from commercially available L-homoserine. The reaction sequence is highlighted by a Ni-catalyzed Grignard addition to a N-protected derivative of L-homoserine. One of the β-amino-γ-keto acids was then used to create a β-peptide trimer composed solely of β-amino-γ-keto acids.

β-Amino acids are key components of many natural products, including bestatin, cryptophycin, and taxol. In addition, many β-amino acids are biologically active compounds in their own right. For example, the β-amino acid emeriamine has been shown to possess potent hypoglycemic and antiketogenic activities,[1] and cispentacin is an antifungal agent (Figure 1).[2]

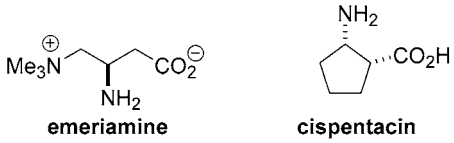


Figure 1. Biologically active β-amino acids.

Oligomers composed entirely of β-amino acids can adopt folded structures in solution and have unique properties relative to their natural α-peptide counterparts.[3] The biological applications of these β-peptides are numerous. For instance, certain β-peptides have shown antimicrobial activity;[4] others can mimic an α-peptide hormone,[5] whereas others have the ability to inhibit cholesterol and fat absorption.[6] Furthermore, it has recently been demonstrated that the β-peptide analogue of the Tat sequence will translocate into mammalian cells.[7]

The incorporation of the ketone functional group into β-peptides would allow for site-specific modification of such macromolecules through the orthogonal reactivity of ketones. In addition, ketones can act as hydrogen bond acceptors, and

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(2) (a) Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749−1755. (b) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756−1762. (c) Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, *1*, 136−140.

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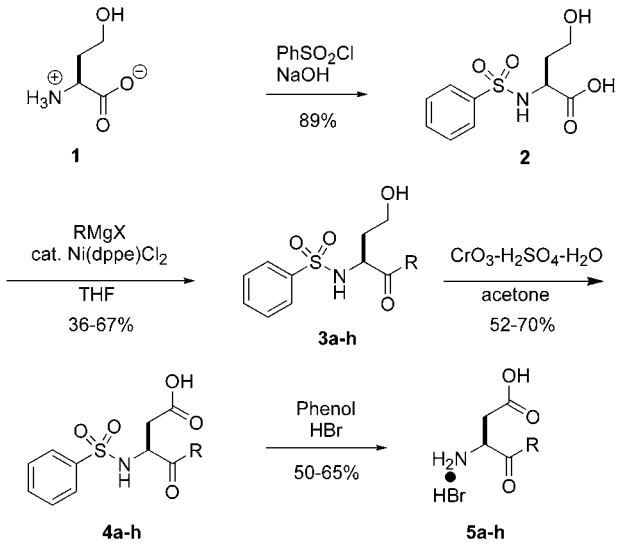
10.1021/ol0345327 CCC: $25.00 © 2003 American Chemical Society
Published on Web 05/17/2003

thus oligomers containing this functionality could have unique hydrogen bonding and folding patterns. We are interested in preparing a wide variety of β-amino-γ-keto acids to explore the oligomeric properties of such compounds, as well as for their use as chiral building blocks in combinatorial library synthesis and as modules in protease inhibitors. While there have been many synthetic efforts directed toward the preparation of β-amino acids,[8] there are almost no reports of the synthesis of β-amino-γ-keto acids.[9] Herein we describe an efficient preparation of several β-amino-γ-keto acids from commercially available L-homoserine and the synthesis of a trimer derived from one of these compounds.

The synthetic route for the preparation of β-amino-γ-keto acids is depicted in Scheme 1. The synthesis commenced

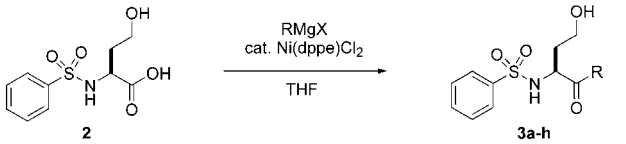
Scheme 1. Synthesis of β-Amino-γ-keto Acids



with protection of the amine of L-homoserine.[10] A robust protecting group was required, as the ketone side chain was to be installed through a Grignard addition. On this basis, L-homoserine was treated with phenylsulfonyl chloride to provide the phenylsulfonamide derivative **2**. Facile crystallization from chilled concentrated HCl gave the pure product in 89% yield.

Under standard Grignard reaction conditions sulfonamide acid **2** was unreactive. However, use of a nickel catalyst[11] enabled the successful addition of several Grignard reagents to the carboxyl group of **2** to provide ketones **3a**−**h** in

Table 1. Reaction of N-Protected Homoserine with Grignard Reagents

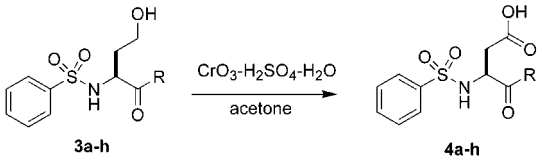


entry	R	X	product	yield[a]
1	propyl	Br	**3a**	67
2	butyl	Br	**3b**	50
3	pentyl	Br	**3c**	56
4	hexyl	Br	**3d**	46
5	cyclohexyl	Cl	**3e**	62
6	cyclopentyl	Br	**3f**	36
7	phenyl	Br	**3g**	47
8	benzyl	Cl	**3h**	51

[a] Yields include a small amount (5−10%) of the secondary alcohol product. This compound, together with **3a**−**h**, is oxidized to **4a**−**h** in the next step of the reaction sequence.

moderate to good yields (Table 1); 6 equiv of the Grignard reagent was used in each transformation. These reactions typically were run for 5−7 days, and even then 20−30% of the unreacted starting material could be recovered. Although a small amount (<10%) of secondary alcohol was also present after this Grignard addition, we did not observe the formation of the tertiary alcohol that would result from over-addition of the Grignard reagent. Subsequent Jones oxidation of the primary alcohol in **3a**−**h** to the carboxylic acid, and of any secondary alcohol to the corresponding ketone, gave the protected β-amino acids **4a**−**h** (Table 2).

Table 2. Jones Oxidation to Provide Protected β-Amino-γ-keto Acids



entry	R	product	yield
1	propyl	**4a**	62
2	butyl	**4b**	52
3	pentyl	**4c**	53
4	hexyl	**4d**	52
5	cyclohexyl	**4e**	64
6	cyclopentyl	**4f**	68
7	phenyl	**4g**	70
8	benzyl	**4h**	50

The direct conversion of carboxylic acid **2** into ketones **3a**−**h** obviated the need for protection of the hydroxyl functionality of **2**. This protection would have been necessary if standard conditions (conversion of the acid into the acid chloride and then reaction with the Grignard reagent) had

(8) (a) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553−2557. (b) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396−2398. (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (d) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983−1004. (e) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965. (f) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159−4161.

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(10) L-Homoserine can be synthesized from L-aspartic acid. See: Sutherland, A.; Caplan, J. F.; Vederas, J. C. *Chem. Commun.* **1999**, 555−556.

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been employed to convert the acid into a ketone. The ability of the nickel catalyst to suppress over-addition to the carboxyl group is consistent with previous literature results.[11]

Removal of the phenylsulfonamide proved to be somewhat troublesome. When SmI_2, Na/Hg amalgam, or $Li-NH_3$ was employed, little or no free β-amino acid was obtained. However, refluxing in HBr/phenol provided the desired β-amino-γ-keto acids **5a**−**h** in good yields and purity without the need for chromatography.

To determine if any racemization of the preexisting stereogenic center had occurred during the course of the synthesis, Mosher amide derivatives of several of the final compounds were synthesized and analyzed. In all cases, the compounds were found to have enantiomeric ratios (ers) of greater than 99.5:0.5. The optical rotations of **5a**−**h** are reported in Figure 2.

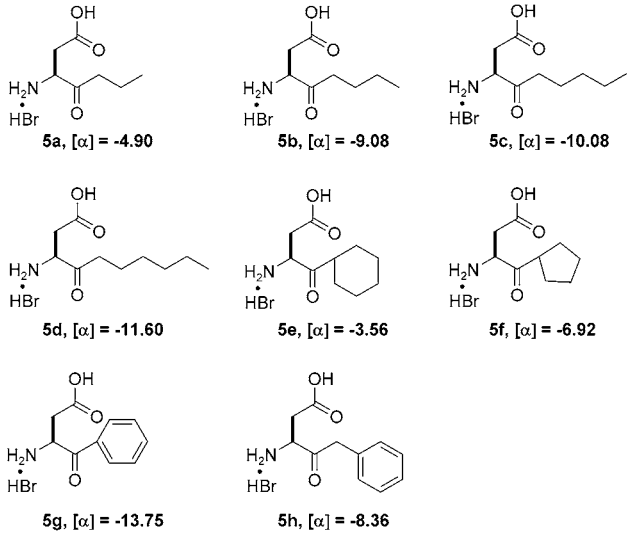
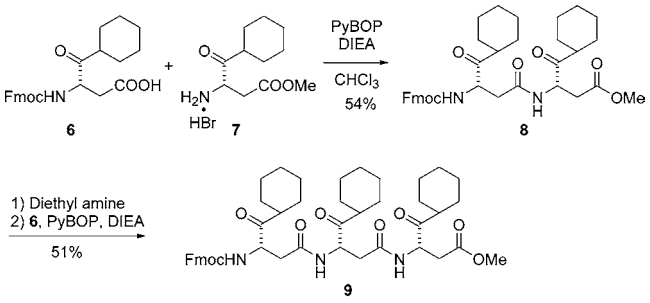


Figure 2. β-Amino-γ-keto acids and their optical rotations.

As ketones provide easily exploitable reactivity, their incorporation into biopolymers allows for facile, site-specific modification of macromolecules.[12] In addition, a peptide composed entirely of β-amino-γ-keto acids would be expected to have markedly different H-bonding properties relative to other β-peptides. To demonstrate that the β-amino-γ-keto acids synthesized herein can readily be incorporated into peptides, we created a β-peptide trimer of the cyclohexyl-substituted β-amino-γ-keto acid **5e** (Scheme 2). The synthesis of this β-amino acid peptide was performed using standard techniques for peptide coupling and purification. Thus, Fmoc-protected acid **6** was coupled to the methyl ester derivative **7** to provide the dimer **8**. After Fmoc deprotection and a further round of coupling, the trimer **9** was obtained (Scheme 2). Although β-peptide **9** is a homopolymer, the synthesis of heteropolymers consisting of various β-amino-γ-keto acids, or the selective incorporation of one ketonic functionality into a standard β-peptide can easily be envisioned. Thus, the facile synthesis of a variety of β-amino-γ-keto acids as described herein should also allow for the production of an array of β-peptides containing ketone side chains.

Scheme 2. Synthesis of a Trimeric β-Peptide Composed of β-Amino-γ-keto Acid Monomers



Described herein is a four-step synthesis of β-amino-γ-keto acids from commercially available L-homoserine. This synthetic route requires only one chromatographic purification, and provides the desired products with no detectable racemization of the stereocenter. These compounds will be useful as chiral building blocks for combinatorial synthesis and as monomers for β-peptide formation. Using standard amino acid couplings, a trimer was created from the cyclohexyl-substituted compound **5e**. Application of these chiral β-amino-γ-keto acids to a variety of problems of biological interest will be reported in due course.

Acknowledgment. We thank the University of Illinois and the National Science Foundation (NSF-CAREER Award to P.J.H., CHE-0134779) for support of this research. P.J.H. is the recipient of a Research Innovation Award from the Research Corporation and of a Beckman Young Investigator Award.

Supporting Information Available: Full experimental protocols and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0345327

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