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New Synthetic Technology for Efficient Construction of α-Hydroxy-β-amino Amides via the Passerini Reaction[1]

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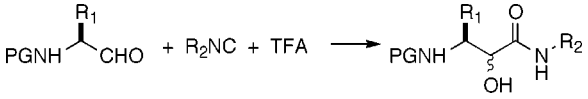
ABSTRACT



The Passerini reaction of *N*-protected amino aldehydes, isonitriles, and TFA using pyridine-type bases proceeds under mild conditions and directly affords α-hydroxy-β-amino amide derivatives in moderate to high yields. These adducts are readily hydrolyzed to α-hydroxy-β-amino carboxylic acids. Application of these key intermediates to concise syntheses of P_1-α-ketoamide protease inhibitors is illustrated.

α-Hydroxy-β-amino carboxylic acid and amide subunits are found in numerous pharmaceuticals and natural products that express potent biological activity.[2] Prominent examples of α-hydroxy-β-amino carboxylates ("norstatines") have recently emerged, underscoring their importance in medicinal chemistry. The clinically proven anticancer drug paclitaxel (Taxol) features *N*-benzoyl-3-phenylisoserine **1** esterified to the C-13 hydroxyl function of baccatin III[3] (Figure 1). Bestatin **2** is a prototypical member of a growing family of peptidyl α-hydroxy-β-amino amide natural products isolated from bacterial cultures that demonstrate potent inhibition of aminopeptidases and prolyl endopeptidases.[4]

These subunits also serve as convenient, chemically stable precursors for the synthesis of α-ketoamide transition-state analogue inhibitors of serine[5] and cysteine[6] proteases. α-Ketoamide scaffolds, including the potent thrombin inhibitor **3**[7] and the calpain inhibitor **4**,[8] serve as useful leads in drug discovery platforms, while the biologically active natural products cyclotheonamide[9] and eurystatin **5**[10] incorporate the reactive α-ketoamide moiety in a macrocyclic array.

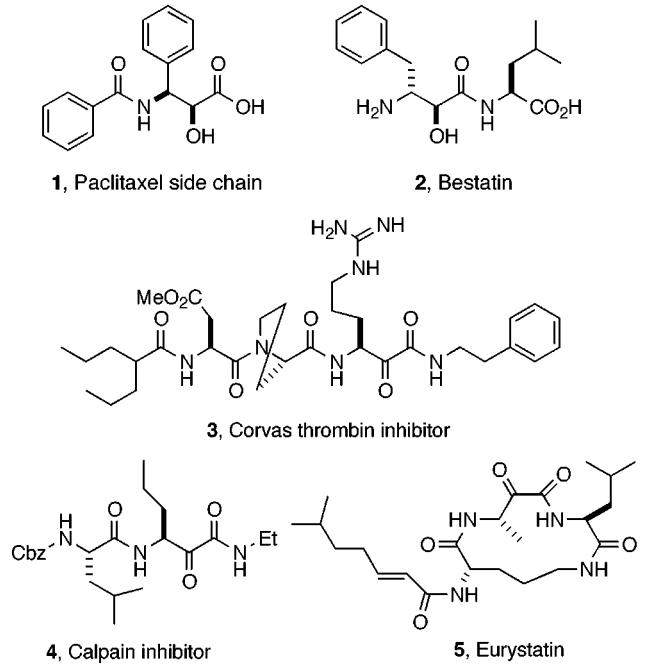


Figure 1. Representative examples of biologically active α-hydroxy-β-amino acid, α-hydroxy-β-amino amide, and α-ketoamide derivatives.

(1) Dedicated to the memory of Joseph E. Semple.

(2) Semple, J. E. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco, CA, March 26−30, 2000; American Chemical Society: Washington, DC, 2000; ORGN.667.

(3) Taxol: (a) Ha, H. J.; Park, G. S.; Ahn, Y. G.; Lee, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1619. (b) Review: Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Intl. Ed. Engl.* **1994**, *106*, 38.

(4) Bestatin: (a) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 600. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235 and references therein.

(5) Semple, J. E.; Rowley, D. C.; Brunck, T. K. Ripka, W. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 315.

(6) Otto, H. H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133.

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As a result of their diverse structural variety, profound biological activity, and synthetic utility, approaches to α-hydroxy-β-amino carboxylate classes have received increased attention over the past decade. Although these methods often proceed with satisfactory to high levels of stereocontrol,[11] final target preparation usually requires many steps. Classical approaches, such as homologation of α-amino aldehydes **6** via cyanohydrin,[12] 2-(TMS)-thiazole,[13] or orthothioformate[14] procedures, continue to receive considerable attention due to their utility and practicality, even though products obtained by these protocols are diastereomeric at the newly created α-hydroxy center. Although each of the above methods has merits, limitations in scope are also evident.

Our exploratory programs on small molecule covalent inhibitors of the blood coagulation proteases thrombin (fIIa)[15] and factor Xa (fXa),[16] the plasminogen activator urokinase (uPA),[17] and the NS3A hepatitis C virus (HCV) protease[18] necessitated the development of new synthetic technology for the rapid construction of diverse α-hydroxy-β-amino carboxylic amide and acid derivatives such as **7** and **8** (Figure 2). In our laboratories, elaboration of these intermediates is followed by a late-stage oxidation step, which minimizes racemization issues with the P_1-α-ketoamide targets **9**.[5,11,14]

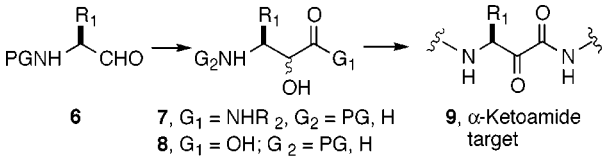


Figure 2. Strategy for the construction of α-hydroxy-β-amino amides **7** and corresponding acids **8** from aldehyde **1** and their potential elaboration into α-ketoamide subunit **9**. PG denotes *N*-protecting group.

We envisioned that application of the classic Passerini reaction employing *N*-α-protected amino aldehydes **6** as substrates would provide a novel, concise approach to these key synthons while complimenting current and more traditional protocols. In this Letter, we report the successful implementation of this strategy, which has demonstrated broad scope and general utility.

The Passerini reaction is a powerful, atom-economical, multiple-component reaction (MCR) between isonitrile, aldehyde (or ketone), and carboxylic acid components[19] that generates a significantly more complex α-acyloxy−carboxamide adduct. Related protic or Lewis acid-catalyzed processes[20] between isonitrile, aldehyde (or ketone), and water components afford α-hydroxyamide derivatives. The scope of the latter reactions may be limited since they occur under vigorous, highly acidic conditions that may not be tolerated by delicate or sensitive functionalities.

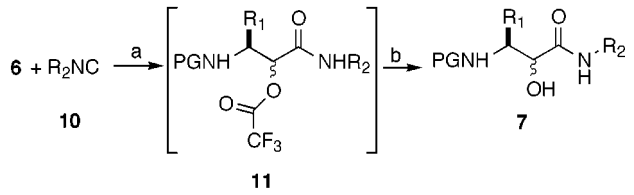
In accordance with the proposed Passerini mechanism,[19c] reaction of protected α-amino aldehydes **6**, isonitriles **10**, and trifluoroacetic acid in the presence of a pyridine-type base leads directly to α-hydroxy-β-amino amide derivatives **7** in moderate to excellent yield (Scheme 1). Presumably, the reaction proceeds through trifluoroacetoxy intermediate **11**, which undergoes facile hydrolysis upon extractive workup with saturated aqueous sodium bicarbonate solution and/or silica gel flash chromatographic purification, and delivers product **7**.[21] Thus, application of this technology allows for the concise construction of α-hydroxy-β-amino amide-containing molecules that traditionally require many steps to prepare.

The reactions proceed under mild, nearly neutral conditions, typically from 0 °C to ambient temperature. Dichloromethane is the solvent of choice. In our hands, this chemistry is readily scalable from 0.1 mmol to 0.5 mol. In cases with less reactive aldehyde or isonitrile components, higher reactant concentrations (ca. 0.5−5 M) or slow removal of solvent affords the best yield of adduct **7**.

To illustrate the scope and generality of the method, 20

(7) Webb, T. R. Miller, T. A.; Vlasuk, G. P. U.S. Pat. 5371072, 1994.
(8) Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett, R.; Carroll, R. M.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. *J. Med. Chem.* **1994**, *37*, 2918.
(9) (a) Fusetani, N.; Matsunaga, S.; Matsumoto, H.; Takebayashi, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7053. (b) Maryanoff, B. E.; Greco, M. N.; Zhang, H. C.; Andrade-Gordon, P.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225.
(10) (a) Schmidt, U. Weinbrenner, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1003. (b) Wasserman, H. H.; Peterson, A. K. *J. Org. Chem.* **1997**, *62*, 8972.
(11) For an excellent compilation of the leading stereospecific and asymmetric approaches to α-hydroxy-β-amino acids and amides, see: Wasserman, H. H.; Xia, M.; Jorgensen, M. R.; Curtis, E. A. *Tetrahedron Lett.* **1999**, *40*, 6163 and references therein.
(12) See refs 4a, 5a, 7, 8, 9b,c and Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kuboto, T.; Umeyama, H.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707.
(13) (a) Review: Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35. (b) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162. (c) Piron, J.; Tourwe, D. *Lett. Pept. Sci.* **1995**, *2*, 229.
(14) (a) Brady, S. F.; Sisko, J. T.; Stauffer, K. J.; Colton, C. D.; Qui, H.; Lewis, S. D.; Ng, A. S.; Shafer, J. A.; Bogusky, M. J.; Veber, D. F.; Nutt, R. F. *Bioorg. Med. Chem.* **1995**, *3*, 1063. (b) Iwanowicz, E. J.; Lin, J.; Roberts, D. G. M.; Michel, I, M.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607.
(15) (a) Minami, N. K.; Reiner, J. E.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2625. (b) Reiner, J. E.; Lim-Wilby, M. S.; Brunck, T. K.; Uong, T. H.; Goldman, E. A.; Abelman, M. A.; Nutt, R. F.; Semple. J. E.; Tamura S. Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 895. (c) Semple, J. E. *Tetrahedron Lett.* **1998**, *39*, 6645.
(16) (a) Tamura, S. Y.; Levy, O. E.; Reiner, J. E.; Uong, T. H.; Goldman, E. A.; Brunck, T. K.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 745. (b) Ho, J. Z.; Levy, O. E.; Gibson, T. S.; Nguyen, K.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3459.
(17) Tamura, S. Y.; Weinhouse, M. I.; Roberts, C. A.; Goldman, E. A.; Masukawa, K.; Anderson, S. M.; Cohen, C. R.; Bradbury, A. E.; Bernadino, V. T.; Dixon, S. A.; Ma, M. G.; Nolan, T. G.; Brunck, T. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 983.
(18) Han, W.; Hu, Z.; Jiang, X.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 711 and references therein.
(19) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M.; Ragni, G.; *Gazz. Chim. Ital.* **1931**, *61*, 964. (c) Ugi, I. in *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971, Chapter 7. (d) Bienayme, H. *Tetrahedron Lett.* **1998**, *39*, 4255. (e) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (f) Ziegler, T.; Kaisers, H. J.; Schlomer, R.; Koch, C. *Tetrahedron* **1999**, *55*, 8397.
(20) (a) Aqueous mineral acid-catalyzed versions: Hagedorn, I.; Eholzer, U. *Chem. Ber.* **1965**, *98*, 936. (b) Lewis-acid catalysis with BF_3·Et_2O or $AlCl_3$ to directly produce α-hydroxyamides: Muller, E.; Zeeh, B. *Liebigs Ann. Chem.* **1966**, *696*, 72. (c) BF_3·Et_2O catalysis: Muller, E.; Zeeh, B. *Liebigs Ann. Chem.* **1968**, *715*, 47. (d) $TiCl_4$ activation: Carofiglio, T.; Cozzi, P. G.; Floriani, C.; Chiesa-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 2726. (f) Seebach, D.; Adam, G.; Gees, T.; Schiess, M.; Weigand, W. *Chem. Ber.* **1988**, *121*, 507. (g) Seebach, D.; Schiess, M. *Helv. Chim. Acta* **1983**, *66*, 1618.

Scheme 1[a]



[a] Reagents and conditions: (a) 2 equiv of TFA, 4 equiv of pyridine, CH_2Cl_2, 0 °C to rt; (b) extractive workup or silica gel flash chromatography.

protected α-amino aldehyde derivatives **6**[22] and 7 representative isonitriles **10**[19] were subjected to the reaction conditions. The resulting products **7a**−**y** are collected in Table 1, where 25 examples embracing a variety of α-*N*-protecting groups and assorted side-chain functionalities are shown.[23] Allyl ester derivatives **7k**−**y**, featuring orthogonal protecting groups, served as versatile intermediates for the construction of focused α-ketoamide protease inhibitor libraries. Full details of this chemistry will be disclosed in a separate communication.[24]

In agreement with literature precedent, formation of the new hydroxy methine center proceeds without appreciable stereoselectivity.[19f,20f] We typically observed ca. 1:1 to 3:1 diastereomeric ratios by NMR and HPLC analysis. However, we note retention of configuration at the original aldehyde and isonitrile (cf. **7j**) chiral centers. For applications to our ultimate α-ketoamide targets (cf. **17** below), the stereochemistry at the α-hydroxy center is inconsequential since it is removed during a late-stage oxidation step. Nonetheless, we are intrigued by the prospect of effecting a stereocontrolled Passerini reaction since this would further enhance the utility of the technology.

Table 1. α-Hydroxy-β-amino Amides **7a**−**y** Produced via TFA-Catalyzed Passerini Reaction of Scheme 1

compd **7**	PG	R_1	R_2	% yield
a	Boc	$(CH_2)_3NHC(=NH)NHNO_2$	*t*-Bu	92
b	Boc	CH_2Ph	*t*-Bu	78[a]
c	Boc	CH_2Chx	*t*-Bu	46
d	Boc	CH_2SMe	CH_2CO_2Me	62
e	Fmoc	$CH(CH_3)_2$	CH_2CO_2t-Bu	68
f	Fmoc	CH_2Ph-4-(*t*-BuO)	CH_2CO_2Et	69
g	Boc	$(CH_2)_3NHC(=NH)NHNO_2$	CH_2CO_2Et	37
h	Fmoc	$(CH_2)_3NHC(=NH)NHPmc$	CH_2CH_2Ph	75
i	Boc	CH_2Ph	CH_2CO_2Allyl	67
j	Cbz	*d*-CH_2Ph	(*S*)-CH(*i*-Bu)CO_2Bn	65
k	Fmoc	H	CH_2CO_2Allyl	77
l	Fmoc	CH_3	CH_2CO_2Allyl	83
m	Fmoc	CH_2CH_3	CH_2CO_2Allyl	73
n	Fmoc	$CH(CH_3)_2$	CH_2CO_2Allyl	68
o	Fmoc	$(CH_2)_2CH_3$	CH_2CO_2Allyl	87
p	Fmoc	$CH_2CH(CH_3)_2$	CH_2CO_2Allyl	85
q	Fmoc	$(CH_2)_3CH_3$	CH_2CO_2Allyl	69
r	Fmoc	CH_2Ph	CH_2CO_2Allyl	67
s	Fmoc	CH_2Ph-4-(*t*-BuO)	CH_2CO_2Allyl	66
t	Fmoc	CH_2Ot-Bu	CH_2CO_2Allyl	68
u	Fmoc	CH_2CO_2t-Bu	CH_2CO_2Allyl	60
v	Fmoc	$(CH_2)_3NHC(=NH)NHPmc$	CH_2CO_2Allyl	76
w	Fmoc	$(CH_2)_4NHBoc$	CH_2CO_2Allyl	79
x	Fmoc	$CH_3(CH)Ot$-Bu	CH_2CO_2Allyl	62
y	Fmoc	*allo*-$CH_3(CH)Ot$-Bu	CH_2CO_2Allyl	74

[a] Yield of **7b** using 2,4,6-collidine as base.

While TFA serves as an essential component of this MCR, it is also a relatively strong acid ($pK_a = 0.3$) whose presence may lead to undesired side reactions. Indeed, in the absence of pyridine, complex mixtures resulted when reactants containing *N*-Boc or *tert*-butyl ester protecting groups were employed. Using the formation of intermediate **7o** from allyl isocyanoacetate and *N*-α-Fmoc-nVal-H as a model reaction, we surveyed a variety of organic bases whose pK_a values ranged from 5 to 11. In general, tertiary trialkylamines gave inferior results. Pyridine, 2,6-lutidine, 2,4,6-collidine, and 2,6-di-*tert*-butylpyridine, with pK_a's of 5.2−7.4, were optimal and provided adduct **7o** in 68−87% yield. Furthermore, utilization of these mild pyridine bases minimizes the potential for α-amino aldehyde racemization that may occur in the presence of stronger trialkylamine bases.[22] Although other more subtle mechanistic factors cannot be excluded,[20d,21] our results suggest that the pyridine-type additives simply serve as mild and efficient bases in these Passerini reactions.

We quickly adapted this technology to a concise synthesis of bestatin **2**[4] (Scheme 2). Thus, reaction of *N*-α-Cbz-*d*-Phe-H **12** and the isonitrile derivative **13** (each freshly prepared in two steps as outlined and utilized immediately) with TFA in pyridine produced adduct **7j** in 65% yield. NMR and HPLC analysis of **7j** indicated a ca. 1.5:1 mixture of diastereomers at the new hydroxy center with retained configuration at the original aldehyde and isonitrile chiral centers. Separation of the α-hydroxy diastereomers, hydrogenolysis, and HPLC separation afforded bestatin **2** in satisfactory overall yield.[25]

(21) Passerini reaction of simple aldehydes and ketones with TFA and pyridine: Lumma, W. *J. Org. Chem.* **1981**, *46*, 3668.

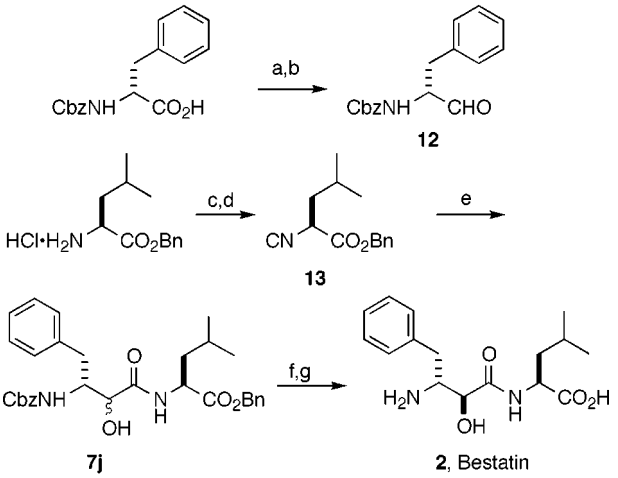
(22) (a) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359. (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (c) Ho, P. T.; Ngu, K. *J. Org. Chem.* **1993**, *58*, 2313. (d) Hyun, S. I.; Kim, Y. G. *Tetrahedron Lett.* **1998**, *39*, 4299. (e) Fehrentz, J. A.; Pothion, C.; Califano, J. C.; Loffet, A.; Martinez, J. *Tetrahedron Lett.* **1994**, *35*, 9031.

(23) All new compounds were characterized by full spectroscopic (NMR, low/high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (≥95% by HPLC, TLC) materials. **General procedure for the synthesis of 7a**−**y**: Trifluoroacetic acid (2.0 equiv) was added dropwise to a cooled solution (−10 to 0 °C) of freshly prepared α-*N*-protected-amino aldehyde (1.0 equiv), isonitrile (1.2−1.5 equiv), and pyridine (4.0 equiv) in dichloromethane [0.25−2.0 M] under a nitrogen atmosphere while maintaining the temperature at ≤0 °C. After 0.5−2 h at 0 °C, the bath was removed and the reaction was stirred at ambient temperature for 12 to 72 h. In cases with sluggish reactants, the solution was slowly concentrated to afford a heavy oil, which was further stirred until TLC or HPLC analysis revealed complete consumption of the α-amino aldehyde component. The resultant slurry was dissolved in ethyl acetate and extracted successively with three portions each of 1 N HCl, a saturated $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was either recrystallized or purified by flash column chromatography on silica gel using ethyl acetate/hexane or dichloromethane/methanol gradient systems. Pure products were obtained as either nearly colorless solids or as colorless to pale yellow viscous oils.

(24) Levy, O. E.; Nguyen, K.; Owens, T. D.; Semple, J. E. 16th American Peptide Symposium, Minneapolis, MN, June 26−July 1, 1999; P.6653.

(25) ^1H NMR and ^{13}C NMR data for bestatin **2** was in full agreement with literature values[4b] and matched an authentic commercial sample (Sigma). Chiral HPLC: $t_R = 14.0$ min (Chiracel AD column; 2-propanol, hexane 10−30% gradient; 0.5 mL/min flow rate).

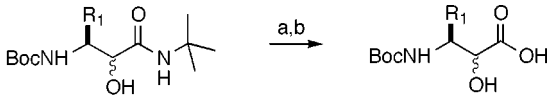
Scheme 2[a]



[a] Reagents and conditions: (a) BH_3·THF, 0 °C to rt, 84%; (b) Pyr·SO_3, Et_3N, DMSO, CH_2Cl_2, ∼5 °C to rt, ∼quant.; (c) CH_3CO_2CHO, Et_3N, 0 °C to rt, 98%; (d) Cl_3CO_2CCl, NMM, CH_2Cl_2, −40 to −15 °C, 86%; (e) **12**, TFA, pyridine, CH_2Cl_2, 0 °C to rt, 65%; (f) H_2, Pd/C; (g) HPLC separation, 29% for two steps.

Selected *tert*-butyl amide intermediates serve as precursors for the preparation of norstatine derivatives (Scheme 3). The

Scheme 3[a]



7a, R = $(CH_2)_3NHC(NH_2)$=N-NO_2
7b, R = CH_2Ph
7c, R = CH_2Chx

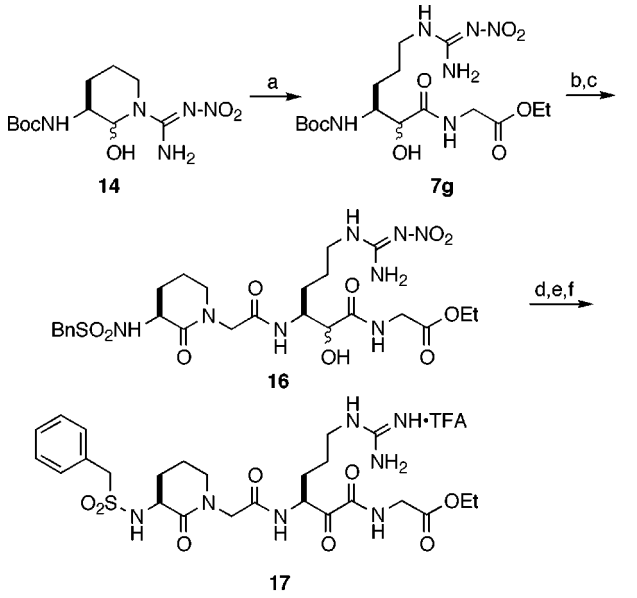
8a, 52%, 250 mg
8b, 93%, 23 g
8c, 72%, 1.7 g

[a] Reagents and conditions: (a) 6 N HCl, 70 °C to reflux; (b) Boc_2O, Na_2CO_3, H_2O; $NaHSO_4$, H_2O.

appropriate *tert*-butylamide precursors **7a**−**c** were obtained in 46−92% yields as described above (Table 1). Interestingly, Passerini adduct **7b** was obtained in 71% or 24% yield with added 2,4,6-collidine or pyridine, respectively, underscoring the importance of judicious base selection. Hydrolysis followed by *N*-*β*-reprotection with Boc_2O to facilitate product isolation and purification afforded the α-hydroxy-*N*-*β*-Boc-amino acid derivatives **8a**−**c** in the listed quantities and in satisfactory overall yields.

Scheme 4 outlines the synthesis of the novel, potent α-ketoargininamide thrombin inhibitor **17** using our new

Scheme 4[a]



[a] Reagents and conditions: (a) $CNCH_2CO_2Et$, TFA, pyridine, CH_2Cl_2, 0 °C to rt, 38%, (see Table 1); (b) HCl, EtOH, 0 °C, 10 min, ∼quant.; (c) (*S*)-2-oxo-3-(BnSO_2-amino)piperidine-1-acetic acid **15**, EDC, HOBt, DIEA, CH_3CN, rt, 68%; (d) H_2, Pd/C, HOAc, EtOH, H_2O, 40 psi, ∼quant.; (e) DMSO, EDC, Cl_2CHCO_2H, toluene, 0 °C to rt; (f) RP-HPLC, 61%.

technology as the key step. In this concise approach, *N*-α-Boc-arginal **14**[26] was reacted with ethyl isocyanoacetate and TFA, employing pyridine as base, and produced the adduct **7g** as a ca. 1:1 mixture of α-hydroxy diastereomers.

Our previous route to this intermediate proceeded in seven steps from **14** via a classical cyanohydrin homologation−peptide coupling protocol.[5,7] Cleavage of the Boc group to generate the corresponding amino alcohol was followed by coupling with lactam acetic acid derivative **15**[26] and delivered the advanced intermediate **16**. Hydrogenolysis, followed by Moffatt oxidation and RP-HPLC purification, provided the α-ketoamide target **17** in good overall yield and with the indicated chirality.

In conclusion, the Passerini reaction of α-amino aldehydes **6**, isonitriles **10**, and TFA in the presence of pyridine-type bases proceeds under mild conditions and provides a concise route to α-hydroxy-*β*-amino amide derivatives **7a**−**y**. Hydrolysis of representative adducts afforded the corresponding α-hydroxy-*β*-amino acids **8a**−**c**. Both classes serve as useful advanced intermediates for the synthesis of biologically active molecules. We envision broad applications of this new technology to α-hydroxy-*β*-amino amides, α-hydroxy-*β*-amino acid derivatives, peptidyl and peptidomimetic α-ketoamide protease inhibitors, and natural products featuring α-ketoamide moieties.[27]

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(26) Semple, J. E.; Rowley, D. C.; Brunck, T. K.; Ha-Uong, T.; Minami, N. K.; Owens, T. D.; Tamura, S. Y.; Goldman, E. A.; Siev, D. V.; Ardecky, R. J.; Carpenter, S. H.; Ge, Y.; Richard, B. M.; Nolan, T. G.; Håkanson, K.; Tulinsky, A.; Nutt, R. F.; Ripka, W. C. *J. Med. Chem.* **1996**, *39*, 4531.

(27) After this paper was submitted, we became aware of a recent related publication: Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985.