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Consecutive catalytic electrophilic fluorination/amination of β-keto esters: toward α-fluoro-α-amino acids?

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This article is dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—Monofluorination of β-keto esters with Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)) using $CpTiCl_3$ as a catalyst, followed by amination with diazodicarboxylates using a Cu/Ph-Box catalyst leads to α-fluoro-α-hydrazino-β-keto esters in good yields and good selectivities (ee up to 94%).

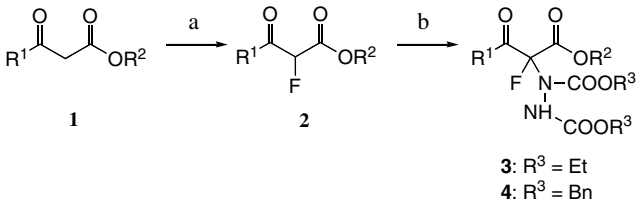
1. Introduction

Organofluorine compounds play an increasingly important role, for example, in medicinal chemistry.[1] Different classes of fluorinated compounds have been investigated, but so far very little has been done toward the synthesis of α-fluorinated amino acids. The reason for this might be the possible inherent instability of α-fluoro-α-amino acids toward the elimination of HF although this has not been unequivocally proven.

An asymmetric synthesis of a protected α-fluoro-glycine via chromatographic separation of its diastereoisomers has been reported.[2] However, the cleavage of a Boc-protected α-fluoro-glycine and reduction of α-fluoro-α-nitro-glycine or -alanine to the corresponding amine were not successful.[3] Recently, the asymmetric synthesis of a phthalimide protected α-fluoro-α-phenyl or α-cyano glycine has been shown to work via stoichiometric deprotonation followed by fluorination with a chiral fluorinating agent derived from chincona alkaloids.[4,5]

Herein, a catalytic asymmetric route was chosen for the preparation of α-fluoro-α-hydrazino β-keto esters, potential precursors for α-fluoro-α-amino acids.

Analogously to the heterodihalogenation of β-keto esters,[6] consecutive fluorination and amination was carried out in two steps (Scheme 1). The α-fluoro-α-hydrazino-β-keto esters were obtained in good yield and good selectivities. The fluorination process with Selectfluor [also called F-TEDA: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2,2,2]octane bis (tetrafluoroborate)] was catalyzed by $CpTiCl_3$, whereas the amination was carried out analogously to the reported procedure for α-alkylated-β-keto esters with a copper–bisoxazoline–catalyst system and azodicarboxylates as an aminating agent.[7–9] The same system was used also for the fluorination or amination of β-keto phosphonates, as recently reported.[10]



Scheme 1. Monofluorination of β-keto esters **1a**–**1f** followed by amination to the products **3** and **4**. Reagents and conditions: (a) F-TEDA, $CpTiCl_3$, MeCN; (b) DEAD or DBnAD, Cu/Ph-Box, solvent.

2. Results and discussion

β-Keto esters **1a**–**1d** (Fig. 1) are commercially available compounds, whereas **1e** and **1f** had to be prepared from diketene.[5] Monofluorination of the unsubstituted β-keto

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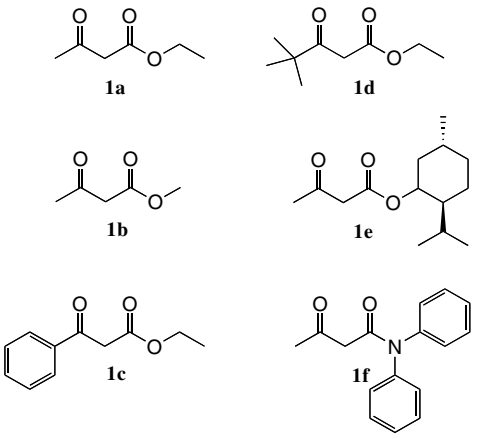

Figure 1. β-Keto esters as substrates for catalytic fluorination and amination reactions used in this study.

esters **1a**–**1e** and β-keto amide **1f** was carried out according to the previously published procedure[6] (Scheme 1). The reactions took place in MeCN as a solvent, Selectfluor was used as a fluorine source, and $CpTiCl_3$ as a catalyst. The ratio of mono versus difluorinated product (>8:1), as well as the yields (>40%) were comparable to those previously reported. In the case of β-keto amide **1f**, the ratio of mono to difluorinated product was significantly lower (1:1).

The amination step was generally carried out with 0.5 mol % of $[Cu((S,S)\text{-Ph-Box})](OTf)_2$ in CH_2Cl_2 and DEAD (diethylazodicarboxylate) or DBnAD (dibenzylazodicarboxylate) as aminating agent.[9]

The best results were obtained when water-free $Cu(OTf)_2$ and the Ph-Box ligand were used. The influence of traces of water is unclear (Table 1). The use of $Cu(OTf)_2$ and Ph-Box, which was stored under air, lowered the enantioselectivity of the reaction of **2a** with DEAD from 93% to 80%. In contrast, the addition of an excess amount of H_2O (40 equiv) to the dry catalyst solution showed only a slight decrease in selectivity over time to 88% ee after 18 h. No uncatalyzed reaction was observed. When the catalytic reaction was carried out in CH_2Cl_2, without the addition of a coordinating ligand, no conversion was observed. After the addition of TMEDA (tetramethylethylenediamine) to the colorless suspension of wet $Cu(OTf)_2$ in CH_2Cl_2, a blue solution was observed. When this TMEDA/$Cu(OTf)_2$ solution was used for catalysis, the reaction proceeded smoothly.

Table 1. Effect of the addition of water on the Cu-catalyzed amination of β-keto ester **2a** with DEAD

Time[a] [h]	Color[b]	Yield [%]	Selectivity [% ee]
—[c]	Green	90	93
2	Green-blue	80	91
4	Blue-green	81	90
18	Pale blue	91	88
Air-exposed chemicals	Pale blue	71	80

[a] Time after the addition of 40 equiv H_2O to the catalyst solution.
[b] Color of the catalyst solution.
[c] Dry catalyst solution was used.

We can, therefore, speak of a ligand accelerated reaction.

For the amination of the α-monofluoro β-keto esters **2a**–**2e** or the β-keto amide **2f**, full conversion and enantiomeric excesses between 81% and 94% were observed after a reaction time of two days. Isolated yields were up to 95% (Table 2).

Table 2. Amination of substrates **2a**–**2d** with DEAD and DBnAD

Substrate	Aminating agent	Product	Yield [%]	Selectivity [% ee]
2a	DEAD	**3a**	90	93
2a	DBnAD	**4a**	73	91
2b	DEAD	**3b**	94	94
2b	DBnAD	**4b**	95	92
2c	DEAD	**3c**	85	87
2c	DBnAD	**4c**	78	81
2d	DEAD	**3d**	84	93
2d	DBnAD	**4d**	84	93

When changing from the Cu/Box system to other Lewis acids ($AlCl_3$, $TiCl_4$, and $[TiCl_2TADDOLato]$ complexes[11]), small amounts of side products were observed. Moreover, the reactions were significantly slower and afforded, in the case of the chiral Ti catalyst only, almost racemic products.

When the catalyst solution was prepared from $[Ni(H_2O)_6](ClO_4)_2$, or $Mg(OTf)_2$, and (*S*,*S*)-Ph-Box as ligand, the reaction took place and went to completion, but again with low selectivities. In fact, product **3a** was obtained in 28% ee and 14% ee using the Ni/Ph-Box and the magnesium catalyst, respectively.

In agreement with recently reported observations[12] concerning the fluorination of indanone-based β-keto esters with NFSI (*N*-fluorobenzenesulfonimide), the sense of induction changes with the choice of the metal. However, in this work, when using copper or nickel catalysts, the sense of induction is the same, as shown by chiral HPLC with the major enantiomer of **3a** eluting first. On the other hand, in the case of magnesium, the opposite sense of induction was observed.

Although we did not determine the absolute configuration of any of our products, it is reasonable to assume that the sense of chiral induction in the amination of our racemic α-fluoro-β-keto esters and amides is the same as originally reported by Jørgensen for α-alkylated β-keto esters, when using the Cu(Ph-Box) system.[9] We, therefore, postulated that for the catalyst containing the (*S*,*S*)-Ph-Box, the delivery of the electrophile preferentially occurs on the *Re*-side of the enolate, thus generating products **3** with an (*S*)-configuration (Jørgensen reported *R*-configured products; however, note that the priority sequence of the substituents in our compounds is different).

Variation of the aminating agent did not seem to have a strong influence on the enantiomeric excess (Table 2). In all cases, the stereoselectivity is above 90% ee and only

in the case of **4c** are selectivities lower. For β-keto esters bearing a methyl or aryl substituent at the α-position, enantiomeric excesses slightly higher than in the case of our α-fluoro compounds were reported.[9]

For the chiral menthyl ester **4e**, a diastereomeric ratio (dr) of 57:43 was observed for the reaction catalyzed by the achiral system Cu/TMEDA. Reaction with the (*S*,*S*)-Ph-Box-ligand gave a dr of 87.5:12.5, whereas using the (*R*,*R*)-Ph-Box-ligand afforded a dr of 98.5:1.5 with inversed selectivity, thus representing the matched case (Table 3). Moreover, when the ester group was replaced by a diphenyl amide function, an enantiomeric excess above 90% could be obtained (Table 3).

Table 3. Amination of substrates **2e** and **2f** with DBnAD

Substrate	Catalyst	Product	Yield [%]	Selectivity [dr or ee]
2e	$Cu(OTf)_2$, TMEDA	**4e**	31	57:43[a]
2e	$Cu(OTf)_2$, (*S*,*S*)-Ph-Box	**4e**	75	87.5:12.5[b]
2e	$Cu(OTf)_2$, (*R*,*R*)-Ph-Box	**4e**	95	98.5:1.5[a]
2f	$Cu(OTf)_2$, (*S*,*S*)-Ph-Box	**4f**	88	92

[a] HPLC: minor isomer first.
[b] HPLC: major isomer first.

When the solvent for the reaction of **2a** with DEAD was changed from CH_2Cl_2 to either toluene or hexane, a slight decrease in selectivity was observed (Table 4). The same trend was apparent with hexane as a solvent for substrates **2b**–**2d**. In this solvent, DBnAD leads to the formation of a biphasic system. When the solvent was changed to the more polar MeCN, the enantiomeric excess drastically dropped to low values around 20% (Table 4). Acetonitrile is a potentially good ligand for copper, thus generating catalytically active achiral species and therefore explaining the low selectivities.

Table 4. Effect of solvent on the selectivity of the amination reaction

Substrate	Product	Solvent	Yield [%]	Selectivity [dr or ee]
2a	**3a**	CH_2Cl_2	90	93
2a	**3a**	Hexane	84	90
2a	**3a**	Toluene	95	85
2a	**3a**	MeCN	82	20
2b	**3b**	CH_2Cl_2	94	94
2b	**3b**	Hexane	90	86
2a	**4a**	CH_2Cl_2	73	91
2a	**4a**	Hexane	—[a,b]	88
2b	**4b**	CH_2Cl_2	95[b]	86

[a] No full conversion of reactant.
[b] A biphasic solution was observed.

We investigated the temperature dependence of the stereoselectivity in the formation of **3a** in CH_2Cl_2 and found a maximum at room temperature (Table 5). Raising the temperature to the boiling point of CH_2Cl_2 afforded only 85% ee, whereas cooling to −40 °C resulted in an almost complete erosion of enantioselectivity to 20% ee. For reactions at low temperatures, full conversion was observed when the reaction was stopped after 5 days.

Table 5. Effect of temperature on the selectivity of the amination reaction of **2a** to **3a**

Temperature [°C]	Yield [%]	Selectivity [% ee]
36	87	85
25	90	93
0	63	89
−40	84	20

The ^{19}F NMR spectra of the α-fluoro-α-hydrazino compounds **3** and **4** showed several broad signals in $CDCl_3$ at room temperature. In the ^1H NMR spectrum the N*H*-proton generates different signals, whereas the quarternary CFN-carbon usually gives rise to two doublets around 100 ppm in the ^{13}C NMR spectrum, whereby all signals are relatively broad. Due to this effect, the observation of the ^{13}C NMR signals for quaternary carbon atoms required rather large amount of substance (>40 mg of **3** or **4**) and long accumulation times (>10,000 pulses). For compound **3a**, ^{19}F NMR and ^1H NMR spectra were recorded at various temperatures between −60 °C and +60 °C. The *H*N proton, which gives rise to several signals at low temperatures, coalesces to one broad resonance at high temperatures, as shown in Figure 2. The behavior of the ^{19}F signal appears to be more complex, with fewer lines at both low and high temperatures, whereas at around 0 °C (Fig. 3) up to

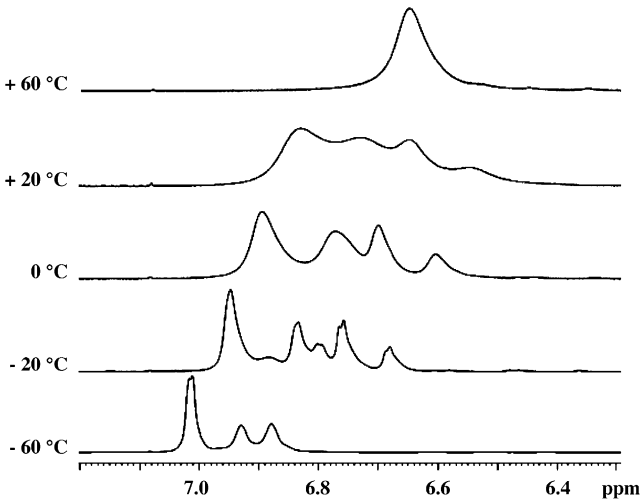

Figure 2. ^1H–N*H* signals at selected temperatures for **3a**.

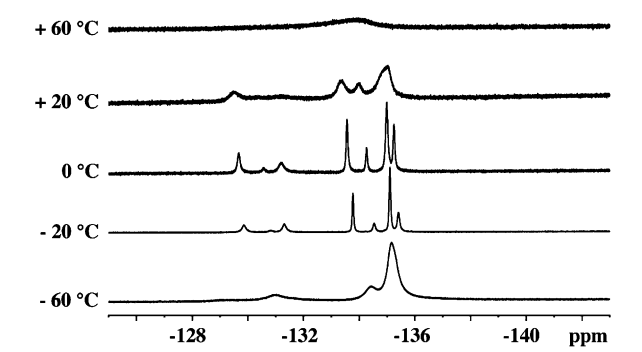

Figure 3. ^{19}F-signals at selected temperatures for **3a**.

seven different signals can be detected. The distinct signals in the NMR spectra are very much likely due to restricted rotation around the N–CO and N–N bonds generating different isomeric forms (Fig. 4). Assuming that the O=C–N–N–C=O structural unit is planar, then eight different isomers may be generated because of this restricted rotation. Seven of these species can be observed in the ^{19}F NMR spectrum at −20 °C, one signal possibly being superposed by another one.

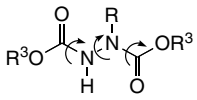

Figure 4. Restricted rotation around N–CO and N–N bonds.

3. Conclusion

Consecutive geminal fluorination and amination has led to compounds containing a quaternary stereocenter having fluorine, nitrogen, and two different carbonyl groups. These new compounds can be obtained in good yield with enantiomeric excesses up to 94%. The further use of hydrazino compounds for the synthesis of α-fluoro-α-amino-β-keto esters has not yet been studied in detail. Preliminary experiments dealing with the cleavage of the N–N bond have so far been unsuccessful. This problem is currently under investigation, along with a possible combination of the two steps—fluorination and amination—into a one-pot procedure.

4. Experimental

4.1. General

Reactions were carried out under an Ar atmosphere using standard Schlenk techniques. Methyl acetoacetate (Fluka), ethyl acetoacetate (Fluka), ethyl pivaloylacetate (ABCR GMbH & Co.), ethyl benzoylacetate (Fluka), F-TEDA (Aldrich), and $CpTiCl_3$ (Acros organics) were purchased and used without further purification. Diethyl azodicarboxylate (Fluka), dibenzyl azodicarboxylate (Acros organics), cupric trifluoromethanesulfonate (Fluka), and (*S*,*S*) or (*R*,*R*) 2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) were purchased and stored under a nitrogen atmosphere. (−)-3-Oxobytyric acid (−)-menthyl ester was prepared according to a published procedure.[6a] Solvents for reactions were distilled.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AVANCE spectrometers AC 200, DPX 250, DPX 300, and DPX 500. ^1H and ^{13}C positive shifts in ppm are downfield from tetramethylsilane. ^{19}F NMR spectra were referenced to external $CFCl_3$. Optical rotations were measured by using a Perkin–Elmer 341 polarimeter with a 1 dm^3 cell. Elemental analysis was carried out by the Laboratory of Microelemental Analysis of the ETH Zurich. Mass spectra were recorded by the MS-service of the Laboratory of Organic Chemistry (ETH Zurich). Enantiomeric excesses were determined by HPLC with Agilent (HPLC 1100 series) or Hewlett Packard (1050 series) instruments using *Diacel* Chiralcel AD-H, OD-H or *ReproSil* Chiral-DP chromatography columns with hexane/^{i}PrOH as an eluent. Conditions are given in the order: machine type, column type, hexane/^{i}PrOH ratio, flow [ml/min], and retention times. Column chromatography was performed with Fluka Silicagel 60.

4.2. General procedure for catalytic fluorination of β-keto esters[6a]

In a Schlenk tube equipped with a magnetic stirrer bar, F-TEDA (1.5 equiv), $CpTiCl_3$ (0.05–0.1 equiv) was added. Under Ar, dry MeCN (F-TEDA < 0.145 M in MeCN) and β-keto ester were added. Conversion was checked by NMR. After the addition of wet TBME, the suspension was filtered over aluminum oxide/silica. Concentration of the liquid phase and chromatography on silica (hexane/TBME = 1:1) gave the product in a pure form as an oily material in 40–70% yield.

4.3. General procedure for catalytic asymmetric fluorination of α-fluoro-β-keto esters[9]

In an oven-dried Schlenk tube equipped with a magnetic stirrer bar, cupric trifluoromethanesulfonate (9 mg, 0.025 mmol) and (*R*,*R*)- or (*S*,*S*)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (10 mg, 0.027 mmol) were added either under Ar atmosphere or in a glovebox. Dry CH_2Cl_2 was added and the solution stirred for 3 h. Then 1 ml of the green solution was transferred to another oven dried Schlenk, 1 ml of dry CH_2Cl_2, and the α-fluoro-β-keto ester (0.5 mmol) and diethyl azodicarboxylate (0.6 mmol) were added. After 48 h at rt, the product was separated from the excess aminating agent by chromatography on silica (hexane/TBME = 5:1) and obtained in its pure form as an oily material in 70–95% yield. Samples for elemental analysis and optical rotations were additionally purified by chromatography on silica (pentane/Et_2O = 5:1). In the case of dibenzyl azodicarboxylate, addition to the Schlenk tube was carried out under Ar atmosphere, then dry CH_2Cl_2, the catalyst solution, and the α-fluoro-β-keto ester were added sequentially.

4.4. 2-Fluoro-3-oxobutyric acid diphenylamide 2f

Preparation according to general procedure for catalytic fluorination. The ratio of mono versus difluorinated product was 1:1. Purification by FC (hexane/ethyl acetate = 2:1) gave a beige solid in 42% yield. ^1H NMR (200 MHz, $CDCl_3$): 7.6–7.2 (m, br, 10 arom. H); 5.31 (d, br, $J_{HF} = 50.0$, 1H, C*H*F); 2.36 (d, br, $J_{HF} = 5.0$, 3H, COCH_3). ^{13}C NMR (63 MHz, $CDCl_3$): 203.15 (d, $J = 28.7$); 164.41 (d, $J = 20.9$); 130.0–126.1 (*m*); 89.86 (d, $J = 191.8$); 26.65 (d, $J = 0.5$). ^{19}F NMR (188.3, $CDCl_3$): −187.4 (qd, $J_{FH} = 50.0$, $J_{FCH3} = 5.0$). IR (NaCl plates): 3062w; 2917w; 1725m; 1678s; 1592m; 1492s; 1377m; 1341m; 1304m; 1208m; 1093m; 755m; 700m. HRMS (EI): calcd 271.1009 (M^+), 272.1042 (M^++1); found 271.1005 (M^+), 272.1030 (M^++1). EA: calcd C: 70.84, H: 5.20, N: 5.16; found C: 70.77, H: 5.27, N: 5.21. Mp: 92 °C.

4.5. 2-Fluoro-*N*′,*N*-bis(ethoxycarbonyl)-2-hydrazino-3-oxobutyric acid ethyl ester 3a

^{1}H NMR (200 MHz, $CDCl_3$): 6.84 (s, br, 1H, N*H*); 4.41–4.24 (m, 6H, CH_2CH$_3$); 2.47 (d, $J_{HF} = 3.8$, 3H, CH_3); 1.71–1.27 (m, 9H, CH$_2$CH_3). ^{13}C NMR (176 MHz, $CDCl_3$): 195.0 (d, br, $J_{CF} = 28.2$, C); 161.8 (d, br, $J_{CF} = 28.2$, C); 155.4 (s, br, C); 154.0 (s, br, C); 102.5 (d, br, $J_{CF} = 239.3$ (s, C)); 101.6 (d, br, $J_{CF} = 241.6$, C); 64.4 (s, CH$_2$); 63.6 (s, br, CH$_2$); 62.8 (s, br, CH$_2$); 25.8 (s, br, CH$_3$); 14.3 (s, CH$_3$); 14.1 (s, CH$_3$); 13.8 (s, CH$_3$). ^{19}F NMR (188.3 MHz, $CDCl_3$): −129.2 (s, br); −132.9 (s, br); −133.4 (s, br); −134.5 (s, br). IR (NaCl plates): 3308*b*m; 2986m; 1743s; 1468m; 1376m; 1333m; 1300s; 1364s; 1238s; 1201m; 1096m; 1049m; 1013m. MS (HResESI): calcd 345.0994 (MNa$^+$), 323.1255 (MH$^+$); found 345.1064 (100, MNa$^+$), 323.1253 (10.6, MH$^+$). EA: calcd C: 44.72, H: 5.94, N: 8.69; found C: 44.77, H: 5.84, N: 8.88. $[\alpha]_D = +16.0$ (*c* 1.00, CH_2Cl_2, 86% ee). HPLC: HP 1050 series, AD-H; 92:8; 0.8; 22/24.

4.6. 2-Fluoro-*N*′,*N*-bis(ethoxycarbonyl)-2-hydrazino-3-oxobutyric acid methyl ester 3b

^{1}H NMR (200 MHz, $CDCl_3$): 6.68 (s, br, 1H, N*H*); 4.28 (q, $J = 7.0$, 2H, CH_2CH$_3$); 4.26 (q, $J = 7.0$, 2H, CH_2CH$_3$); 3.91 (s, 3H, OCH_3); 2.48 (d, $J_{HF} = 4.0$, 3H, CH_3); 1.32 (q, $J = 7.0$, 3H, CH$_2$CH_3). ^{13}C NMR (500 MHz, $CDCl_3$): 195.2 (s, br, C); 162.8 (d, br, $J_{CF} = 32.2$, C); 155.9 (s, br, C); 154.3 (s, br, C); ∼102 (d, br, $J_{CF} = \sim 220$, C); 64.8 (s, br, CH$_2$); 63.3 (s, br, CH$_2$); 54.4 (s, br, CH$_3$); 26.1 (s, br, CH$_3$); 14.7 (s, br, CH$_3$); 14.5 (s, br, CH$_3$). ^{19}F NMR (188.3, $CDCl_3$): −128.9 (s, br); −133.0 (s, br); −133.5 (s, br); −134.3 (s, br). IR (NaCl plates): 3322m; 2987w; 1741s; 1377m; 1239s; 1095m; 770w. MS (MALDI): calcd 331.0918 (MNa$^+$), 332.0951 (MNa$^+$+1); found 331.0911 (100, MNa$^+$), 332.0948 (11.0, MNa$^+$+1). EA: calcd C: 42.86, H: 5.56, N: 9.09; found C: 43.14, H: 5.67, N: 8.99. $[\alpha]_D = +12.5$ (*c* 1.00, CH_2Cl_2, 86% ee). HPLC: HP 1050 series, AD-H; 92:8; 0.8; 24/28.

4.7. 2-Fluoro-*N*′,*N*-bis(ethoxycarbonyl)-2-hydrazino-3-oxo-3-phenylbutyric acid ethyl ester 3c

^{1}H NMR (200 MHz, $CDCl_3$): 8.24 (s, br, 2 arom. H); 7.63 (t, $J = 7.4$, 1 arom. H); 7.49 (t, $J = 7.8$, 2 arom. H); 6.82 (s, br, 1H, N*H*); 4.4–4.2 (m, br, 6H, CH_2CH$_3$); 1.3–1.2, 4.4–4.2 (m, br, 9H, CH$_2$CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 186.6 (d, br, $J_{CF} = 32.0$, C); 162.6 (s, br, C); 155.6 (s, br, C); 154.0 (s, br, C); 133.8 (s, br, CH); 133.3 (s, br, C); 130.2 (s, br, CH); 129.9 (s, br, C); 128.4 (s, br, C); 102.7 (d, br, $J_{CF} = 244.9$, C); 64.2 (s, br, CH$_2$); 63.6 (s, br, CH$_2$); 62.7 (s, br, CH$_2$); 14.3 (s, br, CH$_3$); 13.9 (s, br, CH$_3$); 13.8 (s, br, CH$_3$). ^{19}F NMR (188 MHz, $CDCl_3$): −122.4 (s, br); −126.5 (s, br); −129.2 (s, br). IR (NaCl plates): 3310bw; 2986m; 1747s; 1598w; 1509w; 1468m; 1449m; 1376m; 1301bs; 1232bs; 1096bs; 1032m; 916w; 859w; 765w; 694m. MS (HiResESI): calcd 407.1225 (MNa$^+$); found 407.1218 (MNa$^+$). EA: calcd C: 53.12, H: 5.51, N: 7.29; found C: 53.11, H: 5.59, N: 7.32. $[\alpha]_D = -2.6$ (*c* 1.06, CH_2Cl_2, 87% ee). HPLC: HP 1050 series; AD-H; 90:10; 0.8; 35/45.

4.8. 2-Fluoro-*N*′,*N*-bis(ethoxycarbonyl)-2-hydrazino-2,2-dimethyl-3-oxo-pentanoic acid ethyl ester 3d

^{1}H NMR (200 MHz, $CDCl_3$): 6.8–6.3 (m, br, 1H, N*H*); 4.35 (q, $J = 7.2$, 2H, CH_2CH$_3$); 4.3–4.15 (m, br, 18H, C(CH_3)$_3$, CH$_2$CH_3). ^{13}C NMR (MHz, $CDCl_3$): 201.9 (d, br, $J_{CF} = 145.9$, C); 162.5 (d, br, $J_{CF} = 30.5$, C); 155.9 (d, br, $J_{CF} = 43.7$, C); 154.1 (d, br, $J_{CF} = 19.9$, C); 104.9 (d, br, $J_{CF} = 242.6$, C); 104.6 (d, br, $J_{CF} = 244.5$, C); 64.3 (s, br, CH$_2$); 63.8 (s, br, CH$_2$); 63.0 (s, br, CH$_2$); 45.9 (s, br, C); 27.0 (s, br, CH$_3$); 26.3 (s, br, CH$_3$); 14.8 (s, br, CH$_3$); 14.6 (s, br, CH$_3$); 14.2 (s, br, CH$_3$). ^{19}F NMR (188 MHz, $CDCl_3$): −126.6 (s, br); −129.0 (s, br); −132.1 (s, br); −132.9 (s, br). IR (NaCl plates): 3312bm; 2989m; 1801m; 1732bs; 1504m; 1470m; 1370m; 1232bs; 1096bs; 1058bs; 934w; 860w; 763m. MS (HiResESI): calcd 387.1538 (MNa$^+$); found 387.1533 (MNa$^+$). EA: calcd C: 49.45, H: 6.92, N: 7.69; found C: 49.54, H: 6.81, N: 7.60. $[\alpha]_D = +28$ (*c* 0.94, CH_2Cl_2, 28% ee). HPLC: HP 1050 series; AD-H; 90:10; 0.8; 34/42.

4.9. 2-Fluoro-*N*′,*N*-bis(benzyloxycarbonyl)-2-hydrazino-3-oxobutyric acid ethyl ester 4a

^{1}H NMR (300 MHz, $CDCl_3$, 65 °C): 7.38–7.28 (m, 10 arom. H); 6.81 (s, br, 1H, N*H*); 5.19 (s, 2H, CH_2Ph); 5.16 (s, 2H, CH_2Ph); 4.23 (q, $J = 7.0$, 2H, CH_2CH$_3$); 2.36 (d, $J_{HF} = 3.6$, 3H, CH_3); 1.24 (t, $J = 7.0$, 3H, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 194.8 (d, br, $J_{CF} = 33.7$, C); 161.6 (d, br, $J_{CF} = 32.3$, C); 155.3 (s, br, C); 153.9 (s, br, C); 135.1 (s, br, C); 134.2 (s, br, C); 128.8 (s, br, CH); 128.64 (s, br, CH); 128.59 (s, br, CH); 128.4 (s, br, CH); 102.3 (s, br, $J_{CF} = 217.0$, C); 69.7 (s, br, CH$_2$); 68.4 (s, br, CH$_2$); 63.7 (s, br, CH$_2$); 25.7 (s, br, CH$_3$); 13.7 (s, br, CH$_3$). ^{19}F NMR (282 MHz, $CDCl_3$): −129.0 (s, br); −132.8 (s, br); −134.1 (s, br). IR (NaCl plates): 3311w; 1743w; 1499m; 1456m; 1392m; 1265s; 1230s; 1093m; 745m; 698m. MS (HiResMALDI): calcd 469.1382 (MNa$^+$); found 469.1386 (100, MNa$^+$). EA: calcd C: 59.19, H: 5.19, N: 6.27; found C: 59.29, H: 5.31, N: 6.38. $[\alpha]_D = +10.9$ (*c* 2, CH_2Cl_2, 67% ee). HPLC: HP 1050 series; ReproSil Chiral-DP; 97:3; 0.8; 83/88.

4.10. 2-Fluoro-*N*′,*N*-bis(benzyloxycarbonyl)-2-hydrazino-3-oxobutyric acid methyl ester 4b

^{1}H NMR (200 MHz, $CDCl_3$): 7.36 (m, 10 arom. H); 6.90 (s, br, 1H, N*H*); 5.20 (s, br, 4H, CH_2Ph); 3.71 (s, br, 3H, OCH_3); 2.39 (s, br, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$): 194.7 (d, br, $J_{CF} = 34.3$, C); 162.2 (d, br, $J_{CF} = 34.9$, C); 155.4 (s, br, C); 153.9 (s, br, C); 135.1 (s, br, C); 134.1 (s, br, C); 128.8 (s, br, CH); 128.7 (s, br, CH); 128.6 (s, br, C); 128.5 (s, br, C); 128.4 (s, br, C); 102.9 (d, br, $J_{CF} =$ 240, C); 102.1 (d, br, $J_{CF} = 248$, C); 69.8 (s, br, CH$_2$); 55.0 (s, br, CH$_2$); 29.7 (s, br, $J_{CF} = 2.3$, CH$_3$); 25.8 (s, br, CH$_3$). ^{19}F NMR (188 MHz, $CDCl_3$): −128.4 (s, br); −133.6 (s, br); −133.8 (s, br). IR (NaCl plates): 3315bw; 2959w; 1743s; 1499m; 1456m; 1391m; 1268s:

1225s; 1092m; 746m; 698m. MS (MALDI): calcd 455.1231 (MNa^+); found 455.1233 (100, MNa^+). EA: calcd C: 58.33, H: 4.89, N: 6.48; found C: 58.51, H: 5.15, N: 6.23. $[\alpha]_D = +13.1$ (*c* 2.6, CH_2Cl_2, 90% ee). HPLC: HP 1050 series; ReproSil Chiral-DP; 97:3; 0.8; 93/101.

4.11. 2-Fluoro-*N*′,*N*-bis(benzyloxycarbonyl)-2-hydrazino-3-oxo-3-phenylbutyric acid ethyl ester 4c

^{1}H NMR (300 MHz, $CDCl_3$): 8.18 (s, br, 2 arom. H); 7.56 (s, br, 1 arom. H); 7.43–7.28 (m, br, 12 arom. H); 6.95–6.60 (m, br, 1H, N*H*); 5.14 (s, br, 4H, CH_2Ph); 4.23 (m, br, 2H, CH_2CH$_3$); 1.27 (m, br, 3H, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 186.6 (d, br, $J_{CF} = 29.5$, C); 162.7 (d, br, $J_{CF} = 27.6$, C); 155.3 (s, br, C); 153.9 (s, br, C); 134.3–133.5 (m, br, C, CH); 130.6–129.6 (m, br C, CH); 128.8–123.0 (m, br); 103.4 (d, br, $J_{CF} =$ 233, C); 102.9 (d, br, $J_{CF} = 233$, C); 69.6 (s, br, CH_2); 68.2 (s, br, CH_2); 63.6 (s, br, CH_2); 13.7 (s, br, CH_3). ^{19}F NMR (188 MHz, $CDCl_3$): −122.2 (s, br); −126.6 (s, br); −129.3 (s, br). IR: 3321m; 3073w; 2971w; 1748w; 1598m; 1499m; 1450m; 1226bs; 1084m; 1019m; 910m; 746m; 696s. MS (HiResESI): calcd 531.1538 (MNa^+); found 531.1531 (100, MNa^+). EA: calcd C: 63.77, H: 4.96, N: 5.51; found C: 63.55, H: 5.23, N: 5.57. $[\alpha]_D = -4.8$ (*c* 0.84, CH_2Cl_2, 60% ee). HPLC: Agilent 1100 series, OJ; 90:10; 0.6; 120/160.

4.12. 2-Fluoro-*N*′,*N*-bis(benzyloxycarbonyl)-2-hydrazino-2,2-dimethyl-3-oxopentanoic acid ethyl ester 4d

^{1}H NMR (250 MHz, $CDCl_3$): 7.41–7.30 (m, br, 10 arom. H); 6.78 (s, br, 1H, N*H*); 6.16 (s, br, 4H, CH_2Ph); 4.28 (s, br, $J = 6.6$, 2H, CH_2CH$_3$); 1.28–1.17 (m, br, 12H, CH$_2$CH_3, C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): 201.2 (d, br, $J_{CF} = 25.2$, C); 162.4 (s, br, C); 156.0 (s, br, C); 155.6 (s, br, C); 154.1 (s, br, C); 153.4 (s, br, C); 135.7 (s, br, C); 135.0 (s, br, C); 129.1–128.4 (m, br, CH); 104.8 (d, br, $J_{CF} = 246.5$, C); 104.7 (d, br, $J_{CF} = 246.5$, C); 69.8 (s, br, CH_2); 68.6 (s, br, CH_2); 63.8 (s, br, CH_2); 45.6 (s, br, C); 26.9 (s, br, CH_3); 26.2 (s, br, CH_3); 14.2 (s, br, CH_3). Some signals double due to isomers ^{19}F NMR (188 MHz, $CDCl_3$): −128.2 (s, br); −128.6 (s, br); −131.9 (s, br); −132.6 (s, br). IR: 3321w; 2977m; 1752s; 1499m; 1482m; 1457m; 1396m; 1341m; 1293s; 1225bs; 1097m; 1029m; 920m; 753m; 698m; 597*w*. MS (HiResESI): calcd (MNa^+); found (100, MNa^+). EA: calcd C: 61.47, H: 5.98, N: 5.73; found C: 61.61, H: 6.06, N: 5.59. $[\alpha]_D = +44.0$ (*c* 1.0, CH_2Cl_2, 88% ee). HPLC: HP 1050 series, AD-H; 90:10; 0.8; 30/39.

4.13. 2-Fluoro-*N*′,*N*-bis(benzyloxycarbonyl)-2-hydrazino-3-oxobutyric acid menthyl ester 4e

^{1}H NMR (500 MHz, $CDCl_3$): 7.38 (m, 10 arom. H); 6.91 (s, br, 1H, N*H*); 5.16 (s, br, 4H, CH_2Ph); 4.80 (s, br, C*H*OCO); 2.39 (s, br, 3H, CH_3CO); 1.95 (s, br, 1H); 1.79 (s, br, 1H); 1.70 (s, br, 3H); 1.49 (s, br, 2H); 1.05 (dd, br, $J = 10.5$, 23.0, 2H); 0.90 (s, br, 6H); 0.74 (s, br, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): 195.2 (d, br, $J_{CF} = 35.5$, C); 161.9 (d, br, $J_{CF} = 33.1$, C); 155.6 (s, br, C); 154.3 (s, br, C); 135.6 (s, br, C); 134.7 (s, br, C); 129.1 (s, br, CH); 129.0 (s, br, CH); 128.97 (s, br, CH); 128.9 (s, br, CH); 128.8 (s, br, CH); 128.6 (s, br, CH); 102.9 (d, br, $J_{CF} = 252.6$, C); 79.0 (s, br, CH_2); 70.1 (s, br, CH_2); 68.7 (s, br, CH); 47.1 (s, CH); 40.4 (s, CH_2); 34.4 (s, CH_2); 31.8 (s, CH); 26.6 (s, br, CH_3); 26.0 (s, CH_3); 23.5 (s, CH_2); 22.2 (s, CH); 21.1 (s, CH_3); 16.2 (s, CH_3). ^{19}F NMR (188 MHz, $CDCl_3$): −128.6 (s, br); −130.0 (s, br); −133.0 (s, br); −133.9 (s, br). IR: 3309m; 2957s; 2860m; 1732s; 1497m; 1456s; 1391s; 1391s; 1335bs; 1268bs; 1084s; 1044s; 981s; 909m; 840m; 743s; 697s; 586m. MS (HiResESI): calcd 579.2477 (MNa^+); found 579.2486 (100, MNa^+). EA: calcd C: 64.73, H: 6.70, N: 5.03; found C: 64.75, H: 6.89, N: 5.00. $[\alpha]_D = +44.6$ (*c* 1.2, CH_2Cl_2, 87.5:12.5 dr). HPLC: Agilent 1100 series, OD-H; 98:2; 0.4; 88/97.

4.14. 2-Fluoro-*N*,*N*′-bis(benzyloxycarbonyl)-2-hydrazino-3-oxobutyric acid diphenylamide 4f

^{1}H NMR (300 MHz, $CDCl_3$): 7.4–7.0 (m, 20 arom. H); 6.8–6.6 (s, br, 1H, N*H*); 5.4–5.0 (s, br, 4H, CH_2Ph); 2.2–2.0 (s, br, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 196.6 (s, br, C); 163.2 (d, br, $J_{CF} = 22.7$, C); 155.1 (d, br, $J_{CF} = 85$, C); 135.3 (s, br, C); 134.6 (s, br, C); 104.1 (d, br, $J_{CF} = 230.0$, C); 103.5 (d, br, $J_{CF} = 240$, C); 69.5 (s, br, C); 68.2 (s, br, C); 25.3 (d, br, $J_{CF} = 55.87$, C). ^{19}F NMR (282 MHz, $CDCl_3$): −116.3 (s, br); −120.5 (s, br); −121.8 (s, br); −124.8 (s, br); −126.8 (s, br). IR (NaCl plates): 3283w; 3044w; 1742s; 1674m; 1594w; 1492m; 1455m; 1335m; 1216m; 911m; 734m; 697m. MS (HiResESI): calcd 592.1860 (MNa^+); found 592.1847 (100, MNa^+). EA: calcd C: 67.48, H: 4.95, N: 7.38; found C: 67.47, H: 5.18, N: 7.43. $[\alpha]_D = +23.8$ (*c* 1.00, CH_2Cl_2, 69% ee). HPLC: Agilent 1050 series, OD-H; 94:6; 0.8; 57/88.

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