Photoaffinity-Labeled Peptoids and Depsipeptides by Multicomponent Reactions

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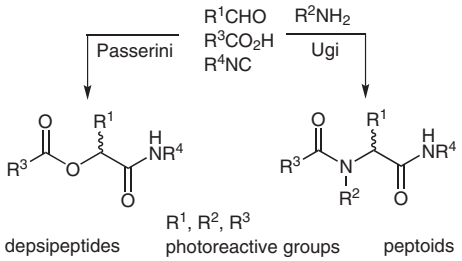
Abstract: Photoaffinity tags can be incorporated easily into peptoids and congeners by the Ugi and Passerini multicomponent reactions. Products related to photo-methionine and photo-leucine can be accomplished by diazirine-containing building blocks. The same protocols can be used to synthesize derivatives with benzophenone photo cross-linkers.

Key words: photo-methionine, photo-leucine, Ugi reaction, Passerini reaction, peptoids

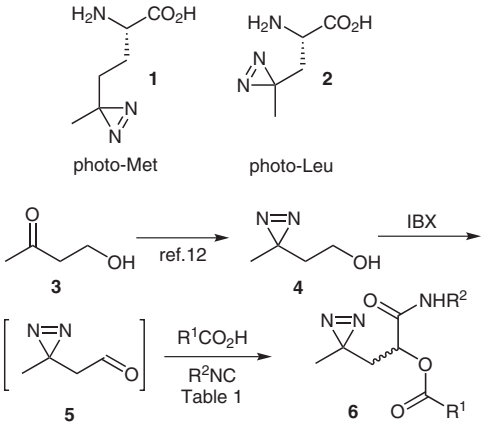
Peptoids (N-substituted glycines) are oligomers that mimic structural and functional features of native peptides. Assets that make peptoids attractive for biological applications are enhanced proteolytic stability, increased cellular permeability, and ease of access by multicomponent reactions (MCRs).[1–3] They have shown promise in regulating a variety of biological phenomena, and can serve as powerful tools to study biomolecular interactions.[4,5] There is currently considerable interest in developing chemical reagents to manipulate protein–protein interactions as tools for chemical biology or as potential drugs. To elucidate the mechanisms, for example, involved in the adhesion to cell surfaces and their biological consequences, the investigation of the molecular interactions between recognition domains and their ligands is of high relevance. For this purpose, photoaffinity-labeling techniques are studied.[6,7] For the synthesis of peptoids, several approaches can be taken; however, the multi-component approach utilizing the Ugi four-component reaction (Ugi-4CR) is most successful for creating diversity.[8,9] As portrayed in Scheme 1, we have applied the Passerini reaction for the synthesis of photoaffinity-labeled α-acyloxy amides and Ugi reaction for peptoids (Scheme 1). In addition, we will describe protocols relying on isonitrile-based MCRs that can be extended to Passerini reactions leading to depsipeptides.

Isonitrile-based MCRs such as the Ugi reaction start from an amine, a carbonyl component, a carboxylic acid, and an isonitrile. If appropriate photoreactive building blocks are used, the labeled peptoids can be utilized further. More specifically, the incorporation of diazirine and benzophenone moieties in different starting materials used for isonitrile-based MCRs will be discussed. The popularity of these photoactive moieties stems from the facile generation of reactive intermediates, namely the formation of carbenes from diazirines or radicals from benzophenone.[10]



Scheme 1 Passerini and Ugi reactions

The first series of photolabeled products represent diazirine derived Passerini and Ugi products. The diazirine modification of peptoids was envisaged due to the close resemblance to photo-methionine **1** and photo-leucine **2**.[11] In Scheme 2 the synthesis of α-acyloxy amides **6** by the Passerini reaction is described.



Scheme 2 Passerini reaction to diazirine-modified α-acyloxy amides **6**

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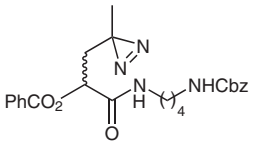
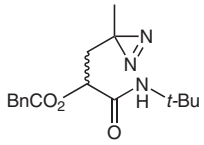
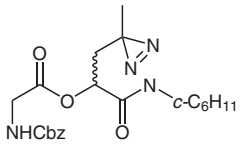
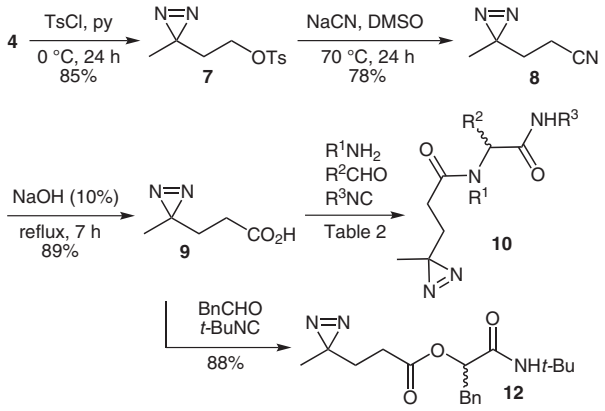
Diazirine containing alcohol **4** can be synthesized starting from **3** in a three-step procedure.[12] Oxidation of **4** to the aldehyde **5** proved to be problematic in our hands; the isolation was always accompanied by decomposition of the material. According to a protocol by Zhu et al., aldehydes employed in MCRs can be synthesized in situ and transformed without further purification.[13] Aldehyde **5** was formed as intermediate via an IBX-oxidation and converted directly to the Passerini products **6** in 52–76% yields (Table 1). As can be seen, the Passerini reaction is not limited to any particular carboxylic acid or isonitrile, leading to a variety of products in only one step.

Table 1 Depsipeptides by Passerini-3CR

	R^1CO_2H	R^4NC	Product
1	$PhCO_2H$	CbzHN–(CH2)4–NC	 **6a** 55%
2	$BnCO_2H$	*t*-BuNC	 **6b** 52%
3	N-Cbz-glycine	*c*-$C_6H_{11}NC$	 **6c** 76%

For diazirine-labeled Ugi products we chose to start from diazirine-modified acid **9** (Scheme 3). Diazirine **9** can be achieved in a three step sequence from **4** in an overall yield of 60%, and can be used subsequently as the carboxylic acid building block (Table 2). The appropriate racemic Ugi products **10a–c** were isolated in 47–88% yields. Of particular interest is the Ugi reaction with isonitrile **11** (entry 3), the resulting amide bond can be transformed into an activated amide bond by formation of an indole amide after acidic cleavage of the acetal. This cleavable isonitrile-derived amide was developed recently by us and shows high versatility.[14] Thus, the complete moiety **10c** (excluding the activation unit) can be retained on its subsequent treatment with nucleophiles affording a variety of carboxylic acid derivatives of interest.[14]

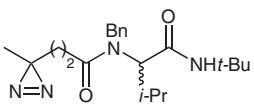
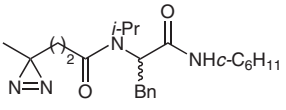
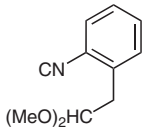
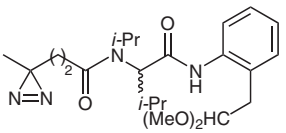
In addition, diazirine **9** can be employed as the carboxylic acid counterpart in Passerini reaction (Scheme 3). The appropriate depsipeptide of this three-component reaction can be isolated in 88% yield, as exemplified for the synthesis of **12**.



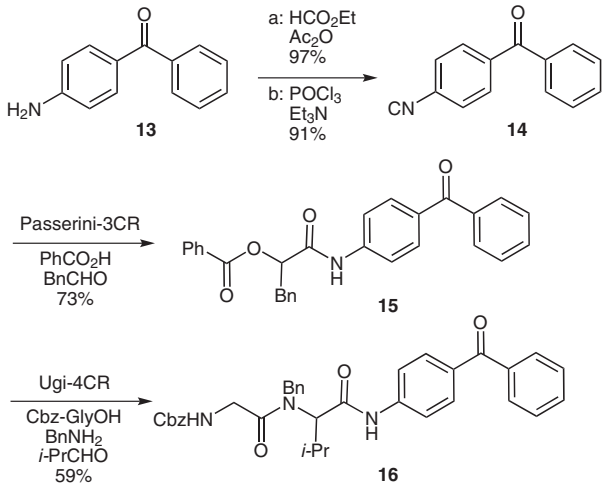
Scheme 3 Ugi reaction to diazirine-modified peptoids **12**

For the synthesis of benzophenone-containing peptoids and depsipeptides, the same established protocols were used (Scheme 4). The synthesis of the isonitrile **14** could be accomplished in two steps by converting amine **13** via the mixed anhydride method to the corresponding formamide followed by dehydration to isonitrile **14**. The overall yield for this two-step procedure was 90%. In Passerini and Ugi reactions this isonitrile behaved as expected leading to the coupled products **15** or **16** in good yields. Func-

Table 2 Peptoids by Ugi-4CR

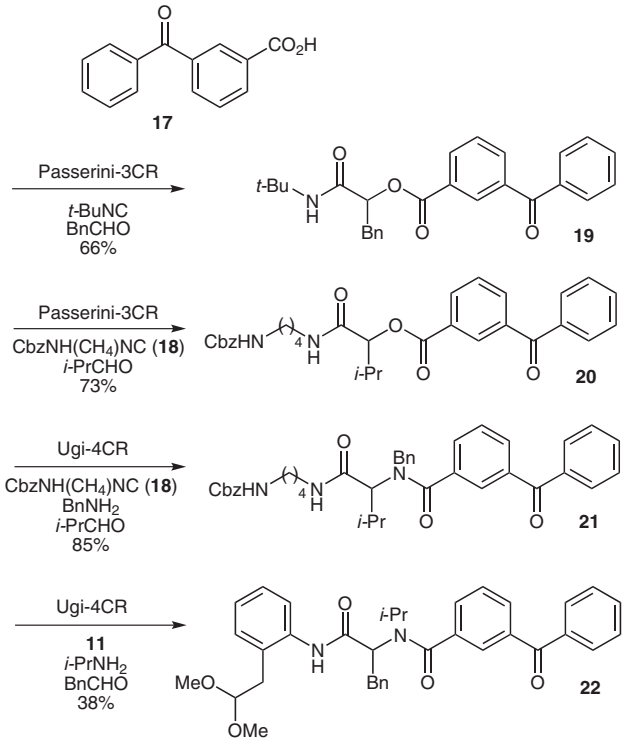
	R^1CHO, R^2NH_2	R^4NC	Product
1	*i*-PrCHO, $BnNH_2$	*t*-BuNC	 **10a** 88%
2	BnCHO, *i*-$PrNH_2$	*c*-$C_6H_{11}NC$	 **10b** 47%
3	*i*-PrCHO, *i*-$PrNH_2$	 **11**	 **10c** 84%

tionalization, for example, by deprotection of the Cbz-group in **16** allows for further manipulations and facile incorporation into larger assemblies.



Scheme 4 MCRs starting from benzophenone-derived isonitrile **14**

Alternatively, the benzophenone-derived carboxylic acid **17**, which is commercially available, can be utilized in the same MCRs (Scheme 5) leading to a modified arrangement of the Ugi starting products.



Scheme 5 Synthesis of benzophenone-derivatives **19–22**

The Passerini products **19** and **20** could be isolated in 66% and 73% yield, respectively; the appropriate Ugi products **21** and **22** were obtained in yields of 85% and 38%. The diversity accomplished by the multicomponent reactions is illustrated by these examples. Further functionalization, for example, the incorporation in peptides synthesis is easily possible. Thus the Cbz-protecting group can be removed to give a free amino terminus and the utilization of the convertible isonitrile **11** allows for cleavage of the C-terminal amide bond.

Further syntheses of chemical probes, especially such that are useful for proteomic studies are currently carried out and will be reported in due course.

All chemicals and solvents used are commercially available and were obtained from Aldrich/Fluka. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Purification of the crude products by column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm), Merck, Germany. TLC identifications of reactants and products were performed on silica gel coated aluminum foil (silica gel 60 F_{254} with fluorescence indicator), Merck, Germany. NMR spectra were recorded on a Varian Mercury 300 spectrometer. All ^{1}H NMR spectra were reported in ppm relative to TMS. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.00 ppm. IR spectra were recorded on Nicolet 5700, Thermo Elektron Co. Electrospray ionization mass spectra (ESI-MS) were recorded on an API 150, Applied Biosystems (ionization condition 70 eV). High-resolution mass spectra (HRMS) were recorded on Bruker BioApex 70 eV FT-ICR spectrometer. Determinations of melting points were accomplished with a Leica DM LS2 microscope (without correction).

2-(3-Methyl-3*H*-diaziren-3-yl)ethanol (4)

4-Hydroxybutan-2-one (**3**; 11.2 g, 127 mmol) was dissolved in liquid ammonia (200 mL) and stirred for 5 h at reflux temperature. The solution was then cooled to –60 °C with a dry ice/EtOH bath and a solution of hydroxylamine *O*-sulfonic acid (16.0 g, 141 mmol) in MeOH (100 mL) was added over a 30-min period. The ice bath was removed and the reaction mixture was stirred at reflux for 1 h. The ammonia was allowed to evaporate overnight and the resulting slurry was filtered and washed several times with MeOH. The combined organic solutions were evaporated under reduced pressure to a volume of about 60 mL until no odor of ammonia could be detected. No further workup was accomplished. The crude methanolic solution of **4** was diluted with MeOH (50 mL) and cooled in an ice bath. Et_3N (12.6 g, 125 mmol) was added keeping the temperature at 0 °C, upon which solid I_2 (19.6 g, 77.4 mmol) was added in small portions (~1 g/min). The I_2 reduction was virtually instantaneous. After complete addition, the red brown color of excess I_2 persisted. The solution was concentrated to a volume of about 80 mL and brine (150 mL) was added and extracted with Et_2O (4 × 100 mL). The combined organic solutions were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to dryness. The residue was distilled (70 °C/32 mbar) to obtain **4** as a colorless liquid (5.45 g, 43%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, CH_3), 1.64 (t, J = 6.3 Hz, 2 H, CH_2), 1.99 (br s, 1 H, OH), 3.54 (t, J = 6.3 Hz, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 24.2, 36.9, 57.6.

ESI-MS: m/z = 102.0 $[M + H]^+$.

Phenyl 3-[(4-{[(Benzyloxy)carbonyl]amino}butyl)amino]-2-[(3-methyl-3*H*-diaziren-3-yl)methyl]-3-oxopropanoate (6a); Typical Procedure for the Sequence of IBX-Oxidation/Passerini-3CR with 2-(3-Methyl-3*H*-diaziren-3-yl)ethanol (4)

Cbz-4-isocyanobutylamine (0.93 g, 4.00 mmol) and **4** (0.50 g, 4.50 mmol) were dissolved in THF (20 mL) and subsequently, benzoic acid (0.93 g, 4.50 mmol) and IBX (2.80 g, 10.0 mmol) were added. The mixture was stirred overnight at 40 °C. After TLC and ESI-MS

monitoring of the formation of the Passerini product, the consumed IBX was filtered off and the solution was evaporated under reduced pressure to give the crude oily product. The residue was purified by column chromatography (EtOAc) to obtain **6a** as a light yellow oil (1.0 g, 55%); R_f = 0.29 (PE–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, CH_3), 1.50–1.52 (m, 4 H, 2 CH_2), 1.85, 1.90 (2 d, J = 9.0 Hz, 1 H, CH_2), 2.15–2.23 (m, 1 H, CH_2), 3.16–3.20 (m, 2 H, CH_2), 3.27–3.29 (m, 2 H, CH_2), 5.00 (br s, 1 H, NH), 5.04 (s, 2 H, CH_2), 5.40–5.44 (m, 1 H, CH), 6.47 (br s, 1 H, NH), 7.27–7.37 (m, 5 H, 5 CH), 7.42–7.52 (m, 2 H, 2 CH), 7.55–7.65 (m, 1 H, CH), 8.06–8.14 (m, 2 H, 2 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 23.5, 26.3, 27.1, 37.0, 39.0, 40.4, 66.5, 70.8, 128.0, 128.0, 128.3, 128.4, 128.6, 128.9, 129.9, 129.9, 133.2, 133.8, 136.5, 156.47, 165.4, 168.8.

ESI-MS: m/z = 475.1 $[M + Na]^+$, 927.8, $[2 M + Na]^+$, 451.4 $[M – H]^–$.

HRMS (ESI): m/z calcd for $C_{24}H_{28}N_4O_5$ as $[M – N_2 + Na]^+$: 439.1957; found: 439.1948.

Benzyl 3-(*tert*-Butylamino)-2-[(3-methyl-3*H*-1,2-diaziren-3-yl)methyl]-3-oxopropanoate (6b)

The IBX-oxidation/Passerini-3CR of **4** (0.50 g, 4.50 mmol), phenylacetic acid (0.61 g, 4.50 mmol), and *tert*-butyl isonitrile (0.33 g, 4.00 mmol) in the presence of IBX (2.80 g, 10.0 mmol) led to the formation of diazirine derivative **6b**. After purification by column chromatography (PE–EtOAc, 1:2), **6b** was obtained as a yellow oil (0.66 g, 52%); R_f = 0.83 (PE–EtOAc, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 3 H, CH_3), 1.16 (s, 9 H, 3 CH_3), 1.60, 1.65 (2 d, J = 8.4 Hz, 2 H, CH_2), 3.79 (s, 2 H, CH_2), 5.14–5.18 (m, 1 H, CH), 5.52 (br s, 1 H, NH), 7.28–7.37 (m, 5 H, 5 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 23.4, 28.3, 36.9, 41.6, 51.1, 70.6, 127.5, 128.9, 129.2, 133.3, 167.4, 169.6.

ESI-MS: m/z = 317.9 $[M + H]^+$, 340.2 $[M + Na]^+$, 316.3 $[M – H]^–$.

HRMS (ESI): m/z calcd for $C_{17}H_{23}N_3O_3$ + Na $[M + Na]^+$: 340.16371; found: 340.16296.

Benzyl {4-(Cyclohexylamino)-3-[(3-methyl-3*H*-diaziren-3-yl)methyl]-2,4-dioxobutyl}carbamate (6c)

The IBX-oxidation/Passerini-3CR of **4** (0.50 g, 4.50 mmol), Cbz-Gly-OH (0.94 g, 4.50 mmol), and cyclohexyl isonitrile (0.44 g, 4.00 mmol) in the presence of IBX (2.80 g, 10.0 mmol) led to the formation of **6c**. After purification by column chromatography (EtOAc), **6c** was obtained as a red-brown oil (1.27 g, 76%); R_f = 0.69 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, CH_3), 1.11–1.35 (m, 6 H, 3 CH_2), 1.57–1.73 (m, 4 H, 2 CH_2), 1.83–1.88 (m, 2 H, CH_2), 3.71–3.75 (m, 1 H, CH), 3.98–4.16 (m, 2 H, CH_2), 5.11–5.21 (m, 2 H, CH_2), 5.25–5.31 (m, 1 H, CH), 5.63 (br s, 1 H, NH), 6.66 (br d, J = 7.7 Hz, 1 H, NH), 7.31–7.37 (m, 5 H, 5 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 24.8, 24.9, 25.4, 32.5, 32.6, 36.8, 43.5, 48.5, 67.3, 71.0, 127.9, 128.3, 128.5, 135.9, 157.1, 167.5, 169.5.

ESI-MS: m/z = 439.0 $[M + Na]^+$, 833.7 $[2 M + H]^+$, 855.1 $[2 M + Na]^+$.

HRMS (ESI): m/z calcd for $C_{21}H_{28}N_4O_5$ as $[M – N_2 + Na]^+$: 411.1896; found: 411.1889.

2-(3-Methyl-3*H*-diaziren-3-yl)ethyl *p*-Toluenesulfonate (7)[15]

2-(3-Methyl-3*H*-diaziren-3-yl)ethanol (**4**; 2.00 g, 20.0 mmol) was dissolved in pyridine (20 mL), cooled down with an ice bath and TsCl (5.71 g, 29.97 mmol) was added in small portions. The reaction mixture was stirred at 0–10 °C for 2 h and allowed to stand overnight at 4 °C. The mixture was poured into concd HCl (40 mL) containing ice (150 g). The oily layer was extracted with Et_2O (3 × 100 mL) and the combined Et_2O extracts were washed first with aq 2 M HCl (100 mL), then with aq 2 M NaOH (100 mL), and finally with brine (100 mL). The organic solution was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to obtain **7** as a light yellow oil (4.34 g, 85%); R_f = 0.70 (PE–EtOAc, 1: 1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 1.68 (t, J = 6.4 Hz, 2 H, CH_2), 2.46 (s, 3 H, CH_3), 3.96 (t, J = 6.3 Hz, 2 H, CH_2), 7.37 (d, J = 8.1 Hz, 2 H, 2 CH), 7.81 (d, J = 8.2 Hz, 2 H, 2 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 21.6, 23.3, 34.0, 65.1, 127.9, 129.8, 132.6, 145.0.

ESI-MS: m/z = 277.0 $[M + Na]^+$, 531.1 $[2 M + Na]^+$.

3-(3-Methyl-3*H*-diaziren-3-yl)propanenitrile (8)

2-(3-Methyl-3*H*-diaziren-3-yl)ethyl tosylate (**7**; 4.21 g, 16.6 mmol) was dissolved in anhyd DMSO (50 mL) and NaCN (1.62 g, 33.1 mmol) was added. The reaction mixture was heated overnight at 60–70 °C, and then H_2O (100 mL) was added to the brown solution. The solution was extracted with Et_2O (3 × 50 mL), and the combined Et_2O extracts were washed with H_2O (2 × 50 mL) and finally with brine (2 × 50 mL). The Et_2O solution was dried (Na_2SO_4), filtered, and the solvent was evaporated to yield **8** as a light yellow liquid (1.41 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, CH_3), 1.76 (t, J = 7.5 Hz, 2 H, CH_2), 2.26 (t, J = 7.5 Hz, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 19.2, 24.4, 30.7, 118.4.

ESI-MS: m/z = 109.3 $[M + H]^+$.

3-(3-Methyl-3*H*-diaziren-3-yl)propanoic Acid (9)

Aq NaOH (10%, 10 mL) was added to **8** (0.68 g, 6.38 mmol). The mixture was refluxed for 7 h and then Et_2O (10 mL) was added. The aqueous layer was separated and acidified with aq 4 M HCl. Subsequently, the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure to afford **9** as a light yellow liquid (0.71 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, CH_3), 1.73 (t, J = 7.3 Hz, 2 H, CH_2), 2.25 (t, J = 7.7 Hz, 2 H, CH_2), 10.98 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 25.0, 28.5, 29.3, 178.7.

MS (ESI): m/z = 126.6 $[M – H]^–$.

Ugi-4CR with 3-(3-Methyl-3*H*-diaziren-3-yl)propanoic Acid (9); N^2-Benzyl-*N*-*tert*-butyl-N^2-[3-(3-methyl-3*H*-diaziren-3-yl)propanoyl]valinamide (10a); Typical Procedure

$BnNH_2$ (0.08 g, 0.78 mmol) and isobutyraldehyde (0.06 g, 0.78 mmol) were dissolved in MeOH (10 mL) and were stirred for 2 h at r.t. to preform the imine. Subsequently, **9** (0.10 g, 0.78 mmol) and *tert*-butyl isonitrile (0.07 g, 0.78 mmol) were added. The mixture was stirred for 1 day. When TLC-monitoring and ESI-MS indicated the formation of the Ugi-4CR product, the mixture was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 4:1) to obtain **10a** as a colorless oil (0.26 g, 88%); R_f = 0.65 (hexane–EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.8 Hz, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 0.96 (d, J = 6.6 Hz, 3 H, CH_3), 1.30 (s, 9 H, 3 CH_3), 1.57–1.78 (m, 2 H, CH_2), 1.87–2.12 (m, 2 H, CH_2), 2.34–2.42 (m, 1 H, CH), 4.38–4.51 (m, 2 H, CH_2), 4.75–4.84 (m, 1 H, CH), 6.26 (br s, 1 H, NH), 7.13–7.20 (m, 2 H, 2 CH), 7.22–7.32 (m, 3 H, 3 CH).

^{13}C NMR (75 MHz; $CDCl_3$): δ = 18.9, 19.6, 19.9, 25.3, 27.4, 28.3, 28.5, 29.5, 48.7, 51.3, 65.8, 126.2, 127.2, 128.5, 137.5, 169.1, 173.8.

ESI-MS: *m/z* = 372.9 $[M + H]^+$, 395.3 $[M + Na]^+$, 371.1 $[M - H]^-$.

HRMS (ESI): *m/z* calcd for $C_{21}H_{32}N_4O_2$ + Na $[M + Na]^+$: 395.24230; found: 395.24181.

_N_-Cyclohexyl-_N_$^{\alpha}$-[3-(3-methyl-3_H_-diaziren-3-yl)propanoyl]-_N_$^{\alpha}$-(1-methylethyl)phenylalaninamide (10b)

The Ugi-4CR of **9** (0.09 g, 0.70 mmol), *i*-$PrNH_2$ (0.04 g, 0.70 mmol), phenylacetaldehyde (0.08 g, 0.70 mmol), and cyclohexyl isonitrile (0.08 g, 0.70 mmol) led to the formation of the diazirine derivative **10b**. After purification by column chromatography (hexanes–EtOAc, 4:1), **10b** was obtained as a yellow oil (0.13 g, 47%); R_f = 0.38 (hexanes–EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.45 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.13 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.16–1.42 (m, 6 H, 3 CH_2), 1.54–2.03 (m, 8 H, 4 CH_2), 2.07–2.16 (m, 1 H, CH), 3.18–3.24 (m, 1 H, CH), 3.64–3.69 (m, 1 H, CH), 3.72–3.82 (m, 2 H, CH_2), 7.14–7.29 (m, 5 H, 5 CH), 7.72 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 20.1, 20.9, 24.5, 25.4, 25.5, 28.8, 29.4, 32.5, 32.7, 35.0, 47.9, 49.6, 63.1, 126.6, 128.3, 129.4, 138.3, 171.6, 172.7.

ESI-MS: *m/z* = 399.4 $[M + H]^+$, 421.3 $[M + Na]^+$, 431.9 $[M - H]^-$.

HRMS (ESI): *m/z* calcd for $C_{23}H_{34}N_4O_2$ + Na $[M + Na]^+$: 421.25795; found: 421.25775.

_N_-[2-(2,2-Dimethoxyethyl)phenyl]-_N_^{2}-[3-(3-methyl-3_H_-diaziren-3-yl)propanoyl]-_N_^{2}-(1-methylethyl)valinamide (10c)

The Ugi-4CR of **9** (0.10 g, 0.78 mmol), *i*-$PrNH_2$ (0.05 g, 0.78 mmol), isobutyraldehyde (0.06 g, 0.78 mmol), and 2-(2,2-dimethoxyethyl)phenyl isonitrile (**11**; 0.15 g, 0.78 mmol) led to the formation of the diazirine derivative **10c**. After purification by column chromatography (hexanes–EtOAc, 3:1), **10c** was obtained as a colorless oil (0.28 g, 84%); R_f = 0.46 (hexanes–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.08 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.10–1.33 (m, 6 H, 2 CH_3), 1.70–1.92 (m, 2 H, CH_2), 2.12–2.31 (m, 2 H, CH_2), 2.84–2.94 (m, 2 H, CH_2), 3.00–3.18 (m, 1 H, CH), 3.33, 3.34 (2 s, 6 H, 2 CH_3), 4.05–4.13 (m, 1 H, CH), 4.45–4.54 (m, 2 H, 2 CH), 7.05–7.11 (m, 1 H, CH), 7.19–7.28 (m, 2 H, 2 CH), 7.77–7.81 (m, 1 H, CH), 9.98 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 20.0, 20.3, 20.9, 21.4, 25.3, 26.8, 28.9, 29.5, 35.7, 49.6, 53.4, 53.9, 68.9, 104.8, 123.8, 124.8, 127.1, 128.8, 130.9, 136.4, 171.1, 172.5.

ESI-MS: *m/z* = 433.4 $[M + H]^+$, 455.2 $[M + Na]^+$, 431.8 $[M - H]^-$.

HRMS (ESI): *m/z* calcd for $C_{23}H_{36}N_4O_4$ + Na $[M + Na]^+$: 455.26343; found: 455.26295.

1-Benzyl-2-(*tert*-butylamino)-2-oxoethyl 3-(3-Methyl-3_H_-diaziren-3-yl)propanoate (12)

t-BuNC (0.05 g, 0.55 mmol) and phenylacetaldehyde (0.07 g, 0.55 mmol) were dissolved in CH_2Cl_2 (4 mL) and subsequently **9** (0.07 g, 0.55 mmol) was added. The mixture was stirred overnight at r.t. When TLC-monitoring and ESI-MS indicated the formation of the Passerini-3CR product, the organic layer was washed with aq sat. $NaHCO_3$ (4 × 4 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude Passerini-3CR product. The residue was purified by column chromatography (PE–EtOAc, 1:2) to afford (0.16 g, 88%) **12** as a light, yellow oil (0.16 g, 88%); R_f = 0.85 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 1.28 (s, 9 H, 3 CH_3), 1.63–1.78 (m, 2 H, CH_2), 2.08–2.15 (m, 2 H, CH_2), 3.13–3.17 (m, 2 H, CH_2), 5.25 (t, *J* = 7.0 Hz, 1 H, CH), 5.70 (br s, 1 H, NH), 7.16–7.31 (m, 5 H, 5 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 25.1, 28.5, 28.5, 29.0, 37.6, 51.3, 74.8, 126.9, 128.3, 129.6, 135.8, 167.8, 170.8.

ESI-MS: *m/z* = 332.4 $[M + H]^+$, 354.4 $[M + Na]^+$, 330.4 $[M - H]^-$.

HRMS (ESI): *m/z* calcd for $C_{18}H_{25}N_3O_3$ + Na $[M + Na]^+$: 354.17936; found: 354.17863.

_N_-(4-Benzoyl)phenyl Isocyanide (14)

N-(4-Benzoylphenyl)formamide: A mixture of Ac_2O (21.0 mL, 222 mmol) and formic acid (12.0 mL, 318 mmol) was heated at 65 °C for 3 h. The mixed anhydride was added under reflux to a solution of 4-aminobenzophenone (**13**; 4.00 g, 20.3 mmol) and Et_3N (9.00 mL, 64.6 mmol) in THF (150 mL). The resulting mixture was refluxed for further 3 h. After cooling to r.t., the solvent was evaporated and the residue was taken up in EtOAc (200 mL) and H_2O (50 mL). The solution was neutralized with solid Na_2CO_3. The organic phase was separated and washed with sat. aq $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL). After drying (Na_2SO_4), the organic solvent was evaporated to yield *N*-(4-benzoyl)phenylformamide (4.43 g, 97%) as a white solid; mp 85.9–87.5 °C; R_f = 0.41 (hexanes–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (m, 2 H, CH), 7.40–7.50 (m, 4 H, CH), 7.52–7.62 (m, 2 H, CH), 7.69–7.87 (m, 10 H), 8.28 (s, 1 H), 8.43 (s, 1 H), 8.89 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.1, 119.1, 128.3, 128.4, 129.7, 129.8, 131.6, 132.2, 132.4, 132.5, 133.3, 133.8, 137.4, 137.6, 140.8, 140.9, 159.4, 162.0, 195.5, 195.9.

ESI-MS: *m/z* = 226.4 $[M + H]^+$, 224.4 $[M - H]^-$.

HRMS (ESI): *m/z* calcd for $C_{14}H_{10}NO_2$ $[M - H]^-$: 224.07115; found: 224.07126.

14: To a solution of *N*-(4-benzoyl)phenylformamide (2.11 g, 9.37 mmol) and Et_3N (12.0 mL, 86.1 mmol) in anhyd THF (200 mL) was added dropwise $POCl_3$ (2.00 mL, 21.5 mmol) at –65 °C. The resulting mixture was allowed to warm to r.t. overnight. The mixture was poured into ice water (200 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the organic solvent was evaporated. The residue was purified on silica gel (hexanes–EtOAc, 3:1) to yield **14** as a pale yellow solid (1.78 g, 91%); mp 101.9–103.4 °C; R_f = 0.72 (hexanes–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.53 (m, 4 H), 7.63 (t, *J* = 7.3 Hz, 1 H), 7.78 (d, *J* = 7.0 Hz, 2 H), 7.85 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.4, 128.5, 130.0, 131.1, 133.0, 136.6, 138.1, 166.9, 194.9.

EI-MS: *m/z* = 207.2 $[M]^+$, 130.1 $[C_8H_4NO]^+$, 105.1 $[C_7H_5O]^+$, 102.1 $[C_7H_4N]^+$, 77.1 $[C_6H_5]^+$.

2-Oxo-1-benzyl-2-{[4-(phenylcarbonyl)phenyl]amino}ethyl Benzoate (15)

To a solution of *N*-(4-benzoyl)phenyl isocyanide (**14**; 0.10 g, 0.48 mmol) and phenylacetaldehyde (0.06 g, 0.48 mmol) dissolved in CH_2Cl_2 (4 mL) was added benzoic acid (0.06 g, 0.48 mmol). The mixture was stirred overnight at r.t. When TLC-monitoring and ESI-MS indicated the formation of the Passerini-3CR product, the organic layer was washed with sat. aq $NaHCO_3$ (4 × 4 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude Passerini-3CR product. After purification by column chromatography (PE–EtOAc, 1:1), **15** was obtained as a brown oil (0.16 g, 73%); R_f = 0.67 (PE–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (d, *J* = 6.0 Hz, 2 H, CH_2), 5.73 (t, *J* = 6.0 Hz, 1 H, CH), 7.17–7.35 (m, 5 H, 5 CH), 7.43–7.65 (m, 7 H, 7 CH), 7.72–7.77 (m, 4 H, 4 CH), 7.96–8.04 (m, 3 H, 3 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7, 75.1, 119.3, 127.2, 128.2, 128.6, 128.7, 128.8, 129.6, 129.8, 129.8, 131.4, 132.3, 133.5, 133.9, 135.4, 137.6, 140.6, 165.4, 167.5, 195.5.

ESI-MS: *m/z* = = 450.3 [M + H]$^+$, 472.4 [M + Na]$^+$, 899.8 [2 M + H]$^+$, 921.5 [2 M + Na]$^+$, 448.1 [M – H]$^-$.

HRMS (ESI): *m/z* calcd for $C_{29}H_{23}NO_4$ + Na [M + Na]$^+$: 472.15248; found: 472.15168.

_N_-[(Benzyloxy)carbonyl]glycyl-_N_^{2}-benzyl-_N_-[4-(phenylcarbonyl)phenyl]valinamide (16)

$BnNH_2$ (0.05 g, 0.48 mmol) and isobutyraldehyde (0.04 g, 0.48 mmol) were dissolved in MeOH (2 mL) and stirred for 2 h at r.t. to preform the imine. Subsequently, Cbz-Gly-OH (0.10 g, 0.48 mmol) and *N*-(4-benzoyl)phenyl isocyanide (**14**; 0.10 g, 0.48 mmol) were added and the mixture was stirred for 1 day. When TLC-monitoring and ESI-MS indicated the formation of the Ugi-4CR product, the mixture was evaporated to dryness under reduced pressure. After purification by column chromatography (PE–EtOAc, 1:3), **16** was obtained as a light brown, amorphous solid (0.16 g, 59%); R_f = 0.67 (PE–EtOAc, 1:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.53–2.67 (m, 1 H, CH), 3.85–3.97, 4.08–4.20 (m, 2 H, CH_2), 4.31–4.60 (m, 2 H, CH_2), 4.69–4.90 (m, 1 H, CH), 5.09 (s, 2 H, CH_2), 5.73 (br s, 1 H, NH), 7.01–7.33 (m, 10 H, 10 CH), 7.42–7.64 (m, 5 H, 5 CH), 7.66–7.76 (m, 4 H, 4 CH), 9.15 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.7, 26.7, 43.4, 49.4, 67.0, 119.1, 126.3, 127.5, 127.9, 128.0, 128.2, 128.5, 128.6, 129.0, 129.8, 131.4, 132.1, 133.0, 135.3, 136.1, 137.8, 141.6, 156.1, 168.1, 171.4, 195.6.

ESI-MS: *m/z* = 578.7 [M + H$^+$], 600.4 [M + Na]$^+$, 1177.6 [2 M + Na]$^+$, 576.8 [M – H]$^-$.

Benzyl 4-Isocyanobutylcarbamate (18)

Benzyl 4-aminobutylcarbamate[16] (8.00 g, 36.0 mmol) was dissolved in ethyl formate (250 mL). The solution was refluxed for 4 h. After complete conversion of the amine, the solution was evaporated to dryness. Benzyl [3-(formylamino)butyl]carbamate was obtained as a colorless oil (8.90 g, 36.0 mmol, 99%) and was used without further purification. To a solution of benzyl [4-(formylamino)butyl]carbamate (8.90 g, 35.5 mmol) in anhyd CH_2Cl_2 (200 mL) was added (*i*-Pr)$_2$NH (15.7 mL, 112 mmol). The solution was cooled to 0 °C and $POCl_3$ (3.90 mL, 42.6 mmol) was added slowly via a syringe. The cooling bath was removed and the solution was allowed to warm to r.t. The solution was stirred for 2 h at r.t. Aq Na_2CO_3 (10%, 100 mL) was then added and the solution was stirred for additional 30 min. CH_2Cl_2 (100 mL) and H_2O (100 mL) were added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated. After column chromatography (CH_2Cl_2–MeOH, 9:1), **18** was obtained as a brown oil (13.0 g, 89%); R_f = 0.71 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (br s, 4 H, 2 CH_2), 3.22 (m, 2 H, CH_2), 3.40 (br s, 2 H, CH_2), 4.91–5.04 (m, 1 H, NH), 5.08 (s, 2 H, CH_2), 7.28–7.43 (m, 5 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 26.9, 39.9, 41.0, 41.1, 41.2, 66.6, 127.9, 127.9, 128.3, 136.2, 155.7, 155.8, 155.9, 156.2.

ESI-MS: *m/z* = 255.4 [M + Na]$^+$.

HRMS (ESI): *m/z* calcd for $C_{13}H_{16}N_2O_2$ + Na [M + Na]$^+$: 255.11096; found: 255.11063.

1-Benzyl-2-(*tert*-butylamino)-2-oxoethyl 3-(Phenylcarbonyl)benzoate (19)

t-BuNC (0.18 g, 2.21 mmol) and phenylacetaldehyde (0.27 g, 2.21 mmol) were dissolved in CH_2Cl_2 (10 mL) and subsequently **17** (0.50 g, 2.21 mmol) was added. The mixture was stirred overnight at r.t. When TLC-monitoring and ESI-MS indicated the formation of the Passerini-3CR product, the organic layer was washed with sat. aq $NaHCO_3$ (4 × 4 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude Passerini-3CR product. After purification by column chromatography (PE–EtOAc, 2:1), **19** was obtained as colorless, amorphous solid (0.63, 66%); R_f = 0.76 (PE–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9 H, *t*-C_4H_9), 3.28 (d, *J* = 5.7 Hz, 2 H, CH_2), 5.47 (t, *J* = 5.7 Hz, 1 H, CH), 5.58 (br s, 1 H, NH), 7.19–7.22 (m, 5 H, 5 CH), 7.49–7.53 (m, 2 H, 2 CH), 7.59–7.66 (m, 2 H, 2 CH), 7.78–7.81 (m, 2 H, 2 CH), 8.05 (dt, *J* = 7.7, 1.4 Hz, 1 H, CH), 8.20 (dt, *J* = 7.9, 1.4 Hz, 1 H, CH), 8.37 (t, *J* = 1.5 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 37.7, 51.3, 75.3, 126.9, 128.3, 128.5, 128.9, 129.5, 129.7, 130.0, 130.9, 132.9, 133.2, 134.6, 135.7, 136.8, 138.0, 164.3, 167.5, 195.4.

ESI-MS: *m/z* = 430.6 [M + H]$^+$, 452.2 [M + Na]$^+$, 859.6 [2 M + H]$^+$, 881.5 [2 M + Na]$^+$.

HRMS (ESI): *m/z* calcd for $C_{27}H_{27}NO_4$ + Na [M + Na]$^+$: 452.18378; found: 452.18336.

1-[(4-{[(Benzyloxy)carbonyl]amino}butyl)carbamoyl]-2-methylethyl 3-(Phenylcarbonyl)benzoate (20)

To a solution of benzyl 4-isocyanobutyl carbamate (**18**; 0.51 g, 2.21 mmol) and isobutyraldehyde (0.16 g, 2.21 mmol) in CH_2Cl_2 (10 mL) was added **17** (0.50 g, 2.21 mmol). The mixture was stirred overnight at r.t. When TLC-monitoring and ESI-MS indicated the formation of the Passerini-3CR product, the organic layer was washed with sat. aq $NaHCO_3$ (4 × 4 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude Passerini-3CR product. After purification by column chromatography (PE–EtOAc, 1:1), **20** was obtained as a colorless, amorphous solid (0.67 g, 57%); R_f = 0.47 (PE–EtOAc, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.42–1.61 (m, 4 H, 2 CH_2), 2.41–2.47 (m, 1 H, CH), 3.17–3.34 (m, 4 H, 2 CH_2), 5.03 (s, 2 H, CH_2), 5.08 (br s, 1 H, NH), 5.24 (d, *J* = 4.6 Hz, 1 H, CH), 6.34 (br s, 1 H, NH), 7.28–7.34 (m, 5 H, 5 CH), 7.47–7.52 (m, 2 H, 2 CH), 7.57–7.65 (m, 2 H, 2 CH), 7.77–7.81 (m, 2 H, 2 CH), 8.01 (dt, *J* = 7.9, 1.4 Hz, 1 H, CH), 8.30 (dt, *J* = 7.9, 1.4 Hz, 1 H, CH), 8.48 (t, *J* = 1.4 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 18.9, 26.5, 27.2, 30.6, 38.8, 40.4, 66.5, 79.1, 128.0, 128.4, 128.4, 128.7, 129.7, 130.0, 131.0, 132.9, 133.3, 134.6, 136.5, 136.7, 138.1, 156.4, 164.8, 169.1, 195.5.

ESI-MS: *m/z* = 531.3 [M + H]$^+$, 553.4 [M + Na]$^+$, 1083.8 [2 M + Na]$^+$, 529.5 [M – H]$^-$.

HRMS (ESI): *m/z* calcd for $C_{31}H_{34}N_2O_6$ + Na [M + Na]$^+$: 553.23146; found: 553.23143.

Benzyl {4-[(_N_-Benzyl-_N_-{[3-(phenylcarbonyl)phenyl]carbonyl}valyl)amino]butyl}carbamate (21)

$BzNH_2$ (0.24 g, 2.21 mmol) and isobutyraldehyde (0.16 g, 2.21 mmol) in MeOH (8 mL) were stirred for 2 h at r.t. to preform the imine. Subsequently, **17** (0.50 g, 2.21 mmol) and benzyl 4-isocyanobutyl carbamate (**18**; 0.51 g, 2.21 mmol) were added and the mixture was stirred for 1 day. When TLC-monitoring and ESI-MS indicated the formation of the Ugi-4CR product, the mixture was evaporated to dryness under reduced pressure. After purification by

column chromatography (PE–EtOAc, 1:3), **21** was obtained as a light brown oil (1.17 g, 85%); R_f = 0.58 (PE–EtOAc, 1:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, J = 6.4 Hz, 3 H, CH_3), 1.04 (d, J = 6.4 Hz, 3 H, CH_3), 1.42–1.58 (m, 4 H, 2 CH_2), 2.64–2.68 (m, 1 H, CH), 3.07–3.32 (m, 4 H, 2 CH_2), 4.27 (d, J = 11.0 Hz, 1 H, CH), 4.47–4.52, 4.70–4.75 (m, 2 H, CH_2), 5.02 (br s, 1 H, NH), 5.08 (s, 2 H, CH_2), 6.88 (br s, 1 H, NH), 7.13–7.23 (m, 5 H, 5 CH), 7.27–7.33 (m, 7 H, 7 CH), 7.39–7.51 (m, 4 H, 4 CH), 7.57–7.66 (m, 3 H, 3 CH), 7.75–7.77 (m, 2 H, 2 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.9, 26.6, 27.0, 27.3, 38.8, 40.5, 51.9, 53.4, 66.5, 67.3, 127.3, 128.0, 128.3, 128.3, 128.4, 129.9, 130.2, 131.1, 132.7, 136.6, 136.8, 137.7, 156.4, 170.0, 173.0, 195.4.

ESI-MS: m/z = 620.6 $[M + H]^+$, 642.4 $[M + Na]^+$, 1262.0 $[2 M + Na]^+$, 618.9 $[M - H]^-$.

HRMS (ESI): m/z calcd for $C_{38}H_{41}N_3O_5$ + Na $[M + Na]^+$: 642.29439; found: 642.29333.

***N*-[2-(2,2-Dimethoxyethyl)phenyl]-*N*$^{\alpha}$-(1-methylethyl)-*N*$^{\alpha}$-{[3-(phenylcarbonyl)phenyl]carbonyl}phenylalaninamide (22)**

i-$PrNH_2$ (0.13 g, 2.21 mmol) and phenylacetaldehyde (0.27 g, 2.21 mmol) in MeOH (8 mL) were stirred for 2 h at r.t. to preform the imine. Subsequently, **17** (0.50 g, 2.21 mmol) and **11** (0.42 g, 2.21 mmol) were added and the mixture was stirred for 1 day. When TLC-monitoring and ESI-MS indicated the formation of the Ugi-4CR product, the mixture was evaporated to dryness under reduced pressure. After purification by column chromatography (PE–EtOAc, 1:3), **22** was obtained as a light yellow oil (0.38 g, 38%); R_f = 0.61 (PE–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.48 (d, J = 6.4 Hz, 3 H, CH_3), 1.16 (d, J = 6.4 Hz, 3 H, CH_3), 2.99–3.06 (m, 2 H, CH_2), 3.31 (s, 3 H, 2 CH_3), 3.35 (s, 3 H, 2 CH_3), 3.44 (d, J = 8.8 Hz, 2 H, CH_2), 3.79 (quint, J = 6.6 Hz, 1 H, CH), 4.05–4.12 (m, 1 H, CH), 4.49 (t, J = 5.5 Hz, 1 H, CH), 7.10–7.34 (m, 9 H, 9 CH), 7.43–7.65 (m, 5 H, 5 CH), 7.69–7.79 (m, 2 H, 2 CH), 7.84–7.88 (m, 2 H, 2 CH), 9.90 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 21.1, 34.4, 36.0, 52.2, 54.6, 62.8, 106.4, 124.3, 125.1, 127.0, 127.1, 127.9, 128.3, 128.4, 128.6, 128.9, 129.7, 129.8, 129.9, 130.5, 130.8, 131.1, 132.7, 136.4, 137.0, 137.7, 137.9, 170.6, 172.3, 195.7.

ESI-MS: m/z = 579.8 $[M + H]^+$, 601.7 $[M + Na]^+$, 1179.5 $[2 M + Na]^+$, 577.8 $[M - H]^-$.

HRMS (ESI): m/z calcd for $C_{36}H_{38}N_2O_5$ + Na $[M + Na]^+$: 601.26784; found: 601.26779.

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