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A New Strategy for the Synthesis of Optically Pure β-Fluoroalkyl β-Amino Acid Derivatives

Santos Fustero,*,†,‡ Carlos del Pozo,‡ Silvia Catalán,‡ José Alemán,§ Alejandro Parra,§ Vanesa Marcos,§ and José Luis García Ruano*,§

Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain, Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain, and Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

santos.fustero@uv.es; joseluis.garcia.ruano@uam.es

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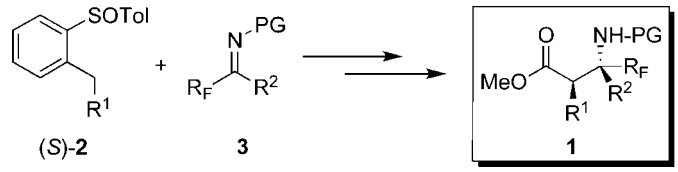
ABSTRACT



The first general approach for the diastereoselective formation of a variety of optically pure *anti*-β-fluoroalkyl β-amino acid derivatives is described. The process relies on the stereocontrolled reaction, mediated by a remote sulfoxide, of fluorinated imines with sulfinylated benzyl carbanions, which are used as synthetic equivalents of chiral ester enolates.

β-Amino acids (β-AAs) play a significant role in medicinal chemistry.[1] They are the structural units of β-peptides, compounds with better pharmacological profiles than natural peptides, displaying highly stable secondary structures and being more resistant to proteolytic degradation.[2] Furthermore, natural products containing β-amino acid units exhibit antibiotic, antifungal, cytotoxic, and other pharmacological properties.[3] In contrast to the wide knowledge about these compounds, very little is known about the chemistry and biological activity of fluorine-containing β-amino acids despite the significant benefits that the substitution of hydrogen by fluorine imparts in organic compounds.[4] Thus, the search for new methodologies for preparing enantiomerically pure fluorinated β-amino acids is of particular interest nowadays.[5]

Among the different substitution patterns of fluorinated β-AAs (Figure 1),[6] α-functionalized β-fluoroalkyl derivatives

† Universidad de Valencia.
‡ Centro de Investigación Príncipe Felipe.
§ Universidad Autónoma de Madrid.

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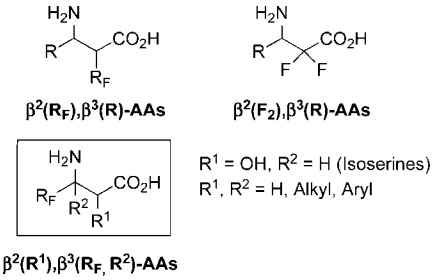


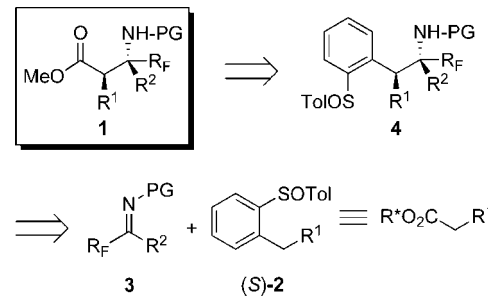
Figure 1. Substitution patterns of acyclic fluorinated β-AAs.

$\beta^2(R^1),\beta^3(R_F,R^2)$-AAs are worth mentioning. Probably, the most representative examples of these are isoserines (R^1 = OH, R^2 = H), substructures found in medicinally relevant molecules such as the antitumoral agents taxol and bestatin. Several stereocontrolled methods for their preparation have been devised.[7] However, methods for synthesizing the α-alkyl analogues (R^1 = alkyl, R^2 = H, alkyl, aryl) are rather scarce. Regarding β-AAs containing a quaternary stereocenter in the β^3 position, their stereoselective synthesis constitutes an enormous challenge for synthetic chemists, which explains why fluorinated β-AAs with this substitution pattern have not been reported to date.[8]

In this sense, Soloshonok reported a chemoenzymatic approach to *anti*- and *syn*-α-methyl-β-trifluoromethyl-β-alanine derivatives.[9] A diastereoselective base-catalyzed [1,3]-proton shift reaction followed by an enzyme-catalyzed resolution allowed for the preparation of all four possible diastereoisomers in enantiomerically pure form. We also developed a highly diastereoselective route to enantiopure *syn*-α-alkyl β-fluoroalkyl β-amino acids, based on a chemo- and diastereoselective reduction of chiral fluorinated β-enamino esters.[10] More recently, these compounds were also obtained by means of an indirect Mannich-type reaction of fluorinated aldimines with aliphatic aldehydes catalyzed by proline.[11] However, to our knowledge, the diastereoselective preparation of the corresponding *anti* derivatives still remains a challenge.

The most direct route to prepare the skeleton of β-fluoroalkyl β-AAs is the reaction of fluorinated imines with α-lithiated esters. Previous results from our laboratory demonstrated that the reaction of 8-phenyl menthol derived ester enolates with fluorinated imines takes places with poor chemical yields and diastereoselectivity.[10] We envisioned the possibility of using 2-*p*-tolylsulfinyl benzyl carbanions as synthetic chiral equivalents of ester enolates, since they have been demonstrated to be highly efficient in controlling the *anti*-stereoselectivity of their reactions with *N*-sulfinylimines[12] as well as *N*-arylimines.[13] Thus, the phenyl-*p*-tolylsulfoxide group would be used both as chiral inducer in its reaction with fluorinated aldimines and ketimines and also as precursor of the carboxylic moiety by a two-step desulfinylation/phenyl ring oxidation sequence. In this paper, we describe a highly efficient stereoselective synthesis of enantiopure *anti*-β-fluoroalkyl β-amino acids by using a chiral sulfinyl group as inducer. This methodology is also suitable for the generation of new types of β-AAs containing a quaternary stereocenter (Figure 1). The retrosynthetic analysis is depicted in Scheme 1.

Scheme 1. Synthetic Strategy



We have recently reported that the deprotonation of sulfoxides (*S*)-**2** at the benzylic position with LDA at −78 °C and subsequent treatment with fluorinated imines **3** [PG = *p*-methoxyphenyl (PMP)] led to the formation of fluorinated indolines in a highly selective fashion after the reaction mixture was allowed to reach room temperature.[14] When the reactions were hydrolyzed at −78 °C, diastereomeric mixtures of fluorinated amines **4** and **5** were obtained, with **4** being formed as the major or exclusive product (Table 1). Thus, with *o*-tolyl derived sulfoxides **2a** (R^1 = H), separable diastereoisomeric mixtures of amines **4** and **5** were obtained (Table 1, entries 1−5). Surprisingly, the best results were

(5) Review: Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711.

(6) For the enantioselective synthesis of enantiomerically pure $\beta^2(R),\beta^3(R_F)$-AAs, see: (a) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060. (b) Fustero, S.; Chiva, G.; Piera, J.; Volonterio, A.; Zanda, M.; González, J.; Morán, A. *Chem. Eur. J.* **2007**, *13*, 8530. (c) Yamauchi, Y.; Kawate, T.; Itahashi, H.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6319. For the enantioselective synthesis of enantiomerically pure $\beta^2(F_2),\beta^3(R)$-AAs, see: (d) Edmonds, M. K.; Graichen, F. H. N.; Gardiner, J.; Abell, A. D. *Org. Lett.* **2008**, *10*, 885. (e) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBiochem* **2004**, *5*, 691. (f) Sorochinsky, A.; Voloshin, N.; Markovski, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Bervasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448. (g) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461.

(7) Jiang, Z.-X.; Qing, F.-L. *J. Org. Chem.* **2004**, *69*, 5486, and references therein.

(8) For recent reviews of creation of quaternary stereocenters, see: (a) Cozzi, P. G.; Hilfrag, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473.

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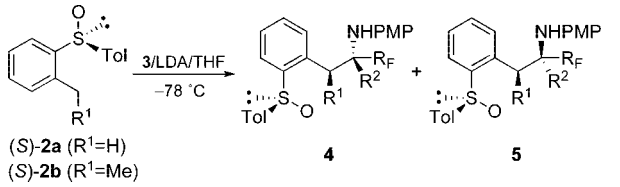
(13) García-Ruano, J. L.; Alemán, J.; Alonso, I.; Parra, A.; Marcos, V.; Aguirre, J. *Chem. Eur. J.* **2007**, *13*, 6169.

(14) García-Ruano, J. L.; Alemán, J.; Catalán, S.; Marcos, V.; Monteagudo, S.; Parra, A.; del Pozo, C.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941.

Table 1. Reaction of Sulfoxides **2** with Imines **3**



entry	3	R^1	R^2	R_F	4, 5 (% yield)[b]	ratio 4:5[c]
1[a]	**3a**	H	H	CF_3	**4a**, **5a** (74)	69:31
2[a]	**3b**	H	H	CF_2Cl	**4b**, **5b** (80)	70:30
3	**3c**	H	H	CF_2CF_3	**4c**, **5c** (75)	67:33
4[a]	**3d**	H	Me	CF_3	**4d**, **5d** (77)	96:4
5	**3e**	H	Me	CF_2CF_3	**4e**, **5e** (45)	>99:1
6[a]	**3a**	Me	H	CF_3	**4f** (69)	>99:1
7[a]	**3b**	Me	H	CF_2Cl	**4g** (71)	>99:1
8	**3c**	Me	H	CF_2CF_3	**4 h**, **5 h** (60)	4:1
9[a]	**3d**	Me	Me	CF_3	**4i** (86)	>99:1
10	**3e**	Me	Me	CF_2CF_3	**4j** (55)	>99:1

[a] See ref 14. [b] Combined yields of **4** + **5**. [c] Diastereoisomeric ratios were determined by ^{19}F NMR.

achieved when the reaction was carried out with ketimines ($R^2 \neq H$), reaching diastereoisomeric ratios of up to 99% (Table 1, entries 4 and 5). We were delighted to find that, using of sulfoxides **2b** with R^1 = Me, the process evolved in a completely stereoselective way, yielding mainly compounds **4** as single diastereoisomers with both fluorinated aldimines and ketimines[15,16] (Table 1, entries 6−10).

Rationalization of the stereochemical results can be made by assuming for the nucleophilic carbanion the structure indicated in Figure 2. The sulfinyl oxygen stabilizes the

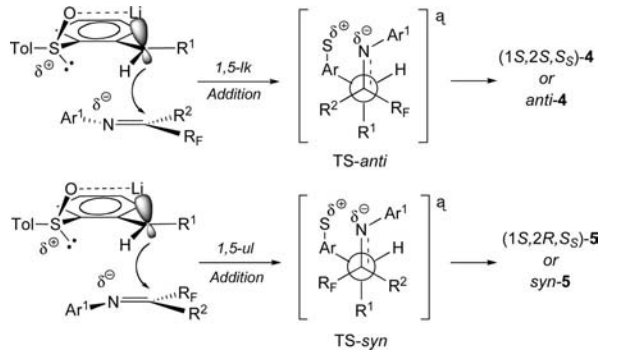


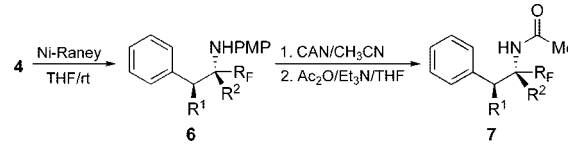
Figure 2. Diastereoselectivity control in the formation of amines **4** and **5**.

benzyllithium by forming a chelated species, which adopts a quasi-boat conformation, with the lone electron pair and the hydrogen occupying the flagpoles.[17] As the metal blocks the upper face, the approach of the electrophile can only take place at the lower face (Figure 2), thus justifying that all compounds obtained in these reactions have the *S* configuration at the benzylic carbon.[18] Two possible approaches of the electrophile can be postulated, respectively yielding the *anti* and *syn* (1,5-like vs 1,5-unlike addition) isomers (Figure 2). Both of them arrange the C═N bond antiperiplanar with respect to the C−R^1 bond, thus maintaining the electrostatic stabilization derived from the interaction of the N (negatively charged in the transition state) with the S (positively charged).[19] This assumption, along with the minimization of steric interactions of R_F with R^1 and the sulfinylated aryl groups, could justify the complete *anti*-selectivity observed in reactions from (*S*)-**2b** as well as the predominance of the *anti* isomers in reactions from (*S*)-**2a** (Table 1).

Addition products **4** were then subjected to the desulfuration/oxidation sequence that gave rise to the corresponding fluorinated β-amino acid derivatives **1**. Removal of the sulfoxide group was achieved by treatment with Raney-Ni, which afforded the desulfurated products **6** in nearly quantitative yields after 12 h at room temperature.

The transformation of the phenyl ring into the carboxylic acid required the previous conversion of the PMP group into other nitrogen protecting groups compatible with the phenyl ring oxidation. With this purpose, compounds **6** were treated with CAN (cerium ammonium nitrate) at 0 °C for 1 h, which provoked the PMP removal. Resulting amines were then *N*-acetylated with acetic anhydride under standard conditions, yielding the fluorinated amides **7** in good to excellent yields (Table 2).

Table 2. Preparation of Fluorinated *N*-Acetyl Amides **7**



entry	substrate	R^1	R^2	R_F	7 (% yield)[a]
1	**4a**	H	H	CF_3	**7a** (90)
2	**4d**	H	Me	CF_3	**7b** (70)
3	**4f**	Me	H	CF_3	**7c** (79)
4	**4g**	Me	H	CF_2Cl	**7d** (72)
5	**4i**	Me	Me	CF_3	**7e** (65)
6	**5a**	H	CF_3	H	**7f** (86)

[a] Isolated yield after three steps, from **4** to **7**.

The final conversion to the amino ester functionality was then carried out by phenyl ring oxidation with ruthenium

(15) Only one exception to this general behavior has been observed; see Table 1, entry 8.

(16) The absolute configuration of the major diastereoisomers was established by X-ray analysis. See ref 14.

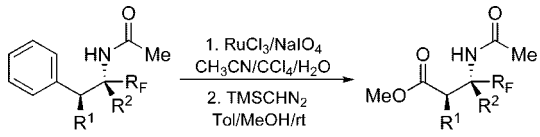
(17) The assumption of this structure as the most stable one for the benzyllithium derived from **2b** is supported by theoretical calculations. See ref 13.

(18) Starting from (*R*)-sulfoxides, resulting compounds would exhibit an (*R*)-configuration at this position.

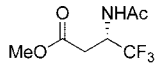
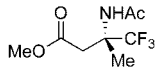
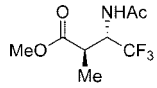
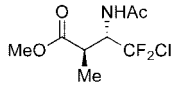
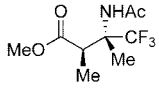
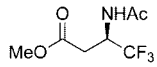
(19) Similar approaches were used for explaining the stereochemical results obtained in reactions of sulfinylated thiomethylcarbanions with ketones. See: Arroyo, Y.; Meana, A.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *Org. Lett.* **2008**, *10*, 2151.

tetraoxide.[20] The isolation of the *N*-acetylamino acids proved to be difficult, and we decided to perform an in situ esterification of the carboxylic acid group by treatment with trimethylsilyl diazomethane. After chromatographic purification, final *N*-acetyl β-amino esters **1** were obtained in good yields (Table 3).

Table 3. Preparation of *anti*-β-Amino Esters **1** from Amides **7**



7 **1**

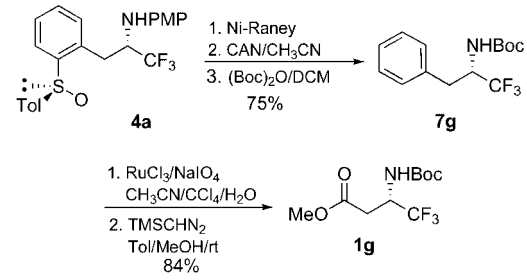
entry	7	product	1 (% yield)[a]
1	**7a**		**1a** (81)
2	**7b**		**1b** (61)
3	**7c**		**1c** (73)
4	**7d**		**1d** (70)
5	**7e**		**1e** (54)
6	**7f**		**1f** (78)

[a] Isolated yields.

It is noteworthy that the use of this methodology allowed for the selective creation of one stereocenter (Table 3, entries 1, 2, and 6) and two vicinal stereocenters, with an *anti* disposition between R^1 and the nitrogen-containing substituent (Table 3, entries 3−5). The generation of quaternary stereocenters was also achieved in an efficient manner (Table 3, entries 2 and 5).

This sequence is also compatible with the presence of other nitrogen protecting groups. To illustrate this possibility, **4a** was transformed into the corresponding *N*-Boc derivative **7g** by reaction of the free amine with di-*tert*-butyl dicarbonate after sulfoxide elimination and PMP release. Following the previously mentioned methodology, **7g** was converted into the *N*-Boc amino ester **1g** in good overall yield (Scheme 2).

Scheme 2. Preparation of *N*-Boc Derivative **1g**



In conclusion, the stereocontrolled preparation of β-fluoroalkyl β-amino acid derivatives has been described. It involves the highly selective addition of 2-(*p*-tolylsulfinyl)-benzylic carbanions to fluorinated imines followed by a desulfuration/oxidation sequence, which allows the synthesis of the final amino acid derivatives **1** in good yields. A combination of steric and electrostatic factors has been invoked to explain the high selectivity found in the addition of benzyllithiums to fluorinated aldimines and ketimines. It is noteworthy that this is one of the first methods described in the literature for the stereoselective preparation of enantiomerically pure *anti*-β-fluoroalkyl-α-alkyl β-amino esters and the first one for compounds containing quaternary centers.

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

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