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A Convenient Enantioselective Synthesis of (*S*)-α-Trifluoromethylisoserine

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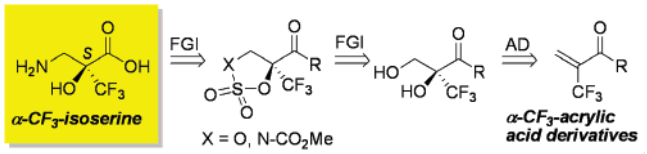
Received March 16, 2005



This report describes two straightforward synthetic methodologies to obtain α-CF_3-isoserine, a new α,α-disubstituted β-amino acid, from α-(trifluoromethyl)acrylic acid. The routes involve the synthesis of five-membered cyclic sulfates (using sulfuryl chloride) or sulfamidates (using the Burgess reagent) from the corresponding chiral diols, which are obtained by a catalytic asymmetric dihydroxylation (AD) reaction.

In recent years, the synthesis of fluorinated organic compounds (FOC) has emerged as an important field in organic chemistry[1] because the unique properties of the fluorine atom give rise to certain general characteristics in FOC. Moreover, it is well known that optically active FOC exhibit high physiological activity and remarkable physical properties.[1] Among such FOC, trifluoromethylated (CF_3) products constitute an important family because of the lipophilicity associated with this substituent.[2]

In this context, fluorinated analogues of naturally occurring amino acids have proved to be of great interest.[3] In the field of amino acids, the study of β-amino acids (β-AA) is a topic of constant attention due to the applications of such compounds in medicinal and peptide chemistry as well as molecular recognition.[4] In this respect,

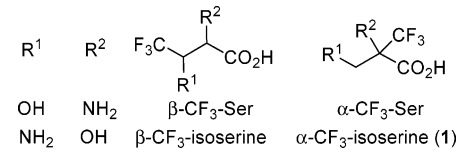


FIGURE 1. The α- and β-trifluoromethylated hydroxy amino acids.

β- or α-substituted β-AA (β^3- or β^2-AA) represent an important class of compounds because these substituents favor folded conformations in β-peptides.[4c,5] Several synthetic approaches have been described for β^3-AA, but very few routes have been reported for β^2-AA and even fewer on the synthesis of chiral geminally α,α-disubstituted β-AA ($\beta^{2,2}$-AA).[6] Consequently, the development of practical methods for the synthesis of β-AA bearing a chiral quaternary center in the α-position would be exceedingly valuable, particularly in cases that bear a CF_3 substituent.[7]

In connection with our project on restricted hydroxy amino acids,[8] and with the aim of combining the two aforementioned aspects, we focused our attention on the synthesis of α-CF_3-β-AA. Our specific aim was to synthesize derivatives of isoserine due to their implications as peptidomimetic units[9] and as important targets in the synthesis of β-lactams and of Taxol analogues (taxoids).[10] In the case of serine, the asymmetric synthesis of α-CF_3-Ser[11] and of *syn*- and *anti*-β-CF_3-Ser have been previously reported.[12] Regarding isoserine, only the asymmetric synthesis of both enantiomers of *syn*- and *anti*-β-CF_3-isoserine has been published.[13] To cover this gap, we report here the enantioselective synthesis of α-CF_3-isoserine **1**. Moreover, to the best of our knowledge, there are only two references concerning the introduction of a CF_3 group in the α-position of a β-AA[14] (Figure 1).

A very short method to obtain enantiomerically pure α-CF_3-isoserine **1** could make use of the Sharpless

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(1) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119−6146 and references therein. (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16. (c) Special issue: *ChemBioChem* **2004**, *5*, 557−726.

(2) Special issue: Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823−4131.

(3) (a) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711−6745 and references therein. (b) Kukhar, V. P.; Soloshonok, V. A. *Fluorine Containing Amino Acids: Synthesis and Properties*; Wiley: New York, 1995. (c) Horng, J. C.; Raleigh, D. P. *J. Am. Chem. Soc.* **2003**, *125*, 9286−9287. (d) Bravo, P.; Bruché, L.; Pesenti, C.; Viani, F.; Volonteiro, A.; Zanda, M. *J. Fluorine Chem.* **2001**, *112*, 153−162. (e) Koksch, B.; Sewald, N.; Hofmann, H.-J.; Burger, K.; Jakubke, H.-D. *J. Pept. Sci.* **1997**, *3*, 157−167. (f) Koksch, B.; Dahl, C.; Radics, G.; Vocks, A.; Arnold, K.; Arnhold, J.; Sieler, J.; Burger, K. *J. Pept. Sci.* **2004**, *10*, 67−81. (g) Koksch, B.; Quaedflieg, P. J. L. M.; Michel, T.; Burger, K.; Broxterman, Q. B.; Schoemaker, H. E. *Tetrahedron: Asymmetry* **2004**, *15*, 1401−1407.

(4) (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (c) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111−1239. (d) Seebach, D.; Kimmerlin, T.; Sebesta, R.; Campo, M. A.; Beck A. K. *Tetrahedron* **2004**, *60*, 7455−7506.

(5) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932−982.

(6) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15.

(7) Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651−4654.

(8) Avenoza, A.; Busto, J. H.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Italy, 2002; pp 231−244.

(9) Volonteiro, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827−1830.

(10) Kuznetsova, L.; Ungureanu, I. M.; Pepe, A.; Zanardi, I.; Wu, X.; Ojima, I. *J. Fluorine Chem.* **2004**, *125*, 487−500.

(11) Synthesis of α-CF_3-Ser: (a) Bravo, P.; Viani, F.; Zanda, M.; Soloshonok, V. *Gazz. Chim. Ital.* **1995**, *125*, 149−150. (b) Bravo, P.; Zanda, M.; Zappalà, C. *Tetrahedron Lett.* **1996**, *37*, 6005−6006.

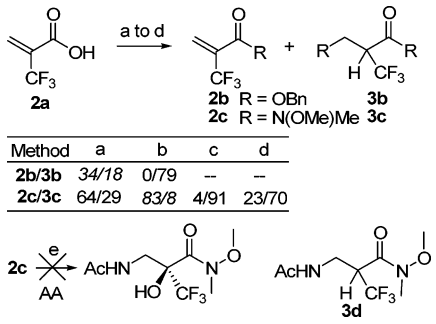
(12) Synthesis of β-CF_3-Ser: Jiang, Z.-X.; Qin, Y.-Y.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 7544−7547 and references therein.

(13) Synthesis of β-CF_3-isoserine: Jiang, Z.-X.; Qing, F.-L. *J. Org. Chem.* **2004**, *69*, 5486−5489 and references therein.

(14) (a) Haddad, M.; Vakselman, C. *J. Fluorine Chem.* **1995**, *73*, 57−59. (b) Sekiguchi, T.; Sato, K.; Ishihara, T.; Konno, T.; Yamanaka, H. *Chem. Lett.* **2004**, *33*, 666−667.

10.1021/jo0505371 CCC: $30.25
Published on Web 06/15/2005

SCHEME 1. Synthesis of Olefins 2b,c and Asymmetric Aminohydroxylation Reaction[a]



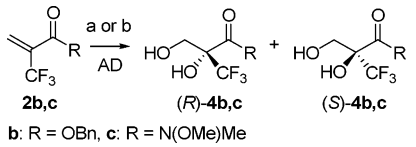
Method	a	b	c	d
2b/3b	*34/18*	0/79	--	--
2c/3c	64/29	*83/8*	4/91	23/70

[a] (a) BnOH/TEA or HCl·HN(OMe)Me/DIEA, Mukaiyama's reagent, CH_2Cl_2, reflux, 16 h; (b) BnOH or HCl·HN(OMe)Me, DIEA, DCC, CH_2Cl_2, 0 °C, 16 h; (c) (i) phthaloyl chloride, 140 °C; (ii) HCl·HN(OMe)Me, Py, CH_2Cl_2, −20 °C, 4 h; (d) (i) PCl_5, CH_2Cl_2, 25 °C; (ii) HCl·HN(OMe)Me, Py, CH_2Cl_2, 0 °C, 2 h; (e) LiOH·H_2O, K_2OsO_4·$2H_2O$ (5%), $(DHQD)_2PHAL$ (5%), AcNHBr, ^{t}BuOH/H_2O (1.5:1), 0 °C, 24 h, 84%.

asymmetric aminohydroxylation[15] of 2-(trifluoromethyl)-acrylic acid derivatives as a key step. We therefore synthesized two derivatives of commercially available 2-(trifluoromethyl)acrylic acid (**2a**) as prochiral fluorine-containing starting materials: compounds **2b** and **2c**. Several coupling methods were tested, and it was found that the best conditions for the synthesis of olefin **2b** involved the use of Mukaiyama's reagent (*N*-methyl-2-chloropyridinium iodide). This approach gave a yield of 34% accompanied by a 15% yield of racemic Michael coupling product **3b**. In contrast, compound **2c** was obtained in 83% yield along with 8% of racemic Michael coupling product **3c** when DCC was used as the coupling agent (Scheme 1). We proceeded to attempt the asymmetric aminohydroxylation reaction on olefin **2c** using the conditions shown in Scheme 1. Under these conditions, all of the starting material was consumed but aminohydroxylation products were not detected. A mixture of two compounds was obtained: dihydroxylation product (10%) and the corresponding racemic compound **3d**, which is formed by Michael addition of acetamide on olefin **2c** (Scheme 1).

Recently, we achieved excellent results in the synthesis of several enantiopure $\beta^{2,2}$-AA from two kinds of chiral building blocks. These precursors were five-membered cyclic α-methylisoserine-derived sulfamidates[16] and α-methyl-α,β-dihydroxypropanoic acid-derived sulfates.[17,18] These compounds were obtained from chiral 1,2-diols, which in turn were synthesized by a Sharpless asymmetric dihydroxylation (AD)[19] on the corresponding olefin using AD-mix α or β.[20] Taking into account these facts, and considering the previous results of asymmetric

SCHEME 2. Sharpless AD Reaction on Olefins 2b,c[a]



[a] (a) AD-mix α, $MeSO_2NH_2$, ^{t}BuOH/H_2O (1:1), 0 °C, 24 h, 87%, ee = 66% of (*R*)-**4b**, 90% of (*R*)-**4c**, ee = 90%; (b) conditions of (a) with AD-mix β, 87%, ee = 66% of (*S*)-**4b**, 90% of (*S*)-**4c**, ee = 90%.

aminohydroxylation on olefin **2c**, we decided to use the sulfamidate and sulfate protocols to achieve the target α-CF_3-isoserine. Therefore, the key step in our synthetic routes will involve the Sharpless AD on olefins **2b,c**.

As outlined in Scheme 2, olefins **2b,c** were subjected to Sharpless dihydroxylation conditions using AD-mix α or β to give the mixture of compounds (*S*)-**4b**,**c** and (*R*)-**4b**,**c** in good yields (87% from **2b** and 90% from **2c**). Nevertheless, the enantioselectivity achieved from **2c** (90% ee) was better than that from **2b** (66% ee).[21] We observed that the reactivity or the degree and sense of the enantioselectivity did not differ from those of similar nonfluorinated substrates (2-methylacrylic acid derivatives).[20] These results are very important, because a recent review concerning asymmetric catalytic reactions on fluorinated carbonyl and olefinic compounds[1b] describes several enantioselective reductions, but only one example of the catalytic enantioselective oxidation of prochiral fluorine-containing carbonyl compounds or olefins.[22] Likewise, these AD reactions on olefins **2b**,**c** constitute the first examples of non-Michael-type functionalization of these types of substrate, which have been described as excellent Michael acceptors.[23]

Treatment of diol (*S*)-**4c** with Burgess reagent[24] gave the corresponding sulfamidate (*S*)-**5** as a single regioisomer[25] in 34% yield when the reaction was carried out at rt. This yield could be improved (51%) by carrying out the reaction under reflux. Sulfamidate (*S*)-**5** was quantitatively hydrolyzed in an acidic medium to give α-CF_3-isoserine (*S*)-**1** in its hydrochloride form (Scheme 3). In this way, (*S*)-**1**·HCl was obtained from olefin **2a** in four

(15) (a) Sharpless, K. B.; Bruncko, M.; Schlingloff, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483−1486. (b) Sharpless, K. B.; Tao, B.; Schlingloff, G. *Tetrahedron Lett.* **1998**, *39*, 2507−2510. (c) Song, C. E.; Oh, C. R.; Roh, E. J.; Lee, S.; Choi, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 671−674. (d) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329.

(16) Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; Peregrina, J. M. *Chem. Commun.* **2004**, 980−981.

(17) Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; París, M.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 131−137.

(18) Avenoza, A.; Busto, J. H.; Corzana, F.; García, J. I.; Peregrina, J. M. *J. Org. Chem.* **2003**, *68*, 4506−4513.

(19) (a) Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070. (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 227−272.

(20) (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949−953. (b) Bennani, Y. L.; Sharpless K. B. *Tetrahedron Lett.* **1993**, *34*, 2079−2082.

(21) The yield was calculated after column chromatography, and the enantiomeric excess (ee) was determined by GC−MS (see Supporting Information).

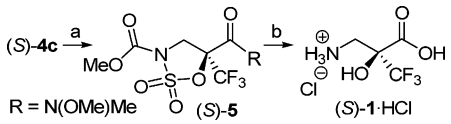
(22) Bennani, Y. L.; Vanhessche, K. P. M.; Sharpless, B. *Tetrahedron: Asymmetry* **1994**, *5*, 1473−1476.

(23) (a) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197−200. (b) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonteiro, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063.

(24) (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 6135−6141. (b) Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 834−838. (c) Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem.-Eur. J.* **2004**, *10*, 5581−5606. (d) Bower, J. F.; Svenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727−4730.

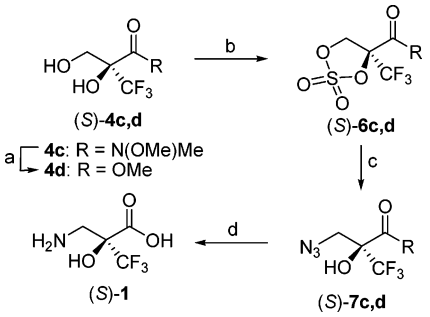
(25) Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581−2616.

SCHEME 3. Synthesis of α-CF_3-Isoserine (*S*)-1 via Sulfamidate[a]



[a] (a) Burgess reagent, THF, reflux, 1 h, 51%; (b) 6 N HCl (aq), 100 °C, 12 h, 90%.

SCHEME 4. Synthesis of α-CF_3-Isoserine (*S*)-1 via Sulfates[a]



[a] (a) (i) LiOH·H_2O, H_2O/MeOH (1:3), 25 °C, 2 h; (ii) AcCl, MeOH, reflux, 12 h, 85%; (b) SO_2Cl_2, TEA, CH_2Cl_2, −20 °C, 1 h, 81% of **6c**, 78% of **6d**; (c) (i) NaN_3, DMF, 70 °C, 12 h, (ii) 20% H_2SO_4 (aq)/CH_2Cl_2 (1:1), 25 °C, 10 h, 99% of **7c**, 90% of **7d**; (d) (i) LiOH·H_2O, H_2O/MeOH (1:3), 25 °C, 2 h; (ii) H_2, Pd−C, MeOH, 25 °C, 48 h, 95% from **7c**.

steps in 34% yield. This moderate overall yield is mainly due to the modest yield of the sulfamidate generation and led us to develop a new synthetic strategy involving the use of chiral sulfates as building blocks followed by regioselective nucleophilic opening with the azide ion.

The use of sulfuryl chloride allowed the preparation with good yields of two chiral gem-disubstituted sulfates [(*S*)-**6c**,**d**] from diols (*S*)-**4c**,**d** (Scheme 4). This last chiral diol [(*S*)-**4d**] was obtained by basic hydrolysis of the amide group in diol (*S*)-**4c** and subsequent esterification with acetyl chloride in MeOH. Furthermore, the ring-opening reaction of these sulfates with sodium azide in DMF and subsequent acid hydrolysis surprisingly gave, in both cases, an exclusive regioisomer: the *β*-azido α-alcohols (*S*)-**7c**,**d**. These surprising results regarding our previous work[17] agree with those reported by Jiang and Qing's[12,13] and are probably due to the effect of the CF_3 group. Compounds (*S*)-**7c**,**d** were subjected to hydrolysis in a basic medium to give the corresponding carboxylic acid derivatives after neutralization. Subsequent hydrogenation using MeOH as solvent and Pd/C as a catalyst quantitatively provided α-CF_3-isoserine (*S*)-**1** (seven steps, 51% from **2a**) (Scheme 4).

The ee (90%) and the absolute configuration of α-CF_3-isoserine (*S*)-**1** was unambiguously determined by transformation of the methyl ester derivative of this $\beta^{2,2}$-AA, obtained by esterification with acetyl chloride in MeOH, into the dipeptide **8**, a chiral derivative with two stereogenic centers, whose absolute configuration was found to be (*S*,*S*) by X-ray analysis (see Supporting Information) of the corresponding monocrystals (Scheme 5).

A theoretical study was undertaken in an effort to understand the behavior of this kind of cyclic α-CF_3-sulfate in the ring-opening S_N2 reaction with the azide

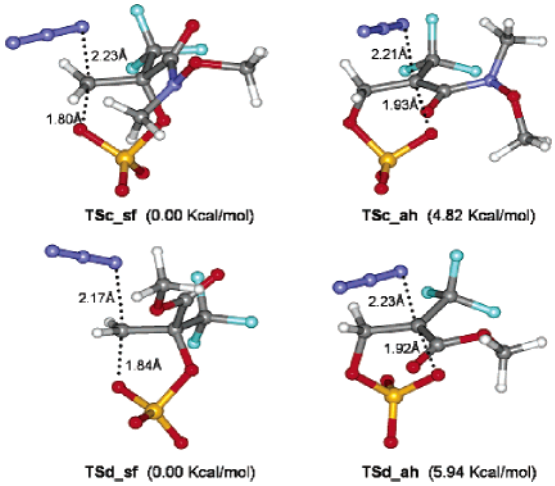
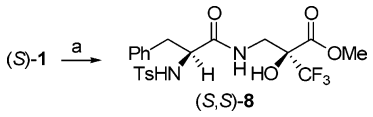


FIGURE 2. Lowest energy TS calculated with (*S*)-**6c** and (*S*)-**6d** and azide anion.

SCHEME 5. Determination of Absolute Configuration of $\beta^{2,2}$-AA[a]



[a] (a) (i) AcCl, MeOH, reflux, 10 h; (ii) *N*-(tosyl)phenylalaninyl chloride, DIEA, CH_2Cl_2, 25 °C, 14 h, 88%.

ion. All ground state and transition state (TS) geometries were located using hybrid DFT (B3LYP)[26] and the 6-31+G(d) basis sets implemented in Gaussian 98.[27] Solvent effects were taken into account through single point energy calculations with the IPCM method[28] at the B3LYP/6-31+G(d) level using the dielectric permittivity of DMF (38.25), which was the solvent used in the experiments.

Two competitive S_N2 pathways were examined: azide attack at the "free" (**f**) secondary position and at the "hindered" (**h**) quaternary position. Each TS was located in the two possible carbonyl conformations, *syn* (**s**) and *anti* (**a**) with regard to the CF_3 group. This led to four possible TS for each sulfate, and these are denoted as **TSc-d_af**, **TSc-d_ah**, **TSc-d_sf**, and **TSc-d_sh**, respectively. Several geometrical features of the minimum energy TS are shown in Figure 2. As far as substrates (*S*)-**6c** and (*S*)-**6d** are concerned, the TS obtained for the S_N2 reaction on the "free" position (**TSc_sf** and **TSd_sf**, respectively) were considerably lower in energy (4.82 and 5.94 kcal/mol more stable) than those resulting from

(26) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377.
(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaroni, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; González, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revisions A.7 and A.11; Gaussian, Inc.: Pittsburgh, PA, 1998.
(28) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098−16104.

nucleophilic attack at the "hindered" position (**TSc_ah** and **TSd_ah**, respectively). This situation is in agreement with the experimentally observed regioselectivity. Moreover, these results confirm the conclusion established by Uneyama et al. on the prevention of nucleophilic substitution in the α-position with respect to a CF_3 group. This effect was attributed to the negatively charged nature of this group, which exhibits strong repulsive interactions toward negatively charged nucleophiles.[29]

In summary, we have developed a simple methodology to obtain a new class of optically active $\beta^{2,2}$-AA with a CF_3-containing quaternary carbon center; α-CF_3-isoserine. The route starts from commercially available α-(trifluoromethyl)acrylic acid and combines the Sharpless AD reaction for the preparation of chiral diols with the generation of cyclic sulfamidates or cyclic sulfates.

(29) (a) Katagiri, T.; Uneyama, K. *Chirality* **2003**, *15*, 4−9. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231.

Acknowledgment. We thank the Ministerio de Ciencia y Tecnología (project PPQ2001-1305), the Ministerio de Educación y Ciencia (Ramon y Cajal contract of J.H.B.), and the Universidad de La Rioja (project API-04/02, doctoral fellowship of G.J.-O.).

Supporting Information Available: Experimental details, spectroscopic characterization of all compounds, crystal structure data, as well as computational energy data and coordinates for the structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0505371