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Efficient preparation of enantiomerically pure α-aryl-α-trifluoromethylglycines via Auto Seeded Programmed Polythermic Preferential Crystallization of 5-aryl-5-trifluoromethylhydantoins

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Dedicated to the memory of Professor Y. L. Yagupol'skii (Institute of Organic Chemistry, Kiev)

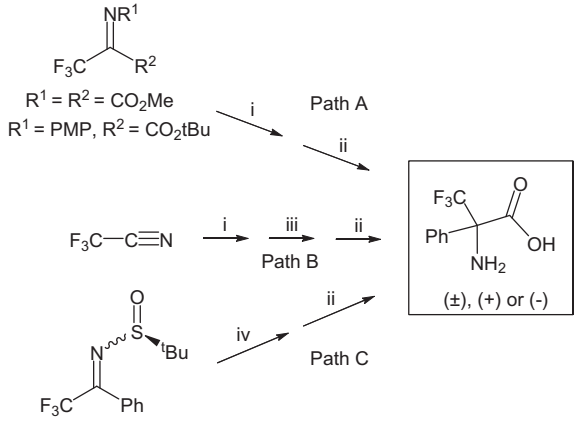
ABSTRACT

Both pure enantiomers of α-phenyl- (or α-(*p*-methoxyphenyl))-α-trifluoromethyl-glycine and their corresponding methyl esters were obtained on a preparative scale using the following four-step sequence: the preparation of 5-aryl-5-trifluoromethylhydantoins by a Bücherer–Bergs reaction starting from trifluoromethyl aryl ketones, optical resolution by Auto Seeded Programmed Polythermic Preferential Crystallization (AS3PC), basic hydrolysis of the enantiopure hydantoins by means of aqueous barium hydroxide, and esterification of the amino acids with trimethylsilyldiazomethane. Hydantoins **5** and **6** were proven to crystallize as conglomerates using first second harmonic generation and then X-ray powder diffraction. The absolute stereochemistry of (+)-5-phenyl-5-trifluoromethylhydantoin **5b** was established to be (*S*) by X-ray diffraction analysis on a single-crystal.

1. Introduction

α-Trifluoromethyl amino acids and their corresponding amino esters are very attractive for the design of biologically active molecules, especially in the application of peptides as pharmaceuticals.[1] Among these compounds, fluorinated non-racemic α,α-disubstituted α-amino acids represent key targets in modern peptide chemistry,[2] because of their remarkable properties. Their restricted conformational flexibility is useful for well-defined secondary structure folding,[3] their increased lipophilicity improves the in vivo absorption rate and permeability through cellular membranes[4] while their higher resistance toward enzymatic hydrolysis enhances bioavailability.[5]

Several syntheses of racemic[6] or enantiopure[7] α-trifluoromethyl α-amino acids have already been reported. Herein we wish to focus on synthetic routes to enantiopure α,α-disubstituted α-trifluoromethyl α-amino acids. There are two general methods described in the literature: (a) the synthesis of racemic α-amino acid derivatives based on reactions between N-protected imines derived from alkyl trifluoropyruvate and various organometallic reagents,[8] followed by resolution using chiral agents or enzymes;[5a,9] and (b) the diastereoselective synthesis using chiral trifluoromethyl building blocks (cyclic 2,5-diketopiperazine,[10] β-sulfinylimines or β-iminosulfoxides,[11] α-CF_3-imines, iminiums, and oxazolidines[7,12]), followed by cleavage of the chiral auxiliary.



Scheme 1. Reagents and conditions: (i) PhMgX; (ii) HCl, HCO_2H_{aq} or (1) CAN_{aq}, (2) HCl_{aq}; (iii) HCN; (iv) TMSCN.

Among fluorinated α,α-disubstituted α-amino acids, there are very few examples concerning α-aryl-α-trifluoromethylglycine derivatives. Only two racemic syntheses and one stereoselective method have been reported (Scheme 1). In the first approach, α-phenyl-α-trifluoromethylglycine was prepared from the reaction of a non chiral trifluoropyruvate imine with a phenyl Grignard reagent

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followed by aqueous acid hydrolysis (Scheme 1: path A: $R^1 = R^2 = CO_2Me$)[13] or oxidative removal of a *p*-methoxyphenyl (PMP) group by treatment with cerium ammonium nitrate (CAN) and acid hydrolysis (Scheme 1: path A: R^1 = PMP, $R^2 = CO_2{}^tBu$).[14] Another racemic synthesis involves a three-step sequence: the reaction of trifluoroacetonitrile with phenyl Grignard reagent to afford the corresponding ketimine; the addition of hydrogen cyanide leading to α-aminonitrile; and then aqueous hydrolysis with hydrochloric acid (Scheme 1: path B).[15]

The non-racemic approach uses an asymmetric Strecker reaction of chiral (*R*)-*N*-*tert*-butylsulfinylketimine with trimethylsilylcyanide followed by aqueous acid hydrolysis to remove the chiral auxiliary (Scheme 1: path C).[16] These three syntheses suffer from several drawbacks: the preparation of racemic mixtures (paths A, B) or the use of a chiral auxiliary in stoichiometric amounts (path C).

2. Results and discussion

2.1. Synthesis of (±)-hydantoins 5–8

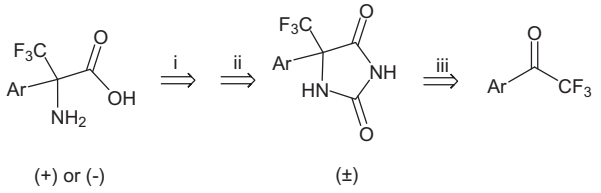
The aim of our strategy was to develop an efficient three-step method for the preparation of both (+)- and (−)-enantiomers of α-aryl-α-trifluoromethylglycine derivatives. The key step is based on an easy resolution of 5-aryl-5-trifluoromethylhydantoins by Auto Seeded Programmed Polythermic Preferential Crystallization (AS3PC).[17] There are several advantages to this approach: there is no need for the use of stoichiometric amounts of resolving agent; it can be carried out on a large multigram scale, and both enantiomers are accessible in high enantiomeric excess (ee >98%).

According to Scheme 2, the two enantiomers of α-aryl-α-CF_3-glycines could be obtained from aqueous basic hydrolysis of enantiopure 5-aryl-5-CF_3-hydantoins, which could be resolved by the AS3PC method and prepared using a Bücherer-Bergs reaction from the corresponding ketones.

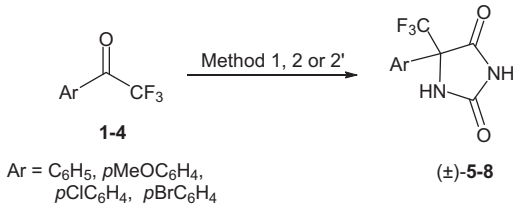
The first step of our sequence was the one pot synthesis of 5-aryl-5-trifluoromethylhydantoins. These compounds are known to exhibit interesting biological activities such as anesthetic or neuroprotective actions on the central nervous system.[18a,b] Two main synthetic pathways to 5-aryl-5-CF_3-hydantoins have previously been reported in the literature. The most general method is based on a Bücherer–Bergs reaction[19] starting from trifluoromethyl aryl ketones or the corresponding cyanohydrins with ammonium carbonate and potassium cyanide.[18] The second method involves the reaction of trifluoromethyl amino ester derivatives with various substituted isocyanates followed by cyclization to the corresponding hydantoins.[20]

We chose the Bücherer-Bergs reaction for the preparation of (±) hydantoins **5**–**8** as their corresponding CF_3-ketones **1**–**4** are commercially available or easily prepared using a Friedel–Craft reaction.

The first experiment was to repeat the reported procedure[18a] starting from α,α,α-trifluoro-acetophenone **1** with ammonium carbonate and potassium cyanide in a sealed container (Scheme 3). Unfortunately, the conversion was not complete and a low yield (~30–40%) of hydantoin **5** was obtained. When the reaction was repeated twice (heating **1** with 1.5 equiv of potassium cyanide and 2.0 equiv of ammonium carbonate for 16 h, then the addition of the same quantities of reagents and again heating for 22 h), the yield of compound **5** reached 53% yield after purification by silica gel column chromatography (Table 1, Method 1: entry 1).



Scheme 2. Reagents and conditions: (i) aqueous basic hydrolysis; (ii) resolution by AS3PC; (iii) Bücherer–Bergs reaction.



Scheme 3. Reagents and conditions. *Method 1*: KCN (3.0 equiv), $(NH_4)_2CO_3$ (4.0 equiv), EtOH–H_2O (50:50), autoclave, 110–120 °C, 38 h. *Method 2* or *2′*: KCN (1.2 equiv), $(NH_4)HCO_3$ (3.6 equiv), NH_4OH (8.6 equiv), EtOH–H_2O (50:50), 65 °C, 2–4 days.

A second optimisation up to 72% yield was performed using the procedure developed by Coquerel et al.[21] starting from an aqueous ammonium hydrogenocarbonate, ammonium hydroxide, and potassium cyanide suspension (Scheme 3, Table 1, Method 2: entry 2). This improvement can be reasonably explained by the increase in reaction mixture solubility. Moreover, it was suspected that ammonium carbamate (a side-product of ammonium carbonate) might inhibit the Bücherer–Bergs reaction.

When performing the same reaction on a large scale (Table 1, entry 3), purification of compound **5** was difficult when using silica gel column chromatography or direct recrystallization of the crude mixture (due to solubility problems). Therefore, the crude mixture was purified by precipitation of the (±)-α-methylbenzylamine (α-MBA)·(±)-hydantoin ammonium salt, filtration, and the release of the corresponding (±) hydantoin by simple heating (Table 1, Method 2′: entry 3) afforded 50% of pure compound **5**. This purification method has already been developed by Coquerel et al.[21] for non-fluorinated hydantoin derivatives.

Our methodology (Method 2 or 2′) was then extended to various *p*-substituted aryl trifluoromethyl ketones **2**–**4** (Scheme 3). *p*-Methoxyphenyl hydantoin **6** was successfully prepared in good yields using Method 2 or 2′ (Table 1, entries 4 and 5). Nevertheless, the reactions of *p*-chloro- and *p*-bromophenyl trifluoromethyl ketones **3** and **4** were more complicated. Although reaction yields were almost quantitative, the corresponding hydantoins **7** and **8** were obtained in 35% and 23% yields, respectively (Table 1, entries 6 and 7). Indeed, several other fluorinated by-products (which were not characterized) were detected in the crude mixture by ^{19}F NMR, indicating possible partial substitution of the halogen or other competitive reactions.

It is worth noting that the aryl trifluoromethyl ketones **1**–**4** react differently compared to the non-fluorinated ones. Almost

Table 1
Synthesis of 5-aryl-5-(trifluoromethyl)hydantoins **5**–**8**

Entry	Ar	Ketone (scale)	Method	Conv.[a] (%)	Yield[b] (%)
1	Ph	**1** (5.7 mmol)	1	87	**5** (53)[c]
2	Ph	**1** (5.7 mmol)	2	~100	**5** (72)[c]
3	Ph	**1** (345 mmol)	2′	~100	**5** (50)[d]
4	$pMeOC_6H_4$	**2** (23.8 mmol)	2	~100	**6** (63)[c]
5	$pMeOC_6H_4$	**2** (107 mmol)	2′	~100	**6** (65)[d]
6	$pClC_6H_4$	**3** (3.6 mmol)	2	~95[e]	**7** (35)[c]
7	$pBrC_6H_4$	**4** (4.1 mmol)	2	~95[e]	**8** (23)[c]

[a] Conversion was estimated by ^{19}F NMR of the crude mixture.
[b] Isolated pure compound.
[c] Purification by silica gel column chromatography.
[d] Purification by crystallization with (±)-αMBA.
[e] Several other fluorinated by-products were detected in the crude mixture by ^{19}F NMR.

quantitative conversion of **1**–**4** into hydantoins **5**–**8** was reached after 2–4 days (in contrast, the corresponding 5-aryl-5-methylhydantoins were obtained in good yields after only 5–10 h).[21]

2.2. Characterisation of hydantoins 5–8

All fluorinated (±)-hydantoins **5**–**8** were characterized using spectroscopic experiments (^{19}F, ^{1}H, ^{13}C NMR, and IR), mass spectrometry, and microanalyses. It was not possible to crystallize the *p*-chloro- and *p*-bromophenylhydantoins **7** and **8**. In contrast, compounds **5** and **6** were easily obtained as solids and were suspected to crystallize as conglomerates by means of first Second Harmonic Generation (SHG) tests.[22]

Moreover, it was shown that the XRPD patterns of the racemic mixtures and of the pure enantiomers were exactly superimposable for hydantoins **5** and **6**, respectively, thus confirming the full chiral discrimination in the solid state. This important property allowed us to perform the resolution of racemic hydantoins **5** and **6** by AS3PC experiments (vide infra).

Suitable single-crystals of compound **5** were obtained by the slow evaporation of a saturated ether/MeOH/CH_2Cl_2 solution. The crystalline structure of hydantoin **5b** was determined by single-crystal X-ray diffraction in the $P2_1$ space group at 296 K. Structure representation (ORTEP drawing) is given in Figure 1. The (*S*)-configuration was assigned to a single crystal of hydantoin **5b**. The calculated XRPD pattern from single-crystal X-ray diffraction was consistent with the experimental XRPD patterns. Therefore, the single-crystal used for this structure study was representative of the bulk.

The stability of the crystalline packing was ensured by an extensive network of hydrogen bonds (Table 2). The crystal structure (see Cambridge Crystallographic Data Centre: Reference No. 684964) shows the usual H-bond network in the shape of a ribbon and with a periodicity of 6.21 ± 0.02 Å.[23]

2.3. Determination of the absolute configuration of hydantoin 5b

The resolution of the crystalline structure of hydantoin **5b** did not allow us to unambiguously determine the absolute configuration because the Flack parameter was not accurate enough. It was, therefore, determined from the resolution of the corresponding ammonium salt. A batch of salt **9** was prepared from (*R*)-(+)-α-methylbenzylamine [(+)-α-MBA] and (+)-hydantoin **5b** (obtained from Pasteurian resolution,[24] see Section 4). Several single-crystals were obtained by slow evaporation of a petroleum ether/MeOH/CH_2Cl_2 solution. The resolution of **9** was performed by single-crystal X-ray diffraction and its configuration was the following: (*R*) for (+)-α-MBA molecules and (*S*) for (+)-hydantoin molecules (Fig. 2).

Table 2
Hydrogen bond lengths and angles

D–H···A	d(D–H) (Å)	d(H···A) (Å)	d(D···A) (Å)	Angle (DHA) (°)
N(1)–H(1)···O(2)	0.86	1.99	2.838(2)	169.3
N(2)–H(2)···O(1)	0.86	1.99	2.781(2)	153.1

2.4. Resolution of (±)-hydantoins 5 and 6 by Auto Seeded Programmed Polythermic Preferential Crystallization experiments

Preferential crystallization, also called entrainment, is a well-known preparative resolution method[25] applicable to racemic mixtures crystallizing as stable conglomerates. This method consists of alternate stereoselective crystallizations of each antipode from a supersaturated mother liquor initially containing an excess of one enantiomer. By means of successive recycling of the mother liquor and the addition of the racemic mixture in order to maintain the same initial concentration, the process quantitatively gave the two enantiomers without the use of a resolving agent. A variant of preferential crystallization known as AS3PC (Auto Seeded Programmed Polythermic Preferential Crystallization),[17,21] which offers improved performances in comparison to the conventional seeded method, was applied here.

2.4.1. Resolution of (±)-5-phenyl-5-trifluoromethylhydantoin 5

Two batches of (±)-5-phenyl-5-trifluoromethylhydantoin **5** were resolved by two campaigns of preferential crystallization (Scheme 4). Seven and twelve entrainments were carried out by successive recycling of the mother liquor. The initial composition

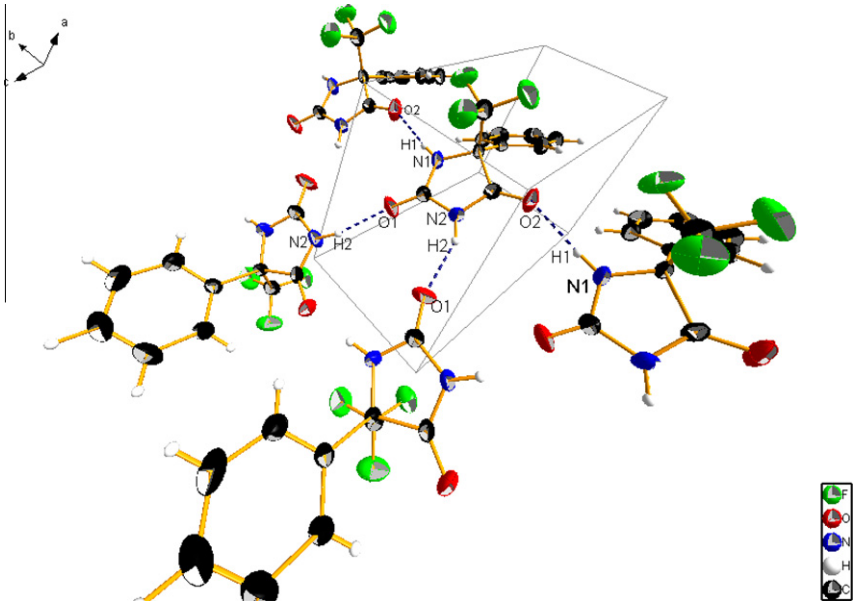


Figure 1. Visualisation of hydrogen bonds between hydantoin molecules (ORTEP drawing) of **5b**. All non-hydrogen atoms are represented by their displacement ellipsoids drawn at a 50% probability level. Hydrogen atoms are drawn with an arbitrary radius.

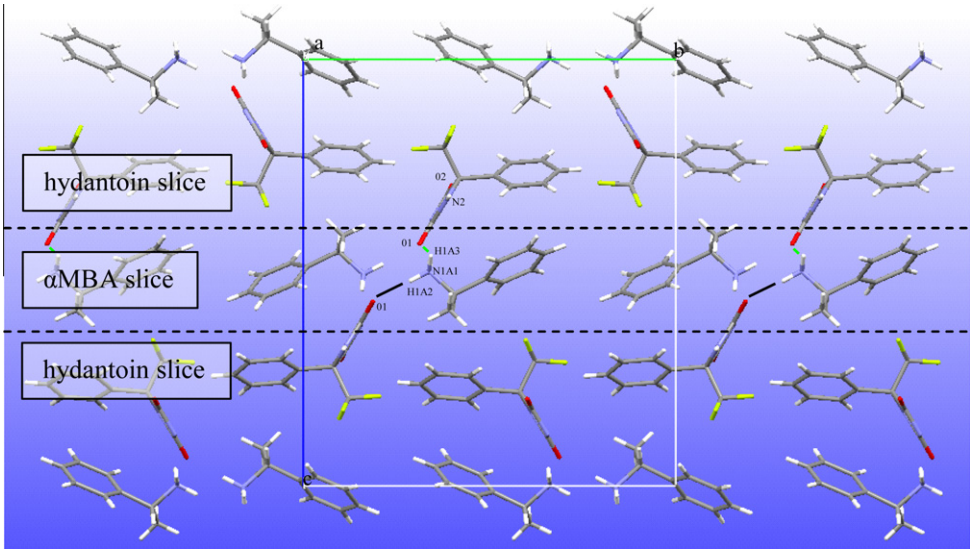


Figure 2. Projections of the crystalline structure of the (*R*)-(+)-α-MBA salt **9** of (+)-(*S*)-hydantoin **5b** along an axis.

of the system for the first attempts, the main AS3PC parameters, and the results are collected in Tables 3 and 4, respectively. The temperature ramp was from 30 °C to −10 °C for the first campaign and from 30 °C to −15 °C for the second one (cooling rate = 0.67 °C/min). The final temperature was held until the end (≈24 h) showing a strong entrainment effect. The evolution of the enantiomeric excess (ee) was measured by using off line polarimetry and HPLC with three or four samples of the mother liquor near completion of the entrainment.

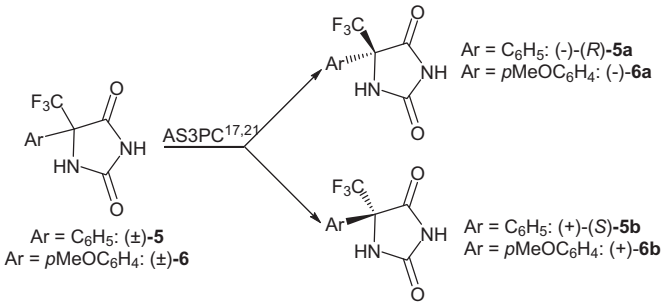
An average mass of 1.2 g (crude crops) was collected with an enantiomeric purity approximately 86% ee. Theoretically, the ee value should be 100%; the lower value obtained is due to the fact that the crystals were partially impregnated by the mother liquor containing the remaining racemic mixture and no washing of the filtration cake had been implemented. We noticed that the final temperature T_F for the second campaign was decreased from −10 °C down to −15 °C in order to increase the driving force of the crystallization. Subsequent purification by recrystallization gave the pure enantiomer with an enantiomeric purity of 99% ee with 87% yield. This result is consistent with the crystal structure with a partial solid solution, that is, complete chiral discrimination occurs in the solid state.

In conclusion, for these small scale AS3PC experiments, the direct resolution of 5-phenyl-5-trifluoromethylhydantoin **5** was characterized by a satisfactory entrainment effect.

2.4.2. Resolution of (±)-5-(*p*-methoxyphenyl)-5-(trifluoromethyl)hydantoin 6

The same AS3PC experiments were performed with (±) 5-(*p*-methoxyphenyl)-5-trifluoromethylhydantoin **6**. Seven entrainments were carried out by successive recycling of the mother liquor. The initial composition of the system for the first attempt, the main AS3PC parameters and the results are given in Table 5. The temperature ramp was from 40 °C to 0 °C for the first four cycles and from 40 °C to −10 °C for the following cycles (cooling rate = 0.67 °C/min). The final temperature was held until the end of entrainment (≈48 h) in order to determine the end of the entrainment effect.

We noticed that after a certain number of crystallizations, several impurities contained in the racemic mixture accumulated in the mother liquor. These components introduced a shift in the temperatures: the final temperatures T_F progressively decreased from 0 °C down to −10 °C. Experimentally, the entrainment effect remained unchanged because the same driving force (supersaturation) was used.



Scheme 4. AS3PC resolution of (±) hydantoins **5** and **6**.

During these entrainments, the crop mass values were scattered because monitoring the mother liquor requires several samples, thus causing a significant loss of material at this scale. An average mass of 777 mg (crude crops) was collected with an enantiomeric purity of approximately 86% ee. Recrystallization in ethanol gave access to the pure enantiomers with an enantiomeric purity of greater than 99% ee.

2.5. Synthesis of α-aryl-α-trifluoromethylglycine derivatives

The most general method for the transformation of hydantoins into the corresponding α-amino acids uses aqueous acid (H_2SO_4 or HCl)[26] or basic (NaOH, LiOH, or $Ba(OH)_2$)[27] hydrolysis. For non-fluorinated hydantoins, several reactions have already been reported in the literature. These transformations usually require strong reaction conditions such as highly concentrated aqueous acid (e.g., H_2SO_4 60%) or base (e.g., NaOH 2 M) solution, long reaction time (12–48 h), high temperature (>120 °C), and give only moderate yields (25–50%) of the amino acid derivatives.[26,27] It is worth noting that basic hydrolysis often gives slightly better yields. On the contrary, there is only one publication that reports the hydrolysis of (*R*)-5-difluoromethyl-5-methylhydantoin into (*R*)-α-difluoromethylalanine hydrochloride (yield: 90%) by refluxing with aqueous $Ba(OH)_2{\cdot}8H_2O$ and subsequent HCl acidification of the reaction mixture.[11b]

Table 3
Results of the preferential crystallization of (±)-5-phenyl-5-trifluoromethylhydantoin **5**—first campaign

	Mass of ethanol (g)	Mass of racemic mixture $M(\pm)$ (g)			Mass of pure enantiomer M_p (g)		
	24.9	4.71			0.45		
Cycle	1	2	3	4	5	6	7
Mass of crops (g)	0.766	1.645	1.082	1.205	0.975	0.949	1.078
Enantiomeric excess by HPLC (% ee)	89	40[a]	91	86	88	91	85
Mass of collected pure enantiomer (g)	0.682	0.658	0.985	1.036	0.858	0.864	0.916
ee_f (%)[b]	6.7	6.5	9.5	9.9	8.3	8.4	8.9

[a] For this batch, nucleation of the antipode was detected before filtration.
[b] ee_f stands for the final enantiomeric excess of the mother liquor at the end of the entrainment. $ee_f = \frac{M_p/2}{M_p/2+M(\pm)}$.

Table 4
Results of preferential crystallization of (±)-5-phenyl-5-trifluoromethylhydantoin **5**—second campaign

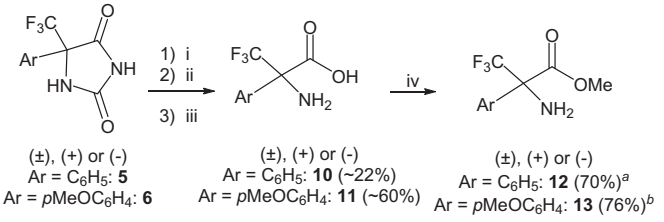
	Mass of ethanol (g)			Mass of racemic mixture $M(\pm)$ (g)					Mass of pure enantiomer M_p (g)			
	31.9			6.0					0.50			
Cycle	1	2	3	4	5	6	7	8	9	10	11	12
Mass of crops (g)	1.084	1.146	1.641	1.617	1.166	1.124	1.349	1.505	1.391	1.389	1.317	0.977
Enantiomeric excess by HPLC (% ee)	88	80	80	90	91	87	88	89	93	95	91	94
Mass of collected pure enantiomer (g)	0.953	0.917	1.313	1.471	1.061	0.978	1.187	1.339	1.293	1.319	1.198	0.918
ee_f (%)	7.3	7.1	9.9	10.9	8.1	7.5	9.0	10.0	9.7	9.9	9.1	7.1

Table 5
Results of preferential crystallization of (±) 5-(*p*-methoxyphenyl)-5-trifluoromethyl-hydantoin **6**

	Mass of ethanol (g)	Mass of racemic mixture $M(\pm)$ (g)			Mass of pure enantiomer M_p (g)			
	21.5	3.2			0.35			
Cycle	1	2	3	4	5	6	7	MEAN
Mass of crops (g)	1.070	1.082	0.534	0.405	0.845	0.613	0.892	0.777
Enantiomeric excess by HPLC (% ee)	58	93	95	92	86	88	89	85.8
Mass of collected pure enantiomer (g)	0.621	1.006	0.508	0.372	0.723	0.549	0.794	0.653
ee_f	8.8%	13.6%	7.3%	5.5%	10.1%	7.9%	11.0%	9.1%

As indicated in the literature[11b] as well in our first preliminary experiment, it was necessary to use mild reaction conditions in order to avoid the loss of the trifluoromethyl group. The hydrolysis of 5-aryl-5-trifluoromethylhydantoins **5** and **6** were performed using Zanda's reaction conditions, but hydrochloric acid was replaced by sulfuric acid in order to increase the precipitation of inorganic salts ($BaSO_4$ is less soluble in water than $BaCl_2$). Reactions were optimized on racemic mixtures, then the transformations were extended to both (+)- and (−)-enantiomers without the isolation of the corresponding amino acid derivatives (see one pot procedure). Nevertheless, we did not notice any variation in the chemical yields in the racemic or enantiopure series. The best conditions were the following: an aqueous suspension of hydantoin **5** or **6** and $Ba(OH)_2{\cdot}8H_2O$ (6 equiv) was refluxed for 3 days (reaction evolution was monitored by ^{19}F NMR of the crude reaction mixture). After H_2SO_4 acidification (pH 1) and removal of the inorganic salts, the resulting α-amino acid was obtained by chromatography on Dowex 50WX, in moderate (∼22% for compound **10**) to good (∼60% for compound **11**) yields (Scheme 5).

α-Amino acids **10** and **11** were characterized by NMR experiments (^{19}F, ^{1}H, ^{13}C), and mass spectrometry (MS, HRMS). Although only one enantiomer of each α-amino acid **10** or **11** was observed using chiral HPLC analysis (stationary phase: Chirobiotic T), the samples were slightly contaminated by inorganic salts (as proved by microanalysis). Therefore, compounds **10** and **11** were derivatized into the corresponding α-amino esters using a solution of trimethylsilyldiazomethane[28] in an MeOH-toluene mixture (Scheme 5). After easy purification by chromatography on silica gel, compounds **12** and **13** were obtained in 70% and 76% yields, respectively. The chemical purities of **12** and **13** were checked by microanalysis. However, all attempts to verify the enantiomeric purity by chiral GC (stationary phase: chirasil-L-val or permethylated-β-cyclodextrin) or HPLC (stationary phase: Chirobiotic T or Chirobiotic V) were unsuccessful.



Scheme 5. Reagents and conditions: (i) $Ba(OH)_2{\cdot}8H_2O$, Δ, 3 days; (ii) H_2SO_4 (0.5 M); (iii) DOWEX chromatography; (iv) $TMSCHN_2$, MeOH–toluene, 25 °C. [a]Overall yield of **12** from **5**: 14%. [b]Overall yield of **13** from **6**: 46%.

For the esterification of (±)-α-amino acid **11**, small amounts of *N*-methyl and *N*,*N*-dimethyl amino esters **14** and **15** (see Section 4) were observed in the crude reaction mixture by NMR and GC–MS.

In order to increase the efficiency of our method, a one pot synthesis of compounds **12** and **13** was performed starting from the corresponding 5-aryl-5-trifluoromethylhydantoins **5** and **6**; overall yields of 14% and 46%, respectively, were obtained (Scheme 5).

As indicated in Scheme 5, yields of α-amino acids **10** (∼22%) and **11** (∼60%) were quite different and this requires explanation. It was hypothesized that after the formation of the α-amino acids,

in situ deprotonation of the carboxylic function of **10** or **11** could be followed by a decarboxylation reaction leading to carbanion **16** (Scheme 6). The latter could then lose a fluoride anion (which is a good leaving group) to give difluoroalkene **17**. This highly reactive intermediate could thus behave as a Michael type acceptor in an aqueous basic medium to afford the corresponding phenylglycine derivative **18** as the final product (Scheme 6). This proposition was supported by the observation of compound **18** (R = H) in the crude reaction mixture of hydantoin **5**, using LC-MS analysis. On the contrary, a *p*-methoxy substituent (which exhibits an electron-donating effect through phenyl conjugation) seems to have a destabilising contribution on the anion **16**, thus preventing the loss of the fluoride anion and, therefore, the formation of *p*-methoxyphenylglycine **18** (R = OMe).

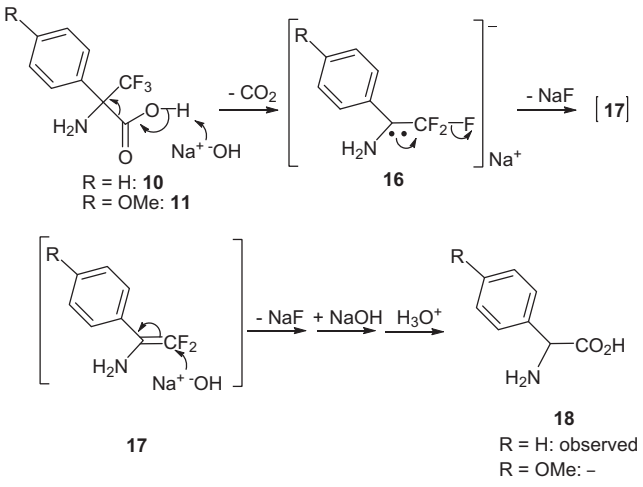
3. Conclusion

We have described a straightforward synthesis of both enantiomers of α-phenyl- and α-(p-methoxyphenyl)-α-trifluoromethylglycines **10** and **11**, from commercially available or easily accessible trifluoromethyl aryl ketones, using a three-step sequence. It is worth noting that there is only one publication which reports the stereoselective synthesis of the α-amino acid **10**.[16] The main advantages of our methodology are the multigram scale synthesis and the access to both the (+)- and (−)-enantiomers in high enantiomeric excess, thanks to efficient resolution of 5-aryl-5-trifluoromethylhydantoins **5** and **6** by the AS3PC process. The fluorinated α,α-disubstituted α-amino acids **10** and **11** as well as α-amino esters **12** and **13** could be involved in new valuable peptide couplings:[29] these aspects are currently under investigation.

4. Experimental

4.1. General methods

Reagents and solvents were generally the best quality commercial grade and used without further purification: α,α,α-trifluoroacetophenone (Acros, 99%), 1-(4-chlorophenyl)-2,2,2-trifluoroeth anone (Aldrich, 99%), 1-(4-bromophenyl)-2,2,2-trifluoroethanone (Aldrich, 99%), (±)-α-methylbenzylamine [(±)-α-MBA, Acros, 99%], ethanol (Acros, absolute), KCN (Aldrich, 99%), NH_4HCO_3 (Prolabo, Rectapur), NH_4OH (Acros, for analysis, 28–30 wt % solution of NH_3 in water), $Ba(OH)_2{\cdot}8H_2O$ (Acros, 98%). Ketone **2** was prepared and purified according to the literature.[30] Small amounts (~100 mg) of enantiopure (+) hydantoins **5b** and **6b** were obtained using Pasteurian resolution starting from (−)-(*S*)-α-methylbenzylamine.[24] Reactions were followed by thin layer chromatography (TLC) on silica gel (Merck, Darmstadt, Germany) and revealed using UV light, using either an ethanolic solution of phosphomolybdic acid or ninhydrin solution (especially for amino acids and amino esters). Purification of compounds **5**–**8** (Table 1) was carried out using flash column chromatography with silica gel (70–200 μm). The purity of the synthetic products was established by HPLC/UV analysis and confirmed by NMR spectroscopic data and MS analysis. HPLC: for hydantoins **5a**,**b** and **6a**,**b**: ThermoQuest P1500, UV Detector: λ = 235 nm, chiral stationary phase: Chiral Pack AD, mobile phase: ethanol, flow: 1 mL/min; for α-amino acids **10a**,**b** and **11a**,**b**: ThermoQuest P1500, UV Detector: λ = 220 nm, chiral stationary phase: Chirobiotic T, 250 mm×4.6 mm, mobile phase: 90% MeOH/10% water/0.1% acetic acid, flow: 1 mL min^{-1}. MS: Thermo Finnigan, LCQ Advantage Max, Electrospray Ionisation, Source heater T = 220 °C, capillary voltage = 33 V. High Resolution Mass Spectra (HRMS) were recorded with a Q-TOF Micromass Instrument in the positive ESI (CV = 30 V) mode. ^1H (300 MHz), ^{19}F (280 MHz), and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Advance DMX 300 instrument. All the experiments were recorded using $CDCl_3$ or CD_3COCD_3 or DMSO-d_6 as solvent. TMS or the deuterated solvent signal was taken as internal reference for ^1H and ^{13}C spectra and the $CFCl_3$ signal for ^{19}F spectra. The enantiomeric purity of the 'crops' of hydantoins **5**, **6** was determined by chiral HPLC. Specific rotations ($[\alpha]^{25\,^\circ C}_{589\ nm}$) were measured with a Perkin–Elmer Model 341 polarimeter using the sodium D line at 589 nm, at 25 °C. XRPD measurements were carried out with a D5000matic Siemens® instrument with a Bragg Brentano geometry, in theta–theta reflection mode. The instrument is equipped with an X-ray tube (copper anticathode, 40 kV, 40 mA, $K_{\alpha1}$ radiation: 1.540598 Å, $K_{\alpha2}$ radiation: 1.544426 Å), a nickel filter, and a scintillation detector. The diffraction patterns were collected with steps of 0.04° (2-theta) over the angular range 3–30°, with a counting time of 4 s per step. No internal standard was used but a sample of quartz was analyzed as an external standard (data processing by using software EVA® v 9.0.0.2). The crystal structures of hydantoin **5b** and ammonium salt **9** were determined from single-crystal X-ray diffraction on a Bruker© SMART APEX diffractometer (with $MoK_{\alpha1}$ radiation: 0.71073 Å). The structures were determined by means of the direct methods and refined with the SHELXTL© package.[31] Single-crystals of **5b** and **9** were obtained by a slow evaporation of a saturated solution of petroleum ether/MeOH/CH_2Cl_2. TG/DSC measurements were performed with a STA 409 PC/PG (Netzsch®) with aluminum crucibles and with a 2 K/min heating rate.



Scheme 6. Proposed mechanism explaining the low yield of α-amino acid **10**.

4.2. General procedure for the synthesis of 5-(trifluoromethyl)-hydantoins 5–8

The (±)-5-(trifluoromethyl)hydantoins **5**–**8** were prepared from the appropriate ketones **1**–**4** using a Bücherer–Bergs reaction.

4.2.1. Typical procedure for Method 1 (Table 1, entry 1)

A solution of ketone **1** (5.74 mmol, 1 equiv) in ethanol (12 mL) was added to a mixture of KCN (0.56 g, 8.61 mmol) and $(NH_4)_2CO_3$ (1.65 g, 17.22 mmol) in water (12 mL). The suspension was heated in an autoclave at 110–120 °C for 16 h. The course of the reaction was controlled by ^{19}F NMR of the crude mixture. After one night of heating, the conversion was not complete. Next, KCN (0.56 g, 8.61 mmol) and $(NH_4)_2CO_3$ (0.55 g, 5.74 mmol) were added. The suspension was again heated at 110–120 °C for 22 h. At the end of reaction, an excess of hydrochloric acid solution (37 wt %, 10 mL) was slowly added to obtain an acidic pH (pH 1–2). The aqueous phase was extracted four times with diethyl ether (4 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude

yellow solid was purified by silica gel column chromatography (eluent: petroleum ether/AcOEt 70:30) affording the desired hydantoin **5** (0.74 g, 53%).

4.2.2. Typical procedure for Method 2 (Table 1, entry 2)

A solution of ketone **1** (5.74 mmol, 1 equiv) in ethanol (23 mL) was added to a mixture of KCN (4.67 g, 6.89 mmol) and $(NH_4)HCO_3$ (17.1 g, 20.66 mmol) in water (23 mL). A solution of NH_4OH (30 wt %, 17.7 mL) was added into the flask provided with a reflux condenser. The mixture was heated at 65 °C for 3 days. At the end of the reaction, an excess of hydrochloric acid solution (37 wt %, 20 mL) was slowly added to obtain an acidic pH (pH 1–2). The same work-up and purification on silica gel column chromatography as Method 1 afforded hydantoin **5** (1.01 g, 72%).

4.2.3. Typical procedure for Method 2′ (Table 1, entry 3)

A solution of ketone **1** (0.345 mol, 1 equiv) in ethanol (140 mL) was added to a mixture of KCN (27.2 g, 0.418 mol) and $(NH_4)HCO_3$ (100 g, 1.260 mol) in water (140 mL). A solution of NH_4OH (30 wt %, 104 mL) was then added. The mixture was heated at 65 °C for 3 days. At the end of the reaction, an excess of hydrochloric acid solution (37 wt %, 70 mL) was slowly added to an obtain acidic pH (pH 1–2). The resulting hydantoin **5** was precipitated and filtered off. The crude was purified by crystallization of ammonium salt with (±)-αMBA as a base. The crude solid (56 g) was dissolved in ethanol (60 mL) then (±)-αMBA (27.8 g, 1.02 equiv) was slowly added. The resulting ammonium salt was formed after 5 min and its solubility was decreased by the slow addition of diethyl ether (100 mL) as an anti-solvent. The suspension was filtrated on a Büchner and the collected mass was around 40 g. The solution was partially evaporated and the process of crystallization was repeated several times. Four successive crystallization/filtration sequences allowed the collection of several fractions of salt. For each crop, the solid was washed with diethyl ether (~20 mL). All solid phases were combined to give 63 g of the ammonium salt. The release of pure hydantoin was performed by simple heating of the ammonium salt at 100–110 °C, in an oven for 48 h. When the loss of mass was about 33% (corresponding to αMBA mass), the solid was kept at room temperature. (±)-5-Phenyl-5-(trifluoromethyl)hydantoin **5** was obtained (42 g, 50% yield) with a 99% chemical purity.

4.2.4. 5-Phenyl-5-(trifluoromethyl)hydantoin 5 (Table 1, entries 1–3)

(±) Hydantoin **5**: solid. Mp 220 °C. ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.4–7.6 (m, 3H Ph), 7.9–8.0 (m, 2H Ph), 8.7 (br s, 1H, NH), 10.2 (br s, 1H, NH). ^{19}F NMR (280 MHz, CD_3COCD_3) δ: −75.0 (s). ^{13}C NMR (75 MHz, CD_3OD) δ: 69.6 (q, $^2J_{C,F}$ = 30.0 Hz, C-5), 124.2 (q, $^1J_{C,F}$ = 284.2 Hz, CF_3), 127.8 (s, 2 × CH Ph), 129.8 (s, 2 × CH Ph), 131.0 (s, CH Ph), 131.7 (s, C_q Ph), 158.2 (s, C-2, CO), 170.1 (s, C-4, CO). GC-MS (EI, %) *m*/*z* 244 [M^+], 175, 132, 104 (100), 77. HRMS (ESI^+) calcd for $C_{10}H_7F_3N_2NaO_2$ *m*/*z* 267.0357, found 267.0359.

4.2.5. 5-(*p*-Methoxyphenyl)-5-(trifluoromethyl)hydantoin 6

(±)-Hydantoin **6** was obtained in 63% yield (4.11 g) using Method 2 (purification by chromatography on silica gel, Table 1, entry 4) and in 65% yield (17.0 g) using Method 2′ (purification by crystallization of ammonium salt, Table 1, entry 5). (±)-Hydantoin **6**: solid. Mp 230 °C. ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.68 (s, 3H, MeO), 6.89 (d, $^3J_{H,H}$ = 8.6 Hz, 2H Ar), 7.63 (d, $^3J_{H,H}$ = 8.6 Hz, 2H Ar), 8.6 (br s, 1H, NH), 10.2 (br s, 1H, NH). ^{19}F NMR (280 MHz, CD_3COCD_3) δ: −75.3 (s). ^{13}C NMR (75 MHz, CD_3COCD_3) δ: 55.6 (s, CH_3O), 68.5 (q, $^2J_{C,F}$ = 29.9 Hz, C-5), 114.8 (s, 2 × CH Ar), 122.9 (s, C_q Ar), 123.9 (q, $^1J_{C,F}$ = 283.9 Hz, CF_3), 128.9 (s, 2 × CH Ar), 155.9 (s, C-2, CO), 161.7 (s, C_q, COMe), 168.9 (s, C-4, CO). IR (KBr, cm^{-1}) 3226, 3019, 2963, 1797, 1751, 1614, 1513, 1403, 1249. GC–MS (EI, %) *m*/*z* 274 [M^+], 205, 134 (100), 91, 44. HRMS (ESI^+) calcd for $C_{11}H_9F_3N_2O_3Na$ *m*/*z* 297.0463, found 297.0464.

4.2.6. (±) 5-(*p*-Chlorophenyl)-5-(trifluoromethyl)hydantoin 7

(±)-Hydantoin **7** was obtained in 35% yield (0.35 g) using Method 2 (Table 1, entry 6) after purification by silica gel column chromatography (eluent: petroleum ether/AcOEt 50/50). Oil. ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.1 (br s, 1H, NH), 7.4 (br s, 1H, NH), 7.52 (d, $^3J_{H,H}$ = 8.7 Hz, 2H Ar), 7.86 (d, $^3J_{H,H}$ = 8.7 Hz, 2H Ar). ^{19}F NMR (280 MHz, CD_3COCD_3) δ: −74.7 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 77.8 (q, $^2J_{C,F}$ = 29.3 Hz, C-5), 123.5 (q, $^1J_{C,F}$ = 286.1 Hz, CF_3), 127.9 (q, $^4J_{C,F}$ = 1.5 Hz, 2 × CH Ar), 129.1 (s, 2 × CH Ar), 132.4 (s, C_q Ar), 136.0 (s, C_q Ar), 160.6 (s, C-2, CO), 170.1 (s, C-4, CO). MS (ESI^-) *m*/*z* 279 [M-H], 277 [M-H]. HRMS (ESI^-) calcd for $C_{10}H_5{}^{35}ClF_3N_2O_2$ *m*/*z* 276.9992, found 277.0000. Several other fluorinated by-products were detected in the crude mixture by ^{19}F NMR but were not separated and assigned.

4.2.7. (±) 5-(*p*-Bromophenyl)-5-(trifluoromethyl)hydantoin 8

(±)-Hydantoin **8** was obtained in 23% yield (0.31 g) using Method 2 (Table 1, entry 7) after purification by silica gel column chromatography (eluent: petroleum ether/AcOEt 60/40). Oil. ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.1 (br s, 1H, NH), 7.4 (br s, 1H, NH), 7.71 (d, $^3J_{H,H}$ = 8.5 Hz, 2H Ar), 7.85 (d, $^3J_{H,H}$ = 8.5 Hz, 2H Ar). ^{19}F NMR (280 MHz, CD_3COCD_3) δ: −74.7 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 77.9 (q, $^2J_{C,F}$ = 29.1 Hz, C-5), 123.6 (q, $^1J_{C,F}$ = 286.0 Hz, CF_3), 124.3 (s, C_q Ar), 128.2 (q, $^4J_{C,F}$ = 1.6 Hz, 2 × CH Ar), 132.0 (s, 2 × CH Ar), 132.8 (s, C_q Ar), 160.6 (s, C-2, CO), 170.2 (s, C-4, CO). MS (ESI^-) *m*/*z* 323 [M-H], 321 [M-H]. HRMS (ESI^-) calcd for $C_{10}H_5{}^{79}BrF_3N_2O_2$ *m*/*z* 320.9486, found 320.9489. Several other fluorinated by-products were detected in the crude mixture by ^{19}F NMR but were not separated and assigned.

4.3. Typical procedure for the Auto Seeded Programmed Poly thermic Preferential Crystallization (AS3PC) of 5-phenyl-5-(trifluoromethyl)hydantoin 5 (Scheme 4, Tables 3–5)

Preferential crystallization (PC) using the Auto-Seeded variant (AS3PC[17,21]) was performed in a thermostated double-wall tube. Temperature was accurately controlled by a cryo/thermostat (Lauda® RE107). The initial system containing an excess of the (*S*)-enantiomer was heated at temperature T_B (T_B = 30 °C for hydantoin **5** and T_B = 40 °C for hydantoin **6**) so that only the (*R*)-enantiomer was completely dissolved. The slurry was composed of crystals of the (*S*)-enantiomer in excess and in a thermodynamic equilibrium with its saturated solution; the suspension was self-seeded by crystals of the pure enantiomer. The auto-seeded preferential crystallization was then ready to start. Thus, the suspension was submitted to an adapted cooling program (30 °C to −10 °C for hydantoin **5**—cooling rate = 0.67 °C/min; and 40 °C to 0 °C for hydantoin **6**—cooling rate = 0.67 °C/min) and magnetic stirring without any need of additional seeds so that the crystal growth was favoured instead of an uncontrolled second nucleation. The course of the entrainment was monitored by off-line polarimetric measurements of the mother liquor. At the end of the entrainment, the crystals of the (*S*)-enantiomer were collected by filtration with a Büchner and the enantiomeric purities of the crops were determined by chiral HPLC. The mother liquor containing an excess of the (*R*)-enantiomer was heated until T_B. A mass of (±)-hydantoin **5** [equal to the collected mass of (*S*) crystals] was then added to the mother liquor. The slurry was thus composed of crystals of the (*R*)-enantiomer and the same cooling program was applied in order to collect a crop of the (*R*)-enantiomer. This process can be repeated as many times as necessary, allowing alternative crystallizations of *S*- and *R*-enantiomers, corresponding to the resolution of the racemic mixture.

4.3.1. (−)-(*R*)- and (+)-(*S*)-Hydantoins 5a and 5b

Enantiopure hydantoins **5a**, **5b** were obtained by an AS3PC procedure and recrystallization in ethanol.

(−)-(*R*)-Hydantoin **5a**: solid. Mp 257 °C. $[\alpha]_{589}^{25} = -34.8$ (*c* 0.01 g/mL, MeOH). HPLC: retention time: 5.3 min; enantiomeric purity: 99.3% e.e.

(+)-(*S*)-Hydantoin **5b**: solid. Mp 257 °C. $[\alpha]_{589}^{25} = +34.7$ (*c* 0.01 g/mL, MeOH). HPLC: retention time: 3.3 min; enantiomeric purity: 99.2% e.e.

The X-ray crystal structure determination of compound **5b** (Fig. 1). $C_{10}H_7F_3N_2O_2$, $M_r = 244.18$, monoclinic, $P2_1$, $a = 7.4111(1)$, $b = 6.1865(1)$, $c = 11.3615(1)$ Å, $\beta = 106.043(2)°$, $V = 500.6$ Å^3, $Z = 2$, $Dx = 1.620$ g cm^{-3}. A total of 3876 reflections were collected at 293 K using MoKα radiation ($\lambda = 0.71073$ Å); 2041 independent reflections (Rint = 0.0238). The structure was solved by direct methods with SHELXTL and refined by least square using F^2 values and anisotropic thermal parameters for non hydrogen atoms.[31] There was one independent molecule in the asymmetric unit (151 parameters). The final reliability values for 2041 unique reflections and 154 parameters are $R_1 = 0.0521$, $wR_2 = 0.1176$ for 1059 reflections with $I > 2\sigma(I)$ and $R_1 = 0.0587$ and $wR_2 = 0.1176$ for all data. The data have been deposited at the Cambridge Crystallographic Data Centre (Reference N° 684964).

4.3.2. (−) and (+) Hydantoins 6a and 6b

Enantiopure hydantoins **6a** and **6b** were obtained by an AS3PC procedure (Table 5) and recrystallized in ethanol.

(−)-Hydantoin **6a**: solid. Mp 261 °C. $[\alpha]_{589}^{25} = -32.8$ (*c* 0.01 g/mL, EtOH). HPLC: retention time: 6.3 min. Enantiomeric purity: 99.6% e.e.

(+) Hydantoin **6b**: solid. Mp 261 °C. $[\alpha]_{589}^{25} = +32.8$ (*c* 0.01 g/mL, EtOH). HPLC: retention time: 3.7 min. Enantiomeric purity: 99.7% e.e.

4.4. General procedure for obtaining enantiopure 5-aryl-5-(trifluoromethyl)-hydantoins 5, 6 by recrystallization of AS3PC crops

In a single operation, each crude enantiomer of hydantoins **5** or **6** (enantiomeric purity ~80% ee) can be purified to > 99.9% ee.

For a typical example: 5 g of hydantoin **5b** (from AS3PC crops) were dissolved in ethanol (3.44 g). The mixture was heated up (T ~ 60 °C) in order to obtain a clear solution. Then, the temperature was progressively decreased to 30 °C. The system was kept at this temperature for 2 h. A filtration of the mixture was carried out on a glass filter n°4 to afford 4.34 g of pure enantiomer (yield: 87%, 99.9% ee).

4.5. Typical procedure for Pasteurian resolution of hydantoins 5 and 6

A solution of (±)-5-phenyl-5-(trifluoromethyl)hydantoin **5** (2.00 g, 8.19 mmol) and (−)-(*S*)-α-methylbenzylamine (0.99 g, 8.19 mmol) in ethanol (44 mL) was stirred in a thermostated bath at 20 °C for 16 h. The ammonium salt was filtered and washed with ethanol (2 mL). The crude was then poured into a solution of hydrochloric acid (50 mL) and stirred at room temperature for 22 h. The resulting solid was filtered to afford 0.54 g (yield: 25%) of enantiopure hydantoin **5b** (99.8% ee).

4.6. Typical procedure for the formation of (+)-(R)-α-MBA. (+)-5-Phenylhydantoin ammonium salt 9; determination of its absolute configuration by X-ray diffraction analysis (Fig. 2)

(+)-Hydantoin **5b** (1.00 g, 4 mmol) was dissolved in ethanol (20 mL), after which enantiopure (+)-(*R*)-α-MBA (0.50 g, 4 mmol) was added slowly. The resulting salt was formed after 5 min and its solubility was decreased by the slow addition of diethyl ether (20 mL). The suspension was filtrated on a Büchner to afford 1.40 g (yield: 90%) of the corresponding ammonium salt **9**.

4.6.1. (+)-(*R*)-α-Methylbenzylamine·(+)-5-phenyl-5-(trifluoromethyl)hydantoin ammonium salt 9

White solid. Mp 190 °C. IR (KBr, cm^{-1}) 3184, 2982, 1792, 1741, 1602, 1452, 1389, 1257. HRMS (ESI$^+$) calcd for $C_{18}H_{19}F_3N_3O_2$ *m*/*z* 366.1429, found 366.1438. The solid was recrystallized in petroleum ether/MeOH/CH_2Cl_2 giving suitable single-crystal for X-ray diffraction analysis. $C_{18}H_{18}F_3N_3O_2$, $M_r = 365.35$, orthorhombic, $P2_12_12_1$, $a = 6.2300(5)$, $b = 16.1133(1)$, $c = 18.5094(1)$ Å, $V = 1858.1$ Å^3, $Z = 4$, $Dx = 1.306$ g cm^{-3}. A total of 14998 reflections were collected at 293 K using MoKα radiation ($\lambda = 0.71073$ Å); 2205 independent reflections (Rint = 0.0475). The structure was solved by direct methods with SHELXTL[31] and refined by least square using F^2 values and anisotropic thermal parameters for non hydrogen atoms. There is one independent molecule (one αMBA molecule and one hydantoin molecule) in the asymmetric unit (237 parameters). The final *R* values for the 2205 unique reflections and 237 parameters are $R_1 = 0.0405$, $wR_2 = 0.0926$ for 1563 reflections with $I > 2\sigma(I)$ and $R_1 = 0.0663$ and $wR_2 = 0.1019$ for all data. The data have been deposited at the Cambridge Crystallographic Data Centre (Reference No. 684965). X-ray diffraction analysis is presented in Figure 2.

4.6.2. (+)-(*R*)-α-Methylbenzylamine.(+)5-(p-methoxyphenyl)-5-(trifluoromethyl)hydantoin ammonium salt

It was not possible to obtain a suitable single-crystal for X-ray diffraction analysis in order to determine the absolute configuration of **6a** or **6b**. White solid. Mp 224 °C. IR (KBr, cm^{-1}) 3232, 2985, 1797, 1745, 1615, 1515, 1403, 1249. HRMS (ESI$^+$) calcd for $C_{19}H_{21}F_3N_3O_3$ *m*/*z* 396.1535, found 396.1550.

4.7. Typical procedure for the preparation of α-aryl-α-trifluoromethylglycines 10 and 11 (Scheme 5)

A suspension of (±)-5-(*p*-methoxyphenyl)-5-(trifluoromethyl)hydantoin **6** (1.00 g, 3.64 mmol) and $Ba(OH)_2{\cdot}8H_2O$ (6.90 g, 21.89 mmol) in water (40 mL) was refluxed for 3 days. The evolution of the reaction was followed by ^{19}F NMR of the crude mixture. After cooling at room temperature, the reaction mixture was acidified with aqueous sulfuric acid solution (0.5 M, 15 mL) until pH 1 ($BaSO_4$ salt precipitated). The suspension was filtered on a Büchner and the resulting filtrate was chromatographed on an ion-exchange DOWEX 50WX8-100 (H^+ form, 280 mL) eluting first with water (~200 mL) until pH 5–6 and then with 10% aqueous ammonia (~300 mL). Solvent removal at reduced pressure of the collected ammonia fractions, afforded ~600 mg (~ 60%) of the free (±)-amino acid **11** as a white powder.

4.7.1. α-(*p*-Methoxyphenyl)-α-trifluoromethylglycine 11

(±)-α-Amino acid **11**: Mp 230 °C (sublimation). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.73 (s, 3H, OCH_3), 6.88 (d, $^3J_{H,H} = 8.8$ Hz, 2H Ar), 7.62 (d, $^3J_{H,H} = 8.8$ Hz, 2H Ar). ^{19}F NMR (280 MHz, DMSO-d_6) δ: −71.3 (s). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.1 (s, OCH_3), 66.1 (q, $^2J_{C,F} = 24.2$ Hz, C-2), 112.8 (s, 2 × CH Ar), 126.7 (q, $^1J_{C,F} = 283.3$ Hz, CF_3), 128.6 (s, 2 × CH Ar), 132.0 (s, C_q Ar), 158.5 (s, C_q, *C*OMe), 169.7 (s, COOH). MS (ESI$^-$): *m*/*z* 248 [M-H]. HRMS (ESI$^+$) calcd for $C_{10}H_{11}F_3NO_3$ *m*/*z* 250.0691, found 250.0692.

The same procedure was applied to both the (−)- and (+)-enantiomers **6a** and **6b**, but the corresponding amino acids **11a** and **11b** were directly engaged in the esterification step.

(−)-α-Amino acid **11a**: Solid. HRMS (ESI$^+$) calcd for $C_{10}H_{11}F_3NO_3$ *m*/*z* 250.0691, found 250.0694. HPLC: retention time: 4.35 min. Enantiomeric purity: 98.1% ee.

(+)-α-Amino acid **11b**: Solid. HRMS (ESI$^+$) calcd for $C_{10}H_{11}F_3NO_3$ *m*/*z* 250.0691, found 250.0692. HPLC: retention time: 3.90 min. Enantiomeric purity: 98.3% ee.

4.7.2. (±) α-Phenyl-α-trifluoromethylglycine 10

(±)-Amino acid **10** was obtained in ~22% yield (~169 mg) using the above described procedure. White powder. Mp 245 °C (sublimation). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 7.27 (m, 3H Ph), 7.74 (m, 2H Ph). ^{19}F NMR (280 MHz, DMSO-d$_6$) δ: −70.8 (s). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 66.6 (q, $^2J_{C,F}$ = 23.6 Hz, C-2), 126.7 (q, $^1J_{C,F}$ = 282.3 Hz, CF_3), 127.1 (s, CH Ph), 127.3 (s, 2 × CH Ph), 127.4 (s, 2 × CH Ph), 140.3 (s, C_q Ph), 168.7 (s, COOH). MS (ESI$^-$): *m*/*z* 218 [M-H]. HRMS (ESI$^-$) calcd for $C_9H_7F_3NO_2$ *m*/*z* 218.0429, found 218.0430.

The same procedure was applied to both the (−)-(*R*)- and (+)-(*S*)-enantiomers **5a** and **5b** but the corresponding amino acids **10a** and **10b** were directly engaged in the esterification step.

(−)-(*R*)-α-Amino acid **10a**: Solid. HRMS (ESI$^-$) calcd for $C_9H_7F_3NO_2$ *m*/*z* 218.0429, found 218.0434. HPLC retention time: 4.06 min. Enantiomeric purity: 98.4% e.e.

(+)-(*S*)-α-Amino acid **10b**: Solid. HRMS (ESI$^-$) calcd for $C_9H_7F_3NO_2$ *m*/*z* 218.0429, found 218.0432. HPLC: retention time: 4.98 min. Enantiomeric purity: 98.2% e.e.

4.8. Typical procedure for the preparation of α-aryl-α-trifluoromethylglycine methyl esters 12 and 13 (Scheme 5)

A solution of trimethylsilyldiazomethane (0.21 g, 1.8 mmol) in diethyl ether (4 mL) was added dropwise to a solution of (±)-amino acid **11** (0.30 g, 1.2 mmol) in a mixture of (3/2) toluene/methanol (10 mL). The reaction mixture (slightly yellow) was stirred at room temperature for 30 min. After solvent removal at reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/AcOEt 70/30) to afford the desired (±)-amino ester **13** (0.20 g, 76%). It is worth noting that small amounts of *N*-methyl and *N*,*N*-dimethyl amino esters **14** and **15** were detected in the crude mixture by ^{1}H, ^{19}F NMR and GC-MS.

The same procedure was also applied to both the (+)- and (−)-enantiomers **11a** and **11b**.

4.8.1. α-(*p*-Methoxyphenyl)-α-trifluoromethylglycine methyl ester 13

(±)-Amino ester **13**. Oil. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 3.02 (s, 2H, NH_2), 3.74 (s, 3H, $COOCH_3$), 3.76 (s, 3H, OCH_3), 6.97 (d, $^3J_{H,H}$ = 8.8 Hz, 2H Ar), 7.46 (d, $^3J_{H,H}$ = 8.8 Hz, 2H Ar). ^{19}F NMR (280 MHz, DMSO-d$_6$) δ: −73.7 (s). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 52.9 (s, COO*C*H$_3$), 55.2 (s, OCH_3), 66.5 (q, $^2J_{C,F}$ = 26.9 Hz, C-2), 113.7 (s, 2 × CH Ar), 124.7 (q, $^1J_{C,F}$ = 284.4 Hz, CF_3), 126.9 (s, C_q Ar), 128.3 (s, 2 × CH Ar), 159.7 (s, C_q, *C*OMe), 169.7 (s, *C*OOCH$_3$). IR (film, cm^{-1}): 3401, 3340, 3009, 2959, 2842, 1745, 1611, 1582. GC-MS (EI, %) *m*/*z* 263 [M$^+$], 204 (100), 134, 109, 94, 77. HRMS (ESI$^+$) calcd for $C_{11}H_{13}F_3NO_3$ *m*/*z* 264.0848, found 264.0843.

(−)-Amino ester **13a**. Oil. $[\alpha]_{589}^{25} = -2.2$ (*c* 0.01 g/mL, MeOH). HRMS (ESI$^+$) calcd for $C_{11}H_{13}F_3NO_3$ *m*/*z* 264.0848, found 264.0845. $C_{11}H_{12}F_3NO_3$ (263.216): calcd. C 50.19, H 4.60, N 5.32; found C 50.24, H 4.69, N 5.29.

(+)-Amino ester **13b**. Oil. $[\alpha]_{589}^{25} = +2.1$ (*c* 0.01 g/mL, MeOH). HRMS (ESI$^+$) calcd for $C_{11}H_{13}F_3NO_3$ *m*/*z* 264.0848, found 264.0841.

It was not possible to determine the enantiomeric purity of these amino esters by chiral GC or HPLC.

(±)-*N*-Methyl α-(*p*-Methoxyphenyl)-α-trifluoromethylglycine methyl ester **14**. Selected data: ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 2.27 (d, $^3J_{H,H}$ = 5.6 Hz, 3H, NH*C*H$_3$), 3.76 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 6.97 (d, $^3J_{H,H}$ = 8.8 Hz, 2H Ar), 7.33 (d, $^3J_{H,H}$ = 8.8 Hz, 2H Ar). ^{19}F NMR (280 MHz, DMSO-d$_6$) δ: −69.6 (s). GC-MS (EI,%) *m*/*z* 277 [M$^+$], 218 (100), 148, 134, 110.

(±)-*N*,*N*-Dimethyl α-(*p*-Methoxyphenyl)-α-trifluoromethylglycine methyl ester **15**. Selected data: ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 2.35 (s, 6H, N(CH_3)$_2$), 3.77 (s, 3H, $COOCH_3$), 3.84 (s, 3H, OCH_3), 6.98 (d, $^3J_{H,H}$ = 8.8 Hz, 2H Ar), 7.29 (d, $^3J_{H,H}$ = 8.8 Hz, 2H Ar). ^{19}F NMR (280 MHz, DMSO-d$_6$) δ: −62.9 (s). GC-MS (EI,%) *m*/*z* 291 [M$^+$], 232 (100), 148, 133, 110.

4.8.2. α-Phenyl-α-trifluoromethylglycine methyl ester 12

(±)-Amino ester **12** was obtained in 70% yield (~185 mg) using the procedure described above. Oil. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 3.08 (s, 2H, NH_2), 3.74 (s, 3H, OCH_3), 7.43 (m, 3H Ph), 7.54 (m, 2H Ph). ^{19}F NMR (280 MHz, DMSO-*d*$_6$) δ: −73.4 (s). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 53.0 (s, OCH_3), 67.6 (q, $^2J_{C,F}$ = 26.3 Hz, C-2), 124.6 (q, $^1J_{C,F}$ = 284.4 Hz, CF_3), 126.9 (s, 2 × CH Ph), 128.4 (s, 2 × CH Ph), 129.0 (s, CH Ph), 135.1 (s, C_q Ar), 169.5 (s, *C*OOCH$_3$). IR (film, cm^{-1}): 3402, 3339, 3011, 3001, 2958, 1748, 1604, 1501. GC–MS (EI,%) *m*/*z* 233 [M$^+$], 174 (100), 104, 96, 79. HRMS (ESI$^+$) calcd for $C_{10}H_{11}F_3NO_2$ *m*/*z* 234.0742, found 234.0746.

(−)-(*R*)-Amino ester **12a**. Oil. $[\alpha]_{589}^{25} = -3.05$ (*c* 0.01 g/mL, MeOH). HRMS (ESI$^+$) calcd for $C_{10}H_{11}F_3NO_2$ *m*/*z* 234.0742, found 234.0744. $C_{10}H_{10}F_3NO_2$ (233.19): calcd. C 51.51, H 4.32, N 6.01; found C 51.62, H 4.39, N 6.12.

(+)-(*S*)-Amino ester **12b**. Oil. $[\alpha]_{589}^{25} = +3.3$ (*c* 0.01 g/mL, MeOH). HRMS (ESI$^+$) calcd for $C_{10}H_{11}F_3NO_2$ *m*/*z* 234.0742, found 234.0745.

It was not possible to determine the enantiomeric purity of these amino esters by chiral GC or HPLC.

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