Pergamon

*Tetrahedron Letters*, Vol. 37, No. 29, pp. 5103-5106, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01044-1

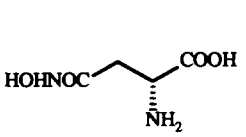
# Synthesis of Nonracemic 3-Fluoro-Aspartic Acids

**F. Burgat Charvillon and R. Amouroux ***

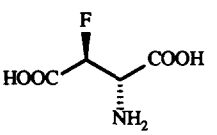
*Laboratoire de Chimie Organique Physique et Synthétique associé au CNRS*
*Université Claude Bernard - Lyon I, 69 622 Villeurbanne, France.*

**Abstract** : The two isomers (2*S*,3*S*) and (2*S*,3*R*) of 3-fluoro-D-aspartic acid were synthesized by two independent routes both starting from D-tartaric acid esters.

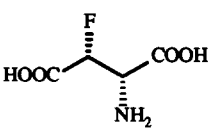

D-aspartic acid β-hydroxamate (DAH, **1**) has been shown to have some antitumoral activity and an interesting antiretroviral effect in Friend disease and HIV replication [1]. In connection with a program for the development of DAH analogues, we are working towards the preparation of analogues containing a fluorine atom in C-3 position, since the introduction of fluorine is generally known to exert an important and, in many cases, useful influence on the bioactivity of organic molecules. To bring about such a modification, we need to synthesize corresponding 3-fluoro-D-aspartic acids which are regarded as good precursors of the targeted β-hydroxamates. In this paper, we describe a convenient access to the two isomers *anti* (2*S*,3*S*) and *syn* (2*S*,3*R*) of 3-fluoro-D-aspartic acid (**10** and **15**) by two independent routes, both starting from D-tartaric acid esters.




DAH **1**



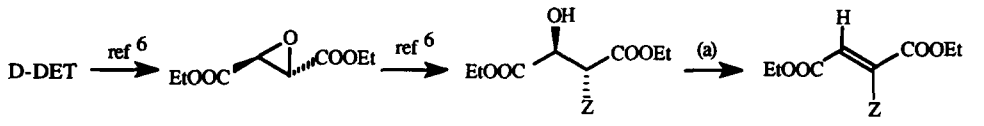

*anti* (2*S*,3*S*) **10**




*syn* (2*S*,3*R*) **15**

Surprisingly, in the view of the literature, no synthesis of 3-fluoro-aspartic acid in an optically active form has been reported. However, a few synthetic methods have been described, all of which lead to either the *anti* or the *syn* isomer but both in a racemic form. The first synthesis of the *anti* isomer of 3-fluoro-aspartic acid was made with a nitrous acid deamination of *meso* diamino-succinic acid in liquid HF [2]. A different approach, giving mainly the *anti* isomer, was also conceived *via* stereoselective reduction of 3-fluoro 2-amino maleic / fumaric acids esters [3]. Furthermore, fluorodehydroxylation procedure involving the use of sulfur tetrafluoride in liquid HF was used with success on 3-hydroxy-aspartic acid esters and the resulting fluoro compounds were either a single [4a] or a mixture of diastereoisomers [4b]. More recently, the synthesis of the *syn* isomer was achieved with the reaction of dibenzyl difluoromaleate with dibenzylamine [5].

In our initial synthesis scheme, we had planned to perform fluorodehydroxylation reaction on both the *syn* and *anti* isomers of 3-amino 2-hydroxy-succinic acid ester or on the corresponding 3-azido derivatives [6]. To obtain this transformation, (diethyl amino)sulfur trifluoride (DAST), a mild reagent known to induce in many cases an inversion of configuration [7], was used. We first tried to make this DAST reaction on *anti* precursors **3** and **4** which are readily available from D-diethyl tartrate (D-DET) *via* epoxysuccinate **2**. Unfortunately, dehydratation was observed, resulting in the elimination products **5** and **6** respectively (scheme 1).




**2**

$Z = N_3$ , **3**
$Z = NH_2$ , **4**

$Z = N_3$ , **5** 71 %
$Z = NH_2$ , **6** 61 %

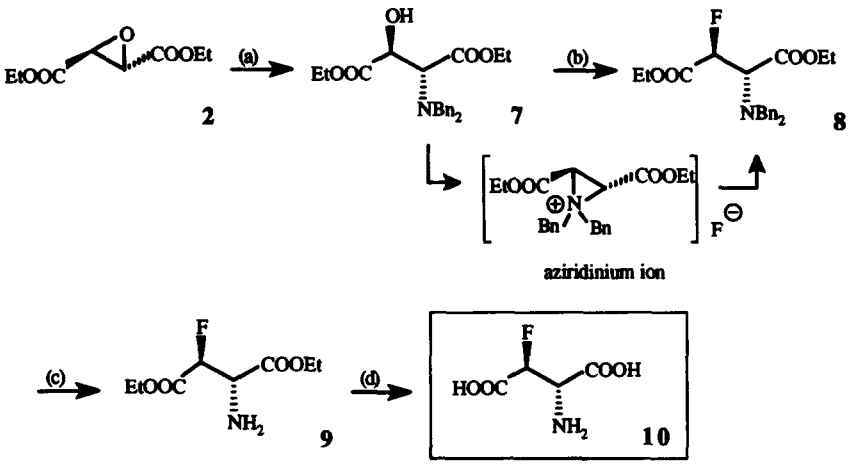
**scheme 1**

Condition (a) : DAST, THF, - 40 °C to r.t., 2h.

To prevent this elimination reaction, we attempted fluorodehydroxylation on N,N dibenzyl derivative of aminoalcohol **4**. This procedure has been successfully used on N,N dibenzyl esters of serine and threonine, to obtain quantitatively the corresponding rearranged N,N dibenzyl α-fluoro β-aminoacid esters [8]. A nucleophilic assistance of the N-protected group leading to an aziridinium ion was proposed to explain this rearrangement. According to this mechanism, the application of such a transformation to N,N dibenzyl 3-hydroxy-aspartic acid ester in the *anti* form **7** should give the fluorinated compound **8** with retention of configuration. In fact, in this case, because of the axial symmetry of the postulated aziridinium ion, the attack by fluorine at C-2 or C-3 position was stereochemically indifferent and therefore resulted in the same fluorinated derivative (scheme 2). We observed that the required N,N dibenzyl derivative **7** could be directly and conveniently synthesized by aminolysis of the epoxide **2**. Thus, the treatment of **2** with excess dibenzylamine in the presence of $LiBF_4$ in refluxed acetonitrile [9] afforded, after 3 days, N,N dibenzyl aminoalcohol **7** in 62 % yield as a single diastereoisomer following $^1H$ and $^{13}C$ NMR analysis (scheme 2). Subsequent DAST reaction was achieved at room temperature and gave rise, with a excellent yield, to the *anti* fluorinated compound **8** [10]. After the hydrogenolysis of the benzyl groups [11], diethyl 3-fluoro-aspartate **9** was obtained quantitatively [12]. Treatment in an aqueous HCl at reflux [4] led to the (2*S*,3*S*) 3-fluoro-D-aspartic acid as the hydrochloride, which was transformed in a 40 % overall yield to the free compound **10** after ion exchange chromatography [13] (scheme 2).

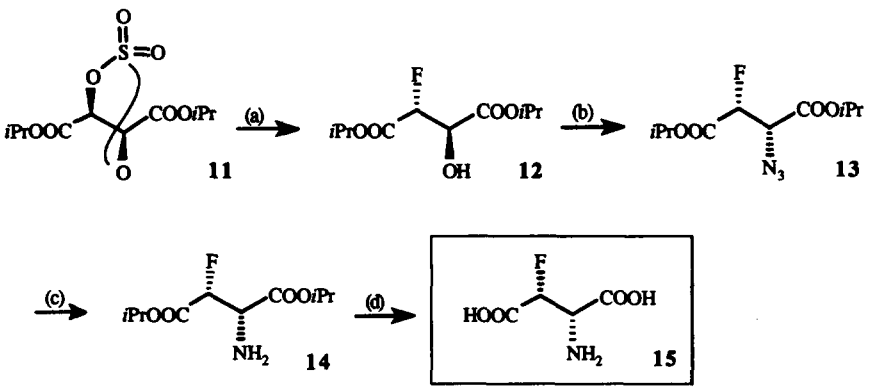
The fluorodehydroxylation procedure described above cannot be used for the synthesis of the *syn* isomer (2*S*,3*R*) because of the *meso* configuration of the aziridinium ion in this case. Therefore, access to this isomer was conceived starting from β-fluoro alcohol **12** (scheme 3). The alcohol was prepared according to Gao et al.[14], after ring opening with fluoride anion, of cyclic sulfate **11** derived from D-di*iso*propyl tartrate. Esterification of the free hydroxyl group with triflic anhydride, followed by treatment of the resulting triflate with sodium azide in dimethylformamide at - 5°C [15], gave the corresponding azide **13**. The displacement of the triflate by azide ion took place with clean inversion of configuration as shown in $^1H$, $^{13}C$, $^{19}F$ NMR spectra [16]. After catalytic hydrogenation, di*iso*propyl 3-fluoro-aspartate **14** was isolated quantitatively [17].

Subsequent acidic hydrolysis [4] provided the (2*S*,3*R*) 3-fluoro-D-aspartic acid **15** in 53 % yield after ion exchange chromatography [18] (scheme 3).




**scheme 2**

Conditions : (a). $HNBn_2$, $LiBF_4$, $CH_3CN$, Δ, 72h, 62 % (b). $Et_2NSF_3$, THF, r.t., 2h, 94 % (c). $H_2$ (1 atm.) Pd/C, EtOH, 4h, quant. (d). 1. HCl 4N, Δ, 48 h ; 2. Resin Dowex formate form ($H_2O$ then HCOOH 1N) ; 40 %.




**scheme 3**

Conditions : (a). 1. $Et_4NF$, acetone, r.t., 6h ; 2. $H_2SO_4$ 20 % aqueous solution, r. t., 7h ; 88 % (b). 1. $Tf_2O$, $CH_2Cl_2$, - 65 °C, 5 min then 2,6-lutidine ; 2. $NaN_3$, DMF, - 5 °C ; 56% (c). $H_2$ (1 atm.) Pd/C, EtOH, 4h, quant. (d). 1. HCl 4N, Δ, 20h ; 2. Resin Dowex formate form ($H_2O$ then HCOOH 1N) ; 53%.

In summary, we have reported here the first synthesis of the two isomers *syn* and *anti* of 3-fluoro-D-aspartic acid in an optically active form by means of stereocontrolled reactions. Further transformations in corresponding β-hydroxamates, the 3-fluorinated analogues of DAH, are in progress in our laboratory.

**References and Notes :**


1. a) Thomasset, N. ; Hamedi-Sangsari, F. ; Tournaire, R. ; Navarro, C. ; Malley, S. ; Goetsch, L. ; Grange, J. ; Vila., J. *Int. J. Cancer* **1991**, *49*, 421-424. b) Tournaire, R. ; Malley, S. ; Hamedi-Sangsari, F. ; Thomasset, N. ; Grange, J. ; Doré, J. F. ; Vila, J. *Int. J. Cancer* **1994**, *58*, 420-425. c) Malley, S. ; Grange, J. ; Hamedi-Sangsari, F. ; Vila, J. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11017-11021.
2. Matsumoto, K. ; Ozaki, Y. ; Iwasaki, T. ; Horikawa, H. ; Miyoshi, M. *Experientia* **1979**, *35*, 850-851.
3. Wanner, M. J. ; Hageman, J. J. M. ; Koomen, G. J. ; Pandit, U. K. *J. Med. Chem.* **1980**, *23*, 85-87.
4. a) Kollonitsch, J. ; Marburg, S. ; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771-777. b) Stern, A. M. ; Foxman, B. M. ; Tashjian, Jr, A. H. ; Abeles, R. H. *J. Med. Chem.* **1982**, *25*, 544-550.
5. Hudlicky, M. *J. Fluorine Chem.* **1988**, *40*, 99-108.
6. a) Burgat Charvillon, F. ; Amouroux, R. *Biomed. Chem. Lett.*, submitted. b) Saito, S. ; Bunya, N. ; Inaba, M. ; Moriwake, T. ; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309-5312.
7. a) Tewson, T. J. ; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090-1092. b) Pansare, S. V. ; Vederas, J. C. *J. Org. Chem.* **1987**, *52*, 4804-4810. c) Hayakawa, H. ; Takai, F. ; Tanaka, H. ; Miyasaka, T. ; Yamaguchi, K. *Chem. Pharm. Bull.* **1990**, *38*, 1136-1139. d) Focella, A. ; Bizzarro, F. ; Exon, C. *Synth. Com.* **1991**, *21*, 2165-2170. e) Pankiewicz, K. W. ; Krzeminski, J. ; Ciszewski, L. A. ; Ren, W-Y. ; Watanabe, K. A. *J. Org. Chem.* **1992**, *57*, 553-559.
8. Somekh, L. ; Shanzer, A. *J. Am. Chem. Soc.* **1982**, *104*, 5836-5837.
9. Chini, M. ; Crotti, P. ; Favero, L. ; Macchia, F. *Tetrahedron Lett.* **1994**, *35*, 761-764.
10. Compound **8** : $^{1}H$ NMR ($CDCl_3$) δ 1.21 (t, 3H, *J* = 7) ; 1.33 (t, 3H, *J* = 7) ; 3.72 (d, 2H, *J* = 14) ; 3.86 (d, 2H, *J* = 14) ; 4.03 (dd, 1H, *J* = 5, *J* = 23) ; 4.28 (q, 4H, *J* = 7) ; 5.27 (dd, 1H, *J* = 5, *J* = 48) ; 7.2-7.3 (m, 10H). $^{19}F$ NMR ($CDCl_3$) δ (from $CCl_3F$) - 196.6 (dd, *J* = 23, *J* = 48). $^{13}C$ NMR ($CDCl_3$) δ 13.9 (q) ; 14.3 (q) ; 55.5 (t) ; 55.6 (t) ; 61.2 (t) ; 61.8 (t) ; 62.7 (dd, *J* = 23) ; 88.5 (dd, *J* = 190) ; 127.3 (2d) ; 128.3 (4d) ; 129.0 (4d) ; 138.6 (2s) ; 167.7 (sd, *J* = 22) ; 168.5 (s). $[\alpha]^{20}_D$ = + 82 (c 0.98, $CH_2Cl_2$).
11. Atmospheric pressure and a short reaction time (4h) are crucial since a higher pressure and a longer time gave rise to an enamine by loss of HF. In addition, because of its relative instability, the fluoroamine **9** must be stored in the hydrochloride form.
12. Compound **9** (HCl form) : $^{1}H$ NMR ($CD_3OD$) δ 1.30 (t, 3H, *J* = 7) ; 1.34 (t, 3H, *J* = 7) ; 3.31 (s, 1H, not exchanged -NH) ; 4.3-4.4 (m, 4H) ; 4.85 (dd, 1H, *J* = 2, *J* = 27) ; 5.59 (dd, 1H, *J* = 2, *J* = 47). $^{19}F$ NMR ($CD_3OD$) δ (from $CCl_3F$) - 201.6 (dd, *J* = 27, *J* = 47). $^{13}C$ NMR ($CD_3OD$) δ 14.2 (q) ; 14.3 (q) ; 55.6 (dd, *J* = 22) ; 63.8 (t) ; 64.6 (t) ; 87.6 (dd, *J* = 192) ; 165.7 (sd, *J* = 5) ; 166.5 (sd, *J* = 23). $[\alpha]^{20}_D$ = - 23 (c 0.85, MeOH).
13. Compound **10** : $^{1}H$ NMR ($D_2O$+DCl) δ 4.77 (dd, 1H, *J* = 2, *J* = 29) ; 5.53 (dd, 1H, *J* = 2, *J* = 48). $^{19}F$ NMR ($D_2O$+DCl) δ (from $CCl_3F$) - 198.5 (dd, *J* = 29, *J* = 48). $^{13}C$ NMR ($D_2O$+DCl) δ 57.6 (dd, *J* = 22) ; 89.7 (dd, *J* = 189) ; 170.1 (sd, *J* = 5) ; 172.4 (sd, *J* = 22). $[\alpha]^{20}_D$ = - 18 (c 0.53, HCl 1N).
14. Gao, Y. ; Sharpless, B. *J. Am. Chem. Soc.* **1988**, *110*, 7538-7539.
15. The elimination of HF was observed in the final product with temperature reaction above 0°C.
16. Compound **13** : $^{1}H$ NMR ($CDCl_3$) δ 1.26 (d, 6H, *J* = 6) ; 1.27 (d, 6H, *J* = 6) ; 4.17 (dd, 1H, *J* = 2 , *J* = 30) ; 5.12 (qq, 2H, *J* = 6) ; 5.31 (dd, 1H, *J* = 2, *J* = 47). $^{19}F$ NMR ($CDCl_3$) δ (from $CCl_3F$) - 202.5 (dd, *J* = 30, *J* = 47). $^{13}C$ NMR ($CDCl_3$) δ 22.2 (2q) ; 22.3 (2q) ; 63.1 (dd, *J* = 20) ; 71.4 (d) ; 71.9 (d) ; 89.4 (dd, *J* = 195) ; 166.3 (sd, *J* = 25) ; 166.5 (s). $[\alpha]^{20}_D$ = + 83 (c 1.03, $Et_2O$).
17. Compound **14** : $^{1}H$ NMR ($CDCl_3$) δ 1.21 (d, 6H, *J* = 6) ; 1.22 (d, 6H, *J* = 6) ; 1,61 (s, 2H) ; 3.87 (dd, 1H, *J* = 2, *J* = 32) ; 5.04 (qq, 1H, *J* = 6) ; 5.11 (qq, 1H, *J* = 6) ; 5.23 (1H, dd, *J* = 2, *J* = 48). $^{19}F$ NMR ($CDCl_3$) δ (from $CCl_3F$) - 206.8 (dd, *J* = 32, *J* = 48). $^{13}C$ NMR ($CDCl_3$) δ 21.6 (2q) ; 21.7 (2q) ; 56.6 (dd, *J* = 21) ; 69.7 (d) ; 69.8 (d) ; 89.8 (dd, *J* = 190) ; 166.9 (sd, *J* = 24) ; 170.9 (sd, *J* = 2). $[\alpha]^{20}_D$ = + 26 (c 1.41, $Et_2O$).
18. Compound **15** : $^{1}H$ NMR ($D_2O$+DCl) δ 4.16 (dd, 1H, *J* = 2, *J* = 29) ; 5.14 (dd, 1H, *J* = 2, *J* = 44). $^{19}F$ NMR ($D_2O$+DCl) δ (from $CCl_3F$) - 196.6 (dd, *J* = 29, *J* = 44). $^{13}C$ NMR ($D_2O$+DCl) δ 56.1 (dd, *J* = 21) ; 88.4 (dd, *J* = 189) ; 169.9 (s) ; 170.9 (sd, *J* = 24). $[\alpha]^{20}_D$ = + 5 (c 0.19, HCl 1N).


(*Received in France* 18 *April* 1996; *accepted* 29 *May* 1996)