Tetrahedron 68 (2012) 7028–7034

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of fluorinated *N*-aminoaziridines: access to new CF_3-peptidomimetics

Bertrand Schweitzer-Chaput, Massaba Keita, Thierry Milcent *, Sandrine Ongeri, Benoit Crousse

Univ Paris-Sud, BioCIS, UMR8076, Faculté de Pharmacie, 5 rue J.-B. Clément, 92290 Châtenay-Malabry, France

ARTICLE INFO

Article history:
Received 21 February 2012
Received in revised form 8 June 2012
Accepted 21 June 2012
Available online 28 June 2012

Keywords:
N-Amino aziridine
Fluorine
Peptidomimetic
Iodobenzene diacetate
Amino acids

ABSTRACT

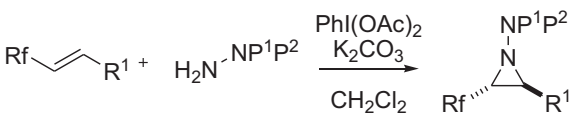
A series of fluorinated *N*-aminoaziridines have been synthesized by the $PhI(OAc)_2$-mediated aziridination procedure. The reaction was carried out with various protected hydrazides and fluorinated alkenes. The reaction was extended to alkenes bearing an amino acid and the ring opening of the CF_3–*N*-aminoaziridines has been investigated.

1. Introduction

The synthesis of aziridines has attracted important attention because of their use as central precursors in the preparation of various compounds, such as α and β-amino acids, amino alcohols, β-lactam etc.[1–3] Due to their structural analogy with epoxides, aziridines can provide similar types of reaction, for example, ring opening with nucleophiles,[4] giving access to a large number of valuable compounds. However, the *N*-amino analogues of aziridines have been less studied whereas they are synthetic precursors of α and β-hydrazino acids.[5,6] Furthermore, they can be considered as constrained analogues of those hydrazino acids structures, which have a growing interest in the synthesis of peptidomimetics with particular structural and biological properties,[7,8] such as antibiotic activity[9] or inhibition of the human leukocyte elastase.[10] Some papers report the synthesis of *N*-aminoaziridines,[11] and the main method is based on the oxidative addition of *N*-aminoheterocycles to olefins. These oxidative aminoaziridination proceed via nitrenoids, which can be generated from various *N*-aminoheterocycles.[12,13] This reaction can be performed in the presence of lead tetraacetate,[14–22] iodobenzene diacetate ($PhI(OAc)_2$)[23–26] or other oxidizing agents, such as *m*CPBA[27] or KO_2.[28] As part of our continuing interest on the synthesis of fluorinated compounds and in particular the access to original fluorinated peptidomimetic units, we focused our attention on the synthesis of fluorinated *N*-aminoaziridines. Indeed these units combine the unique physical and biological properties of fluorine (steric and electronic constraints, increase of the oxidative and proteolytic stability)[29–32] and the structural characteristics of the three member ring heterocycles. Furthermore, the ring opening of the CF_3–*N*-aminoaziridines carboxylates, provides an interesting access to α-substituted-β-CF_3-β-hydrazino acids, which might be of interest in the inhibition of the proteasome. Indeed, β-CF_3-β-hydrazino acids have been useful scaffold in the design and synthesis of peptidomimetic inhibitors of the 20S proteasome.[33] Finally, to our knowledge there is no precedent on the synthesis and reactivity of fluorinated *N*-aminoaziridines.

2. Results and discussion

The *N*-aminoaziridines **2** were synthesized using the iodobenzene diacetate mediated aziridination of alkenes developed by Che and coll.[23] (Scheme 1). Compared to lead tetraacetate, $PhI(OAc)_2$ provides better yields, can be applied to a wide range of alkenes and is less toxic.



Scheme 1. $PhI(OAc)_2$-mediated N-aminoaziridination of fluorinated alkenes.

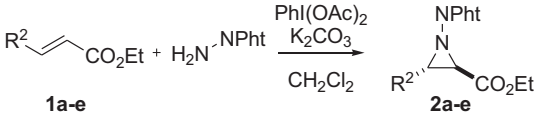
We first investigated the aziridination reaction of the commercially available *N*-aminophthalimide with the ethyl (*E*)-trifluorocrotonate **1a**[34] in dichloromethane (1.5 equiv of $PhI(OAc)_2$

* Corresponding author. Tel.: +33 (0)146835744; fax: +33 (0)146835740; e-mail address: thierry.milcent@u-psud.fr (T. Milcent).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.06.093

and 2.8 equiv of K_2CO_3). The trifluoromethyl *N*-aminoaziridine **2a** was obtained in good yield (64%) although lower than for its non-fluorinated counterpart **2b** (Table 1, entries 1 and 2). The reaction was then applied to various fluorinated Michael acceptors: the ethyl (*E*)-4,4,5,5,5-pentafluoropentenoate **1c**,[34] the ethyl (*E*)-4,4-difluorobutenoate **1d**[34] and the ethyl (*E*)-3-(perfluorophenyl) acrylate **1e**,[35] which were reacted under the same conditions with the *N*-aminophthalimide, giving rise to the corresponding aziridines **2c**–**e** in reasonable yields (Table 1, entries 3–5).

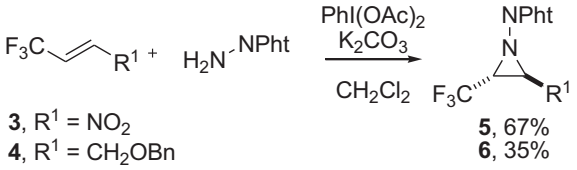
Table 1
Synthesis of fluorinated *N*-aminoaziridines[a]



Entry	Starting material	R^2	Product	Yield %
1	**1a**	CF_3	**2a**	64
2	**1b**	CH_3	**2b**	78
3	**1c**	C_2F_5	**2c**	31
4	**1d**	CHF_2	**2d**	58
5	**1e**	C_6F_5	**2e**	55

[a] Reaction conditions: *N*-aminophthalimide (1.4 equiv), alkene (1 equiv), iodobenzene diacetate (1.5 equiv) and K_2CO_3 (2.8 equiv) in dichloromethane at room temperature.

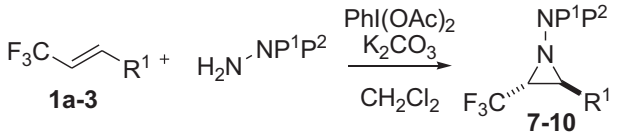
The reaction was also extended to the (*E*)-trifluoronitropropene **3**[36] and the (*E*)-benzyloxy-trifluorobutene **4**,[37] leading to the CF_3–*N*-aminoaziridines **5** and **6** in 67 and 35% yields, respectively (Scheme 2).



Scheme 2. Synthesis of trifluoromethyl *N*-aminoaziridines.

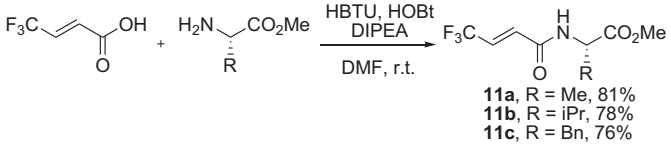
In order to use these motifs as central units for novel constrained peptides, the reaction was then carried out with nitrene precursors bearing protective groups consistent with further peptide coupling. We investigated the N-aminoaziridination reaction using the *N*,*N*-di-*tert*-butylcarbazate (NH_2NBoc_2),[38] the commercially available *N*-methyl-*N*-*tert*-butylcarbazate ($NH_2N(CH_3)Boc$) and the *N*,*N*-dibenzylcarbazate (NH_2NCbz_2).[20] Ethyl (*E*)-trifluorocrotonate **1a** or (*E*)-trifluoronitropropene **3** were reacted with the latter carbazates to lead to the corresponding *N*-aminoaziridines **7**–**9** and **10** in satisfactory yields (Table 2).

Table 2
N-Aminoaziridination reaction with carbazates



Entry	R^1	Reagent	P^1	P^2	Product	Yield %
1	CO_2Et	**1a**	Boc	Boc	**7**	65
2	CO_2Et	**1a**	Boc	Me	**8**	37
3	CO_2Et	**1a**	Cbz	Cbz	**9**	76
4	NO_2	**3**	Boc	Boc	**10**	57

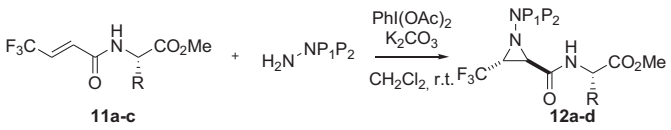
We next extended this reaction to the CF_3-crotonic acid previously coupled with an amino acid in order to access directly to fluorinated constrained peptidomimetics. The starting olefins **11a**–**c** were obtained in good yields by coupling various amino acids methyl ester hydrochloride with the commercially available (*E*)-trifluorocrotonic acid in the presence of usual coupling agents, HBTU and HOBt (Scheme 3).



Scheme 3. Coupling of (*E*)-trifluorocrotonic acid with amino acids.

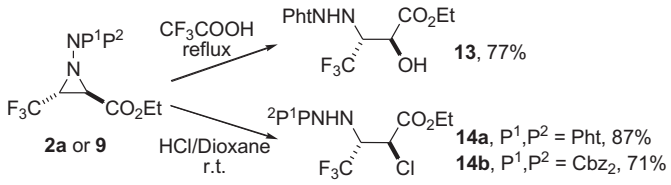
The N-aminoaziridination of compounds **11a**–**c**, using *N*-aminophthalimide or *N*,*N*-di-*tert*-butylcarbazate was carried out following the same reaction conditions as previously described. The corresponding peptidomimetics **12a**–**d** were obtained in satisfactory yields as a mixture of diastereoisomers in a 1:1 ratio (Table 3). In the case of the products **12a** and **12b**, the two diastereoisomers were separated by chromatography on silica gel, leading to the enantiopure peptidomimetics.

Table 3
N-Aminoaziridination reaction with compounds **9a**–**c**



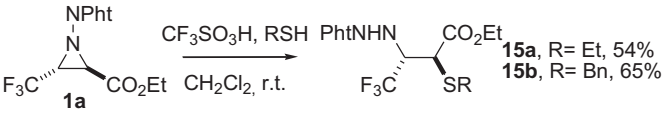
Entry	Reagent	R	P^1	P^2	Product	Yield %
1	**11a**	Me	Pht		**12a**	68
2	**11b**	^{i}Pr	Pht		**12b**	64
3	**11c**	Bn	Pht		**12c**	72
6	**11c**	Bn	Boc	Boc	**12d**	79

We then focused our attention on the reactivity and stability of those new fluorinated building blocks in the ring opening reaction towards various nucleophiles. Many ways to open aziridines are described in the literature, using both hard or soft nucleophiles,[4] whereas in the few examples of *N*-aminoaziridines ring opening, an excess of reagent[6,9,39] or an activation by an acid is required.[40–43] Furthermore, the ring opening of CF_3-aziridines is more difficult than their non-fluorinated counterparts and requires special conditions, such as the presence of an electron-withdrawing group on the nitrogen atom.[44] In order to check the reactivity of the trifluoromethyl *N*-aminoaziridine, we first investigated the ring opening under the standard nucleophilic conditions. As expected, the ring opening of the CF_3–*N*-aminoaziridine **2a** with NaN_3, NaCN or benzylamine did not lead to the expected products even in the presence of Lewis acids. This shows the stability of these patterns towards various nucleophiles. We then investigated the ring opening under strong acidic conditions, based on the previously reported work of Prati and coll. who described the ring opening of the non-activated *trans*-*N*-benzyl-3-trifluoromethyl-aziridine-2-carboxylate in hydrochloric acid or trifluoroacetic acid.[45] Thus, the ring opening of *N*-aminoaziridine **2a** in refluxing trifluoroacetic acid led to the α-hydroxy-β-hydrazino ester **13** in 77% yield, whereas the α-chloro-β-hydrazino esters **14a** and **14b** were obtained in good yields, by reacting the *N*-aminoaziridines **2a** and **9**, respectively, in a solution of HCl/dioxane (Scheme 4).



Scheme 4. *N*-Aminoaziridine ring opening in acidic conditions.

The ring opening was then extended to thiol containing nucleophiles. The reaction occurred only in the presence of trifluoromethanesulfonic acid,[46] leading to the thioethers **15a**,**b** were obtained in 54 and 65% yield, respectively (Scheme 5).



Scheme 5. *N*-Aminoaziridine ring opening with thiol containing derivatives.

As previously reported for the CF_3-aziridines ring opening in acidic conditions,[46] compounds **13**–**15** were obtained as a single regioisomer resulting from the C2-attack of the nucleophiles and were assumed to have an *anti* relative configuration according to the previously reported work of Dali and coll.[45]

3. Conclusion

In summary, we reported the efficient synthesis of various fluorinated *N*-aminoaziridines obtained by $PhI(OAc)_2$-mediated aziridination using fluorinated olefins and nitrene precursors. Furthermore we extended the scope of the reaction to the synthesis of peptidomimetics containing constrained CF_3–*N*-aminoaziridines consistent for peptide coupling. Finally, the stability towards nucleophiles has been investigated and the ring opening of *N*-aminoaziridine under strong acidic conditions led to the α-substituted-β-CF_3-hydrazino acids, which could be scaffold of great interest in medicinal chemistry.

4. Experimental part

4.1. General methods

All reagents were used as purchased from commercial suppliers without further purification. Melting points were measured on a Stuart® SMP10 apparatus. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker® ARX apparatus at, respectively, 300, 75 and 188 MHz in $CDCl_3$ with TMS as internal standard for ^1H and ^{13}C and $CFCl_3$ for ^{19}F NMR. Mass spectra were performed on a Bruker® Esquire-LC apparatus. IR spectra were recorded on a Bruker® Vector 22 apparatus. Elemental analyses were carried out on an Ankersmit CAHN® 25 apparatus. Optical rotations were measured on an Optical Activity LTD Automatic polarimeter polAAr 32 apparatus at 589 nm. Column chromatography was performed on silica gel Merk® silica gel (43–60 μm) with a cyclohexane/ethyl acetate or ether/cyclohexane as a system eluent.

4.2. General procedure for the synthesis of products 2

N,*N*-Disubstituted hydrazines (1.4 equiv) were added to a solution of alkene **1a** (1 equiv), iodobenzene diacetate (1.5 equiv) and K_2CO_3 (2.8 equiv) in dichloromethane. The resulting solution was stirred at room temperature until the disappearance of the starting alkene (monitored by ^{19}F NMR). The reaction medium was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel.

*4.2.1. Ethyl 1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(trifluoromethyl)aziridine-2-carboxylate (**2a**).* Yield: 64%. Yellow light oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=1.34 (t, $^3J_{H,H}$=7 Hz, 3H, $CH_{3\ ester}$), 3.61 (d, $^3J_{H,H}$=4.6 Hz, 1H, $CH_{aziridine}$), 4.20 (qd, $^3J_{H,H}$=4.6 Hz, $^3J_{H,F}$=4.9 Hz, 1H, $CH_{aziridine}$), 4.22 (q, ^3J=7 Hz, 2H, $CH_{2\ ester}$), 7.92–7.77 (m, 4H, $H_{phthalimide}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.81 ($CH_{3\ ester}$), 40.44 ($CH_{aziridine}$), 45.71 (q, $^2J_{C,F}$=41 Hz, $CH_{aziridine-CF3}$), 62.93 ($CH_{2\ ester}$), 121.73 (q, $^1J_{C,F}$=273 Hz, CF_3), 123.48 ($CH_{phthalimide}$), 129.83 ($C_{phthalimide}$), 134.42 ($CH_{phthalimide}$), 164.96 ($C{=}O_{phthalimide}$), 164.18 ($C{=}O_{ester}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−70.88 (d, $^3J_{F,H}$=4.9 Hz, 3F). $C_{14}H_{11}F_3N_2O_4$ (328): calcd. C 51.23, H 3.38, N 8.53; found C 51.62, H 3.25, N 8.64.

*4.2.2. Ethyl 1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(pentafluoroethyl)aziridine-2-carboxylate (**2c**).* Yield: 78%. Colourless light oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=1.20 (t, $^3J_{H,H}$=7.3 Hz, 3H, $CH_{3\ ester}$), 3.56 (d, $^3J_{H,H}$=4.5 Hz, 1H, $CH_{aziridine}$), 4.18 (q, $^3J_{H,H}$=7.3 Hz, 2H, $CH_{2\ ester}$), 4.24 (m, 1H, C*H*$_{aziridine}$), 7.84–7.65 (m, 4H, $H_{phthalimide}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.77 ($CH_{3\ ester}$), 39.29 ($CH_{aziridine}$), 42.35 (dd, $^2J_{C,F}$=24 Hz, $^2J_{C,F}$=31 Hz, $CH_{aziridine}$), 62.90 ($CH_{2\ ester}$), 123.41 ($CH_{phthalimide}$), 129.76 ($C_{phthalimide}$), 134.38 ($CH_{phthalimide}$), 163.96 ($C{=}O_{phthalimide}$), 164.18 ($C{=}O_{ester}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−84.19 (t, $^3J_{F,F}$=1.27 Hz, 3F, CF_3), −121.49 (ddq, $^2J_{F,F}$=276.8 Hz, $^3J_{H,F}$=8.1 Hz, $^3J_{F,F}$=1.27 Hz, 1F, CF_2), −124.79 (ddq, $^2J_{F,F}$=276.8 Hz, $^3J_{H,F}$=8.1 Hz, $^3J_{F,F}$=1.27 Hz, 1F, CF_2) ppm. $C_{15}H_{11}F_5N_2O_4$ (378): calcd. C 47.63, H 2.93, N 7.41; found C 47.21, H 2.71, N 7.32.

*4.2.3. Ethyl 3-(difluoromethyl)-1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)aziridine-2-carboxylate (**2d**).* Yield: 58%. Yellow light oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=1.33 (t, $^3J_{H,H}$=7 Hz, 3H, $CH_{3\ ester}$), 3.57 (d, $^3J_{H,H}$=4.8 Hz, 1H, $CH_{aziridine}$), 3.89 (dddd, $^3J_{H,H}$=2.5 Hz, $^3J_{H,H}$=4.8 Hz, $^3J_{H,F}$=5.5 Hz, $^3J_{H,F}$=13.2 Hz, 1H, $CH_{aziridine}$), 4.22 (q, $^3J_{H,H}$=7 Hz, 2H, $CH_{2\ ester}$), 6.05 (dd, $^3J_{H,H}$=2.5 Hz, $^2J_{F,H}$=56 Hz, 1H, C*H*F_2), 6.25 (dd, $^3J_{H,H}$=2.5 Hz; $^2J_{F,H}$=55 Hz, 1H, C*H*F_2), 7.95–7.65 (m, 4H, $H_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−121.22 (ddd, $^3J_{F,H}$=5.5 Hz, $^2J_{F,H}$=55 Hz, $^2J_{F,F}$=297 Hz, 1F), −127.13 (ddd, $^3J_{F,H}$=13.2 Hz, $^2J_{F,H}$=56 Hz, $^2J_{F,F}$=297 Hz, 1F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.82 ($CH_{3\ ester}$). 39.76 ($CH_{aziridine}$), 45.95 (dd, $^3J_{C,F}$=27 Hz; $^3J_{C,F}$=35 Hz, $CH_{aziridine}$), 62.56 ($CH_{2\ ester}$), 111.89 (t, $^2J_{C,F}$=242 Hz, CHF_2), 123.31 (2C, $CH_{phthalimide}$), 129.94 ($C_{phthalimide}$), 134.26 (2C, $CH_{phthalimide}$), 164.26 ($CO_{phthalimide}$), 164.92 (CO_{ester}) ppm. $C_{14}H_{12}F_2N_2O_4$ (310): calcd. C 54.20, H 3.90, N 9.03; found C 53.95, H 4.06, N 9.21.

*4.2.4. Ethyl 1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(pentafluorophenyl)aziridine-2-carboxylate (**2e**).* Yield: 55%. White solid, mp 152 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=1.29 (t, $^3J_{H,H}$=7 Hz, 3H, $CH_{3\ ester}$), 3.87 (d, 1H, $^3J_{H,H}$=5.1 Hz, $CH_{aziridine}$), 4.20 (q, 2H, $^3J_{H,H}$=7 Hz, $CH_{2\ ester}$), 4.53 (d, 1H, $^3J_{H,H}$=5.1 Hz, $CH_{azirindine}$), 7.85–7.65 (m, 4H, $H_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−142.87 (m, 2F), −152.94 (tt, 1F, $^3J_{F,F}$=2.2 Hz, $^3J_{F,F}$=21 Hz), −161.75 (m, 2F) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.87 ($CH_{3\ ester}$), 40.86 ($CH_{aziridine}$), 43.79 ($CH_{aziridine}$), 62.55 ($CH_{2\ ester}$), 108.68 (C_{C6F5}), 123.51 ($CH_{phthalimide}$), 134.20 ($C_{phthalimide}$), 130.05 ($CH_{phthalimide}$), 136.01 (CF_{C6F5}), 139.37 (CF_{C6F5}), 143.13 (CF_{C6F5}), 164.27 (CO_{ester}), 165.51 ($CO_{phthalimide}$) ppm. $C_{19}H_{11}F_5N_2O_4$ (426): calcd. C 53.53, H 2.60, N 6.57; found C 54.13, H 2.57, N 6.61.

*4.2.5. 2-[2-Nitro-3-(trifluoromethyl)aziridin-1-yl]-1H-isoindole-1,3(2H)-dione (**5**).* Yield: 67%. White solid, mp 123 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.85 (broad, 1H, C*H*$_{aziridine}$–CF_3), 5.55

(broad, 1H, C*H*$_{aziridine}$–NO$_2$), 7.9–7.7 (m, 4H, H$_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−69.69 (br s, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=30.89 (CH$_{aziridine}$), 44.15 (q, $^2J_{C,F}$=42 Hz, CH$_{aziridine}$), 120.55 (q, $^1J_{C,F}$=275 Hz, CF$_3$), 124.01 (CH$_{phthalimide}$), 129.42 (C$_{phthalimide}$), 134.96 (CH$_{phthalimide}$), 163.34 (C=O) ppm. $C_{11}H_6F_3N_3O_4$ (301): calcd. C 43.87, H 2.01, N 13.95; found C 43.07, H 1.94, N 13.29.

*4.2.6. 2-{2-[(Benzyloxy)methyl]-3-(trifluoromethyl)aziridin-1-yl}-1H-isoindole-1,3(2H)-dione (**6**).* Yield: 35%. White solid, mp 108 °C. ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ=3.08 (td, 1H, $^3J_{H,H}$=3.9 Hz, $^3J_{H,H}$=5.0 Hz, CH$_{aziridine}$), 3.62 (d, $^3J_{H,H}$=3.9 Hz, 2H, CH$_2$OBn), 4.15 (qt, $^3J_{H,H}$=4.9 Hz, $^3J_{H,F}$=4.9 Hz, 1H, CH$_{aziridine}$), 4.24 (d, 1H, $^3J_{H,H}$=11.7 Hz, O–CH$_2$–Ph), 4.32 (d, 1H, $^3J_{H,H}$=11.7 Hz, O–CH$_2$–Ph), 7.1–6.8 (m, 5H, H$_{aromatic\ benzyl}$), 7.7–7.5 (m, 4H, H$_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−71.09 (d, $^3J_{H,F}$=4.9 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=39.39 (q, $^2J_{C,F}$=40 Hz, CH$_{aziridine}$), 42.89 (CH$_{aziridine}$), 63.54 (CH$_2$), 73.23 (CH$_2$), 122.85 (q, $^1J_{C,F}$=273 Hz, CF$_3$), 123.21 (2C, CH$_{phthalimide}$), 127.54 (CH$_{benzyl}$), 127.81 (CH$_{benzyl}$), 128.28 (CH$_{benzyl}$), 134.18 (CH$_{phthalimide}$), 130.12 (C$_{phthalimide}$), 136.59 (C$_{benzyl}$), 164.93 (C=O) ppm. $C_{19}H_{15}F_3N_2O_3$ (376): calcd. C 60.64, H 4.02, N 7.44; found C 60.30, H 4.32, N 6.97.

*4.2.7. Ethyl 1-[bis(tert-butoxycarbonyl)amino]-3-(trifluoromethyl) aziridine-2-carboxylate (**7**).* Yield 65%. Colourless oil. ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ=1.29 (t, $^3J_{H,H}$=7 Hz, 3H, CH$_{3\ ester}$), 1.48 (s, 18H, CH$_{3\ Boc}$), 3.32 (d, $^3J_{H,H}$=4.6 Hz, 1H, CH$_{aziridine}$), 3.60 (qd, $^3J_{H,H}$=4.5 Hz, $^3J_{H,F}$=4.9 Hz, 1H, CH$_{aziridine}$–CF$_3$), 4.30–4.05 (m, 2H, CH$_{2\ ester}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−70.20 (d, $^3J_{H,F}$=4.6 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=13.86 (CH$_{3\ ester}$), 27.77 (CH$_{3\ Boc}$), 27.88 (CH$_{3\ Boc}$), 43.41 (CH$_{aziridine}$), 48.33 (q, $^3J_{C,F}$=41.4 Hz, CH$_{aziridine}$), 62.24 (CH$_{2\ ester}$), 84.37 (C$_{quat\ Boc}$), 84.78 (C$_{quat\ Boc}$), 121.99 (q, $^2J_{C,F}$=274 Hz, CF$_3$), 148.6 (CO$_{Boc}$), 150.41 (CO$_{Boc}$), 164.50 (CO$_{ester}$) ppm. $C_{16}H_{25}F_3N_2O_6$ (398): calcd. C 48.24, H 6.33, N 7.03; found C 48.61, H 5.95, N 6.87.

*4.2.8. Ethyl 1-[(tert-butoxycarbonyl)(methyl)amino]-3-(trifluoromethyl)aziridine-2-carboxylate (**8**).* Yield 37%. Colourless oil. ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ=1.30 (t, $^3J_{H,H}$=7 Hz, 3H, CH$_{3\ ester}$), 1.42 (s, 9H, CH$_{3\ Boc}$), 2.93 (s, 3H, CH$_3$–N), 3.32 (d, $^3J_{H,H}$=4.5 Hz, 1H, CH$_{aziridine}$), 3.45 (qd, $^3J_{H,H}$=4.5 Hz, $^3J_{H,F}$=4.9 Hz, 1H, CH$_{aziridine}$), 4.21 (m, 2H, CH$_{2\ ester}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−70.94 (d, $^3J_{H,F}$=4.9 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=13.87 (CH$_{3\ ester}$), 28.11 (CH$_{3\ Boc}$), 35.41 (CH$_3$–N), 44.20 (CH$_{aziridine}$), 45.40 (q, $^3J_{C,F}$=40 Hz, CH$_{aziridine}$), 62.12 (CH$_{2\ ester}$), 81.58 (C$_{quat\ Boc}$), 122.13 (q, $^2J_{C,F}$=273 Hz, CF$_3$), 154.83 (CO$_{Boc}$), 164.02 (CO$_{ester}$) ppm. $C_{12}H_{19}F_3N_2O_4$ (312): calcd. C 46.15, H 6.13, N 8.97; found C 46.52, H 6.54, N 8.41.

*4.2.9. Ethyl 1-[bis(benzyloxycarbonyl)amino]-3-(trifluoromethyl) aziridine-2-carboxylate (**9**).* Yield 76%. Colourless oil. ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ=1.12 (t, $^3J_{H,H}$=7.2 Hz, 3H, CH$_{3\ ester}$), 3.33 (d, $^3J_{H,H}$=4.7 Hz, 1H, CH$_{aziridine}$), 3.61 (qd, $^3J_{H,H}$=4.7 Hz, $^3J_{H,F}$=4.8 Hz, 1H, CH$_{aziridine}$–CF$_3$), 3.95 (m, 2H, CH$_{2\ ester}$), 5.11 (d, $^2J_{H,H}$=12.2 Hz, 2H, CH$_{2\ benzyl}$), 5.21 (d, $^2J_{H,H}$=12.2 Hz, 2H, CH$_{2\ benzyl}$), 7.33–7.45 (m, 10H, H$_{aromatic}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−70.53 (d, $^3J_{H,F}$=4.8 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=13.79 (CH$_{3\ ester}$), 43.50 (CH$_{aziridine}$), 48.51 (q, $^3J_{C,F}$=40.6 Hz, CH$_{aziridine}$), 62.43 (CH$_{2\ ester}$), 69.49 (O–CH$_2$–Ph), 121.95 (q, $^2J_{C,F}$=273.5 Hz, CF$_3$), 128.41 (CH$_{aromatic}$), 128.54 (CH$_{aromatic}$), 128.57 (CH$_{aromatic}$), 134.52 (C$_{aromatic}$), 151.35 (CO$_{Cbz}$), 164.37 (CO$_{ester}$) ppm. $C_{22}H_{21}F_3N_2O_6$ (466): calcd. C 56.65, H 4.54, N 6.01; found C 56.78, H 4.41, N 6.12.

*4.2.10. Di-tert-butyl [2-nitro-3-(trifluoromethyl)aziridin-1-yl]imidodicarbonate (**10**).* Yield 57%. White solid, mp 80 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=1.52 (s, 18H, CH$_{3\ Boc}$), 4.18 (qd, $^3J_{H,H}$=2.8 Hz, $^3J_{H,F}$=4.9 Hz, 1H, CH$_{aziridine}$), 5.35 (d, $^3J_{H,H}$=2.8 Hz, 1H, CH$_{aziridine}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−68.56 (d, $^3J_{H,F}$=4.9 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=27.74 (CH$_{3\ Boc}$), 48.08 (q, $^2J_{C,F}$=41 Hz, CH$_{aziridine}$), 72.05 (CH$_{aziridine}$), 85.73 (C$_{quat\ Boc}$), 120.70 (q, $^1J_{C,F}$=275 Hz, CF$_3$), 149.58 (CO Boc) ppm. $C_{13}H_{20}F_3N_3O_6$ (371): calcd. C 42.05, H 5.43, N 11.32; found C 42.38, H 5.49, N 11.03.

4.3. General procedure for the synthesis of products 11a–c

To a solution of trifluorocrotonic acid (1.0 equiv) in DMF, was added the amino acid methyl ester hydrochloride (1.2 equiv), DIPEA (4.0 equiv), HBTU (1.2 equiv) and HOBt (1.2 equiv) in this order. The mixture was stirred overnight at room temperature under argon atmosphere. The solvent was evaporated under vacuum and the residue dissolved in ethyl acetate. The organic layer was washed with 10% citric acid aqueous solution (two times), water, 10% K_2CO_3aqueous solution (two times) and brine, dried over Na_2SO_4, filtrated and evaporated. The crude product was purified by column chromatography (EtOAc/cyclohexane: 3/7) to afford the corresponding alkene.

*4.3.1. Methyl (2S)-2-{[(2E)-4,4,4-trifluorobut-2-enoyl]amino}propanoate (**11a**).* Yield 81%. Colourless solid, mp 156 °C. $[\alpha]_D^{25}$=+35 (*c* 1, CH_2Cl_2). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ=1.45 (d, $^3J_{H,H}$=7.2 Hz, 3H, CH$_3$), 3.75 (s, 3H, CH$_{3\ ester}$), 4.68 (qt, $^3J_{H,H}$=7.2 Hz, 1H, CH$_\alpha$–CH$_3$), 6.61 (dq, $^3J_{H,H}$=15.4 Hz, $^4J_{H,F}$=1.4 Hz, 1H, CH$_{alkene}$), 6.76 (dq, $^3J_{H,H}$=15.4 Hz, $^3J_{H,F}$=6.4 Hz, 1H, CH$_{alkene}$–CF$_3$), 7.02 (d$_{broad}$, $^3J_{H,H}$=7.2 Hz, 1H, NH) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−65.56 (dd, $^4J_{H,F}$=1.4 Hz, $^3J_{H,F}$=6.4 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=18.21 (CH$_3$), 48.44 (CH$_\alpha$), 52.69 (CH$_{3\ ester}$), 124.19 (q, $^1J_{C,F}$=280 Hz, CF$_3$), 128.86 (q, $^2J_{C,F}$=36 Hz, CH–CF$_3$), 130.40 (q, $^3J_{C,F}$=5.5 Hz, CH$_{alkene}$), 162.03 (CO$_{amide}$), 173.14 (CO$_{ester}$) ppm. $C_8H_{10}F_3NO_3$ (225): calcd. C 42.67, H 4.48, N 6.22; found C 42.61, H 4.52, N 6.31.

*4.3.2. Methyl (2S)-3-methyl-2-{[(2E)-4,4,4-trifluorobut-2-enoyl]amino}butanoate (**11b**).* Yield 78%. Colourless solid, mp 178 °C. $[\alpha]_D^{25}$=+78 (*c* 1, CH_2Cl_2). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ=0.85 (d, $^3J_{H,H}$=6.1 Hz, 3H, CH$_3$), 0.95 (d, $^3J_{H,H}$=6.1 Hz, 3H, CH$_3$), 2.22 (m, 1H, CH$_{isopropyl}$), 3.73 (s, 3H, CH$_{3\ ester}$), 4.66 (dd, $^3J_{H,H}$=5.2 Hz, $^3J_{H,H}$=8.9 Hz, 1H, CH$_\alpha$), 6.62 (dq, $^3J_{H,H}$=15.3 Hz, $^4J_{H,F}$=1.5 Hz, 1H, CH$_{alkene}$), 6.73 (dq, $^3J_{H,H}$=15.3 Hz, $^3J_{H,F}$=6.8 Hz, 1H, CH$_{alkene}$–CF$_3$), 7.15 (d$_{broad}$, $^3J_{H,H}$=8.9 Hz, 1H, NH) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=−65.55 (dd, $^4J_{H,F}$=1.5 Hz, $^3J_{H,F}$=6.8 Hz, 3F, CF$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=17.82 (CH$_3$), 18.08 (CH$_3$), 30.15 (CH$_{isopropyl}$), 51.42 (CH$_\alpha$), 56.34 (OCH$_3$), 48.44 (CH$_{3\ ester}$), 52.69 (CH$_\alpha$), 56.03 (OCH$_{3\ ester}$), 123.48 (q, $^1J_{C,F}$=278 Hz, CF$_3$), 128.82 (q, $^2J_{C,F}$=38 Hz, CH–CF$_3$), 129.87 (q, $^3J_{C,F}$=5.7 Hz, CH$_{alkene}$), 161.73 (CO$_{amide}$), 172.84 (CO$_{ester}$) ppm. $C_{10}H_{14}F_3NO_3$ (253): calcd. C 47.43, H 5.57, N 5.53; found C 47.84, H 5.52, N 5.41.

*4.3.3. Methyl (2S)-3-phenyl-2-{[(2E)-4,4,4-trifluorobut-2-enoyl]amino}propanoate (**11c**).* Yield 76%. White solid. Mp 102 °C. $[\alpha]_D^{25}$=+128 (*c* 1, MeOH). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ=3.07 (dd, $^3J_{H,H}$=5.7, $^2J_{H,H}$=13.9 Hz, 1H, CH$_{2a}$), 3.15 (dd, $^3J_{H,H}$=5.7, $^2J_{H,H}$=13.9 Hz, 1H, CH$_{2b}$), 3.69 (s, 3H, CH$_{3\ ester}$), 4.90 (dd, $^3J_{H,H}$=5.7 Hz, $^3J_{H,H}$=13.9 Hz, 1H, CH–CH$_2$), 6.32 (d, $^3J_{H,H}$=6.6 Hz, 1H, NH), 6.42 (dq, $^3J_{H,H}$=15.6 Hz, $^4J_{H,F}$=1.2 Hz, 1H, CH=CO), 6.62 (qd, $^3J_{H,F}$=6.7 Hz, $^3J_{H,H}$=15.6 Hz, 1H, CH=CF$_3$), 7.01 (d, $^3J_{H,H}$=7.0 Hz, 2H, CH$_{aromatic}$), 7.19 (m, 3H, CH$_{aromatic}$) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ=65.53 (dd, $^3J_{H,F}$=6.7 Hz, $^4J_{H,F}$=1.2 Hz, CF$_3$), ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ=37.6 (CH$_2$), 52.6 (CH$_{3\ ester}$), 53.5 (CH–CH$_2$), 122.3 (q, $^1J_{C,F}$=270.8 Hz, CF$_3$), 129.1 (q, $^3J_{C,F}$=35 Hz, CH–CF$_3$), 129.2; 129.7 (CH$_{aromatic}$), 130.1 (q, $^4J_{C,F}$=5.7 Hz, CH–CO),

135.3 ($C_{aromatic}$), 161.9 (CO_{amide}), 171.5 (CO_{ester}) ppm. $C_{14}H_{14}F_3NO_3$ (301.26): calcd. C 55.82, H 4.68, N 4.65; found C 55.98, H 4.83, N 4.63. MS: ESI^+ (M+Na)=324.

4.4. Products 12a–d were synthesized using the general procedure for the synthesis of *N*-aminoaziridines

*4.4.1. Methyl (2S)-2-({[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(trifluoromethyl)aziridin-2-yl]carbonyl}amino)propanoate (**12a**).* Yield 68%. $C_{16}H_{14}F_3N_3O_5$ (385): calcd. C 49.88, H 3.66, N 10.91; found C 50.07, H 3.65, N 10.38.

Diastereoisomer A: white solid, mp 198 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.25 (d, $^3J_{H,\ H}$=7.3 Hz, 3H, CH_3), 3.53 (d, $^3J_{H,\ H}$=4.5 Hz, 1H, $CH_{aziridine}$), 3.76 (s, 3H, $CH_{3\ ester}$), 4.35 (dq, $^3J_{H,\ H}$=4.5 Hz, $^3J_{H,\ H}$=4.9 Hz 1H, CH–CF_3), 4.50 (qt, $^3J_{H,\ H}$=7.3 Hz CH_α), 7.26 (d_{broad}, $^3J_{H,\ H}$=7.3 Hz, 1H, NH), 7.67–7.77 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−70.54 (d, $^3J_{H,\ F}$=4.9 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=17.15 (CH_3), 42.43 ($CH_{aziridine}$), 43.15 (q, $^2J_{C,\ F}$=40 Hz, $CH_{aziridine}$–CF_3), 48.87 (CH_α), 52.72 (OCH_3), 121.92 (q, $^1J_{C,\ F}$=272 Hz, CF_3), 123.27 ($CH_{phthalimide}$), 129.91 ($C_{phthalimide}$), 134.28 ($CH_{phthalimide}$), 161.09 ($CO_{phthalimide}$), 164.11 (CO_{amide}), 172.82 (CO_{ester}) ppm. $[\alpha]_D^{25}$=+96 (*c* 1, CH_2Cl_2).

Diastereoisomer B: white solid, mp 224 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.31 (d, $^3J_{H,\ H}$=7.4 Hz, 3H, CH_3), 3.33 (d, $^3J_{H,\ H}$=4.6 Hz, 1H, $CH_{aziridine}$), 3.65 (s, 3H, $CH_{3\ ester}$), 4.28 (dq, $^3J_{H,\ H}$=4.6 Hz, $^3J_{H,\ H}$=4.8 Hz 1H, CH–CF_3), 4.42 (qt, $^3J_{H,\ H}$=7.4 Hz, CH_α), 7.15 (d_{broad}, $^3J_{H,\ H}$=7.4 Hz, 1H, NH), 7.54–7.68 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−70.73 (d, $^3J_{H,\ F}$=4.8 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=16.93 (CH_3), 41.61 ($CH_{aziridine}$), 42.74 (q, $^2J_{C,\ F}$=41 Hz, $CH_{aziridine}$–CF_3), 48.58 (CH_α), 52.19 (OCH_3), 121.13 (q, $^1J_{C,\ F}$=274 Hz, CF_3), 123.17 ($CH_{phthalimide}$), 129.80 ($C_{phthalimide}$), 134.20 ($CH_{phthalimide}$), 161.75 ($CO_{phthalimide}$), 164.27 (CO_{amide}), 172.93 (CO_{ester}) ppm.

*4.4.2. Methyl (2S)-2-({[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(trifluoromethyl)aziridin-2-yl]carbonyl}amino)-3-methylbutanoate (**12b**).* Yield 64%. $C_{18}H_{18}F_3N_3O_5$ (413): calcd. C 52.30, H 4.39, N 10.17; found C 52.01, H 4.12, N 10.47.

Diastereoisomer A: colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ=0.87 (d, $^3J_{H,\ H}$=6.8 Hz, 3H, CH_3), 0.92 (d, $^3J_{H,\ H}$=6.8 Hz, 3H, CH_3), 2.09 (m, 1H, $CH_{isopropyl}$), 3.64 (d, $^3J_{H,\ H}$=4.6 Hz, 1H, $CH_{aziridine}$), 3.75 (s, 3H, $CH_{3\ ester}$), 4.44 (m, 2H, CH–CF_3, CH_α), 7.45 (d_{broad}, $^3J_{H,\ H}$=8.6 Hz, 1H, NH), 7.59–7.81 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−70.77 (d, $^3J_{H,\ F}$=4.9 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=17.68 (CH_3), 18.47 (CH_3), 31.44 ($CH_{isopropyl}$), 42.11 ($CH_{\ aziridine}$), 42.95 (q, $^2J_{C,\ F}$=41 Hz, $CH_{\ aziridine}$–CF_3), 52.48 (CH_α), 58.08 (OCH_3), 121.76 (q, $^1J_{C,\ F}$=273 Hz, CF_3), 123.26 ($CH_{phthalimide}$), 129.90 ($C_{phthalimide}$), 134.30 ($CH_{phthalimide}$), 161.84 ($CO_{phthalimide}$), 164.19 (CO_{amide}), 172.21 (CO_{ester}) ppm. $[\alpha]_D^{25}$=+67(*c* 1, CH_2Cl_2).

Diastereoisomer B: white solid, mp 206 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ=0.92 (d, $^3J_{H,\ H}$=7.2 Hz, 3H, CH_3), 0.96 (d, $^3J_{H,\ H}$=7.2 Hz, 3H, CH_3), 2.15 (m, 1H, $CH_{isopropyl}$), 3.55 (d, $^3J_{H,\ H}$=4.5 Hz, 1H, $CH_{aziridine}$), 3.72 (s, 3H, $CH_{3\ ester}$), 4.38 (m, 2H, CH–CF_3 and CH_α), 7.19 (d_{broad}, $^3J_{H,\ H}$=8.1 Hz, 1H, NH), 7.65–7.78 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−70.69 (d, $^3J_{H,\ F}$=4.9 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=18.07 (CH_3), 18.72 (CH_3), 31.16 ($CH_{isopropyl}$), 42.08 ($CH_{aziridine}$), 42.10 (q, $^2J_{C,\ F}$=40.6 Hz, $CH_{aziridine}$–CF_3), 52.31 (CH_α), 58.34 (OCH_3), 122.55 (q, $^1J_{C,\ F}$=274 Hz, CF_3), 123.33 ($CH_{phthalimide}$), 129.98 ($C_{phthalimide}$), 134.18 ($CH_{phthalimide}$), 162.01 ($CO_{phthalimide}$), 164.08 (CO_{amide}), 171.29 (CO_{ester}) ppm. $[\alpha]_D^{25}$=−51 (*c* 1, CH_2Cl_2).

*4.4.3. Methyl (2S)-2-({[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(trifluoromethyl)aziridin-2-yl]carbonyl}amino)-3-phenylpropanoate (**12c**).* Yield 72%. White foam. The two diastereoisomers were separated.

Diastereoisomer A: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.93 (dd, $^3J_{H,\ H}$=5.9 Hz, $^2J_{H,\ H}$=13.7 Hz, 1H, CH_{2a}), 3.10 (dd, $^3J_{H,\ H}$=4.7 Hz, $^2J_{H,\ H}$=13.9 Hz, 1H, CH_{2b}), 3.43 (d, $^3J_{H,\ H}$=4.0 Hz, 1H, $CH_{aziridine}$), 3.68 (s, 3H, $CH_{3\ ester}$), 4.35 (m, 1H, $CH_{aziridine}$), 4.83 (dd, $^3J_{H,\ H}$=5.2 Hz, $^3J_{H,\ H}$=7.8 Hz, 1H, C*H*–CH_2), 6.92 (d, $^3J_{H,\ H}$=8.3 Hz, 1H, NH), 7.27 (m, 5H, $CH_{aromatic}$), 7.71 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=70.26 (m, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=37.9 (CH_2), 41.9 ($CH_{aziridine}$), 43.0 (q, $^3J_{C,\ F}$=43.2 Hz, *C*H–CF_3), 52.4 (CH–CH_2), 53.6 ($CH_{3\ ester}$), 123.3; 123.4 ($CH_{aromatic}$), 123.8 (q, $^1J_{C,\ F}$=272.1, CF_3), 128.7; 128.9 ($CH_{phthalimide}$), 129.4 ($C_{aromatic}$), 134.2 ($CH_{phthalimide}$), 135.1 ($C_{phthalimide}$), 163.3 ($CO_{phthalimide}$), 164.0 (CO_{ester}), 171.1 (C_{amide}) ppm.

Diastereoisomer B: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.05 (dd, $^3J_{H,\ H}$=5.6 Hz, $^2J_{H,\ H}$=13.7 Hz, 1H, CH_{2a}), 3.17 (dd, $^3J_{H,\ H}$=6.0 Hz, $^3J_{H,\ H}$=14 Hz, 1H, CH_{2b}), 3.54 (d, $^3J_{H,\ H}$=4.5 Hz, 1H, $CH_{aziridine}$), 3.64 (s, 3H, $CH_{3\ ester}$), 4.38 (m, 1H, $CH_{aziridine}$), 4.72 (m, 1H, CH–CH_2), 6.83 (d, $^3J_{H,\ H}$=7.9 Hz, 1H, NH), 7.25 (m, 5H, $CH_{aromatic}$), 7.75 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=70.38 (m, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=37.3 (CH_2), 41.7 ($CH_{aziridine}$), 43.4 (q, $^3J_{C,\ F}$=43.2 Hz, *C*H–CF_3), 52.6 (CH–CH_2), 54.2 ($CH_{3\ ester}$), 123.4; 127.4 ($CH_{aromatic}$), 128.6; 129.1 ($CH_{phthalimide}$), 130.0 ($C_{aromatic}$), 134.2 ($CH_{phthalimide}$), 135.2 ($C_{phthalimide}$), 161.5 ($CO_{phthalimide}$), 164.2 (CO_{ester}), 171.3 (CO_{amide}) ppm.

*4.4.4. Methyl (2S)-2-({[1-(bis(tert-butoxycarbonyl)amino)-3-(trifluoromethyl)aziridin-2-yl]carbonyl}amino)-3-phenylpropanoate (**12d**).* Yield 79%. White foam. Mixture of diastereoisomers in a 1:1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.50 (s, 9H, $CH_{3\ Boc}$), 1.52 (s, 9H, $CH_{3\ Boc}$), 3.14 (m, 2H, C*H*$_2$–CH), 3.27 (d, $^3J_{H,\ H}$=4.5 Hz, 1H, $CH_{aziridine}$), 3.65 (s, 1.5H, $CH_{3\ ester\ dia\ 1}$), 3.72 (s, 1.5H, $CH_{3\ ester\ dia\ 2}$), 3.74 (m, 1H, $CH_{aziridine}$), 4.85 (m, 1H, C*H*–CH_2), 7.09 (m, 1H, NH), 7.27 (m, 5H, $CH_{aromatic}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=69.51 (m, $CF_{3\ dia\ 1}$), 69.59 (m, $CF_{3\ dia\ 2}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=27.9; 28.0 ($CH_{3\ Boc}$), 37.9; 38.0 (CH_2), 44.8 ($CH_{aziridine}$), 52.2 (CH_{ester}), 52.3 (CH–CF_3), 84.3; 84.9 ($C_{quat\ Boc}$), 127.0 (q, $^1J_{C,\ F}$=272.0 Hz, CF_3), 128.6; 128.7; 129.2 ($CH_{aromatic}$), 148.3 (CO_{Boc}), 150.9 (CO_{Boc}), 164.3 (CO_{ester}), 171.2 (CO_{amide}) ppm. $C_{24}H_{32}F_3N_3O_7$ (571.52): calcd. C 54.23, H 6.07, N 7.91; found C 54.68H 6.42, N 7.62. MS: ESI^+ (M+Na)=554.

*4.4.5. Ethyl 3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-4,4,4-trifluoro-2-hydroxybutanoate (**13**).* A large excess of trifluoroacetic acid (8 mL) was added to the aziridine **2a** (250 mg, 0.76 mmol) and the reaction was refluxed for 18 h. Then the trifluoroacetic acid was removed under pressure and the residue was diluted in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was dried on $MgSO_4$ and the solvent was removed under reduced pressure followed by purification by column chromatography on silica gel (cyclohexane/AcOEt 7/3) to yield the compound **13** as a white solid (202 mg, 77%), mp 139 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.23 (t, $^3J_{H,\ H}$=7 Hz, 3H, $CH_{3\ ester}$), 3.52 (d, $^3J_{H,\ H}$=6.4 Hz, 1H, OH), 3.89 (qd, $^3J_{H,\ H}$=7.4 Hz, $^3J_{H,\ H}$=2.9 Hz, 1H, CH–CF_3), 4.21 (m, 2H, $CH_{2\ ester}$), 4.62 (dd, $^3J_{H,\ H}$=1.3 Hz, $^3J_{H,\ H}$=2.9 Hz, 1H, CH–OH), 5.42 (d, $^3J_{H,\ H}$=7.5 Hz, 1H, NH), 7.65 (m, 2H, $CH_{phthalimide}$), 7.85 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−69.58 (dd, $^3J_{H,\ F}$=7.4 Hz, $^3J_{H,\ F}$=1.3 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.90 ($CH_{3\ ester}$), 62.67 ($CH_{2\ ester}$), 63.30 (q, $^2J_{C,\ F}$=27 Hz, CH–CF_3), 68.73 (CH–OH), 123.95 (q, $^1J_{C,\ F}$==282 Hz, CF_3), 123.77 ($CH_{phthalimide}$), 129.83 ($C_{phthalimide}$), 134.62 ($CH_{phthalimide}$), 165.81 ($CO_{phthalimide}$), 170.42 (CO_{ester}) ppm. $C_{14}H_{13}F_3N_2O_5$ (346): calcd. C 48.56, H 3.78, N 8.09; found C 48.91, H 3.91, N 7.88.

*4.4.6. Ethyl 2-chloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-4,4,4-trifluorobutanoate (**14a**).* Hydrogen chloride 4 M (2.5 mL) in dioxane was added to the compound **2a** (100 mg,

0.31 mmol) at 0 °C. The reaction mixture was stirred for 5 h at room temperature and the solvent was removed under pressure. The residue was diluted with CH_2Cl_2 (15 mL) and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was dried on $MgSO_4$ and the solvent was removed under pressure to yield the compound **14a** as a colourless oil (98 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.35 (t, $^3J_{H,\ H}$=7.2 Hz, 3H, CH_3 ester), 4.22 (q, $^3J_{H,\ H}$=7.2 Hz, 2H, CH_2 ester), 4.26 (qdd, $^3J_{H,\ H}$=3.8 Hz, $^3J_{H,\ H}$=6.2 Hz, $^3J_{H,\ H}$=7.7 Hz, 1H, CH–CF_3), 4.92 (d, $^3J_{H,\ H}$=3.8 Hz, 1H, CH–Cl), 5.46 (d, $^3J_{H,\ H}$=7.7 Hz, 1H, NH), 7.9–7.65 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−69.78 (d, $^3J_{H,\ F}$=6.2 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.78 (CH_3 ester), 54.95 (CH–Cl), 63.24 (q, $^2J_{C,\ F}$=28.5 Hz, CH–CF_3), 63.27 (CH_2 ester), 123.5 (q, $^1J_{C,\ F}$==284 Hz, CF_3), 123.72 ($CH_{phthalimide}$), 129.76 ($C_{phthalimide}$), 134.64 ($CH_{phthalimide}$), 165.5 ($CO_{phthalimide}$), 165.7 ($CO_{phthalimide}$), 168.10 (CO_{ester}) ppm. $C_{14}H_{12}ClF_3N_2O_4$ (364): calcd. C 46.11, H 3.32, N 7.68; found C 46.54, H 3.45, N 7.89.

*4.4.7. Dibenzyl 2-(3-chloro-4-ethoxy-1,1,1-trifluoro-4-oxobutan-2-yl)hydrazine-1,1-dicarboxylate (**14b**).* Hydrogen chloride 4 M (2.5 mL) in dioxane was added to the compound **9** (100 mg, 0.21 mmol) at 0 °C. The reaction mixture was stirred for 5 h at room temperature and the solvent was removed under pressure. The residue was diluted with CH_2Cl_2 (15 mL) and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was dried on $MgSO_4$ and the solvent was removed under pressure to yield the compound **14b** as a colourless oil (77 mg, 71%). ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ=1.24 (t, $^3J_{H,\ H}$=7.2 Hz, 3H, CH_3 ester), 4.21 (qd, $^3J_{H,\ H}$=7.2 Hz, $^3J_{H,\ H}$=2.1 Hz, 2H, CH_2 ester), 4.39 (qd, $^3J_{H,\ H}$=3.8 Hz, $^3J_{H,\ H}$=7.2 Hz, 1H, CH–CF_3), 4.95 (dd, $^3J_{H,\ H}$=3.8 Hz, $^3J_{H,\ H}$=0.8 Hz, 1H, CH–Cl), 5.25 (d, $^2J_{H,\ H}$=12.2 Hz, 2H, CH_2 benzyl), 5.29 (d, $^2J_{H,\ H}$=12.2 Hz, 2H, CH_2 benzyl), 7.31–7.45 (m, 10H, $CH_{aromatic}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−69.45 (d, $^3J_{H,\ F}$=6.9 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.83 (CH_3 ester), 54.74 (CH–Cl), 63.16 (CH_2 ester), 63.56 (q, $^2J_{C,\ F}$=27.9 Hz, CH–CF_3),69.82 (OCH_2–Ph), 123.8 (q, $^1J_{C,\ F}$==284 Hz, CF_3), 128.47 ($CH_{aromatic}$), 128.63 ($CH_{aromatic}$), 128.71 ($CH_{aromatic}$), 134.43 ($C_{aromatic}$), 153.01 (CO_{Cbz}), 165.71 (CO_{ester}) ppm. $C_{22}H_{22}ClF_3N_2O_6$ (502): calcd. C 52.55, H 4.41, N 5.57; found C 51.95, H 4.09, N 5.03.

4.5. General method for the ring opening with thiol

To a solution of aziridine (100 mg, 0.30 mmol, 1 equiv) in CH_2Cl_2, (5 mL), the thiol (0.33 mmol, 1.1 equiv) and the trifluoromethanesulfonic acid (0.33 mmol, 1.1 equiv) were added to the solution and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then washed with a saturated aqueous solution of $NaHCO_3$ and the organic layer was dried on $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane/AcOEt 8/2) to lead to the corresponding pure compound.

*4.5.1. Ethyl 3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-2-(ethylsulfanyl)-4,4,4-trifluorobutanoate (**15a**).* Yield 54%. Colourless oil, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.35 (t, $^3J_{H,\ H}$=7.2 Hz, 3H, CH_3 ester), 1.42 (t, $^3J_{H,\ H}$=7.5 Hz, 3H, S–CH_2–CH_3), 2.71 (q, $^3J_{H,\ H}$=7.5 Hz, 2H, S–CH_2–CH_3), 3.75 (d, $^3J_{H,\ H}$=3.9 Hz, 1H, CH–SEt), 4.22 (m, 1H, CH–CF_3), 4.34 (q, $^3J_{H,\ H}$=7.2 Hz, 2H, CH_2 ester), 6.18 (d, $^3J_{H,\ H}$=7.8 Hz, 1H, NH), 7.72 (m, 2H, $CH_{phthalimide}$), 7.85 (m, 2H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−71.94 (d, $^3J_{H,\ F}$=7.0 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.98/14.07 (CH_3 ester and *C*H_3–CH_2–S), 27.21 (CH_3–CH_2–S), 44.99 (CH–SEt), 61.94 (q, $^2J_{C,\ F}$=28 Hz, CH–CF_3), 62.24 (CH_2 ester), 121.15 (q, $^1J_{C,\ F}$=280 Hz, CF_3), 123.54 ($CH_{phthalimide}$), 130.00 ($C_{phthalimide}$), 134.38 ($CH_{phthalimide}$), 165.24 ($CO_{phthalimide}$), 169.32 (CO_{ester}) ppm. $C_{16}H_{17}F_3N_2O_4S$ (390): calcd. C 49.23, H 4.39, N 7.18; found C 49.01, H 4.03, N 7.29.

*4.5.2. Ethyl 2-(benzylsulfanyl)-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-4,4,4-trifluorobutanoate (**15b**).* Yield 65%. Colourless oil, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.33 (t, $^3J_{H,\ H}$=7.1 Hz, 3H, CH_3 ester), 3.69 (d, $^3J_{H,\ H}$=3.8 Hz, 1H, CH–SBn), 3.97 (d, $^3J_{H,\ H}$=13.4 Hz, 1H, CH_2–Ph), 4.03 (d, $^3J_{H,\ H}$=13.4 Hz, 1H, CH_2–Ph), 4.15 (m, 1H, CH–CF_3), 4.25 (q, $^3J_{H,\ H}$=7.1 Hz, 1H, CH_2 ester), 6.18 (d, $^3J_{H,\ H}$=8 Hz, 1H, NH), 7.31–7.52 (m, 5H, CH_{benzyl}), 7.80–8.02 (m, 4H, $CH_{phthalimide}$) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ=−72.03 (d, $^3J_{H,\ F}$=7.5 Hz, 3F, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.96 (CH_3 ester), 37.11 (S–CH_2–Ph), 44.02 (CH–SBn), 61.90 (q, $^2J_{C,\ F}$=28 Hz, CH–CF_3), 62.23 (CH_2 ester), 123.51 ($CH_{phthalimide}$), 124.18 (q, $^1J_{C,\ F}$=285 Hz, CF_3), 127.61, 128.69, 129.20 (CH_{benzyl}), 130.02 ($C_{phthalimide}$), 134.34 ($CH_{phthalimide}$), 136.31 (C_{benzyl}), 165.14 ($CO_{phthalimide}$), 169.28 (CO_{ester}) ppm. $C_{21}H_{19}F_3N_2O_4S$ (452): calcd. C 55.75, H 4.23, N 6.19; found C 55.31, H 9.98, N 6.52.

Acknowledgements

Central Glass is thanked for the kind gift of trifluorocrotonic acid and the (*E*)-benzyloxy-trifluorobutene. We thank A. Solgadi for performing mass spectra analysis (SAMM platform, Châtenay-Malabry).

References and notes

1. Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.
2. Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911–4919.
3. Padwa, A.; Murphree, S. S. *Arkivoc* **2006**, 6–33.
4. Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743.
5. Leighton, J. L.; Valdez, S. C. *J. Am. Chem. Soc.* **2009**, *131*, 14638–14642.
6. Kapron, J. T.; Santarsiero, B. D.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1074–1076.
7. Vidal, J. Synthesis and Chemistry of α-Hydrazino Acids In *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley-VCH GmbH & KGaA: 2009; pp 35–92.
8. Günther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2000**, *123*, 247–255.
9. Chakraborty, T. K.; Ghosh, A. *Indian J. Chem., Sect. B* **2001**, *40*, 895–897.
10. Guy, L.; Vidal, J.; Collet, A.; Amour, A.; Reboud-Ravaux, M. *J. Med. Chem.* **1998**, *41*, 4833–4843.
11. Sweeney, J. B. Synthesis of Aziridines In *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH GmbH & KGaA: 2006; pp 117–144.
12. Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519–1558.
13. Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. *Tetrahedron* **1989**, *45*, 2875–2886.
14. Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. C* **1970**, 576–582.
15. Atkinson, R. S.; Rees, C. W. *J. Chem. Soc. C* **1969**, 772–778.
16. Yang, K.-S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676–1679.
17. Yang, K. S.; Chen, K. M. *Org. Lett.* **2002**, *4*, 1107–1109.
18. Ulukanli, S.; Karabuga, S.; Celik, A.; Kazaz, C. *Tetrahedron Lett.* **2005**, *46*, 197–199.
19. Diaper, C. M.; Sutherland, A.; Pillai, B.; James, M. N. G.; Semchuk, P.; Blanchard, J. S.; Vederas, J. C. *Org. Biomol. Chem.* **2005**, *3*, 4402–4411.
20. Milcent, R.; Guevrekian-Soghomoniantz, M.; Barbier, G. *J. Heterocycl. Chem.* **1986**, *23*, 1845–1848.
21. Duan, Z.; Li, Z. X.; Kang, J. X.; Wang, H. Q.; Yu, L. J.; Wu, Y. J. *Tetrahedron* **2008**, *64*, 1924–1930.
22. Butkevich, A. N.; Zibinsky, M.; Kuznetsov, M. A. *Tetrahedron Lett.* **2008**, *49*, 5505–5507.
23. Li, J. Y.; Liang, J. L.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2004**, *45*, 2685–2688.
24. Richardson, R. D.; Desaize, M.; Wirth, T. *Chem.—Eur. J.* **2007**, *13*, 6745–6754.
25. Kuznetsov, M. A.; Zibinsky, M.; Stewart, T.; Prakash, G. K. S. *Eur. J. Org. Chem.* **2009**, 3635–3642.
26. Hernandez-Toribio, J.; Hussain, M. M.; Cheng, K.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 6094–6097.
27. Li, J. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2005**, *7*, 5801–5804.
28. Singh, K. N.; Singh, S. *Synth. Commun.* **2005**, *35*, 2597–2602.
29. Begue, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992–1012.
30. Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303–319.
31. Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27–33.
32. Bégué, J.-P.; Bonnet-Delpon, D. Fluorinated Drugs In *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons: 2007; pp 279–351.
33. Formicola, L.; Marechal, X.; Basse, N.; Bouvier-Durand, M.; Bonnet-Delpon, D.; Milcent, T.; Reboud-Ravaux, M.; Ongeri, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 83–86.
34. Jagodzinska, M.; Huguenot, F.; Zanda, M. *Tetrahedron* **2007**, *63*, 2042–2046.

35. Vicente, J.; Chicote, M. T.; Fernandezbaeza, J.; Fernandezbaeza, A. *New J. Chem.* **1994**, *18*, 263–268.
36. Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887–3890.
37. Wang, B. L.; Fei, Y.; Qiu, X. L.; Jiang, Z. X.; Qing, F. L. *J. Fluorine Chem.* **2006**, *127*, 580–587.
38. Brosse, N.; Pinto, M. F.; Jamart-Gregoire, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3685–3688.
39. Egli, M.; Hoesch, L.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 220–230.
40. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3096–3106.
41. Du, X.; Yang, S.; Yang, J.; Liu, Y. *Chem.—Eur. J.* **2011**, *17*, 4981–4985.
42. Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597–2600.
43. Jefford, C. W.; Jaggi, D.; Kohmoto, S.; Timari, G.; Bernardinelli, G.; Canfield, C. J.; Milhous, W. K. *Heterocycles* **1998**, *49*, 375–383.
44. Bonnet-Delpon, D.; Rinaudo, G.; Narizuka, S.; Askari, N.; Crousse, B. *Tetrahedron Lett.* **2006**, *47*, 2065–2068.
45. Davoli, P.; Forni, A.; Franciosi, C.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2361–2371.
46. Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Begue, J. P. *Synlett* **2001**, 679–681.