Organic LETTERS

Letter

pubs.acs.org/OrgLett

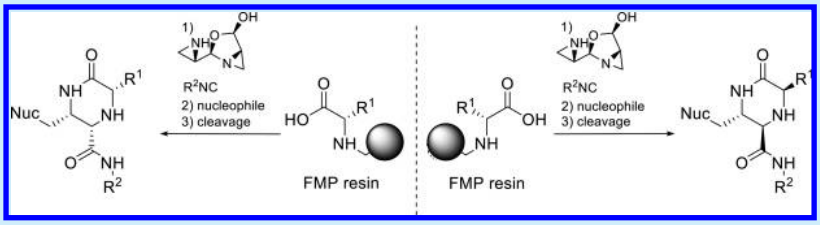
Solid-Phase Synthesis of Piperazinones via Disrupted Ugi Condensation

Adam P. Treder,[†] Marie-Claude Tremblay,[†] Andrei K. Yudin,[‡] and Eric Marsault*[,†]

[†]Département de Pharmacologie, Institut de Pharmacologie de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, Canada J1H 5N4

[‡]Department of Chemistry, University of Toronto, Davenport Building, rm. 362, 80 St. George, Toronto, ON, Canada M5S 3H6

Supporting Information



ABSTRACT: The first application of aziridine aldehyde dimers in solid-phase synthesis is reported. The solid-supported disrupted Ugi condensation between an aziridine aldehyde dimer, isonitrile, and backbone-anchored amino acids delivered *N*-acyl aziridine intermediates, which were reacted with nucleophiles to yield the corresponding piperazinones. Subsequent cleavage from the resin provided a diverse set of 2,3,6-trisubstituted piperazinones starting from various amino acids, aziridine aldehydes, and nucleophiles.

The Ugi multicomponent reaction plays an important role in drug discovery, natural products synthesis, and combinatorial chemistry as a source of peptidomimetic scaffolds.[1] Recently, the Yudin group reported novel aziridine aldehyde dimers (Figure 1)[2] as a new class of amphoteric reagents, which

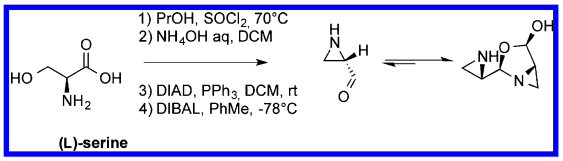


Figure 1. Synthesis of (*S*)-aziridine aldehyde dimer derived by Serine.

has found utility in a wide variety of applications in organic synthesis, including multicomponent reactions.[3] Aziridine aldehydes lead to disrupted Ugi four-component condensations, generating cyclic products that do not correspond to conventional Ugi-type outcomes, thereby improving the diversity of accessible structures. The resulting bicyclic aziridines can be reacted with nucleophiles under mild conditions. This approach offers four diversity elements on pharmaceutically important scaffolds such as macrocycles and piperazinones.[4]

The piperazine moiety has been frequently used in drug discovery and introduced in many valuable biologically active compounds,[5] including antineoplastics,[6] antivirals,[7] coagulation regulators,[8] insecticides,[9] and antischisostomal agents.[10] They have been applied to a variety of targets such as elastase,[11] fibrinogen,[12] oxytocin,[13] melanocortin-4,[14] dopamine receptors,[15] or $GABA_A$ chloride ion channel.[16] The piperazinone ring is also found in multiple natural products (Figure 2) possessing activities such as serine protease inhibitors,[17] cytostatic,[18] antibacterial,[19] and immunomodulating agents[20] (Figure 2).

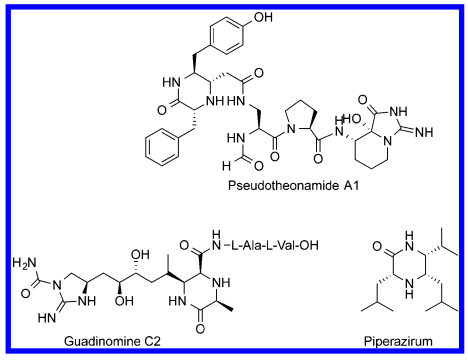


Figure 2. Representative biologically active piperazinones.

Recent efforts by the Yudin group in the field of parallel synthesis of piperazinones have focused on the application of microfluidics.[21] On the other hand, solid-phase synthesis represents a powerful tool to support the rapid generation of diversity, both via parallel synthesis or split-pool combinatorial chemistry.[22] In order to further exploit the potential of aziridine aldehydes, we embarked on the development of a solid-phase synthetic method to enable the parallel synthesis of piperazinones.

Received: August 4, 2014
Published: August 25, 2014

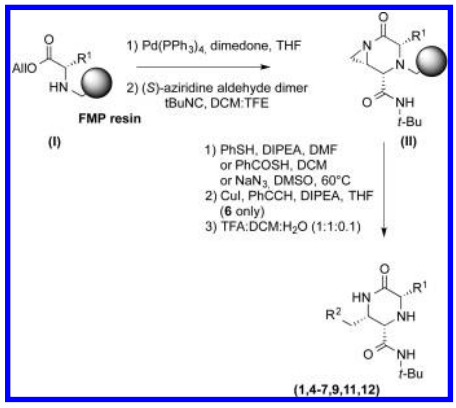
dx.doi.org/10.1021/ol5023118 | *Org. Lett.* 2014, 16, 4674–4677

Several approaches to solid-supported Ugi reactions have been reported.[23] Synthesis of substituted piperazinones on solid-phase has also been explored. Among the known methods of piperazine ring formation are polyamine cyclization on MBHA resin,[24] cyclization of dipeptides immobilized on BAL resin to diketopiperazines,[25] or traceless synthesis of piperazinones on Wang resin.[26] Applications of Merrifield,[27] Rink,[28] and trityl[29] resins as well as a polymer-supported trialkylsilylethyl linker[30] have also been reported.

We sought a solid-supported precursor displaying free amino and carboxylate ends, turning our attention to the immobilization of amino acids by anchoring the backbone on FMP resin using reductive amination.[25,31,32] This site of resin anchoring was expected to enhance the nucleophilicy of the amine, and to facilitate chain folding for cyclization.

Direct reductive amination of unprotected amino acids and resin aldehyde proved difficult due to the poor solubility of unprotected amino acids in organic solvents. We thus chose allyl esters, which are subsequently deallylated on solid phase (Scheme 1). As described previously,[4] the cyclization reaction

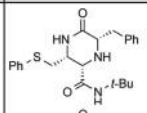
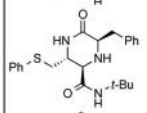
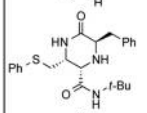
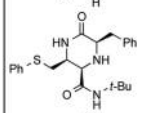
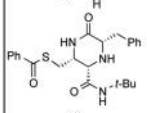
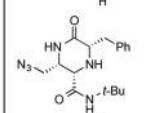
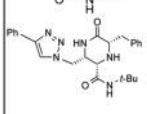
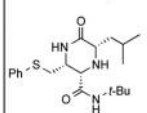
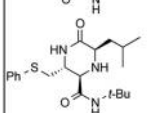
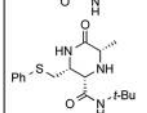
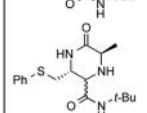
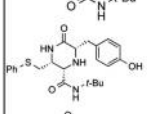
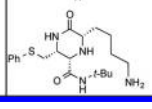
Scheme 1. Representative Synthesis of Piperazinones



is best performed in TFE as a solvent, yet the physical properties of polystyrene-based resins precluded the use of neat TFE due to poor swelling. To ensure appropriate swelling of the resin, a variety of solvent and solvent mixtures were tested to finally identify a mixture of TFE and DCM (1:1) as the best combination. In the first step of cyclization, a secondary FMP-anchored amino acid (**I**) was reacted with an aziridine aldehyde dimer and *t*-BuNC to yield the bicyclic aziridine derivative (**II**). Our efforts to cleave and isolate the bicyclic aziridine product (**II**) were unsuccessful due to the instability of the compounds under cleavage conditions. Only decomposition products were observed by LC/MS. In subsequent experiments, the aziridine was opened *in situ* with a variety of nucleophiles, including thiol, azide, and thioacid (Scheme 1, Table 1). The cyclization reactions (**I**–**II**, Scheme 1) occurred in good yields and gave products in high purity when the amino acid configuration matched that of the aziridine aldehyde dimer [matched chemistry: (*S*)-dimer and L-amino acid, or (*R*)-dimer and D-amino acid; mismatched chemistry: (*S*)-dimer and D-amino acid; Figure 3]. L- and D-Phe anchored to FMP resin were chosen to assess the robustness of the cyclization to deliver (*S*)-(**1**–**6**).

In the subsequent step, the corresponding bicyclic aziridine intermediate (**II**) was reacted with a series of nucleophiles such as thiophenol (**1**–**3**), thiobenzoic acid (**4**), and sodium azide (**5**). In the case of azido derivative (**5**), the azide moiety was subsequently reacted with phenylacetylene in a "click" cyclo-

Table 1. Piperazinones Obtained in This Study

nr	product	substrates			yield [%]*
		a. acid	dimer	nucleophile	
1		L-Phe	(*S*)	PhSH	30
2a		D-Phe	(*S*)	PhSH	19
2b		D-Phe	(*S*)	PhSH	6
3		D-Phe	(*R*)	PhSH	36
4		L-Phe	(*S*)	PhCOSH	30
5		L-Phe	(*S*)	NaN_3	34
6		L-Phe	(*S*)	NaN_3, then PhCCH/ CuI	17
7		L-Leu	(*S*)	PhSH	38
8		D-Leu	(*S*)	PhSH	19
9		L-Ala	(*S*)	PhSH	36
10		D-Ala	(*S*)	PhSH	16
11		L-Tyr	(*S*)	PhSH	23
12		L-Lys	(*S*)	PhSH	36

[a]Overall yields for 4–5 steps including RP-HPLC purification and lyophilization, calculated based on initial resin loading.

addition displaying an alternative method for piperazinone derivatization (**6**).[33] Several other FMP-attached amino acids were cyclized with the (*S*)-aziridine aldehyde dimer and *t*-BuNC: L-Leu, D-Leu, L-Ala, D-Ala, L-Tyr, and L-Lys. The bicyclic aziridine intermediates were further reacted with thiophenol, yielding thioether derivatives (**7**–**12**). Figure 3 shows a representative chromatogram of a matched (**2a**) and a mismatched (**2b**) cyclization. Matched combinations were typically of superior purity and gave higher yields. The configurations of newly

dx.doi.org/10.1021/ol5023118 | *Org. Lett.* 2014, 16, 4674–4677

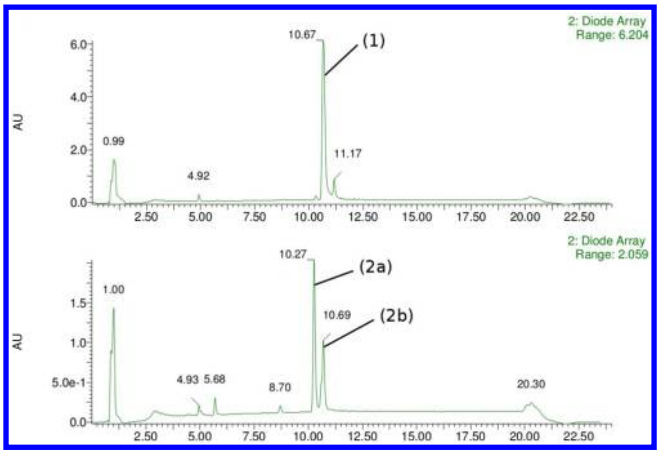


Figure 3. Typical HPLC traces of crude cyclizations in matched (**1**) and mismatched (**2a**, **2b**) cases.

synthesized compounds were determined by NMR, particularly positions 3 and 6 of the piperazinone scaffold (Figure 4).

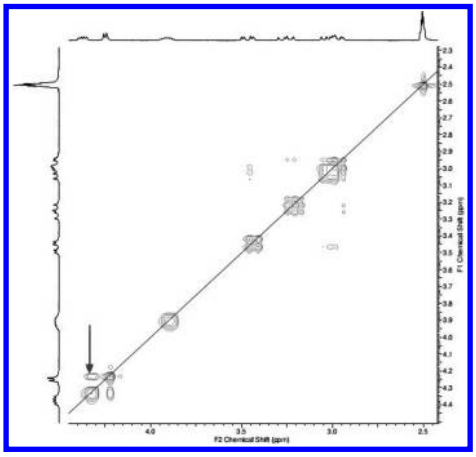


Figure 4. NOESY experiment for (**1**). Diagnostic crosspeak between two axial protons (Figure 5) marked by arrow.

The relative configuration of the new stereocenter in position 2 was confirmed by analysis of ^{1}H NMR coupling constants followed by 2D NOESY experiments for a subset of compounds (**1**, **2a**,**b**, **7**). For product **1**, the ^{1}H NMR coupling constant between protons in positions 2 and 3 was characteristic of axial−equatorial or equatorial−equatorial protons (4.7 Hz). A ^{1}H−^{1}H NOESY experiment (Figures 4 and 5) showed cross-peaks for axial protons in positions 2 and 6, confirming the (2*S*) configuration. Similar results were obtained for **7**.

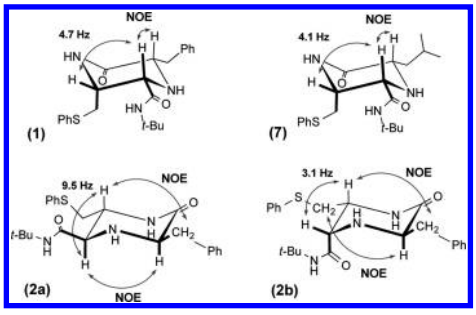


Figure 5. Structural elucidation of products.

For product **2a** obtained from FMP-D-Phe and the (*S*)-aziridine aldehyde dimer, the coupling constant between protons in positions 2 and 3 was characteristic of a *trans*-diaxial orientation (9.5 Hz). NOESY analysis further confirmed the configuration as (2*R*) (Figure 5). As a side product of FMP-D-Phe cyclization with the (*S*)-dimer, (2*S*)-diastereomer **2b** was isolated. For **2b**, only a long distance NOE was observed, along with a low coupling constant (3.1 Hz), which is indicative of an axial−equatorial relationship (Figure 5). Configurations of other compounds in this series were assigned by comparison of ^{1}H NMR coupling constants to **1**, **2a**,**b**, and **7**.

The configuration at position 2 of the piperazinones obtained on *solid phase* was determined by the configuration of the starting amino acid. By virtue of resin anchoring, which converts the amino acid into a secondary amine, piperazinones derived from the solid-phase method yield the *cis* diastereomer. This is in contrast to *solution phase*, which yields the *trans* diastereomer predominantly when primary amino acids are cyclized (Figure 6).[4a] Thus, the solid-phase approach provides complementary access to the opposite diastereomer for the cyclization of primary amino acids such as Leu and Phe.

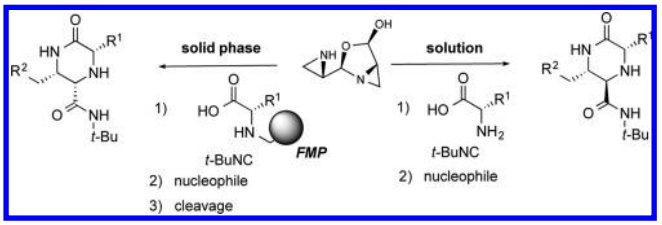


Figure 6. Comparison of *solid-phase* and *solution-phase* outcomes for (*S*) matched chemistry.

In summary, we have developed a new and efficient solid-supported method to synthesize 2,3,6-trisubstituted piperazinones via disrupted Ugi condensation between amine-anchored amino acids, isocyanides, and aziridine aldehyde dimers. The cyclization diastereoselectivity strongly depends on the stereochemistry of both the amino acid and the aziridine aldehyde. The reaction yields a single *cis* diastereomer when the amino acid and aziridine aldehyde dimer possess matched stereochemistry. The solid-phase cyclization approach presented herein represents a viable method for the synthesis of combinatorial libraries of piperazinones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, chromatograms, and NMR and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: eric.marsault@usherbrooke.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

CQDM (Consortium Québécois sur la Découverte du Médicament, www.cqdm.org) is acknowledged for funding. We also thank Serge Zaretsky and Jennifer L. Hickey (University of Toronto) for constructive comments.

REFERENCES

(1) For reviews, see: (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439−4486. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (c) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083−3135.

(2) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772−14773.

(3) For examples of applications of this new reagent, see: (a) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 16404−16406. (b) He, Z.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 1607−1610. (c) Bakthara-man, S.; Afagh, N.; Vandersteen, A.; Yudin, A. K. *Org. Lett.* **2010**, *12*, 240−243. (d) Assem, N.; Natarajan, A.; Yudin, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 10986−10987. (e) Cheung, L. L. W.; He, Z.; Decker, S. M.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1179−1180.

(4) (a) Hili, R.; Rai, V.; Yudin, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 2889−2891. (b) Rotstein, B. H.; Mourtada, R.; Kelly, Sh. O.; Yudin, A. K. *Chem.—Eur. J.* **2011**, *17*, 12257−12261. (c) Roxin, A.; Chen, J.; Scully, C. C. G.; Rotstein, B. H.; Yudin, A. K.; Zheng, G. *Bioconjugate Chem.* **2012**, *23*, 1387−1395. (d) Rotstein, B. H.; Winterheimer, D. J.; Yin, L. M.; Deber, Ch. M.; Yudin, A. K. *Chem. Commun.* **2012**, *48*, 3775−3777. (e) Zaretsky, S.; Scully, C. C. G.; Lough, A. J.; Yudin, A. K. *Chem.—Eur. J.* **2013**, *19*, 17668−17672.

(5) For reviews, see: (a) Borthwick, A. D. *Chem. Rev.* **2012**, *112*, 3641−3716. (b) Williams, R. M. *J. Org. Chem.* **2011**, *76*, 4221−4259. (c) Ressureicao, A. S. M.; Delatouche, R.; Gennari, C.; Piarulli, U. *Eur. J. Org. Chem.* **2011**, 217−228.

(6) Bergman, J. M.; Abrams, M. T.; Davide, J. P.; Greenberg, I. B.; Robinson, R. G.; Buser, C. A.; Huber, H. E.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Graham, S. L.; Hartman, G. D.; Williams, T. M.; Dinsmore, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1411−1415.

(7) (a) Nishizawa, R.; Nishiyama, T.; Hisaichi, K.; Matsunaga, N.; Minamoto, C.; Habashita, H.; Takaoka, Y.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 727−731. (b) Habashita, H.; Kokubo, M.; Hamano, S.; Hamanaka, M.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, *49*, 4140−4152.

(8) Su, T.; Yang, H.; Volkots, D.; Woolfrey, J.; Suiko, D.; Wong, P.; Sinha, U.; Scarborough, R. M.; Zhu, B. Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 729−732.

(9) Watanabe, T.; Arisawa, M.; Narusuye, K.; Alam, M. S.; Yamamoto, K.; Mitomi, M.; Ozoe, Y.; Nishida, A. *Bioorg. Med. Chem.* **2009**, *17*, 94−110.

(10) Cao, H.; Liu, H.; Dömling, A. *Chem.—Eur. J.* **2010**, *16*, 12296−12298.

(11) Seibel, J.; Brown, D.; Amour, A.; MacDonald, S. J.; Oldham, N. J.; Schoefield, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 387−389.

(12) Sugihara, H.; Fukushi, H.; Myawaki, T.; Imai, Y.; Tereshita, Z.; Kawamura, M.; Fujisawa, Y.; Kita, S. *J. Med. Chem. Chem.* **1998**, *41*, 489−502.

(13) Liddle, J.; Allen, M. J.; Borthwick, A. D.; Brooks, D. P.; Davies, D. E.; Edwards, R. M.; Exall, A. M.; Hamlett, C.; Irving, W. R.; Mason, A. M.; McCafferty, G. P.; Nerozzi, F.; Peace, S.; Philp, J.; Pollard, D.; Pullen, M. A.; Shabbir, S. S.; Sollis, S. L.; Westfall, T. D.; Woollard, P. M.; Wu, C.; Hickey, M. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90−94.

(14) Tian, X.; Mishra, R. K.; Switzer, A. G.; Hu, X. E.; Kim, N.; Mazur, A. W.; Ebetino, F. H.; Wos, J. A.; Crossdoersen, D.; Pinney, B. B.; Farmer, J. A.; Sheldon, R. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4668−4673.

(15) Yu, K.-L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1988**, *31*, 1430−1436.

(16) Jacobsen, E. J.; Stelzer, L. S.; TenBrink, R. E.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. K.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D.; Zhong, W.-Z.; Mickelson, J. W. *J. Med. Chem.* **1999**, *42*, 1123−1144.

(17) (a) Nakao, Y.; Masuda, A.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, *121*, 2425−2431. (b) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K.; Phalgune, U. D. *Tetrahedron Lett.* **2002**, *43*, 1897−1900.

(18) El-Desouky, S. K.; Ryub, S. Y.; Kima, Y.-K. *Tetrahedron Lett.* **2007**, *48*, 4015−4017.

(19) Hirose, T.; Sunazuka, T.; Tsuchiya, S.; Tanaka, T.; Kojima, Y.; Mori, R.; Iwatsuki, M.; Omura, S. *Chem.—Eur. J.* **2008**, *14*, 8220−8238.

(20) (a) Jacquot, D. E. N.; Zöllinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295−2298. (b) Shigematsu, N.; Setoi, H.; Uchida, I.; Shibata, T.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 5147−5150.

(21) Jebrail, M. J.; Ng, A. H. C.; Rai, V.; Hili, R.; Yudin, A. K.; Wheeler, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 8625−8629.

(22) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. *Chem. Rev.* **2009**, *109*, 1999−2060.

(23) (a) Liu, Z.; Nefzi, A. *Tetrahedron Lett.* **2012**, *53*, 1013−1014. (b) Henkel, B.; Sax, M.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 7015−7018. (c) Lin, Q.; Neill, J. C.; Blackwell, H. E. *Org. Lett.* **2005**, *7*, 4455−4458. (d) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8350−8354. (e) Liu, Z.; Nefzi, A. *J. Comb. Chem.* **2010**, *12*, 566−570. (f) Golebiowski, A.; Jozwik, J.; Klopfenstein, S. R.; Colson, A.-O.; Grieb, L. A.; Russel, A. F.; Rastogi, V. L.; Diven, C. F.; Portlock, D. E.; Chen, J. J. *J. Comb. Chem.* **2002**, *4*, 584−590.

(24) (a) Nefzi, A.; Giulianotti, M. A.; Houghten, R. A. *Tetrahedron Lett.* **1999**, *40*, 8539−8542. (b) Nefzi, A.; Santos, R. T. *J. Org. Chem.* **2005**, *70*, 9622−9625. (c) Nefzi, A.; Mimna, R. A.; Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 542−545. (d) Nefzi, A.; Giulianotti, M. A.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 68−70.

(25) (a) Del Fresno, M.; Alsina, J.; Royo, M.; Barany, G.; Albericio, F. *Tetrahedron Lett.* **1998**, *39*, 2639−2642. (b) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441−5452. (c) Royo, M.; Van Den Nest, W.; Del Fresno, M.; Frieden, A.; Yahalom, D.; Rosenblatt, M.; Chorev, M.; Albericio, F. *Tetrahedron Lett.* **2001**, *42*, 7387−7391.

(26) Shreder, K.; Zhang, L.; Gleeson, J. P.; Ericsson, J. A.; Yalamoori, V. V.; Goodman, M. *J. Comb. Chem.* **1999**, *1*, 383−387.

(27) Li, W.-R.; Peng, S.-Z. *Tetrahedron Lett.* **1998**, *39*, 7373−7376.

(28) Goff, D. A.; Zuckermann, R. *Tetrahedron Lett.* **1996**, *37*, 6247−6250.

(29) Sabatino, G.; Chelli, M.; Mazzuco, S.; Ginanneschi, M.; Papini, A. M. *Tetrahedron Lett.* **1999**, *40*, 809−812.

(30) Wang, B.; Chen, L.; Kim, K. *Tetrahedron Lett.* **2001**, *42*, 1463−1466.

(31) For examples of applications, see (a) Bourne, G. T.; Meutermans, W. D. F.; Alewood, P. F.; McGeary, R. P.; Scanlon, M.; Watson, A. A.; Smythe, M. L. *J. Org. Chem.* **1999**, *64*, 3095−3101. (b) Royo, M.; Farrera-Sinfreu, J.; Sole, L.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 2029−2032. (c) Bourne, G. T.; Meutermans, W. D. F.; Smythe, M. L. *Tetrahedron Lett.* **1999**, 7271−7274. (c) Bourne, G. T.; Golding, S. W.; Meutermans, W. D. F.; Smythe, M. L. *Lett. Pept. Sci.* **2001**, *7*, 311−316. (d) Alsina, J.; Yokum, T. S.; Albericio, F.; Barany, G. *J. Org. Chem.* **1999**, *64*, 8761−8769. (e) Bianco, A.; Fournel, S.; Wieckowski, S.; Hoebeke, J.; Guichard, G. *Org. Biomol. Chem.* **2006**, *4*, 1461−1463. (f) Rew, Y.; Goodman, M. *J. Org. Chem.* **2002**, *67*, 8820−8826. (g) Gu, W.; Silverman, R. B. *J. Org. Chem.* **2003**, *68*, 8774−8779.

(32) For reviews, see (a) Boas, U.; Brask, J.; Jensen, K. J. *Chem. Rev.* **2009**, *109*, 2092−2118. (b) Virta, P.; Katajisto, J.; Nittymäki, T.; Lönberg, H. *Tetrahedron* **2003**, *59*, 5137−5174.

(33) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905−4979.

dx.doi.org/10.1021/ol5023118 | *Org. Lett.* 2014, 16, 4674−4677