OL Organic Letters

pubs.acs.org/OrgLett Letter

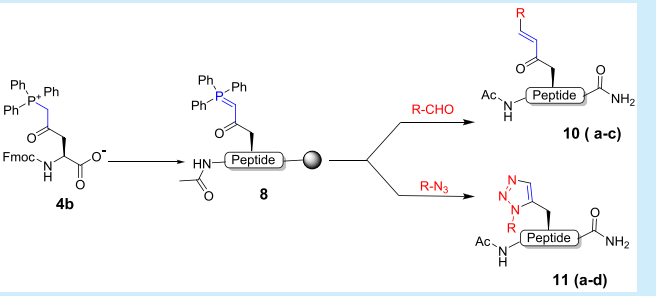
Side-Chain Modification of Peptides Using a Phosphoranylidene Amino Acid

Enaam Masri, Ahsanullah, Matteo Accorsi, and Jörg Rademann*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00713 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The flexible variation of peptidomimetics is of great interest for the identification of optimized protein ligands. Here we present a general concept for introducing side-chain modifications into peptides using triarylphosphonium amino acids. Building blocks **4a** and **4b** are activated for amidation and incorporated into stable peptides. The obtained phosphoranylidene peptides undergo Wittig olefinations and 1,3-dipolar cycloaddition reactions, yielding peptidomimetics with vinyl ketones and 5-substituted 1,2,3-triazoles as non-native peptide side chains.

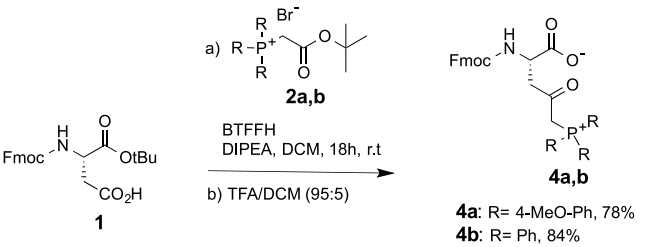


Peptidomimetics are structurally modified peptides and can modulate the biological activity and enhance the therapeutic potential of peptides.[1] Often, peptidomimetics have been designed to overcome the limitations of native peptides with respect to the metabolic stability,[2] membrane permeability,[3] binding affinity,[4] and specificity of the parent peptides.[5] In typical peptidomimetics, the peptide backbone, the termini, or the side chains of peptides are modified.[6] Incorporation of phosphorus into the side chains of amino acids has been reported for phosphonates.[7] We have earlier introduced a set of methods for the C-terminal variation of peptides based on C-acylation of polymer-attached phosphoranylidene acetonitriles or acetate esters with activated amino acids followed by standard peptide couplings.[8] The reactions proceeded racemization-free, and the obtained peptidyl-ylides have been employed in oxidation reactions furnishing peptidyl-keto amides, diketoesters, and 2-keto-aldehydes,[9] in Wittig reactions,[10] and in 1,3-dipolar cycloadditions yielding 1,5-disubstituted 1,2,3-triazoles as stable mimetics of *cis* peptide bonds.[11] The latter reaction proceeded without a metal catalyst, in contrast to the Cu^{I}-catalyzed reaction of azides and alkynes forming a 1,4-disubstituted heterocycle[12] and the Ru^{II}-catalyzed reaction giving a 1,5-disubstituted product.[13] On the basis of this phosphorus-ylide chemistry, the Bode group has utilized sulfur-ylides to synthesize C-terminal peptide α-ketoacids for peptide ligation purposes.[14]

Here, we have exploited the described C-acylation methodology for the flexible variation of side chains in peptides. The approach enables the introduction of diverse non-native residues in a defined amino acid position to identify best binding and most active peptide derivatives. For this purpose, an amino acid building block carrying a reactive phosphonium salt in the side chain has been developed, tested for compatibility with the conditions of solid phase peptide synthesis, and then applied in peptide preparation and subsequent side-chain variations.

N-Fmoc-L-aspartic acid-α-*tert*-butylester **1** was selected as the starting material for the C-acylation of the soluble triarylphosphonium bromide salts **2a** and **2b** and of the polymeric triarylphosphonium bromide salts **3a** and **3b** (Scheme 1). **2a** and **2b** were obtained from the P-alkylation

Scheme 1. Synthesis of Triarylphosphoranylidene Building Blocks 4a (R = 4-methoxyphenyl) and 4b (R = phenyl)



of tris(4-methoxy-phenyl)-phosphine (for **2a**) and triphenyl-phosphine (for **2b**), respectively, with *tert*-butyl-2-bromoacetate. The two different phosphines were used to provide phosphorane-ylides with different reactivity by varying the energy level of the highest occupied molecular orbital (HOMO). For a solid-supported approach, Wang resin was

Received: February 24, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00713
Org. Lett. XXXX, XXX, XXX−XXX

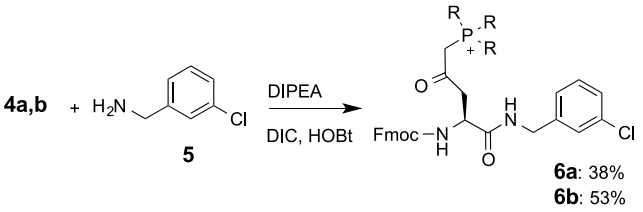
esterified with 2-bromoacetyl bromide.[15] The polymer-bound bromoacetate was then used to alkylate the two triarylphosphines yielding the polymer-supported phosphonium salts **3a** and **3b** (see the Supporting Information).

Next, phosphonium salts **2a** and **2b** were converted into the corresponding phosphoranylidene acetates *in situ* with an excess of *N,N*-diisopropylethylamine (DIPEA) and then C-acylated with Fmoc-L-aspartic acid-*α*-*tert*-butylester **1**. Various condensing reagents were investigated for this purpose, namely, *N,N′*-diisopropyl carbodiimide (DIC) with 1-hydroxybenzotriazole (HOBt), *O*-(7-aza-benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyl-uronium hexafluorophosphate (HATU), benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), *N,N,N′,N′*-bis-tetramethylene-fluoro-formamidinium hexafluorophosphate (BTFFH), and *N,N,N′,N′*-tetramethyl-fluoro-formamidinium hexafluorophosphate (TFFH). Cleavage of the *tert*-butyl ester from the intermediary product using trifluoroacetic acid (TFA) proceeded with instantaneous decarboxylation and furnished the desired building blocks **4a** and **4b**, which were isolated by reversed phase C18-MPLC on a 1−2 g scale. The best results were obtained for the reagents forming intermediary acyl fluorides (TFFH and BTFFH) with yields of 78% (**4a**) and 84% (**4b**), respectively. Likewise, the polymer-supported triarylphosphonium salts **3a** and **3b** were converted into triarylphosporanylidene acetates by treatment with DIPEA. The supported ylides were C-acylated with Fmoc-L-aspartic acid-*α*-*tert*-butylester **1** (5 equiv), through BTFFH activation. The success of the supported C-acylation reaction was quantified by cleavage and spectrophotometric determination of the Fmoc group from a dried and weighed resin sample giving turnovers of 88% for **3a** and 94% for **3b**. Cleavage with TFA released the building blocks **4a** and **4b** from the resin in isolated yields of 60% and 71%, respectively (see the Supporting Information).

The thermostability of **4a** and **4b** was investigated by heating solutions of these compounds in DMSO and DMF to 120 °C for 5 h. HPLC-MS analysis showed that both **4a** and **4b** were not stable at this temperature and led to several degraded products. The main product mass corresponded to the open-chain and cyclic dimers of building blocks **4a** and **4b**, which were formed after cleavage of the *N*-Fmoc group and presumably imine condensation reactions. This observation was in accordance with a literature report indicating that Fmoc is cleaved at this temperature without the presence of base.[16] In addition, traces of tris(4-methoxyphenyl)-phosphine oxide and triphenyl phosphine oxide were found; however, the phosphonium moiety remained stable under these conditions, suggesting that follow-up reactions with peptides containing building blocks **4a** and **4b** should be feasible at elevated temperatures.

Next, the Asp-derived triarylphosphonium-containing amino acids, building blocks **4a** and **4b**, were investigated in a simple amidation reaction in solution using 3-chlorobenzylamine **5** as the nucleophile. In the first attempt, the phosphonium salt **4a** was activated with DIC and HOBt in DMF followed by addition of **5** (Scheme 2). No amide bond formation was observed by HPLC-MS monitoring after reaction for 18 h at room temperature. When, however, 2 equiv of DIPEA was added to the reaction mixture, the reaction proceeded smoothly and furnished the amides **6a** and **6b** as shown in SFigure 21. Presumably, the formation of the ylide derivatives of **4a** and **4b** was required to prevent the protonation of the

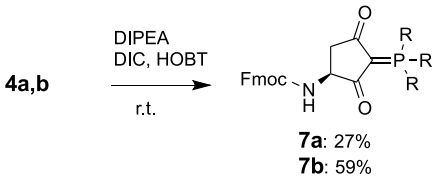
Scheme 2. Amide-Forming Reaction of Building Blocks 4a and 4b



amine by the phosphonium salt and thus to enable the amidation reaction. Isolated yields after RP-HPLC were 38% and 53% for compounds **6a** and **6b**, respectively. The results showed that the triphenylphosphonium building block **4b** provided better results than the tris(4-methoxyphenyl)-phosphine building block **4a** as observed before in the building block synthesis.

To investigate the self-reactivity of the activated building blocks, i.e. the possibility of cyclizing the activated amino acid through an intramolecular C-acylation, reagents **4a** and **4b** were activated under the same conditions (HOBt/DIC and DIPEA) without a primary amine as a reactive nucleophile present (Scheme 3). LC-MS analysis after 18 h at room

Scheme 3. Formation of *N*-Fmoc-Protected (*S*)1-Amino-(2,4-dioxo-3-(triaryl phosphoranylidene)-cyclopentyl) carbamates 7a and 7b



temperature revealed the formation of the cyclized intramolecular C-acylation product as the major product. The *N*-Fmoc-protected (*S*)1-amino-[2,4-dioxo-3-(triaryl phosphanylidene) cyclopentyl] carbamates **7a** and **7b** were isolated in yields of 27% and 59%, respectively. When building blocks **4a** and **4b** were activated with BTFFH, LC-MS analysis revealed a complex mixture of products. This mixture included the cyclization products **7a** and **7b**, but in addition, masses were detected corresponding to dimeric C-acylation products that were not isolated.

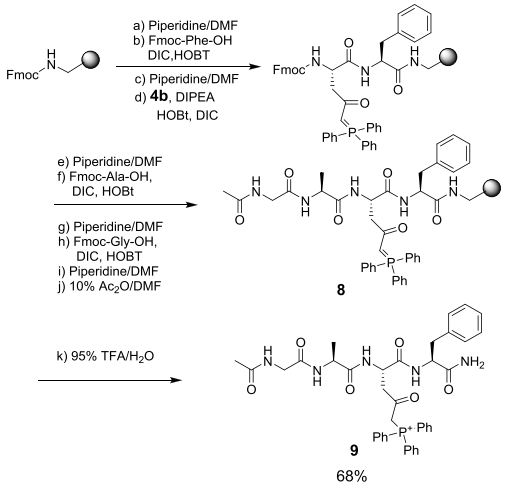
Subsequently, the reactivity of the phosphoranylidene moiety of the Fmoc-protected amino acid building blocks **4a** and **4b** was tested with azides and with aldehydes. For example, treatment of building blocks **4a** and **4b** with 3 equiv of DIPEA and 2 equiv of 4-azidobenzoic acid in dry THF as a solvent at 70 °C for 16 h yielded the corresponding 1,2,3-triazole. HPLC-MS analysis revealed that building block **4b** was more reactive than building block **4a**, showing 73% of the product and 26% of unconverted starting material (according to the integration of HPLC traces as shown in SFigure 60). In contrast, under the same conditions, **4a** gave only 15% of the product with 85% of the starting material remaining. This observation contradicted earlier results indicating that the phosphorus ylide of **4a** should be more reactive due to its higher electron density. To ensure that ylide formation from **4a** was not hampered by the lower acidity of the electron-rich phosphonium salt, bases stronger than DIPEA, namely 1,8-

https://dx.doi.org/10.1021/acs.orglett.0c00713
Org. Lett. XXXX, XXX, XXX−XXX

diazabicyclo(5.4.0)undec-7-ene (DBU) and lithium bis-trimethylsilyl amide (LiHMDS) were used as well but without improvement. Therefore, we decided to employ the building block **4b** for peptide synthesis and for peptide side-chain variations onward.

The triarylphosphonium derivative of aspartic acid **4b** was incorporated into a model tetrapeptide using Rink amide resin (Scheme 4). While the couplings of the standard Fmoc-protected amino acids phenylalanine, alanine, and glycine were conducted using DIC/HOBt for activation, building block **4b** was incorporated in the second coupling step using DIC/HOBt with an additional 5 equiv of DIPEA as discussed above. Incorporation of **4b** was quantified using Fmoc cleavage and photometric determination from a small resin sample that indicated complete conversion. N-Terminal capping of the peptide chain with 20% acetic anhydride in DMF was problematic due to partial C-acylation of the phosphoranylidene as observed in HPLC-MS in SFigure 40. Thus, capping instead was performed using 10% acetic anhydride in DMF. With these adjustments, tetrapeptide **9** carrying the triphenylphosphonium side chain was cleaved from the resin with a crude purity of 88% and was isolated by preparative RP-HPLC in 68% yield. The NMR spectrum of **9** was fully assigned, and the identity was confirmed with high-resolution MS. 2D NMR spectra displayed a single set of signals suggesting the absence of racemization.

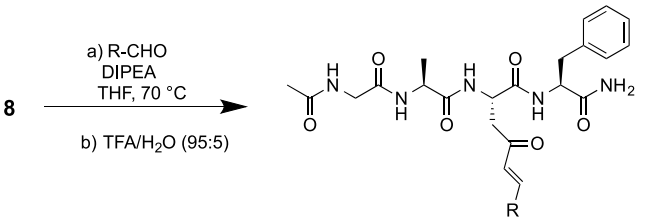
Scheme 4. Incorporation of Building Block 4b in the Peptide Chain



To examine the synthetic potential of peptides bearing the phosphorane side chain, the resin-bound tetrapeptide **8** was reacted with three aliphatic and aromatic aldehydes (Scheme 5) in THF using 10 equiv of aldehyde and 5 equiv of DIPEA at 70 °C for 18 h. Crude purities of peptides **10a−c** after cleavage from the resin were found to be 65%, 72%, and 79% with isolated yields of 57%, 62%, and 70%, respectively (Table 1). NMR analysis revealed that the reactions delivered vinyl ketones with exclusively *E*-configured olefins.

In another application, the resin-bound peptide **8** was subjected to 1,3-dipolar cycloaddition reactions with various aromatic and aliphatic azides (Scheme 6). Reaction of the aromatic azides, 4-azido-benzoic acid and methyl 4-azido-benzoate, with polymer-bound **8** at 70 °C using DIPEA followed by cleavage from resin resulted in selective formation

Scheme 5. Wittig Reactions of Peptidyl-phosphoranes to Form Vinyl Ketones



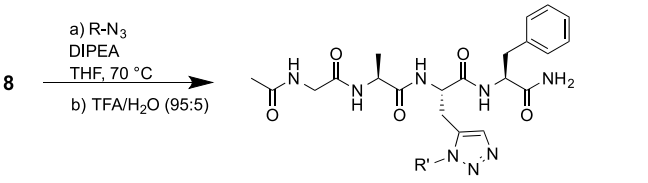
10a: R = methyl
10b: R = 2-isopropyl
10c: R = 4-chlorophenyl

Table 1. Selected Vinyl Ketone Ligation Products

compound	aldehyde	crude purity[a]	yield (%)[b]
10a	acetaldehyde	65	57
10b	isobutyraldehyde	72	62
10c	4-chlorobenzaldehyde	79	70

[a]Purity determined in the crude mixture at 210 nm before purification. [b]Yields of isolated product after purification by HPLC.

Scheme 6. 1,3-Dipolar Cycloaddition Reactions of Peptidyl-phosphoranes to Form 1,5-Disubstituted 1,2,3-Triazoles



11a: R,R′ = 4-carboxy-phenyl
11b: R,R′ = 4-(methoxy-carbonyl)-phenyl
11c: R,R′ = 2-methoxy-2-oxoethyl
11d: R = 4-toluyl-sulfonyl, R′ = H

of the 1,5-disubstituted 1,2,3-triazoles **11a** and **11b** in isolated yields of 63% and 56%, respectively (Table 2). No traces of the 1,4-disubstituted regioisomer, formed in classical copper-catalyzed cycloadditions, could be detected. The reaction between resin-bound peptide **8** and aliphatic azide, methyl 2-azidoacetate, under similar conditions proceeded at much lower rate with 24% conversion and 15% isolated yield of **11c** after RP-HPLC. The lower reaction rate and decreased yield for methyl 2-azidoacetate in comparison with 4-azido-benzoic acid and methyl 4-azido-benzoate could be attributed to relatively increased electron density at the azide center. The

Table 2. Selected Triazole Ligation Products

compound	azide	crude purity[a]	yield (%)[b]
11a	4-azidobenzoic acid	74	63
11b	methyl 4-azidobenzoate	63	56
11c	methyl 2-azidoacetate	24	15
11d	4-toluenesulfonylazide, R′ = H[c]	73	69

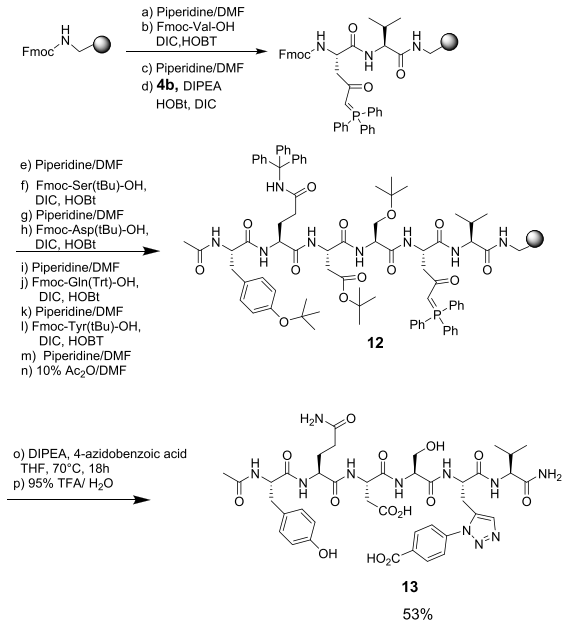
[a]Purity determined in the crude at 210 nm before purification. [b]Yields of isolated products after purification by HPLC. [c]The reaction with *p*-toluenesulfonylazide led to the desulfonylated 1*H*-1,2,3-triazole product **11d**.

https://dx.doi.org/10.1021/acs.orglett.0c00713
Org. Lett. XXXX, XXX, XXX−XXX

influence of electron density on reaction rate was further confirmed by the reaction of 4-toluenesulfonyl azide, the most electron deficient member of the series, with peptide **8** which proceeded smoothly at room temperature with 73% conversion and 69% isolated yield. The cleaved product, however, underwent desulfonylation under reaction conditions leading to the 1*H*-1,2,3-triazole **11d**.

To test the compatibility of this chemistry with diversely protected functional groups in the peptide side chains, building block **4b** was incorporated into the hexapeptide, Ac-Tyr-Gln-Asp-Ser-X-Val-NH_2, that contained a protected phenol, primary amide, carboxylic acid, and aliphatic alcohol residues (Scheme 7). The identity of hexapeptide **12** was confirmed

Scheme 7. Incorporation of Building Block 4b into a Hexapeptide Chain with Diverse Side Chain Functionalities and Cycloaddition Product Formed from Reaction between Peptidyl-phosphorane and 4-Azidobenzoic Acid



after TFA cleavage from the resin and precipitation from cold diethyl ether giving fully deprotected hexapeptide **12** in a purity of 77% and an isolated yield of 57%. Protected peptide **12** attached to the Rink amide resin, carrying the phosphonium residue of **4b** in position 5, was reacted with the aromatic azide, 4-azido-benzoic acid, at 70 °C. After TFA cleavage from the resin and precipitation from cold diethyl ether, fully deprotected hexapeptide **13**, bearing 1,5-disubstituted 1,2,3-triazole, was obtained in 65% purity in the crude mixture and 53% yield after RP-HPLC.

In summary, we have converted *N*-Fmoc-protected L-aspartic acid into the unnatural amino acids **4a** and **4b** carrying triarylphosphonium salts in their side chains. Building blocks **4a** and **4b** could be activated with DIC/HOBt and coupled efficiently with a nucleophilic amine **5** in solution yielding amides **6a** and **6b**; also, they were successfully incorporated into peptides using Fmoc-based solid phase peptide synthesis as demonstrated by the preparation of model peptides **9** and **12** in excellent yields and purities. These peptides were finally employed in side-chain variations using Wittig reactions to provide *E*-configured *α,β*-unsaturated ketones and 1,3-dipolar cycloaddition reactions to form regioselectively 1,5-disubstituted 1,2,3-triazole **10a−c**, **11a−d**, and **13**. In general, the triphenylphosphonium salt **4b** provides higher yields both in the building block synthesis, amidation reactions and in 1,3-dipolar cycloadditions compared to the more electron-rich tris(4-methoxyphenyl) phosphonium reagent **4a**. The presented methodology enables the systematic variation and replacement of native amino acid residues by alternative fragments and will allow for the optimization of peptides for applications in medicinal chemistry and chemical biology. Furthermore, the peptides bearing vinyl ketones as Michael acceptors in the side chain might serve as electrophilic probes and as intermediates for subsequent reactions, including addition of (bis)-nucleophiles leading to diverse heterocycles. Another interesting application of this chemistry that is currently under investigation is the cyclization of peptides through side-chain reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00713.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jörg Rademann − *Department of Chemistry, Biology, and Pharmacy, Institute of Pharmacy/Medicinal Chemistry, Freie Universität Berlin, 14195 Berlin, Germany;* orcid.org/0000-0001-6678-3165; Phone: +4930 83853272; Email: joerg.rademann@fu-berlin.de

Authors

Enaam Masri − *Department of Chemistry, Biology, and Pharmacy, Institute of Pharmacy/Medicinal Chemistry, Freie Universität Berlin, 14195 Berlin, Germany*

Ahsanullah − *Department of Chemistry, Biology, and Pharmacy, Institute of Pharmacy/Medicinal Chemistry, Freie Universität Berlin, 14195 Berlin, Germany; Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan*

Matteo Accorsi − *Department of Chemistry, Biology, and Pharmacy, Institute of Pharmacy/Medicinal Chemistry, Freie Universität Berlin, 14195 Berlin, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00713

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Deutsche Forschungsgemeinschaft (DFG) Grants Ra895/11, SFB 765, and by DAAD granting a PhD fellowship to E.M.

■ REFERENCES

(1) (a) Neefjes, J.; Dantuma, N. P. *Nat. Rev. Drug Discovery* **2004**, *3*, 58−69. (b) Qvit, N.; Rubin, S. J. S.; Urban, T. J.; Mochly-Rosen, D.; Gross, E. R. *Drug Discovery Today* **2017**, *22*, 454−462. (c) Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133* (3), 462−477. (d) Hruby, V. J.; Cai, M. *Annu. Rev. Pharmacol. Toxicol.* **2013**, *53*, 557−580.

https://dx.doi.org/10.1021/acs.orglett.0c00713
Org. Lett. XXXX, XXX, XXX−XXX

(2) (a) Croft, N. P.; Purcell, A. W. *Expert Rev. Vaccines* **2011**, *10*, 211−226. (b) Fransson, R.; Sköld, C.; Kratz, J. M.; Svensson, R.; Artursson, P.; Nyberg, F.; Hallberg, M.; Sandström, A. *J. Med. Chem.* **2013**, *56*, 4953−4965. (c) Veber, D. F.; Freidinger, R. M. *Trends Neurosci.* **1985**, *8*, 392−396.
(3) (a) Rafi, S. B.; Hearn, B. R.; Vedantham, P.; Jacobson, M. P.; Renslo, A. R. *J. Med. Chem.* **2012**, *55* (7), 3163−3169. (b) Stone, T. A.; Deber, C. M. *Biochim. Biophys. Acta, Biomembr.* **2017**, *1859* (4), 577−585. (c) Brodin, B.; Nielsen, C. U.; Steffansen, B.; Frøkjær, S. *Pharmacol. Toxicol.* **2002**, *90*, 285−296. (d) Giacomini, K. M.; Huang, S. M.; Tweedie, D. J.; et al. *Nat. Rev. Drug Discovery* **2010**, *9*, 215−236. (e) Witt, K. A.; Gillespie, T. J.; Huber, J. D.; Egleton, R. D.; Davis, T. P. *Peptides* **2001**, *22*, 2329−2343.
(4) Neffe, A. T.; Bilang, M.; Grüneberg, I.; Meyer, B. *J. Med. Chem.* **2007**, *50*, 3482−3488.
(5) (a) Teveroni, E.; Lucà, R.; Pellegrino, M.; Ciolli, G.; Pontecorvi, A.; Moretti, F. *Expert Opin. Ther. Pat.* **2016**, *26*, 1417−1429. (b) Humphrey, M. J.; Ringrose, P. S. *Drug Metab. Rev.* **1986**, *17* (3−4), 283−310. (c) Turcotte, S.; Mellal, K.; Chingle, R.; Mulumba, M.; Omri, S.; Dif-Yaiche, L.; Chemtob, S.; Ong, H.; Lubell, W. D. *Biomedicines* **2018**, *6*, 98.
(6) (a) Fletcher, M. D.; Campbell, M. M. *Chem. Rev.* **1998**, *98*, 763−796. (b) Grauer, A.; König, B. *Eur. J. Org. Chem.* **2009**, *2009*, 5099−5111. (c) Hallberg, M.; Nyberg, F. *Curr. Protein Pept. Sci.* **2003**, *4*, 31−44. (d) Claerhout, S.; Sharma, S.; Sköld, C.; Cavaluzzo, C.; Sandström, A.; Larhed, M.; Thirumal, M.; Parmar, V. S.; Van der Eycken, E. V. *Tetrahedron* **2012**, *68*, 3019−3029. (e) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; et al. *J. Med. Chem.* **1993**, *36*, 3039−3049. (f) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2* (4), 441−452. (g) Vagner, J.; Qu, H. C.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292−296. (h) van De Waterbeemd, H.; Smith, D. A.; Beaumont, K.; Walker, D. K. *J. Med. Chem.* **2001**, *44*, 1313−1333. (i) Mir, F. M.; Atmuri, N. D. P.; Bourguet, C. B.; Fores, J. R.; Hou, X.; Chemtob, S.; Lubell, W. D. *J. Med. Chem.* **2019**, *62*, 4500−4525. (j) Geranurimi, A.; Cheng, C. W. H.; Quiniou, C.; Zhu, T.; Hou, X.; Rivera, J. C.; St-Cyr, D. J.; Beauregard, K.; Bernard-Gauthier, V.; Chemtob, S.; Lubell, W. D. *Front. Chem.* **2019**, *7*, 23. (k) Atmuri, N. D. P.; Reilley, D. J.; Lubell, W. D. *Org. Lett.* **2017**, *19*, 5066−5069. (l) Zhang, J.; Mulumba, M.; Ong, H.; Lubell, W. D. *Angew. Chem., Int. Ed.* **2017**, *56*, 6284−6288.
(7) (a) Arribat, M.; Cavelier, F.; Rémond, E. *RSC Adv.* **2020**, *10*, 6678−6724. (b) Cortes-Clerget, M.; Jover, J.; Dussart, J.; Kolodziej, E.; Monteil, M.; Migianu-Griffoni, E.; Gager, O.; Deschamp, J.; Lecouvey, M. *Chem. - Eur. J.* **2017**, *23*, 6654−6662. (c) Real-Fernández, F.; Colson, A.; Bayardon, J.; Nuti, F.; Peroni, E.; Meunier-Prest, R.; Lolli, F.; Chelli, M.; Darcel, C.; Jugé, S.; Papini, A. M. *Biopolymers* **2008**, *90*, 488−495.
(8) (a) El-Dahshan, A.; Ahsanullah; Rademann, J. *Biopolymers* **2010**, *94*, 220−228. (b) El-Dahshan, A.; Weik, S.; Rademann, J. *Org. Lett.* **2007**, *9*, 949−52. (c) Weik, S.; Rademann, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2491−2494.
(9) El-Dahshan, A.; Nazir, S.; Ahsanullah; Ansari, F. L.; Rademann, J. *Eur. J. Org. Chem.* **2011**, *2011*, 730−739.
(10) Holland-Nell, K.; Fernández-Bachiller, M. I.; Ahsanullah; Rademann, J. *Org. Lett.* **2014**, *16*, 4428−31.
(11) (a) Ahsanullah; Schmieder, P.; Kühne, R.; Rademann, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5042−5045. (b) Ahsanullah; Rademann, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5378−5382.
(12) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−64. (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952−3015.
(13) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999.
(14) (a) Ju, L.; Bode, J. W. *Org. Biomol. Chem.* **2009**, *7*, 2259−2264. (b) Bode, J. W. *Acc. Chem. Res.* **2017**, *50* (9), 2104−2115. (c) Murar, C. E.; Thuaud, F.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 18140−18148.
(15) Ahsanullah; Al-Gharabli, S. I.; Rademann, J. *Org. Lett.* **2012**, *14*, 14−17.
(16) Höck, S.; Marti, R.; Riedl, R.; Simeunovic, S. *Chimia* **2010**, *64*, 200−202.

https://dx.doi.org/10.1021/acs.orglett.0c00713
Org. Lett. XXXX, XXX, XXX−XXX