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Asymmetric Synthesis of β-Substituted α-Methyl-β-amino Esters by Mannich Reaction of (*S*,*S*)-(+)-Pseudoephedrine Acetamide Derived Enolate with Imines

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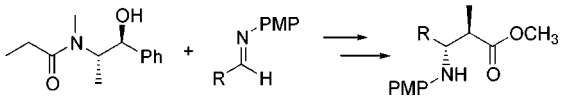
ABSTRACT



The reaction of an (*S*,*S*)-(+)-pseudoephedrine acetamide based enolate with several imines afforded smoothly and with full stereochemical control a series of β-substituted α-methyl-β-aminoamides that upon hydrolysis/esterification afforded the corresponding β-aminoester derivatives in good yields and in almost enantiomerically pure form.

Chiral β-amino acids, although less abundant than their α-counterparts, are important components of numerous natural products and therapeutic agents[1] (e.g., taxol side chain), and they are also key precursors in the synthesis of β-lactam antibiotics.[2] Furthermore, the substitution of α-amino acids for β-amino acids in biologically active peptides has also been used very recently as a promising tactic to prepare peptide analogues with increased potency and enzymatic stability. For these reasons, the asymmetric synthesis of β-amino acid derivatives with different substitution patterns at the carbon chain has become a field of increasing interest in synthetic organic chemistry during the past few years.[3] Among the different methodologies found in the literature for this purpose, one of the most widely used is the nucleophilic addition of an enolate across a C=N bond of an imine or related species.[4] In this context, the strategies employed to exert stereocontrol in the newly created chiral centers involve the introduction of the chiral information at the imine[5] the enolate[6] or by incorporating chiral ligands in the reaction medium either in a stoichiometric[7] or catalytic[8] way.

If we assume that an enolate with one substituent at the α-possition and with a determined geometry (*E* or *Z*) undergoes a Mannich reaction with an imine, four possible estereoisomers can be formed (Figure 1). Under kinetic conditions, the stereochemistry of the first chiral center would be controlled by the approach of the imine from one of the two diastereotopic faces of the enolate (the so-called enan-

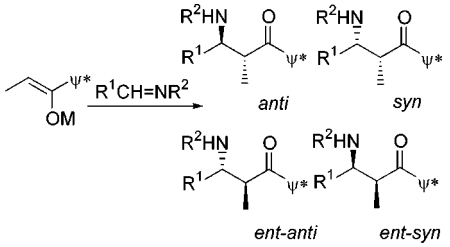


Figure 1.

(1) See, for example: (a) Drey, C. N. C. In *Chemistry and Biochemistry of Amino Acids*; Barret, G. C., Ed.; Chapman and Hall: London, New York, 1985. (b) Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Wiley & Sons: New York, 1983.

(2) For reviews, see: (a) van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503. (b) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (c) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447.

(3) For some reviews, see: (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. See also: (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

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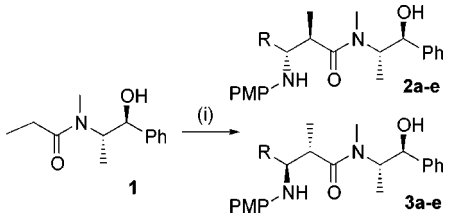
tiofacial differenciation or diastereofacial selectivity) and therefore by the presence of the chiral information attached to the enolate.[9] The stereochemistry of the second chiral center would be controlled by the approach of the imine from one of its two enantiotopic faces (named as simple diastereoselection) and therefore by the steric requirements derived from a cyclic transition state such as a Zimmermann−Traxler-like or related mechanism.[10] The main target when planning a Mannich reaction is to achieve complete stereocontrol in both of the aforementioned aspects, thus allowing the preparation of a single isomer from the four possible ones.

In a previous paper[11] we have reported a very efficient procedure for performing asymmetric aldol reactions in which (*S*,*S*)-(+)-pseudoephedrine acetamide based enolates smoothly reacted with several aldehydes, yielding the corresponding α,*β*-disubstituted *β*-hydroxy acid derivatives in an almost enantiomerically pure form. A further advantage of this methodology is that the amide aldol adducts can be derivatized to a wide range of other synthetically useful chiral synthons and that the auxiliary can be easily removed and recovered.[12] With these results in mind and in connection with our research in the field of asymmetric synthesis,[13] we report herein the further extension of the aforementioned methodology to the reaction of enolates with imines, which has provided access to chiral nonracemic α,*β*-disubstituted *β*-amino acid derivatives.

Propionamide **1** was deprotonated with 2 equiv of LDA, and the dianion formed was reacted with several *p*-anisidine-based imines, leading to the desired *β*-aminoamides in good yields after flash column chromatography purification (Scheme 1).[14]

Scheme 1[a]



[a] (i) 1. LDA, LiCl, THF, −78 °C; 2. RCH=NPMP, THF, 0 °C.

In all cases, the reaction proceeded with extremely high simple (*anti*/*syn* ratio >99:1, Table 1) and facial (**2**/**3** ratio >99:1, Table 1) diastereoselection, and amides **2a**−**e** were obtained as one diastereoisomer out of the four possible ones, attending to the configuration of the two newly created chiral centers, which was verified by HPLC analysis of the crude reaction mixtures under conditions previously optimized for

(4) Recent reviews: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069 (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(5) (a) Müller, R.; Röttele, H.; Henke, H.; Waldmann, H. *Chem. Eur. J.* **2000**, *6*, 2032. (b) Kawecki, R. *J. Org. Chem.* **1999**, *64*, 8724. (c) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (d) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489. (e) Guenoun, F.; Zair, T.; Lamaty, F.; Pierrot, M.; Lazaro, R.; Viallefont, P. *Tetrahedron Lett.* **1997**, *38*, 1563. (f) Kunz, H.; Burgard, A.; Schanzenbach, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 386. (g) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *52*, 1685. (h) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. (i) Cozzi, P. G.; di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691. (j) van Maanen, H. L.; Kleijn, H.; Jastrzebski, J. T. B. H.; Verweij, J.; Kieboom, A. P. G.; van Koten, G. *J. Org. Chem.* **1995**, *60*, 4331. (k) Matsumura, Y.; Tomita, T. *Tetrahedron Lett.* **1994**, *35*, 3737. (l) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1993**, *34*, 6921. (m) Davis, F. A.; Reddy, R. T.; Teddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (n) Andrés, C.; González, A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895. (o) Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1991**, *56*, 1933.

(6) (a) Palomo, C.; Oiarbide, M.; González-Rego, C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063. (b) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Org. Lett.* **1999**, *1*, 107. (c) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1999**, *64*, 8731. (d) Barbaro, G.; Battaglia, A.; Guerrini, A.; Bertucci, C. *J. Org. Chem.* **1999**, *64*, 4643. (e) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. (f) Shimizu, M.; Teramoto, Y.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 729. (g) Braun, M.; Sacha, H.; Galle, D.; El-Alali, A. *Tetrahedron Lett.* **1995**, *36*, 4213. (h) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (i) Nagao, Y.; Dai, W.-M.; Ochiai, M. *Tetrahedron Lett.* **1988**, *29*, 6133. (j) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227. (k) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. (l) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

(7) (a) Fujieda, H.; Janai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (b) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; van Meervelt, L. Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4671. (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Molteni, V.; Raimondi, L. *Tetrahedron* **1995**, *51*, 8941. (d) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (e) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.

(8) For a review, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. See also: (b) Arend, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2873 and references therein. (c) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (d) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (e) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949. (f) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (g) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

(9) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 2.

(10) (a) Bernardi, A.; Gennari, C.; Raimondi, L.; Villa, M. B. *Tetrahderon* **1997**, *53*, 7705. (b) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. (c) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(11) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754.

(12) For the use of (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary, see: (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(13) (a) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *Tetrahedron: Asymmetry* **2000**, *11*, 3779. (b) Carrillo, L.; Badía, D.; Domínguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem.* **1999**, *64*, 1115. (c) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610. (d) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L.; Anakabe, E. *Tetrahedron Lett.* **1999**, *40*, 7123. (e) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1947. (f) Carrillo, L.; Badía, D.; Domínguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716.

(14) In a general experimental procedure, 1 mmol of amide **1** was slowly added to a suspension of LDA (2 mmol) and LiCl (5 mmol) in THF at −78 °C. After 1 h of stirring at this temperature, the mixture was allowed to reach room temperature and stirred for another 15 min. The reaction was then cooled to 0 °C, and a solution of the corresponding imine (4 mmol) was slowly added. The mixture was stirred until TLC analysis of aliquots indicated full conversion (typically 4−6 h). The reaction was quenched with water and extracted with CH_2Cl_2, the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, affording the wanted amides after flash column chromatography purification (hexanes:AcOEt 2:8). All amides gave physical and spectroscopic data consistent with the proposed structures.

Table 1. Stereocontrolled Reaction of Amide **1** with Several Imines

prod.	R	yield (%)[a]	**2**/**3**[b]	*anti*/*syn*[b]
2a	Ph	86	>99:1	>99:1
2b	3,4-$(MeO)_2C_6H_3$	77	>99:1	>99:1
2c	2-furyl	80	>99:1	>99:1
2d	2-thienyl	83	>99:1	>99:1
2e	$(CH_3)_3C$	69	>99:1	>99:1

[a] Yield of product after flash column chromatography purification. [b] Calculated by HPLC (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 70:30, 1.00 mL/min).

a mixture of the four possible isomers (see Supporting Information).

It should also to be pointed out that the presence of LiCl is necessary in the reaction medium, as in its absence only starting materials were recovered. This contrasts with the parent reaction of the same enolate with aldehydes, in which the presence of LiCl was not necessary.[11] We believe that since imines have a much less electrophilic character than aldehydes, a reactivity enhancement on the enolate species is necessary which is provided by the presence of lithium salts as has previously been reported.[15] Also, the fact that an excess of imine (4 equiv) is needed for the reaction to complete in a reasonable time should be interpreted in the same terms.

The results relating to the high diastereofacial control are in accordance with a previously proposed mechanism[12a,13c] in which the adduct of the pseudoephedrine amide Mannich reaction should arise from the attack to the preformed *Z* enolate from the less hyndered *Si* face of an intermediate in an opened staggered conformation, which remains rigid by the help of bridging solvent or ^{i}PrNH (from LDA) molecules (Figure 2). With respect to the high simple diastereoselection,

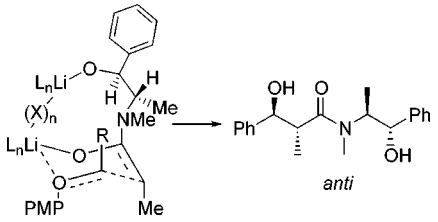
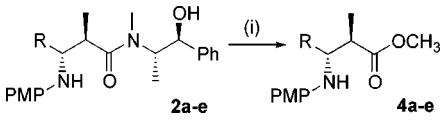


Figure 2. Proposed mechanism for the Mannich reaction. (X) denotes THF or $^{i}Pr_2NH$ molecules.

it is in agreement with a pseudo-chair conformation for the transition state[10] in which the PMP substituent on the imine would lie in an axial possition in order to allow the only available electron couple at the imine nitrogen to coordinate with the lithium atom. Assuming an *E* configuration for the C═N azomethyne bond,[16] this would place the imine R substituent in an axial possition in the cyclic transition state and therefore afford the diastereoisomer of relative *anti* configuration.

The resulting amides **2a**−**e** were subjected to a hydrolysis/esterification procedure, affording the target α-methyl-*β*-amino acid derivatives as their corresponding methyl esters (Scheme 2).[17]

Scheme 2[a]



[a] (i) 1. 4 M H_2SO_4/dioxane, reflux; 2. MeOH, H_2SO_4, reflux.

The aminoesters **4a**−**e** were obtained in good yields after flash chromatography purification and were almost enantiomerically pure as proven by HPLC analysis in a chiral stationary phase under conditions previously optimized for a racemic mixture (see Supporting Information). This also indicates that both conversions performed on the amides **2a**−**e** (hydrolysis and esterification) proceeded without racemization in any of the chiral centers (Table 2).

Table 2. Hydrolysis/Esterification of Amides **2a**−**e**

prod.	R	yield (%)[a]	ee (%)[b]
4a	Ph	83	>99
4b	3,4-$(MeO)_2C_6H_3$	78	>99
4c	2-furyl	68	>99
4d	2-thienyl	72	>99
4e	$(CH_3)_3C$	86	>99

[a] Yield of product after flash column chromatography purification. [b] Calculated by HPLC (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 90:10, 1.00 mL/min).

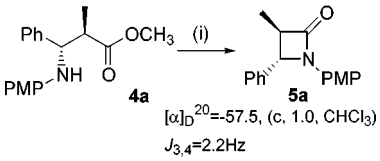
To unambiguously assign the absolute configuration of both chiral centers created in the first reaction, *β*-aminoester

(15) For the effect of LiCl in the reaction of pseudoephedrine amide enolates, see: (a) Rück, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433. See also: (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339 and references therein. (c) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271 and references therein.

(16) All starting imines showed one ^{13}C NMR resonance for the C═N group indicating that only one of the two possible *E*/*Z* isomers of the azomethyne bond was present. The preference for the *E* configuration in imines in which the C═N bond is conjugated with one or more aromatic rings has already been described. Hine, J.; Yeh, C. Y. *J. Am. Chem. Soc.* **1967**, *89*, 2669.

(17) In a typical procedure, a solution of the starting amide (1 mmol) in dioxane (10 mL) was added to a 4 M H_2SO_4 solution (10 mL) and refluxed for 6 h. The volatiles were removed in vacuo and MeOH (15 mL) was added. The mixture was then heated to reflux temperature for an additional 6 h. Water (10 mL) was added, and the mixture was carefully basified with NaOH and extracted with CH_2Cl_2. The collected organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo, affording the desired *β*-aminoesters after flash column chromatography purification (hexanes:AcOEt 1:1). All products gave physical and spectroscopic data consistent with the proposed structures.

Scheme 3[a]



[a] (i) LiN(TMS)$_2$, THF, −20 °C.

4a was transformed under a previously reported base-promoted cyclization[18] into the known β-lactam **5a** (Scheme 3).[19] Comparison of the observed $J_{3,4}$ coupling constants in the ^{1}H NMR spectrum with those reported in the literature[20] ($J_{3,4}$ = 5.8 Hz for the *syn* isomer and $J_{3,4}$ = 2.2 Hz for the *anti* isomer) allowed us to propose an *anti* relative configuration between the two adjacent chiral centers. A comparison of the obtained $[\alpha]^{20}_D$ value for **5a** with that reported in the literature[20] allowed us to establish the absolute configuration of **5a** as (3*R*,4*S*) which should be extended to the rest of the b-aminoesters **4a**−**e** and amides **2a**−**e**.

In summary, a very easy and efficient synthetic protocol for the preparation of chiral α,β-disubstituted-β-aminoesters in almost enantiomerically pure form has been developed using (*S*,*S*)-(+)-pseudoephedrine as a chiral auxiliary. The methodology involves the addition of a pseudoephedrine acetamide enolate to a C=N imine bond followed by hydrolysis/esterification of the resulting adducts. In view of the large number of amides and imines amenable to this process, broad application of this method should be anticipated, thus opening up access to a full range of chiral nonracemic β-amino acid derivatives with different substitution patterns at the alkyl chain. In addition, the fact that pseudoephedrine is inexpensive and commercially available in both enantiomeric forms makes the reported procedure even more attractive from both a synthetic and economic point of view.

Acknowledgment. Financial support from the Basque Government (a fellowship to J.L.V. and Project GV00170.30-7307/19) is gratefully acknowledged.

Supporting Information Available: Experimental details for the determination of *anti*/*syn* and **2**/**3** ratios and ee values of aminoesters **4** by HPLC. This information is available free of charge via the Internet at http://pubs.acs.org.

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(18) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331.

(19) The ^{1}H NMR spectrum of the reaction crude showed the presence of only one diastereoisomer with respect to the relative configuration between both chiral centers. HPLC analysis under conditions optimized for racemic (±)-**5a** (ChiralcelOD, UV detector, *n*-hexane/2-propanol 95:5, 0.80 mL/min) indicated the presence of only one of the two possible ones.

(20) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060.