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A 1,4-Diphenyl-1,2,3-Triazole-Based β-Turn Mimic Constructed by Click Chemistry

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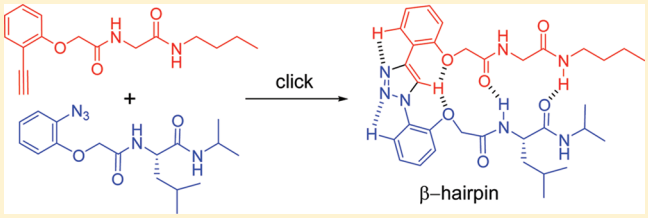
Supporting Information

ABSTRACT: A series of 1,4-diphenyl-1,2,3-triazole-incorporated amide derivatives have been designed and prepared. X-ray crystallographic and (1D and 2D) ^{1}H NMR studies reveal that these compounds fold into stable U-shaped conformations driven by three-center intramolecular C−H···O hydrogen-bonding formed between the triazole C-5 H atom and the two ether O atoms. Such folded structures make this 1,4-diphenyl-1,2,3-triazole skeleton a good candidate to be used as β-turn mimic. To prove this, the formation of a β-hairpin structure induced by this β-turn motif has been further demonstrated.



INTRODUCTION

As one of the most typical secondary structures, β-sheets have been found in most proteins.[1] To facilitate the formation of a β-sheet, one peptide strand usually needs to adopt a U-shaped conformation, in which two segments of the peptide strand can be arranged in a parallel or antiparallel manner stabilized by intramolecular C═O···H—N hydrogen bonds formed between the amides of the two peptide segments arranged in reverse directions. In nature, this process is usually induced by several specific glycin- and proline-rich peptide sequences named β-turns.[2] For this reason, β-turns have been considered to be extremely important in many biological processes including protein−protein, protein−peptide, and protein−DNA interactions, biomolecular recognition, phosphorylation, glycosylation, and hydroxylation.[3] In the past decades, the development of artificial β-turn mimics has attracted a great deal of interest because progress along this line not only provides insight into the basic principles governing the high-order structures of biological macromolecules, but also is useful in designing potential drug candidates that can mimic the functions of natural β-turns.

Currently, a variety of chemical structures have been designed to resemble β-turns. The representative examples include 2,2′-substituted tolan adopted by the Kemp group,[4] phenoxathiin derivatives developed by Figel[5] and Sogah,[6] dibenzofuran-based amino acids reported by Kelly et al.,[7] tetrasubstituted alkenes reported by the Gellman group,[8] as well as amino(oxo)piperidinecarboxylate scaffolds designed by Borggraeve and co-workers.[9] In these examples, β-turn motifs have been constructed through arranging two docking sites (amino group and carboxyl group) in nearby positions on a rigid skeleton, and then two peptide strands designed to construct artificial β-sheet structures could be attached to the β-turn skeleton in a step by step manner. In another approach, the mimics of β-turn structures have been achieved by employing acyclic artificial peptides, which folded into U-shaped conformations driven by intramolecular N−H···O hydrogen-bonding. In this context, the Nowick group succeeded in designing a series of urea derivatives[10] and 5-amino-2-methoxybenzoic acid,[11] on the basis of which a variety of mimic structures have been constructed. On the other hand, a convergent method, in which two peptide strands are first constructed respectively and then combined by intermolecular ligation to form a β-sheet structure, should also be attractive because it provides an efficient access to structurally diverse β-turn-containing molecules. In 2006, Guan et al. reported a convergent synthesis of β-turn mimics via the Cu (I)-catalyzed azide−alkyne cycloaddition,[12] in which the β-turn structures were induced and stabilized by intramolecular N—H···O═C hydrogen bonds between the two clicked dipeptide strands.[13] A similar strategy has also been employed by Burgess et al. to construct cyclic β-turn motifs.[14] We recently reported a series of 1,4-di(2-methoxyl and/or *i*-butoxy)phenyl-1,2,3-triazole derivatives whose structures were fixed into folded conformations through the formation of intramolecular six-membered three-center C−H···O hydrogen bonding between the C−H of triazole unit and the oxygen atoms of the methoxyl or *i*-butoxy groups substituted at the ortho positions of the phenyl rings.[15] We anticipated that this skeleton could be further exploited as a novel β-turn mimic because of the stable folded conformation, the high efficiency structure construction (via click chemistry), and most importantly, the convergent approach to independently introduce two peptide strands. In this paper, we report a systematic investigation on the feature of this 1,4-diphenyl-1,2,3-triazole-based β-turn mimic through X-ray crystallographic and (1D and 2D) ^{1}H NMR studies on a series of rationally designed derivatives. We further demonstrate the

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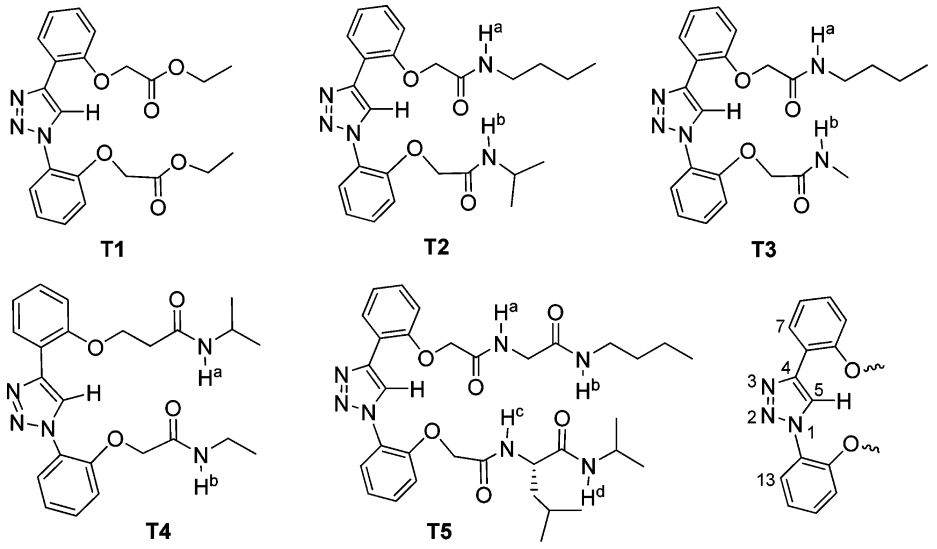
Scheme 1. Structures of Compounds T1−T5 and the 1,4-Diphenyl-1,2,3-triazole Skeleton with Related Atoms Being Labeled



capacity of this motif by using it to nucleate a β-hairpin, the shortest β-sheet structure.

RESULTS AND DISCUSSION

Design and Synthesis. Compound **T1** was designed as the model of β-turn mimic, while compounds **T2**−**T4** carry two amide chains with different terminal alkyl groups and different spacer lengths between the triazole unit and a docking site to test the conformation and stability of this β-turn mimic. **T5** was designed to examine the capability of this β-turn mimic to induce the formation of β-sheet structure (Scheme 1).

All the target compounds were synthesized using a convergent strategy. That is, coupling one segment bearing an azide group with another one bearing an alkynyl group via Cu (I)-catalyzed azide−alkyne cycloaddition. For the synthesis of **T1** (Scheme 2), 2-iodophenol was first reacted with ethyl 2-chloroacetate in the presence of potassium carbonate to give compound **2** in 97% yield, which was then coupled with trimethylsilylacetylene catalyzed by $PdCl_2(PPh_3)_2$ and CuI to afford compound **3** in 95% yield. Treatment of **3** with TBAF generated alkyne **4** in 80% yield. For the azide segment, 2-aminophenol was first treated with sodium nitrite and hydrochloric acid (2 M), and then the resulting solution was treated with sodium azide to give compound **6** in 85% yield. This intermediate was further treated with ethyl 2-chloroacetate to generate azide **7** in 95% yield. With the alkyne and azide precursors available, compound **T1** was obtained via a 1,3-dipolar cycloaddition reaction in the presence of sodium ascorbate and copper sulfate in 70% yield. For the preparation of compounds **T2**−**T5**, similar procedures were followed using corresponding phenylacetylenes and azides, which are shown in Scheme 2. Compounds **T1**−**T5** have been characterized by ^{1}H and ^{13}C NMR spectroscopies and (high resolution) mass spectrometry, and their signals in the ^{1}H NMR spectra have been assigned on the basis of the 2D NOESY, and COSY ^{1}H NMR and/or DEPT135°, HMQC, HMBC experiments.

Crystal Structure of T1. Single crystals of compound **T1** suitable for X-ray crystallographic analysis were grown from a mixture of ethyl acetate and cyclohexane by slow evaporation of the solvent. As shown in Figure 1, its crystal structure revealed the formation of two intramolecular C^5−H···O hydrogen bonds. One is six-membered ring with the H···O distance being 2.31 Å, while the other ring has a little bit longer distance of 2.34 Å. The H···N distance between N^2 of the triazole unit and C^{13}−H of the N^1-substituted benzene ring was 2.38 Å, and the H···N distance between N^3 of the triazole unit and C^7−H of the C^4-substituted benzene ring was 2.47 Å. Both of them were notably shorter than the sum of the van der Waals radii (2.65 Å), indicating the formation of two five-membered C−H···N hydrogen bonds. Furthermore, intramolecular hydrogen bonding was also observed between the OCH_2CO of the upper chain and the oxygen of the carbonyl group of the bottom chain with a distance of 2.35 Å. The torsion angles between the triazole unit and the two benzenes are 2.62° (the one at C^4) and 3.43° (the one at N^1), respectively, suggesting that all the three rings almost lay in the same plane. With the cooperation of these hydrogen bonds, compound **T1** adopts a planar U-shaped conformation, which nicely meets the structural requirement for a β-turn unit. Thus, it should facilitate the formation of β-sheets when the two carboxyl units are extended by suitable peptide strands.

Structures in Solution. The conformations of compounds **T1**−**T4** were investigated in $CDCl_3$ solutions by ^{1}H NMR spectroscopy. For compound **T1**, the signal of the triazole C^5−H appeared at 9.20 ppm, which is considerably lower than the C^5−H resonance of 1,4-bis(4-methoxyphenyl)-1,2,3-triazole (8.00 ppm).[14] Compared with the corresponding signals of its precursors **4** and **7**, the signals of C^7−H and C^{13}−H of **T1** were also shifted downfield pronouncedly by 1.00 and 0.96 ppm, respectively (Figure S2, Supporting Information), suggesting that both protons were also hydrogen-bonded, which is in agreement with the observation in its crystal structure. In the case of **T2**, compared to those of its precursors **9** and **12** of the same concentration, its amide proton H^a was shifted downfield by 0.68 ppm, while the amide H^b just showed very little change (ca. 0.06 ppm) (Figure 2). This result suggests that the former amide proton was hydrogen-bonded, while the latter was mainly solvent-exposed. Furthermore, the resonances of C^5−H, C^7−H, and C^{13}−H also appeared in the far-low field. All these observations support the existence of the intramolecular hydrogen-bonds that induce the molecule to form a U-shaped conformation similar to that shown by **T1** in the crystal structure.

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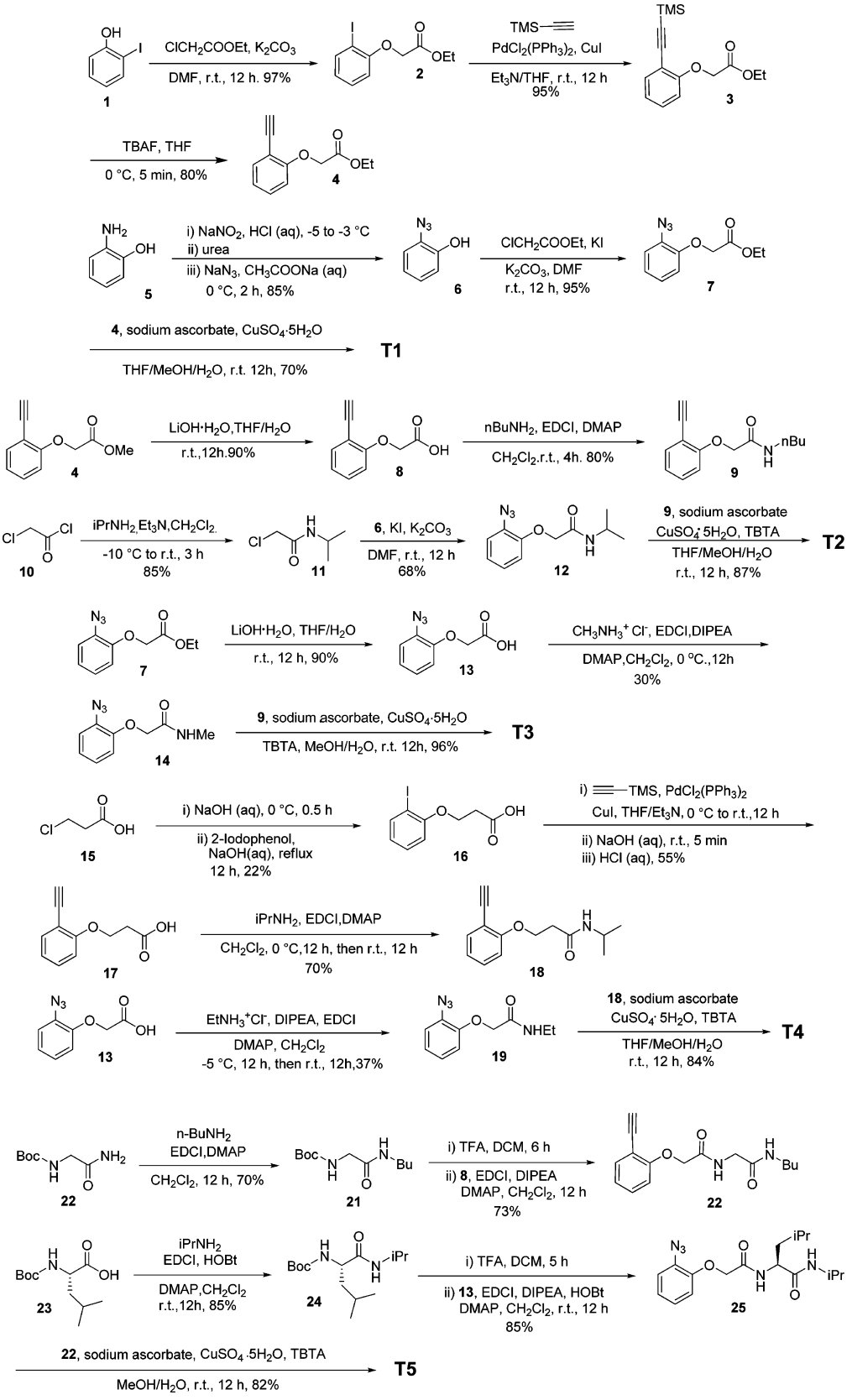
Scheme 2. Synthetic Routes for Compounds T1−T5



The ^{1}H NMR spectra of compounds **T3**−**T4** in $CDCl_3$ exhibit similar trends (Figures S3−S4, Supporting Information), supporting the *β*-turn feature of their structures. In addition to the large downfield shifting of the C^5−H, C^7−H, and C^{13}−H signals, which could be attributed to the formation of the C−H···O and C−H···N hydrogen bonds, as revealed by **T1** and **T2**, the amide proton H^a of **T3** was shifted downfield by 0.69 ppm with respect to the amide signal of its precursors.

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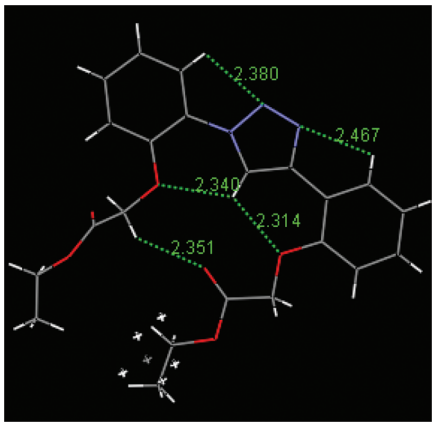

Figure 1. The crystal structure of compound **T1**, highlighting its β-turn character.

The shifting value is the same as that of **T2**, indicating that the terminal alkyl groups in these molecules did not have much impact on the turn conformation. After combining the two strands by the click chemistry, the amide proton of the bottom chain of **T4** exhibited a downfield shift of 0.35 ppm. This result suggested that this hydrogen was also involved in the formation of the intramolecular hydrogen bonding, and the molecule also adopted a U-shaped conformation. However, the change of this chemical shifting for **T4** is just half of the value observed for **T2** and **T3**, implying that the folded conformation of **T4** is not as stable as those of **T2** and **T3**. This might be attributed to the longer distance (one more carbon) between the β-turn unit and the docking site (carboxyl group) in **T4** than that in **T2** and **T3**, which weakens the β-sheet-inducing capability of the triazole moiety. ^{1}H NMR dilution experiments were also carried out for compounds **T2**−**T4** (Figure S5−S7, Supporting Information). It was found that diluting their solutions from 50 mM to 0.5 mM just caused very small shifting of the NH signals, suggesting that no important intermolecular hydrogen-bonding-driven aggregation took place in the range of the concentrations tested.

More compelling evidence for the formation of β-turn mimics were provided by 2D NOESY ^{1}H NMR experiments. The NOESY spectrum of **T2** is provided in Figure 3 as an example. The spectrum gave rise to a number of NOE contacts, including those between the C^5−H of the triazole ring and amide protons H^a and H^b and methylene protons H^1 and that between the terminal methyl groups ($CH_3{}^2$ and $CH_3{}^3$). Similar NOE correlations were also observed for a solution of **T2** at 2 mM (Figure S9, Supporting Information). These results clearly indicated **T2** folded into a β-turn conformation driven by intramolecular hydrogen-bonding.

For compounds **T1** and **T3**−**T4**, similar interstrand NOE contacts were observed (Figures S8, S10, and S11, Supporting Information). In the case of **T1**, C^5−H of the triazole exhibited NOE connections with protons of both the OCH_2CO units of upper and bottom strands. For compound **T3**, in addition to the similar NOE connections as described above for **T1**, NOEs between the C^5−H of the triazole ring and the two amide protons and between the NCH_2 of the upper strand and the terminal methyl group of the lower strand were also observed. The NOESY spectrum of compound **T4** also revealed NOEs between the C^5−H of the triazole ring and the amide protons as well as the protons of two OCH_2 units and between the terminal methyl group of the upper strand and the amide proton of the lower strand. The NOE contacts are summarized in Figure 4. These results confirmed that all these compounds adopted β-turn structures in solution. The fact that NOEs are observed between the C^5−H of triazole unit and both the amide protons of the upper and lower strands for **T2**−**T4** suggests that the two strands might rotate to some extent, which leads to two folded conformations. On the basis of the ^{1}H NMR results above, conformer-a was considered to be favorable over conformer-b.

Construction of a β-Hairpin Structure. Compound **T5**, which bears two artificial dipeptide strands, was further prepared to test the capability of this "clicked" unit to induce the formation of β-hairpin, the shortest β-sheet analogue. The ^{1}H NMR spectra of **T5** and its precursors **22** and **25** of the same concentration in $CDCl_3$ are provided in Figure 5. It can be found that, compared to the related signals of the two controls, the amide protons of the two strands of **T5** are all shifted downfield considerably, indicating that they are involved in intramolecular hydrogen bonding. In principle, the two peptide chains of **T5** may form two different conformations (**T5**-a and **T5**-b), both of which can be stabilized by the intramolecular hydrogen bonds, as illustrated in Figure 5. Since amide proton H^a experienced a larger downfield shifting (0.53 ppm) than amide proton H^c (0.32 ppm), conformer **T5**-a may be the preferred one. Diluting the solution of **T5** from 100 mM to 0.5 mM caused the signals of the H^a, H^b, H^c, and H^d protons to shift upfield by 0.16, 0.30, 0.37, and 0.44 ppm, respectively (Figure S12, Supporting Information). The fact that H^a experienced the smallest shift seems to indicate that it was involved in the strongest intramolecular hydrogen-bonding, while the other protons might be engaged in intermolecular hydrogen bonding to a higher extent at high concentration.

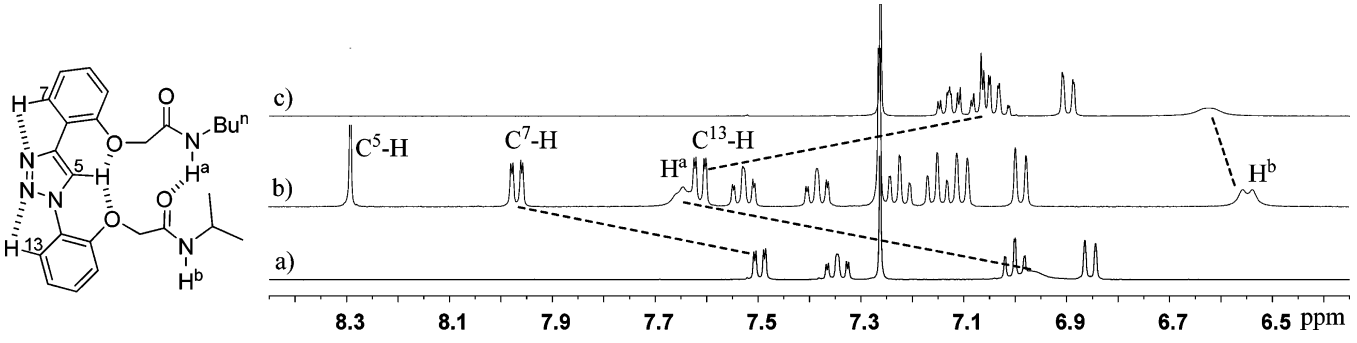

Figure 2. Partial ^{1}H NMR (400 MHz) spectra of (a) **9**, (b) **T2**, and (c) **12** in $CDCl_3$ (20 mM) at 25 °C.

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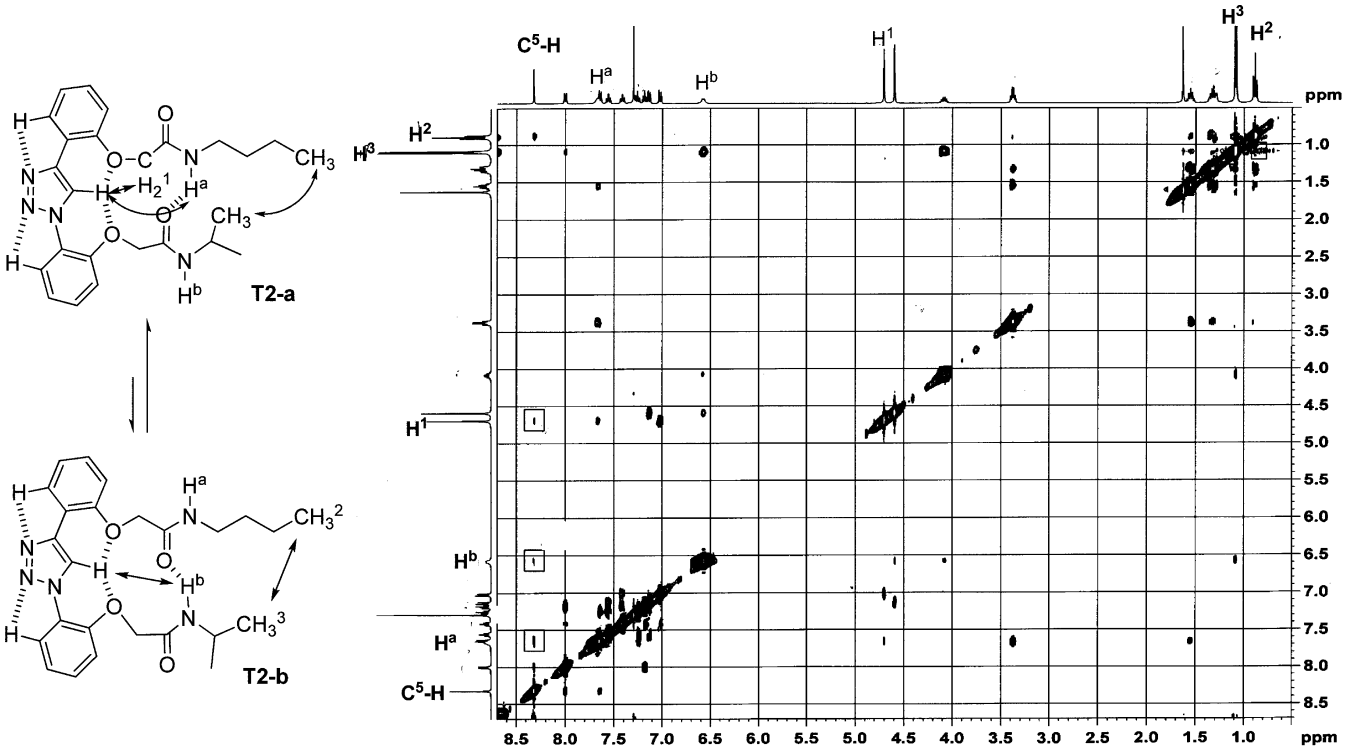

Figure 3. NOESY spectrum (400 MHz) of compound **T2** in $CDCl_3$ (20 mM) at 25 °C (mixing time = 0.8 s).

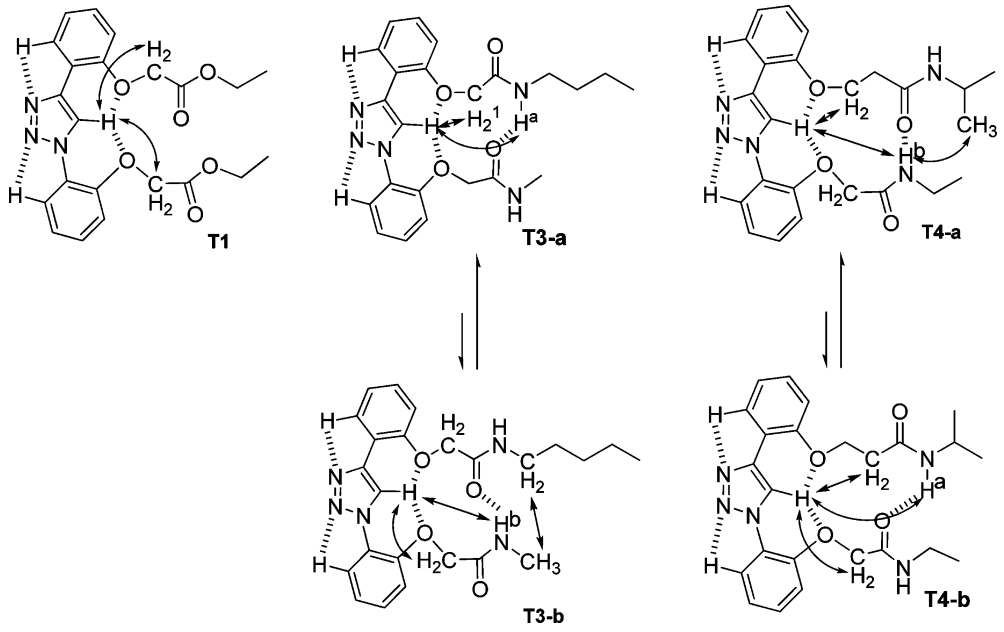

Figure 4. NOE contacts observed for compounds **T1**, **T3**, and **T4** in $CDCl_3$.

This result again supports that conformer **T5**-a is favorable over conformer **T5**-b.

2D NOESY ^{1}H NMR experiment was further carried out for compound **T5** to obtain more evidence for the formation of β-hairpin structure (Figure 6). Strong NOE connections were exhibited between C^5–H of the trazole ring and the methylene protons H^1 and H^5 as well was the amide protons H^a and H^c. Furthermore, interstrand NOE cross-peaks were also observed between H^2 and H^6, H^2 and H^c, H^7 and H^b, and H^4 and H^7. These results clearly indicated that the two dipeptide strands were orientated in close proximity, well corresponding to the typical structure of a β-hairpin. The existence of NOE connections between C^5–H and both H^1 and H^5 also suggested that compound **T5** adopted two different conformations. Further analysis of the NOESY spectrum of **T5** revealed that the intensity of NOE between C^5–H and H^5 was weaker than that between C^5–H and H^1, which again supported that conformer **T5**-a was favorable over conformer **T5**-b. In contrast, under similar condition no NOE correlations between the protons of the two dipeptide strands could be observed for a mixture of compounds **22** and **25** (1:1, 20 mM), the precursors of **T5** (Figure S14, Supporting Information). This

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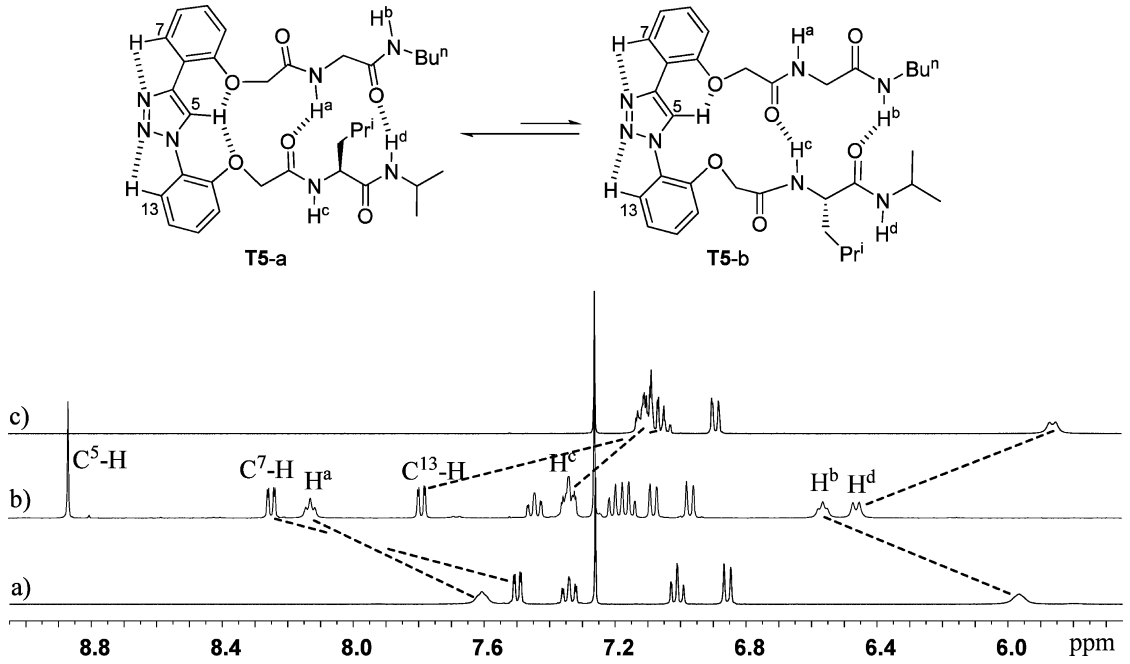

Figure 5. Partial ^{1}H NMR (400 MHz) spectra of (a) **22**, (b) **T5**, and (c) **25** in $CDCl_3$ (20 mM) at 25 °C.

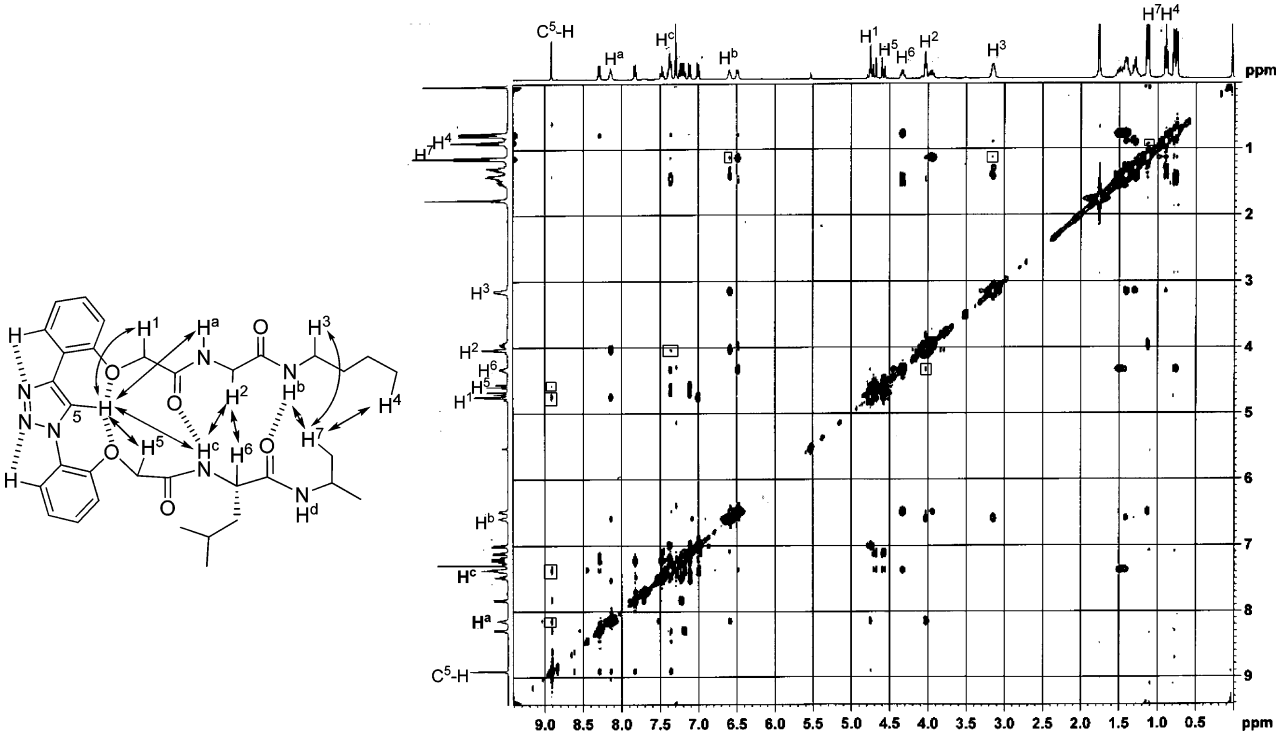

Figure 6. NOESY spectrum (400 MHz) of **T5** in $CDCl_3$ (20 mM) at 25 °C (mixing time = 0.6 s). NOESY spectrum (600 MHz) was also performed for a solution of **T5** in $CDCl_3$ at 2 mM, and a similar result was obtained; see Figure S13 (Supporting Information) for details.

control experiment confirmed again that the NOE connections detected in **T5** should originate from a β-hairpin structure, not from a result of intermolecular aggregation of the molecules.

CONCLUSION

To conclude, we have developed a novel β-turn mimic based on a hydrogen-bonded triazole motif. Different from previously reported rigid cyclic skeletons, which point two docking sites in the same direction, or artificial acylic peptides, which fold into U-shaped conformation mediated by intramolecular N—H···O hydrogen-bonding, the new β-turn mimic is realized by the formation of a folded conformation driven by intramolecular C—H··O hydrogen-bonding. Because of the unique feature of the click chemistry, this approach provides some advantages: (i) mild reaction condition, high efficiency, and tolerance of various functional groups, (ii) a convergent approach by which the two peptide strands designed to construct artificial β-sheets can be prepared separately and efficiently, and (iii)

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synchronously forming β-turn motif when the two peptide strands are intermolecular ligated. The successful construction of β-hairpin structure **T5** here implies that more complex β-sheet structures nucleated by this triazole-based β-turn mimic could be expected. This potential will be explored in the next step.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under a dry nitrogen atmosphere. All solvents were dried before use following the standard procedures. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica 60 coated on glass plates with F254 indicator. The ^{1}H and ^{13}C NMR spectra were recorded on 300 or 400 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (chloroform δ 7.26 ppm).

Safety Comment. Sodium azide is very toxic, and personal protection precautions should be taken. As low molecular weight organic azides are potential explosives, care must be taken during their handling. Generally, when the total number of carbon (NC) plus oxygen (NO) atoms is less than the total numbers of nitrogen atoms (NN) by a ratio of three, i.e., $(NC + NO)/NN < 3$, the compound is considered as an explosive hazard. In those instances, the compound was prepared prior to use and used immediately. A standard PVC blast shield should be used when necessary.

Compound 2. A suspension of 2-iodophenol (6.62 g, 30 mmol), K_2CO_3 (14.45 g, 90 mmol), and ethyl 2-chloroacetate (3.8 mL, 36 mmol) in DMF (35 mL) was stirred for 12 h at room temperature, and then the solid was filtrated off. The filtrate was concentrated under reduced pressure, and the resulting residuum was dissolved in ethyl acetate (100 mL). The organic phase was washed with water (50 mL) and brine (50 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (PE/EA, 15:1) to give compound **2** as a colorless oil (8.91 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1 H), 7.28 (t, J_1 = 8.4 Hz, J_2 = 7.5 Hz, 1 H), 6.75(t, J_1 = 8.4 Hz, J_2 = 7.8 Hz, 1 H), 6.73 (d, J = 8.4 Hz, 1 H), 4.68 (s, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 1.30 (t, J = 7.6 Hz,3 H); MS (ESI) m/z 306.9 $[M + 1]^+$.

Compound 3. Compound **2** (4.60 g, 15 mmol), $PdCl_2(PPh_3)_2$ (199 mg, 0.28 mmol), and CuI (57 mg, 0.28 mmol) were placed in a two-neck flask, which was degassed under a high vacuum and backfilled with argon three times. Degassed tetrahydrofuran (15 mL) and triethylamine (15 mL) were added and then followed by dropwise addition of trimethylsilylacetylene (2.6 mL, 18 mmol). The reaction mixture was stirred for 12 h at room temperature. The solid was filtrated off, the filtrate was concentrated with a rotary evaporator, and the resulting residuum was washed with water (50 mL), extracted with diethyl ether (2 × 60 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE/EA, 25:1) to give compound **3** as a yellow oil (3.95 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1 H), 7.25 (dd, J_1 = 6.3 Hz, J_2 = 1.2 Hz 1 H), 6.94 (t, J = 7.8 Hz, 1 H), 6.79 (d, J = 8.1 Hz,1H), 4.70 (s, 2 H), 4.28 (q, J = 7.2 Hz, 2 H), 1.30 (t, J = 7.2 Hz, 3 H), 0.26 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 158.8, 134.2, 129.8, 121.7, 113.4, 113.2, 100.8, 99.0, 66.4, 61.3, 14.2, 0.0 (3C); MS (ESI) m/z 277.2 $[M + 1]^+$. HRMS (ESI) Calcd. for $C_{15}H_{20}O_3SiNa$ $[M + Na]^+$: 299.10739. Found: 299.10684.

Compound 4. A flask was charged with compound **3** (1.03 g, 3.73 mmol) and THF (15 mL), and the mixture was stirred in ice bath. A solution of tetrabutyl ammonium fluoride (TBAF, 1.08 g, 4.12 mmol) in THF (12 mL) was added dropwise to the former solution during 5 min. After work up, the reaction mixture was concentrated under reduced pressure. The resulting residuum was dissolved in ethyl acetate (40 mL), washed with water (20 mL) and brine (20 mL), and dried over sodium sulfate. After being concentrated, the crude product was purified by flash chromatography (PE/CH_2Cl_2, 3:1) to give compound **4** as an oily liquid (607 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 7.5 Hz, 1 H), 7.29 (t, J = 7.5 Hz, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 4.73 (s, 2 H), 4.26 (q, J = 7.2 Hz, 2 H), 3.32 (s, 1 H), 1.29 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 159.0, 134.4, 130.1, 121.6, 112.4, 112.1, 81.7, 79.6, 66.0, 61.4, 14.1; MS (ESI) m/z 205.0 $[M + 1]^+$. HRMS (ESI) Calcd. for $C_{12}H_{12}O_3Na$ $[M + Na]^+$: 227.06787. Found: 227.06810.

Compound 6. 2-Aminophenol (764 mg, 7 mmol) was dissolved in 2 M HCl (aq, 10 mL) and chilled with stirring in an ice−salt mixture. An ice-cold solution of sodium nitrite (580 mg, 8.4 mmol) in water (2 mL) was added dropwise during 5 min with the temperature of the reaction mixture maintained at −3 to −5 °C. After a further 5 min, urea (50 mg) was added to destroy the excess of nitrous acid. This diazonium salt solution was then added dropwise to a stirred ice-cold solution of sodium azide (910 mg, 14 mmol) and sodium acetate (1.65 mg) in water (10 mL). The mixture was stirred in an ice-bath for 2 h. The black oily product was then extracted into diethyl ether (2 × 25 mL). The combined organic phase was dried with sodium sulfate. After being concentrated, the crude product was purified by flash chromatography (PE/CH_2Cl_2, 5:1) to give compound **6** as a black solid (805 mg, 85%): mp 35−36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1 H), 7.01 (m, 2 H), 6.89 (m, 2 H).

Compound 7. A suspension of **6** (752 mg, 5.6 mmol), K_2CO_3 (1.84 g, 11.4 mmol), KI (1.85 g, 16.8 mmol), and ethyl 2-chloroacetate (1.2 mL, 11.4 mmol) in DMF (30 mL) was stirred for 12 h, and then the solid was filtrated off. The filtrate was concentrated with a rotary evaporator, and the resulting residuum was dissolved in ethyl acetate (100 mL). The organic phase was washed with water (50 mL) and brine (50 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (PE/CH_2Cl_2, 2:1) to give compound **7** as a yellow oil (1.15 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (m, 3 H), 6.82 (d, J = 8.0 Hz, 1 H), 4.68 (s, 2 H), 4.27 (q, J = 7.6 Hz, 2 H), 1.29 (t, J = 7.6 Hz,3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 150.3, 129.3, 125.6, 122.8, 120.9, 114.0, 66.4, 61.6, 14.2; MS (ESI) m/z 244.1 $[M + Na]^+$ HRMS (EI) Calcd. for $C_{10}H_{11}N_3O_3$: 221.0800. Found: 221.0797.

Compound T1. Compound **4** (135 mg, 0.61 mmol), compound **7** (112 mg, 0.55 mmol), $CuSO_4{\cdot}5H_2O$ (9 mg, 0.036 mmol), and sodium ascorbate (15 mg, 0.076 mmol) were placed in a two-neck flask, which was degassed under a high vacuum and backfilled with argon three times. THF (4 mL), methanol (4 mL), and water (4 mL) were added. The mixture was stirred about 12 h. After removal of the solvents under vacuo, the resulting residuum was dissolved in CH_2Cl_2 (40 mL). The solution was washed with water (20 mL × 2) and brine (20 mL × 2) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was purified by recrystallization (ethyl acetate/petroleum ether) to give compound **T1** as a white crystal (173 mg, 70%): mp 114−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 8.48 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1 H), 7.93 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.39 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.30 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.17 (m, 2 H), 7.00 (d, J = 7.8 Hz, 1 H), 6.87 (d, J = 7.8 Hz, 1 H), 4.79 (s, 2 H), 4.76 (s, 2 H), 4.24 (m, 4 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.23 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.4, 153.8, 149.6, 142.6, 129.6, 128.7, 128.1, 127.4, 126.2, 125.7, 122.4, 122.1, 120.4, 113.7, 111.6, 66.1, 65.5, 61.5, 61.4, 14.2, 14.1; MS (ESI) m/z 426.4 $[M + 1]^+$. Anal. Calcd. For $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 61.92; H, 5.49; N, 9.86.

Compound 8. A solution of compound **4** (208 mg, 1.02 mmol) and $LiOH{\cdot}H_2O$ (85 mg, 2.02 mmol) in a 1:1 mixture of THF/H_2O (8 mL) was stirred at room temperature for 12 h. After removal of the organic solvents, water was added (7 mL), followed by the addition of hydrochloric acid until pH = 4. The resulting solid was filtrated and dried to give compound **8** (163 mg, 90%): mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1 H), 7.32 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 4.78 (s, 2 H), 3.35 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 158.5, 134.4, 130.3, 122.2, 112.8, 112.3, 82.1, 79.4, 65.7; MS

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(ESI) m/z 175.04 $[M - 1]^-$. HRMS (ESI) Calcd. for $C_{10}H_7O_3$: 175.04007. Found: 175.03935.

Compound 9. A solution of compound **8** (352 mg, 2 mmol), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) (192 mg, 2.4 mmol), DMAP (10 mg), and butylamine (0.2 mL 2 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 4 h. The solution was then washed with saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$. After being concentrated, the crude product was purified by column chromatography (PE/EA, 8:1) to give compound **9** as a yellow oil (566 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1 H), 7.35 (m, 1 H), 7.00 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1 H), 6.96 (b, 1 H), 6.85 (d, J = 8.0 Hz,1 H), 4.54 (s, 2 H), 3.36 (m, 2 H), 3.32 (s, 1 H), 1.55 (m, 2 H), 1.39 (m, 2 H), 0.94 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 158.5, 134.0, 130.6, 121.9, 112.5, 111.8, 81.7, 79.8, 67.9, 38.7, 31.4, 20.0, 13.7; MS (ESI) m/z 232.2 $[M + 1]^+$. HRMS (EI) Calcd. for $C_{14}H_{17}N_1NaO_2$ $[M + Na]^+$: 254.11515. Found: 254.11557.

Compound 11. Isopropylamine (0.85 mL, 10 mmol) and Et_3N (2.7 mL, 20 mmol) were dissolved in CH_2Cl_2 (50 mL) and chilled with stirring in an ice−salt mixture. Then chloro-acetyl chloride (1 mL, 13 mmol) was added dropwise to the solution, and stirring was continued for 3 h in the ice−salt bath. The solution was then washed with water (20 mL) and brine (20 mL) and dried over sodium sulfate. After being concentrated, the crude product was purified by recrystallization (ethyl acetate/petroleum ether) to give compound **11** as a yellow powder (1.15 g, 85%): mp 50−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (b, 1 H), 4.10 (m, 1 H), 4.029 (s, 2 H), 1.21 (d, J = 6.4 Hz, 6 H); MS (ESI) m/z 136.0 $[M + 1]^+$.

Compound 12. Prepared in 68% yield as a yellow powder from the reaction of compounds **6** and **11** according to a procedure similar to that described for compound **7**: mp 55−56 °C; ^{1}H NMR (400 MHz, DMSO) δ (d, J = 7.6 Hz, 1 H), 7.13 (m, 1 H), 7.05 (m, 1 H), 7.00 (m, 2 H), 4.53 (s, 2 H), 3.92 (m, 1 H), 1.08 (d, J = 7.6 Hz, 6 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 166.9, 151.7, 129.3, 127.0, 123.4, 121.8, 115.5, 69.5, 41.7, 22.7 (2C); MS (ESI) m/z 257.0 $[M + Na]^+$. HRMS (EI) Calcd. for $C_{11}H_{14}N_4O_2$: 234.1117. Found: 234.1111.

Compound T2. Compound **9** (143 mg, 0.6 mmol), **12** (143 mg, 0.6 mmol), $CuSO_4{\cdot}5H_2O$ (14 mg, 0.056 mmol), sodium ascorbate (24 mg, 0.12 mmol), and TBTA (tris-(benzyl-triazolylmethyl)amine) (16 mg, 0.03 mmol) were placed in a two-neck flask, which was degassed under a high vacuum and backfilled with argon three times. THF (5 mL), methanol (5 mL), and water (5 mL) were added. The mixture was stirred about 12 h. After removal of the solvents under vacuo, the resulting residuum was dissolved in CH_2Cl_2 (80 mL). The solution was washed with water (30 mL × 2) and brine (30 mL × 2) and dried over sodium sulfate. After being concentrated, the crude product was purified by column chromatography (PE/EA, 1:4) to give compound **T2** as a white powder (241 mg, 87%): mp 122−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.97 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz,1 H), 7.64 (b, 1 H), 7.61 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 7.52 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 7.38 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.55 (d, J = 8.0 Hz, 1 H), 4.67 (s, 2 H), 4.56 (s, 2 H), 4.05 (m, 1 H), 3.33 (m, 2 H), 1.52 (m, 2 H), 1.29 (m, 2 H), 1.06 (d, J = 6.4 Hz, 6 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 166.2, 154.3, 150.7, 144.4, 131.6, 130.1, 128.9, 126.6, 126.4, 124.1, 122.6, 122.4, 119.4, 113.9, 112.9, 68.1, 68.0, 41.3, 39.1, 31.6, 22.5 (2C), 20.2, 13.8; MS (ESI) m/z 466.4 $[M + 1]^+$. Anal. Calcd. for $C_{25}H_{31}N_5O_4$: C, 64.50; H, 6.71; N, 15.04. Found: C, 64.65; H, 6.71; N, 15.13.

Compound 13. A solution of compound **7** (450 mg, 2.03 mmol) and $LiOH{\cdot}H_2O$ (168 mg, 4 mmol) in a 1:1 mixture of THF−H_2O (20 mL) was stirred at room temperature for 12 h. After removal of the organic solvents, water was added (5 mL), followed by the addition of hydrochloric acid until pH = 4. The resulting solid was filtrated and dried. The crude product was purified by recrystallization (ethyl acetate/n-hexane) to give compound **13** as a yellow powder (351 mg, 80%): mp 106−107 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.08 (m, 3 H), 6.86 (d, J = 7.2 Hz, 1 H), 4.74 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 149.5, 129.3, 125.6, 123.1, 120.6, 114.2, 65.8; MS (ESI) m/z 192.0 $[M - 1]^-$. HRMS (ESI) Calcd. for $C_8H_6N_3O_3$: 192.04146. Found: 192.04138.

Compound 14. A solution (in a sealed tube) of compound **13** (386 mg, 2 mmol), EDCI (499 mg, 2.6 mmol), DMAP (10 mg), aminomethane hydrochloride (675 mg, 10 mmol), and DIPEA (*N*,*N*-diisopropyl ethyl amine) (1.7 mL) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 12 h. The solution was then washed with saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$. After being concentrated, the crude product was purified by column chromatography (PE/EA, 2:1) to give compound **14** as a yellow power (125 mg, 30%): mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 3 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.78 (b, 1 H), 4.51 (s, 2 H), 2.92 (d, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 149.4, 128.8, 126.2, 123.1, 120.6, 114.4, 68.6, 25.9; MS (ESI) m/z 229.0 $[M + Na]^+$. HRMS (ESI) Calcd. for $C9H_{10}N_4O_2Na$ $[M + Na]^+$: 229.06960, Found: 229.06983.

Compound T3. Prepared in 96% yield as white powder from the reaction of compounds **9** and **14** according to a procedure similar to that described for compound **T2**: mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.96 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1 H), 7.65 (b, 1 H), 7.60 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz,1 H), 7.52 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz,1 H), 7.39 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1 H), 7.22 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.16 (t, J = 7.2 Hz, 1 H), 7.12 (d, J = 8.0 Hz, 1 H), 6.99 (d, J = 8.0 Hz, 1 H), 6.90 (b, 1 H), 4.67 (s, 2 H), 4.62 (s, 2 H), 3.35 (m, 2 H), 2.83 (d, J = 4.8 Hz, 3 H), 1.53 (m, 2 H), 1.31 (m, 2 H), 0.86 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 168.0, 154.1, 150.1, 143.9, 130.8, 129.6, 128.4, 126.5, 125.9, 124.5, 122.4, 122.1, 119.3, 113.8, 112.6, 68.0, 67.8, 38.9, 31.3, 25.7, 20.0, 13.6; MS (ESI) m/z 438.5 $[M + 1]^+$. HRMS (MALDI-TOF) Calcd. for $C_{23}H_{28}N_5O_4$: 438.2128. Found: 438.2136.

Compound 16. To a stirred solution of 3-chloropropanoic acid (1.08 g, 10 mmol) in ice−water (3 mL), a solution of NaOH (0.4 g, 10 mmol) in ice−water (3 mL) was added. The resulting cold solution was stirred for 30 min and added dropwise to a refluxing aqueous solution (4 mL) containing 9 mmol of sodium 2-iodophenolate (prepared from 1.98 g of 2-iodophenol and 0.4 g NaOH). After the addition was completed, the reaction mixture was refluxed for an additional 12 h. Upon being cooled to room temperature, the aqueous solution was washed with CH_2Cl_2 (5 mL × 3). The aqueous solution was then acidified to pH = 1 with dilute HCl and extracted with ether (20 mL × 2). The combined ether extracts were washed with water and brine and dried over sodium sulfate. After being concentrated, the crude product was purified by recrystallization (ethyl acetate/petroleum ether) to give compound **16** as a yellow powder (632 mg, 22%): mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 7.30 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 6.85 (d, J = 8.0 Hz, 1 H), 6.73 (t, J = 7.6 Hz, 1 H), 4.31 (t, J = 6.4 Hz, 2 H), 2.94 (t, J = 6.4 Hz, 2 H); MS (ESI) m/z 290.9 $[M - 1]^-$.

Compound 17. Compound **16** (584 mg, 2 mmol), $PdCl_2$ $(PPh_3)_2$ (42 mg, 0.06 mmol), and CuI (30 mg, 0.16 mmol) were placed in a two-neck flask, which was degassed under a high vacuum and backfilled with argon three times. Degassed THF (5 mL) and Et_3N (5 mL) were added and followed by the dropwise addition trimethylsilylacetylene (0.31 mL, 22 mmol). The reaction mixture was stirred for 12 h at room temperature. The solid was filtrated off, and the filtrate was concentrated with a rotavapor. The resulting residuum was dissolved in aqueous NaOH (1 M, 10 mL) and stirred for 5 min. The aqueous solution was then acidified to pH = 1 with dilute HCl and extracted with ether (20 mL × 2). The combined ether extracts were washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE/EA, 3:1) to give compound **17** as a yellow powder (211 mg, 55%): mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1 H), 7.30 (t, J = 8.0 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 6.92 (t, J = 8.0 Hz, 1 H), 4.34 (t, J = 5.6 Hz, 2 H), 3.25 (s, 1 H), 2.93 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 159.5, 134.2,130.2, 121.2, 112.2, 112.2, 81.4, 79.7, 64.2, 34.2; MS (ESI) m/z 189.0 $[M - 1]^-$. HRMS (ESI) Calcd. for $C_{11}H_9O_3$:189.05572. Found: 189.05599.

Compound 18. A solution (in a sealed tube) of compound **17** (190 mg, 1 mmol), EDCI (230 mg, 1.2 mmol), DMAP (10 mg), and 2-aminopropane (1.2 mL, 14 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 12 h. After being stirred an additional 12 h at room temperature, the solution was then washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. After being concentrated, the crude product was purified by chromatography (PE/EA, 2:1) to give compound **18** as a white powder (160 mg, 70%): mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 1 H), 7.32 (t, J = 7.2 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 1 H), 6.13 (b, 1 H), 4.28 (t, J = 6.0 Hz, 2 H), 4.09 (m, 1 H), 3.26 (s, 1 H), 2.69 (t, J = 5.2 Hz, 2 H), 1.15 (t, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 159.3, 134.2, 130.4, 121.0, 111.8, 111.4, 81.4, 80.2, 65.0, 41.5, 37.1, 29.7, 22.7, 22.7; MS (ESI) m/z 232.2 $[M + 1]^+$. HRMS (ESI) Calcd. for $C_{14}H_{17}N_1NaO_2$ $[M + Na]^+$: 254.11515. Found: 254.11566.

Compound 19. Prepared in 37% yield as a white powder from the reaction of compound **13** and aminoethane hydrochloride according to a procedure similar to that described for compound **14**: mp 54−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (m, 3 H), 6.90 (d, J = 7.6 Hz, 1 H), 6.76 (b, 1 H), 4.52 (s, 2 H), 3.41 (m, 2 H), 1.20 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 149.5, 128.7, 126.0, 123.0, 120.6, 114.3, 68.6, 34.0, 14.6; MS (ESI) m/z 243.1 $[M + Na]^+$. HRMS (ESI) Calcd. for $C_{10}H_{12}N_4O_2Na$ $[M + Na]^+$: 243.08576. Found: 243.08525.

Compound T4. Prepared in 84% yield as a white powder from the reaction of compounds **18** and **19** according to a procedure similar to that described for compound **T2**: mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 8.37 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1 H), 7.64 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.19 (t, J = 7.6 Hz, 1 H), 7.10 (m, 3 H), 7.03 (d, J = 8.4 Hz, 1 H), 5.74 (d, J = 6.4 Hz, 1 H), 4.58 (s, 2 H), 4.43 (t, J = 6.4 Hz, 2 H), 3.93 (m, 1 H), 3.30 (m, 2 H), 2.65 (t, J = 6.4 Hz, 2 H), 1.08 (t, J = 7.6 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 169.2, 167.4, 154.5, 150.5, 143.1, 130.7, 129.2, 128.0, 126.9, 126.2, 125.0, 122.5, 121.5 119.4, 113.9, 111.9, 68.2, 64.4, 41.5, 36.6, 34.2, 22.4 (2C), 14.4; MS (ESI) m/z 452.5 $[M + 1]^+$. HRMS (ESI) Calcd. for $C_{24}H_{30}N_5O_4$: 452.22923. Found: 452.22996.

Compound 21. A solution of Boc-Glycine (5.26 g, 30 mmol), EDCI (6.91 g, 36 mmol), DMAP (50 mg), and *n*-butylamine (3 mL) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 h. The solution was then washed with saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$. After being concentrated, the crude product was purified by column chromatography (PE/EA, 2:1) to give compound **21** as a colorless oil (4.83 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (b, 1 H), 5.28 (b, 1 H), 3.75 (d, J = 6.4 Hz, 2 H), 3.24 (q, J = 6.4 Hz, 2 H), 1.47 (m, 2 H), 1.43 (s, 9 H), 1.26 (m, 2 H), 0.90 (t, 3 H).

Compound 22. A solution of **21** (553 mg, 2.4 mmol) and trifluoroacetic acid (1.9 mL, 24 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 6 h. Upon removal of the solvents under vacuo, the resulting residuum was dissolved in CH_2Cl_2 (25 mL). Compound **8** (418 mg, 2.4 mmol), EDCI (600 mg. 3.1 mmol), DMAP (20 mg), and DIPEA (1.2 mL) were added into the solution and stirred for 12 h at room temperature. The solution was then washed with saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$. After being concentrated, the crude product was purified by column chromatography (PE/EA, 3:1) to give compound **22** as a white powder (500 mg, 73%): mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (b, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.34 (t J = 7.6 Hz, 1 H), 7.01 (t J = 7.6 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 5.93 (b, 1 H), 4.60 (s, 2 H), 4.01 (d, J = 5.6 Hz, 2 H), 3.43 (s, 1 H), 3.27 (q, J = 6.8 Hz, 2 H), 1.49 (m, 2 H), 1.34 (m, 2 H), 0.92 (t, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.0, 158.3, 134.0, 130.5, 122.2, 112.5, 112.2, 82.5, 79.3, 67.7, 43.1, 39.4, 31.5, 20.0, 13.7; MS (ESI) m/z 289.2 $[M + 1]^+$. HRMS (ESI) Calcd. for $C_{16}H_{21}N_2O_3$: 289.15467. Found: 289.15546.

Compound 24. Prepared in 85% yield from the reaction of Boc-L-Leu-OH (**23**) and isopropylamine according to a procedure similar to that described for compound **21**: mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.6 Hz, 1 H), 6.71 (d, J = 8.4 Hz, 1 H), 3.89 (m, 1 H), 3.80 (m, 1 H), 1.56 (m, 1 H), 1.37 (m, 11 H), 1.03 (dd, J_1 = 10 Hz, J_2 = 6.4 Hz, 6 H), 0.85 (t, J = 7.2 Hz, 6 H); MS (ESI) m/z 273.3 $[M + 1]^+$.

Compound 25. Prepared in 85% yield as a yellow powder from the reaction of compounds **13** and **24** according to a procedure similar to that described for compound **22**: mp 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (m, 4 H), 6.90 (d, J = 8.0 Hz, 1 H), 5.86 (d, J = 7.6 Hz 1 H), 4.55 (s, 2 H), 4.43 (m, 1 H), 4.04 (m, 1 H), 1.73 (m, 1 H), 1.61 (m, 2 H), 1.14 (m,6 H), 0.94 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.1, 149.5, 129.4, 126.1, 123.5, 120.7, 115.0, 68.9, 51.7, 41.7, 41.0, 24.9, 23.0, 22.8, 22.7, 22.2; MS (ESI) m/z 348.2 $[M + 1]^+$. Anal. Calcd. for $C_{17}H_{25}N_5O_3$: C, 58.77; H, 7.25; N, 20.16. Found: C, 58.75; H, 7.30; N, 19.99.

Compound T5. Prepared in 82% yield as white powder from the reaction of compounds **22** and **25** according to a procedure similar to that described for compound **T2**: mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1 H), 8.27 (d, J = 7.6 Hz, 1 H), 8.06 (t, J = 4.2 Hz, 1 H), 7.8 (d, J = 8 Hz, 1 H), 7.45 (t, J = 8 Hz, 1 H), 7.35 (t, J = 7.6 Hz, 2 H),7.19 (m, 2 H), 7.09 (d, J = 8 Hz, 1 H), 6.97 (d, J = 8 Hz, 1 H), 6.52 (m, 1 H), 6.38 (d, J = 8 Hz, 1 H), 4.72 (d, J = 2.8 Hz, 2 H), 4.62 (dd, J_1 = 48.4 Hz, J_2 = 14 Hz, 2 H), 4.29 (m, 1 H), 4.00 (t, J = 6.4 Hz, 2 H), 3.93 (m, 1 H), 3.13 (m, 2 H), 1.37 (m, 7 H), 1.10 (t, J = 6.8 Hz, 6 H), 0.86 (t, J = 7.2 Hz, 3 H), 0.73 (dd, J_1 = 14.8 Hz, J_2 = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.4, 168.9, 168.1, 154.2, 150.0, 143.4, 130.6, 129.5, 128.8, 127.0, 126.2, 125.2, 122.7, 122.6, 120.0, 113.8, 112.6, 68.4, 68.2, 52.0, 43.2, 41.7, 40.7, 39.4, 31.5, 24.8, 22.8, 22.6, 22.5, 21.9, 20.1, 13.8; MS (ESI) m/z 636.4 $[M + 1]^+$. Anal. Calcd. For $C_{33}H_{45}N_7O_6$: C, 62.34; H, 7.13; N, 15.42. Found: C, 62.13; H, 7.26; N, 15.30.

■ ASSOCIATED CONTENT

Supporting Information

Thermal ellipsoid plot of the crystal structure of compound **T1** and CIF file, copies of additional ^{1}H NMR and 2D COSY and NOESY ^{1}H NMR spectra. Copies of ^{1}H NMR and ^{13}C NMR spectra of the new compounds. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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