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Efficient Synthesis of β^2-Amino Acid by Homologation of α-Amino Acids Involving the Reformatsky Reaction and Mannich-Type Imminium Electrophile

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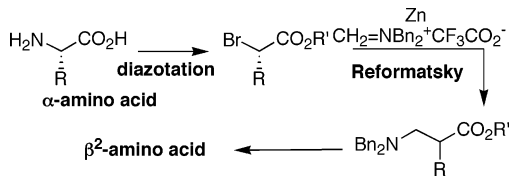

Development of new methods for the synthesis of β-amino acids is important as polymers of these compounds are promising peptidomimetic candidates in medicinal chemistry. We report here our findings on a new and highly efficient general strategy for the synthesis of β^2-amino acids by homologation of α-amino acids, involving the Reformatsky reaction and Mannich-type imminium electrophile.

The control of both stability and three-dimensional structure of peptides and proteins by chemical modifications of proteinogenic amino acids has been the keystone of peptide chemistry for the past decades. The aim of these studies is the development of compounds with improved selectivity, bioavailability, stability, and permeability.[1] Such goals may be successfully reached with β-peptides. Indeed, Gellman[2] and Seebach[3] have shown that short polymers made of β-amino acids can fold to form predictable secondary structures in solution. Moreover, these compounds are stable to cleavage by peptidases[4] and can mimic α-peptides in biological interactions.[3,5]

Apart from polysubstituted derivatives, β^2- and β^3-amino acids can be distinguished regarding the position of the side chain on the 3-aminopropanoic acid skeleton. If most of the β^3-amino acids bearing proteinogenic side chains are easily obtained by Arndt−Eistert homologation of α-amino acids,[6] preparation of β^2-amino acids is much more difficult. Several methodologies have been suggested for this purpose,[7] involving, for instance, the diastereoselective alkylation of a chiral derivative of β-alanine,[8] Curtius rearrangement of a chiral succinate,[9] or conjugate addition of nitrogen[10] or carbon nucleophile[11] to the appropriate Michael acceptor. One of the most useful strategies, based on the pioneering work of Evans[12] and Oppolzer,[13] is the aminomethylation of a chiral precursor, which bears the side chain of the amino acid.[14] Noticeably, Seebach et al. have successfully used this methodology for the preparation of a wide range of β^2-amino acids.[9b,15] However, the low reactivity of the used aminomethylating reagent makes this method inefficient in some cases; in particular, the preparation of amino acids bearing a functional group on their side chain required multistep procedures. In some cases, it was necessary to use an alternative, which consists of the introduction of a carboxymethyl group followed by Curtius rearrangement.[9b] Although good yields and diastereoselectivities are generally obtained, the multiplication of the number of steps limits the application of such a method to laboratory scale. Thus, it appears necessary to us to develop a new scalable strategy for the synthesis of these compounds, particularly for amino acids bearing a functional group on their side chain. The aim of this work is the production of these compounds on an industrial scale.

We report here our findings on a new and highly efficient general strategy for the synthesis of β^2-amino acids starting from α-amino acids, via the Reformatsky reaction and Mannich-type iminium electrophile. The classical Reformatsky reaction in-

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(1) Karoyan, P.; Sagan, S.; Lequin, O.; Quancard, J.; Lavielle, S.; Chassaing, G. *Targets Heterocycl. Syst.* **2004**, *8*, 216.

(2) Cheng, P. R.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.

(3) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiv.* **2004**, *1*, 1111.

(4) (a) Frakenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445. (b) Sagan, S.; Milcent, T.; Ponsinet, R.; Convert, O.; Tasseau, O.; Chassaing, G.; Lavielle, S.; Lequin, O. *Eur. J. Biochem.* **2003**, *270*, 939.

(5) Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.* **2005**, *13*, 11.

(6) Ellmerer-Müller, E. P.; Brössner, D.; Maslouh, N.; Tako, A. *Helv. Chim. Acta* **1998**, *81*, 59.

(7) Lelais, G.; Seebach, D. *Biopolymers (Peptide Sci.)* **2004**, *76*, 206.

(8) (a) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553. Juaristi, E.; Quintana, D.; Balderas, M.; Garcia-Perez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233. (b) Seebach, D.; Boog, A.; Schweizer, W. B. *Eur. J. Org. Chem.* **1999**, 335. (c) Ponsinet, R.; Chassaing, G.; Vaissermann, J.; Lavielle, S. *Eur. J. Org. Chem.* **2000**, 83. (d) Gutiérez-Garcia, V. M.; Reyes-Rangel, G.; Lopez-Ruiz, H.; Juaristi, E. *Tetrahedron* **2001**, *57*, 6487. Gutiérez-Garcia, V. M.; Reyes-Rangel, G.; Munoz-Muniz, O.; Juaristi, E. *Helv. Chim. Acta*, **2002**, *85*, 4189. (e) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527.

(9) (a) Sibi, M. P.; Deshpande, P. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1461. (b) Seebach, D.; Schaeffer, L.; Gessier, F.; Bindschädler, P.; Jäger, C.; Josien, D.; Kopp, S.; Lelais, G.; Mahayan, Y. R.; Micuch, P.; Sebesta, R.; Schweiser, B. W. *Helv. Chim. Acta* **2003**, *86*, 1852.

(10) Lee, H. S.; Park, J. S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575. Bedow, J. E.; Davies, S. G.; Smith, A. D.; Russel, A. J. *J. Chem. Soc., Chem. Commun.* **2004**, 2778.

(11) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79. Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189. Dursma, A.; Minard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700.

(12) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(13) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.

(14) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437. Arvanatis, T. E.; Ernst, H.; Ludwig, A. A.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 521.

(15) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093. Sebesta, R.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4061. Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2460. Seebach, D.; Namoto, K.; Mahajan, Y. R.; Bindschädler, P. *Chem. Biodiversity* **2004**, *1*, 65.

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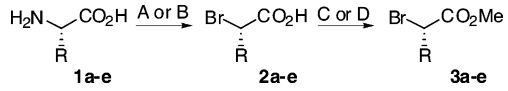
SCHEME 1. Synthesis of α-Bromoacetate Esters[a]



[a] Key: (A) $NaNO_2$, NaBr, 2.5 M H_2SO_4; (B) $NaNO_2$, NaBr, 0.75 M HBr; (C) MeOH, cat. H_2SO_4, reflux; (D) CH_3COCl, MeOH, rt.

TABLE 1. Reaction Conditions (RC) for the Synthesis of α-Bromoacetate Esters

			yield (RC) (%)	
L-amino acids	entry	R	**2**	**3**
Ala	**a**	CH_3	ca[a]	
Leu	**b**	*i*Bu	70 (A)	79 (C)
Phe	**c**	CH_2Ph	90 (A)	94 (C)
Trp(*N*-Boc)	**d**	CH_2-(3-indolyl-*N*-Boc)	67 (B)	59 (D)
Asp (O-*t*-Bu)	**e**	CH_2CO_2tBu	86 (B)	51 (D)

[a] ca: commercially available.

volved nucleophilic species resulting from zinc insertion into carbon−halogen bonds of α-haloacetate esters.[16] Such esters, bearing proteinogenic side chains, when not commercially available, are easily obtained starting from α-amino acids as originally reported by Izumiya and others[17] (Scheme 1). The amine moiety can be diazotized and converted to the α-bromo acid, which is subsequently esterified under conditions suitable for classical protective groups for peptide synthesis, as described in Table 1.

In the classical Reformatsky reaction, the nucleophilic zinc enolate intermediate is reacted with aldehydes or ketones, leading to β-hydroxyalkanoates. The scope of the reaction has been extended to various electrophiles.[16] Gilman and Speeter have first reported the addition of the zinc enolate on benzalaniline-type Schiff bases in refluxing toluene.[18] In that case, the intermediately formed zinc complex cyclized to give the β-lactam. In a more detailed study of this reaction, Dardoize et al.[19] have reported that cyclization might be avoided and β^3- or $\beta^{2,3}$-amino esters could be obtained with aldimine Schiff bases, depending on the Schiff base, temperature, and solvent used for the reaction. The addition of the zinc enolate on nonsubstituted Schiff bases (i.e., formylimine derivatives that would lead to β^2-amino esters) was not reported due to the inaccessibility of reactive formylimine equivalent. Interestingly, Mannich-type iminium ions are very reactive aminomethylating agents,[20] but no example of the Reformatsky reaction involving this type of ion and zinc enolate of esters was described. Recently, Millot et al. have reported the aminomethylation of organozinc and Grignard reagents using iminium trifluoroacetates.[21]

We have thus explored the scope of these iminium trifluoroacetates regarding the Reformatsky reaction (Scheme 2).

SCHEME 2. Reformatsky's Reaction with Imminium Trifluoroacetate

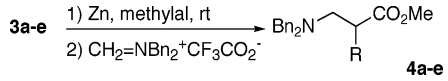
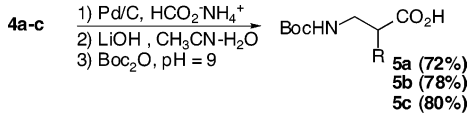


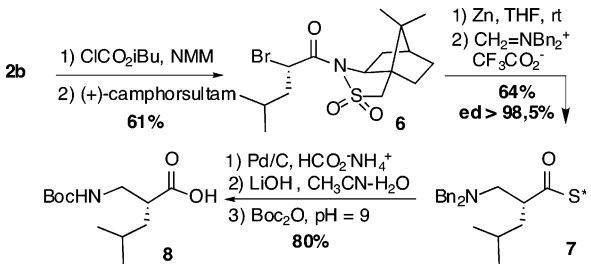
TABLE 2. Yields for the Reformatsky Reaction with Imminium Trifluoroacetate

entry	R	**4** (yield, %)
a	CH_3 (**3a**)	**4a** (43)
b	*i*Bu (**3b**)	**4b** (66)
c	CH_2Ph (**3c**)	**4c** (74)
d	CH_2-(3-indolyl-*N*-Boc) (**3d**)	**4d** (73)
e	CH_2CO_2-*t*-Bu (**3e**)	**4e** (72)

SCHEME 3. Deprotection



SCHEME 4. Asymmetric Aminomethylation



Starting from the α-bromoesters **3a**−**e**, the zinc intermediate was generated, as reported by Dardoize et al,[19a] in formaldehyde−dimethyl acetal at room temperature and reacted with dibenzylidene iminium trifluoroacetate, leading to compounds **4a**−**e** with good yields (Table 2).

Subsequent debenzylation with ammonium formate over palladium charcoal[22] was performed for the derivatives **4a**−**c**. This debenzylation was followed by ester saponification and *N*-Boc protection leading to racemic β^2-amino acids **5a**−**c** suitably protected for peptide synthesis (Scheme 3).

The ease of this reaction led us to explore the asymmetric version of this aminomethylation of the Reformatsky reagent for the synthesis of β^2-homoleucine (Scheme 4), which was needed for our structure−activity relationship studies of biologically active peptides. In the classical Reformatsky reaction, the attachment of chiral auxiliaries (derived from menthol, oxazolidines, or oxazinanes) to halo precursors led to some diastereoselectivity and enantiofacial differentiation.[16] We have chosen Oppolzer's sultam,[23] since good to excellent diastereoselectivities were usually observed with this chiral auxiliary (Scheme 4).

The sodium salt of (+)-10,2-camphorsultam was introduced after activation of the carboxylic function of **2b** with isobutyl chloroformate leading to compound **6**. The aminomethylation was performed in THF, as described above for the racemate, leading to a single stereoisomer according to NMR analysis. The stereochemistry of compound **7** obtained through the

(16) Fürstner, A. *Synthesis* **1989**, 571. Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325.

(17) (a) Izumiya, N.; Nagamtsu, A. *Bull. Chem. Soc. Jpn*. **1952**, *52*, 265. (b) Souers, A. J.; Schürer, S.; Kwack, H.; Virgilio, A. A.; Ellman, J. A. *Synthesis* **1999**, *4*, 583. (c) Shin, I.; Lee, M.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem*. **2000**, *65*, 7667.

(18) Gilman, H.; Speeter, M. *J. Am. Chem. Soc*. **1943**, *65*, 2255.

(19) (a) Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Bull. Soc. Chim. Fr*. **1973**, *5*, 1668 and references therein. (b) Hart, D. J.; Deok-Chang, H. *Chem. Rev*. **1989**, *89*, 1447.

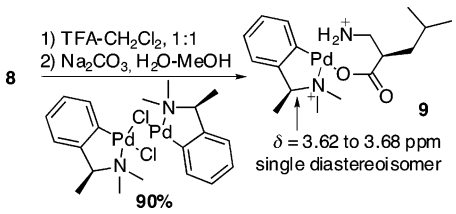
(20) Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* **1979**, *35*, 613.

(21) Millot, N.; Piazza, C.; Avolio, S.; Knochel, P. *Synthesis* **2000**, *7*, 941.

(22) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929.

(23) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009.

SCHEME 5. Enantiomeric Excess



aminomethylation reaction was deduced from comparison of compound **8** optical rotation with an authentic sample[8c] and confirmed by NMR analysis following the methodology reported by Böhm et al (Scheme 5).[24] It should be noted that the stereochemical course of this aminomethylation reaction is identical to that usually observed with Oppolzer's sultam for glycinate-derived enolate.[23]

In conclusion, it has been shown that β^2-amino acids can be prepared by homologation of α-amino acids in few steps. The strategy reported here involved iminium trifluoroacetate that appeared to be an efficient aminomethylating agent in the Reformatsky reaction. The asymmetric synthesis has been successfully tested. We believe that this strategy is of great value for rapid generation of β^2-amino acids. Moreover, the possibility of preparation of β^2-amino acids bearing a functionalized side chain in few steps is particularly attractive, since the procedures described for this purpose are generally long and tedious. Finally, this methodology can be easily scaled up for the industrial production of these compounds, and we are currently working toward this goal.

Experimental Section

General Procedure for the Reformatsky Reaction. To a suspension of zinc dust (1.5 equiv) in methylal (0.5 mL/mmol) was added dibromoethane (20 μL/mmol). The mixture was refluxed for few minutes. A solution of the α-bromo acid (1 equiv) in methylal (1 mL/mmol) was added dropwise. The reaction was stirred at room temperature for 15 min, and the solution of imminium trifluoroacetate was added. The reaction mixture was stirred at room temperature for 1.5 h, quenched with saturated solution of NH_4Cl, and extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, 5% aqueous $Na_2S_2O_3$, and saturated aqueous NH_4Cl and dried ($MgSO_4$). After evaporation of the solvents, the crude product was purified by flash column chromatography.

(*R*)-*N*-(2-Dibenzylaminomethyl-4-methylpentanoyl)camphorsultam 7. Compound **7** was obtained by precipitation from methanol−chloroform as a single diastereoisomer (7.2 g; 64%). Mp = 108 °C. $[\alpha]^{20}_D$: +69.9 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18−7.33 (m, 10H); 3.87 (dd, J = 5 Hz, 7.6 Hz, 1H); 3.68 (d, J = 13,9 Hz, 2H); 3.41−3.52 (m, 5H); 2.76 (dd, J = 6.3 Hz, 12.4 Hz, 1H); 2.50 (dd, J = 12.4 Hz, 7.3 Hz, 1H); 2.00−2.11 (m, 2H); 1.86−1.92 (m, 4H); 1.46−1.56 (m, 3H); 1.31−1.42 (m, 2H); 1.22 (s, 3H); 0.97 (s, 3H); 0.87 (d, J = 5.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.9; 139.1; 129.1; 128.0; 126.8; 65.5; 58.1; 56.5; 53.2; 48.2; 47.8; 44.6; 42.6; 38.8; 38.6; 32.9; 26.5; 26.0; 23.0; 22.7; 21.0; 19.9. Anal. Calcd for $C_{31}H_{42}N_2O_3S$: C, 71.23; H, 8.10; N, 5.36. Found: C, 71.05; H, 8.30; N, 5.11.

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Supporting Information Available: Experimental procedures for all compounds and NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Böhm, A.; Seebach, D. *Helv. Chim. Acta* **2000**, *83*, 3262.