ChemPubSoc Europe

DOI: 10.1002/ejoc.201700472

EurJOC European Journal of Organic Chemistry

Full Paper

Meldrum's Acid

A Meldrum's Acid Based Multicomponent Synthesis of *N*-Fmoc-isoxazolidin-5-ones: Entry to *N*-Fmoc-β-amino Acids

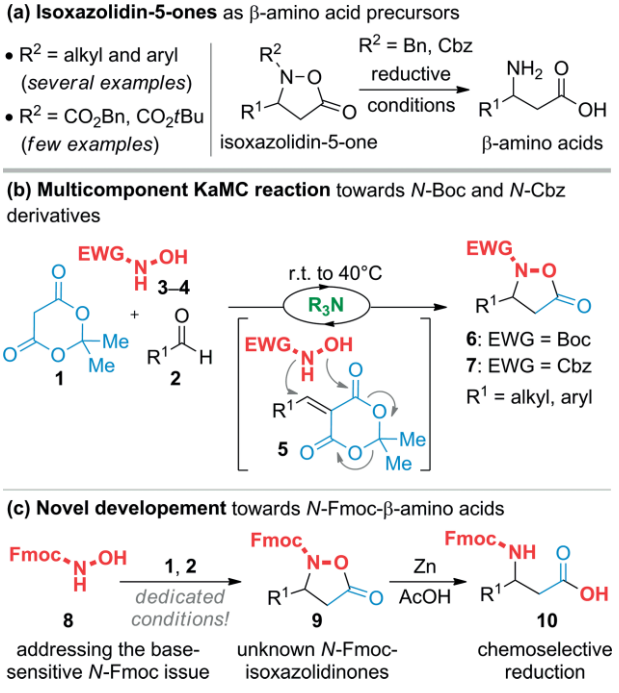
Alexandra Le Foll Devaux,[a][‡] Emmanuel Deau,[a][‡] Emilie Corrot,[a] Laurent Bischoff,[a] Vincent Levacher,[a] and Jean-François Brière*[a]

Abstract: A multicomponent Knoevenagel–aza-Michael cyclocondensation (KaMC) reaction starting from Meldrum's acid has been developed with base-sensitive *N*-Fmoc-hydroxylamine. The reaction takes place under very mild basic conditions, providing a straightforward synthetic route to various unprecedented *N*-Fmoc-isoxazolidin-5-ones. Subsequent chemoselective reductive cleavage of the N–O bond in the presence of Zn/AcOH allowed a short synthesis of the corresponding *N*-Fmoc-β-amino acids.

Introduction

The isoxazolidin-5-one structure is a motif that is present in biologically active compounds (Scheme 1a),[1] but it has also been used in building blocks for the synthesis of nucleoside mimics and aminosugar architectures.[2,3] Most importantly, this five-membered heterocycle has found significant application as a readily available precursor of β-amino acid derivatives, after the usually facile reductive cleavage of the N–O bond (Scheme 1a).[4,5] Thus, owing to the importance of the β-amino acid motif in naturally occurring molecules and β-peptides, and in modern peptidomimetic strategies in medicinal chemistry, the development of straightforward routes to new isoxazolidin-5-ones is an appealing goal.[6]

Most synthetic approaches to date have led to the formation of *N*-alkyl- (mainly benzyl-) or *N*-aryl-isoxazolidin-5-ones.[4,7] Only a handful of examples have described the construction of isoxazolidinones having an *N*-alkoxycarbonyl ($R^2 = CO_2R$) moiety such as *N*-Boc or *N*-Cbz, despite the great utility of these orthogonal protective functional groups.[4b,4d,8] Córdova, Bode, Takemoto, and others have carried out one- or two-step syntheses of *N*-Boc- (*tert*-butyloxycarbonyl-) or *N*-Cbz- (benzyloxycarbonyl-) -isoxazolidin-5-ones[4d,8] for subsequent transformation into β-amino acid derivatives. On the other hand, Rinehart achieved the multistep synthesis of an *N*-Boc-isoxazolidinone, which was then transformed into ADDA [(2*S*,3*S*,4*E*,6*E*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid], a β-amino acid structure found in numerous cyanobacterial toxins.[4b] In this context,[8b] we have recently described an unprecedented multicomponent reaction (MCR) for the synthesis of *N*-Boc- or *N*-Cbz-isoxazolidin-5-ones **6** and **7** from the corresponding hydroxylamines **3** and **4**, respectively (Scheme 1b).[9] This approach is based on a Knoevenagel–aza-Michael cyclocondensation (KaMC) sequence promoted by a catalytic amount of DABCO (1,4-diazabicyclo[2.2.2]octane) or a pyrrolidine as an organocatalyst. This MCR was successful with both aromatic and aliphatic aldehydes **2**, thanks to the transient formation of the highly electrophilic alkylidene Meldrum's acid intermediates **5**, which may be seen as acrylate equivalents.[10] Historically speaking, the aza-Michael addition reaction of hydroxylamines to less reactive native acrylates was limited to electron-rich *N*-alkyl derivatives (R^2-NHOH, R^2 = alkyl), which



Scheme 1. Multicomponent KaMC reaction: new objectives and challenges.

[a] *Normandie Université, INSA Rouen, Université de Rouen, CNRS, COBRA (UMR 6014), 76000 Rouen, France*
E-mail: jean-francois.briere@insa-rouen.fr
http://www.lab-cobra.fr/thematique/lorganocatalyse
[‡] These s contributed equally to this work.
Supporting information and ORCID(s) from the (s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201700472.

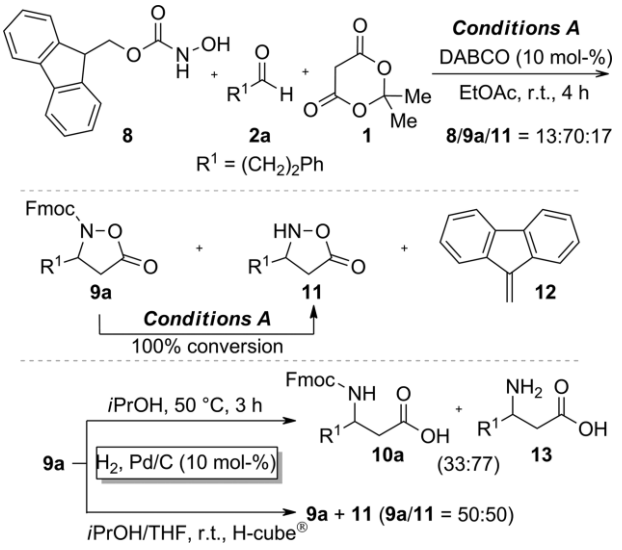
led to the formation of the corresponding *N*-alkylisoxazolidinones.[4a,11]

The products **6** and **7**, obtained by means of the multicomponent KaMC reaction, were eventually used for the diastereoselective synthesis of β-amino acid derivatives, pyrrolizidines, and a lactone.[9] At first glance, we hypothesized that this MCR would be easily extrapolated to *N*-(9-fluorenylmethyloxycarbonyl)- (*N*-Fmoc-) -hydroxylamine (**8**), which would open up a route to the corresponding *N*-Fmoc heterocycle **9**, an *N*-functionalized isoxazolidin-5-one that has not been reported before (Scheme 1c). Then, reductive cleavage of the N–O bond would open up a rapid route to highly valuable *N*-Fmoc-β-amino acids **10** with an orthogonal acid-stable protective group, which could be used in peptide synthesis.[12] However, *N*-Fmoc derivatives **8** and **9** proved to be tremendously labile to amine bases and also to standard reductive conditions for N–O bond cleavage; this required the development of dedicated reaction conditions. In this paper, we report an innovative development of the multicomponent KaMC reaction with *N*-Fmoc-hydroxylamine (**8**) for the synthesis of *N*-Fmoc-isoxazolidin-5-ones **9**. The reaction takes advantage of the unique acidity of Meldrum's acid (pK_a = 4.9 in water), which gives rise to the corresponding soft conjugated base.[10] Furthermore, this work highlights Zn/AcOH reagents, which allow remarkably chemoselective N–O bond-cleavage reactions. This approach was compatible with various functional groups, and this allowed the synthesis of a range of *N*-Fmoc-β-amino acid derivatives, especially those having the aliphatic side-chains found in the proteinogenic α-amino acids.

Results and Discussion

Using our previously developed conditions for the synthesis of *N*-Boc- and *N*-Cbz-isoxazolidinone derivatives **6** and **7**,[9] Meldrum's acid (**1**), dihydrocinnamaldehyde (**2a**), and *N*-Fmoc-hydroxylamine (**8**) were mixed in the presence of DABCO (10 mol-%) at room temperature (Scheme 2). Although aldehyde **2a** was rapidly consumed, a mixture of *N*-Fmoc-isoxazolidinone **9a** and the corresponding NH counterpart **11** was formed. The base-promoted *N*-Fmoc deprotection was shown by the presence of a dibenzofulvene side-product **12**, which could be identified in the ^{1}H NMR spectrum of the crude product.

When an isolated sample of *N*-Fmoc-isoxazolidine **9a** was subjected to the reaction conditions, complete deprotection to give product **11** took place within 4 h. Similarly, the *N*-Fmoc-hydroxylamine (**8**) underwent a loss of the Fmoc moiety to give the corresponding hydroxylamine (72 % conversion after 4 h). Thus, it was clear that these derivatives were incompatible even with a soft base such as DABCO. The reductive cleavage of the N–O bond of **9a** was also explored. Under standard conditions (H_2, Pd/C, 50 °C), the desired *N*-Fmoc-β-amino acid **10a** was obtained in addition to the deprotected β-amino acid **13** (Scheme 2). When milder conditions were used (H_2, Pd/C, room temp., continuous flow with H-Cube), the incomplete but exclusive formation of *NH*-isoxazolidin-5-one **11** (**9a**/**11**, 50:50) was



Scheme 2. Limitations of the base-catalysed conditions with *N*-Fmoc-hydroxylamine derivatives.

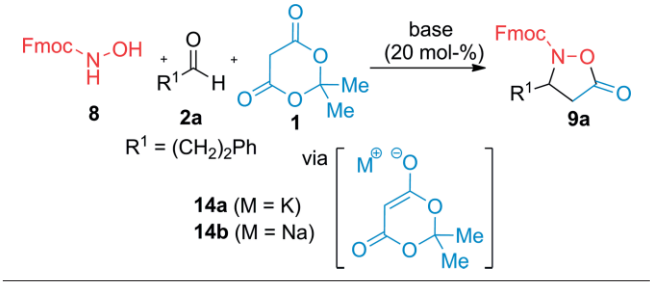
observed, already before the N–O-bond cleavage. The sensitivity of the *N*-Fmoc group to reductive conditions has been observed previously,[12a] but this turned out to be a major issue for isoxazolidinone **9a**.

Preliminary investigations using $Mo(CO)_6$ or SmI_2 in THF did not improve the outcome. In summary, the multicomponent KaMC reaction with *N*-Fmoc-hydroxylamine (**8**) was demonstrated, together with the subsequent reduction of the resulting isoxazolidinone **9a** into *N*-Fmoc-β-amino acid **10a**. Nevertheless, the facile removal of the *N*-Fmoc group from isoxazolidinone **9a** and precursor **8** under basic or reductive conditions precludes any further development without a complete reinvestigation.

On this basis, we turned our attention to the optimization of the KaMC sequence using a catalytic amount of a heterogeneous base, Cs_2CO_3 or K_2CO_3 (20 mol-%), hoping to minimize the *N*-Fmoc deprotection side reaction (Table 1). Pleasingly, by using these carbonate bases together with a stoichiometric amount of each component **1**, **2a**, and **8**, the formation of isoxazolidinone **9a**, derived from dihydrocinnamaldehyde (**2a**), was observed in good 72–74 % yields (by NMR spectroscopy) at room temperature (Table 1, Entries 1 and 2). The reaction proceeded with complete conversion of aldehyde **2a** in a relatively clean fashion as deduced from the NMR spectrum of the crude product. When the reaction temperature was raised to 40 °C, conditions previously required to broaden the scope of the multicomponent KaMC reaction with *N*-Boc-hydroxylamine **3**,[9] this led to decreased yields of 66 and 47 % with K_2CO_3 and Cs_2CO_3, respectively (Table 1, Entries 3 and 4). This is probably due to some decomposition events. In the presence of sodium *tert*-butoxide (20 mol-%), a good 73 % yield was also obtained after 4 h, although a temperature of 40 °C was required (Table 1, Entries 5–7). We reasoned that K_2CO_3 and *t*BuOK simply generated a significant amount of the potassium enolate of Meldrum's acid **14a**, which was required to trigger the subsequent domino process (Table 1, Entry 8). Accordingly, we carried out

the reaction with Meldrum's acid anions **14a** or **14b** (20 mol-%) at room temperature, and we observed the formation of isoxazolidinone **9a** in 72 and 73 % yields, respectively (Table 1, Entries 9 and 10); thus, changing between the potassium and sodium salts had minimal effect on the result. The same outcome was observed at 40 °C, despite the presence of *N*-Fmoc as a base-sensitive functional group (Table 1, Entry 11); this demonstrates the mildness of these conditions. In our hands, the addition of a quaternary ammonium salt as a phase-transfer catalyst did not result in any significant improvement (Table 1, Entry 11). Although the dihydrocinnamaldehyde (**2a**) and Meldrum's acid (**1**) were completely consumed, the crude NMR spectrum revealed the presence of small amounts of *N*-Fmoc-hydroxylamine (**8**). Consequently, a reaction was carried out using 1.3 equiv. of both aldehyde **2a** and Meldrum's acid (**1**), and this gave an improved 91 % yield determined by NMR spectroscopy; a similar outcome was not observed when Meldrum's acid (**1**; 1.3 equiv.) was used as the only component in excess (Table 1, Entry 12; 72 % yield by NMR spectroscopy). The MCR was then evaluated with other solvents, including THF, acetonitrile, and toluene, but slightly lower yields were obtained (Table 1, Entries 13–15). Thus, the multicomponent KaMC reaction allows the straightforward construction of *N*-Fmoc-isoxazolidinone **9a** simply in the presence of Meldrum's acid anion **14b** (20 mol-%), very mild reaction conditions indeed.

Table 1. Optimization of the multicomponent KaMC reaction with *N*-Fmoc-hydroxylamine.[a]

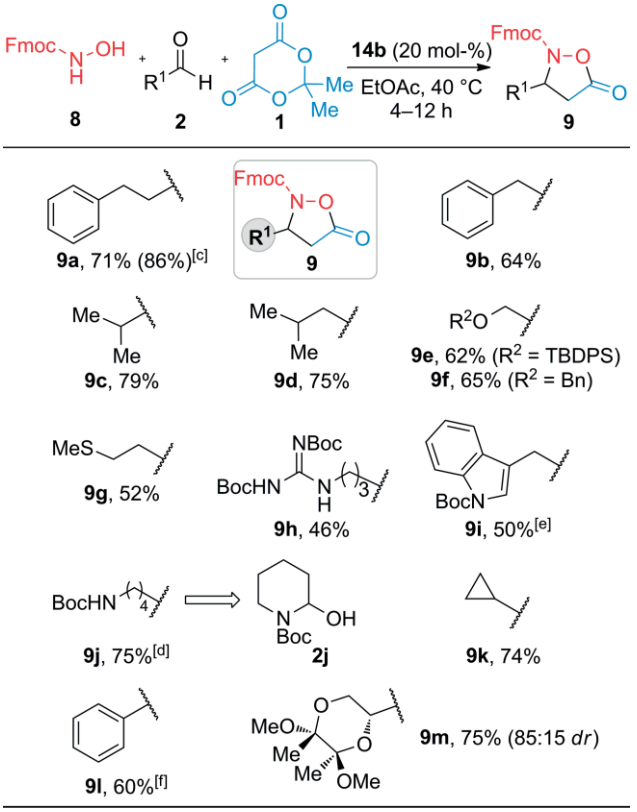


Entry	Base	Solvent	Temp.	Time [h]	Yield [%][b]
1	Cs_2CO_3	EtOAc	r.t.	4	72
2	K_2CO_3	EtOAc	r.t.	4	74
3	Cs_2CO_3	EtOAc	40 °C	4	47
4	K_2CO_3	EtOAc	40 °C	4	66
5	*t*BuOK	EtOAc	r.t.	4	51
6	*t*BuOK	EtOAc	r.t.	12	57
7	*t*BuOK	EtOAc	40 °C	4	73
8	–	EtOAc	r.t.	4	0
9	**14a**	EtOAc	r.t.	4	72
10	**14b**	EtOAc	r.t.	4	73 (71)[c]
11	**14b**	EtOAc	40 °C	4	73 (75)[d]
12	**14b**	EtOAc	40 °C	4	91[e] (72)[f]
13	**14b**	THF	40 °C	4	67
14	**14b**	MeCN	40 °C	4	71
15	**14b**	toluene	40 °C	4	69

[a] Reaction carried out at a concentration of 0.25 M on a 0.25 mmol scale with 1 equiv. of each component and 20 mol-% of base. [b] Yield by NMR spectroscopy, determined using an internal standard. [c] Isolated yield after silica gel column chromatography. [d] In the presence of nBu_4NBr (10 mol-%). [e] With 1.3 equiv. of Meldrum's acid (**1**) and aldehyde **2a**. [f] With 1.3 equiv. of Meldrum's acid (**1**).

Having established these convenient conditions, we went on to explore the scope and limitations of the multicomponent KaMC reaction with various aldehydes **2** together with Meldrum's acid (**1**) (Table 2). The model *N*-Fmoc substrate **9a** was formed from dihydrocinnamaldehyde (**2a**) in 71 % isolated yield after purification by silica gel column chromatography. By increasing the amount of **1** and **2a** from 1.0 to 1.3 equiv., the yield was improved to 86 %. We then focussed on the construction of *N*-Fmoc-isoxazolidinones **9** with side-chains found in the proteinogenic α-amino acids. Accordingly, products with alkyl chains **9b**–**9d** (for phenylalanine-, valine-, and leucine-like derivatives, 64–79 % yields), together with those having various functionalities such as ethers **9e** and **9f** (for serine-like compounds, 62–65 % yields), thioether **9g** (for a methionine-like compound, 52 % yield), a protected guanidine **9h** (for an arginine-like compound, 46 % yield), and an *N*-Boc-indole **9i** (for a tryptophan-like compound, 50 % yield) were smoothly synthesized in moderate to good yields (46–79 %). Interestingly, isoxazolidinone **9j**, an analogue of *N*-Boc-protected lysine, was easily obtained in 75 % yield from the corresponding piperidin-2-ol derivative **2j** as a convenient aldehyde surrogate. Com-

Table 2. Scope of the multicomponent KaMC reaction with *N*-Fmoc-hydroxylamine.[a,b]

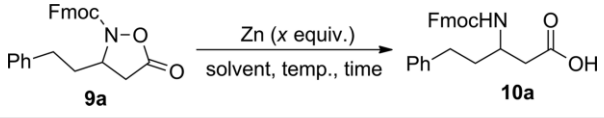


[a] Reaction carried out at a concentration of 0.25 M on a 0.5 mmol scale with 1 equiv. of each component **1**, **2**, and **8**, and 0.2 equiv. of the sodium salt of Meldrum's acid **14b** in EtOAc at 40 °C for 12–16 h. [b] Isolated yield with respect to hydroxylamine **5** after silica gel column chromatography. [c] Reaction carried out with 1.3 equiv. of aldehyde **2** and 1.3 equiv. of Meldrum's acid (**1**). [d] Reaction carried out with *tert*-butyl 2-hydroxypiperidine-1-carboxylate **2j** (1 equiv.). [e] Reaction carried out with 1.5 equiv. of aldehyde **2** and 1.5 equiv. of Meldrum's acid (**1**). [f] Reaction carried out for 4 h.

pound **9k**, with a cyclopropyl substituent, was formed in 74 % yield. Moreover, a congener bearing a phenyl moiety **9l** was also obtained in 60 % yield. Finally, a diastereoselective sequence was demonstrated starting from Ley's aldehyde **2m** that gave rise to the corresponding product **9m** in 75 % yield with a diastereoisomeric ratio of 85:15.

As mentioned above (Scheme 2), preliminary investigations revealed that the *N*-Fmoc protective group on the isoxazolidin-5-one ring **9** is markedly prone to elimination, even under mild palladium-catalysed hydrogenolysis conditions. Pleasingly, we found that zinc-promoted N–O bond cleavage occurred without affecting the *N*-Fmoc moiety of the new structure **9a** as a model substrate (Table 3). Optimization of the conditions established that THF is essential for the proper dissolution of the substrate in the reaction mixture, leading to complete reaction within 4 h (Table 3, Entries 1 and 2). Raising the amount of THF in the solvent mixture to 80 % led to complete conversion of substrate **9a** into the desired *N*-Fmoc-β-amino acid **10a** in 88 % yield by NMR spectroscopy (Table 3, Entry 3). In an attempt to optimize the amount of metal by decreasing the amount of zinc to 20 or 10 equiv. resulted in higher degradation rates and decreased yields of 68 and 75 %, respectively (Table 3, Entries 4 and 5). Consequently, the conditions given in Table 3, Entry 3 were used as the optimum conditions for the Zn-assisted reductive isoxazolidinone ring opening.

Table 3. Optimization of the Zn-promoted N–O bond cleavage.[a,b]



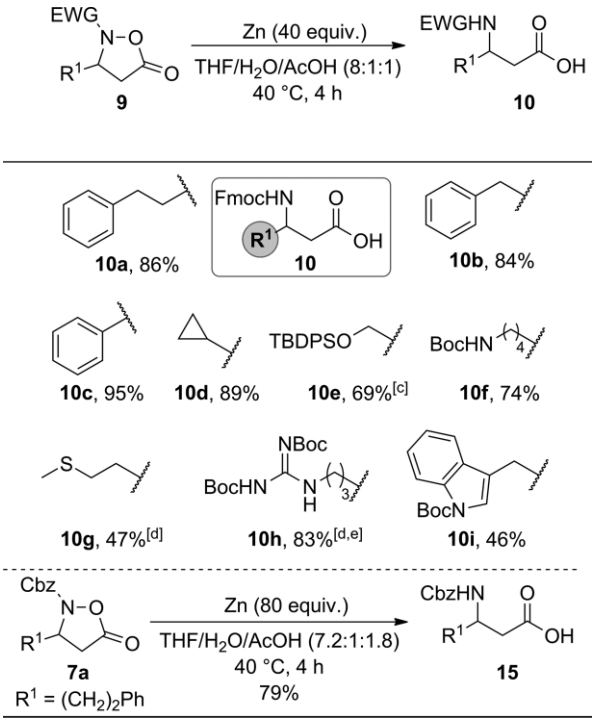
9a **10a**

Entry	Zn [equiv.]	Solvent	Temp. [°C]	Time [h]	Yield [%][b]
1	40	AcOH/H_2O (1:1)	40	4	49 (70)[c]
2	40	THF/AcOH/H_2O (1:2:2)	40	4	55 (92)[c]
3	40	THF/AcOH/H_2O (8:1:1)	40	4	88 (100)[c]
4	20	THF/AcOH/H_2O (8:1:1)	40	4	68 (97)[c]
5	10	THF/AcOH/H_2O (8:1:1)	40	4	75 (83)[c]

[a] Reaction carried out at a concentration of 0.05 M on a 0.2 mmol scale. [b] Yield by NMR spectroscopy, determined using an internal standard. [c] Conversion determined by NMR spectroscopy using an internal standard, based on remaining starting material.

Next, we explored a set of isoxazolidinone substrates **9** in order to probe the functional-group compatibility of this zinc-promoted transformation into β-amino acids **10** (Table 4). The products were isolated after workup and purification on silica gel, or a precipitation sequence, to give sufficiently pure compounds. First of all, β-amino acids **10a**–**10c**, bearing $(CH_2)_2Ph$, benzyl, and phenyl side-chains, were easily synthesized in high isolated yields ranging from 84 to 95 %. Compound **10d**, bearing a cyclopropyl moiety, was also formed in 89 % yield. In terms of functional-group tolerance, we were pleased to find that *O*-*tert*-butyldiphenylsilyl (TBDPS) precursor **9e** was compatible with the Zn/AcOH conditions, and gave the corresponding ring-opened product **10e** in 69 % yield. Importantly, *N*-Boc derivatives such as lysine homologue **10f** (74 % yield) and tryptophan homologue **10i** (46 % yield) were synthesized by this acidic protocol, albeit in lower yield in the latter case, probably due to precipitation issues.

Table 4. Scope of the Zn-promoted isoxazolidinone ring-opening reaction.[a,b]



[a] Reaction carried out at 0.05 M on a 0.4–0.5 mmol scale. [b] Isolated yield with regard to hydroxylamine **5** after workup and precipitation. [c] Required 4.5 h reaction time. [d] Isolated yield after purification by column chromatography on silica gel (*n*-pentane/EtOAc/AcOH, 1:1:0.1). [e] Required 80 equiv. of activated Zn in a THF/H_2O/AcOH (7.2:1:1.8) mixture at 40 °C for 4 h.

Pleasingly, *N*-Fmoc-β-homoarginine **10h** was conveniently synthesized in 83 % yield, with retention of both Boc protective groups; this demonstrates the mild conditions of the zinc-assisted ring-opening reaction. Under the same conditions, thioether **9g** underwent a smooth N–O bond cleavage to yield **10g**, as shown by ^1H NMR spectroscopic analysis of the crude product. Unfortunately, significant degradation (most likely sulfoxide formation, as determined by MS analysis) occurred before purification, and *N*-Fmoc-β-homomethionine **10g** was isolated in only a moderate 47 % yield. To our delight, this reductive protocol could be successfully applied to *N*-Cbz-isoxazolidinone **7a**, allowing the formation of the corresponding *N*-Cbz-β-amino acid **15** in 79 % yield (Table 4). Interestingly, this chemoselective approach nicely complements the usual palladium-promoted hydrogenolysis reaction, which would also cleave the *N*-Cbz functional group.

Conclusions

We have demonstrated that very mild and newly developed conditions allow a multicomponent Knoevenagel-aza-Michael cyclocondensation (KaMC) reaction between Meldrum's acid (**1**), aldehydes and *N*-Fmoc-hydroxylamine (**8**). This results in the straightforward construction of various *N*-Fmoc-isoxazolidin-5-ones **9**, heterocycles that were previously only known as their

N-Boc or *N*-Cbz derivatives. A chemoselective reductive N–O bond cleavage using Zn/AcOH provided a short route to the corresponding β^3-amino acids **10** and **15**; a wide range of nitrogen- or oxygen-containing functional groups were unaffected. This synthetic strategy involves a multicomponent approach, and is expected to be useful for the formation of valuable *N*-Fmoc-β^3-amino acid derivatives **10**. The development of enantioselective variants of this multicomponent process is currently under investigation.

Experimental Section

General Information: Reactions were carried out using oven-dried glassware under dry argon or nitrogen with freshly distilled or purified aldehydes. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers, and were used as received. THF, toluene, MeCN and CH_2Cl_2 were dried with an MBRAUN MB SPS-800 apparatus. EtOAc was freshly distilled from K_2CO_3. Reactions were monitored by thin-layer chromatography on silica gel 60 F254 precoated aluminium plates (0.25 mm). Visualization was carried out under UV light, or by oxidation with phosphomolybdic acid or $KMnO_4$. Chromatographic purification of compounds was carried out on silica gel 60 (40–63 μm).[13] Melting points were measured with a WME Kofler hot-stage (Stuart SMP3). Infrared spectra (IR) were recorded with a Perkin–Elmer Spectrum 100 Series FTIR spectrometer. Liquids and solids were applied onto the single-reflection attenuated total reflectance (ATR) accessories. Data are reported in cm^{-1}. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with a Bruker Avance 300 spectrometer. Processing and analysis of the spectra were carried out with the Topspin 3.5 software from Bruker using a PC workstation. Data are reported in the following order: chemical shifts in ppm, which were referenced to the internal solvent signal, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets, ddd, doublet of doublets of doublets, dt, doublet of triplets; ddt, doublet of doublets of triplets, td, triplet of doublets; tdd, triplet of doublets of doublets; m, multiplet, AB_q, AB system), coupling constant *J* in Hertz, and number of protons. Note: NMR spectroscopic data obtained in $CDCl_3$ are consistent with literature data, but compounds were also characterized in [D_6]DMSO in order to minimize the appearance of interconverting rotamers. Accurate mass measurements (HRMS) were carried out by the Mass Spectrometry Laboratory of the University of Rouen, and were recorded with a Waters LCP 1er XR spectrometer.

General Procedure (GP1) for the Synthesis of 14a and 14b: A freshly prepared solution of NaOEt or KOEt (2.02 mmol, 1.01 equiv.) in EtOH (8 mL) was added dropwise to a stirred solution of Meldrum's acid (288 mg, 2 mmol, 1 equiv.) in EtOH (8 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, then it was warmed to room temperature and stirred at room temperature for 1 h. The solution was then concentrated in vacuo. The solid residue was triturated with Et_2O, then collected by filtration through a Büchner funnel to give the desired compound in analytically pure form.

Potassium 2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-olate (14a): Prepared according to GP1 to give **14a** (270 mg, 74 %) as an orange solid. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.23 (br. s, 1 H), 1.43 (s, 6 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 165.9 (C_q), 99.6 (C_q), 62.3 (CH), 26.0 (CH_3) ppm.

Sodium 2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-olate (14b): Prepared according to GP1 to give **14b** (276 mg, 83 %) as a pale yellow solid. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.25 (s, 1 H), 1.43 (s, 6 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 166.1 (C_q), 99.9 (C_q), 62.5 (CH), 26.0 (CH_3) ppm.

General Procedure (GP2) for the Synthesis of *N*-Fmoc-isoxazolidinones 9a–9m: At room temperature, **14b** (16.6 mg, 100 μmol, 20 mol-%) was added in one portion to a stirred suspension of *N*-(9-fluorenylmethoxycarbonyloxy)hydroxylamine (**8**; 128 mg, 0.5 mmol, 1 equiv.), Meldrum's acid (72 mg, 0.5 mmol, 1 equiv.), and the appropriate aldehyde (1 equiv.) in freshly distilled EtOAc (2 mL). The mixture was heated at 40 °C (preheated oil bath) for the appropriate amount of time. The solution was warmed to room temperature, diluted with EtOAc, and washed with a saturated aqueous solution of sodium hydrogen carbonate. The aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel to give the desired isoxazolidinone.

(±)-(9*H*-Fluoren-9-yl)methyl 5-Oxo-3-phenethylisoxazolidine-2-carboxylate (9a): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9a** (147 mg, 71 %) as a colourless solid. M.p. 131–133 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.76 (app d, *J* = 7.5 Hz, 2 H), 7.66–7.61 (app t, *J* = 7.5 Hz, 2 H), 7.46–7.16 (m, 9 H), 4.65 (dd, *J* = 10.5, 6.9 Hz, 1 H), 4.55 (dd, *J* = 10.5, 6.9 Hz, 1 H), 4.45 (tdd, *J* = 8.4, 5.4 Hz, 2.4 Hz, 1 H), 4.30 (app t, *J* = 6.6 Hz, 1 H), 2.84 (dd, *J* = 18, 9 Hz, 1 H), 2.77–2.52 (m, 2 H), 2.41 (dd, *J* = 17.7, 2.4 Hz, 1 H), 2.15–2.03 (m, 1 H), 1.85–1.73 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C_q), 157.4 (C_q), 143.3 (C_q), 143.1 (C_q), 141.5 (C_q), 140.4 (C_q), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 126.5 (CH), 125.3 (CH), 125.2 (CH), 120.2 (CH), 69.0 (CH_2), 60.4 (CH), 47.0 (CH), 36.0 (CH_2), 34.1 (CH_2), 31.9 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3024, 2953, 2926, 1802, 1722, 1448, 1314, 1126, 762 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{26}H_{27}N_2O_4$ 431.1964; found 431.1989.

(±)-(9*H*-Fluoren-9-yl)methyl 3-Benzyl-5-oxoisoxazolidine-2-carboxylate (9b): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9b** (128 mg, 64 %) as a colourless solid. M.p. 103–105 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (app d, *J* = 7.4 Hz, 2 H), 7.62–7.57 (m, 2 H), 7.47–7.27 (m, 7 H), 7.15–7.06 (m, 2 H), 4.71–4.50 (m, 3 H), 4.27 (app t, *J* = 6.5 Hz, 1 H), 3.06 (dd, *J* = 13.8, 6.1 Hz, 1 H), 2.77 (dd, *J* = 13.8, 8.3 Hz, 1 H), 2.67 (dd, *J* = 17.9, 8.7 Hz, 1 H), 2.48 (dd, *J* = 17.9, 2.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C_q), 156.7 (C_q), 143.2 (C_q), 143.1 (C_q), 141.4 (C_q), 135.5 (C_q), 129.4 (CH), 128.9 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 125.3 (CH), 125.1 (CH), 120.3 (CH), 120.2 (CH), 68.7 (CH_2), 61.4 (CH), 47.0 (CH), 39.7 (CH_2), 33.1 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3064, 3037, 2959, 2921, 2854, 1798, 1728, 1447, 1307, 1125, 763 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{25}H_{25}N_2O_4$ 417.1809; found 417.1816.

(±)-(9*H*-Fluoren-9-yl)methyl 3-Isopropyl-5-oxoisoxazolidine-2-carboxylate (9c): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9c** (135 mg, 79 %) as a colourless solid. M.p. 94–96 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (app d, *J* = 7.5 Hz, 2 H), 7.62 (dd, *J* = 7.1, 4.1 Hz, 2 H), 7.42 (app t, *J* = 7.4 Hz, 2 H), 7.33 (app t, *J* = 7.4 Hz, 2 H), 4.66 (dd, *J* = 10.5, 6.5 Hz, 1 H), 4.52 (dd, *J* = 10.5, 6.7 Hz, 1 H), 4.29 (app t, *J* = 6.6 Hz, 1 H), 4.19–4.09 (m, 1 H), 2.74 (dd, *J* = 18.0, 9.4 Hz, 1 H), 2.49 (dd, *J* = 18.0, 2.2 Hz, 1 H), 1.95–1.71 (m, 1 H), 0.91 (app d, *J* = 4.9 Hz, 3 H), 0.89 (app d, *J* = 4.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (C_q), 157.5 (C_q), 143.4 (C_q), 143.2 (C_q), 141.5 (C_q), 128.1 (CH), 127.5 (CH), 127.4 (CH), 125.3 (CH), 125.2 (CH), 120.2 (CH), 68.8 (CH_2), 65.7 (CH), 47.1 (CH), 31.9 (CH), 31.3 (CH_2), 18.0 (CH), 17.9 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 2966, 1804, 1724, 1447, 1289, 1150, 758, 736 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{24}H_{23}N_2O_4$ 403.1652; found 403.1651.

(±)-(9*H*-Fluoren-9-yl)methyl 3-Isobutyl-5-oxoisoxazolidine-2-carboxylate (9d): Isolated according to GP2 (petroleum ether/

CH_2Cl_2, 1:9 to 0:1) to give **9d** (137 mg, 75 %) as a colourless solid. M.p. 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (app d, J = 7.4 Hz, 2 H), 7.62 (dd, J = 7.3, 3.8 Hz, 2 H), 7.42 (app t, J = 7.3 Hz, 2 H), 7.33 (app t, J = 7.4 Hz, 2 H), 4.72 (dd, J = 10.6, 6.4 Hz, 1 H), 4.53 (dd, J = 10.6, 6.6 Hz, 1 H), 4.47–4.36 (m, 1 H), 4.28 (app t, J = 6.4 Hz, 1 H), 2.72 (dd, J = 17.6, 8.6 Hz, 1 H), 2.32 (dd, J = 17.6, 1.9 Hz, 1 H), 1.80–1.58 (m, 2 H), 1.34–1.12 (m, 1 H), 0.89 (app d, J = 6.2 Hz, 3 H), 0.84 (app d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (C_q), 157.6 (C_q), 143.3 (C_q), 143.2 (C_q), 141.5 (C_q), 141.4 (C_q), 128.3 (CH), 127.5 (CH), 127.4 (CH), 125.3 (CH), 125.1 (CH), 120.2 (CH), 120.2 (CH), 68.6 (CH_2), 59.4 (CH), 47.1 (CH), 42.9 (CH_2), 34.3 (CH_2), 24.9 (CH), 22.7 (CH), 21.8 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 2960, 1811, 1720, 1448, 1323, 1126, 761 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{22}H_{27}N_2O_4$ 383.1965; found 383.1974.

(±)-(9*H*-Fluoren-9-yl)methyl 3-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-5-oxoisoxazolidine-2-carboxylate (9e): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9e** (179 mg, 62 %) as a colourless solid. M.p. 59–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (dd, J = 7.5, 2.6 Hz, 2 H), 7.66–7.56 (m, 6 H), 7.37 (m, 10 H), 4.60–4.50 (m, 2 H), 4.49–4.39 (m, 1 H), 4.28 (app t, J = 7.0 Hz, 1 H), 3.88 (dd, J = 10.9, 3.7 Hz, 1 H), 3.66 (dd, J = 11.0, 3.1 Hz, 1 H), 2.99–2.73 (m, 2 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C_q), 156.5 (C_q), 143.3 (C_q), 143.2 (C_q), 141.5 (C_q), 141.4 (C_q), 135.8 (CH), 135.7 (CH), 132.8 (C_q), 132.4 (C_q), 130.2 (CH), 130.1 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 125.4 (CH), 125.3 (CH), 120.3 (CH), 120.2 (CH), 69.1 (CH_2), 64.8 (CH_2), 60.8 (CH), 46.9 (CH), 31.0 (CH_2), 26.8 (CH_3), 19.3 (C_q) ppm. IR (ATR): $\tilde{\nu}$ = 3077, 2926, 2857, 1807, 1722, 1316, 1149, 1105, 738, 700 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{35}H_{39}N_2O_5Si$ 595.2623; found 595.2645.

(±)-(9*H*-Fluoren-9-yl)methyl 3-[(Benzyloxy)methyl]-5-oxoisoxazolidine-2-carboxylate (9f): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9f** (140 mg, 65 %) as a colourless solid. M.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (app d, J = 7.5 Hz, 2 H), 7.63 (dd, J = 7.2, 4.7 Hz, 2 H), 7.47–7.27 (m, 9 H), 4.68–4.42 (m, 5 H), 4.29 (app t, J = 7.0 Hz, 1 H), 3.64 (dd, J = 10.0, 4.9 Hz, 1 H), 3.56 (dd, J = 10.1, 3.9 Hz, 1 H), 2.88 (dd, J = 17.7, 9.0 Hz, 1 H), 2.77 (dd, J = 17.7, 3.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2 (C_q), 156.6 (C_q), 143.3 (C_q), 143.2 (C_q), 141.5 (C_q), 141.4 (C_q), 137.4 (C_q), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 125.4 (CH), 125.3 (CH), 120.2 (CH), 73.7 (CH_2), 70.0 (CH_2), 69.1 (CH_2), 59.4 (CH), 46.9 (CH), 31.3 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3031, 2867, 1805, 1721, 1450, 1318, 1140, 1119, 759, 737 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{26}H_{27}N_2O_5$ 447.1914; found 447.1923.

(±)-(9*H*-Fluoren-9-yl)methyl 3-[2-(Methylthio)ethyl]-5-oxoisoxazolidine-2-carboxylate (9g): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9g** (123 mg, 64 %) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (app d, J = 7.5 Hz, 2 H), 7.62 (app d, J = 7.4 Hz, 2 H), 7.42 (app t, J = 7.4 Hz, 2 H), 7.34 (app t, J = 7.5 Hz, 2 H), 4.65 (dd, J = 10.5, 6.6 Hz, 1 H), 4.60–4.49 (m, 2 H), 4.28 (app t, J = 6.6 Hz, 1 H), 2.84 (dd, J = 17.8, 8.9 Hz, 1 H), 2.59–2.37 (m, 3 H), 2.08 (s, 3 H), 2.05–1.95 (m, 1 H), 1.82–1.66 (m, 1 H) ppm. IR (ATR): $\tilde{\nu}$ = 3037, 3064, 2918, 2854, 1805, 1722, 1449, 1139, 740 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{21}H_{22}NO_4S$ 384.1264; found 384.1277.

(±)-(9*H*-Fluoren-9-yl)methyl 3-{3-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]propyl}-5-oxoisoxazolidine-2-carboxylate (9h): Isolated according to GP2 (petroleum ether/CH_2Cl_2/EtOAc, 1:9:0 to 0:1:0 to 0:95:5) to give **9h** (140 mg, 46 %) as a colourless solid. M.p. 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.49 (br. s, 1 H), 8.31 (t, J = 5.7 Hz, 1 H), 7.78 (app d, J = 7.4 Hz, 2 H), 7.61 (dd, J = 7.2, 2.5 Hz, 2 H), 7.42 (app t, J = 7.4 Hz, 2 H), 7.33 (app t, J = 7.5 Hz, 2 H), 4.67 (dd, J = 10.5, 6.4 Hz, 1 H), 4.54 (dd, J = 10.5, 6.6 Hz, 1 H), 4.43–4.33 (m, 1 H), 4.28 (app t, J = 6.5 Hz, 1 H), 3.51–3.25 (m, 2 H), 2.83 (dd, J = 17.8, 8.9 Hz, 1 H), 2.40 (dd, J = 17.8, 2.3 Hz, 1 H), 1.82–1.55 (m, 4 H), 1.50 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 (C_q), 163.7 (C_q), 157.3 (C_q), 156.4 (C_q), 153.4 (C_q), 143.3 (C_q), 143.1 (C_q), 141.6 (C_q), 141.5 (C_q), 128.2 (CH), 128.1 (CH), 127.5 (CH), 125.3 (CH), 125.2 (CH), 120.3 (CH), 120.2 (CH), 83.4 (C_q), 79.5 (C_q), 68.8 (CH_2), 60.4 (CH), 47.0 (CH), 40.0 (CH_2), 34.1 (CH_2), 31.6 (CH_2), 28.5 (CH_3), 28.2 (CH_3), 25.5 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3332, 2977, 1807, 1718, 1636, 1614, 1325, 1130, 740 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{32}H_{41}N_4O_8$ 609.2919; found 609.2927.

(±)-(9*H*-Fluoren-9-yl)methyl 3-{[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]methyl}-5-oxoisoxazolidine-2-carboxylate (9i): Isolated according to GP2 (petroleum ether/CH_2Cl_2/EtOAc, 1:9:0 to 0:1:0 to 0:95:5) to give **9i** (135 mg, 50 %) as a colourless solid. M.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.0 Hz, 1 H), 7.74 (dd, J = 7.3, 2.3 Hz, 2 H), 7.59 (dd, J = 7.2, 2.5 Hz, 2 H), 7.50–7.20 (m, 8 H), 4.84–4.72 (m, 1 H), 4.63 (dd, J = 10.5, 6.8 Hz, 1 H), 4.53 (dd, J = 10.5, 6.9 Hz, 1 H), 4.26 (app t, J = 6.8 Hz, 1 H), 3.21 (dd, J = 14.7, 5.5 Hz, 1 H), 2.90 (dd, J = 14.6, 9.0 Hz, 1 H), 2.76 (dd, J = 17.9, 8.6 Hz, 1 H), 2.59 (dd, J = 17.9, 3.0 Hz, 1 H), 1.67 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (C_q), 156.8 (C_q), 149.6 (C_q), 143.3 (C_q), 143.1 (C_q), 141.5 (C_q), 141.4 (C_q), 135.6 (C_q), 130.1 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 125.3 (CH), 125.2 (CH), 125.0 (CH), 124.3 (CH), 123.0 (CH), 120.2 (CH), 118.9 (CH), 115.6 (CH), 114.7 (C_q), 84.1 (CH), 69.0 (CH_2), 60.1 (CH), 47.0 (CH), 33.6 (CH_2), 29.6 (CH_2), 28.4 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3129, 3057, 2977, 2933, 1801, 1723, 1706, 1450, 1393, 1347, 1141, 735 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{32}H_{34}N_3O_6$ 556.2442; found 556.2460.

(±)-(9*H*-Fluoren-9-yl)methyl 3-{4-[(*tert*-Butoxycarbonyl)amino]butyl}-5-oxoisoxazolidine-2-carboxylate (9j): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9j** (180 mg, 75 %) as a colourless solid. M.p. 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (app d, J = 7.5 Hz, 2 H), 7.61 (app d, J = 7.2 Hz, 2 H), 7.42 (app t, J = 7.2 Hz, 2 H), 7.38–7.30 (m, 1 H), 4.69 (dd, J = 10.5, 6.4 Hz, 1 H), 4.58–4.43 (m, 2 H), 4.36–4.23 (m, 2 H), 3.13–3.02 (m, 2 H), 2.76 (dd, J = 17.9, 8.8 Hz, 1 H), 2.45–2.31 (m, 1 H), 1.80–1.63 (m, 1 H), 1.56–1.47 (m, 1 H), 1.44 (s, 9 H), 1.43–1.15 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C_q), 157.4 (C_q), 156.1 (C_q), 143.3 (C_q), 143.2 (C_q), 141.5 (C_q), 128.1 (CH), 127.5 (CH), 127.4 (CH), 125.3 (CH), 125.2 (CH), 120.2 (CH), 120.1 (CH), 79.4 (C_q), 68.7 (CH_2), 60.5 (CH), 47.1 (CH), 40.2 (CH_2), 34.0 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 28.6 (CH_3), 22.6 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3380, 2932, 2861, 1805, 1740, 1684, 1525, 1450, 1275, 1147, 738 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{27}H_{36}N_3O_6$ 498.2599; found 498.2607.

(±)-(9*H*-Fluoren-9-yl)methyl 3-Cyclopropyl-5-oxoisoxazolidine-2-carboxylate (9k): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9k** (129 mg, 74 %) as a colourless solid. M.p. 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (app d, J = 7.5 Hz, 2 H), 7.62 (app d, J = 7.0 Hz, 2 H), 7.47–7.38 (m, 2 H), 7.38–7.29 (m, 2 H), 4.65 (dd, J = 10.5, 6.6 Hz, 1 H), 4.50 (dd, J = 10.5, 6.8 Hz, 1 H), 4.28 (app t, J = 6.6 Hz, 1 H), 4.04–3.90 (m, 1 H), 2.84 (dd, J = 17.7, 9.1 Hz, 1 H), 2.56 (dd, J = 17.8, 2.1 Hz, 1 H), 1.23–0.98 (m, 1 H), 0.65–0.49 (m, 2 H), 0.43–0.30 (m, 1 H), 0.30–0.15 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1 (C_q), 157.1 (C_q), 143.3 (C_q), 143.2 (C_q), 141.5 (C_q), 141.5 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 125.3 (CH), 125.2 (CH), 120.2 (CH), 68.8 (CH_2), 63.9 (CH), 47.0 (CH), 34.3 (CH_2), 15.0 (CH), 3.5 (CH_2), 2.5 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 2968, 1804, 1724, 1448, 1384, 1289, 1150, 758, 736 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{21}H_{23}N_2O_4$ 367.1652; found 367.1660.

(±)-(9*H*-Fluoren-9-yl)methyl 5-Oxo-3-phenylisoxazolidine-2-carboxylate (9l): Isolated according to GP2 (petroleum ether/CH_2Cl_2, 1:9 to 0:1) to give **9l** (116 mg, 60 %) as a colourless solid.

M.p. 52–54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.6 Hz, 2 H), 7.55 (t, J = 7.1 Hz, 2 H), 7.46–7.27 (m, 10 H), 5.50 (dd, J = 9.5, 3.4 Hz, 1 H), 4.62 (dd, J = 10.5, 6.8 Hz, 1 H), 4.51 (dd, J = 10.5, 6.9 Hz, 1 H), 4.26 (t, J = 6.8 Hz, 1 H), 3.22 (dd, J = 17.8, 9.5 Hz, 1 H), 2.82 (dd, J = 17.8, 3.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C_q), 156.5 (C_q), 143.2 (C_q), 143.1 (C_q), 141.4 (C_q), 141.3 (C_q), 138.3 (C_q), 129.3 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.4 (CH), 127.3 (CH), 125.7 (CH), 125.3 (CH), 125.2 (CH), 120.2 (CH), 120.1 (CH), 69.0 (CH_2), 63.0 (CH), 46.9 (CH), 37.0 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 2920, 1803, 1722, 1449, 1283, 1165, 1124, 737 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{24}H_{23}N_2O_4$ 403.1652; found 403.1651.

(±)-(9*H*-Fluoren-9-yl)methyl 3-[(2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]-5-oxoisoxazolidine-2-carboxylate (9m): Isolated according to GP2 to give **9m** (181 mg, 75 %) as a white foam, a mixture of two diastereoisomers [*dr* 85:15; the diastereoisomeric ratio was determined by integration of the signal for the minor diastereoisomer at δ = 2.97 ppm (dd) in the ^{1}H NMR spectrum]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.62 (t, J = 7.1 Hz, 2 H), 7.28–7.44 (m, 4 H), 4.68 (dd, J = 6.3, 10.5 Hz, 1 H), 4.52 (dd, J = 6.7, 10.5 Hz, 1 H), 4.34 (dt, J = 2.4, 10 Hz, 1 H), 4.28 (app t, J = 6.4 Hz, 1 H), 3.87 (dt, J = 2.8, 11 Hz, 1 H), 3.67 (app t, J = 11.1 Hz, 1 H), 3.25 (m, 1 H), 3.23 (s, 3 H), 3.21 (s, 3 H), 2.78 (dd, J = 9.9, 17.6 Hz, 1 H), 2.64 (dd, J = 1.8, 17.6 Hz, 1 H), 1.26 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C_q), 157.2 (C_q), 143.3 (CH), 143.0 (CH), 141.5 (CH), 128.2 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 125.3 (CH), 125.1 (CH), 120.2 (CH), 120.2 (CH), 99.8 (C_q), 98.2 (C_q), 68.9 (CH_2), 68.5 (CH_2), 59.6 (CH), 59.5 (CH), 48.4 (CH_3), 48.2 (CH_3), 47.0 (CH), 30.3 (CH_2), 17.6 (2 × CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2949, 1807, 1723, 1450, 1375, 1309, 1143, 1117, 1035, 965, 875, 740 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{26}H_{33}N_2O_8$ 501.2237; found 501.2221.

General Procedure (GP3) for the Zn-Assisted Isoxazolidinone Ring-Opening (10a–10h): At room temperature, activated zinc dust (1.308 g, 20 mmol, 40 equiv.) was added to a stirred solution of the appropriate isoxazolidinone (0.5 mmol, 1 equiv.) in a THF/H_2O/AcOH (8:1:1) mixture (10 mL). The heterogeneous solution was stirred at 40 °C for 4 h. When the reaction was complete, the mixture was c to room temperature, and filtered through a pad of diatomaceous earth. The pad was rinsed with THF. The filtrate was partially concentrated in vacuo and diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude white residue was triturated or precipitated from an appropriate solvent mixture (see details below) to give the desired β-amino acid in analytically pure form.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-5-phenylpentanoic Acid (10a): Isolated according to GP3 (trituration with *n*-pentane) to give **10a** (179 mg, 86 %) as a colourless solid. M.p. 129–131 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.13 (br. s, 1 H), 7.89 (app d, J = 7.5 Hz, 2 H), 7.77–7.67 (m, 2 H), 7.41 (app t, J = 7.4 Hz, 2 H), 7.36–7.22 (m, 5 H), 7.22–7.11 (m, 3 H), 4.41–4.17 (m, 3 H), 3.81 (app q, J = 7.3 Hz, 1 H), 2.66–2.52 (m, 2 H), 2.43–2.25 (m, 2 H), 1.78–1.62 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.6 (C_q), 155.6 (C_q), 144.0 (C_q), 143.8 (C_q), 141.8 (C_q), 140.7 (C_q), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 125.7 (CH), 125.2 (CH), 120.1 (CH), 65.1 (CH_2), 47.8 (CH), 46.9 (CH), 39.8 (CH_2), 36.2 (CH_2), 31.7 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 335, 3070, 3024, 2952, 1696, 1538, 1296, 1250, 1046, 741 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{26}H_{26}NO_4$ 416.1856; found 416.1871.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-phenylbutanoic Acid (10b):[14] Isolated according to GP3 (dissolved in CH_2Cl_2 and precipitated with *n*-pentane at 0 °C) to give **10b** (169 mg, 84 %) as a colourless solid. M.p. 140–142 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.05 (s, 1 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.64 (d, J = 7.4 Hz, 2 H), 7.48–7.03 (m, 10 H), 4.29–4.08 (m, 3 H), 4.07–3.86 (m, 1 H), 2.72 (d, J = 6.6 Hz, 2 H), 2.42–2.27 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.7 (C_q), 155.3 (C_q), 143.9 (C_q), 143.9 (C_q), 140.7 (C_q), 138.6 (C_q), 129.2 (CH), 128.2 (CH), 127.6 (CH), 127.1 (CH), 126.1 (CH), 125.2 (CH), 120.1 (CH), 65.2 (CH_2), 49.7 (CH), 46.7 (CH), 39.7 (CH_2), 38.9 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3345, 3031, 2959, 1722, 1687, 1529, 1228, 1084, 1044, 739 cm^{-1}. HRMS: calcd. for $[M - H]^-$ $C_{25}H_{22}NO_4$ 400.1554; found 400.1531.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-3-phenylpropanoic Acid (10c): Isolated according to GP3 (trituration with *n*-pentane) to give **10c** (184 mg, 95 %) as a colourless solid. Spectroscopic data are consistent with literature data.[15] M.p. 197–199 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.21 (br. s, 1 H), 7.95 (app d, J = 8.6 Hz, 1 H), 7.88 (app d, J = 7.3 Hz, 2 H), 7.67 (app d, J = 7.2 Hz, 2 H), 7.50–7.11 (m, 9 H), 4.93 (app q, J = 8.4, 7.8 Hz, 1 H), 4.42–4.03 (m, 3 H), 2.83–2.56 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.0 (C_q), 155.4 (C_q), 144.0 (C_q), 143.8 (C_q), 143.0 (C_q), 140.7 (C_q), 128.3 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.4 (CH), 125.2 (CH), 125.2 (CH), 120.2 (CH), 65.4 (CH_2), 51.7 (CH), 46.7 (CH), 41.2 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3367, 3037, 2952, 1703, 1526, 1284, 1227, 1026, 740 cm^{-1}. HRMS: calcd. for $[M - H]^-$ $C_{24}H_{20}NO_4$ 386.1398; found 386.1395.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-3-cyclopropylpropanoic Acid (10d): Isolated according to GP3 (trituration with *n*-pentane/CH_2Cl_2, 1:1) to give **10d** (155 mg, 89 %) as a colourless solid. M.p. 177–179 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.12 (br. s, 1 H), 7.89 (app d, J = 7.4 Hz, 2 H), 7.68 (app d, J = 7.2 Hz, 2 H), 7.41 (app t, J = 7.3 Hz, 2 H), 7.32 (app t, J = 7.8 Hz, 3 H), 4.38–4.06 (m, 3 H), 3.44–3.33 (m, 1 H), 2.49–2.41 (m, 2 H), 0.97–0.80 (m, 1 H), 0.44–0.21 (m, 3 H), 0.14 (m, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 172.5 (C_q), 155.6 (C_q), 144.0 (C_q), 143.8 (C_q), 140.7 (C_q), 127.6 (CH), 127.1 (CH), 125.2 (CH), 120.1 (CH), 65.2 (CH_2), 51.5 (CH), 46.8 (CH), 40.1 (CH_2), 16.0 (CH), 2.9 (CH_2), 2.2 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3333, 2958, 1806, 1698, 1449, 1255, 1105, 1051, 736 cm^{-1}. HRMS: calcd. for $[M - H]^-$ $C_{21}H_{20}NO_4$ 350.1398; found 350.1402.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-[(*tert*-butyldiphenylsilyl)oxy]butanoic Acid (10e): Isolated according to GP3 (dissolved in Et_2O and precipitated from *n*-pentane at 0 °C) to give **10e** (200 mg, 69 %) as a colourless solid. M.p. 82–84 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.22 (br. s, 1 H), 7.88 (app d, J = 7.5 Hz, 2 H), 7.68 (dd, J = 7.3, 3.4 Hz, 2 H), 7.64–7.57 (m, 4 H), 7.50–7.33 (m, 9 H), 7.32–7.22 (m, 2 H), 4.30–4.11 (m, 3 H), 4.10–3.96 (m, 1 H), 3.64–3.47 (m, 2 H), 2.64–2.35 (m, 2 H), 0.98 (s, 9 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.4 (C_q), 155.6 (C_q), 143.9 (C_q), 143.8 (C_q), 140.7 (C_q), 135.1 (CH), 132.9 (C_q), 132.8 (C_q), 129.9 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 125.2 (CH), 120.1 (CH), 65.4 (CH_2), 65.1 (CH_2), 49.6 (CH), 46.7 (CH), 35.8 (CH_2), 26.6 (CH_2), 18.8 (C_q) ppm. IR (ATR): $\tilde{\nu}$ = 3341, 3064, 2956, 2861, 1805, 1723, 1697, 1449, 1278, 1112, 737 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{35}H_{38}NO_5Si$ 580.2514; found 580.2516.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-7-[(*tert*-butoxycarbonyl)amino]heptanoic Acid (10f): Isolated according to GP3 (dissolved in Et_2O and precipitated from *n*-pentane at 0 °C) to give **10f** (174 mg, 74 %) as a colourless solid. Spectroscopic data are consistent with literature data.[14,16] M.p. 85–87 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.13 (br. s, 1 H), 7.89 (app d, J = 7.4 Hz, 2 H), 7.68 (app d, J = 7.1 Hz, 2 H), 7.41 (app t, J = 7.4 Hz, 2 H), 7.32 (app t, J = 7.3 Hz, 2 H), 7.20 (app d, J = 8.7 Hz, 1 H), 6.76 (app t, J = 5.3 Hz, 1 H), 4.35–4.13 (m, 3 H), 3.74 (s, 1 H), 2.87 (app q, J = 5.6 Hz, 2 H), 2.41–2.15 (m, 2 H), 1.36 (s, 9 H), 1.33–1.05 (m, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.5 (C_q), 155.5 (C_q), 155.5 (C_q),

143.9 (C_q), 143.8 (C_q), 140.7 (C_q), 127.6 (CH), 127.0 (CH), 126.9 (CH), 125.2 (CH), 125.1 (CH), 120.1 (CH), 77.3 (C_q), 65.1 (CH_2), 47.8 (CH), 46.7 (CH), 39.6 (CH_2), 39.4 (CH_2), 33.9 (CH_2), 29.3 (CH_2), 28.2 (CH_3), 22.7 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3344, 2979, 2939, 1691, 1534, 1252, 1169, 739 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{27}H_{38}N_3O_6$ 500.2755; found 500.2762.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-5-(methylthio)pentanoic Acid (10g): At room temperature, activated zinc dust (1.046 g, 16 mmol, 40 equiv.) was added portionwise to a stirred solution of isoxazolidinone **9g** (153 mg, 0.4 mmol, 1 equiv.) in a THF/H_2O/AcOH (8:1:1) mixture (8 mL). The heterogeneous solution was stirred at 40 °C for 4 h. When the reaction was complete, the mixture was cooled to room temperature, and filtered through a pad of diatomaceous earth. The pad was rinsed with THF. The filtrate was partially concentrated in vacuo and diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (*n*-pentane/EtOAc/AcOH, 1:1:0.1) to give *N*-Fmoc-β^3-homoMet-OH **10i** (72 mg, 187 µmol, 47 %) as a colourless solid. M.p. 129–131 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 12.18 (br. s, 1 H), 7.89 (app d, *J* = 7.5 Hz, 2 H), 7.68 (dd, *J* = 7.5, 3.6 Hz, 2 H), 7.41 (app t, *J* = 7.4 Hz, 2 H), 7.32 (app t, *J* = 7.5 Hz, 2 H), 7.27 (app d, *J* = 8.5 Hz, 1 H), 4.38–4.16 (m, 3 H), 3.95–3.81 (m, 1 H), 2.47–2.24 (m, 4 H), 2.01 (s, 3 H), 1.80–1.57 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 172.4 (C_q), 155.6 (C_q), 144.0 (C_q), 143.8 (C_q), 140.8 (C_q), 127.6 (CH), 127.1 (CH), 125.2 (CH), 120.1 (CH), 65.1 (CH_2), 47.2 (CH), 46.8 (CH), 39.5 (CH_2), 33.7 (CH_2), 29.7 (CH_2), 14.6 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3311, 3070, 2917, 2887, 2854, 1694, 1543, 1259, 1051, 735 cm^{-1}. HRMS: calcd. for $[M + NH_4]^+$ $C_{21}H_{27}N_2O_4S$ 403.1686; found 403.1689.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-6-[2,3-bis(*tert*-butoxycarbonyl)guanidino]hexanoic Acid (10h): Freshly activated zinc dust (2.615 g, 80 equiv.) was added portionwise to a stirred solution of isoxazolidinone **9h** (304 mg, 0.5 mmol) in a THF/H_2O/AcOH (7.2:1:1.8) mixture (10 mL). The heterogeneous solution was stirred at 40 °C for 4 h. When the reaction was complete, the mixture was brought back to room temperature, and filtered off on a pad of diatomaceous earth. The pad was rinsed with THF and CH_2Cl_2. The filtrate was concentrated in vacuo, and filtered through a short pad of silica gel (*n*-pentane/EtOAc/AcOH, 1:1:0.1) to give analytically pure *N*-Fmoc-β^3-homoArg(*N*,*N*′-diBoc)-OH **10h** (253 mg, 0.41 mmol, 83 %) as a colourless foamy solid. Spectroscopic data are consistent with literature data.[17] M.p. 115–117 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 12.12 (br. s, 1 H), 11.50 (br. s, 1 H), 8.28 (app t, *J* = 5.7 Hz, 1 H), 7.88 (app d, *J* = 7.4 Hz, 2 H), 7.67 (dd, *J* = 7.1, 2.9 Hz, 2 H), 7.40 (app t, *J* = 7.4 Hz, 2 H), 7.31 (app t, *J* = 7.4 Hz, 2 H), 7.24 (app d, *J* = 8.6 Hz, 1 H), 4.39–4.13 (m, 3 H), 3.86–3.73 (m, 1 H), 3.30–3.15 (m, 2 H), 2.36 (app d, *J* = 6.8 Hz, 2 H), 1.42 (d, *J* = 24.4 Hz, 22 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 172.5 (C_q), 163.2 (C_q), 155.6 (C_q), 155.3 (C_q), 152.1 (C_q), 144.0 (C_q), 143.8 (C_q), 140.7 (C_q), 127.6 (CH), 127.0 (CH), 125.2 (CH), 120.1 (CH), 82.9 (C_q), 78.1 (C_q), 65.1 (CH_2), 47.8 (CH), 46.8 (CH), 40.2 (CH_2), 39.7 (CH_2), 31.6 (CH_2), 28.0 (CH_3), 27.6 (CH_3), 25.4 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3332, 2978, 2933, 1716, 1643, 1614, 1327, 1228, 1132, 739 cm^{-1}. HRMS: calcd. for $[M + H]^+$ $C_{32}H_{43}N_4O_8$ 611.3075; found 611.3068.

(±)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-4-[1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]butanoic Acid (10i): Isolated according to GP3 (dissolved in Et_2O/CH_2Cl_2, 95:5, and precipitated from *n*-pentane at 0 °C) to give **10i** (124 mg, 46 %) as a colourless solid. Spectroscopic data are consistent with literature data.[16,18] M.p. 118–120 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 12.26 (br. s, 1 H), 8.02 (app d, *J* = 8.3 Hz, 1 H), 7.88 (app d, *J* = 7.5 Hz, 2 H), 7.70 (app d, *J* = 7.6 Hz, 1 H), 7.65–7.56 (m, 2 H), 7.55–7.15 (m, 8 H), 4.28–3.99 (m, 4 H), 2.84 (d, *J* = 6.8 Hz, 2 H), 2.49–2.37 (m, 2 H), 1.55 (s, 9 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 172.7 (C_q), 155.5 (C_q), 149.0 (C_q), 143.8 (C_q), 140.7 (C_q), 134.8 (C_q), 130.5 (C_q), 127.6 (CH), 127.0 (CH), 125.2 (CH), 125.1 (CH), 124.3 (CH), 123.7 (CH), 122.5 (CH), 120.1 (CH), 119.3 (CH), 117.4 (CH), 114.7 (CH), 83.4 (C_q), 65.3 (CH_2), 48.1 (CH), 46.7 (CH), 39.0 (CH_2), 29.7 (CH_2), 27.6 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3339, 3044, 2979, 1729, 1691, 1532, 1452, 1367, 1250, 1159, 1085, 732 cm^{-1}. HRMS: calcd. for $[M - H]^-$ $C_{21}H_{20}NO_4$ 539.2188; found 539.2196.

(±)-3-{[(Benzyloxy)carbonyl]amino}-5-phenylpentanoic Acid (15): Prepared according to GP3 using activated Zn dust (80 equiv.) in a THF/H_2O/AcOH (7.2:1:1.8) mixture (10 mL), and precipitated from *n*-pentane at 0 °C after dissolution in CH_2Cl_2 to give **15** (129 mg, 79 %) as a colourless solid. Spectroscopic data are consistent with literature data.[19] M.p. 148–150 °C. ^{1}H NMR (300 MHz, [D_4]methanol): δ = 9.00–8.56 (m, 10 H), 6.72–6.49 (m, 2 H), 5.63–5.37 (m, 1 H), 4.25–4.05 (m, 2 H), 4.06–3.86 (m, 2 H), 3.49–3.22 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 176.4 (C_q), 155.6 (C_q), 142.1 (C_q), 137.4 (C_q), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 125.6 (CH), 65.1 (CH_2), 48.5 (CH), 41.6 (CH_2), 35.9 (CH_2), 31.9 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3388, 3034, 2944, 1693, 1568, 1414, 1252, 1050, 697 cm^{-1}. HRMS: calcd. for $[M - H]^-$ $C_{19}H_{20}NO_4$ 326.1398; found 326.1392.

Acknowledgments

This work has been partially supported by INSA Rouen, Rouen University, the Centre National de la Recherche Scientifique (CNRS), EFRD, and Labex SynOrg (ANR-11-LABX-0029), and by Region Normandie (CRUNCh network). This work is part of CrisOrg – LabCom V6 (ANR-14-LAB6-0002), Laboratoires communs organismes de recherche publics – PME/ETI – 2014.

Keywords: Amino acids · Isoxazolidinones · Heterocycles · Meldrum's acid · Reduction · Multicomponent reactions

[1] a) T. Janecki, T. Wąsek, M. Różalski, U. Krajewska, K. Studzian, A. Janecka, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1430; b) Shamsuzzaman, H. Khanam, A. Mashrai, N. Siddiqui, *Tetrahedron Lett.* **2013**, *54*, 874.
[2] G. Romeo, U. Chiacchio, A. Corsaro, P. Merino, *Chem. Rev.* **2010**, *110*, 3337.
[3] D. Socha, M. Jurczak, M. Chmielewski, *Tetrahedron* **1997**, *53*, 739.
[4] For representative examples, see: a) J. E. Baldwin, L. M. Harwood, M. J. Lombard, *Tetrahedron* **1984**, *40*, 4363; b) C. Pearson, K. L. Rinehart, M. Sugano, J. R. Costerison, *Org. Lett.* **2000**, *2*, 2901; c) M. Shindo, K. Itoh, K. Ohtsuki, C. Tsuchiya, K. Shishido, *Synthesis* **2003**, *9*, 1441; d) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849; e) S. A. Bentley, S. G. Davies, J. A. Lee, P. M. Roberts, A. J. Russell, J. E. Thomson, S. M. Toms, *Tetrahedron* **2010**, *66*, 4604.
[5] For a review on the synthesis of isoxazolidin-5-ones, see: J. Annibaletto, S. Oudeyer, V. Levacher, J.-F. Brière, *Synthesis* **2017**, *49*, 2117.
[6] For selected leading reviews, see: a) E. Juaristi, V. A. Soloshonok (Eds.), *Enantioselective Synthesis of β-Amino Acids*, 2nd ed., Wiley, **2005**; b) M.-I. Aguilar, A. W. Purcell, R. Devi, R. Lew, J. Rossjohn, A. I. Smith, P. Perlmutter, *Org. Biomol. Chem.* **2007**, *5*, 2884; c) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366; d) S. M. Kim, J. W. Yang, *Org. Biomol. Chem.* **2013**, *11*, 4737; e) C. Cabrele, T. A. Martinek, O. Reiser, Ł. Berlicki, *J. Med. Chem.* **2014**, *57*, 9718.
[7] For representative examples, see: a) T. Okino, Y. Hoashi, Y. Takemoto, *Tetrahedron Lett.* **2003**, *44*, 2817; b) J. Seayad, P. K. Patra, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 953; c) S. Postikova, T. Tite, V. Levacher, J.-F. Brière, *Adv. Synth. Catal.* **2013**, *355*, 2513; d) F. Nawaz, M. Zaghouani, D. Bonne, O. Chuzel, J. Rodriguez, Y. Coquerel, *Eur. J. Org. Chem.* **2013**, 8253.

[8] a) M. E. Juarez-Garcia, S. Yu, J. W. Bode, *Tetrahedron* **2010**, *66*, 4841; b) T. Tite, M. Sabbah, V. Levacher, J.-F. Brière, *Chem. Commun.* **2013**, *49*, 11569; c) A. Pou, A. Moyano, *Eur. J. Org. Chem.* **2013**, 3103; d) S. Izumi, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2016**, *18*, 696.
[9] C. Berini, M. Sebban, H. Oulyadi, M. Sanselme, V. Levacher, J.-F. Brière, *Org. Lett.* **2015**, *17*, 5408 and references cited therein.
[10] For recent reviews on Meldrum's acid, see: a) A. M. Dumas, E. Fillion, *Acc. Chem. Res.* **2010**, *43*, 440; b) E. Pair, T. Cadart, V. Levacher, J.-F. Brière, *ChemCatChem* **2016**, *8*, 1882.
[11] a) K. R. Fountain, R. Erwin, T. Early, H. Kehl, *Tetrahedron Lett.* **1975**, *16*, 3027; b) for conjugate addition of BnNHOH to chiral acrylates, see: D. Niu, K. Zhao, *J. Am. Chem. Soc.* **1999**, *121*, 2456; c) A. G. Moglioni, E. Muray, J. A. Castillo, Á. Álvarez-Larena, G. Y. Moltrasio, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2002**, *67*, 2402 and references cited therein.
[12] a) A. Isidro-Llobet, M. Álvarez, F. Albericio, *Chem. Rev.* **2009**, *109*, 2455; b) P. G. M Wuts, *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., Hoboken, NJ, **2014**; c) R. Behrendt, P. White, J. Offer, *J. Pept. Sci.* **2016**, *22*, 4.
[13] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[14] G. Guichard, S. Abele, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 187.
[15] Y. Bandala, J. Aviña, T. González, I. A. Rivero, E. Juaristi, *J. Phys. Org. Chem.* **2008**, *21*, 349.
[16] D. M. Pahlke, U. Diederichsen, *J. Pept. Sci.* **2016**, *22*, 636.
[17] M. Rueping, Y. R. Mahajan, B. Jaun, D. Seebach, *Chem. Eur. J.* **2004**, *10*, 1607.
[18] K. Gademann, T. Kimmerlin, D. Hoyer, D. Seebach, *J. Med. Chem.* **2001**, *44*, 2460.
[19] C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188.

Received: April 5, 2017

