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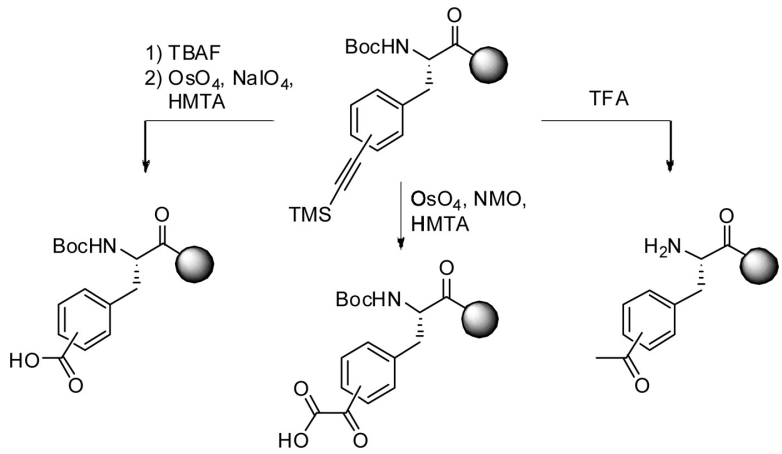

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Divergent Pathway for the Solid-Phase Conversion of Aromatic Acetylenes to Carboxylic Acids, α-Ketocarboxylic Acids, and Methyl Ketones

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An efficient divergent pathway for the selective and quantitative solid-phase conversion of aromatic acetylenes to the corresponding carboxylic acids, α-keto-carboxylic acids, and methyl ketones is presented. A range of aromatic trimethylsilyl-protected acetylene building blocks was synthesized in excellent yields using a Sonogashira cross-coupling protocol and used in solid-phase synthesis on PEGA resin. Dependent on the selection of conditions, the same solid-supported alkyne could be quantitatively converted to an aromatic carboxylic acid, an aromatic α-ketocarboxylic acid, or an aromatic methyl ketone. The conversion to carboxylic acid involved an OsO_4/$NaIO_4$/HMTA-mediated oxidative cleavage of the silyl-deprotected alkyne to provide the aromatic carboxylate in excellent yield. The α-ketocarboxylic acids were obtained by direct treatment of the trimethylsilyl-protected alkyne with OsO_4/NMO/HMTA, while the ketones were obtained by simple acid-mediated hydration of the alkyne using aqueous TFA. In general, all products were obtained in excellent purities, typically above 90%. In addition, it was shown that the alkyne-containing building blocks could easily be incorporated into resin-bound peptides and after chemoselective conversion of the alkyne the new functional groups could be used for further derivatization into peptidomimetic compounds.

Introduction

The field of peptide-research has emerged as one of the leading fields in modern bioorganic and medicinal chemistry. It has been estimated that, apart from peptides already being marketed as pharmaceuticals, more than 200 peptide-based drugs are currently in development, and approximately half of these are in clinical trials or waiting for approval.[1] Peptides display a broad range of activities in living organisms. They function as hormones, neurotransmitters, cytokines, and growth factors[2,3] and therefore constitute attractive endogenous leads for drug discovery. Their direct use as pharmaceuticals has often been limited by rapid degradation and clearance, and particularly by poor membrane permeability leading to low oral bioavailability. However new techniques for peptide formulation greatly enhance the potential for peptides and peptidomimetics as pharmaceuticals.[4] Their biological activity is often related to the accurate display of a few pharmacophores, and the spatial arrangement is critical for selective interaction with target receptors. Initially, upon the introduction of solid-phase peptide synthesis (SPPS), an impressive number of syntheses of natural peptide hormones was described and has facilitated the biochemical investigation of hormone−receptor interaction. It was soon realized that the natural peptides were not suited for drug development. However, the development of unnatural amino acid building blocks and combinatorial methods for assembly of biochemically more viable peptidomimetic analogues of the natural hormones has changed this situation dramatically.

Today, a major effort of pharmaceutical auxiliary industry is to develop building blocks that facilitate incorporation during peptide and peptidomimetic synthesis. However, despite the easy access to these building blocks, the development of site-selective and reliable chemical solid-phase methods for different transformations of a common functional group is a valuable alternative, particularly important in case of incompatibility of the target functional group with standard SPPS procedures. Such functional groups often require specific protecting group manipulations and elaborate synthetic protocols. Furthermore, site-selective chemical modification of peptidic molecules[5–8] may allow for the conjugation to biologically relevant molecules by incorporation of novel handles for chemical derivatization.[9–11]

With the aim of developing solid-phase methods amenable to the construction of split/mix libraries incorporating peptides with diverse display of pharmacophores, we here present a selective and divergent pathway for the conversion of peptide-supported aromatic acetylenes into three different functionalities.

During previous studies on the solid-phase synthesis of carboxylic and oxamic acids via an OsO_4/$NaIO_4$/hexamethylenetetramine (HMTA)-mediated oxidative cleavage of aliphatic acetylenic peptides (Scheme 1),[12] a range of minor byproducts were observed, depending on the reaction conditions. We have examined the nature of these products and have, on that basis, developed new methods for the transformation of the alkyne moiety on the solid support into the α-ketocarboxylic acid and methyl ketone functional groups. These moieties have previously proven of great interest in

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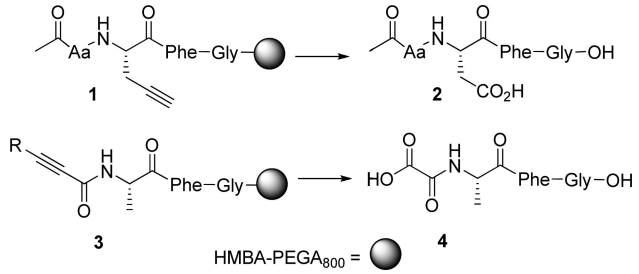
Scheme 1. OsO_4/$NaIO_4$/HMTA-Mediated Oxidative Cleavage of Solid-Supported Alkyne-Containing Peptides[12]



medicinal chemistry. Various aromatic α-ketocarboxylic acids have for instance been found to inhibit the protein tyrosine phosphatase (PTP) of *Yersinia enterocolitica*.[13–16] Phosphatases constitute an important class of biological targets because of their role in a number of diseases,[17] and they are notably emerging targets for the treatment of type 2 diabetes.[18] Furthermore, peptides incorporating carboxy-substituted phenylalanines have been found to be inhibitors of PTP 1B[19] and potent inhibitors of the protein tyrosine kinase $pp60^{c\text{-}src}$.[20] Finally, a cyclic enkephalin analogue incorporating a crucial 4-acetylphenylalanine residue has been shown to possess nanomolar μ- and δ-opioid agonist activities.[21] It may therefore be assumed that libraries exhibiting a combinatorial display of these three pharmacophores will serve as valuable tools for structure−activity studies or even drug-lead generation for these and other targets.

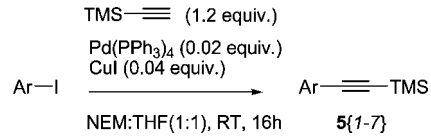
Alkynes constitute versatile functional groups in organic chemistry, and their applications are numerous. They can, for instance, participate as coupling partners in transition-metal-mediated coupling reactions, thus enabling the creation of *C−C bonds*, for example, in the Pd−Cu-catalyzed Sonogashira cross-coupling reaction or in the Cu-mediated coupling of terminal alkynes (Gläser reaction). The recently described Cu(I)-mediated cycloaddition of azides to alkynes,[22–24] displaying "click"properties[25] adds yet another important transformation of the alkyne moiety to the chemist's toolbox. The present reactions are known from solution-phase synthesis,[26–37] but no reports seem to exist on the solid-phase conversion of aromatic acetylenes to carboxylic acids, α-ketocarboxylic acids, or methyl ketones.

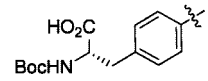
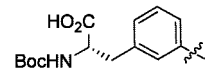
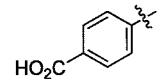
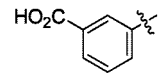
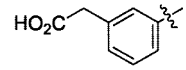
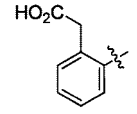
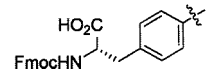
Results and Discussion

Aromatic acetylene building blocks, each containing a free carboxylic acid handle for attachment to the solid phase, were synthesized in solution by Sonogashira cross-coupling. A range of different substituted aryl iodides were reacted with trimethylsilyl-acetylene (TMS-acetylene) under catalysis with a Pd/Cu-couple ($Pd(PPh_3)_4$ and CuI) in the presence of *N*-ethylmorpholine (NEM). The TMS-protected aromatic acetylene products **5**{*1*−*7*} were all obtained in excellent yields, ranging from 87% to >95% (Table 1). Alternatively, the Sonogashira-coupling with aryl iodides can be performed on the solid support after their incorporation into peptides.[38,39]

The base-labile linker, 4-hydroxymethylbenzoic acid (HMBA), was attached to the PEGA resin, and substrates **6**{*1*−*7*} were prepared by standard Fmoc-based solid-phase synthesis (Table 2).[40–42] 1-(Mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) and *N*-methylimidazole were used as coupling reagents for the attachment of Fmoc amino acids to the linker.[43] Assembly of the peptide was performed by *N*-[1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU) activation of Fmoc amino acids and acetylene building blocks.[44] Fmoc cleavage was mediated with piperidine in DMF. The solid-phase chemical transformations, presented herein, were specifically developed for the PEGA resin, which is the resin of choice for in-house on-bead screening assays.

Table 1. Synthesis of Aromatic Acetylenes **5** via Sonogashira Cross-Coupling Reactions

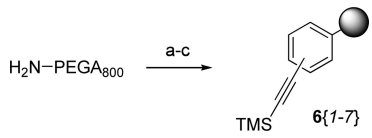


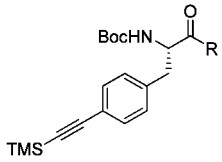
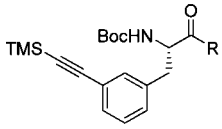
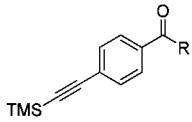
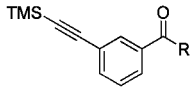
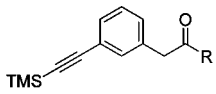
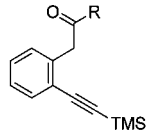
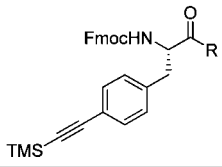
entry	Ar	yield (%)[a]
1		**5**{*1*}, 89
2		**5**{*2*}, 92
3		**5**{*3*}, >95
4		**5**{*4*}, 94
5		**5**{*5*}, >95
6		**5**{*6*}, 87
7		**5**{*7*}, >95

[a] Isolated yield after flash silica gel chromatography.

Solid-Phase Synthesis of Aromatic Carboxylic Acids. Initially, the conversion of the acetylenes into the corresponding carboxylic acids was investigated. The trimethylsilyl-protecting group of peptide substrates **6**{*1*−*7*} was removed prior to oxidation by treatment with fluoride using tetrabutylammonium fluoride. The desilylated substrates were then subjected to OsO_4/$NaIO_4$/HMTA-mediated oxidative cleavage conditions.[12] The conditions involve the use of catalytic amounts of OsO_4 in combination with large excesses of co-oxidant ($NaIO_4$) and HMTA as base. The nature of the base was essential to obtain clean conversion without formation of byproducts. In all cases, the desired products were obtained in excellent purities (>95%) after cleavage from the solid-support (Table 3). This oxidative cleavage protocol gives access to a number of solid-supported aromatic carboxylic acids. Notably, the amino acid-derived building blocks **5**{*1*}, **5**{*2*}, and **5**{*7*} can be applied, thus providing the opportunity for their direct use as precursors for 3- and

Table 2. Solid-Phase Synthesis of Peptide Substrates **6**[a]



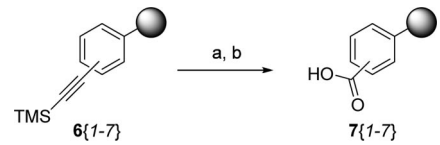
entry	product,[b] purity (%)[c]
1	 **6**{*1*}, >95
2	 **6**{*2*}, >95
3	 **6**{*3*}, >95
4	 **6**{*4*}, >95
5	 **6**{*5*}, >95
6	 **6**{*6*}, >95
7	 **6**{*7*}, >95[d]

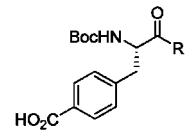
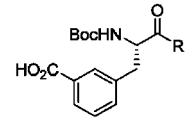
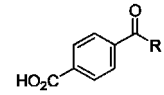
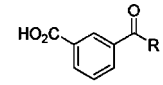
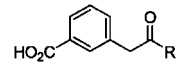
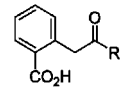
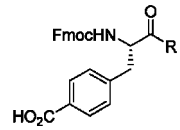
[a] Reagents and conditions: (a) HMBA, TBTU, NEM, DMF; (b) Fmoc-Gly-OH, MSNT, 1-methylimidazole, CH_2Cl_2; (c) cycles of Fmoc deprotection with 20% piperidine in DMF and TBTU-mediated couplings of Fmoc-Aa-OH or acetylene building blocks **5**{*1*−*7*}. [b] R = Ala-Phe-Gly-HMBA-$PEGA_{800}$. [c] The compounds were released from the solid phase with 0.1 M NaOH (aq), and the purities were determined by RP-HPLC. [d] The compound was treated with 20% piperidine (DMF) before cleavage of the compound off the solid-support.

4-carboxyphenylalanine in solid-phase peptide synthesis. The OsO_4/$NaIO_4$-mediated conversion of alkynes into carboxylic acids, generally, proved highly compatible with most amino acids as previously reported.[12]

Solid-Phase Synthesis of Aromatic α-Ketocarboxylic Acids. It was speculated that the oxidation procedure could be shortened if the TMS-protected acetylenes could be directly converted to the carboxylate in the oxidative cleavage, that is, without prior fluoride treatment. To our surprise, even though full conversion of the substrate could be achieved, the oxidative cleavage conditions did not yield the expected carboxylic acid in satisfying purity (∼50%). Examination of the reaction mixture revealed the presence of a more hydrophilic product detected by RP-HPLC. This

Table 3. Solid-Phase Oxidative Cleavage of Aromatic TMS-Protected Acetylenes **6** to Carboxylic Acids **7**[a]



entry	peptide substrate	product,[b] purity (%)[c]
1	**6**{*1*}	 **7**{*1*}, >95
2	**6**{*2*}	 **7**{*2*}, >95
3	**6**{*3*}	 **7**{*3*}, >95
4	**6**{*4*}	 **7**{*4*}, >95
5	**6**{*5*}	 **7**{*5*}, >95
6	**6**{*6*}	 **7**{*6*}, >95
7	**6**{*7*}	 **7**{*7*}, 78[d]

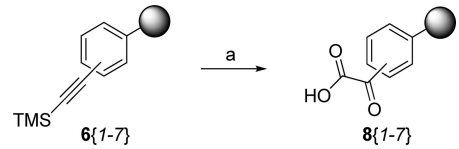
[a] Reagents and conditions: (a) TBAF; (b) OsO_4, $NaIO_4$, HMTA, THF/H_2O (1:1). [b] R = Ala-Phe-Gly-HMBA-$PEGA_{800}$. [c] The compound was released from the solid phase with 0.1 M NaOH (aq), and the purity was determined by RP-HPLC. [d] The compound was treated with 20% piperidine (DMF) before cleavage of the compound off the solid-support.

product was characterized as the α-ketocarboxylic acid, arising from the oxidation of the alkyne by a different pathway. Attempts to fully convert the α-ketocarboxylic acid to the carboxylate under the oxidative cleavage conditions were unsuccessful, and once formed, the product proved completely stable to the oxidation conditions.

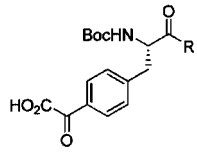
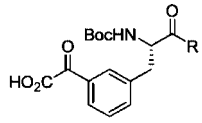
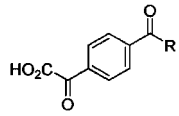
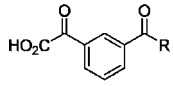
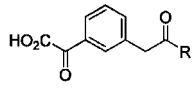
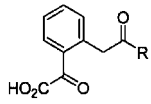
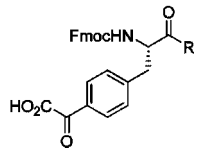
Aware of previous solution-phase studies on the conversion of alkynes to α-ketocarboxylic acids and diketo derivatives,[29–37] we attempted the quantitative conversion of the TMS-protected aromatic acetylene into the corresponding α-ketocarboxylic acid. The use of $NaIO_4$ as an oxidizing agent should be avoided because of its general ability to cleave unsaturated *C*−*C* bonds. *N*-Methylmorpholine-oxide (NMO), on the other hand, is a mild co-oxidant, and to our delight, the reaction with a combination of NMO, OsO_4, and HMTA provided the α-ketocarboxylic acid **8**{*1*} in excellent purity (>95%, Table 4, entry 1).

The NMO-mediated transformation was applied to substrates **6**{*2*−*7*} (Table 4). In general, products were obtained

Table 4. Solid-Phase Oxidation of Aromatic TMS-Protected Acetylenes **6** to α-Ketocarboxylic Acids **8**[a]



6{*1-7*} **8**{*1-7*}

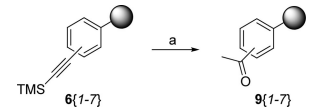
entry	peptide substrate	product,[b] purity (%)[c]
1	**6**{*1*}	 **8**{*1*}, >95
2	**6**{*2*}	 **8**{*2*}, >95
3	**6**{*3*}	 **8**{*3*}, 73[d]
4	**6**{*4*}	 **8**{*4*}, 90
5	**6**{*5*}	 **8**{*5*}, 92
6	**6**{*6*}	 **8**{*6*}, 0[e]
7	**6**{*7*}	 **8**{*7*}, 92[f]

[a] Reagents and conditions: (a) OsO_4, NMO, HMTA, THF/H_2O (1:1). [b] R = Ala-Phe-Gly-HMBA-$PEGA_{800}$. [c] The compound was released from the solid phase with 0.1 M NaOH (aq), and the purity was determined by RP-HPLC. [d] The presence of 20% carboxylic acid **7**{*3*} was observed. [e] LC-MS analysis showed the presence of 50% unconverted acetylene, while the rest of the product mixture appeared as an inseparable mixture of peaks. [f] The compound was treated with 20% piperidine (DMF) before cleavage of the compound off the solid-support with 0.1 M NaOH (aq).

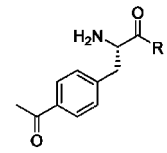
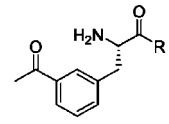
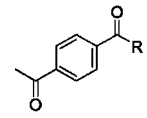
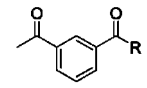
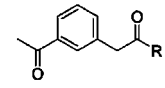
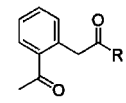
almost quantitatively (>90%).[45] Longer reaction times (20 h) were necessary for the complete conversion of the substrates as compared to the $NaIO_4$-mediated conversion into carboxylic acids. Furthermore, in most cases, the presence of a tiny amount of the carboxylic acid was noted (<5%). Attempts to optimize the procedure to completely suppress the formation of the carboxylic acid by using shorter reaction times, and different stoichiometries were not successful. The compatibility of the NMO-mediated transformation with various amino acids was not investigated further.

Solid-Phase Synthesis of Aromatic Methyl Ketones. The catalytic addition of water to an alkyne (hydration) is a well-investigated reaction.[46] Numerous catalysts can be used, among which Brønsted acid and base catalysts are the most simple. Notably, electron-rich aryl-alkynes are known to react readily upon acid catalysis.[46] The alkyne in substrates **6**{*2*−*7*} could be hydrated to the corresponding methyl ketones when these were subjected to acidic treatment with 95% TFA (aq) or 50% TFA (CH_2Cl_2) overnight. The desired methyl ketones **9**{*1*−*7*} were obtained in excellent purities (>95%) (Table 5). It is important to note that, for substrates **6**{*1*} and **6**{*2*}, the acidic reaction conditions also cleaved off the Boc-protecting group at the *N*-terminus of the peptide.

Table 5. Solid-Phase Hydration of Aromatic TMS-Protected Acetylenes **6** to Methyl Ketones **9**[a]



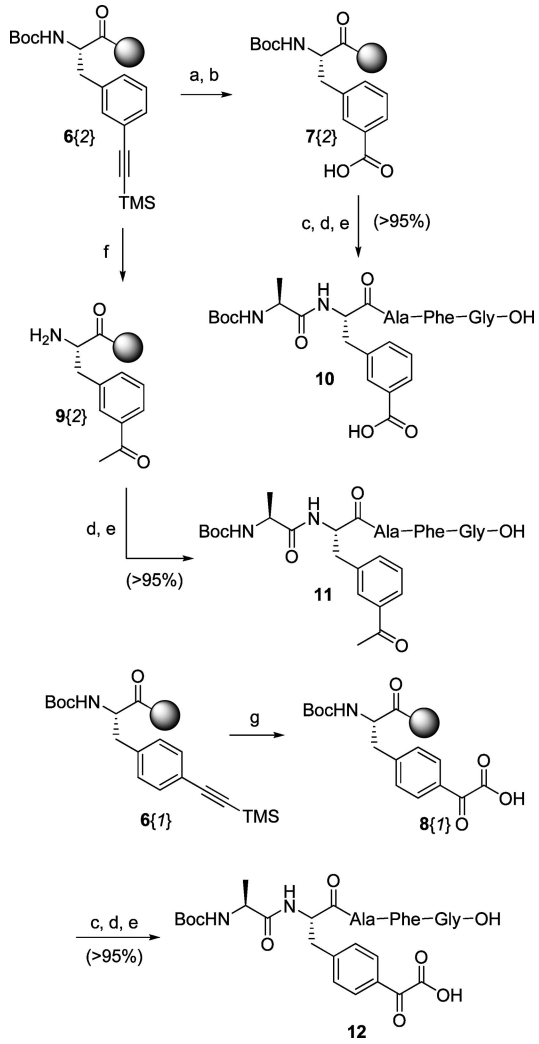
6{*1-7*} **9**{*1-7*}

entry	peptide substrate	product,[b] purity (%)[c]
1	**6**{*1*}	 **9**{*1*}, >95
2	**6**{*2*}	 **9**{*2*}, >95
3	**6**{*3*}	 **9**{*3*}, >95
4	**6**{*4*}	 **9**{*4*}, >95
5	**6**{*5*}	 **9**{*5*}, >95
6	**6**{*6*}	 **9**{*6*}, >95
7	**6**{*7*}	 **9**{*7*}, >95[d]

[a] Reagents and conditions: (a) 95% TFA (aq). [b] R = Ala-Phe-Gly-HMBA-$PEGA_{800}$. [c] The compound was released from the solid phase with 0.1 M NaOH (aq), and the purity was determined by RP-HPLC. [d] The compound was treated with 20% piperidine (DMF) before cleavage of the compound off the solid-support with 0.1 M NaOH (aq).

Solid-Phase Incorporation and Derivatization of Functionalities in Peptides. The present methodology thus enabled the completely selective transformation of one functional group, namely, the TMS-protected acetylene, into

Scheme 2. Solid-Phase Elongation of Peptides **6**{*1*} and **6**{*2*}[a]



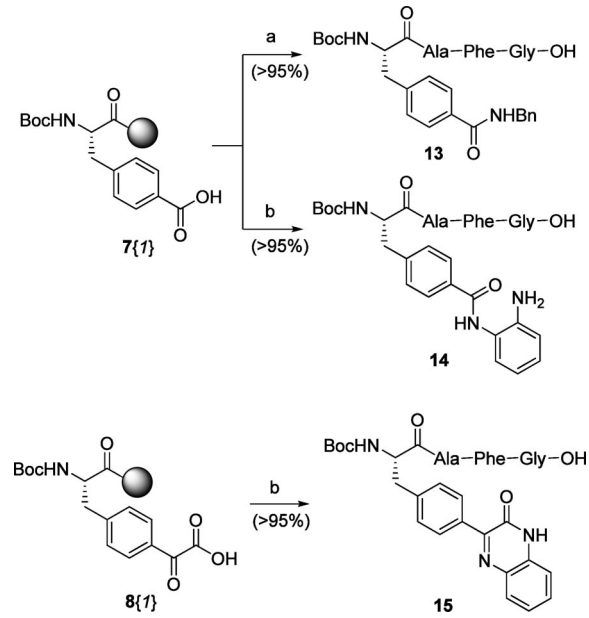
[a] Reagents and conditions: (a) TBAF; (b) OsO_4, $NaIO_4$, HMTA, THF/H_2O (1:1); (c) 50% TFA (CH_2Cl_2); (d) Boc-Ala-OH, TBTU, NEM, DMF; (e) 0.1 M NaOH (aq); (f) 95% TFA (aq); (g) OsO_4, NMO, HMTA, THF:H_2O (1:1).

three different functionalities: a carboxylic acid, an α-ketocarboxylic acid, and a methyl ketone. Bearing in mind the previous success of the oxidative cleavage of aliphatic alkynes to carboxylic acids,[12] the conversion of nonaromatic acetylenes into the α-ketocarboxylic acids, and the methyl ketones was attempted, however without any success, indicating that the conjugation with the phenyl ring is crucial for these reactions.

Amino acid building blocks **5**{*1*}, **5**{*2*}, and **5**{*7*} with their reactive acetylene functionality may be used for incorporation into peptidic structures for further transformation. We therefore investigated if products **7**{*2*} and **9**{*2*} could be further elongated using standard Boc-based SPPS, thereby effectively incorporating side-chain modified amino acids into peptides (Scheme 2).

The resin-bound compound **6**{*2*} was subjected to acidic treatment with 95% TFA (aq) for 20 h to cause a simultaneous hydration of the alkyne-moiety and Boc-deprotection. The product **9**{*2*} was subsequently quantitatively converted into peptide **11**, demonstrating the compatibility of the methyl

Scheme 3. Solid-Phase Derivatization of Peptides **7**{*1*} and **8**{*1*}[a]



[a] Reagents and conditions: (a) BnNH2, TBTU, NEM, DMF; (b) 1,2-diaminobenzene, TBTU, NEM, DMF.

ketones with Boc-based peptide synthesis and the insertion of 3-acetylphenylalanine into a peptide. Similarly, treatment of **6**{*2*} with $NaIO_4$, OsO_4, and HMTA, followed by Boc cleavage and peptide coupling, afforded **10** in 95% purity. Finally, the insertion of the α-ketocarboxylic acid was also demonstrated by short acidic treatment of peptide **8**{*1*} to remove the Boc group, followed by amino acid coupling, providing the desired 4-(α-ketocarboxy)-phenylalanine containing peptide **12** in excellent purity (>95%).

The high efficiency of the present conversions for the insertion of synthetically modified phenylalanines into peptides has been demonstrated. To explore the scope for combinatorial chemistry, further transformation of the new functionalities were investigated for the carboxylic acids and the α-ketocarboxylic acids (Scheme 3). The usefulness of keto derivatives has previously been studied for the functionalization of proteins incorporating a 4-acetylphenylalanine, where the keto functionality was used as reactive handle for the biotinylation or glycosylation of the proteins.[47,48] Compound **7**{*1*} was successfully derivatized with benzylamine using standard TBTU coupling procedures, providing compound **13** in excellent purity.

Similarly, compounds **7**{*1*} and **8**{*1*} were reacted with 1,2-diaminobenzene to afford new heterocycles by sequential amide formation and condensation reaction. The α-ketocarboxylic acid **8**{*1*} provided the desired quinoxalinone **15**, in excellent purity (>95%). The same reaction of the carboxylic acid resulted in the monocoupling of the diaminobenzene to yield compound **14**, which under these conditions did not yield the bicyclic benzoimidazole by condensation with the formed amide carbonyl even at elevated temperature.

Conclusions

A new and general solid-phase protocol for the selective conversion of aromatic acetylenes into three different func-

tionalities, namely, the carboxylic acid, the α-ketocarboxylic acid, and the acetyl-moiety, has been developed. In most cases, the transformations were quantitative. Furthermore, the synthetic potential of the present methodology for the incorporation of amino acids containing chemically modified side-chains has been demonstrated. These functionalities can also serve as handles for further derivatization of the peptides, as shown by the conversion of an α-ketocarboxylic acid into a quinoxalinone moiety and the coupling of a 4-carboxyphenylalanine with amines.

We expect that these quantitative and diverse solid-phase transformations of a common and easily accessible acetylene group might be, after appropriate evaluation of the transformations with more sophisticated peptides, useful in structure−activity studies with biological receptors. In addition, carboxylates and α-ketocarboxylates have metal-chelating properties,[49,50] and may be used in a combinatorial fashion to provide peptide-based specific metal binders. The acetylene building blocks presented and their solid-phase conversion expands the repertoire for combinatorial chemistry. Finally, the in situ conversion into reactive intermediates, such as the α-ketocarboxylate, allows the clean solid-phase transformation into new heterocyclic systems attached to the peptide scaffold.

Experimental Section

General Methods. General methods are reported in the Supporting Information.

Solid-Phase Procedures. For all solid-phase transformations, a volume of solvent just adequate to fully swell and cover the beads was used to keep the concentration of reagents as high as possible.

Attachment of the 4-hydroxymethylbenzoic acid (HMBA) linker to the amino-functionalized resin was carried out by premixing 4-hydroxymethylbenzoic acid (HMBA, 3.0 equiv), *N*-ethylmorpholine (NEM, 4.0 equiv), and *N*-[1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU, 2.88 equiv) for 5 min in DMF. The resulting solution was added to resin in DMF and allowed to react for 2 h, followed by washing with DMF (6×) and CH_2Cl_2 (6×). Coupling of Fmoc-Gly-OH to the HMBA-derivatized resin was accomplished by treatment of the lyophilized resin with a mixture of Fmoc-Gly-OH (3.0 equiv), 1-methylimidazole (MeIm, 2.25 equiv), and 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT, 3.0 equiv) in dry CH_2Cl_2:THF (20:1). The coupling was repeated once. Peptide synthesis and attachment of the different building blocks to the Gly-HMBA-functionalized resin was subsequently accomplished by standard amino acid coupling procedures (Fmoc-Aa-OH, TBTU, NEM, DMF) as described above for the attachment of the HMBA linker. Completion of the reaction was monitored using the Kaiser test. The resin was washed with DMF (6×) after each coupling step. Fmoc cleavage was accomplished with 20% piperidine in DMF, first for 2 min, and then for 18 min, followed by washing with DMF (6×).

The solid-phase silyl-deprotection of TMS-acetylenes was carried out by addition of tetrabutylammonium fluoride (TBAF, 4 equiv, 1.0 M solution in THF), buffered with AcOH (4.5 equiv), to the resin in THF. The reaction was left for 2 h at RT, at which time the resin was washed with THF (3×), water (6×), DMF (6×), and CH_2Cl_2 (6×).

The oxidative cleavage of solid-phase peptide olefins to carboxylic acids was carried out by addition of $NaIO_4$ (10.0 equiv) and hexamethylenetetramine (HMTA, 5.0 equiv) to the resin in THF:water (1:1), followed by addition of OsO_4 (0.05 equiv, 2.5 wt % solution in 2-methyl-2-propanol). The reaction mixture was gently shaken overnight at RT. Subsequently, the resin was washed with water (6×), 10% TFA (aq) (3×), water (6×), DMF (6×), and CH_2Cl_2 (6×) in a plastic syringe fitted with a Teflon filter.

The solid-phase oxidation of TMS-acetylenes to α-ketocarboxylic acids was carried out by addition of *N*-methylmorpholine-*N*-oxide (NMO, 10.0 equiv) and hexamethylenetetramine (HMTA, 5.0 equiv) to the resin in THF/water (1:1), followed by addition of OsO_4 (0.05 equiv, 2.5 wt % solution in 2-methyl-2-propanol). The reaction mixture was gently shaken overnight at RT. Subsequently, the resin was washed with water (6×), 10% TFA (aq) (3×), water (6×), DMF (6×), and CH_2Cl_2 (6×).

The solid-phase hydration of solid-supported TMS-acetylenes was carried out by treatment of the resin with 95% TFA (aq) overnight at room temperature. The resin was then washed with water (6×), DMF (6×), and CH_2Cl_2 (6×).

The functionalization of solid-supported carboxylic acids and α-ketocarboxylic acids was carried out by addition of a solution of TBTU (3.0 equiv) and NEM (4.0 equiv) in DMF at room temperature. After 5 min, the amine (6.0 equiv) was added. The reaction was left at room temperature for 3 h. The resin was then washed with DMF (6×), CH_2Cl_2 (6×), and DMF (6×).

All compounds were released from the solid support by basic hydrolysis with 0.1 M NaOH (aq) and neutralized with 0.1 M HCl (aq). Corrected for the added NaCl contents, crude lyophilized products arising from solid-phase transformations were typically isolated in 70−90% yield. Upon purification by preparative RP-HPLC, purified and desalted products were isolated in 45−85% yield.

Synthesis of Trimethylsilylethynyl Carboxylic Acid Building Blocks by Sonogashira Cross-Coupling Reactions. General Procedure for the Sonogashira Cross-Coupling Reactions. A flame-dried Schlenk flask was charged with aryl iodide (0.5 mmol), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol), and CuI (3.8 mg, 0.02 mmol). After three successive vacuum/argon cycles, a degassed mixture of THF (2.5 mL) and *N*-ethylmorpholine (2.5 mL) was added via syringe to give a clear, yellow solution. Trimethylsilylacetylene (59.5 mg, 86 μL, 0.6 mmol) was immediately introduced via syringe, and after 1 min of stirring, a white precipitate started to form. The mixture was stirred at RT for 15 h before removal of the solvent by rotary evaporation. The black, solid residue was dissolved in CH_2Cl_2 (20 mL) and treated with a mixture of water (20 mL) and aqueous HCl (1.0 M, 4 mL) for 2 min. The organic layer was separated, and the aqueous phase was washed with further amounts of CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4,

filtered, and concentrated on Celite. The product was purified by flash column chromatography on silica gel as described below.

Boc-Phe(4-(TMS-ethynyl))-OH (5{*1*}). Following the general method, the reaction of Boc-Phe(4-Iodo)-OH (300 mg, 0.767 mmol), TMS-acetylene (90 mg, 130 μL, 0.92 mmol), CuI (6 mg, 0.03 mmol), and $Pd(PPh_3)_4$ (mg, 0.015 mmol) gave, after flash column chromatography (heptane/EtOAc/HOAc 50:50:1) on silica gel, the title compound **5**{*1*} as a solid (247 mg, 89%): R_f 0.19; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 4.16−4.00 (m, 1H), 3.03 (dd, J = 13.7, 4.2 Hz, 1H), 2.83 (dd, J = 13.4, 10.4 Hz, 1H), 1.32 (s, 9H), 0.22 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 155.4, 139.3, 131.4, 129.4, 120.1, 105.3, 93.7, 78.1, 54.8, 36.3, 28.1, −0.1; HRMS (ESI) calcd for $C_{14}H_{20}NO_2Si$ $[M - Boc + H]^+$ 262.1263, found 262.1251.

Boc-Phe(3-(TMS-ethynyl))-OH (5{*2*}). Following the general method, the reaction of Boc-Phe(3-Iodo)-OH (300 mg, 0.767 mmol), TMS-acetylene (90 mg, 130 μL, 0.92 mmol), CuI (6 mg, 0.03 mmol), and $Pd(PPh_3)_4$ (mg, 0.015 mmol) gave, after flash column chromatography (heptane/EtOAc/HOAc 50:50:1) on silica gel, the title compound **5**{*2*} as a solid (255 mg, 92%): R_f 0.19; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.61 (bs, 1H), 7.33 (bs, 1H), 7.27 (m, 3H), 7.08 (d, J = 8.4 Hz, 1H), 4.08 (m, 1H), 3.02 (dd, J = 3.9 Hz, J = 13.7 Hz, 1H), 2.79 (m, 1H), 1.31 (s, 9H), 0.21 (s, 9H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 173.3, 155.3, 138.7, 132.4, 129.9, 129.5, 128.5, 121.9, 105.4, 93.7, 78.0, 54.8, 36.0, 28.1, 0.12; HRMS (ESI) calcd for $C_{14}H_{20}NO_2Si$ $[M - Boc + H]^+$ 262.1263, found 262.1261.

4-Trimethylsilylethynylbenzoic Acid (5{*3*}). Following the general method, the reaction of 4-iodo-benzoic acid (500 mg, 2.02 mmol), TMS-acetylene (238 mg, 347 μL, 2.42 mmol), CuI (15 mg, 0,08 mmol), and $Pd(PPh_3)_4$ (47 mg, 0,04 mmol) gave, after flash column chromatography (heptane/EtOAc/HOAc 70:30:1) on silica, the title compound **5**{*3*} as white crystals (430 mg, >95%): R_f 0.18; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 0.25 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.9, 132.0; 130.0, 128.7, 103.9, 98.3, −0.2; HRMS (ESI) calcd for $C_{12}H_{15}O_2Si$ $[M + H]^+$ 219.0841, found 219.0851.

3-Trimethylsilylethynylbenzoic Acid (5{*4*}). Following the general method, the reaction of 3-iodo-benzoic acid (500 mg, 2.02 mmol), TMS-acetylene (238 mg, 347 μL, 2.42 mmol), CuI (15 mg, 0,08 mmol), and $Pd(PPh_3)_4$ (47 mg, 0,04 mmol) gave after flash column chromatography (heptane/EtOAc/HOAc 70:30:1) on silica gel, the title compound **5**{*4*} as an off-white solid (413 mg, 94%): R_f 0.18; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.22 (t, J = 1.6 Hz, 1H), 8.04 (dt, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.68 (dt, J = 7.7 Hz, J = 1.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 0.27 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.5, 136.9, 133.7, 130.0, 129.5, 128.5, 103.6, 95.7, −0.1; HRMS (ESI) calcd for $C_{12}H_{14}NaO_2Si$ $[M + Na]^+$ 241.0661, found 241.0665.

3-Trimethylsilylethynylphenylacetic Acid (5{*5*}). Following the general method, the reaction of 3-iodophenylacetic acid (524 mg, 2 mmol), TMS-acetylene (236 mg, 339 μL, 2.4 mmol), CuI (15 mg, 0.08 mmol), and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) gave, after flash column chromatography on silica gel (heptane/EtOAc/HOAc 80:20:1), the title compound **5**{*5*} as an off-white solid (463 mg, >95%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.21 (m, 1H), 3.61 (s, 2H), 0.25 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.8, 133.2, 132.8, 130.9, 129.5, 128.5, 123.5, 104.6, 94.5, 40.6, −0.1; HRMS (ESI) calcd for $C_{13}H_{16}NaO_2Si$ $[M + Na]^+$ 255.0817, found 255.0833.

2-Trimethylsilylethynylphenylacetic Acid (5{*6*}). Following the general method, the reaction of 2-iodophenylacetic acid (1048 mg, 4 mmol), TMS-acetylene (472 mg, 678 μL, 4.8 mmol), CuI (38 mg, 0.2 mmol), and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) gave after flash column chromatography on silica gel (heptane/EtOAc/HOAc 80:20:1), the title compound **5**{*6*} as an off-white solid solid (806 mg, 87%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49−7.46 (m, 1H), 7.33−7.20 (m, 3H), 3.87 (s, 1H), 0.24 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.2, 135.8, 132.2, 129.8, 128.7, 127.2, 99.5, 39.5, −0.1; HRMS (ESI) calcd for $C_{13}H_{17}O_2Si$ $[M + H]^+$ 233.0998, found 233.1005.

Fmoc-Phe(4-TMS-ethynyl)-OH (5{*7*}). Following the general method, the reaction of Fmoc-(4-iodo)-Phe-OH (513 mg, 1 mmol), TMS-acetylene (118 mg, 170 μL, 1.2 mmol), CuI (8 mg, 0.04 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) gave, after flash column chromatography on silica gel (heptane/EtOAc/HOAc 100:100:1), the title compound **5**{*7*} as a slightly brown solid (479 mg, >95%): ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.94−7.13 (m, 12H), 4.20 (m, 3H), 3.16 (dd, 1H, J = 4.3 Hz, J = 13.8 Hz), 2.92 (dd, 1H, J = 10.8 Hz, J = 13.6 Hz), 0.27 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.9, 155.7, 143.6, 143.5, 140.5, 139.1, 131.3, 129.3, 127.4, 126.9, 125.1, 125.0, 119.9, 105.2, 93.6, 65.5, 55.0, 46.4, 36.2, −0.1; HRMS (ESI) calcd for $C_{29}H_{30}NO_4Si$ $[M + H]^+$ 484.1944, found 484.1926.

Characterization of Carboxylic Acid Compounds 7{*1*−*7*}. Compound 7{*1*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.24 (t, J = 5.3 Hz, 1H), 8.09 (t, J = 6.9 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.24−7.13 (m, 5H), 6.96 (d, J = 8.5 Hz, 1H), 4.53 (dt, J = 4.2 Hz, J = 8.6 Hz, 1H), 4.32−4.15 (m, 2H), 3.72 (d, J = 6.0 Hz, 2H), 3.09−2.97 (m, 2H), 2.87−2.68 (m, 2H), 1.26 (s, 9H), 1.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.7, 170.9, 170.9, 167.3, 155.1, 143.5, 137.6, 129.3, 129.1, 128.9, 127.9, 126.1, 78.0, 55.2, 53.6, 48.2, 41.0, 37.4, 37.2, 28.0, 18.2; HRMS (ESI) calcd for $C_{29}H_{36}N_4O_9$ $[M + H]^+$ 585.2555, found 585.2542.

Compound 7{*2*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.24 (t, J = 5.5 Hz, 1H), 8.10 (m, 2H), 7.90 (s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.25−7.10 (m, 5H), 6.98 (d, J = 8.8 Hz, 1H), 4.52 (dt, J = 4.2 Hz, J = 8.6 Hz, 1H), 4.32−4.11 (m, 2H), 3.72 (d, J = 5.9 Hz, 2H), 3.09−2.95 (m, 2H), 2.88−2.65 (m, 2H), 1.24 (s, 9H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.8, 171.1, 171.0, 170.9, 167.4, 155.1, 138.7, 137.6, 133.6, 130.7, 130.2, 129.1, 127.9, 127.9, 127.1, 126.1, 77.9, 55.5, 53.6, 48.2, 41.0, 37.4, 37.1, 28.0, 18.2; HRMS (ESI) calcd for $C_{29}H_{36}N_4O_9$ $[M + H]^+$ 585.2555, found 585.2558.

Compound 7{*3*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.89 (bs, 1H), 8.70 (d, J = 7.3 Hz, 1H), 8.35 (t, J = 5.8 Hz, 1H), 8.05−7.95 (m, 5H), 7.26−7.09 (m, 5H), 4.54 (dt, J = 4.5 Hz, J = 9.0 Hz, 1H), 4.44 (p, J = 6.9 Hz, 1H), 3.77 (dd, J = 1.2 Hz, J = 5.8 Hz, 2H), 3.06 (dd, J = 4.4 Hz, J = 13.9 Hz, 1H), 2.85 (dd, J = 9.3 Hz, J = 13.8 Hz, 1H), 1.26 (d, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 171.8, 171.1, 170.9, 166. 7, 165.4, 137.6, 137.6, 133.07, 129.2, 129.0, 127.8, 127.7, 126.1, 53.6, 49.1, 40.3, 37.3, 17.4; HRMS (ESI) calcd for $C_{22}H_{23}N_3O_7$ $[M + H]^+$ 442.1609, found 442.1604.

Compound 7{*4*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.89 (bs, 1H), 8.75 (d, J = 7 Hz 1H), 8.45 (t, J = 1.5 Hz, 1H), 8.34 (t, J = 5.7 Hz, 1H), 8.11 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.25−7.08 (m, 5H), 4.54 (dt, J = 4.1 Hz, J = 8.6 Hz, 1H), 4.45 (p, J = 7.2 Hz, 1H), 3.76 (dd, J = 2.2 Hz, J = 5.7 Hz, 2H), 3.06 (dd, J = 4.4 Hz, J = 13.8 Hz, 1H), 2.84 (dd, J = 9.2 Hz, J = 13.9 Hz, 1H), 1.26 (d, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.8, 171.1, 170.9, 166.8, 165.3, 137.6, 134.2, 131.8, 131.7, 130.9, 129.2, 128.5, 128.3, 127.8, 126.1, 53.6, 49.1, 40.7, 37.4, 17.3; HRMS (ESI) calcd for $C_{22}H_{23}N_3O_7$ $[M + H]^+$ 442.1609, found 442.1616.

Compound 7{*5*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.36 (d, J = 7.4 Hz, 1H), 8.14−8.08 (m, 2H), 7.84 (s, 1H), 7.78 (td, J = 1.4 Hz, J = 7.4 Hz, 1H), 7.46 (td, J = 1.4 Hz, J = 7.6 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.18 (m, 5H), 4.56−4.44 (m, 1H), 4.23 (p, J = 6.9 Hz, 1H), 3.66 (d, J = 5.5 Hz, 2H), 3.52 (d, J = 4.8 Hz, 2H), 3.04 (dd, J = 4.5 Hz, J = 13.8 Hz, 1H), 2.81 (dd, J = 9.4 Hz, J = 13.8 Hz, 1H), 1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.8, 171.0, 170.7, 169.5, 167.4, 137.6, 136.4, 133.0, 131.4, 129.9, 129.0, 128.0, 127.8, 127.1, 126.0, 53.7, 48.2, 41.4, 37.3, 18.1; HRMS (ESI) calcd for $C_{23}H_{26}N_3O_7$ $[M + H]^+$ 456.1771, found 456.1751.

Compound 7{*6*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.41 (d, J = 6.8 Hz, 1H), 8.19−8.14 (m, 2H), 7.77 (dd, J = 1.5 Hz, J = 7.5 Hz, 1H), 7.37 (dt, J = 1.6 Hz, J = 7.4 Hz, 1H), 7.31−7.14 (m, 7H), 4.48−4.39 (m, 1H), 4.06 (p, J = 7.0 Hz, 1H), 3.93 (d, J = 15.0 Hz, 1H), 3.71 (d, J = 15.0 Hz, 1H), 3.56 (d, J = 6.0 Hz, 2H), 3.09 (dd, J = 4.5 Hz, J = 13.9 Hz, 1H), 2.97 (dd, J = 10.0 Hz, J = 13.9 Hz, 1H), 1.07 (d, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.0, 171.1, 171.0, 170.9, 170.2, 138.0, 135.9, 134.3, 131.4, 130.0, 129.8, 129.0, 127.8, 126.2, 126.0, 54.0, 48.8, 41.5, 41.1, 37.0, 17.6; HRMS (ESI) calcd for $C_{23}H_{26}N_3O_7$ $[M + H]^+$ 456.1771, found 456.1761.

Compound 7{*7*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.51 (d, J = 6.7 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.10 (t, J = 5.3 Hz, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.28−7.07 (m, 5H), 4.60−4.45 (m, 1H), 4.35−4.17 (m, 1H), 3.75 (dd, J = 7.3 Hz, J = 4.6 Hz, 1H), 3.66 (d, J = 5.1 Hz, 2H), 3.18−2.98 (m, 2H), 2.92−2.71 (m, 2H), 1.16 (d, J = 6.8 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.5, 171.0, 170.6, 170.4, 167.4, 141.7, 137.7, 129.8, 129.4, 129.2, 129.0, 128.8, 127.8, 126.0, 54.2, 53.7, 48.2, 41.5, 40.4, 37.2, 18.3; HRMS (ESI) calcd for $C_{24}H_{29}N_4O_7$ $[M + H]^+$ 485.2036, found 485.2047.

Characterization of α-Ketocarboxylic Acid Compounds 8{*1*−*7*}. Compound 8{*1*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.36 (t, J = 5.5 Hz, 1H), 8.12−8.09 (m, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.27−7.10 (m, 5H), 6.97 (d, J = 8.7 Hz, 1H), 4.54 (dt, J = 4.6 Hz, J = 8.8 Hz, 1H), 4.28−4.16 (m, 2H), 3.77 (dd, J = 2.1 Hz, J = 5.5 Hz, 2H), 3.09−2.99 (m, 2H), 2.88−2.70 (m, 2H), 1.26 (s, 9H), 1.17 (d, J = 6.9 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) 193.5, 171.7, 171.1, 170.9, 170.8, 168.9, 155.0, 144.3, 137.5, 131.7, 129.3, 129.1, 128.7, 127.8, 126.0, 77.9, 55.0, 53.5, 48.2, 40.6, 37.3, 37.2, 27.9, 18.1; HRMS (ESI) calcd for $C_{24}H_{29}N_4O_7$ $[M + H]^+$ 485.2036, found 485.2015.

Compound 8{*2*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.07 (bs, 1H), 8.26 (t, J = 5.3 Hz, 1H), 8.02 (m, 2H), 7.78 (s, 1H), 7.64 (dJ = 7.6 Hz, 1H,), 7.51 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.17−7.07 (m, 5H), 6.93 (d, J = 8.8 Hz, 1H), 4.47 (dt, J = 4.9 Hz, J = 8.7 Hz, 1H), 4.15 (m, 2H), 3.71 (d, J = 5.5 Hz, 2H), 3.03−2.91 (m, 2H), 2.82−2.60 (m, 2H), 1.19 (s, 9H), 1.11 (d, J = 6.7 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.8, 171.1, 170.9, 167.9, 155.1, 139.1, 137.6, 134.9, 132.9, 129.7, 129.1, 128.3, 127.9, 127.5, 126.1, 78.0, 55.3, 53.5, 48.3, 40.6, 37.4, 37.0, 28.0, 18.1; HRMS (ESI) calcd for $C_{30}H_{36}N_4O_9$ $[M + H]^+$ 613.2510, found 613.2501.

Compound 8{*3*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.63 (d, J = 7.3 Hz, 1H), 8.29 (t, J = 5.8 Hz, 1H), 8.04−7.94 (m, 5H), 7.25−7.11 (m, 5H), 4.59−4.50 (m, 1H), 4.45 (t, J = 7.2 Hz, 1H), 3.78 (d, J = 5.7 Hz, 2H), 3.06 (dd, J = 4.3 Hz, J = 13.6 Hz, 1H), 2.83 (dd, J = 9.4 Hz, J = 14.1 Hz, 1H), 1.26 (d, 3H, J = 7.1 Hz); HRMS (ESI) calcd for $C_{23}H_{24}N_3O_8$ $[M + H]^+$ 470.1563, found 470.1567.

Compound 8{*4*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.73 (t, J = 7.4 Hz, 1H), 8.36−8.29 (m, 2H), 8.10 (d, J = 7.8 Hz, 1H), 8.02−7.99 (m, 2H), 7.61 (t, J = 7.7 Hz, 1H), 7.25−7.11 (m, 5H), 4.59−4.43 (m, 2H), 3.77 (d, J = 5.0 Hz, 2H), 3.06 (dd, J = 4.4 Hz, J = 13.8 Hz, 1H), 2.84 (dd, J = 9.2 Hz, J = 13.8 Hz, 1H), 1.26 (d, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 193.9, 171.8, 171.1, 170.8, 168.7, 165.4, 137.5, 134.3, 134.0, 131.8, 131.8, 129.1, 128.4, 127.9, 127.8, 126.0, 53.5, 49.1, 40.6, 37.3, 17.3; HRMS (ESI) calcd for $C_{23}H_{24}N_3O_8$ $[M + H]^+$ 470.1563, found 470.1539.

Compound 8{*5*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.36−8.24 (m, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.85−7.70 (m, 2H), 7.52−7.39 (m, 2H), 7.19 (m, 5H), 4.54−4.45 (m, 1H), 4.21 (t, J = 7.1 Hz, 1H), 3.75 (dd, J = 2.8 Hz, J = 5.4 Hz, 2H), 3.53 (d, J = 5.5 Hz, 1H), 3.05 (dd, J = 4.4 Hz, J = 13.7 Hz, 1H), 2.82 (dd, J = 9.6 Hz, J = 13.8 Hz, 1H), 1.13 (d, J = 7.0 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 170.8, 170.7, 170.0, 169.8, 168.4, 136.6, 136.5, 135.6, 133.0, 128.5, 128.0, 127.2, 126.8, 126.2, 125.0, 52.5, 47.3, 40.3, 39.5, 36.1, 16.9; HRMS (ESI) calcd for $C_{24}H_{26}N_3O_8$ $[M + H]^+$ 484.1720, found 484.1709.

Compound 8{*7*}. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.79 (d, J = 6.9 Hz, 1H), 8.28−8.21 (m, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.29−7.12 (m, 5H), 4.59−4.50 (m, 1H), 4.28 (t, J = 6.9 Hz, 1H), 3.94 (dd, J = 5.1 Hz, J = 7.1 Hz, 1H), 3.71 (d, J = 6.2 Hz, 2H), 3.19−2.80

(m, 4H), 1.17 (d, J = 9.1 Hz, 3H); HRMS (ESI) calcd for $C_{25}H_{29}N_4O_8$ $[M + H]^+$ 513.1985, found 513.2009.

Characterization of Methyl Ketones 9{*1*−*7*}. Methyl Ketone 9{*1*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.80 (d, J = 7.4 Hz, 1H), 8.38 (t, J = 5.7 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.30−7.11 (m, 5H), 4.57 (dt, J = 4.7 Hz, J = 8.9 Hz, 1H), 4.33 (t, J = 7.1 Hz, 1H), 4.08 (t, J = 6.1 Hz, 1H), 3.77 (dd, J = 1.4 Hz, J = 5.8 Hz, 2H), 3.21−2.93 (m, 3H), 2.84 (dd, J = 9.3 Hz, J = 13.8 Hz, 1H), 2.54 (s, 3H), 1.20 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 197.5, 171.3, 171.1, 170.9, 167.4, 140.651, 137.7, 135.6, 129.9, 129.1, 128.2, 127.9, 126.1, 53.6, 52.9, 48.3, 40.6, 37.5, 36.7, 26.6, 18.3; HRMS (ESI) calcd for $C_{25}H_{30}N_4O_6$ $[M + H]^+$ 483.2244, found 483.2255.

Methyl Ketone 9{*2*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.75 (d, J = 7.4 Hz, 1H), 8.36 (t, J = 5.7 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.93 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.38−7.11 (m, 6H), 4.55 (dt, J = 4.5 Hz, J = 8.8 Hz, 1H), 4.33 (t, J = 7.2 Hz, 1H), 4.07 (dd, J = 5.1 Hz, J = 7.7 Hz, 1H), 3.76 (dd, J = 1.0 Hz, J = 5.7 Hz, 2H), 3.15 (dd, J = 4.8 Hz, J = 14.1 Hz, 1H), 3.05 (dd, J = 4.6 Hz, J = 13.9 Hz, 1H), 2.95 (dd, J = 8.3 Hz, J = 14.3 Hz, 1H), 2.83 (dd, J = 9.4 Hz, J = 13.9 Hz, 1H), 2.55 (s, 3H), 1.21 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 197.8, 171.3, 171.1, 170.9, 167.6, 137.7, 136.9, 135.7, 134.4, 129.5, 129.2, 128.7, 127.9, 126.7, 126.1, 53.7, 53.2, 48.3, 40.6, 37.5, 36.7, 26.7, 18.4; HRMS (ESI) calcd for $C_{25}H_{30}N_4O_6$ $[M + H]^+$ 483.2244, found 483.2252.

Methyl Ketone 9{*3*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.65 (d, J = 7.3 Hz, 1H), 8.30 (t, J = 5.8 Hz, 1H), 8.06−7.95 (m, 5H), 7.25−7.10 (m, 5H), 4.56 (dt, J = 4.3 Hz, J = 8.8 Hz, 1H), 4.45 (p, J = 7.2 Hz, 1H), 3.78 (dd, J = 1.0 Hz, J = 5.8 Hz, 2H), 3.06 (dd, J = 4.9 Hz, J = 14.3 Hz, 1H), 2.83 (dd, J = 9.2 Hz, J = 13.8 Hz, 1H), 2.63 (s, 3H), 1.27 (d, J = 7.2 Hz, 3H); HRMS (ESI) calcd for $C_{23}H_{26}N_3O_6$ $[M + H]^+$ 440.1822, found 440.1809.

Methyl Ketone 9{*4*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.53 (bs, 1H), 8.71 (d, J = 7.3 Hz, 1H), 8.42 (t, J = 1.5 Hz, 1H), 8.30 (t, J = 5.8 Hz, 1H), 8.11 (dd, J = 1.7 Hz, J = 7.8 Hz, 2H), 7.96 (d, J = 8.3 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.25−7.08 (m, 5H), 4.55 (dt, J = 4.1 Hz, J = 8.7 Hz, 1H), 4.47 (p, J = 7.1 Hz, 1H), 3.78 (dd, J = 0.9 Hz, J = 5.8 Hz, 2H), 3.06 (dd, J = 4.5 Hz, J = 13.8 Hz, 1H), 2.83 (dd, J = 9.3 Hz, J = 13.9 Hz, 1H), 2.64 (s, 3H), 1.28 (d, J = 7.2 Hz, 3H); HRMS (ESI) calcd for $C_{23}H_{26}N_3O_6$ $[M + H]^+$ 440.1822, found 440.1812.

Methyl Ketone 9{*5*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.34 (d, J = 7.4 Hz, 1H), 8.27 (t, J = 5.8 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.84−7.79 (m, 2H), 7.52−7.40 (m, 2H), 7.25−7.11 (m, 5H), 4.56−4.46 (m, 1H), 4.29−4.18 (m, 1H), 3.73 (dd, J = 4.3 Hz, J = 5.5 Hz, 2H), 3.54 (s, 2H), 3.04 (dd, J = 4.5 Hz, J = 13.8 Hz, 1H), 2.81 (dd, J = 9.3 Hz, J = 13.8 Hz, 1H), 2.55 (s, 3H), 1.14 (d, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 197.7, 171.8, 171.0, 170.8, 169.4, 137.6, 136.8, 136.6, 133.8, 129.1, 128.6, 128.3, 127.8, 126.2, 126.0, 53.5, 48.2, 41.4, 40.6, 37.3, 26.6, 18.0; HRMS (ESI) calcd for $C_{24}H_{27}N_3O_6Na$ $[M + Na]^+$ 476.1797, found 476.1776.

Methyl Ketone 9{*6*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.12 (d, J = 7.0 Hz, 1H), 8.05 (t, J = 5.7 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.80 (dd, J = 1.4 Hz, J = 7.5 Hz, 1H), 7.46 (dt, J = 1.5 Hz, J = 7.4 Hz, 1H), 7.37 (dt, J = 1.5 Hz, J = 7.5 Hz, 1H), 7.29−7.17 (m, 6H), 4.57−4.44 (m, 1H), 4.20−4.09 (m, 1H), 3.73 (s, 2H), 3.63 (m, 2H), 3.07 (dd, J = 4.4 Hz, J = 13.9 Hz, 1H), 2.80 (dd, J = 9.7 Hz, J = 13.9 Hz, 1H), 2.53 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 202.1, 171.8, 170.9, 170.7, 170.0, 138.3, 137.6, 134.6, 131.8, 131.0, 129.0, 128.8, 127.9, 126.5, 126.0, 53.5, 48.4, 40.7, 37.2, 29.3, 17.8; HRMS (ESI) calcd for $C_{24}H_{27}N_3O_6Na$ $[M + Na]^+$ 476.1797, found 476.1763.

Methyl Ketone 9{*7*}: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.40 (d, J = 7.0 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.95 (t, J = 5.1 Hz, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.28−7.11 (m, 5H), 4.54−4.45 (m, 1H), 4.28−4.23 (m, 1H), 3.65−3.61 (m, 1H), 3.59 (d, J = 5.2 Hz, 2H), 3.10−2.73 (m, 4H), 2.54 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 197.4, 171.6, 171.1, 170.4, 143.4, 137.8, 135.0, 129.6, 129.0, 127.9, 127.8, 126.0, 54.8, 53.8, 48.1, 42.0, 37.2, 26.5, 18.4; HRMS (ESI) calcd for $C_{25}H_{31}N_4O_6$ $[M + H]^+$ 483.2244, found 483.2235.

Characterization of Functionalized and Derivatized Compounds 10−15. Compound 10: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.79 (bs, 1H), 8.30 (t, J = 5.7 Hz, 1H), 8.19 (d, J = 6.9 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.94−7.69 (m, 3H), 7.46 (d, J = 7.6 Hz, 1H), 7.39−7.08 (m, 6H), 6.84 (d, J = 7.3 Hz, 1H), 4.60−4.46 (m, 2H), 4.24 (t, J = 7.2 Hz, 1H), 3.93−3.73 (m, 1H), 3.76 (dd, J = 5.7 Hz, J = 1.2 Hz, 2H), 3.14−2.95 (m, 2H), 2.91−2.69 (m, 2H), 1.34 (s, 9H), 1.16 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.2, 171.5, 171.0, 170.8, 170.3, 167.2, 138.0, 137.5, 133.7, 130.4, 130.2, 129.1, 127.8, 127.1, 126.0, 78.0, 69.6, 53.4, 53.1, 48.1, 40.6, 37.4, 28.0, 18.0, 17.9; HRMS (ESI) calcd for $C_{27}H_{34}N_5O_8$ $[M - Boc + H]^+$ 556.2409, found 556.2427.

Compound 11: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.32−8.19 (m, 2H), 8.06 (d, J = 8.3 Hz, 1H), 7.94−7.81 (m, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.40−7.09 (m, 6H), 6.85 (d, J = 7.3 Hz, 1H), 4.64−4.44 (m, 2H), 4.24 (t, J = 7.1 Hz, 1H), 3.96−3.77 (m, 1H), 3.73 (d, J = 5.7 Hz, 2H), 3.15−2.96 (m, 2H), 2.92−2.71 (m, 2H), 2.54 (s, 3H), 1.33 (s, 9H), 1.17 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 197.8, 172.4, 171.6, 170.9, 170.2, 138.1, 137.6, 136.4, 134.1, 129.3, 129.1, 128.0, 127.8, 126.0, 125.8, 77.9, 53.6, 53.0, 49.8, 48.2, 40.8, 37.4, 37.2, 28.0, 26.6, 18.0; HRMS (ESI) calcd for $C_{33}H_{44}N_5O_9$ $[M + H]^+$ 654.3139, found 654.3146.

Compound 12: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.37 (t, J = 5.7 Hz, 1H), 8.24 (d, J = 7.0 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.33−7.10 (m, 5H), 6.92 (d, J = 7.2 Hz, 1H), 4.67−4.45 (m, 2H), 4.23 (p, J = 6.8 Hz, 1H), 3.96−3.80 (m, 1H), 3.77 (dd, J = 5.6, 2.5 Hz, 2H), 3.15−2.96 (m, 2H), 2.93−2.74 (m, 2H), 1.34 (s, 9H), 1.16 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.4, 171.5, 171.1, 170.8, 170.0, 167.7, 154.8, 144.4, 137.5, 131.0, 129.7, 129.1, 128.8, 127.8,

126.0, 78.0, 53.5, 52.7, 49.8, 49.8, 48.2, 40.6, 37.4, 37.4, 28.0, 18.0, 17.9; HRMS (ESI) calcd for $C_{33}H_{42}N_5O_{11}$ $[M + H]^+$ 684.2881, found 684.2874.

Compound 13: ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.07 (t, J = 5.9 Hz, 1H), 8.25−8.01 (m, 3H), 7.82 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.33−7.08 (m, 10H), 6.96 (d, J = 8.6 Hz, 1H), 4.62−4.46 (m, 1H), 4.47 (d, J = 5.9 Hz, 2H), 4.35−4.10 (m, 2H), 3.67 (d, J = 5.2 Hz, 2H), 3.14−2.92 (m, 2H), 2.90−2.64 (m, 2H), 1.26 (s, 9H), 1.19 (d, J = 6.7 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.7, 171.0, 170.7, 165.9, 155.1, 141.7, 139.7, 137.6, 132.0, 129.0, 129.0, 128.0, 127.8, 127.0, 126.8, 126.5, 126.0, 77.9, 69.6, 55.2, 53.6, 48.1, 42.4, 41.4, 37.3, 28.0, 18.2; HRMS (ESI) calcd for $C_{36}H_{44}N_5O_8$ $[M + H]^+$ 674.3190, found 674.3191.

Compound 14: ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.69 (s, 1H), 8.29−8.05 (m, 3H), 7.92 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.31−7.09 (m, 6H), 7.03−6.90 (m, 2H), 6.78 (dd, J = 7.9 Hz, J = 1.2 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.54 (dt, J = 8.8 Hz, J = 4.6 Hz, 1H), 4.36−4.07 (m, 2H), 3.69 (d, J = 5.4 Hz, 2H), 3.15−2.94 (m, 2H), 2.91−2.65 (m, 2H), 1.28 (s, 9H), 1.20 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.7, 171.1, 171.0, 170.7, 165.0, 155.1, 142.9, 142.0, 137.6, 132.3, 129.1, 128.9, 127.8, 127.4, 126.5, 126.2, 126.0, 123.4, 116.1, 116.0, 77.9, 69.6, 55.3, 53.6, 48.2, 41.3, 37.3, 28.0, 18.2; HRMS (ESI) calcd for $C_{35}H_{43}N_6O_8$ $[M + H]^+$ 675.3142, found 675.3141.

Compound 15: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.40−8.14 (m, 3H), 8.07−7.94 (m, 2H), 7.82 (d, J = 7.9 Hz, 1H), 7.60−7.45 (m, 1H), 7.45−7.07 (m, 9H), 6.96 (d, J = 8.4 Hz, 1H), 4.64−4.48 (m, 1H), 4.41−4.05 (m, 2H), 3.78 (d, J = 6.2 Hz, 2H), 3.14−2.92 (m, 2H), 2.90−2.69 (m, 2H), 1.29 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 171.7, 171.1, 171.0, 170.8, 155.1, 154.4, 153.8, 140.7, 137.6, 133.5, 131.9, 129.9, 129.0, 128.7, 128.6, 128.5, 127.8, 126.0, 123.2, 115.0, 77.9, 55.3, 53.6, 48.2, 40.7, 37.3, 37.0, 28.0, 18.2; HRMS (ESI) calcd for $C_{36}H_{41}N_6O_8$ $[M + H]^+$ 685.2986, found 685.3008.

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Supporting Information Available. Analytical data (HPLC, MS, and NMR) for building blocks and compounds cleaved from the solid support. This material is available free of charge via the Internet at http://pubs.acs.org.

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