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Ruthenium catalyzed synthesis of 5-amino-1,2,3-triazole-4-carboxylates for triazole-based scaffolds: beyond the Dimroth rearrangement

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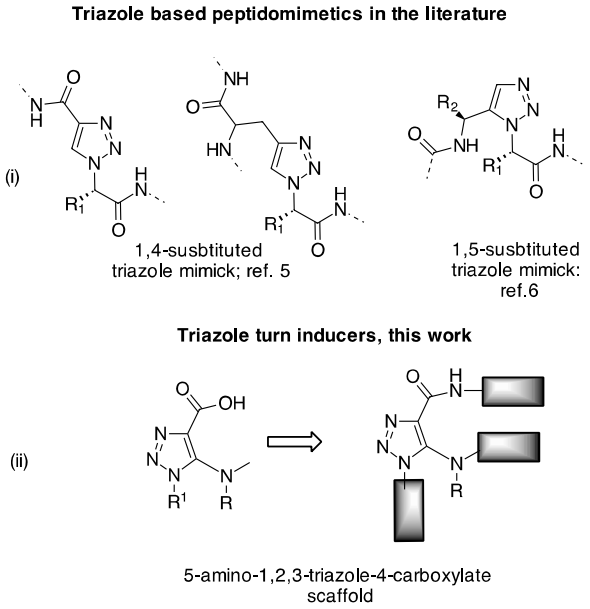
ABSTRACT. The 5-amino-1,2,3-triazole-4-carboxylic acid is a suitable molecule for the preparation of collections of peptidomimetics or biologically active compounds based on the triazole scaffold. However, its chemistry may be influenced by the possibility to undergo the Dimroth rearrangement. To overcome this problem, a protocol based on the ruthenium catalyzed cycloaddition of N-Boc-ynamides with azides has been developed to give a protected version of this triazole amino acid. When aryl or alkyl azides are reacted with N-Boc-aminopropiolates or arylynamides, the cycloaddition occurs with a complete regiocontrol, while N-Boc-alkyl-ynamides yield a mixture of regioisomers. The prepared amino acids were employed for the preparation of triazole containing dipeptides having the structural motives typical of turn inducers. In addition, triazoles active as HSP90 inhibitors (as compound **41**, IC_{50} = 29 nM) were synthesized.

Introduction

The development of compounds that mimic peptide secondary structure is one of the most useful approaches for the design and synthesis of new chemical entities interacting with biological targets.[1] Over the years, a big effort has been devoted to the synthesis of constrained peptidomimetics in order to better understand the bioactive conformations or to improve bioavailability or generic metabolic stability.[2] The incorporation into a peptide chain of (hetero)cyclic scaffolds able to restrict conformational freedom has been shown to be a valuable tool to enhance some molecular properties such as stability to proteases, potency and receptor selectivity.[3] Of particular interest is the use of aromatic and heteroaromatic structures as dipeptide isosters that have found interesting applications in the preparation of active peptidomimetics.[2a] In the wake of the recent increase of interest for triazoles, several examples of triazole based amino acids or peptide scaffolds have been described.[4] 1,2,3-Triazoles have demonstrated to be effective turn inducers for conformationally constrained peptide analogues. In the first papers, the triazole scaffold was produced by Cu catalyzed cycloaddition between α-azido acids (derived from α-amino acids) and N- or C-propargyl derivatives.[5] Afterwards, the Ru catalyzed synthesis of a 1,5-disubstituted 1,2,3-triazole as a proline mimicker has been described.[6] However most of the examples reports 1,4 or 1,5 disubstituted triazoles carrying the carboxyl and the amino groups on the carbon chain relatively far from the triazole itself (Scheme 1, (i)).

SCHEME 1.



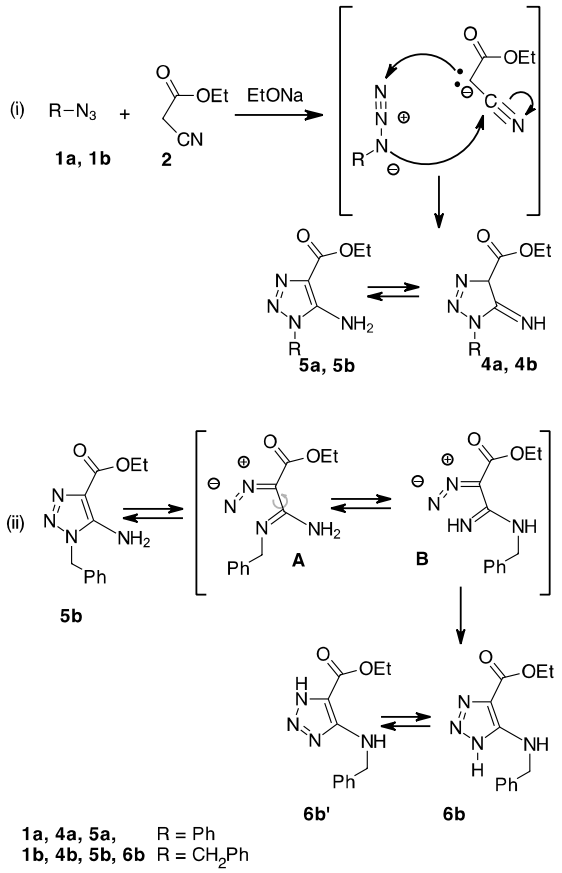
A potentially useful alternative is the 5-amino-(1H)-1,2,3-triazole-4-carboxylate scaffold (Scheme 1, (ii)), a triazole amino acid with three different points for substituent attachment. While the amino and the carboxylic groups can be used to insert the scaffold into a peptide chain using standard peptide couplings, the substituent in position 1 may be used as a group that mimics the side chain of the dipeptide involved in the turn. Alternatively, with another functional group placed on the chain bonded in position 1, the scaffold can be modeled according to the turn required and/or the reagents employed. Nevertheless, although known since the beginning of the 20th century,[7] the 5-amino-1,2,3-triazole 4 carboxylates have found relatively few applications.[8]

Results and Discussion

Intrigued by the possibility to use structures as **5a** or **5b** (Scheme 2) for the preparation of triazole based peptide scaffolds, we decided to investigate the synthesis and the reactivity of

these amino-triazoles towards standard peptide chemistry. Compound **5a** and **5b** were prepared following the approach described in the literature[9] reacting phenyl and benzyl azide (**1a** and **1b** respectively) with ethyl cyanomalonate **2** in the presence of EtONa (Scheme 2, (i)). The malonate anion attacks the terminal nitrogen of the azide and the more nucleophilic part of the azide reacts with the nitrile to give an imino triazole intermediate (**4a** or **4b**) that immediately tautomerizes to the aromatic ethyl-5-amino-1,2,3-triazole-4-carboxylate (**5a** or **5b**).

SCHEME 2.



While aryl azide **1a**, after 6 h in refluxing ethanol, produced exclusively compound **5a** (65% isolated yield), the benzyl azide **2b** gave a 2:1 mixture of the expected 5-amino-1-benzyl triazole **5b** together with the 5-benzylamino derivative **6b** (Scheme 2, (ii)). This compound was produced

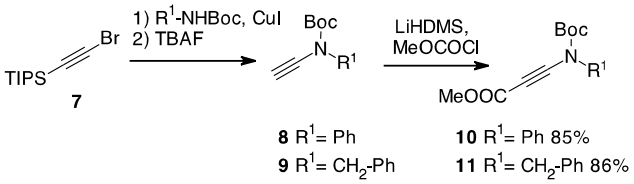
by the Dimroth rearrangement,[10] that proceeds through the ring opening at the bond between N1-N2 with formation of a diazo intermediate (**A**, Scheme 2, (ii)) where rotation is now possible. A further cyclisation may occur on the less substituted nitrogen with formation of a new 1-NH-triazole **6b** (and its tautomer **6b'**). The Dimroth rearrangement is known to be accelerated by the presence of electron withdrawing substituents in position 4 of the triazole and by strong acid or basic media. After purification, the two 5-amino triazoles **5a** and **5b** were submitted to standard peptide bond formation with N-CbzAlaOH in the presence of different coupling agents (e.g. DCC, EDC, HATU, DMTMM). Unfortunately, acylation occurred with low yields and the rearranged compound always contaminated the products.

Since this approach seemed not suitable for an easily functionalization of the 5-amino-1,2,3-triazole-4 carboxylate (as, for example, its introduction in a peptide chain) we decided to explore the possibility to carry out a [3+2] cycloaddition between an alky or aryl azide and a N-protected ynamide in order to control the introduction of nitrogen in position 5. This reaction has been described using terminal ynamides carrying a tosyl or an oxazolidinone group on the ynamide nitrogen. The reaction was carried out thermally[11] or under Cu[12] or Ru catalysis,[13] giving simple 4 amido or 5 amido 1,2,3 triazoles, structures on which removal of the substituent on the nitrogen was not easy.

With the idea to exploit the Ru catalyzed Huisgen cycloaddition for the synthesis of a stable and synthetically versatile analogue of 5-amino-1,2,3-triazole-4-carboxylate, we decided to investigate the cycloaddition of alkyl or aryl azides with methyl-N-Boc-aminopropiolates **10** and **11** (Scheme 3). These are new highly functionalized ynamides equipped with a protected amino group and a carboxylate ester, both moieties suitable for easy tag introduction after the cycloaddition has taken place. Compounds **10** and **11** were prepared by Ullmann type

condensation of N-Boc-aniline or N-Boc-benzylamine respectively with triisopropylsilyl-bromoacetylene[14] in the presence of catalytic amount of the complex phenanthroline/CuI. The silyl protection was then removed and compounds **8** and **9** were acylated through lithiation with LHMDS followed by reaction with methylchloroformate to give **10** and **11** in 85-86% overall yield (Scheme 3).

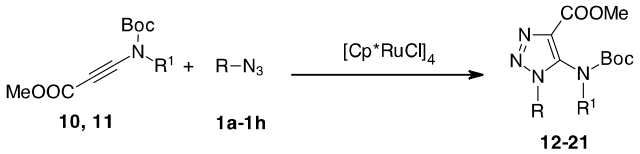
SCHEME 3. Preparation of N-Boc-ynamides

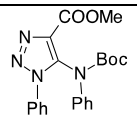
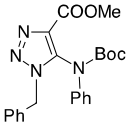
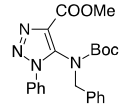
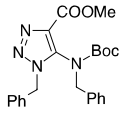
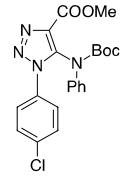
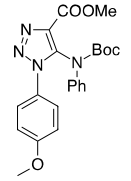
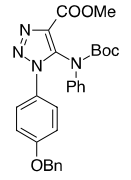
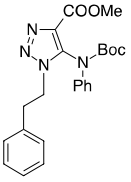
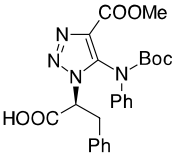


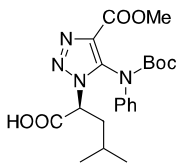
When **10** was submitted to cycloaddition with azide **1a** in DMF at rt for 2 h in the presence of $[Cp^*RuCl]_4$ as the catalyst the corresponding N-Boc-5-aminotriazole **12** was isolated in good yield. The cycloaddition produced a single diastereomer as revealed by ^1H and ^{13}C NMR analysis. Analogously, cycloaddition of ynamide **10** with azide **1b** gave triazole **13** in good yield. Following the same synthetic scheme, different azides (**1c-1h**, see Table 1) were cyclized to give the corresponding N-Boc-5-amino-1,2,3-triazole-4-carboxylates **16-21** in good yields. Also ynamide **11,** in the cycloaddition with azides **1a-1b,** gave triazoles **14** and **15**, respectively. (Table 1) .

The reaction worked well with aromatic and aliphatic azides and even with α-azido amino acids giving the triazole amino acids **20** and **21** (entries 9 and 10 in Table 1) always in good yield and with complete regiocontrol. The regiochemistry presenting the carboxylate in position 4 and the nitrogen in position 5 was postulated on the basis of the orientation proposed in analogous reactions with aryl substituted ynamides[11] or phenylpropiolate (see below).[15]

TABLE 1. Ruthenium cycloaddition between methyl-N-Boc-aminopropiolates 10 and 11 and azides.



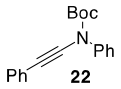
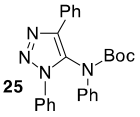
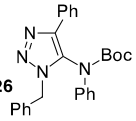
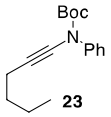
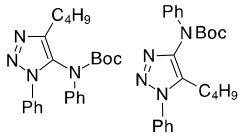
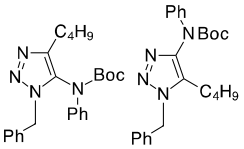
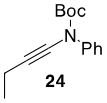
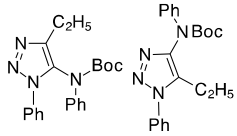
Entry	Azide	Ynamide	Product		Yield[a] (%)
1	PhN_3 **1a**	**10**		**12**	86
2	$PhCH_2N_3$ **1b**	**10**		**13**	88
3	PhN_3 **1a**	**11**		**14**	81
4	$PhCH_2N_3$ **1b**	**11**		**15**	90
5	*p*-$ClC_6H_4N_3$ **1c**	**10**		**16**	81
6	*p*-$MeOC_6H_4N_3$ **1d**	**10**		**17**	79
7	p-$OBnC_6H_4N_3$ **1e**	**10**		**18**	83
8	$PhCH_2CH_2N_3$ **1f**	**10**		**19**	88
9	(*S*)-$PhCH_2CH(COOH)N_3$ **1g**	**10**		**20**	86

10	*(S)*-$Me_2CHCH_2CH(COOH)N_3$ **1h**	**10**		**21**	83

[a] Yield of isolated products.

As the regiochemical control in the cycloaddition was complete and due to the potential applications of the reaction for the synthesis of diverse 5-amino-1,2,3-triazoles, the influence on the regiochemistry of the ynamide C-substituent was investigated (Table 2).

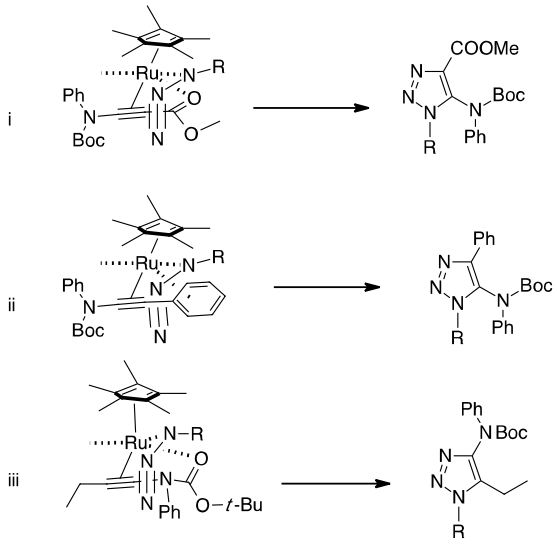
TABLE 2. Ru mediated cycloaddition of different ynamides.

entry	Azide	Ynamide[a)]	Product	Yield[b)] (%)
1	**1a**	 **22**	 **25**	72
2	**1b**	**22**	 **26**	82
3	**1a**	 **23**	 **27a** : **27b** 4 : 1	76[c)]
4	**1b**	**23**	 **28a** : **28b** 4 : 1	79[c)]
5	**1a**	 **24**	 **29a** : **29b** 3 : 1	73[c)]

[a)] Prepared as described for compound **10**. [b)] Yield of isolated compound. [c)] Yield relative to the regioisomer mixture.

To our surprise, while the regiocontrol was complete also with the phenylethyny derivative **22** (entries 1 and 2 in Table 2), in the presence of an alkyl chain (not too large, as for ynamides **23** and **24**) a mixture of regioisomers was obtained, even though the 5 amino-substituted triazole prevailed (entries 3-5 in Table 2). This last quite unexpected result[16] suggests that probably the high regiocontrol observed with ynamides **10**, **11** and **22** may be explained by a possible additional interaction between the Ru atom and the full non-bonding orbitals of the carboxymethyl group (for **10** and **11**) or the π aromatic orbitals of the phenyl in compound **22** (Scheme 4).[11] In absence of these effects, the interaction of Ru with the N-Boc-aminoaryl substituent drives the orientation towards the opposite regioisomers (as **27b-29b** in Table 2).

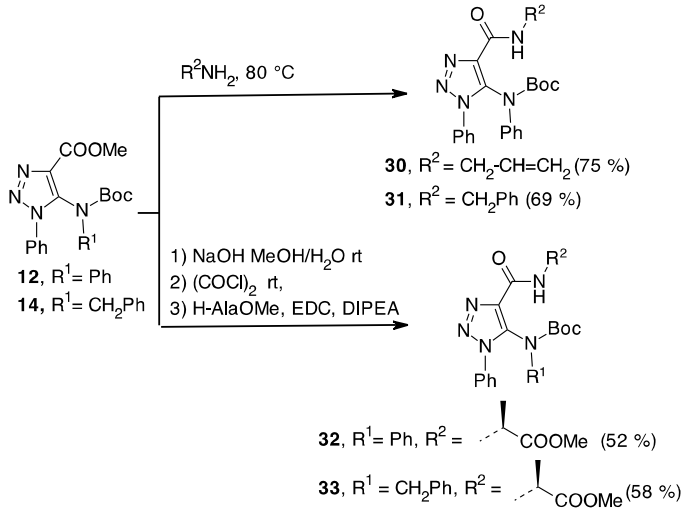
SCHEME 4. Proposed intermediates for the different regiochemical outcome: i and ii justify the selectivity toward the 5-amino substituted triazole, iii justifies the formation of the 4-amino substituted triazole in the reaction with alkyl N-Boc-ynamides.



To explore the synthetic potential and the scope of the reaction, a general functionalization around the triazole ring was explored. The carboxymethyl group in position 4 of triazole **12** was directly transformed into amide by displacement with a primary amine such as allylamine or

benzylamine giving compounds **30** and **31** in 75 and 69% yield respectively. Alternatively, the hydrolysis of the ester in position 4 of **12** or **14** produced the carboxylic acids that were further transformed into the corresponding acyl chlorides (Scheme 5).

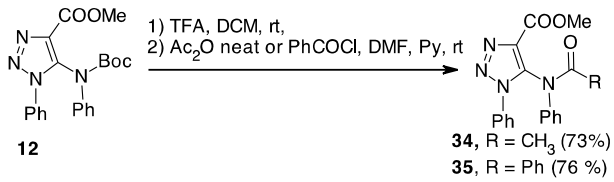
SCHEME 5. Functionalization at position 4.



The further coupling with (*S*)-alanine methyl ester mediated by DIPEA and DMAP in DMF gave triazole dipeptides **32** and **33** respectively in 52 and 58% isolated yield.[17]

The functionalization in position 5 of triazole passed through the removal of Boc that was accomplished with TFA (Scheme 6).

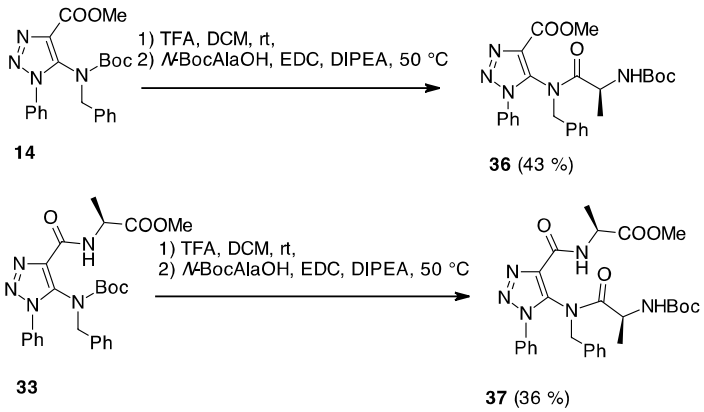
SCHEME 6. Functionalization at position 5



Unfortunately, the aniline-type NH in position 4 of the product derived from **12**, was a poor nucleophile as it reacted exclusively with acetic anhydride or benzoyl chloride to yield compounds **34** and **35** in acceptable yields.

The reaction between the deprotected 5-amino triazoles and different carboxylic acids using the most common peptide-coupling agents (DCC, EDC HATU, PyBOP) was also attempted. Starting from the N-benzyl derivative **14**, and subsequent TFA mediated Boc removal, EDC coupling with N-Boc protected alanine methyl ester gave product **36** in moderate yield (Scheme 7).

SCHEME 7. Preparation of triazole based peptides

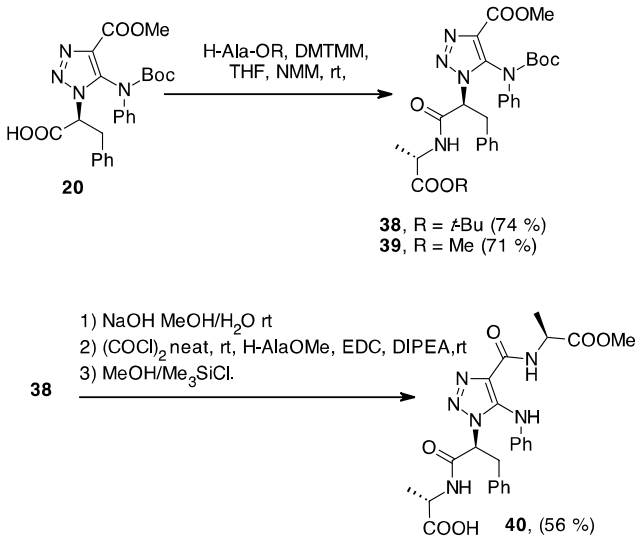


Analogously, starting from compound **33**, removal of the Boc and further EDC mediated coupling with (*S*)- alanine methyl ester gave the triazole containing dipeptide **37** in 36% yield (Scheme 7).

The enantiomeric integrity of products **20, 21 32 33** and **36** was determined by HPLC analysis on a chiral column in comparison with the chromatograms recorded with the coupling products obtained from the racemic amino acids.

Finally, the carboxylic group of the α-azido acids inserted in position 1 of the triazole (compound **20**) was reacted with (L)-alanine *tert*-butyl or methyl esters in the presence of DMTMM[18] as the coupling agent to generate the triazole containing peptides **38** and **39** (Scheme 8).

SCHEME 8. Preparation of triazole based dipeptide.



Elongation of the peptide could be possible by methyl ester hydrolysis of **38** followed by EDC mediated coupling with (*S*)-alanine methyl ester. Final treatment with HCl in MeOH removed the Boc and the *t*-butyl protections to yield the triazole containing (inverted) peptide **40**. In all the cases described above, formation of products derived from the Dimroth rearrangement was never observed. This is a remarkable result especially regarding products having an alkyl group in position 1 that, coupled with an electron-withdrawing group in position 4, is known to promote this rearrangement.[19] Compound **39** crystallized on standing in H_2O to give crystals that were submitted to X-ray analysis, confirming the stereochemistry outcome of the cycloaddition (SI).

To investigate the suitability of aminotriazole scaffold to mimic peptides, with particular reference to reverse turns, comparison of derivative **39** with this structural element was made in detail. Our molecular prototype was subjected to thorough computational analysis of its conformational properties by Molecular Mechanics (MM), Quantum Mechanics (QM) and Molecular Dynamics (MD). The conformational analysis showed that **39** has some populated conformers satisfying reverse turn requirements. In particular, two geometries have a β value much smaller than ±90° and a d_α < 7 Å. Moreover, one of the two most stable conformers show the CO−HN H-bond typical of β turns. In addition, at trial and error-type approach to classify β-turn type was attempted, based on the atom-by-atom superposition of the two conformers onto a built-on-purpose template. This method suggested a type-I' β-turn reference frame for one conformer and a V' β-turn reference for the other. The superposition of both lowest energy conformers of **39** onto, respectively, a standard type-I' and standard type-V' β-turns, are shown in Figure 1 and 2, confirming, as outlined by the X-ray data, that compound **39** can be considered as a good candidate to mimic a reverse turn. A more detailed explanation of the molecular modeling study is reported in the SI.

FIGURE 1. Conformer of 39 colored by atom types (crossed stereoview), superimposed with standard type-I' β-turn (yellow structure with omitted hydrogen atoms).

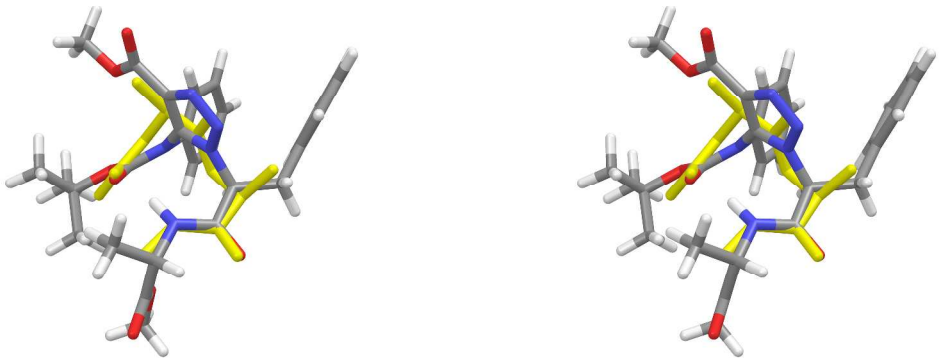
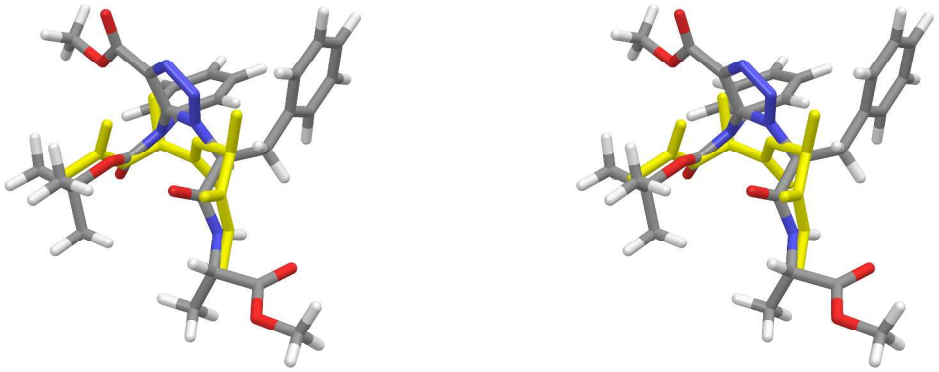


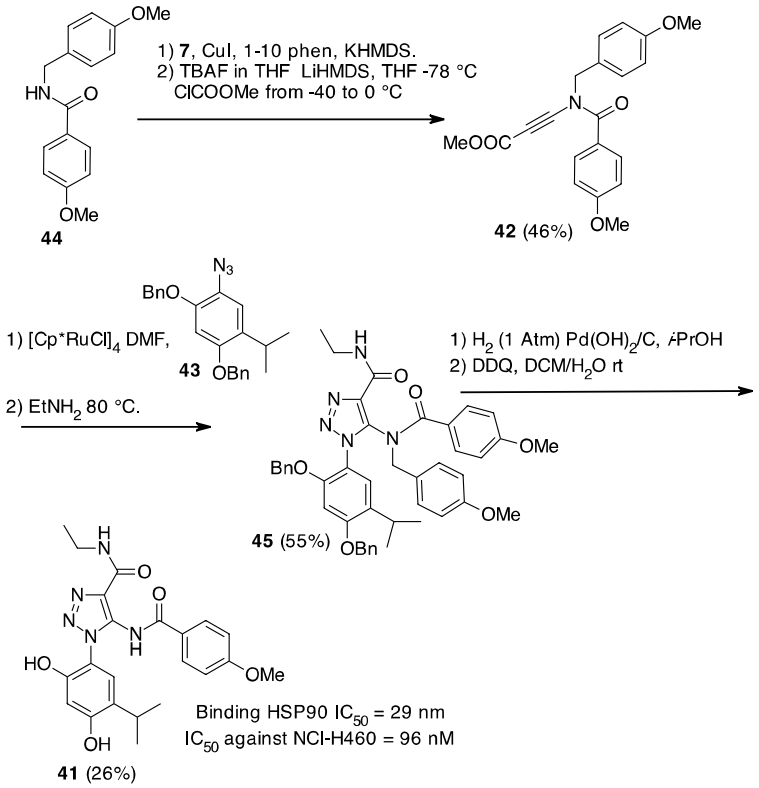
FIGURE 2. Conformer of 39 colored by atom types (crossed stereoview), superimposed with a standard type-V' β-turn (yellow structure with omitted hydrogen atoms).



The 5-amino, 1,2,3-triazole carboxylates can also find interesting applications as scaffold for the preparation of bioactive compound in medicinal chemistry. Based on a recent report that points out how substituted amido-isoxazole or -triazole carboxylates can be employed in HSP90 binding,[20] we prepared 5-amido- 4-carboxy triazole **41** through Ru mediated cycloaddition of the cumenediol azide **43**[20b] and the ynamido propiolate **42.**

This product was prepared by Ullmann type reaction of amide **44** with TIPS-bromoacetylene **7** followed by deprotection and carboxylation with LiHMDS and methyl chloroformate (Scheme 9). Ru mediated cycloaddition between **42** and **43** gave the triazole carboxylate that was transformed into amide by reaction with ethylamine and further deprotected first using H_2 on $Pd(OH)_2/C$ to remove the benzyl groups and then with DDQ in DCM/H_2O to remove the *p*-methoxybenzoyl protecting group, to give amidotriazole **41** in 26% yield. Compound **41** was submitted to a binding text with HSP90 determined by a fluorescence polarization assay (FP Assay) to give an IC_{50} of 29±4 nM (mean value with n = 4). Cytotoxicity on NCI-H460 non-small cell lung carcinoma cells confirmed promising IC_{50} value of 96±2 nM (n =4).

SCHEME 9. Preparation of a triazole based HSP90 inhibitor



Conclusion

In conclusion, we have developed a regiocontrolled synthesis of 5-amino trisubstitued triazoles via Ru mediated cycloaddition of ynamides and azides. The regiocontrol of the reaction was possible only if a group able to interact with the Ru-catalyst were present on the other side of the triple bond with respect to the ynamide moiety. This is an efficient example of the possibility to control the regiochemistry of the addition based on the substrate/catalyst structure. This procedure avoids the event of the Dimroth rearrangement that may give different (and sometimes unpredictable) substituted triazoles. The N-Boc 5-amino triazoles were transformed into the trifluoroacetates after deprotection and reacted as their free amine during the coupling. The reaction products can be used as stereodefined scaffolds for the preparation of triazole containing peptidomimetics or as generic scaffolds for the preparation of diverse trisubstituted amino triazoles. The procedure can be also applied to the preparation of triazoles containing a substituent arrangement suitable for producing antitumor compounds based on HSP90 inhibition.

Experimental Section

General methods. All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven dried or flamed vessels and performed under nitrogen. Solvents were dried and purified by conventional methods prior use. Flash column chromatography was performed with silica gel 60, 0.040-0.063 mm (230-400 mesh). Aluminium backed plates pre-coated with silica gel 60 (UV254) were used for thin layer chromatography and were visualized by staining with $KMnO_4$. NMR spectra were recorded under conditions that are specified for each spectrum (temperature 25 °C unless specified). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual

solvent peak, $CHCl_3$ (7.27 ppm, 1H; 77.16 ppm, the middle peak, 13C). High and low resolution mass spectroscopy analyses were recorded at 70 eV by electrospray ionization using a triple quadrupole mass spectrometer. Melting points were determined in open capillary tubes and are uncorrected. Specific rotations were measured with a 10 cm cell with a Na 589 nm filter: values are given in 10-1 deg.cm3.g-1.

Methyl N-Phenyl, N-Boc-3-aminopropiolate (10). Compound **8** (434 mg, 2 mmol, prepared as described in ref 14) was dissolved in dry THF (10 mL) under nitrogen; the solution was cooled down to -78 °C and LiHMDS (3.5 µl of a solution 1 M in THF, 3.5 mmol) was added. The mixture was slowly warmed up to -40 °C and maintained at this temperature for 1 h. The solution was transferred via cannula to a flask containing methyl chloroformate (620 mg µl, 6.5 mmol) in THF (6 mL) at -40 °C and the solution was warmed up to room temperature. Saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL) were added and the organic phase was extracted (3 x 15 mL EtOAc) and dried over Na_2SO_4. The title compound was obtained after purification by column chromatography (Pet. Et. 40-60/EtOAc from 80:20 to 75:25) (467 mg, 85%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.48-7.12 (m, 5H), 3.71 (s, 3H), 1.50 (s, 9H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 154.4, 151.5, 137.4, 128.7(2C), 127.2(2C), 124.5, 84.6, 82.5, 65.3, 51.86, 27.3(3). HRMS (ESI): *m/z* calcd for $C_{15}H_{17}NO_4Na^+$ 298.1055. Found 298.1050.

Methyl N-Phenyl, N-Boc-3-aminopropiolate (11). Column chromatography (Pet. Et. 40-60/EtOAc from 80:20 to 75:25) gave compound **11** (497 mg, 86%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.53-7.18 (m, 5H), 4.24 (s, 2H), 3.71 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 154.4, 151.5, 137.4, 128.8(2C), 127.3(2C), 124.5, 84.6, 82.6, 65.3, 60.8, 51.8, 27.3(3C). HRMS (ESI): *m/z* calcd for $C_{16}H_{19}NO_4Na^+$ 312.1212. Found 312.1206.

Methyl 1-phenyl-5-(*N*-phenyl-*tert*-butoxycarbonyl-amino)-1*H*-1,2,3-triazole-4-carboxylate 12, general procedure. To phenyl azide **1a** (120 mg, 1 mmol) dissolved in dry DMF (2.5 mL) at rt, compound **10** (275 mg, 1 mmol) was added. The flask was subjected to three vacuum-nitrogen cycles, then $(Cp^*RuCl)_4$ (49 mg, 0.045 mmol) was added followed other three vacuum-nitrogen cycles. The reaction was stirred at room temperature until completion (monitored by TLC, 2h). EtOAc (10 mL) and water (5 mL) were then added. The organic phase was extracted four times with EtOAc (5 mL each) washed with water (2 mL, three times) and brine (5 mL, one time) and dried over Na_2SO_4; the solvent was removed and the mixture was purified by column chromatography (Pet. Et. 40-60:EtOAc 60:40). The title compound was obtained as a purple oil with a tendency to solidify on standing (339 mg, 86%). An analytical sample was crystallized two times from $EtOH/H_2O$, m.p. 123-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-6.99 (m, 8H), 6.90 (dm, 2H), 3.87 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 138.9, 134.3, 132.9, 129.9(2C), 129.18(2C), 128.4(2C), 126.3(2C), 124.8(2C), 123.9, 122.5, 82.9, 51.7, 27.4(3C). ESI/MS $(M+Na)^+$ 417. Anal. calcd for $C_{21}H_{22}N_4O_4$ C, 63.95; H, 5.62; N, 14.20; O, 16.23. Found: C, 63.89; H, 5.65; N, 14.17.

Methyl 1-benzyl-5-(*N*-phenyl-*tert*-butoxycarbonyl-amino)-1*H*-1,2,3-triazole-4-carboxylate 13. Column chromatography (Pet. Et. 40-60:EtOAc 60:40) gave compound **13** (359 mg, 88%) as a waxy material. An analytical sample was crystallized from *i*-PrOH, m.p. 113-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-6.89 (m, 10H), 5.44 (bs, 1H), 4.88 (bs, 1H), 3.87 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.6, 159.9, 150.8, 138.7, 138.1, 133.9, 133.0, 128.7(2C),

128.4(2C), 127.2(2C), 126.1, 124.3(2C), 82.7, 51.7, 51.3, 27.2(3C). ESI/MS $(M+Na)^+$ 431. Anal. calcd for $C_{22}H_{24}N_4O_4$ C, 64.69; H, 5.92; N, 13.72; O, 15.67. Found C, 64.62; H. 5.94; N, 13.70.

Methyl 1-phenyl-5-(*N*-benzyl-*tert*-butoxycarbonyl-amino)-1*H*-1,2,3-triazole-4-carboxylate 14. Column chromatography (Pet. Et. 40-60:EtOAc 50:50) gave compound **14** (331 mg, 81%) as a dense oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-6.57 (m, 10H), 4.75 (d, J = 14.2 Hz, 1H), 4.48 (d, J = 14.3 Hz, 1H), 3.89 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 152.5, 134.3, 129.3(2C), 129.0(2C), 128.8(2C), 128.0(2C), 127.7 (2C), 124.4, 123.6(2C), 82.3, 52.4, 51.7, 27.5(3C). HRMS (ESI): *m/z* calcd for $C_{22}H_{24}N_4O_4Na^+$ 431.1695. Found 431.1690.

Methyl 1-benzyl-5-(*N*-benzyl-*tert*-butoxycarbonyl-amino)-1*H*-1,2,3-triazole-4-carboxylate 15 Column chromatography (Pet. Et. 40-60:EtOAc 65:45) gave compound **15** (380 mg, 90%) as a waxy material. An analytical sample was crystallized from EtOH/H_2O, m.p. 127-129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 6.83 (m, 10H), 4.99 (m 2H), 4.40 (m, 2H), 3.82 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 152.8, 139.4, 135.4, 133.1, 132.2, 129.1(2C), 128.4(2C), 128.3(2C), 128.0(3C), 127.6, 81.9, 52.8, 51.6, 50.4, 27.2(3C). ESI/MS $(M+Na)^+$ 445. Anal. calcd for $C_{23}H_{26}N_4O_4$ C, 65.39; H, 6.20; N, 13.26; O, 15.15. Found: C, 65.34; H, 6.22; N, 13.24.

Methyl 1-*p*-chlorophenyl-5-(*N*-phenyl-*tert*-butoxy-carbonylamino)-1*H*-1,2,3-triazole-4-carboxylate 16 Column chromatography (Pet. Et. 40-60:EtOAc 65:45) gave compound **16** (346 mg, 81 %) as a waxy material. An analytical sample was crystallized from EtOH/H_2O, m.p. 117-119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (m 2H), 7.45 (m, 4H), 7.33-7.10 (m, 2H), 7.03 - 6.96 (m, 1H), 3.31 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 151.9, 139.7, 138.7, 136.6(2C), 134.1, 133.4(2C), 131.4(2C), 129.2(2C), 126.7, 125.8, 125.4, 83.8, 50.8,

28.1(3C). ESI/MS $(M+Na)^+$. 451 Anal. calcd for $C_{21}H_{21}ClN_4O_4$ C, 58.81; H, 4.94; N, 13.06; O, 14.92; Cl, 8.27;. Found: C, 58.77; H, 4.97; N, 13.04.

Methyl 1-*p*-methoxyphenyl-5-(*N*-phenyl-*tert*-butoxy-carbonylamino)-1*H*-1,2,3-triazole-4-carboxylate 17. Column chromatography (Pet. Et. 40-60:EtOAc 65:45) gave compound **17** (334 mg, 79%) as a dense oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-6.67 (m, 9H), 3.80 (s 3H), 3.30 (s, 3H), 1.45-1.20 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 148.7, 139.7, 139.6, 133.8, 129.4(2C), 129.1(2C), 126.8(2C), 126.1, 125.4, 114.9(2C), 83.4, 55.9, 53.3, 28.2(3C). HRMS (ESI): *m/z* calcd for $C_{22}H_{24}N_4O_5Na^+$ 447.1645. Found 447.1643.

Methyl 1-*p*-benzyloxyphenyl-5-(*N*-phenyl-*tert*-butoxy-carbonylamino)-1*H*-1,2,3-triazole-4-carboxylate 18. Column chromatography (Pet. Et. 40-60:EtOAc 65:45) gave compound **18** (465 mg, 93%) as a red waxy material. An analytical sample was crystallized from $EtOH/H_2O$, m.p. 105-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45- 6.69 (m, 14H), 4.75 (d, J = 14.3 Hz, 1H), 4.48 (d, J = 14.3 Hz, 1H), 3.89 (s, 3H), 1.38 - 1.07 (m, 9H). ^{13}C NMR (101 MHz d-DMSO) δ 160.3, 151.7, 149.2, 134.7, 133.1, 129.3(4C), 129.1 (4C), 128.9 (3C), 128.7 (4C), 124.8 (2C), 83.9, 52.1, 50.5, 28.0(3C). ESI/MS (M+Na). Anal. calcd for $C_{28}H_{28}N_4O_5$ C, 67.19; H, 5.64; N, 11.19; O, 15.98. Found: C, 67.14; H, 5.61; N, 11.16.

Methyl 1-phenethyl-5-(*N*-phenyl-*tert*-butoxycarbonyl-amino)-1*H*-1,2,3-triazole-4-carboxylate 19. Column chromatography (Pet. Et. 40-60:EtOAc 65:45) gave compound **19** (371 mg, 88%) as a dense oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 6.93 (m, 10H), 4.33 - 4.17 (m, 4H), 3.29 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 152.0, 139.3, 136.7, 134.0, 129.6(2C), 129.1(2C), 129.0(2C), 128.1, 128.0, 127.0, 126.6, 125.3, 83.5, 61.5, 50.5, 34.5, 28.1 (3C) .HRMS (ESI): *m/z* calcd for $C_{23}H_{26}N_4O_4Na^+$ 445.1852. Found 445.1849.

(*S*)-2-(5-(*tert*-Butoxycarbonyl(phenyl)amino)-4-(methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-propanoic acid 20. Column chromatography (Pet. Et. 40-60:EtOAc from 15:85 to 0:100) gave compound **20** (400 mg, 86%) as a dense oil. An analytical sample was obtained by crystallization of the dimethylamine salt in acetone. $[\alpha]_D^{21}$ (of dimethylamine salt)= - 9.96 (c = 0.67 in MeOH/H_2O 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (bs, 1H), 7.54 - 6.83 (m, 10H), 4.86 (bs, 1H), 3.88 (s, 3H), 2.41 (m, 1H), 2.02 - 1.84 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 164.0, 160.4, 160.3, 160.0, 151.7, 151.7, 138.9, 138.7, 128.2(2C), 128.1(2C), 126.8(2C), 126.6(2C), 124.8, 82.7, 51.0, 36.6, 27.5(3C). ESI/MS $(M-H)^-$: 449. Anal. calcd for $C_{26}H_{33}N_5O_6$ (dimethylamine salt) C, 61.04; H, 6.50; N, 13.69; O, 18.77. Found C, 60.99; H, 6.53; N, 13.73.

(*S*)-2-(5-(*tert*-Butoxycarbonyl(phenyl)amino)-4-(methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)-4-methyl-pentanoic acid 21. Column chromatography (Pet. Et. 40-60:EtOAc from 15:85 to 0:100) gave compound **21** (358 mg, 83%) as a dense oil. An analytical sample was obtained by crystallization of the dimethylamine salt in acetone. $[\alpha]_D^{21}$ (of dimethylamine salt)= - 13.66 (c = 0.86 in MeOH/H_2O 1/1). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.73 (t, *J* = 7.6 Hz, 2H), 7.50 - 7.12 (m, 3H), 4.64 (m, 1H), 3.95 (s, 3H), 2.40 (m 1H), 2.34 - 2.06 (m, 2H), 1.58 (s, 9H), 0.95 (d, *J* = 5.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 150.7, 139.1, 138.4, 133.0, 128.5, 128.4(2C), 127.9, 127.7, 127.2(2C), 83.3, 62.5, 56.2, 51.2, 39.8, 25.2(3C), 18.5. ESI/MS (M-H) 431. Anal. calcd. for $C_{23}H_{35}N_5O_6$ (dimethylamine salt) C, 57.85; H, 7.39; N, 14.67; O, 0.10 . Found: C, 57.80; H, 7.42; N, 14.71.

***tert*-Butyl-(1,4-diphenyl-1*H*-1,2,3-triazol-5-yl)phenyl-carbamate 25**. Column chromatography (Pet. Et. 40-60:EtOAc 70:30) gave compound **24** (297 mg, 72%) as a dense oil with a tendency to solidify on standing. An analytical sample was obtained by crystallization from *i*-

PrOH m.p. 154-156(dec) °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 3H), 7.64 - 6.76 (m, 12H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 140.9, 139.2, 134.9, 133.7, 129.3, 129.0, 128.4(2C), 128.1(2C), 125.5(6C), 125.4(2C), 123.9(2C), 123.2(2C), 82.8, 27.3. ESI/MS $(M+Na)^+$ 435. Anal. calcd for $C_{25}H_{24}N_4O_2$ C, 72.80; H, 5.86; N, 13.58; O, 7.76. Found C, 72.77; H, 5.88; N, 13.56.

***tert*-Butyl (1-benzyl-4-phenyl-1*H*-1,2,3-triazol-5-yl)phenyl-carbamate 26.** Column chromatography (Pet. Et. 40-60;EtOAc 70:30) gave compound **26** (349 mg, 82%) as a dense oil with a tendency to solidify on standing. An analytical sample was obtained by cristallyzation from *i*-PrOH m.p. 168(dec) °C. ^{1}H NMR (400 MHz $CDCl_3$) δ 8.20 -6.83 (m, 15H), 5.47 (d, J = 10.2 Hz, 1H), 4.77 (d, J = 10.2 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 141.7, 138.6, 133.7, 129.1, 128.8(2C), 128.5(2C), 128.3(2C), 128.0, 127.9(2C), 127.2(2C), 125.4, 125.0(2C), 122.8(2C), 82.4 51.2, 26.9(3C). ESI/MS (M+Na) 449. Anal. calcd for $C_{26}H_{26}N_4O_2$ C, 73.22; H, 6.14; N, 13.14; O, 7.50. Found: C, 73.18; H, 6.17; N, 13.12.

***tert*-Butyl (4-butyl-1-phenyl-1*H*-1,2,3-triazol-5-yl)-phenylcarbamate 27a.** Column chromatography (Pet. Et. 40-60:EtOAc 70:30) gave compound **27** (298 mg, 76%) as a mixture of isomers. The ratio was determined by ^{1}H NMR. A second column chromatography with Pet. Et. 40-60/EtOAc from 100:0 to 80:20 allowed the isolation of pure **27a** as a dense oil. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.60 - 6.90 (m, 10H), 2.62 - 2.49 (m, 1H), 2.49 - 2.34 (m, 1H), 1.39 - 1.25 (m, 3H), 1.17 (s, 10 H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz $CDCl_3$) δ 153.2, 143.7, 141.1, 136.3, 132.7, 129.3, 129.1, 128.3(2C), 125.7(2C), 125.5(2C), 124.9(2C), 81.4, 28.9, 27.7(3C), 22.2, 21.9, 13.0. HRMS (ESI): *m/z* calcd for $C_{23}H_{28}N_4O_2Na^+$ 415.2110. Found 415.2116.

***tert*-Butyl (4-butyl-1-benzyl-1*H*-1,2,3-triazol-5-yl)phenylcarbamate 28a** Column chromatography (Pet. Et. 40-60:EtOAc 70:30) gave compound **28** (320 mg, 79%) as a mixture

of isomers. The ratio was determined by ^{1}H NMR. A second column chromatography with Pet. Et. 40-60:EtOAc from 100:0 to 80:20 allowed the isolation of pure **28a** as a dense oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 - 6.67 (m, 10H), 5.33 (d, *J* = 15.2 Hz, 1H), 4.94 (d, *J* = 15.2 Hz, 1H), 2.49 (m, 2H), 1.78 - 1.52 (m, 2H), 1.41 - 1.17 (m, 11H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 143.0, 139.2, 133.9, 132.2, 128.4(3C), 128.3, 127.8(2C), 127.3, 125.3(2C), 123.5, 82.3, 51.2, 29.8, 27.3(2C), 24.0, 22.2, 13.3. HRMS (ESI): *m/z* calcd for $C_{24}H_{30}N_4O_2Na^+$ 429.2267. Found 429.2263

***tert*-Butyl (4-ethyl-1-phenyl-1*H*-1,2,3-triazol-5-yl)phenylcarbamate 29a** Column chromatography (Pet. Et. 40-60:EtOAc 70:30) gave compound **29** (266 mg, 73%) as a mixture of isomers. The ratio was determined by ^{1}H NMR. A second column chromatography with Pet. Et. 40-60/EtOAc from 100:0 to 80:20 allowed the isolation of pure **29a** as a dense oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.36 (m, 7H), 7.17 -7.13 (m, 3H), 2.86 - 2.73 (t-like, 2H), 1.38 (s, 9H), 0.93 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (101 MHz,) δ 154.6, 143.0, 140.6, 135.6, 129.2, 128.5(2C), 127.9(2C), 127.8(2C), 125.3(2C), 124.7(2C), 81.1, 30.3, 28.0(3C), 11.9. HRMS (ESI): *m/z* calcd for $C_{21}H_{24}N_4O_2Na^+$ 387.1797. Found 387.1793

***tert*-Butyl {4-[(allylamino)carbonyl]-1-phenyl-1*H*-1,2,3-triazol-5-yl}phenylcarbamate 30.** Allylamine (142 mg, 2.5 mmol) was added to compound **12** (100 mg, 0.25 mmol) dissolved in dry MeOH (0.5 mL) and the mixture was heated for 6 hours at 80 °C in a sealed tube. The solvent and the excess of the amine were removed under reduced pressure and the residue was crystallized from MeOH/H_2O to give compound **30** (83 mg, 80%). M.p. 186-187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 6.90 (m, 11H), 6.06 - 5.77 (m, 1H), 5.35 - 5.07 (m, 2H), 4.07 (d, *J* = 14.0 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (101 MHz $CDCl_3$) δ 158.6(2C), 134.5, 133.5, 129.9, 129.8(2C), 129.3, 129.3(2C), 129.1, 128.4, 128.4, 128.3, 126.4, 125.5, 124.1, 116.2, 82.7, 40.87

27.5(3C). ESI/MS (M+Na) 442. Anal. calcd for $C_{23}H_{25}N_5O_3$ C, 65.85; H, 6.01; N, 16.70; O, 11.44. Found: C, 65.81; H, 6.04; N, 16.68.

***tert*-Butyl {4-[(benzylamino)carbonyl]-1-phenyl-1*H*-1,2,3-triazol-5-yl}phenylcarbamate 31**. Starting from **14** and following the same procedure described for **30**, **c**ompound **31** was crystallized from MeOH/H_2O (95 mg, 81%). M.p. 202(dec) °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.64 - 7.10 (m, 13H), 5.48 (d, *J* = 15.2 Hz, 1H), 4.78 (d, *J* = 15.3 Hz, 1H), 0.93 (s, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 141.7, 138.6, 133.8, 132.5, 129.8, 129.2, 128.9(2C), 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.2, 125.4, 125.0(2C), 122.9, 122.8, 82.4, 51.2, 51.2, 26.9(3C). ESI/MS (M+Na) 492. Anal. calcd for $C_{27}H_{27}N_5O_3$ C, 69.07; H, 5.80; N, 14.92; O, 10.22. Found: C, 69.01; H, 5.83; N, 14.90.

Methyl *N*-({5-[(*tert*-butoxycarbonyl)(phenyl)amino]-1-phenyl-1*H*-1,2,3-triazol-4-yl}carbonyl)-*L*-alaninate 32, general procedure. Compound **12** (100 mg, 0.25 mmol) was dissolved in MeOH (0.5 mL) and the solution added to 2 mL of a 1M solution of NaOH at rt. The solution was stirred for 2 h, then cooled to 0°C and 3 mL of a 1 M solution of HCl added. EtOAc (10 mL) was then added and the organic phase separated and dried over anhydrous Na_2SO_4. The solvent was evaporated, the residue taken in dry toluene (5 mL) and the solvent evaporated under reduced pressure in order to dry the product. Oxalyl chloride (2 mL) was added and the solution stirred at rt for 3 h. The liquid phase was removed under vacuum (10 mmHg) and the residue dissolved in dry CH_2Cl_2 (0.5 mL). This solution was added to a solution containing H-AlaOMe (41 mg, 0.4 mmol), DIPEA (0.39 mL, 2.5 mmol) and DMAP (5 mg) in dry CH_2Cl_2 (1 mL). The solution was stirred at rt for 6 h, then CH_2Cl_2 (10 mL) added and the organic phase was washed with a solution of HCL 1 M, (2 x 4 mL), $NaHCO_3$ 1 M (2 x 25 mL), water (2 mL) and brine (15 mL). The organic phase was separated, dried over anhydrous Na_2SO_4

and the solvent evaporated. Column chromatography (Pet. Et. 40-60:EtOAc from 40:60 to 0:100) gave compound **32** (60 mg, 52%) as a waxy material. $[\alpha]_D^{21}$ = - 15.36 (c = 0.5 in $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.33 (m, 6H), 7.23 - 7.04 (m, 4H), 6.63 (d, *J* = 7.9 Hz, 1H), 4.76 (m, 1H), 3.74 (s, 3H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz $CDCl_3$) δ 172.5, 161.7, 141.3, 139.2, 135.7, 134.5, 129.8, 129.2, 128.4(4C), 126.4, 126.3, 125.5, 124.1, 123.4, 122.7, 120.1, 120.1, 82.6, 52.1, 47.3, 27.56(3C), 17.9. HRMS (ESI): *m/z* calcd for $C_{24}H_{27}N_5O_5Na^+$ 488.1910. Found 488.1906

Methyl *N*-({5-[(*tert*-butoxycarbonyl)(phenyl)amino]-1-benzyl-1*H*-1,2,3-triazol-4-yl}carbonyl)-*L*-alaninate 33. Starting from **14** and following the same procedure described for **32, c**olumn chromatography (Pet. Et. 40-60:EtOAc from 40:60 to 0:100) gave compound **33** (67 mg, 58%) as a waxy material. $[\alpha]_D^{21}$ = - 17.67 (c = 0.5 in $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.83 - 6.92 (m, 10H), 5.16 (s, 2H), 4.75 (q, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 1.44 (s and d, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 158.0, 149.1, 144.3, 137.6, 135.1, 129.2, 128.5, 128.3(2C), 127.9(2C), 127.8(2C), 127.3(2C), 119.8, 81.2, 52.1, 50.7, 49.9, 27.8(3), 19.8. HRMS (ESI): *m/z* calcd for $C_{25}H_{29}N_5O_5Na^+$ 502.2067. Found 502.2064

Methyl 5-[acetyl(phenyl)amino]-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate 34. Trifluoaroacetic acid (0.16 mL, 2 mmol) was added to a solution of **12** (120 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The solution was stirred at this temperature for 20 min and then warmed up to room temperature and stirred for 4 h. The TFA was removed under vacuum and, to the residue, acetic anhydride (1 mL) and AcONa (0.1 gr) were added and the solution was stirred at rt overnight. The reaction was quenched with 3 mL of a 1 M solution of HCl and extracted with CH_2Cl_2 (10 mL x 3). The organic solution was then dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on (Pet.

Et. 40-60/EtOAc 80: 20) to give compound **34** (74 mg, 73%). An analytical sample was crystallized from EtOH/H_2O. M.p.123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 6.98 (m, 8H), 6.81 (d, *J* = 7.4 Hz, 2H), 3.96 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 160.3, 139.5, 134.0, 130.3, 130.3, 129.8(2C), 129.2(2C), 129.0(2C), 128.6, 127.1, 124.9, 115.9, 53.8, 51.8. ESI/MS (M+Na) 359. Anal. calcd for $C_{18}H_{16}N_4O_3$ C, 64.28; H, 4.79; N, 16.66; O, 14.27. Found: C, 64.24; H, 4.81; N, 16.64.

Methyl 5-[benzoyl(phenyl)amino]-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate 35. The Boc was removed as described for **34** then the residue was dissolved in dry DMF (1 mL) and the solution cooled to 0°C. Pyridine (0.5 mL) was added followed by DMAP (20 mg) and benzoyl chloride (140 mg, 1 mmol). The solution stirred at rt for 12 h. The same work up of **34** gave product **35** (91 mg, 76%). An analytical sample was crystallized from *i*-PrOH. M.p. 164-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-6.92 (m, 15H), 3.87 (s, 3H). ^{13}C NMR (101 MHz $CDCl_3$) δ 164.3, 157.5, 147.3, 136.6, 135.9, 129.5, 129.0, 128.5(2C), 128.4(2C), 128.0(3C), 127.8(2C), 127.5(2C), 127.2(2C), 122.0(2C), 51.9. ESI/MS (M+Na) 421. Anal. calcd for $C_{23}H_{18}N_4O_3$ C, 69.34; H, 4.55; N, 14.06; O, 12.05. Found: C, 69.30; H, 4.57; N, 14.02.

Methyl 5-[[*N*-(*tert*-butoxycarbonyl)-L-alanyl](phenyl)-amino]-1-benzyl-1*H*-1,2,3-triazole-4-carboxylate 36, general procedure. Compound **14** (48 mg, 0.1 mmol) was deprotected from Boc as previously described. The residue was dissolved in dry DMF (1 mL) and this solution was added to a solution containing *N*-Boc-AlaOH (96 mg, 0.5 mmol), DIPEA (0.39 mL, 2.5 mmol) and DMAP (5 mg) in dry DMF (1 mL) cooled to 0 °C. The mixture was gently warmed up to 50°C (water bath) and stirred at this temperature for 12. Then $CHCl_3$ (10 mL) was added and the organic phase was washed with a solution of HCl 1 M, (2 x 4 mL), $NaHCO_3$ 1 M (2 x 25

mL), water (2 mL) and brine (15 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent evaporated. Column chromatography (Pet. Et. 40-60:EtOAc from 40:60 to 0:100) gave compound **36** (103 mg, 43%) as a waxy material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51- 6.52 (m, 11H), 4.75 (d, *J* = 14.3 Hz, 1H), 4.48 (d, *J* = 14.3 Hz, 1H), 3.89 (s, 3H), 3.78 - 3.61 (m, 1H), 1.38 - 1.16 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 160.37, 152.7, 139.0, 134.4, 134.2, 129.4, 129.1, 128.9, 128.3(2C), 128.0(2C), 127.7, 127.3, 125.9, 124.3, 123.6, 82.3, 52.4, 51.7, 27.5(3), 19.1. HRMS (ESI): *m/z* calcd for $C_{25}H_{29}N_5O_5Na^+$ 502.2067. Found 502.2063.

Methyl *N*-({1-benzyl-5-[[*N*-(*tert*-butoxycarbonyl)-L-alanyl](phenyl)amino]-1*H*-1,2,3-triazol-4-yl}carbonyl)-L-alaninate 37. Starting from **33** and following the same procedure described for **36**, column chromatography (Pet. Et. 40-60:EtOAc 40:60 to EtOAc:MeOH 98:2) gave compound **37** (20 mg, 36%) as a waxy material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-6.86 (m, 12H), 5.66 - 5.45 (m, 2H), 4.73 (d, *J* = 7.8 Hz, 1H), 4.66 - 4.55 (m, 1H), 3.88 - 3.53 (s, 3H), 1.49 - 1.31 (m, 12H), 1.23 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 168.1, 152.7, 151.0, 140.3, 138.20, 138.1, 136.0, 134.3, 126.3(2C), 125.9(2C), 125.6(2C), 125.2, 124.8, 121.3, 82.5, 55.8, 54.4, 53.1, 51.3, 27.8, 26.6(3C), 18.5. HRMS (ESI): *m/z* calcd for $C_{28}H_{34}N_6O_6Na^+$ 573.2438. Found 573.2434.

Dipeptide 38, general procedure. Compound **20** (46 mg, 0.1 mmol) was dissolved in DMF (1 mL) followed by H-Ala(O-*t*Bu) (73 mg, 0.5 mmol) and NMM (100 mg, 1 mmol). To this solution, DMTMM-Cl (138 mg, 0.5 mmol) was added and the mixture stirred at rt for 6h. Then $CHCl_3$ (5 mL) was added and the organic phase washed with a solution of HCl 1 M, (2 x 2 mL), $NaHCO_3$ 1 M (4 x 2 mL), water (2 mL) and brine (2 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent evaporated. Column chromatography (Pet. Et. 40-

60:EtOAc 40:60 to EtOAc:MeOH 98:2) gave compound **38** (42 mg, 71%) as a waxy material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.13 (m, 10H), 6.67 - 6.52 (m, 1H), 5.10 (d, *J* = 7.8 Hz, 1H), 4.40 (d, *J* = 6.9 Hz, 1H), 3.95 (s, 4H), 3.80 - 3.62 (m, 1H), 1.59 - 1.32 (m, 18H), 1.31 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 164.9, 159.1, 152.8, 150.5, 139.4, 138.8, 129.3, 128.9, 128.5, 127.9, 127.8, 122.0, 80.2, 78.8, 65.0, 55.9, 52.0, 51.1, 32.1, 25.4, 25.4, 25.3, 25.1(3C), 25.0(3C), 25.05, 18.94. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}N_5O_7Na^+$ 616.2748. Found 616.2744.

Dipetide 39. Column chromatography (Pet. Et. 40-60:EtOAc 40:60 to EtOAc:MeOH 98:2) gave compound **39** (41 mg, 74%) as a waxy material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.87 - 7.57 (m, 2H), 7.53 - 7.03 (m, 7H), 6.61 (t, *J* = 7.1 Hz, 1H), 5.23 - 4.98 (m, 1H), 4.08 - 3.78 (m, 4H), 3.79 - 3.57 (m, 4H), 3.57 - 3.42 (m, 1H), 1.72 (s, 9H), 1.29 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 164.0, 160.4, 160.3, 160.0, 151.7, 151.7, 138.8, 138.7, 128.2(2C), 128.1(2C), 126.7(2C), 126.6(2C), 124.7, 82.7, 54.9, 51.0, 42.8, 37.9, 36.6, 27.5(3C), 20.2. HRMS (ESI): *m/z* calcd for $C_{28}H_{33}N_5O_7Na^+$ 574.2278. Found 574.2280.

Peptide 40. Compound **38** (40 mg, 0.072 mmol) was dissolved in MeOH (0.5 mL) and the solution added to 0.5 mL of a 1 M solution of NaOH at rt. The solution was stirred for 2 h, then cooled to 0°C and 0.6 mL of a 0.1 M solution of HCl added. EtOAc (5 mL) was added and the organic phase rapidly separated and dried over anhydrous Na_2SO_4. The solvent was evaporated, the residue taken in dry toluene (5 mL) and the solvent evaporated under reduced pressure in order to dry the product. Oxaly chloride (1 mL) was added and the solution stirred at rt for 3 h. The liquid phase was removed under vacuum (10 mmHg) and the residue dissolved in dry DMF (0.5 mL). This solution was added to a solution containing H-AlaOMe (20 mg, 0.2 mmol), EDC (77 mg, 0.5 mmol) DIPEA (0.2 mL, 1.3 mmol) and DMAP (5 mg) in dry CH_2Cl_2 (1 mL). The

solution was stirred at rt for 6 h, then CH_2Cl_2 (10 mL) added and the organic phase was washed with a 10 aqueous solution of citric acid (2 x 4 mL), $NaHCO_3$ 1 M (2 x 25 mL), water (2 mL) and brine (15 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent evaporated. A solution prepared dissolving Me_3SiCl (0.127 mL, 1 mmol) in dry MeOH (0.5 mL) was added and the mixture stirred at rt for 2 h. The solvent was evaporated and the residue dissolved in MeOH and passed through a LC-SCX cartridge for weak acids. First elution was done with MeOH, then H_2O and NH_4OH 2% in MeOH. The product was removed with 2% formic acid in MeOH. The solvent was evaporated to give compound **40** (20 mg, 56 %). ^1H NMR (400 MHz, $CDCl_3$) δ 11.06 (bs, 1H), 9.02 - 8.66 (m, 3H), 8.05-7.85 (m, 2H), 7.54 - 7.01 (m, 7H), 6.74 - 6.46 (m, 1H), 5.15 - 4.94 (m, 1H), 4.86 - 4.62 (m, 1H), 4.53 (m, 1H), 4.13 - 3.89 (m, 1H), 3.90 - 3.67 (m, 4H), 1.55 - 1.22 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$*d*) δ 170.2, 168.1, 164.8, 160.3, 139.3, 137.6, 136.1, 130.3(2C), 129.2(2C), 128.6, 127.0(2C), 124.9(2C), 124.9, 119.9, 64.1, 54.5, 53.8, 51.9, 36.8, 22.7, 21.9. HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_6O_6Na^+$ 531.1968. Found 531.1962.

Methyl *p*-(Methoxyphenyl)methyl](*p*-anisoyl)amino}propiolate 42. Amide **44** (1.03 g, 3.8 mmol) was dissolved in toluene (8 mL) and to this solution CuI (0.224 g, 1.17 mol), 1.10 phenatroline (0.252 g, 1.4 mmol) and KHMDS (10 mL of a 0.5 M solution in toluene, 5 mmol) were added under nitrogen. After 30 min of stirring an rt, silane **7** (1.04 g, 4 mmol) was added, the flask sealed and heated at 90 °C for 6 h under stirring. After cooling, the solid was filtered away, the toluene evaporated and substituted with dry THF (10 mL). The solution was cooled to 0 °C, TBAF (0.954 g, 3.02 mmol) was added and the solution stirred at this temperature for 4 h. The solution was diluted with EtOAc(25 mL) and washed with a saturated solution of NH_4Cl and water. The organic layer was separated, dried over Na_2SO_4 and the solvent evaporated. A

passage on a short column of silica gel gave the desilylated product practically pure for the next step (MS/ESI 296 $[M+1]^+$). This product (0.950 g) was dissolved in dry THF (20 mL) and cooled to -78 °C. LHMDS (5.58 mL of a 1 M solution in THF, 5.58 mmol) was slowly added and the mixture stirred 30 min at -78 °C and 1 h at -40 °C. At this temperature, methylchloroformiate (0.404 g, 4.28 mmol) in dry THF (4 mL) was slowly added and the solution gently warmed to rt and stirred for 2 h. Standard aqueous work-up followed by flash chromatography on silica gel, (Pet. Et. 40-60:EtOAc from 100:0 to 90:10) gave compound **42** (0.788 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.1 Hz, 2H), 6.94 (d, J = 6.7 Hz, 2H), 6.79 (d, J = 7.3 Hz, 2H), 4.81 (s, 2H), 3.95 (s, 3H), 3.74 (d, J = 30.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 161.6, 159.0, 130.6, 130.0, 127.9, 125.4, 113.4, 112.5, 99.1, 71.3, 54.9, 54.8, 52.2. ES/MS 376 $[M+Na]^+$. Anal. calcd for $C_{20}H_{19}NO_5$ C, 67.98; H, 5.42; N, 3.96. Found: C, 67.99; H, 5.39; N, 3.98.

Triazole amide 45. To arylazide **43** (186 mg, 0.5 mmol) dissolved in dry DMF (2.5 mL) at rt, compound **42** (160 mg, 0.45 mmol) was added. The flask was subjected to three vacuum-nitrogen cycles, then $(Cp^*RuCl)_4$ (24 mg, 0.022 mmol) was added followed other three vacuum-nitrogen cycles. The reaction was stirred at room temperature until completion (monitored by TLC, 2h). EtOAc and water were then added. The organic phase was extracted four times with EtOAc, washed with water (three times) and brine (one time) and dried over Na_2SO_4; the solvent was removed and the mixture was purified by passage on a shorth path of silica. The crude was dissolved in $EtNH_2$ (2.0 mL of a solution 2 M in MeOH) and the mixture was heated for 24 h at 80 °C in a sealed tube. The solvent and the excess of amine were removed under reduced pressure and the residue submitted to column chromatography (Pet. Et. 40-60/EtOAc 60:40). Compound **45** was obtained as a purple oil with a tendency to solidify on standing (175 mg,

55%). An analytical sample was obtained by crystallization from MeOH/water, M.p. 96-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 20.7, 5.1 Hz, 1H), 8.44-8.17 (m, 2H), 7.51 (dd, *J* = 21.6, 7.3 Hz, 7H), 7.40-7.05 (m, 10H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.29 (s, 1H), 5.53 (s, 2H), 5.15-4.91 (m, 4H), 3.93 (s, 3H), 3.78 (s, 3H), 3.51 (q, *J* = 7.2 Hz, 2H), 3.35 (d, *J* = 6.9 Hz, 1H), 1.32-1.01 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 160.0, 138.7, 138.2, 133.9, 133.0, 128.8, 128.4, 128.1, 127.2, 126.2, 124.4, 82.7, 65.7, 61.5, 58.7, 51.7, 51.4, 34.5, 27.2. MS-ESI 764 $[M + MeOH + Na]^+$. Anal. calcd for $C_{43}H_{43}N_5O_5$ C, 72.76; H, 6.11; N, 9.87. Found: C, 72.79; H, 6.09; N, 9.86.

Amidotriazolylamide 41. Compound **45** (150 mg, 0.211 mmol) was dissolved in EtOH (5 mL), and $Pd(OH)_2/C$ (10 mg of a 10% dispersion on C, 0.01 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (balloon) for 5 h while the reaction progress was minitored by tlc. The catalyst was filtered off through Celite, and the ethanol was removed under reduced pressure. The residue was dissolved in a mixture of DCM /water 3 / 1 (2 mL) and DDQ (95 mg, 0.42 mmol) was added and the mixture stirred for 3 h at rt. The solvent was evaporated and the residue submitted to flash chromatography (DCM/ MeOH, 90/10) to give **41** as a waxy material (24 mg, 26 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.10 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.46 (s, 1H), 3.82 (s, 3H), 3.40 (d, *J* = 7.3 Hz, 2H), 3.24-3.06 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 162.9, 156.7, 152.2, 149.8, 145.2, 133.8, 129.2, 126.6, 125.9, 124.5, 124.2, 113.8, 113.1, 102.1, 54.2, 33.2, 25.7, 21.2, 13.2. HRMS (ESI): *m/z* calcd for $C_{22}H_{25}N_5O_5Na^+$ 462.1754. Found 462.1751.

Supporting Information. Spectra of compounds **10-21**, **25-42** and **45**. This material is available free of charge via the Internet at http://pubs.acs.org."

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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[17] The enantiomeric integrity products **21**, **22**, **25** and **27** was determined by HPLC analysis on a chiral column in comparison with the chromatograms obtained from the products of coupling starting from the racemic amino acids.

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TOC Graph: