DOI: 10.1002/ejoc.200901290

Access to a Novel Class of Tetracyclic 1,4-Benzodiazepin-5-ones Starting from α-Amino Acids by Pd-Catalyzed Amination/1,3-Dipolar Cycloaddition as the Key Steps

Luca Basolo,[a] Egle M. Beccalli,*[a] Elena Borsini,[a] Gianluigi Broggini,[b] Maisaa Khansaa,[b] and Micol Rigamonti[b]

Keywords: Fused-ring systems / Nitrogen heterocycles / Palladium / Cycloaddition / Diastereoselectivity

A convenient procedure for the preparation of the novel class of tetracyclic imidazo[2,1-*c*]pyrazolo[1,5-*a*][1,4]benzodiazepine-5,8-diones is reported. The protocol uses cheap and easily accessible α-amino acids as chiral-pool starting materials and leads to products in an enantiopure form. An intramolecular palladium-catalyzed amination process to form the imidazole nucleus and an intramolecular 1,3-dipolar cycloaddition reaction to simultaneously achieve the pyrazole and 1,4-diazepine rings are the key steps.

Introduction

1,4-Benzodiazepines play an important role in medicinal chemistry due to a wide range of pharmaceutical applications.[1] 1,4-Benzodiazepin-5-ones, one of the most significant classes of these structures, are recognized as being endowed with anxiolytic, anticonvulsant, antiepileptic, muscle relaxant, antidepressant, sedative, and hypnotic activities related to the treatment of CNS disorders.[2] Moreover, this range of therapeutic activities has been significantly enhanced by annulation of the benzodiazepine skeleton to another carbo- or heterocyclic ring. Tricyclic 1,4-benzodiazepin-5-one systems, beyond solving anxiety and stress problems, as in the case of flumazenil (**1**),[3] are also antihistaminic compounds, for example, tarpane (**2**),[4] antibiotics, like the pyrrolo-fused abbeymicin[5] (**3**), and antitumor agents, such as structures **4** (Figure 1).[6] More recently, inspired by the attention given to bretazenil (**5**) due to its potential application in neurodegenerative diseases,[7] some tetracyclic 1,4-benzodiazepinones have appeared in the literature. These structures have the benzodiazepine nucleus fused to different hetero- and carbocycles such as pyrimidines, imidazoles, 1,2,4-triazoles, pyrazoles, benzopyrans, or naphthalenes.[8–10]

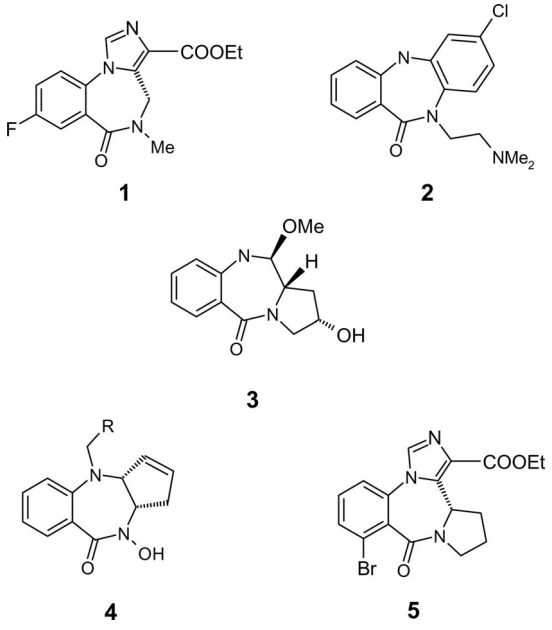


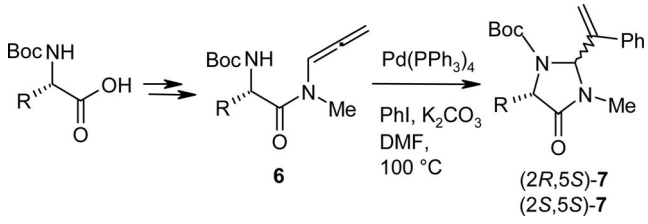
Figure 1. Tri- and tetracyclic pharmacologically active 1,4-benzodiazepin-5-ones.

Among the several procedures reported in articles and patents to synthesize 1,4-benzodiazepin-5-ones, approaches involving the formation of the 1–2 nitrogen–carbon bond as the final step are commonly used. Intramolecular cyclization of amines with carbonyls[11] or acetals/thioacetals,[12] reductive cyclization of nitro derivatives with carbonyls,[13] intramolecular 1,3-dipolar cycloadditions of azides[14] and nitrilimines[15] to alkenes and/or alkynes, aza-Wittig ring-closure of iminophosphoranyls with carbonyls,[16] intramolecular Michael addition of amines to enones,[17] intramo-

[a] DISMAB, Sezione di Chimica Organica "A. Marchesini", Università di Milano,
Via Venezian 21, 20133 Milano, Italy
Fax: +39-02-50314476
E-mail: egle.beccalli@unimi.it
[b] Dipartimento di Scienze Chimiche e Ambientali, Università dell'Insubria,
Via Valleggio 11, 22100 Como, Italy
Fax: +39-031-2386449
E-mail: gianluigi.broggini@uninsubria.it

lecular nucleophilic substitutions by aniline derivatives,[18] ring-opening reactions of amines on furan moieties,[19] intramolecular Pd-catalyzed cyclizations,[6,20] and the cyclization of amines with nitriles[21] on differently substituted benzamides have proven to be fruitful methodologies for promoting the formation of the nitrogen–carbon bond, eventually with the simultaneous construction of a new ring.

This paper concerns a protocol for the synthesis of a new class of tetracyclic 1,4-benzodiazepin-5-ones that we have developed through our recent interest in allenylamide heterocyclization[22] and long-time experience of 1,3-dipolar cycloaddition reactions.[23] The starting point for planning the new synthetic strategy arose from the recent synthesis of the enantiopure 2-vinylimidazolidinones **7**, obtained by heteroannulation of the amino-allenylamides **6** (Scheme 1).[22b] The imidazolidinones **7** are envisaged as building blocks for the construction of 1,3-dipolar substrates suitable for intramolecular cycloaddition due to the presence of the ethylenic C–C double bond as a potential dipolarophile.

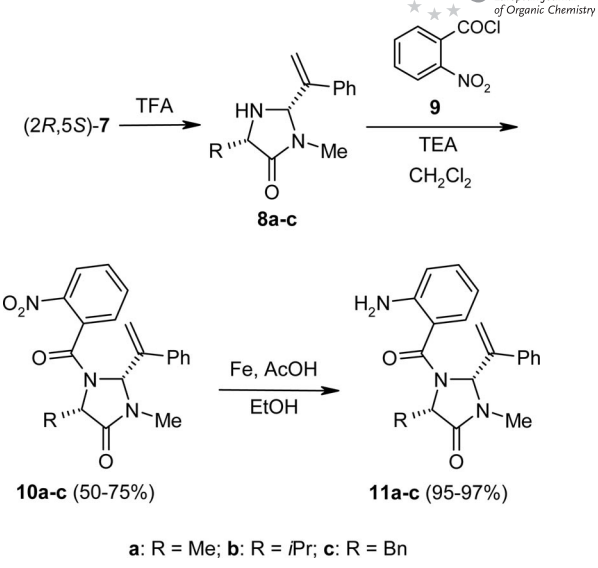


Scheme 1. Synthesis of imidazolidinones **7**.

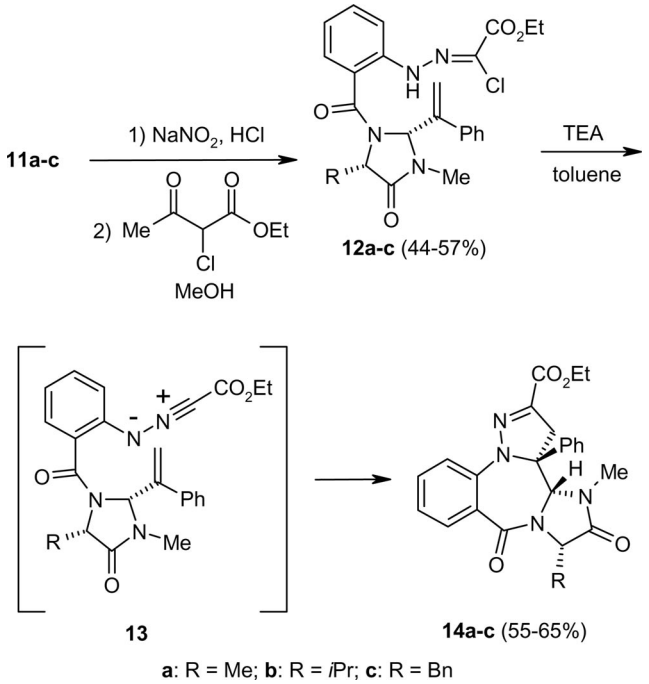
Results and Discussion

First, having recognized the major diastereoisomer imidazolidinone (2*R*,5*S*)-**7** as a convenient starting material, our approach required the synthesis of 2-aminobenzamides **11** as suitable compounds for accessing the azide and nitrilimine 1,3-dipoles due to the presence of the aniline moiety. With this aim, the Boc-protecting group was removed by treatment with TFA to give imidazolidinones **8** (Scheme 2). These latter compounds were functionalized by reaction with 2-nitrobenzoyl chloride (**9**) to give the 2-nitrobenzamides **10**, which in turn were reduced to the 2-aminobenzamides **11**.

The diazotization of the aniline moiety permitted access to the corresponding azido compounds, but their intramolecular 1,3-dipolar cycloaddition furnished unstable 4,5-dihydro-1,2,3-triazole products, which decomposed into complex mixtures with no synthetic interest. Such a failure prompted us to turn our attention to the nitrilimine 1,3-dipole, a well-established functional group in the synthesis of variously substituted azoles.[24] To this end, compounds **11** were submitted to diazotization and subsequent Japp–Klingemann reaction,[25] that is, coupling with ethyl 2-chloroacetoacetate, furnished the hydrazonyl chlorides **12**, precursors of the transient nitrilimine species **13**. In fact, treatment of **12** with triethylamine in boiling toluene gave directly the tetracyclic imidazo[2,1-*c*]pyrazolo[1,5-*a*][1,4]-benzodiazepine-5,8-dione systems **14** (Scheme 3).



Scheme 2. Synthesis of 2-aminobenzamides **11**.



Scheme 3. Generation of nitrilimines and their intramolecular cycloaddition reaction.

Further to the total regiochemical outcome that was expected as a consequence of the propargylic nature of the 1,3-dipole, the cycloaddition reaction was totally diastereoselective giving rise to only one diastereoisomeric product. This feature, highly important from a synthetic point of view, probably arises from the bulky phenyl substituent and the rather rigid imidazolidinone moiety working against the intramolecular approach of the dipole to the *si* face of the dipolarophile, so dictating the exclusive formation of the *cis*

(Ph,H) diastereoisomer **14**. The absolute configuration was assigned on the basis of ^{1}H NMR NOESY experiments carried out on compound **14a**. As shown in Figure 2, further to obvious interactions between the hydrogen atoms at the 2- and 5-positions of the imidazole nucleus, the cross-peak between the hydrogen at the 2-position of the imidazolidinone and the *ortho* hydrogen atoms on the phenyl group resulted in the determination of the *S* configuration of the newly created stereocenter and thus the (3a*S*,3b*R*,6*S*) diastereoisomer. The enantiomeric purity was proven to be better than 99.5% by HPLC analysis of compound **14a** with an AD chiral column and in comparison with a sample of the corresponding racemic mixture synthesized starting from (±)-alanine.

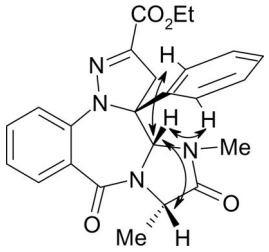
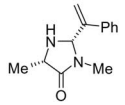
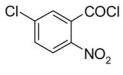
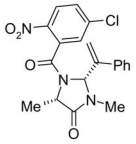
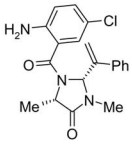
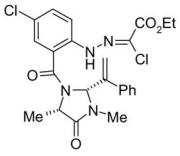
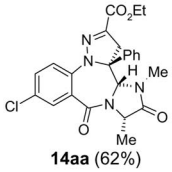
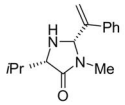
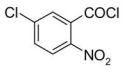
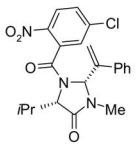
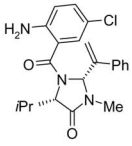
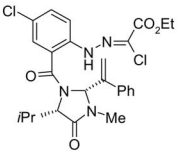
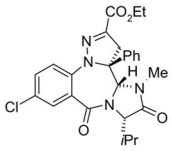
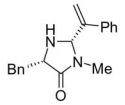
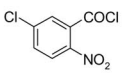
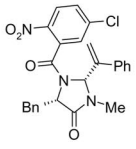
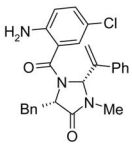
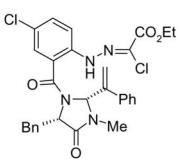
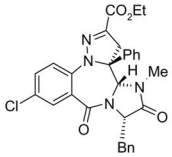
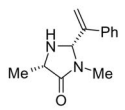
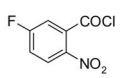
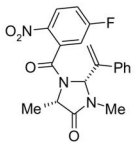
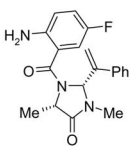
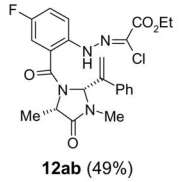
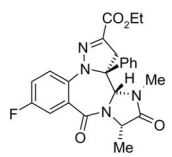
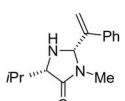
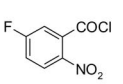
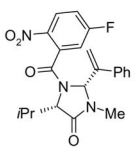
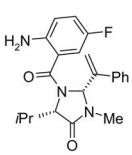
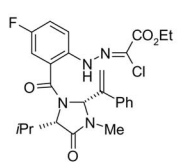
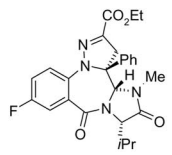
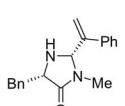
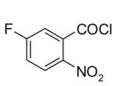
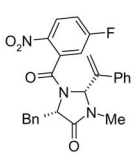
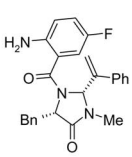
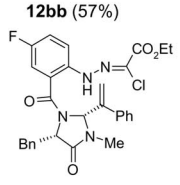
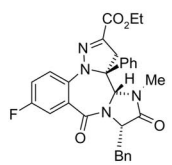


Figure 2. Selected NOESY correlations for compound **14a**.

We next examined the reactions of imidazolidinones **7** and 5-chloro- and 5-fluoro-2-nitrobenzoyl chlorides (**9a** and **9b**, respectively) to broaden the scope of the reaction and

Table 1. Scope of the procedure.

Entry	Imidazolidinones (**8**)	2-Nitrobenzoyl chlorides (**9**)	2-Nitrobenzamides (**10**)	2-Aminobenzamides (**11**)	Hydrazonyl chlorides (**12**)	Benzodiazepinones (**14**)
1	 **8a**	 **9a**	 **10aa** (55%)	 **11aa** (96%)	 **12aa** (62%)	 **14aa** (62%)
2	 **8b**	 **9a**	 **10ba** (34%)	 **11ba** (84%)	 **12ba** (82%)	 **14ba** (53%)
3	 **8c**	 **9a**	 **10ca** (62%)	 **11ca** (79%)	 **12ca** (43%)	 **14ca** (44%)
4	 **8a**	 **9b**	 **10ab** (60%)	 **11ab** (87%)	 **12ab** (49%)	 **14ab** (71%)
5	 **8b**	 **9b**	 **10bb** (49%)	 **11bb** (93%)	 **12bb** (57%)	 **14bb** (46%)
6	 **8c**	 **9b**	 **10cb** (65%)	 **11cb** (60%)	 **12cb** (47%)	 **14cb** (77%)

the interest of the products from a biological point of view, having a halo-substituted 1,4-benzodiazepine nucleus. The halide-containing products, 2-nitrobenzamides **10**, 2-aminobenzamides **11**, hydrazonyl chlorides **12**, and tetracyclic products **14**, are presented in Table 1. The preparation of hydrazonyl chlorides as well as the nitrilimine cycloaddition reactions occurred analogously to those described for the unsubstituted 2-nitrobenzoyl chloride.

Conclusions

We have reported a new procedure for the synthesis of a new class of tetracyclic 1,4-benzodiazepin-5-ones bearing the imidazo[2,1-*c*]pyrazolo[1,5-*a*][1,4]benzodiazepine-5,8-dione structure. The synthetic protocol consists of the following key steps: i) a palladium-catalyzed heteroannulation of allenyl amides starting from α-amino acids to give the imidazole ring and ii) an intramolecular nitrilimine cycloaddition reaction leading to the simultaneous formation of the 1,4-diazepine and pyrazole rings. Moreover, the novel scaffold of these heteropolycyclic systems was accessible in an enantiopure form, as inferred by the starting α-amino acids and conserved during the synthetic sequence.

Experimental Section

General: Melting points were determined by the capillary method with a Büchi B-540 apparatus. Optical rotations were measured with a Jasco P-1010 polarimeter. NMR spectra were recorded with an AVANCE 400 Bruker spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectroscopy. Chemical shifts are given as δ values in ppm relative to residual solvent peaks ($CHCl_3$ or DMSO) as the internal reference. ^{13}C NMR spectra were ^{1}H-decoupled and the multiplicities were determined by the APT pulse sequence. IR spectra were measured with a Jasco FT/IR 5300 spectrometer. Elemental analyses were executed with a Perkin–Elmer CHN Analyzer Series II 2400. Thin-layer chromatographic separations were performed on Merck silica gel 60 F_{254} precoated sheets. Preparative separations were performed by flash chromatography by using Merck silica gel 0.035–0.070 mm. The enantiomeric purity was determined by HPLC (pump: Merck–Hitachi L 7100; detector: DAD HP 1050; column: Chiralpak® AD; flow: 0.8 mL/min; eluent: hexane/2-propanol, 4:1).

General Procedure for the Synthesis of Compounds 8: A solution of (2*R*,5*S*)-**7**[22b] (2.55 mmol) in TFA (6 mL) was stirred at room temperature for 3 h. The solvent was then evaporated under reduced pressure and the residue purified by column chromatography using light petroleum ether/AcOEt (4:1) as eluent.

(2*S*,5*S*)-3,5-Dimethyl-2-(1-phenylvinyl)imidazolidin-4-one (8a): Yield 93%; pale-yellow oil. $[\alpha]_D^{25}$ = +27.5 (*c* = 0.37, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1670, 3430 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 7.1 Hz, 3 H), 3.04 (s, 3 H), 4.08 (q, *J* = 7.1 Hz, 1 H), 5.71 (s, 1 H), 5.72 (s, 1 H), 5.89 (s, 1 H), 6.57 (br. s, 1 H), 7.28–7.30 (m, 2 H), 7.42–7.48 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.7 (q), 28.1 (q), 54.1 (d), 74.2 (d), 122.9 (t), 126.9 (d), 129.2 (d), 129.8 (d), 134.5 (s), 139.5 (s), 169.3 (s) ppm. MS: *m*/*z* = 216 $[M]^+$. $C_{13}H_{16}N_2O$ (216.28): calcd. C 72.19, H 7.46, N 12.95; found C 72.26, H 7.38, N 12.86.

(2*S*,5*S*)-5-Isopropyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (8b): Yield 95%; cream crystals; m.p. 93 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +22.5 (*c* = 0.45, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1664, 3428 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 7.1 Hz, 3 H), 2.39 (dqq, *J* = 3.9, 7.0, 7.1 Hz, 1 H), 3.05 (s, 3 H), 4.19 (d, *J* = 3.9 Hz, 1 H), 5.74 (s, 1 H), 5.87 (s, 1 H), 5.98 (s, 1 H), 7.28–7.32 (m, 2 H), 7.41–7.50 (m, 3 H), 11.07 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.4 (q), 18.2 (q), 28.1 (d), 28.9 (q), 60.1 (d), 74.6 (d), 124.7 (t), 127.5 (d), 129.9 (d), 130.7 (d), 133.6 (s), 139.3 (s), 168.6 (s) ppm. MS: *m*/*z* = 244 $[M]^+$. $C_{15}H_{20}N_2O$ (244.33): calcd. C 73.74, H 8.25, N 11.47; found C 73.82, H 8.09, N 11.25.

(2*S*,5*S*)-5-Benzyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (8c): Yield 93%; white crystals; m.p. 91 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = –30.3 (*c* = 0.27, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1682, 3444 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.86 (s, 3 H), 3.13–3.20 (m, 2 H), 4.14–4.18 (m, 1 H), 5.14 (s, 1 H), 5.38 (s, 1 H), 5.54 (s, 1 H), 5.75 (br. s, 1 H), 7.08–7.36 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 28.8 (d), 34.3 (t), 59.3 (q), 74.9 (d), 124.1 (t), 127.3 (d), 129.2 (d), 129.8 (d), 129.9 (d), 130.2 (d), 130.4 (d), 132.1 (s), 134.0 (s), 139.6 (s), 168.4 (s) ppm. MS: *m*/*z* = 292 $[M]^+$. $C_{19}H_{20}N_2O$ (292.37): calcd. C 78.05, H 6.89, N 9.58; found C 77.93, H 7.02, N 9.74.

General Procedure for the Synthesis of Compounds 10: TEA (0.51 mL, 3.64 mmol) was added to a solution of **8** (0.7 mmol) in dry CH_2Cl_2 (3 mL). The mixture was cooled to 0 °C and a solution of **9** in dry CH_2Cl_2 (2 mL) was added dropwise whilst stirring. After 24 h at room temperature the mixture was washed with 5% HCl (30 mL) and with aq. $NaHCO_3$ (30 mL) and then the organic layer was dried with Na_2SO_4. The solvent was evaporated and the crude mixture was purified by silica gel column chromatography with light petroleum ether/AcOEt (1:1) as eluent to give **10**.

(2*R*,5*S*)-3,5-Dimethyl-1-(2-nitrobenzoyl)-2-(1-phenylvinyl)imidazolidin-4-one (10a): Yield 51% (as a mixture of two conformers in a ratio of 2:1); pale-yellow crystals; m.p. 160 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = –10.2 (*c* = 0.10, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1652, 1704 cm^{-1}. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.41 (d, *J* = 6.9 Hz, 3 H), 3.04 (s, 3 H), 3.78 (q, *J* = 6.9 Hz, 1 H), 5.56 (s, 1 H), 5.77 (s, 1 H), 6.06 (s, 1 H), 6.98–8.26 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.2 (q), 27.5 (q), 55.6 (d), 79.2 (d), 122.3 (t), 124.9 (d), 128.0 (d), 128.8 (d), 129.0 (d), 129.4 (d), 131.0 (d), 132.0 (s), 134.8 (d), 138.1 (s), 144.4 (s), 144.8 (s), 167.5 (s), 170.2 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (d, *J* = 6.9 Hz, 3 H), 2.84 (s, 3 H), 4.65 (q, *J* = 6.9 Hz, 1 H), 4.69 (s, 1 H), 5.13 (s, 1 H), 5.31 (s, 1 H), 6.98–8.26 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.9 (q), 27.4 (q), 55.8 (d), 80.1 (d), 122.4 (t), 125.2 (d), 128.0 (d), 128.9 (d), 129.2 (d), 129.7 (d), 130.5 (d), 132.2 (s), 134.8 (d), 136.8 (s), 144.4 (s), 144.9 (s), 167.5 (s), 170.9 (s) ppm. MS: *m*/*z* = 365 $[M]^+$. $C_{20}H_{19}N_3O_4$ (365.38): calcd. C 65.74, H 5.24, N 11.50; found C 65.98, H 5.09, N 11.44.

(2*R*,5*S*)-1-(5-Chloro-2-nitrobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (10aa): Yield 55% (as a mixture of two conformers in a ratio of 1.25:1); pale-yellow crystals; m.p. 62 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = –13.5 (*c* = 26.7, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1640, 1690 cm^{-1}. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.40 (d, *J* = 6.8 Hz, 3 H), 2.97 (s, 3 H), 3.74 (q, *J* = 6.8 Hz, 1 H), 5.50 (s, 1 H), 5.70 (s, 1 H), 5.98 (s, 1 H), 6.97–8.12 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.8 (q), 27.1 (q), 55.0 (d), 78.6 (d), 121.8 (t), 126.0 (d), 126.4 (d), 127.3 (d), 128.4 (d), 128.7 (d), 130.6 (d), 133.0 (s), 137.5 (s), 141.1 (s), 142.8 (s), 143.8 (s), 165.3 (s), 169.4 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz,

$CDCl_3$, 25 °C): δ = 1.21 (d, J = 6.5 Hz, 3 H), 2.81 (s, 3 H), 4.57 (q, J = 6.5 Hz, 1 H), 4.75 (s, 1 H), 5.20 (s, 1 H), 5.32 (s, 1 H), 6.98–8.12 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.4 (q), 26.9 (q), 55.3 (d), 79.4 (d), 122.1 (t), 126.0 (d), 126.4 (d), 127.3 (d), 128.5 (d), 128.9 (d), 130.6 (d), 133.1 (s), 136.2 (s), 141.1 (s), 142.7 (s), 144.2 (s), 165.3 (s), 170.1 (s) ppm. MS: m/z = 399 $[M]^+$. $C_{20}H_{18}ClN_3O_4$ (399.83): calcd. C 60.08, H 4.54, N 10.51; found C 60.20, H 4.31, N 10.73.

(2*R*,5*S*)-1-(5-Fluoro-2-nitrobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)-imidazolidin-4-one (10ab): Yield 60% (as a mixture of two conformers in a ratio of 2:1); yellow oil. $[\alpha]_D^{25}$ = –4.9 (c = 5.2, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1638, 1702 cm^{-1}. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.45 (d, J = 6.9 Hz, 3 H), 3.04 (s, 3 H), 3.77 (q, J = 6.9 Hz, 1 H), 5.57 (s, 1 H), 5.76 (s, 1 H), 6.03 (s, 1 H), 6.86–8.30 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.8 (q), 27.0 (q), 54.9 (d), 78.6 (d), 116.7 (dd, $^2J_{C\text{-}F}$ = 23.2 Hz), 117.6 (dd, $^2J_{C\text{-}F}$ = 23.0 Hz), 121.8 (t), 127.4 (d), 128.0 (dd, $^3J_{C\text{-}F}$ = 9.9 Hz), 128.4 (d), 128.7 (d), 134.4 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 137.5 (s), 140.7 (s), 143.8 (s), 165.2 (d, $^1J_{C\text{-}F}$ = 259.6 Hz), 169.4 (s), 170.1 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (d, J = 6.9 Hz, 3 H), 2.86 (s, 3 H), 4.64 (q, J = 6.9 Hz, 1 H), 4.80 (s, 1 H), 5.25 (s, 1 H), 5.33 (s, 1 H), 6.86–8.30 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.4 (q), 26.9 (q), 55.3 (d), 79.2 (d), 115.9 (dd, $^2J_{C\text{-}F}$ = 23.4 Hz), 117.5 (dd, $^2J_{C\text{-}F}$ = 22.9 Hz), 122.0 (t), 127.3 (d), 127.7 (dd, $^3J_{C\text{-}F}$ = 9.7 Hz), 128.4 (d), 128.8 (d), 134.5 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 136.3 (s), 140.6 (s), 144.4 (s), 165.4 (d, $^1J_{C\text{-}F}$ = 260.2 Hz), 169.3 (s), 169.9 (s) ppm. MS: m/z = 383 $[M]^+$. $C_{20}H_{18}FN_3O_4$ (383.37): calcd. C 62.66, H 4.73, N 10.96; found C 62.88, H 4.56, N 11.07.

(2*R*,5*S*)-5-Isopropyl-3-methyl-1-(2-nitrobenzoyl)-2-(1-phenylvinyl)-imidazolidin-4-one (10b): Yield 75% (as a mixture of two conformers in a ratio of 3:1); yellow oil. $[\alpha]_D^{25}$ = –18.3 (c = 0.21, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1665, 1688 cm^{-1}. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (d, J = 5.9 Hz, 3 H), 1.11 (d, J = 6.6 Hz, 3 H), 1.44 (dqq, J = 5.9, 6.6, 9.2 Hz, 1 H), 2.84 (s, 3 H), 4.40 (d, J = 9.2 Hz, 1 H), 4.86 (s, 1 H), 5.34 (s, 1 H), 5.54 (s, 1 H), 6.92–6.94 (m, 2 H), 7.23–7.31 (m, 3 H), 7.31–7.38 (m, 2 H), 7.54–7.63 (m, 1 H), 8.16–8.20 (m, 1 H) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.51 (d, J = 5.9 Hz, 3 H), 0.63 (d, J = 6.3 Hz, 3 H), 1.23–1.34 (m, 1 H), 2.94 (s, 3 H), 3.60–3.65 (m, 1 H), 5.54 (s, 1 H), 5.67 (s, 1 H), 6.18 (s, 1 H), 6.91–8.24 (m, 9 H) ppm. ^{1}H NMR (400 MHz, $[D_6]$DMSO, 100 °C): δ = 0.83 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 1.55 (dqq, J = 6.7, 6.9, 7.3 Hz, 1 H), 2.77 (s, 3 H), 4.06 (d, J = 7.3 Hz, 1 H), 5.15 (s, 1 H), 5.27 (s, 1 H), 5.71 (s, 1 H), 7.11–7.12 (m, 2 H), 7.13–7.31 (m, 3 H), 7.46 (dd, J = 1.3, 7.5 Hz, 1 H), 7.68 (ddd, J = 1.3, 7.7, 8.2 Hz, 1 H), 7.76 (ddd, J = 1.1, 7.5, 7.7 Hz, 1 H), 8.16 (dd, J = 1.1, 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO, 100 °C): δ = 20.1 (q), 20.9 (q), 27.8 (d), 32.4 (q), 63.5 (d), 78.9 (d), 120.6 (s), 122.6 (t), 125.7 (d), 128.7 (d), 128.9 (d), 129.1 (d), 129.8 (d), 131.6 (d), 132.3 (s), 135.8 (d), 138.1 (s), 144.9 (s), 145.0 (s), 169.7 (s) ppm. MS: m/z = 393 $[M]^+$. $C_{22}H_{23}N_3O_4$ (393.44): calcd. C 67.16, H 5.89, N 10.68; found C 67.34, H 5.67, N 10.75.

(2*R*,5*S*)-1-(5-Chloro-2-nitrobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (10ba): Yield 34% (as a mixture of two conformers in a ratio of 5:1); white crystals; m.p. 145 °C (iPr$_2$O). $[\alpha]_D^{25}$ = +55.7 (c = 13.0, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1644, 1710 cm^{-1}. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (d, J = 5.5 Hz, 3 H), 1.09 (d, J = 6.6 Hz, 3 H), 1.58 (dqq, J = 5.5, 6.6, 8.9 Hz, 1 H), 2.85 (s, 3 H), 4.36 (d, J = 8.9 Hz, 1 H), 4.91 (s, 1 H), 5.26 (s, 1 H), 5.34 (s, 1 H), 6.95–8.07 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.4 (q), 19.7 (q), 27.2 (d), 32.2 (q), 63.3 (d), 78.6 (d), 120.0 (s), 121.3 (t), 125.9 (d), 127.2 (d), 128.3 (d), 128.6 (d), 128.8 (d), 130.4 (d), 133.4 (s), 137.1 (s), 141.1 (s), 142.8 (s), 144.7 (s), 169.8 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.55 (d, J = 5.6 Hz, 3 H), 0.67 (d, J = 5.9 Hz, 3 H), 1.20–1.26 (m, 1 H), 2.93 (s, 3 H), 3.57–3.63 (m, 1 H), 5.52 (s, 1 H), 5.62 (s, 1 H), 6.15 (s, 1 H), 6.95–8.07 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.8 (q), 20.4 (q), 28.0 (d), 31.9 (q), 64.9 (d), 77.4 (d), 120.0 (s), 121.3 (t), 126.3 (d), 127.8 (d), 128.1 (d), 128.6 (d), 129.5 (d), 130.6 (d), 133.4 (s), 137.1 (s), 141.1 (s), 142.8 (s), 144.7 (s), 169.8 (s) ppm. MS: m/z = 427 $[M]^+$. $C_{22}H_{22}ClN_3O_4$ (427.88): calcd. C 61.75, H 5.18, N 9.82; found C 61.89, H 5.03, N 10.02.

(2*R*,5*S*)-1-(5-Fluoro-2-nitrobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (10bb): Yield 49% (as a mixture of two conformers in a ratio of 4:1); yellow oil. $[\alpha]_D^{25}$ = +0.24 (c = 28.7, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1640, 1698 cm^{-1}. Major conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (d, J = 5.9 Hz, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 1.55 (dqq, J = 5.9, 6.6, 9.0 Hz, 1 H), 2.82 (s, 3 H), 4.33 (d, J = 9.0 Hz, 1 H), 4.94 (s, 1 H), 5.24 (s, 1 H), 5.35 (s, 1 H), 6.91–8.15 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.3 (q), 19.8 (q), 27.2 (d), 32.2 (q), 63.4 (d), 78.4 (d), 116.6 (dd, $^2J_{C\text{-}F}$ = 27.4 Hz), 117.4 (dd, $^2J_{C\text{-}F}$ = 23.1 Hz), 120.9 (t), 127.2 (d), 127.6 (dd, $^3J_{C\text{-}F}$ = 9.4 Hz), 128.3 (d), 128.6 (d), 134.4 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 137.3 (s), 140.7 (s), 144.8 (s), 165.1 (d, $^1J_{C\text{-}F}$ = 259.7 Hz), 166.4 (s), 169.8 (s) ppm. Minor conformer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.49 (d, J = 6.2 Hz, 3 H), 0.64 (d, J = 6.6 Hz, 3 H), 1.32–1.42 (m, 1 H), 2.89 (s, 3 H), 3.54–3.61 (m, 1 H), 5.48 (s, 1 H), 5.60 (s, 1 H), 6.12 (s, 1 H), 6.70–8.29 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.6 (q), 20.4 (q), 28.0 (d), 31.8 (q), 64.8 (d), 77.3 (d), 116.4 (dd, $^2J_{C\text{-}F}$ = 27.2 Hz), 117.6 (dd, $^2J_{C\text{-}F}$ = 23.5 Hz), 120.0 (t), 127.2 (d), 127.8 (dd, $^3J_{C\text{-}F}$ = 9.0 Hz), 128.0 (d), 128.6 (d), 134.2 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 138.0 (s), 139.9 (s), 144.2 (s), 165.4 (d, $^1J_{C\text{-}F}$ = 259.4 Hz), 166.8 (s), 170.1 (s) ppm. MS: m/z = 411 $[M]^+$. $C_{22}H_{22}FN_3O_4$ (411.43): calcd. C 64.22, H 5.39, N 10.21; found C 64.44, H 5.12, N 10.32.

(2*R*,5*S*)-5-Benzyl-3-methyl-1-(2-nitrobenzoyl)-2-(1-phenylvinyl)imidazolidin-4-one (10c): Yield 50% (as a mixture of two conformers in a ratio of 1:1); yellow oil. $[\alpha]_D^{25}$ = +4.3 (c = 0.1, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1658, 1706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.46–2.52 (m, 2 H), 2.81 (s, 3 H), 3.10 (s, 3 H), 3.15–3.22 (m, 2 H), 3.93–4.12 (m, 1 H), 4.17 (s, 1 H), 4.85–4.88 (m, 1 H), 5.17 (s, 1 H), 5.43 (s, 1 H), 5.59 (s, 1 H), 5.71 (s, 1 H), 6.19 (s, 1 H), 6.48–7.92 (m, 28 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.9 (q), 27.6 (q), 36.8 (t), 39.0 (t), 60.5 (d), 61.4 (d), 76.7 (d), 78.7 (d), 121.4 (t), 121.8 (t), 125.1 (d), 125.7 (d), 126.2 (d), 127.0 (d), 127.5 (d), 128.0 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d, overlapped), 128.6 (d), 129.3 (d), 129.4 (d), 129.8 (d), 130.0 (d), 130.3 (d), 130.4 (d), 130.8 (d), 132.4 (d), 133.0 (d), 136.1 (s), 136.9 (s), 137.2 (s), 137.4 (s), 141.1 (s), 141.4 (s), 142.5 (s), 142.7 (s), 143.9 (s), 144.0 (s), 168.6 (s), 168.8 (s), 169.2 (s), 169.6 (s) ppm. MS: m/z = 441 $[M]^+$. $C_{26}H_{23}N_3O_4$ (441.48): calcd. C 70.73, H 5.25, N 9.52; found C 70.50, H 5.51, N 9.43.

(2*R*,5*S*)-5-Benzyl-1-(5-chloro-2-nitrobenzoyl)-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (10ca): Yield 62% (as a mixture of two conformers in a ratio of 1:1); pale-yellow crystals; m.p. 75 °C (iPr$_2$O). $[\alpha]_D^{25}$ = +4.4 (c = 11.9, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1636, 1688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.79 (s, 3 H), 2.84–2.95 (m, 2 H), 3.07 (s, 3 H), 3.12–3.20 (m, 2 H), 3.93–4.15 (m, 1 H), 4.21 (s, 1 H), 4.80–4.86 (m, 1 H), 5.16 (s, 1 H), 5.44 (s, 1 H), 5.57 (s, 1 H), 5.68 (s, 1 H), 6.18 (s, 1 H), 6.47–6.51 (m, 2 H), 6.75–7.48 (m, 22 H), 7.84–7.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.9 (q), 27.6 (q), 36.8 (t), 39.0 (t), 60.5 (d),

61.4 (d), 76.9 (d), 78.6 (d), 121.5 (t), 121.7 (t), 125.7 (d), 126.1 (d), 126.3 (d), 126.9 (d), 127.2 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.6 (d, overlapped), 128.7 (d), 129.4 (d), 129.7 (d), 129.8 (d), 130.0 (d), 130.3 (d), 130.4 (d), 132.4 (s), 133.0 (s), 136.1 (s), 136.9 (s), 137.2 (s), 137.7 (s), 141.0 (s), 141.2 (s), 142.4 (s), 142.5 (s), 144.0 (s), 168.6 (s), 168.7 (s), 169.1 (s), 169.4 (s) ppm. MS: *m*/*z* = 475 $[M]^+$. $C_{26}H_{22}ClN_3O_4$ (475.92): calcd. C 65.62, H 4.66, N 8.83; found C 65.43, H 4.81, N 8.96.

(2*R*,5*S*)-5-Benzyl-1-(5-fluoro-2-nitrobenzoyl)-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (10cb): Yield 65% (as a mixture of two conformers in a ratio of 1:1); white crystals; m.p. 88 °C (*i*Pr_2O). $[a]_D^{25}$ = –4.0 (*c* = 19.1, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1660, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.48–2.56 (m, 2 H), 2.79 (s, 3 H), 3.08 (s, 3 H), 3.01–3.20 (m, 2 H), 3.92–4.13 (m, 1 H), 4.21 (s, 1 H), 4.82–4.89 (m, 1 H), 5.15 (s, 1 H), 5.44 (s, 1 H), 5.58 (s, 1 H), 5.69 (s, 1 H), 6.21 (s, 1 H), 6.25–6.42 (m, 1 H), 6.48–6.51 (m, 3 H), 6.75–7.08 (m, 7 H), 7.25–7.48 (m, 12 H), 7.98–8.05 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.9 (q), 27.6 (q), 36.8 (t), 39.1 (t), 60.6 (d), 61.5 (d), 76.7 (d), 78.6 (d), 116.0 (dd, $^2J_{C-F}$ = 21.8 Hz), 116.2 (dd, $^2J_{C-F}$ = 22.0 Hz), 117.1 (dd, $^2J_{C-F}$ = 21.6 Hz), 117.4 (dd, $^2J_{C-F}$ = 21.9 Hz), 121.3 (t), 121.7 (t), 126.2 (d), 126.8 (dd, $^3J_{C-F}$ = 11.6 Hz), 127.4 (dd, $^3J_{C-F}$ = 11.0 Hz), 128.4 (d), 128.6 (d, overlapped), 130.0 (d), 133.5 (d, $^3J_{C-F}$ = 5.6 Hz), 134.3 (d, $^3J_{C-F}$ = 6.2 Hz), 136.3 (s), 136.6 (s), 136.7 (s), 137.0 (s), 137.4 (s), 137.7 (s), 144.0 (s), 144.2 (s), 165.1 (d, $^1J_{C-F}$ = 231.6 Hz), 166.4 (s), 167.6 (d, $^1J_{C-F}$ = 259.3 Hz), 168.7 (s), 168.8 (s), 169.1 (s) ppm. MS: *m*/*z* = 459 $[M]^+$. $C_{26}H_{22}FN_3O_4$ (459.47): calcd. C 67.97, H 4.83, N 9.15; found C 67.84, H 4.99, N 9.26.

General Procedure for the Synthesis of Compounds 11: A solution of **10** (1.04 mmol) in EtOH (10 mL) and 20% aq. AcOH (2.5 mL) was treated with Fe powder (0.464 g, 8.32 mmol) and heated at reflux for 5 h under vigorous stirring. The mixture was diluted with AcOEt (50 mL) and filtered through a pad of Celite. The filtrate was washed with aq. $NaHCO_3$ (50 mL) and water (2 × 25 mL) and then the organic layer was dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by column chromatography with light petroleum ether/AcOEt (1:1) as eluent.

(2*R*,5*S*)-1-(2-Aminobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)imidazolidin-4-one (11a): Yield 96%; yellow oil. $[a]_D^{25}$ = +25.3 (*c* = 0.22, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1648, 1698, 3488 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.66 (d, *J* = 6.9 Hz, 3 H), 2.96 (s, 3 H), 4.13 (br. s, 2 H), 4.30 (q, *J* = 6.9 Hz, 1 H), 5.36 (s, 2 H), 5.87 (s, 1 H), 6.70–6.75 (m, 2 H), 7.00–7.35 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.3 (q), 27.5 (q), 55.9 (d), 79.5 (d), 117.1 (d), 118.2 (d), 119.2 (s), 121.3 (s), 121.8 (t), 127.2 (d), 127.6 (d), 128.8 (d), 128.9 (d), 131.4 (d), 137.8 (s), 144.7 (s), 144.9 (s), 171.1 (s) ppm. MS: *m*/*z* = 335 $[M]^+$. $C_{20}H_{21}N_3O_2$ (335.40): calcd. C 71.62, H 6.31, N 12.53; found C 71.45, H 6.52, N 12.33.

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)imidazolidin-4-one (11aa): Yield 96%; yellow crystals; m.p. 106 °C (*i*Pr_2O). $[a]_D^{25}$ = +21.4 (*c* = 24.1, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1636, 1694, 3448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.55 (d, *J* = 6.6 Hz, 3 H), 2.80 (s, 3 H), 4.15 (q, *J* = 6.6 Hz, 1 H), 4.26 (br. s, 2 H), 5.16 (s, 1 H), 5.20 (s, 1 H), 5.68 (s, 1 H), 6.51–6.54 (m, 1 H), 6.90–6.97 (m, 4 H), 7.13–7.21 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 16.6 (q), 26.9 (q), 55.2 (d), 79.0 (d), 117.4 (d), 121.4 (t), 121.5 (s), 121.6 (s), 126.5 (d), 128.0 (d), 128.3 (d), 128.4 (d), 130.6 (d), 137.1 (s), 143.1 (s), 144.2 (s), 170.0 (s), 170.3 (s) ppm. MS: *m*/*z* = 369 $[M]^+$. $C_{20}H_{20}ClN_3O_2$ (369.84): calcd. C 64.95, H 5.45, N 11.36; found C 64.87, H 5.61, N 11.27.

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-3,5-dimethyl-2-(1-phenylvinyl)imidazolidin-4-one (11ab): Yield 87%; colorless oil. $[a]_D^{25}$ = +9.9 (*c* = 2.43, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1654, 1702, 3450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.67 (d, *J* = 7.0 Hz, 3 H), 2.96 (s, 3 H), 3.87 (br. s, 2 H), 4.12 (q, *J* = 7.0 Hz, 1 H), 5.37 (s, 2 H), 5.82 (s, 1 H), 6.61–7.35 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.2 (q), 27.4 (q), 55.7 (d), 79.4 (d), 113.8 (dd, $^2J_{C-F}$ = 23.7 Hz), 118.1 (dd, $^2J_{C-F}$ = 22.1 Hz), 118.3 (dd, $^3J_{C-F}$ = 7.2 Hz), 121.9 (t), 122.0 (d, $^3J_{C-F}$ = 6.6 Hz), 128.6 (d), 128.8 (d), 129.0 (d), 137.5 (s), 140.7 (s), 144.8 (s), 155.5 (d, $^1J_{C-F}$ = 238.3 Hz), 168.4 (s), 170.8 (s) ppm. MS: *m*/*z* = 353 $[M]^+$. $C_{20}H_{20}FN_3O_2$ (353.39): calcd. C 67.97, H 5.70, N 11.89; found C 67.86, H 5.82, N 11.74.

(2*R*,5*S*)-1-(2-Aminobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (11b): Yield 95%; colorless oil. $[a]_D^{25}$ = +56.1 (*c* = 0.38, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1640, 1690, 3492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.75 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.26–1.29 (qqd, *J* = 6.5, 6.8, 9.1 Hz, 1 H), 2.81 (s, 3 H), 4.15 (br. s, 2 H), 4.35 (d, *J* = 9.1 Hz, 1 H), 5.24 (s, 1 H), 5.36 (s, 1 H), 5.64 (s, 1 H), 6.70–6.75 (m, 2 H), 7.13–7.34 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.3 (q), 20.6 (q), 28.0 (d), 32.6 (q), 63.6 (d), 79.5 (d), 117.1 (d), 117.7 (d), 120.7 (s), 121.2 (t), 128.2 (d), 128.4 (d), 128.7 (d), 128.8 (d), 131.7 (d), 138.3 (s), 145.4 (s), 145.8 (s), 170.6 (s), 172.5 (s) ppm. MS: *m*/*z* = 363 $[M]^+$. $C_{22}H_{25}N_3O_2$ (363.45): calcd. C 72.70, H 6.93, N 11.56; found C 72.58, H 7.02, N 11.78.

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (11ba): Yield 84%; colorless oil. $[a]_D^{25}$ = +63.7 (*c* = 12.0, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1654, 1706, 3466 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.67 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 6.3 Hz, 3 H), 1.23–1.25 (m, 1 H), 2.78 (s, 3 H), 4.30 (br. s, 2 H), 4.32–4.36 (m, 1 H), 5.15 (s, 1 H), 5.36 (s, 1 H), 5.51 (s, 1 H), 6.63–6.65 (m, 1 H), 7.11–7.31 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.0 (q), 20.0 (q), 27.5 (d), 32.1 (q), 62.9 (d), 79.5 (d), 117.8 (d), 120.9 (s), 121.5 (t), 121.9 (s), 127.9 (d), 128.0 (d), 128.4 (d), 128.5 (d), 131.0 (d), 137.4 (s), 143.7 (s), 145.0 (s), 170.0 (s), 171.0 (s) ppm. MS: *m*/*z* = 397 $[M]^+$. $C_{22}H_{24}ClN_3O_2$ (397.90): calcd. C 66.41, H 6.08, N 10.56; found C 66.53, H 6.01, N 10.44.

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-5-isopropyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (11bb): Yield 93%; white crystals; m.p. 44 °C (*i*Pr_2O). $[a]_D^{25}$ = +26.7 (*c* = 21.8, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1640, 1696, 3438 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.73 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.32 (qqd, *J* = 6.5, 6.8, 9.0 Hz, 1 H), 2.83 (s, 3 H), 3.47 (br. s, 2 H), 4.29 (d, *J* = 9.0 Hz, 1 H), 5.20 (s, 1 H), 5.36 (s, 1 H), 5.60 (s, 1 H), 6.65–7.35 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.8 (q), 20.1 (q), 27.5 (d), 32.1 (q), 63.1 (d), 78.9 (d), 114.3 (dd, $^2J_{C-F}$ = 23.8 Hz), 117.7 (dd, $^3J_{C-F}$ = 8.1 Hz), 117.8 (dd, $^2J_{C-F}$ = 20.2 Hz), 120.9 (t), 121.2 (d, $^3J_{C-F}$ = 6.1 Hz), 127.9 (d), 128.3 (d), 128.4 (d), 137.6 (s), 140.8 (s), 145.2 (s), 154.8 (d, $^1J_{C-F}$ = 236.3 Hz), 169.9 (s), 170.6 (s) ppm. MS: *m*/*z* = 381 $[M]^+$. $C_{22}H_{24}FN_3O_2$ (381.44): calcd. C 69.27, H 6.34, N 11.02; found C 69.41, H 6.12, N 11.29.

(2*R*,5*S*)-1-(2-Aminobenzoyl)-5-benzyl-3-methyl-2-(1-phenylvinyl)-imidazolidin-4-one (11c): Yield 97%; yellow crystals; m.p. 130 °C (*i*Pr_2O). $[a]_D^{25}$ = +130.0 (*c* = 0.28, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1642, 1696, 3472 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.87–1.94 (m, 1 H), 2.37–2.43 (m, 1 H), 2.93 (s, 3 H), 4.01 (br. s, 2 H), 4.50–4.54 (m, 1 H), 5.19 (s, 1 H), 5.46 (s, 1 H), 5.80 (s, 1 H), 6.71–7.40 (m, 14 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.5 (q), 38.7 (t), 60.5 (d), 79.0 (d), 117.2 (d), 118.3 (d), 121.1 (s), 121.7 (t), 126.8 (d), 127.4 (d), 128.5 (d), 128.8 (d, overlapped), 128.9 (d),

129.8 (d), 131.5 (d), 137.4 (s), 138.0 (s), 144.8 (s), 145.0 (s), 169.9 (s), 170.2 (s) ppm. MS: *m*/*z* = 411 $[M]^+$. $C_{26}H_{25}N_3O_2$ (411.50): calcd. C 75.89, H 6.12, N 10.21; found C 76.02, H 5.97, N 10.40.

(2*R*,5*S*)-1-(2-Amino-5-chlorobenzoyl)-5-benzyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (11ca): Yield 79%; yellow oil. $[\alpha]_D^{25}$ = +13.7 (*c* = 8.47, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1650, 1696, 3480 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.03–2.36 (m, 2 H), 2.93 (s, 3 H), 4.15 (br. s, 2 H), 4.56–4.60 (m, 1 H), 5.12 (s, 1 H), 5.36 (s, 1 H), 5.70 (s, 1 H), 6.58–7.41 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.1 (q), 38.2 (t), 60.0 (d), 78.9 (d), 113.4 (d), 118.0 (d), 121.4 (s), 121.7 (t), 122.4 (s), 126.6 (d), 127.1 (d), 128.2 (d), 128.4 (d), 128.6 (d), 129.3 (d), 129.4 (d), 130.9 (d), 131.3 (d), 136.9 (s), 137.3 (s), 143.2 (s), 144.4 (s), 168.7 (s), 169.3 (s) ppm. MS: *m*/*z* = 445 $[M]^+$. $C_{26}H_{24}ClN_3O_2$ (445.94): calcd. C 70.03, H 5.42, N 9.42; found C 70.18, H 5.31, N 9.38.

(2*R*,5*S*)-1-(2-Amino-5-fluorobenzoyl)-5-benzyl-3-methyl-2-(1-phenylvinyl)imidazolidin-4-one (11cb): Yield 60%; white crystals; m.p. 142 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +4.7 (*c* = 5.07, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1662, 1708, 3490 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.03–2.36 (m, 2 H), 2.93 (s, 3 H), 4.15 (br. s, 2 H), 4.56–4.60 (m, 1 H), 5.12 (s, 1 H), 5.36 (s, 1 H), 5.70 (s, 1 H), 6.58–7.41 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.1 (q), 38.2 (t), 60.0 (d), 78.6 (d), 113.7 (dd, $^2J_{C-F}$ = 23.7 Hz), 117.9 (dd, $^2J_{C-F}$ = 22.6 Hz), 118.1 (dd, $^3J_{C-F}$ = 7.4 Hz), 121.5 (t), 121.2 (d, $^3J_{C-F}$ = 6.1 Hz), 126.6 (d), 128.2 (d), 128.4 (d), 128.6 (d, overlapped), 129.4 (d), 137.6 (s), 137.4 (s), 140.4 (s), 144.4 (s), 155.2 (d, $^1J_{C-F}$ = 236.8 Hz), 168.6 (s), 169.4 (s) ppm. MS: *m*/*z* = 429 $[M]^+$. $C_{26}H_{24}FN_3O_2$ (429.49): calcd. C 72.71, H 5.63, N 9.78; found C 72.60, H 5.81, N 9.61.

General Procedure for the Synthesis of Compounds 12: $NaNO_2$ (0.156 g, 2.26 mmol) was added portionwise to a solution of **11** (1.13 mmol) in MeOH (2 mL) and 6 M HCl (0.65 mL) cooled to 0 °C. After 30 min AcONa was added until pH 5 and then a solution of ethyl 2-chloroacetoacetate (1.13 mmol, 0.122 mL) in MeOH (1 mL) was added dropwise under vigorous stirring at room temperature. After 24 h the solvent was evaporated under reduced pressure and the residue extracted with Et_2O (2 × 15 mL). The organic layer was washed with aq. $NaHCO_3$ (15 mL) and water (30 mL) and then dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by silica gel column chromatography with light petroleum ether/AcOEt (1:1) as eluent.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{2-[3,5-dimethyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)acetate (12a): Yield 57%; pale-yellow crystals; m.p. 65 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +2.1 (*c* = 0.15, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1650, 1703, 1716, 3338 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.62 (d, *J* = 6.6 Hz, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H), 2.98 (s, 3 H), 4.35 (q, *J* = 6.6 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 5.38 (s, 1 H), 5.40 (s, 1 H), 5.91 (s, 1 H), 7.00–7.61 (m, 9 H), 9.40 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 17.1 (q), 27.5 (q), 56.2 (d), 63.3 (t), 79.9 (d), 116.7 (d), 118.5 (s), 121.0 (s), 122.1 (t), 122.4 (d), 127.3 (d), 128.8 (d), 128.9 (d), 132.1 (d), 132.2 (d), 137.4 (s), 140.3 (s), 144.7 (s), 159.2 (s), 168.5 (s), 170.7 (s) ppm. MS: *m*/*z* = 468 $[M]^+$. $C_{24}H_{25}ClN_4O_4$ (468.93): calcd. C 61.47, H 5.37, N 11.95; found C 61.34, H 5.48, N 11.77.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{4-chloro-2-[3,5-dimethyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)acetate (12aa): Yield 62%; pale-yellow crystals; m.p. 174 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +2.4 (*c* = 17.8, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1646, 1694, 1728, 3392 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.66 (d, *J* = 6.5 Hz, 3 H), 1.37 (t, *J* = 6.9 Hz, 3 H), 2.94 (s, 3 H), 4.31–4.37 (m, 3 H), 5.37 (s, 2 H), 5.83 (s, 1 H), 7.04–7.47 (m, 8 H), 9.33 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 16.7 (q), 27.0 (q), 55.6 (d), 63.0 (t), 79.6 (d), 117.8 (d), 118.6 (s), 121.7 (s), 121.8 (s), 121.9 (t), 127.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 131.4 (d), 136.8 (s), 138.4 (s), 144.1 (s), 159.1 (s), 167.0 (s), 170.1 (s) ppm. MS: *m*/*z* = 502 $[M]^+$. $C_{24}H_{24}Cl_2N_4O_4$ (503.38): calcd. C 57.26, H 4.81, N 11.13; found C 57.40, H 4.62, N 11.21.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{2-[3,5-dimethyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]-4-fluorophenyl}hydrazono)acetate (12ab): Yield 49%; yellow crystals; m.p. 125 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = –0.35 (*c* = 10.3, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1642, 1708, 1732, 3412 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.64 (d, *J* = 6.3 Hz, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 2.96 (s, 3 H), 4.30 (q, *J* = 6.3 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 5.38 (s, 2 H), 5.86 (s, 1 H), 6.95–7.51 (m, 8 H), 9.22 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 16.7 (q), 27.0 (q), 55.7 (d), 62.9 (t), 79.4 (d), 113.8 (dd, $^2J_{C-F}$ = 24.3 Hz), 118.0 (s), 118.2 (dd, $^3J_{C-F}$ = 7.5 Hz), 118.5 (dd, $^2J_{C-F}$ = 22.4 Hz), 121.8 (t), 128.3 (d), 128.5 (d), 128.6 (d), 136.1 (s), 136.8 (s), 140.6 (s), 144.1 (s), 157.5 (d, $^1J_{C-F}$ = 242.8 Hz), 159.2 (s), 166.8 (s), 170.1 (s) ppm. MS: *m*/*z* = 486 $[M]^+$. $C_{24}H_{24}ClFN_4O_4$ (486.92): calcd. C 59.20, H 4.97, N 11.51; found C 59.08, H 5.12, N 11.31.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{2-[5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)acetate (12b): Yield 51%; cream crystals; m.p. 69 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +45.6 (*c* = 0.4, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1656, 1688, 1724, 3436 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.72 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.17–1.21 (m, 1 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 2.83 (s, 3 H), 4.39–4.45 (m, 3 H), 5.32 (s, 1 H), 5.42 (s, 1 H), 5.68 (s, 1 H), 7.01 (dd, *J* = 7.4, 7.5 Hz, 1 H), 7.10–7.13 (m, 2 H), 7.27–7.36 (m, 3 H), 7.40 (d, *J* = 7.5 Hz, 1 H), 7.45 (dd, *J* = 7.4, 8.2 Hz, 1 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 9.51 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 19.3 (q), 20.5 (q), 28.0 (d), 32.6 (q), 63.3 (t), 63.8 (d), 79.7 (d), 116.7 (d), 118.9 (s), 120.6 (s), 121.4 (t), 122.0 (d), 128.2 (d), 128.3 (d), 128.9 (d), 129.0 (d), 132.4 (d), 138.1 (s), 140.8 (s), 145.8 (s), 159.9 (s), 170.3 (s), 171.2 (s) ppm. MS: *m*/*z* = 496 $[M]^+$. $C_{26}H_{29}ClN_4O_4$ (496.99): calcd. C 62.83, H 5.88, N 11.27; found C 62.71, H 5.96, N 11.10.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{4-chloro-2-[5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)-acetate (12ba): Yield 82%; pale-yellow oil. $[\alpha]_D^{25}$ = –0.81 (*c* = 6.20, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1634, 1686, 1716, 3424 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.62 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 1.00–1.09 (m, 1 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 2.77 (s, 3 H), 4.27–4.35 (m, 3 H), 5.18 (s, 1 H), 5.36 (s, 1 H), 5.53 (s, 1 H), 7.05–7.48 (m, 8 H), 9.49 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1 (q), 18.9 (q), 19.9 (q), 27.4 (d), 32.0 (q), 62.9 (t), 63.0 (d), 79.6 (d), 117.7 (d), 118.8 (s), 121.2 (s), 121.7 (t), 126.7 (s), 127.8 (d), 127.9 (d), 128.3 (d), 128.5 (d), 131.6 (d), 137.2 (s), 138.9 (s), 145.0 (s), 159.2 (s), 169.8 (s), 169.9 (s) ppm. MS: *m*/*z* = 530 $[M]^+$. $C_{26}H_{28}Cl_2N_4O_4$ (531.43): calcd. C 58.76, H 5.31, N 10.54; found C 58.54, H 5.44, N 10.43.

Ethyl (2*R*,5*S*)-2-Chloro-2-(2-{4-fluoro-2-[5-isopropyl-3-methyl-4-oxo-2-(1-phenylvinyl)imidazolidin-1-ylcarbonyl]phenyl}hydrazono)-acetate (12bb): Yield 57%; colorless oil. $[\alpha]_D^{25}$ = +16.4 (*c* = 5.00, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1638, 1710, 1722, 3384 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.70 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.18–1.23 (m, 1 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 2.83 (s, 3 H), 4.33–4.41 (m, 3 H), 5.29 (s, 1 H), 5.42 (s, 1 H), 5.64 (s, 1 H), 7.08–7.17 (m, 4 H), 7.27–7.33 (m, 3 H), 7.53–7.57 (m, 1 H), 9.30 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 18.9 (q), 20.3 (q), 27.5 (d), 32.1 (q), 62.9 (t), 63.3 (d), 79.2 (d), 114.7 (dd, $^2J_{C-F}$ = 24.4 Hz), 118.1 (dd, $^3J_{C-F}$ = 7.4 Hz), 118.5

(s), 118.8 (dd, $^2J_{C-F}$ = 22.3 Hz), 121.3 (t), 127.8 (d), 128.6 (d), 128.9 (d), 136.6 (s), 137.3 (s), 140.0 (s), 145.2 (s), 157.2 (d, $^1J_{C-F}$ = 242.7 Hz), 159.3 (s), 169.5 (s), 169.7 (s) ppm. MS: *m*/*z* = 514 $[M]^+$. $C_{26}H_{28}ClFN_4O_4$ (514.98): calcd. C 60.64, H 5.48, N 10.88; found C 60.88, H 5.23, N 10.65.

Ethyl (2*R*,5*S*)-2-(2-{2-[5-Benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]phenyl}hydrazono)-2-chloroacetate (12c): Yield 44%; yellow oil. $[\alpha]_D^{25}$ = –33.8 (*c* = 0.21, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1646, 1692, 1720, 3404 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.42 (t, *J* = 7.1 Hz, 3 H), 2.01–2.05 (m, 1 H), 2.08–2.13 (m, 1 H), 2.98 (s, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 4.60 (t, *J* = 4.7 Hz, 1 H), 5.23 (s, 1 H), 5.37 (s, 1 H), 5.83 (s, 1 H), 6.75–7.56 (m, 14 H), 9.31 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 27.5 (q), 38.7 (t), 60.9 (d), 63.3 (t), 79.4 (d), 116.8 (d), 118.5 (s), 120.9 (s), 122.0 (t), 122.4 (d), 126.5 (d), 126.9 (d), 127.5 (d), 128.6 (d), 128.8 (d), 129.3 (d), 129.7 (d), 132.1 (d), 136.8 (s), 137.8 (s), 140.3 (s), 144.8 (s), 159.8 (s), 168.9 (s), 169.6 (s) ppm. MS: *m*/*z* = 544 $[M]^+$. $C_{30}H_{29}ClN_4O_4$ (545.03): calcd. C 66.11, H 5.36, N 10.28; found C 65.98, H 5.54, N 10.12.

Ethyl (2*R*,5*S*)-2-(2-{2-[5-Benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]-4-chlorophenyl}hydrazono)-2-chloroacetate (12ca): Yield 43%; yellow oil. $[\alpha]_D^{25}$ = +0.022 (*c* = 4.49, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1650, 1702, 1726, 3456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, *J* = 7.1 Hz, 3 H), 2.22–2.26 (m, 2 H), 2.98 (s, 3 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 4.65 (t, *J* = 6.4 Hz, 1 H), 5.19 (s, 1 H), 5.40 (s, 1 H), 5.79 (s, 1 H), 6.77–6.80 (m, 2 H), 7.10–7.43 (m, 11 H), 9.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 27.1 (q), 38.3 (t), 60.3 (d), 63.0 (t), 79.3 (d), 117.8 (d), 118.7 (s), 121.3 (s), 122.0 (t), 126.6 (d), 127.0 (s), 127.1 (d), 128.3 (d), 128.7 (d), 128.8 (d, overlapped), 129.1 (d), 130.2 (d), 131.5 (d), 136.3 (s), 137.3 (s), 138.6 (s), 144.2 (s), 159.2 (s), 167.4 (s), 169.0 (s) ppm. MS: *m*/*z* = 578 $[M]^+$. $C_{30}H_{28}Cl_2N_4O_4$ (579.47): calcd. C 62.18, H 4.87, N 9.67; found C 61.95, H 5.04, N 9.87.

Ethyl (2*R*,5*S*)-2-(2-{2-[5-Benzyl-3-methyl-4-oxo-2-(1-phenylvinyl)-imidazolidin-1-ylcarbonyl]-4-fluorophenyl}hydrazono)-2-chloroacetate (12cb): Yield 47%; yellow crystals; m.p. 105 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = –0.13 (*c* = 4.43, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1647, 1704, 1728, 3462 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (t, *J* = 7.1 Hz, 3 H), 2.17–2.25 (m, 2 H), 2.96 (s, 3 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.60 (t, *J* = 6.4 Hz, 1 H), 5.17 (s, 1 H), 5.37 (s, 1 H), 5.83 (s, 1 H), 6.78–7.44 (m, 13 H), 9.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 27.1 (q), 38.3 (t), 60.4 (d), 63.0 (t), 79.0 (d), 114.1 (dd, $^2J_{C-F}$ = 24.3 Hz), 118.0 (s), 118.3 (dd, $^3J_{C-F}$ = 7.5 Hz), 118.5 (dd, $^2J_{C-F}$ = 22.4 Hz), 121.5 (s), 121.8 (t), 126.6 (d), 128.2 (d), 128.3 (d, overlapped), 128.6 (d), 129.2 (d), 136.1 (s), 136.3 (s), 137.3 (s), 144.2 (s), 157.4 (d, $^1J_{C-F}$ = 243.0 Hz), 159.3 (s), 167.3 (s), 169.1 (s) ppm. MS: *m*/*z* = 562 $[M]^+$. $C_{30}H_{28}ClFN_4O_4$ (563.02): calcd. C 64.00, H 5.01, N 9.95; found C 63.81, H 5.13, N 10.07.

General Procedure for the Synthesis of Compounds 14: A solution of **12** (0.2 mmol) in toluene (9 mL) was treated with TEA (0.11 mL, 0.8 mmol) and heated at reflux for 24 h. The organic layer was washed with aq. $NaHCO_3$ (10 mL) and water (20 mL) and then it was dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the products purified by silica gel column chromatography with light petroleum ether/AcOEt (1:1) as eluent.

Ethyl (3a*S*,3b*R*,6*S*)-4,6-Dimethyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*][1,4]diazepine-2-carboxylate (14a): Yield 55%; yellow crystals; m.p. 90 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +667.0 (*c* = 0.20, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1652, 1705, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.32 (d, *J* = 6.8 Hz, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 3.25 (s, 3 H), 3.60 (d, *J* = 16.1 Hz, 1 H), 3.82 (d, *J* = 16.1 Hz, 1 H), 4.25 (q, *J* = 6.8 Hz, 1 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 5.57 (s, 1 H), 7.13 (dd, *J* = 7.4, 8.0 Hz, 1 H), 7.18–7.21 (m, 2 H), 7.36–7.38 (m, 3 H), 7.52 (ddd, *J* = 1.6, 7.4, 8.7 Hz, 1 H), 7.84 (d, *J* = 8.7 Hz, 1 H), 8.11 (dd, *J* = 1.6, 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 14.6 (q), 30.5 (q), 44.7 (t), 55.9 (d), 62.4 (t), 77.4 (d), 81.7 (s), 116.8 (s), 118.1 (d), 122.4 (d), 126.5 (d), 129.5 (d), 129.9 (d), 133.3 (d), 134.0 (d), 137.9 (s), 141.5 (s), 143.4 (s), 162.1 (s), 164.5 (s), 172.4 (s) ppm. MS: *m*/*z* = 432 $[M]^+$. $C_{24}H_{24}N_4O_4$ (432.47): calcd. C 66.65, H 5.59, N 12.96; found C 66.41, H 5.70, N 12.82.

Ethyl (3a*S*,3b*R*,6*S*)-10-Chloro-4,6-dimethyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (14aa): Yield 62%; yellow crystals; m.p. 143 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +89.7 (*c* = 2.31, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1647, 1704, 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.32 (d, *J* = 6.7 Hz, 3 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 3.21 (s, 3 H), 3.57 (d, *J* = 16.1 Hz, 1 H), 3.82 (d, *J* = 16.1 Hz, 1 H), 4.17 (q, *J* = 6.7 Hz, 1 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 5.53 (s, 1 H), 7.11–7.40 (m, 6 H), 7.76–7.79 (m, 1 H), 8.04 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.7 (q), 14.2 (q), 30.1 (q), 44.4 (t), 55.5 (d), 62.1 (t), 76.7 (d), 81.1 (s), 117.2 (s), 119.3 (d), 126.6 (d), 127.2 (s), 129.1 (d), 129.6 (d), 132.1 (d), 133.4 (d), 137.2 (s), 139.7 (s), 143.5 (s), 161.4 (s), 162.7 (s), 171.8 (s) ppm. MS: *m*/*z* = 466 $[M]^+$. $C_{24}H_{23}ClN_4O_4$ (466.92): calcd. C 61.74, H 4.97, N 12.00; found C 61.48, H 5.23, N 12.27.

Ethyl (3a*S*,3b*R*,6*S*)-10-Fluoro-4,6-dimethyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (14ab): Yield 71%; white crystals; m.p. 145 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +912.1 (*c* = 3.23, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1655, 1690, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.29 (d, *J* = 6.7 Hz, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 3.24 (s, 3 H), 3.58 (d, *J* = 16.1 Hz, 1 H), 3.82 (d, *J* = 16.1 Hz, 1 H), 4.21 (q, *J* = 6.7 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 5.54 (s, 1 H), 7.15–7.40 (m, 6 H), 7.78–7.83 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.7 (q), 14.2 (q), 30.1 (q), 44.4 (t), 55.6 (d), 62.0 (t), 76.7 (d), 81.1 (s), 118.1 (s), 118.3 (dd, $^2J_{C-F}$ = 24.6 Hz), 119.7 (dd, $^3J_{C-F}$ = 6.7 Hz), 121.1 (dd, $^2J_{C-F}$ = 22.7 Hz), 126.7 (d), 129.2 (d), 129.6 (d), 137.4 (s), 137.5 (s), 142.9 (s), 157.8 (d, $^1J_{C-F}$ = 240.7 Hz), 161.5 (s), 162.8 (s), 171.8 (s) ppm. MS: *m*/*z* = 450 $[M]^+$. $C_{24}H_{23}FN_4O_4$ (450.46): calcd. C 63.99, H 5.15, N 12.44; found C 64.08, H 5.02, N 12.31.

Ethyl (3a*S*,3b*R*,6*S*)-6-Isopropyl-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (14b): Yield 62%; yellow crystals; m.p. 138 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +975.0 (*c* = 0.38, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1644, 1702, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.16 (qqd, *J* = 6.6, 6.7, 9.8 Hz, 1 H), 0.45 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 3.20 (s, 3 H), 3.55 (d, *J* = 15.9 Hz, 1 H), 3.76 (d, *J* = 15.9 Hz, 1 H), 4.04 (d, *J* = 9.8 Hz, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 5.42 (s, 1 H), 7.12 (dd, *J* = 7.3, 8.1 Hz, 1 H), 7.26–7.37 (m, 5 H), 7.50 (ddd, *J* = 1.6, 7.3, 8.6 Hz, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 8.19 (dd, *J* = 1.6, 8.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 19.3 (q), 22.2 (q), 30.1 (d), 33.3 (q), 45.0 (t), 62.5 (t), 63.5 (d), 79.9 (d), 81.1 (s), 116.7 (s), 118.5 (d), 122.4 (d), 127.7 (d), 129.3 (d), 129.7 (d), 133.7 (d), 134.4 (d), 137.8 (s), 142.3 (s), 145.6 (s), 161.9 (s), 166.5 (s), 172.1 (s) ppm. MS: *m*/*z* = 460 $[M]^+$. $C_{26}H_{28}N_4O_4$ (460.52): calcd. C 67.81, H 6.13, N 12.17; found C 67.54, H 6.24, N 12.02.

Ethyl (3a*S*,3b*R*,6*S*)-10-Chloro-6-isopropyl-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (14ba): Yield 53%; yellow crystals; m.p. 135 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +818.0 (*c* = 3.94, $CHCl_3$). IR

(Nujol): $\tilde{\nu}$ = 1652, 1688, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.18 (qqd, J = 6.6, 6.5, 9.7 Hz, 1 H), 0.42 (d, J = 6.6 Hz, 3 H), 0.80 (d, J = 6.5 Hz, 3 H), 1.36 (t, J = 7.2 Hz, 3 H), 3.20 (s, 3 H), 3.56 (d, J = 16.1 Hz, 1 H), 3.76 (d, J = 16.1 Hz, 1 H), 4.03 (d, J = 9.7 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 5.42 (s, 1 H), 7.22–7.44 (m, 6 H), 7.79 (d, J = 9.1 Hz, 1 H), 8.18 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 18.9 (q), 21.7 (q), 29.8 (d), 32.9 (q), 44.7 (t), 62.2 (t), 63.2 (d), 76.5 (d), 80.6 (s), 117.1 (s), 119.7 (d), 127.1 (d), 127.4 (s), 129.0 (d), 129.4 (d), 132.6 (d), 133.8 (d), 137.1 (s), 140.4 (s), 145.3 (s), 161.4 (s), 164.8 (s), 171.5 (s) ppm. MS: m/z = 494 $[M]^+$. $C_{26}H_{27}ClN_4O_4$ (494.97): calcd. C 63.09, H 5.50, N 11.32; found C 63.27, H 5.29, N 11.44.

Ethyl (3a*S*,3b*R*,6*S*)-10-Fluoro-6-isopropyl-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (14bb): Yield 46%; yellow crystals; m.p. 144 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +207.4 (c = 2.23, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1644, 1701, 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.07 (d, J = 6.6 Hz, 3 H), 0.45 (qqd, J = 6.6, 6.5, 9.1 Hz, 1 H), 0.82 (d, J = 6.5 Hz, 3 H), 1.22 (t, J = 7.2 Hz, 3 H), 3.19 (s, 3 H), 3.53 (d, J = 16.0 Hz, 1 H), 3.75 (d, J = 16.0 Hz, 1 H), 4.02 (d, J = 9.1 Hz, 1 H), 4.31 (q, J = 7.2 Hz, 2 H), 5.32 (s, 1 H), 7.10–7.83 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 18.9 (q), 21.9 (q), 29.7 (d), 32.8 (q), 44.5 (t), 62.1 (t), 63.1 (d), 76.5 (d), 81.2 (s), 114.5 (d), 118.7 (d), 119.3 (dd, $^2J_{C\text{-}F}$ = 23.7 Hz), 120.0 (dd, $^3J_{C\text{-}F}$ = 7.5 Hz), 125.2 (dd, $^2J_{C\text{-}F}$ = 22.4 Hz), 127.2 (d), 127.3 (d), 137.5 (s), 137.8 (s), 143.2 (s), 156.9 (d, $^1J_{C\text{-}F}$ = 244.1 Hz), 160.8 (s), 163.0 (s), 170.6 (s) ppm. MS: m/z = 478 $[M]^+$. $C_{26}H_{27}FN_4O_4$ (478.52): calcd. C 65.26, H 5.69, N 11.71; found C 65.51, H 5.44, N 11.43.

Ethyl (3a*S*,3b*R*,6*S*)-6-Benzyl-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo[5,1-*c*]-[1,4]diazepine-2-carboxylate (14c): Yield 65%; yellow oil. $[\alpha]_D^{25}$ = +94.6 (c = 0.20, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1643, 1691, 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82–0.91 (m, 1 H), 1.39 (t, J = 7.1 Hz, 3 H), 2.34–2.38 (m, 1 H), 3.24 (s, 3 H), 3.64 (d, J = 16.1 Hz, 1 H), 3.84 (d, J = 16.1 Hz, 1 H), 4.29–4.38 (m, 3 H), 5.56 (s, 1 H), 7.15–8.16 (m, 14 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 28.7 (q), 35.0 (t), 44.7 (t), 60.6 (d), 60.8 (t), 76.8 (d), 81.7 (s), 116.8 (s), 118.2 (d), 122.5 (d), 126.8 (d), 127.5 (d), 128.5 (d), 129.6 (d), 129.8 (d), 130.2 (d), 133.3 (d), 134.1 (d), 137.9 (s), 138.3 (s), 141.6 (s), 143.7 (s), 162.0 (s), 164.5 (s), 171.2 (s) ppm. MS: m/z = 508 $[M]^+$. $C_{30}H_{28}N_4O_4$ (508.57): calcd. C 70.85, H 5.55, N 11.02; found C 70.69, H 5.67, N 11.13.

Ethyl (3a*S*,3b*R*,6*S*)-6-Benzyl-10-chloro-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (14ca): Yield 44%; yellow crystals; m.p. 141 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +914.0 (c = 1.89, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1641, 1708, 1722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.86–0.92 (m, 1 H), 1.37 (t, J = 7.2 Hz, 3 H), 2.18–2.26 (m, 1 H), 3.23 (s, 3 H), 3.64 (d, J = 16.1 Hz, 1 H), 3.83 (d, J = 16.1 Hz, 1 H), 4.33–4.41 (m, 3 H), 5.52 (s, 1 H), 7.13–8.13 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 30.3 (q), 34.6 (t), 44.5 (t), 60.3 (d), 62.2 (t), 76.3 (d), 81.1 (s), 117.2 (s), 119.4 (d), 126.5 (d), 126.9 (d), 127.7 (s), 128.2 (d), 129.2 (d), 129.3 (d), 129.9 (d), 132.2 (d), 133.6 (d), 137.2 (s), 137.8 (s), 139.7 (s), 143.6 (s), 161.4 (s), 162.7 (s), 170.7 (s) ppm. MS: m/z = 542 $[M]^+$. $C_{30}H_{27}ClN_4O_4$ (543.01): calcd. C 66.36, H 5.01, N 10.32; found C 66.12, H 5.14, N 10.55.

Ethyl (3a*S*,3b*R*,6*S*)-6-Benzyl-10-fluoro-4-methyl-5,8-dioxo-3a-phenyl-3,3a,3b,4,5,6-hexahydro-8*H*-benzo[*e*]imidazo[1,2-*a*]pyrazolo-[5,1-*c*][1,4]diazepine-2-carboxylate (14cb): Yield 77%; yellow crystals; m.p. 146 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +0.64 (c = 2.2, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1646, 1692, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82–0.88 (m, 1 H), 1.37 (t, J = 7.1 Hz, 3 H), 2.30–2.35 (m, 1 H), 3.23 (s, 3 H), 3.62 (d, J = 16.0 Hz, 1 H), 3.82 (d, J = 16.0 Hz, 1 H), 4.31–4.37 (m, 3 H), 5.53 (s, 1 H), 7.13–7.79 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (q), 29.9 (q), 34.6 (t), 44.2 (t), 60.3 (d), 62.0 (t), 76.4 (d), 81.2 (s), 114.0 (s), 119.7 (dd, $^2J_{C\text{-}F}$ = 23.2 Hz), 120.2 (dd, $^3J_{C\text{-}F}$ = 7.4 Hz), 125.6 (dd, $^2J_{C\text{-}F}$ = 21.8 Hz), 126.4 (d), 127.1 (s), 128.1 (d), 129.2 (d), 129.8 (d), 130.2 (d), 130.3 (d), 135.4 (s), 137.6 (s), 137.9 (s), 142.1 (s), 157.8 (d, $^1J_{C\text{-}F}$ = 245.6 Hz), 164.0 (s), 170.8 (s) ppm. MS: m/z = 526 $[M]^+$. $C_{30}H_{27}FN_4O_4$ (526.56): calcd. C 68.43, H 5.17, N 10.64; found C 68.20, H 5.34, N 10.88.

Acknowledgments

Ministero dell'Università e della Ricerca (MIUR) is acknowledged for financial support and for a Ph. D. fellowship to M. R. (Progetto Giovani 2006). We are also grateful to the Centro Interuniversitario sulle Reazioni Pericicliche.

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Received: November 10, 2009
Published Online: February 4, 2010

