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Highly Diastereoselective Synthesis of 1-Carbamoyl-4-aminoindoloazepinone Derivatives via the Ugi Reaction

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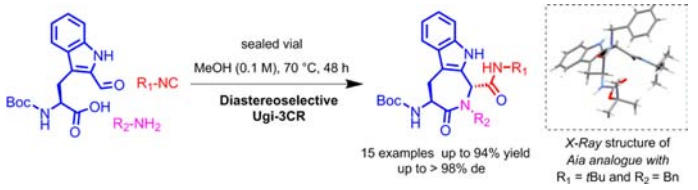
ABSTRACT



A one-pot procedure for the highly diastereoselective synthesis of 1-carbamoyl-4-amino-1,2,4,5-tetrahydroindolo[2,3-*c*]azepin-3-one derivatives is described. Using 2-formyl-L-tryptophan as a bifunctional building block, a catalyst-free Ugi-three-component reaction (Ugi-3CR) was developed to present trisubstituted indoloazepinones in good yields and excellent diastereomeric excess.

Multicomponent reactions (MCRs) are one-pot processes during which three or more substrates react in a single chemical step to produce a product that incorporates all of the educts.[1] Since MCRs represent one of the most powerful approaches for combinatorial chemistry and diversity-oriented synthesis, they play an important role in the development of drug discovery methodology and biological probes.[2] The Ugi four-component reaction (Ugi-4CR)[3] is one of the most widely applied MCRs, and great efforts have been dedicated to the exploration of its synthetic potential.[4] The Ugi-4CR involves a condensation of a carbonyl component, an isonitrile, an amine, and a carboxylic acid to present α-acylaminoamides. Concomitantly, a new stereogenic center is created. Hence, it provides a powerful tool to access diversity as well as complexity in a one-step procedure. Several strategies have been applied to control the chirality of the newly formed stereocenter by using chiral substrates or chiral auxiliaries.[4a,5] For example, chiral amines such as (*S*)-α-phenylethylamines,[6] ferrocenylamines,[7] glycosylamines,[8] xylopyranose-derived peracylated thiosugar,[9] and esters of α-amino acids[10] are capable to induce excellent stereoselectivity in Ugi-4CRs. In contrast, chiral oxo components

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(1) (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (b) Ramon, D. J.; Yus, M. *Angew. Chem.* **2005**, *117*, 1628. (c) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

(2) (a) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (b) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Bindu, A. R.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (c) Akakritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324. (d) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796. (e) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153.

(3) (a) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632. (b) Ugi, I. *Angew. Chem.* **1962**, *74*, 9. (c) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 8.

(4) (a) Domling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Domling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300. (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (d) Ugi, I.; Werner, B.; Domling, A. *Molecules* **2003**, *8*, 53. (e) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *44*, 1602.

(5) Asymmetric Isocyanide-based MCRs:Banfi, L.; Basso, A. ; Guanti, G. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 1−32.

(6) Ugi, I.; Kaufhold, G. *Liebigs Ann. Chem.* **1967**, *709*, 11.

(7) Marquarding, D.; Hoffman, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969.

(8) Kunz, H.; Sager, W. *Angew. Chem., Int. Ed.* **1987**, *26*, 557.

(9) Ross, F. G.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, *58*, 6127.

(10) Faggi, C.; Mercaccini, S.; Pepino, R.; Pozo, C. M. *Synthesis* **2002**, 2756.

(11) (a) Zhdanko, A. G.; Nenajdenko, V. G. *Eur. J. Org. Chem.* **2009**, *74*, 884. (b) Banfi, L.; Basso, A.; Riva,R. In *Isocyanide Chemistry*; Nenajdenko, V., Eds.; Wiley-VCH: Weinheim, 2012; pp 1−33. (c) Carney, D. W.; Truong, J. V.; Sello, J. K. *J. Org. Chem.* **2011**, *76*, 10279.

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and chiral isocyanides do not have a great influence on the stereoselectivity of the reaction.[11] Furthermore, a negligible stereoselectivity was observed when chiral carboxylic acids were used.[12] Additionally, using 1,8-naphthalaldehydic acid, 2-formylphenoxyacetic acid, and 2-formylphenoxy-2-benzoic acid as bifunctional reagents in Ugi condensations, a series of rare six-, seven-, and eight-membered heterocyclic rings was obtained.[13] In all cases, the compounds were isolated in low yield and racemic form and with poor diastereoselectivity. The steric biases imposed by a cyclic transition state can, however, facilitate the achievement of good diastereoselectivity in intramolecular Ugi reactions.[14] As such, a diastereomeric ratio of 9:1 was observed by a 1,4 long-range asymmetric induction for the formation of 2,5-substituted tetrahydrobenzoxazepines.[14c]

Seven-membered N-heterocycles, including pyrrolo- and indoloazepinones, are very interesting in medicinal chemistry, where they represent an important class of "privileged scaffolds".[15] Previously, we have suggested that the 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one **1a** (Aba), 4-aminoindoloazepinone **1b** (Aia), and 4-aminotriazolodiazepinone **1c** (Ata)[16] (Figure 1) might also serve as privileged templates since these scaffolds were used to obtain a variety of peptide and peptidomimetic ligands for several G protein-coupled receptors. Examples include opioid GPCRs,[17] neurokinin 1,[18] and somatostatin receptors.[19] 1-Substituted analogues such as **2** (Figure 1), having three points of diversification, are therefore interesting in medicinal chemistry.

Only the 1-phenyl-substituted analogues of **1a** have been reported.[20] As a continuation of our studies on isocyanide-based multicomponent reactions,[21] we proposed that the 1-carboxamido-substituted Aia scaffold **2** (R_3 = CO-NHR$_3$) could be synthesized via the intramolecular Ugi

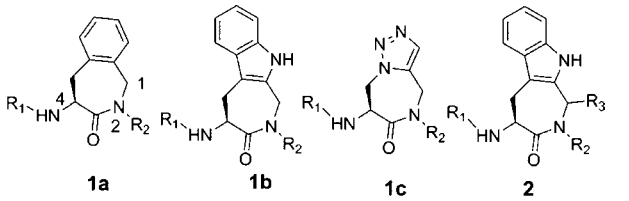


Figure 1. Conformationally constrained amino acid scaffolds Aba **1a**, Aia **1b/2**, and Ata **1c**.

reaction using an *N*-protected 2-formyltryptophan reagent **3** that was previously developed by us[22] (see the Supporting Information for more details). The preparation of racemic 5- or 7-carboxamidoindolobenzazepinones was reported by application of an intramolecular Ugi-3CR.[23]

In this paper, we report the development of a new stereoselective Ugi-3CR that allows the synthesis of novel, optically pure 1-carbamoyl-Aia heterocycles by condensation of 2-formyl-L-Trp **3** with different amines and isocyanides. In order to find the best reaction conditions for the synthesis of the prototype Aia derivatives, Boc-2-formyl-L-tryptophan **3**, 4-methoxy-benzylamine **5d**, and *tert*-butyl isocyanide **4c** were chosen as model substrates to optimize the reaction conditions (Table 1).

Because we recently investigated microwave-assisted, solvent- and catalyst-free conversions,[24] the development of such conditions was of particular interest.

In a first step, we optimized the microwave irradiation parameters. Initially, under solvent-free microwave conditions,[24b] the reaction did not proceed when the mixture was heated at 100 °C for 3 min (entry 1, Table 1). In addition, performing the reaction in MeOH (0.1 M) under microwave conditions and increasing the temperature to 80 °C for 2 h did not lead to the desired Ugi product (entries 2 and 3, Table 1). To our delight, the desired product was, however, observed upon further increase of the temperature (entries 4−9, Table 1). Successive temperature increase from 80 to 175 °C and applying a reaction time of 1 h 30 to 2 h afforded total conversion to **6f** (75% yield, 44/56 dr, entry 8, Table 1). Two diastereomers were observed by HPLC and ^{1}H NMR, and these could be separated by silica gel column chromatography (see the Supporting Information). No reaction occurred at room temperature in methanol with reaction times of up to 48 h (entry 10, Table 1). Because of a lack in stereoselectivity, we turned our attention to exploring lower temperatures and prolonged reaction

(12) (a) Yamada, T.; Motoyama, N.; Taniguchi, T.; Kazuta, Y.; Miyazawa, T.; Matsumoto, K.; Sugiura, M. *Chem. Lett.* **1987**, 723. (b) Golebioski, A.; Klopfenstein, S. R.; Shao, X.; Chen, J. J.; Colson, A. O.; Grieb, A. L.; Russel, A. F. *Org. Lett.* **2000**, *2*, 2615.

(13) (a) Ley, S. V.; Taylor, S. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1813. (b) Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591.

(14) (a) Basso, A.; Banfi, L.; Riva, R. *Eur. J. Org. Chem.* **2010**, 1831. (b) van Berkel, S. S.; Bögels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, 3543. (c) Banfi, L.; Bagno, A.; Basso, A.; De Stanis, C.; Riva, R.; Rastrelli, F. *Eur. J. Org. Chem.* **2013**, 5064.

(15) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *3*, 2235.

(16) Buysse, K.; Farad, J.; Nikolaou, A.; Vanderheyden, P.; Vauquelin, G.; Sejer Pedersen, D.; Tourwé, D.; Ballet, S. *Org. Lett.* **2011**, *13*, 6468.

(17) Novoa, A.; Van Drope, S.; Wynendaele, E.; Spetea, M.; Bracke, N.; Stalmans, S.; Betti, C.; Chung, N. N.; Lemieux, C.; Zuegg, J.; Cooper, M. A.; Tourwé, D.; De Spiegeleer, B.; Schiller, P. W.; Ballet, S. *J. Med. Chem.* **2012**, *55*, 9549.

(18) Ballet, S.; Feytens, D.; Buysse.; Chang, N. C.; Lemieux, C.; Tumati, S.; Keresztes, A.; Van Duppen, J.; Lai, J.; Varga, E.; Porreca, F.; Schiller, P. W.; Vanden Broeck, J.; Tourwé, D. *J. Med. Chem.* **2011**, *54*, 2467.

(19) Feytens, D.; De Vlaeminck, M.; Cescato, R.; Tourwé, D.; Reubi, J. C. *J. Med. Chem.* **2009**, *52*, 95.

(20) Ballet, S.; Urbanczyk-Lipkowska, Z.; Tourwé, D. *Synlett* **2005**, *18*, 2791.

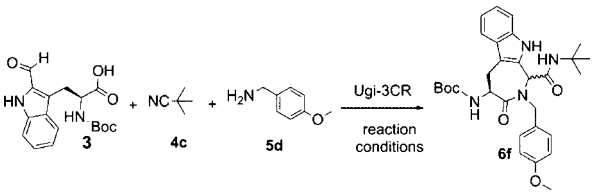
(21) Malaquin, S.; Jida, M.; Gesquiere, J.-C.; Deprez-Poulain, R.; Deprez, B.; Laconde, G. *Tetrahedron Lett.* **2010**, *51*, 2983.

(22) Pulka, K.; Feytens, D.; Van den Eynde, I.; De Wachter, R.; Kosson, P.; Misicka, A.; Lipkowski, A.; Chung, N. N.; Schiller, P. W.; Tourwé, D. *Tetrahedron* **2007**, *63*, 1459.

(23) Beaumont, S.; Retailleau, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2008**, 5162.

(24) For selected examples, see: (a) Jida, M.; Deprez-Poulain, R.; Malaquin, S.; Roussel, P.; Agboussou-Niedercorn, F.; Deprez, B.; Laconde, G. *Green Chem.* **2010**, *12*, 961. (b) Jida, M.; Malaquin, S.; Deprez-Poulain, R.; Laconde, G.; Deprez, B. *Tetrahedron Lett.* **2010**, *51*, 5109. (c) Jida, M.; Soueidan, O. M.; Deprez, B.; Laconde, G.; Deprez-Poulain, R. *Green Chem.* **2012**, *14*, 909.

Table 1. Optimization of Ugi-3CR Reaction Conditions[a]



entry	temp (°C)	time (h)	conv[b] (%)	dr[b]
1[c]	100	3 min	0	
2[d]	50	8	0	
3[d]	80	2	traces	
4[d]	100	2	40	80:20
5[d]	120	2	78	78:22
6[d,e]	150	2	100	42:58
7[d]	150	1.5	90	44:56
8[d,f]	175	1.5	100	44:56
9[d]	175	1	84	50:50
10[g]	25	48	0	
11[h]	40	48	traces	
12[h]	60	48	46	>99:1
13[h]	70	12	48	>99:1
14[h]	70	16	53	>99:1
15[h]	70	18	61	>99:1
16[h]	70	40	93	>99:1
17[h]	70	42	95	>99:1
18[h,i]	**70**	**48**	**100**	**>99:1**
19[d]	70	48	100	>99:1

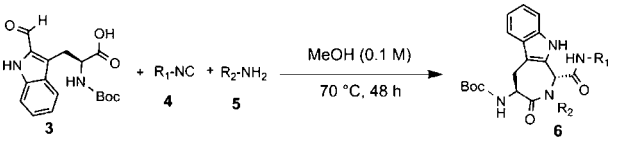
[a] Reaction conditions: **3**, **4**, and **5** (0.3 mmol), MeOH (3 mL). [b] Determined by HPLC of the crude reaction mixture. [c] The reaction was performed under solvent-free microwave irradiation. [d] The reaction was performed in MeOH (0.1 M) under microwave irradiation. [e] Isolated in 75% yield, and diastereomers **6f** and **6f'** were separated by silica gel column chromatography. [f] The substrate partially decomposed, and secondary products appeared. [g] The reaction was carried out at room temperature in methanol for 48 h. [h] The reaction was performed in a sealed vial in an oil bath. [i] Isolated in 92% yield as a single *trans* diastereomer.

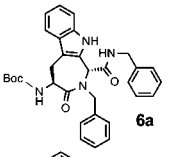
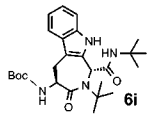
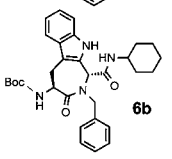
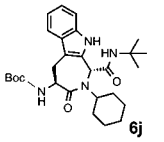
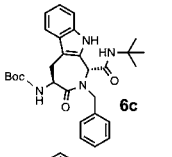
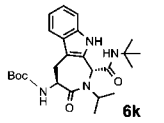
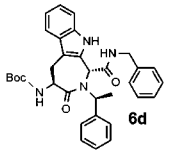
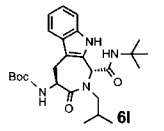
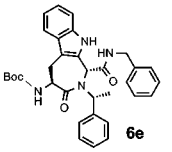
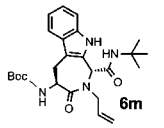
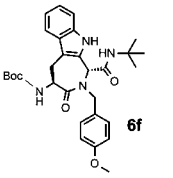
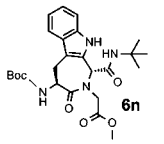
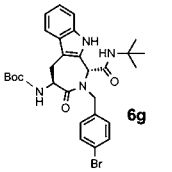
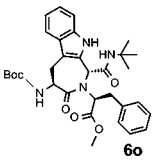
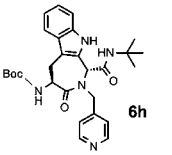
times. For this purpose, the optimization of the Ugi reaction was performed in sealed vials which were placed in an oil bath (entries 11−18, Table 1). Gratifyingly, when using conventional heating, only one diastereomer was obtained in all cases. In order to determine the origin of the stereoselectivity, we compared the optimal reaction conditions obtained for conventional heating (entry 18, 70 °C for 48 h) to the equivalent conditions under microwave irradiation (entry 19, Table 1). As expected, the microwave conditions also give way to one diastereomer, concluding that the stereoselectivity is dependent on temperature.

Next, the optimal conditions (entry 18, Table 1) were chosen to explore the substituent scope of this protocol. At this temperature and reaction time, full conversion and high diastereomeric excesses were obtained. Detailed results for a wide array of enantiopure Aia scaffolds are summarized in Table 2.

With enantiopure *N*-Boc-2-formyl-Trp-OH **3** as a chiral formylcarboxylic acid in hand, we initiated a study to explore the scope of this new stereoselective Ugi-3CR. In

Table 2. Substrate Scope[a]



entry	ugi product (Aia)	yield (%)[b] de (%)[c]	entry	ugi product (Aia)	yield (%)[b] de (%)[c]
1	 **6a**	82 (> 98)	9[e]	 **6i**	66 (> 98)
2	 **6b**	81 (> 98)	10	 **6j**	85 (> 98)
3	 **6c**	78 (> 98)	11	 **6k**	80 (> 98)
4	 **6d**	90 (> 98)	12	 **6l**	89 (> 98)
5	 **6e**	84 (> 98)	13	 **6m**	86 (> 98)
6	 **6f**	92 (> 98)	14[d]	 **6n**	72 (> 98)
7[d]	 **6g**	94 (> 98)	15[d]	 **6o**	91 (> 98)
8	 **6h**	94 (> 98)			

[a] Reaction conditions: **3**, **4**, and **5** (0.3 mmol), MeOH (3 mL), 48 h, 70 °C. [b] Isolated yields after silica gel column chromatography. [c] Diastereomeric excess determined by ^{1}H and ^{13}C NMR spectra or HPLC. [d] 1 equiv of Et_3N was added. [e] The reaction was stopped after 1 week.

all cases, excellent diastereoselectivity and high yields were observed for various amines and isocyanides. The reaction of three different isocyanides with benzylamine was examined (entries 1−3, Table 2), and the desired

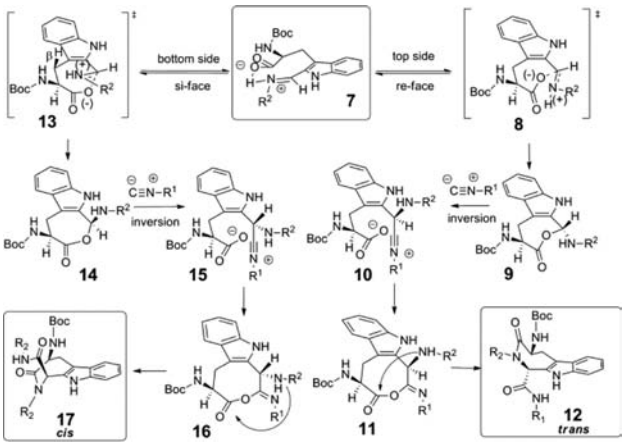
products **6a**−**c** were isolated with high yields and excellent de (%). To check that no racemization takes place during the cyclization step, a reaction with (*S*)-1-methylbenzylamine and (*R*)-1-methylbenzylamine was realized. Only single diastereomeric Aia's (**6d**,**e**) were observed by ^{1}H NMR and HPLC (entries 4 and 5, Table 2). The electron-donating or electron-withdrawing properties of the substituent of the amine component were well tolerated and have no influence on the yield and diastereomeric excess of the reaction, and the compounds (**6f**,**g**) were isolated in an enantiopure form (entries 6 and 7, Table 2). Also, a heteroaromatic amine could be used to give compound **6h** (entry 8, Table 2). A moderate yield of Ugi product **6i** was observed upon use of *tert*-butylamine (entry 9, Table 2). This result could be attributed to its weak reactivity (and hence long reaction times) and lower thermal stability leading to possible byproducts.

In contrast, a cyclic, an aliphatic α-branched and α-unbranched amine gave the expected compounds (**6j**,**k**) in excellent yields and diastereomeric excess (entries 10−13, Table 2). Finally, amino esters such as glycine and phenylalanine methyl ester could also be used and reacted smoothly with Boc-2-formyl-L-Trp **3** to give the desired dipeptidomimetics **6n** and **6o** in high yield and diastereomeric ratio (entries 8−10). It is noteworthy that the reported procedure is an attractive methodology for the single step synthesis of conformationally constrained Aia-Xxx dipeptides (with Xxx: a variable α-amino acid residue) in its enantiopure form. The configuration of the Ugi-Aia products was confirmed by NOESY studies of **6f** and X-ray crystallographic analysis of **6c** (see the Supporting Information).

Mechanistically, the reaction proceeds via the formation of an imine, formed *in situ* from formyltryptophan **3** and an amine (Scheme 1). A pseudocyclic intermediate **7** is proposed by intramolecular protonation of the imine by the carboxylic acid, in which the bulky *N*-Boc substituent adopts a pseudoequatorial conformation and which fixes the orientation of the imine. The isocyanide can add immediately to the iminium ion or the iminium ion is first attacked by the carboxylate, especially in polar media, followed by a substitution by the isocyanide with inversion of configuration.[25]

Since the second mechanism involves an intramolecular addition in the present case, this may be the preferred pathway. Addition of the carboxylate can occur from the top side (reface) through a boatlike transition state **8** in which the NH-R^2 substituent is placed in a pseudoequatorial position, thus avoiding unfavorable allylic strain with the indole N−H. Substitution by the isocyanide with inversion of configuration then leads to intermediate **10**, which rearranges to **11**, followed by acyl transfer to the *trans*-diastereoisomer **12**. Alternatively, addition of the carboxylate from the bottom side (*si*-face) of the iminium ion occurs through another boatlike transition state **13**, in which the pseudoaxial NH-R^2 substituent has unfavorable transannular interactions with one of protons at C$^\beta$ of the Trp structure. The formation of intermediate **14**, ultimately leading to the *cis*-isomer **17**, is therefore proposed to be disfavored compared to **9**.

Scheme 1. Suggested Rationale for Induction of Diastereoselectivity



In conclusion, we have described an efficient and useful stereoselective Ugi-3CR reaction for the synthesis of optically pure amino indoloazepinone (Aia) derivatives starting from *N*-Boc-2-formyl-L-tryptophan **3** as a chiral formylcarboxylic acid. The desired seven-membered products are formed in excellent yields and diastereomeric excess under catalyst-free conditions and simple experimental procedures. Dipeptide building blocks of type **6n** and **6o** can be applied to different bioactive peptide chains by incorporation of enantiopure and trisubstituted Aia scaffolds into peptide sequences but also used to prepare new combinatorial libraries with a wide structural diversity. The complexity of and substitution patterns in these compounds will allow their use in various biological applications.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(25) (a) Banfi, L.; Basso, A.; Chiappe, C.; De Moliner, F.; Riva, R.; Sonaglia, L. *Org. Biomol. Chem.* **2012**, *10*, 3819. (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587.