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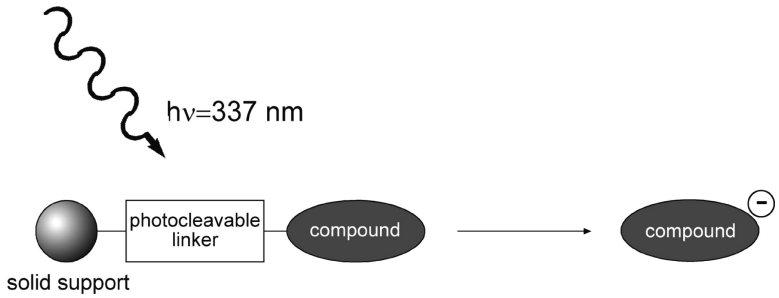

Direct Mass Spectrometric Monitoring of Solid Phase Organic Syntheses

Jantje M. Gerdes and Herbert Waldmann*

Max-Planck-Institut für molekulare Physiologie, Abt. Chemische Biologie, Otto-Hahn-Strasse 11, D-44227 Dortmund and Fachbereich 3, Organische Chemie, Universität Dortmund, Dortmund, Germany

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Direct on-bead monitoring of solid-phase reactions is possible with soft laser desorption time-of-flight mass spectrometry (SLD-TOF MS) without prior cleavage from the resin if photocleavable phenacyl ester or *o*-nitroveratryl linker groups are employed.

Combinatorial and parallel synthesis of compound libraries on solid support have emerged as key technologies for the generation of substance collections with a predetermined profile of properties, in particular, in medicinal chemistry and chemical biology. The synthesis of such libraries often includes a diverse set of transformations in multistep sequences leading to large libraries with each library member present in only (very) small amounts (in the extreme case, a different compound on every bead). To develop such solid-phase reaction sequences and to assay the content of small bead numbers, i.e., in a split-pool synthesis, efficient analytical methods are in urgent demand. Ideally, these methods should allow for direct monitoring of the reactions on the solid support, i.e., without a separate cleavage step, and they should reliably detect very small amounts of material. While Fourier transform infrared spectroscopy (FT-IR) and magic angle spinning nuclear magnetic resonance (MAS NMR)[1] can be employed for this purpose, due to signal overlap the information gained by these methods often is not sufficient for unambiguous compound identification.

Additionally, there have been approaches that utilized mass spectrometric analysis for compound identification. In most cases, the method consisted of a two-step process, cleavage from the resin, and subsequent analysis by electrospray ionization ESI-MS[2] or matrix-assisted laser desorption ionization (MALDI-TOF)[3−5]analysis. Meldal et al. augmented this technique by purification of the cleavage solution via thin-layer chromatography before submitting the samples to MALDI-TOF analysis.[6] An interesting if somewhat harsh experiment involved the fragmentation of whole functionalized polystyrene beads in an electron impact EI mass spectrometer.[7,8] The rupture of an ester bond by secondary ion SI mass spectrometry serves as a source of negatively charged ions detectable in the spectrometer.[9,10]

In principle, mass spectrometry would be an ideal technique if simultaneous cleavage of compounds from the solid support and ionization could be achieved, for instance, via cleavage of a photolabile linker in a MALDI mass spectrometer. In two inaugurating reports, Siuzdak et al.[11] and Carrasco et al.[12] demonstrated the feasibility of this approach. However, the reported methods suffer from two major drawbacks: (i) To guarantee ionization in the MALDI machine a charged peptidic tag had to be introduced, thereby significantly raising the complexity of the entire synthesis. (ii) Due to the presence of matrix peaks the method did not seem to be appropriate for the routine detection of low molecular weight compounds (MW < 500) typically required in medicinal chemistry applications. To overcome these drawbacks, a peptidic prelinker was introduced rendering the entire process somewhat lengthy. We now report that a variety of different types of organic compounds with MW < 300 can be detected and that different reaction sequences typical for regular compound library synthesis can be followed by direct and matrix-free on-bead-monitoring by means of SLD-TOF MS employing an appropriate photolabile linker group.

Figure 1 demonstrates the principle of our approach. The compound library is attached to the solid support via a photolabile linker that is cleaved by a short laser pulse and releases a detectable ion. A solid support polystyrene was employed. Because commercial MALDI-TOF spectrometers commonly are equipped with lasers emitting at a wavelength of 337 nm, photolabile linkers were used whose absorption spectra provide sufficient overlap with the lasers' emission wavelength. This precondition is fulfilled by the phenacyl linker **1** which usually is cleaved by irradiation at 350 nm and the *o*-nitroveratryl linker incorporated into **2**, which is labile if irradiated at 365 nm (Figure 1). It was planned to release negatively charged carboxylates upon irradiation, and it was hoped that photolysis would equip the analyte with sufficient energy to be released into the gas phase. Thereby, the use of an additional matrix could be omitted and

* To whom correspondence should be addressed. Fax: (+49)231−133−2499. E-mail: herbert.waldmann@mpi-dortmund.mpg.de.

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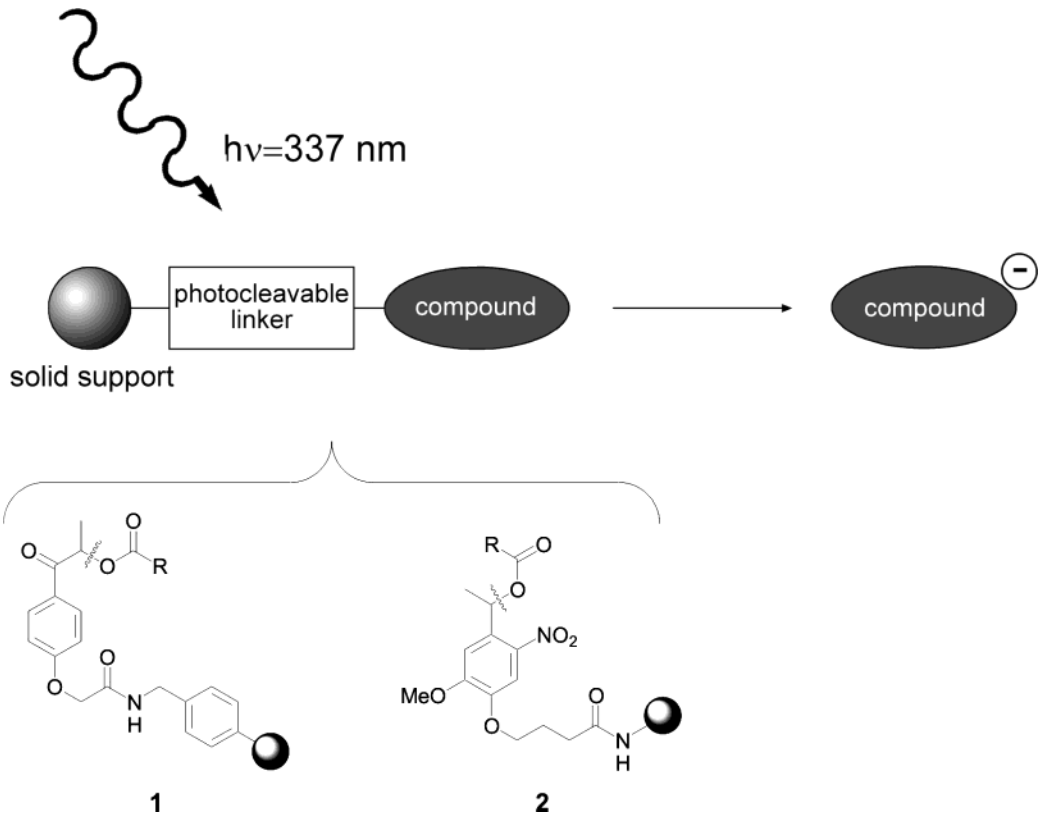


Figure 1. Basic principle of direct mass spectrometric monitoring of solid-phase organic synthesis with phenacyl ester (**1**) and *o*-nitro veratryl ester (**2**) as photolabile linker groups.

molecular ions with *m*/*z*-ratios < 300 would become detectable.

To investigate the feasibility of the approach, a variety of different carboxylic acids was attached to the polymeric support carrying either of the linker groups. Direct analysis of the loading was performed in the MALDI-TOF instrument without addition of matrix.[15] The results of this investigation are depicted in Table 1.

In the overwhelming majority of the cases were the expected signals detected. Thus, differently functionalized aromatic compounds such as iodobenzoic acids **3** and **4**, 6-chloronicotinic acid **6**, and 2,5-dihydroxybenzoic acid **7**, as well as hydroxy-functionalized aliphatic acids (**5**, **13**, **22**) and unsaturated carboxylic acids gave strong peaks. Also β-lactam **14**, β- and ϵ-amino acids **16** and **17** as well as keto acids **18** and **19** responded positively. The absorbance characteristics of the carboxylic acids varied in such a way that compounds with absorption bands around 350 nm or at different wavelengths could be detected. In these experiments, phenacyl ester **1** proved to be superior to *o*-nitroveratryl ester **2**.

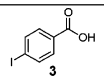
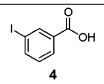
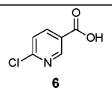
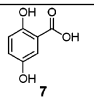
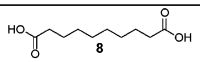
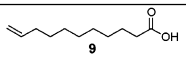
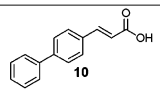
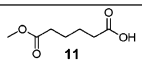
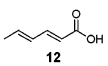
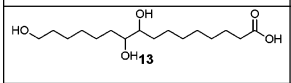
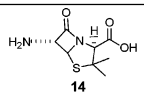
These results clearly and convincingly demonstrate that structurally diverse solid-phase-bound compounds with molecular weights < 300 can be detected with this mass spectrometric technique. We found the lowest mass detectable to be ca. $m/z = 120$; however, in certain cases, e.g., acrylic acid **20**, even masses < 100 could be detected.

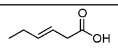
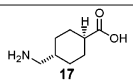
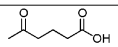
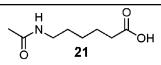
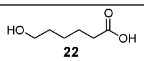
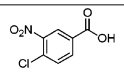
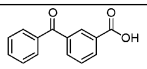
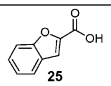
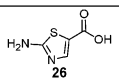
Not unexptectedly, compounds with pronounced photoreactivity are not amenable to analysis via the SLD-TOF method. Thus, nitrobenzoic acid **23**, benzophenone derivative **24**, as well as 2-benzofuranoic acid **25** and 2-aminothiazole carboxylic acid **26**, which have complex photoreactivity patterns,[13,14] were not detectable. For instance, nitro compounds are known to react via Norrish type reactions, a property that was exploited in the development of *o*-nitrobenzyl based protecting groups and linkers such as *o*-nitroveratryl ester **2**. Resulting radicals are likely to react with the surrounding polymer scaffold and hence cannot be detected in the time-of-flight mass detector. Benzophenone and related structures on the other hand display photoreactivity patterns that are exploited f.e. in photolabeling experiments in protein biochemistry. Upon irradiation with wavelengths of 350 nm, the benzophenone forms a triplet excited state which can be interpreted as biradical and which in turn abstracts rapidly a hydrogen radical from the surroundings. The hydroxydibenzyl radical formed in turn is prone to react with the polymer scaffold again rendering the molecule covalently bound to the polymer scaffold and thus likewise undetectable for the mass detector.

To demonstrate the applicability of this on-resin mass-spectrometric monitoring technique to solid-phase chemistry, two syntheses of pharmacologically and biologically relevant compound classes employing different types of transformations were investigated.[15]

On one hand, 1,4-benzodiazepines, i.e., a compound class with a privileged structure[16] were synthesized following the method of Mayer et al. (Scheme 1).[17] To this end, Fmoc-protected amino acids **27** were coupled to Merrifield resin. Similar to the observation of Siuzdak et al.[11] we could not detect this compound class by SLD-TOF. But after deprotection using 20% piperidine in dimethyl formamide and subsequent acylation with anthranilic acid, intermediates **28**

Table 1. Structures of Compounds Tested for Detectability in the MALDI TOF Spectrometer[a]

Structure	MW	Linker **1**	Linker **2**
 **3**	248.02	+	+
 **4**	248.02	+	n. d.
 **5**	76.05	+	-
 **6**	157.55	+	+
 **7**	154.12	+	+
 **8**	202.25	+	n. d.
 **9**	184.28	+	-
 **10**	224.25	+	-
 **11**	160.17	+	-
 **12**	112.13	-	+ (dimer/tetramer)
 **13**	304.42	+	-
 **14**	216.26	+	n. d.

Structure	MW	Linker **1**	Linker **2**
 **15**	114.14	+	n. d.
 **16**	143.18	+	n. d.
 **17**	157.21	+	n. d.
 **18**	130.14	+	+
 **19**	88.06	+	n. d.
 **20**	72.06	+	n. d.
 **21**	173.21	+	n. d.
 **22**	132.16	+	n. d.
 **23**	201.56	-	-
 **24**	226.23	-	-
 **25**	162.14	-	-
 **26**	144.15	-	-

[a] "+" mass signal detected. "−" no mass signals observed. n.d., this combination has not been tested.

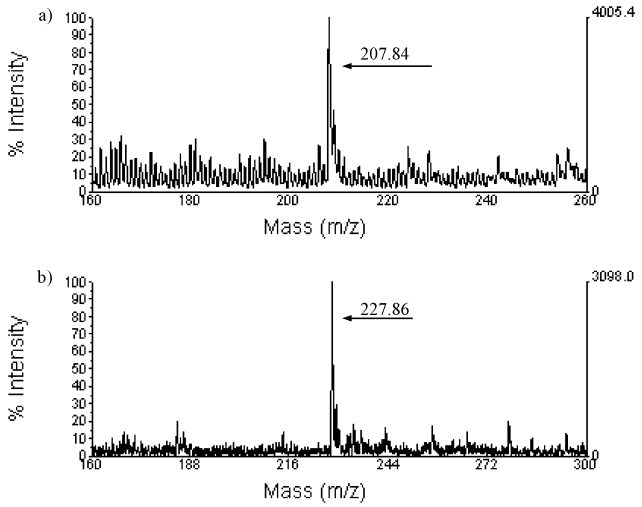


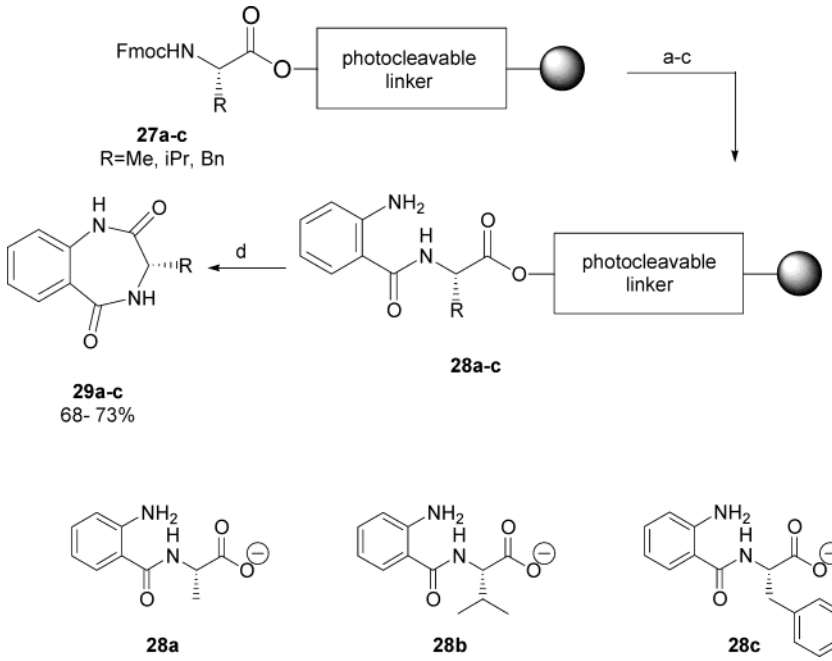
Figure 2. (a) Mass spectrum of H-Abz-Ala-OH **28a** on phenacyl PS resin, (b) Mass spectrum of **31c** (before cleavage with N_2H_4) on phenacyl PS resin; arrows indicate in both cases $[M - H]^-$ signals. Detected masses are slightly greater than expected because of the bead diameter which causes a shorter flight path.

gave strong signals in the mass spectrometer (Figure 2a), irrespective of the linker employed. Finally, benzodiazepines **29** were released from the solid support by treatment with potassium *tert*-butyl alcoholate in tetrahydrofuran at 60 °C. If the *o*-nitroveratryl linker **2** was used the yields were similar to the values reported by Mayer et al.[17] who employed the Wang linker. The phenacyl linker gave somewhat lower yields.

On the other hand, a Pd^0-catalyzed biaryl synthesis employing the Suzuki reaction was carried out. Biaryls are among the most frequently found structural subunits of all drugs[18−20] and Pd^0-catalyzed transformations belong to the most frequently applied solid-phase reactions. Thus, *m*- and *p*-iodobenzoic acid were attached to the solid support using both linker groups and then subjected to Suzuki-coupling with different boronic acids (Scheme 2). While upon use of the *o*-nitroveratryl linker solid-phase bound biaryls could not be detected, in the presence of the phenacyl ester strong product peaks were recorded (Figure 2b). Release of the products from the solid support was achieved by irradiation with a mercury vapor lamp or nucleophilic cleavage using hydrazine hydrate in dimethyl formamide.

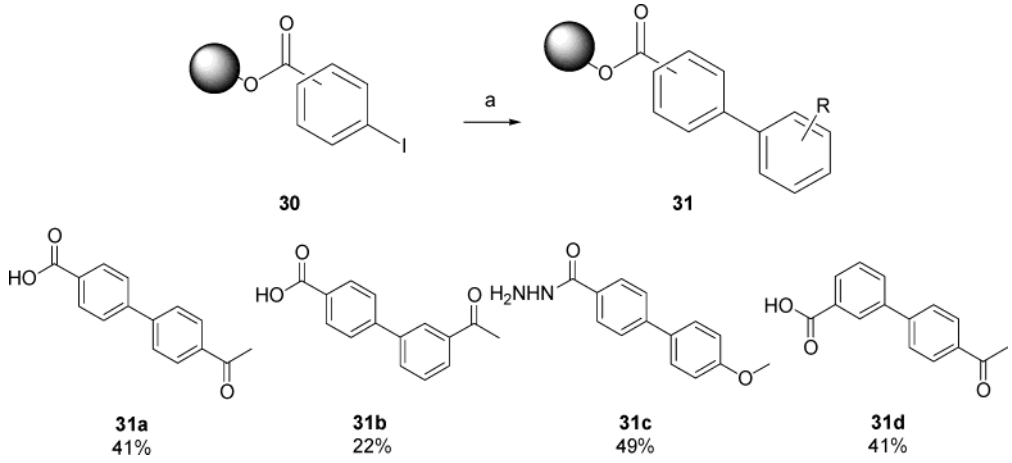
Finally, a two-step sequence employing an oxidation and a Grignard reaction was investigated (Scheme 3). Thus,

Scheme 1. Synthesis of 1,4-Benzodiazepine-2,5-diones on Linker **2** and Structures of Mass Spectrometrically Detected Intermediates **28a**−**c**[a]



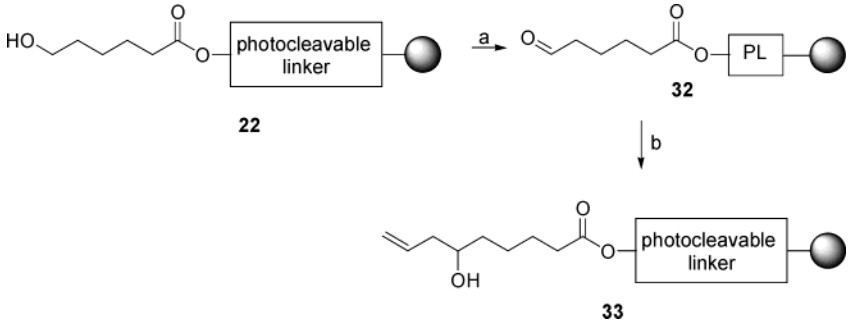
[a] (a) 20% piperidine, DMF (4 × 5 min), (b) Fmoc- Abz-OH, HBTU, HOBt, DIPEA, DMF (2 × 2 h), (c) 20% piperidine DMF (4 × 5 min), (d) NaO*t*Bu, THF, 60 °C, 24 h.

Scheme 2. Suzuki Cross Coupling Reaction of Iodobenzoic Acid with Boronic Acids on Linker **1** and Structures of Mass Spectrometrically Detected Intermediates **31**[a]



[a] (a) 10 equiv of boronic acid, 3 equiv of K_3PO_4*$3H_2O$, 20 mol % $Pd(PPh_3)_4$, DMF/H_2O 6:1.

Scheme 3. Synthesis of 6-Hydroxynon-8-enoic Acid (**33**) from **22**[a]



[a] (a) IBX in DMSO, THF, 24 h. (b) Allyl magnesium chloride, THF, −25 °C, 12 h.

6-hydroxycaproic acid **22** was attached to the polystyrene resin by means of the phenacyl linker. Oxidation with the hypervalent iodine compound IBX in a mixture of dimethyl sulfoxide and tetrahydrofuran followed by addition of allylmagnesium chloride to the aldehyde formed gave immobilized homoallylic alcohol **33**. Both steps were readily monitored in the MALDI-TOF spectrometer.

In a small series of orienting experiments, we investigated

the immobilization and subsequent mass spectrometric detection of functional groups other than carboxylic acids. To determine if amines can be detected, 2-aminobenzoyllysine allyl ester was coupled to nitroveratryl linker **2**. This molecule was linked to the resin as a urethane via the free ϵ-amino group. After Pd^0-mediated cleavage of the allyl ester in the presence of $NHMe_2*BH_3$, the borane complex of the expected product was detected in the positive ion mode.

For application to a broader range of functional groups, a dual handle strategy as demonstrated already by Carrasco et al.[10] could be envisioned. Preliminary experiments showed that 4-hydroxymethylphenoxyacetic acid HMPA, a common linker group,[21] could be detected when coupled to linker **1**.

In conclusion, we have demonstrated that different organic transformations and compound classes can be monitored and detected on solid support by means of SLD-TOF mass spectrometry if the photolabile *o*-nitroveratryl or the phenacyl linker are employed. The method omits the use of a disturbing matrix and is fast and very practical, i.e., it is suitable for application in regular MALDI-TOF machines. It detects masses with *m*/*z* ratios down to 100−200 reliably.

Thus, the method should be applicable in the development of compound library syntheses on polymeric carriers. Preliminary tests have confirmed the applicability of this method not only to carboxylic acids but also to amines linked to the solid support.

Mass spectrometric analysis requires only very small amounts of analyte (ca. 10^{-15} mol).[22] Thus, given the spatial resolution of the laser, in principle a single bead is sufficient for compound identification. This indicates that MALDI-TOF mass spectrometry could be employed very advantageously to deconvolute compound libraries generated in split-mix syntheses.

Experimental Section

The bromophenacyl and the *o*-nitorveratryl functionalized styrene were purchased from Novabiochem. All chemicals were purchased from Acros, Aldrich, Avocado (palladium catalyst), Biolsolve, and Fluka. With the exception of *N*,*N*-dimethyl formamide DMF, *N*,*N*-dimethyl acetamide, and *N*-methyl pyrrolidone NMP, all solvents were distilled prior to use. Dry DMF was purchased from Fluka.

Solution-phase NMR spectra were measured on a Varian Mercury 400 MHz spectrometer (reference tetramethylsilane TMS, $\delta = 0$ ppm). The HPLC-MS measurements were carried out on a HPLC system 1100 series by Hewlett-Packard and a Finnigan LCQ ESI spectrometer using C18 reversed phase column material and a linear gradient of acetonitrile and water. Mass spectra were measured on a Voyager DE Pro MALDI-TOF spectrometer equipped with a LeCroy Digitizer and an internal laser, sample plates are presented horizontally in this type of spectrometer. Spectra were measured in the linear operation mode with delayed extraction, mostly in the negative ion mode. Other settings were optimized laser rate type, bin size 0.5 ns; vertical scale, 1000 mV with full input bandwidth; accelerating voltage: 20000 V; grid voltage: 95%; and guide wire voltage: 0.05%. Loading of resins was determined by measuring the UV absorption of the dibenzofulvene-piperidine adduct at 301 nm.[23]

General Procedure for the Loading of Bromophenacyl Polystyrene. A 0.5 M solution of 3 equiv of carboxylic acid, 0.3 equiv of cesium iodide, and 3 equiv of DIEA in dry DMF was added to a suspension of 1 equiv of brominated phenacyl resin in little dry DMF and the suspension was agitated overnight. Subsequently, the resin was washed with DMF (2*5 mL), with DCM (3*5 mL), and successively with MeOH, DCM, ethyl acetate, and MeOH (5 mL each). The immobilized carboxylic acid was dried under reduced pressure.

General Procedure for the Loading of *o*-Nitroveratryl Polystyrene. To a solution of 5 equiv of carboxylic acid in a mixture of THF and DCM was subsequently added 3.75 equiv of MeIm and 5 equiv of MSNT. After a few minutes, the reaction mixture were added to a suspension of 1 equiv of *o*-nitroveratryl PS resin in DCM. After 2 h of agitation of the sample at room temperature, the resin was washed successively with DCM (3*5 mL), DMF (3*5 mL), DCM, ethyl acetate, and methanol (5 mL each). The immobilized carboxylic acid was dried under reduced pressure.

H-Abz-Ala 28a on *o*-Nitroveratryl PS Resin. A suspension of 121 mg (30.3 μmol) of Fmoc-alanine on *o*-nitroveratryl PS resin in 3 mL of 20% piperidine in DMF was agitated at room temperature for 10 min. The solution was filtrated and the resin repeatedly agitated in 20% piperidine in DMF for 10 min (3 times). Again, the resin was filtrated and the resin was washed with DMF (4*3 mL) and suspended in 1.5 mL of dry DMF. At the same time a solution of 54.0 mg (150 μmol, 5.0 equiv) of Fmoc-anthranilic acid, 38.2 mg (249 μmol, 8.2 equiv) of HOBt, and 55.6 mg (147 μmol, 4.8 equiv) of HBTU in 1.5 mL of DMF was preactivated with 50.0 μL (292 μmol, 9.6 equiv) of DIEA for 5 min before addition to the resin. The reaction mixture was agitated at room temperature overnight. The resin was washed with DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Loading (Fmoc):[23] 0.22 mmol/g. The product was suspended in 2.5 mL of 20% piperidine in DMF and agitated at room temperature for 15 min before filtration. This procedure was repeated once. Subsequently, the resin was washed with DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Isolated material: 92.6 mg of yellow polymer beads. MS: *m*/*z* calc. 207.2; found 207.8.

3-Methyl-3,4-dihydro-1*H*-benzo[*e*]-1,4-diazepin-2,5-dione (29a). A suspension of 92.6 mg (20.4 μmol) of H-Abz-Ala **28a** on *o*-nitroveratryl PS resin in 1.5 mL of dry THF was treated with 4.3 mg (44.7 μmol, 2.2 equiv) of NaO*t*Bu and heated at 70 °C for 24 h. The resin was washed with dry THF (2*3 mL), DCM (3*3 mL) and subsequently with MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The solvent was removed and the residue dried under reduced pressure. Yield: 2.8 mg (14.8 μmol, 73%) white solid, ESI-MS: 191.1 $[M + H]^+$; ^{1}H NMR (400 MHz, D_2O) (approximately 30% impurity of the open chain amide): δ=

1.32 (d, $J = 7.2$ Hz, 3H, Me), 4.22 (q, $J = 7.2$ Hz, 1H, αCH), 6.73−6.79 (m, 2H, arom. H), 7.23 (t, $J = 7.8$ Hz, 1H, arom. H), 7.40 (d, $J = 7.5$ Hz, 1H, arom. H).

H-Abz-Val-OH on *o*-Nitroveratryl PS Resin 28b. A suspension of 214 mg (38.4 μmol) of Fmoc-valin on *o*-nitroveratryl PS resin in 3 mL of 20% piperidine in DMF was agitated 10 min at room temperature. The solution was filtrated and the resin repeatedly agitated in 20% piperidine in DMF for 10 min (3 times). The resin was washed with DMF (4*3 mL) and suspended in 1.5 mL of dry DMF. At the same time a solution of 70.6 mg (150 μmol, 5.0 equiv) of Fmoc-anthranilic acid, 42.2 mg (249 μmol, 8.2 equiv) of HOBt, and 72.3 mg (190 μmol, 4.95 equiv) of HATU in 1.5 mL of DMF was preactivated with 32.9 μL (192 μmol, 5 equiv) of DIEA for 2 min before addition to the resin. The reaction mixture was agitated at room temperature overnight. The resin was washed with DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Loading (Fmoc):[23] 0.16 mmol/g. The product was suspended in 2.5 mL of 20% piperidine in DMF and agitated at room temperature for 15 min before filtration. This procedure was repeated once. Subsequently, the resin was washed with DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Isolated material: 92.6 mg of yellow polymer beads. MS: *m*/*z* calc. 235.3; found 235.6.

3-*iso*-Propyl-3,4-dihydro-1*H*-benzo[*e*]-1,4-diazepin-2,5-dione (29b). A suspension of 199 mg (31.8 μmol) of H-Abz-Val **28b** on *o*-nitroveratryl PS resin in 3 mL of dry THF was treated with 7.6 mg (79.1 μmol, 2.2 equiv) of NaO*t*Bu and heated at 70 °C for 24 h. The resin was washed with dry THF (2*3 mL), DCM (3*3 mL) and subsequently with MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The solvent was removed and the residue dried under reduced pressure. Yield: 4.7 mg (21.5 μmol, 68%) white solid, ESI-MS: 219.2 $[M + H]^+$; ^{1}H NMR (400 MHz, D_2O) (approximately 10% impurity of the open chain amide): $\delta =$ 1.04 (d, $J = 6.8$ Hz, 6H, 2 Me),2.56−2.63 (m, 1H, −C*H*$(CH_3)_2$), 3.90−3.93 (m, 1H, αCH), 6.73−6.75 (m, 1H, arom. H), 6.90−6.94 (m, 1H, arom. H), 7.12−7.20 (m, 2H, arom. H), 7.53 (d, $J = 7.4$ Hz, 1H, arom. H).

H-Abz-Phe-OH on *o*-Nitroveratryl PS Resin 28c. A suspension of 214 mg (38.4 μmol) of Fmoc-phenylalanine on *o*-nitroveratryl PS resin in 3 mL of 20% piperidine in DMF was agitated 10 min at room temperature. The solution was filtrated and the resin repeatedly agitated in 20% piperidine in DMF for 10 min (3 times). The resin was washed with DMF (4*3 mL) and suspended in 1.5 mL of dry DMF. At the same time a solution of 99.2 mg (271 μmol, 5.0 equiv) of Fmoc-anthranilic acid, 58.3 mg (380 μmol, 7.0 equiv) of HOBt, and 100.9 mg (265 μmol, 4.9 equiv) of HATU in 1.5 mL of DMF was preactivated with 46.4 μL (270 μmol, 5 equiv) of DIEA for 2 min before addition to the resin. The reaction mixture was agitated at room temperature overnight. The resin was washed with DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The coupling procedure was repeated once. The resin was dried under reduced pressure. Loading (Fmoc):[23] 0.21 mmol/g. The product was suspended in 2.5 mL of 20% piperidine in DMF and agitated at room temperature for 15 min before filtration. This procedure was repeated once. Subsequently, the resin was washed with DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Isolated material: 92.6 mg of yellow polymer beads. MS: *m*/*z* calc. 283.3; found 283.8.

3-Benzyl-3,4-dihydro-1*H*-benzo[*e*]-1,4-diazepin-2,5-dione (29c). A suspension of 230 mg (48.3 μmol) of H-Abz-Phe **28c** on *o*-nitroveratryl PS resin in 3 mL of dry THF was treated with 7.6 mg (79.1 μmol, 2.2 equiv) of NaO*t*Bu and heated at 70 °C for 24 h. The resin was washed with dry THF (2*3 mL), DCM (3*3 mL) and subsequently with MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The solvent was removed and the residue dried under reduced pressure. Yield: 8.0 mg (35.4 μmol, 73%) white solid, ESI-MS: 267.2 $[M + H]^+$; ^{1}H NMR (400 MHz, D_2O): $\delta =$ 3.86−3.89 (m, 1H, αC*H*), 5.71−5.72 (m, 2H, −CH_2Ph), 7.08 (d, $J = 7.6$ Hz, 1H, arom. H), 7.16−7.25 (m, 5H, phenyl), 7.29 (d, $J = 8.0$ Hz, 1H, arom. H), 7.48 (dd, $J_1 = J_2 = 7.6$ Hz, 1H, arom. H), 7.65 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H, arom. H).

General Procedure for the Suzuki Coupling of Immobilized Iodobenzoic Acid. A suspension of 1 equiv of immobilized iodobenzoic acid, 2.5 equiv of potassium phosphate hydrate, and 10 equiv of boronic acid in degassed DMF/water 6:1 was treated with 0.05 equiv of $Pd(PPh_3)_4$ and gently agitated at 80 °C for 24 h. The resin was washed with DMF (5 mL), DMF/water 6:1 (2*5 mL), DMF (2*5 mL), DCM (3*5 mL), MeOH, DCM, ethyl acetate, and MeOH (5 mL each). The product was dried under reduced pressure.

4′-Acetylbiphenyl-4-carboxylic Acid (31a). According to the general procedure the Suzuki coupling was carried out with 99.1 mg (79.3 μmol) of 4-iodobenzoic acid on phenacyl ester PS resin, 136 mg (806 μmol, 10.2 equiv) of 4-acetylphenylboronic acid, and 34.1 mg (161 μmol, 2.0 equiv) of K_3PO_4*$3H_2O$ in 3.5 mL DMF/water 6:1. Isol. Mat.: 92.1 mg of gray polymer beads. MS: *m*/*z* calc. 239.3, found 239.6. The product was suspended in 3 mL of 1% ethanolamine in THF under argon and irradiated with a Hg vapor lamp overnight. The resin was washed with THF (2*3 mL), DCM (2*3 mL), MeOH, DCM, ethyl acetate, and MeOH. The filtrate was evaporated to dryness and the residue dried under reduced pressure. Yield: 4.8 mg (20 μmol, 41%) of white solid. LCMS: 239.1 $[M - H]^-$; ^{1}H NMR (400 MHz, $CDCl_3$, little CD_3OD): $\delta = 2.58$ (s, 3H, −CH_3), 7.59−7.70 (m, 4H, arom. H), 7.93 (d, $J = 8.6$ Hz, 2H, arom. H), 8.22 (d, $J =$ 8.4 Hz, 2H, arom. H).

3′-Acetylbiphenyl-4-carboxylic Acid (31b). According to the general procedure, the Suzuki coupling was carried out with 255 mg (239 μmol) of 4-iodobenzoic acid on phenacyl ester PS resin, 254 mg (1.55 mmol, 6.5 equiv) of 3-acetylphenylboronic acid, and 81 mg (382 μmol, 2 equiv) of K_3PO_4*$3H_2O$ in 5 mL of DMF/water. Isol. Mat.: 114.1 mg of gray polymer beads. MS: *m*/*z* calc. 239.3, found 239.6. The product was suspended in 3 mL of 1% ethanolamine in

THF under argon and irradiated with a Hg vapor lamp overnight. The resin was washed with THF (2*3 mL), DCM (2*3 mL), MeOH, DCM, ethyl acetate, and MeOH. The filtrate is evaporated to dryness and the residue dried under reduced pressure. Yield: 3.2 mg (13.3 μmol, 22%) of white solid. LCMS: 239.1 $[M - H]^-$; ^{1}H NMR (400 MHz, $CDCl_3$, little CD_3OD): $\delta = 2.56$ (s, 3H, $-CH_3$), 7.41−7.43 (m, 1H, arom. H), 7.66−7.70 (m, 3H, arom. H), 7.82−84 (m, 1H, arom. H), 8.11−8.20 (m, 3H, arom. H).

4′-Methoxybiphenyl-4-carboxylic Acid (31c). According to the general procedure the Suzuki coupling was carried out with 207 mg (124 μmol) of 4-iodobenzoic acid on phenacyl ester PS resin, 190 mg (1.25 mmol, 10 equiv) of 4-methoxyphenylboronic acid, and 52.8 mg (249 μmol, 2 equiv) of K_3PO_4*$3H_2O$ in 4.9 mL of DMF/water. Isol. Mat.: 197.5 mg of gray polymer beads. MS: *m*/*z* calc. 227.2, found 227.9. The product was suspended in 2 mL of 5% hydrazine hydrate in DMF. After 2 h of gentle agitation, the resin was washed with DMF (2*3 mL), DCM (2*3 mL), MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The filtrate is evaporated to dryness and the residue dried under reduced pressure. Yield: 10.6 mg (44.0 μmol, 42%) of white solid; ESI-MS: 243.2 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$, little CD_3OD): $\delta = 3.44$ (s, 3H, $-CH_3$), 6.74 (d, $J = 9.1$ Hz, 2H, arom. H), 7.40−7.49 (m, 3H, arom. H), 7.71−7.74 (m, 1H, arom. H), 7.88−7.91 (m, 1H, arom. H), 8.17 (s, 1H, arom. H).

3′-Acetylbiphenyl-3-carboxylic Acid (31d). According to the general procedure the Suzuki coupling was carried out with 73.5 mg (44.1 μmol) 3-iodobenzoic acid on phenacyl ester PS resin, 73.9 mg (442 μmol, 10 equiv) of 3-acetylphenylboronic acid, and 20.8 mg (98 μmol, 2.2 equiv) of K_3PO_4*$3H_2O$ in 4.9 mL of DMF/water. Isol. Mat.: 55.6 mg of gray polymer beads. MS: *m*/*z* calc. 239.3, found 239.8. The product was suspended in 3 mL of 1% ethanolamine in THF under Argon and irradiated with a Hg vapor lamp overnight. The resin was washed with THF (2*3 mL), DCM (2*3 mL), MeOH, DCM, ethyl acetate, and MeOH. The filtrate is evaporated to dryness and the residue dried under reduced pressure. Yield: 2.8 mg (13.3 μmol, 39%) white solid. LCMS: 239.1; ^{1}H NMR (400 MHz, $CDCl_3$, little CD_3OD): $\delta = 2.54$ (s, 3H, $-CH_3$), 7.43−7.57 (m, 3H, arom. H), 7.80−7.85 (m, 2H, arom. H), 8.08−8.11 (m, 2H, arom. H), 8.38 (s, 2H, arom. H).

6-Oxohexanoic Acid on Phenacylester PS Resin (32). A suspension of 158 mg (82.0 μmol) of 6-hydroxyhexanoic acid on phenacylester PS resin in 1 mL of dry THF was treated with a solution of 118.4 mg (423 μmol, 5 equiv) of IBX in 1.3 mL of dry DMSO. The mixture was agitated for 24 h and subsequently washed with DMSO (3 mL), DMSO/THF 1:1 (3*5 mL), DCM (3*3 mL), MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Isol. Mat.: 145.8 mg white resin, MS: *m*/*z* calc 129.1, found 129.9.

6-Hydroxy-8-nonenoic Acid (33). A suspension of 127 mg (53.3 μmol) of **32** in 3 mL of dry THF was cooled to −30 °C and subsequently reacted with 0.76 mL (1.52 mmol, 29 equiv) of 2 M allylmagnesium chloride in THF and gently agitated overnight. The mixture was stopped by addition of 2 mL of MeOH and the resin subsequently washed with DCM (5 mL), DMF (2*3 mL), DCM (3*3 mL), MeOH, DCM, ethyl acetate, and MeOH (3 mL each). The resin was dried under reduced pressure. Isol. Mat.: 145.8 mg of white resin, MS: *m*/*z* calc 171.2, found 171.9.

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(15) Typically after the reaction, the resin is washed with DMF, methylene chloride, MeOH, methylene chloride, ethyl acetate, and MeOH successively. For MS analysis, a small sample (ca. 50 beads) is removed from the suspension of the final MeOH wash and diluted with about five times the volume of water. Now, the sample is simply pipetted onto the MALDI plate (Eppendorf pipet, volume about 1.5 μL) and left in the dark until the solution is evaporated. In presence of basic functionalities (i.e., amino groups), signal intensity can be improved significantly by adding 1% ammonium hydroxide in water.
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