JOC The Journal of Organic Chemistry

Article

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Helical Peptide-Foldamers Having a Chiral Five-Membered Ring Amino Acid with Two Azido Functional Groups

Makoto Oba,[†] Hiroomi Takazaki,[‡] Naomi Kawabe,[‡] Mitsunobu Doi,[§] Yosuke Demizu,[∥] Masaaki Kurihara,[∥] Hiromu Kawakubo,[⊥] Masanobu Nagano,[‡] Hiroshi Suemune,[‡] and Masakazu Tanaka*[,†]

[†]Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bukyo-machi, Nagasaki 852-8521, Japan

[‡]Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan

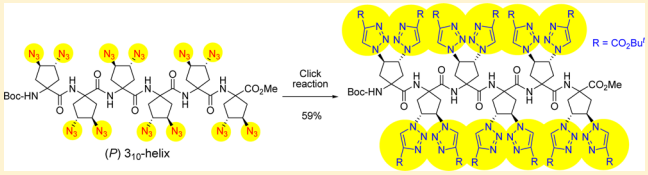
[§]Osaka University of Pharmaceutical Sciences, Osaka 569-1094, Japan

[∥]Division of Organic Chemistry, National Institute of Health Sciences, Tokyo 158-8501, Japan

[⊥]Department of Pharmaceutical Sciences, Nihon Pharmaceutical University, Saitama 362-0806, Japan

Supporting Information

ABSTRACT: A chiral five-membered ring α,α-disubstituted α-amino acid (R,R)-Ac$_5$c^{dN3} having two azido functional groups has been designed and synthesized. The cyclic amino acid (R,R)-Ac$_5$c^{dN3} could be efficiently converted into several cyclic amino acids with various two 1,2,3-triazole functional groups. (R,R)-Ac$_5$c^{dN3} homochiral peptides (up to hexapeptide) and (R,R)-Ac$_5$c^{dN3}-containing L-Leu-based peptides were prepared, and their conversion of azido functional groups into triazole groups was completed. The preferred conformation of oligomers, before and after the "click reaction", together with the azido *gauche* effect of amino acid residues were studied using FT-IR absorption, CD, ^{1}H NMR, and X-ray crystallographic analysis. The cyclic amino acid (R,R)-Ac$_5$c^{dN3} could be used as a helical conformation controlling residue and also has a versatile functionalizing site in its oligopeptides.



INTRODUCTION

Foldamers are any oligomers folding into well-defined three-dimensional structures.[1] Various helical foldamers, such as β-peptides,[1] peptoids,[2] arene-oligomers,[3] and urea-oligomers,[4] have been reported to date. α,α-Disubstituted α-amino acid-containing peptides (foldamers) are reported to form 3_{10}-helices, α-helices, and fully planar extended structures.[5−7] Recently, we have reported that homochiral oligopeptides composed of a chiral five-membered ring α,α-disubstituted α-amino acid, (3*S*,4*S*)-1-amino-3,4-(dimethoxy)cyclopentanecarboxylic acid $\{(S,S)$-Ac$_5$c$^{dOM}\}$, having two methoxy functional groups, in which chiral centers exist at the side chain of the amino acid, but not at the α-carbon atom, preferentially formed one-handed helical secondary structures.[8,9] In this case, one helical-screw direction was exclusively controlled by the side-chain chiral centers at Cγ-carbons with a methoxy group. On the other hand, we reported that homopeptides composed of a chiral bicyclic amino acid, (1*R*,6*R*)-8-aminobicyclo[4.3.0]non-3-ene-8-carboxylic acid $\{(R,R)$-Ab$_{5,6=}$c$\}$, having only side-chain chiral centers at the fused-ring junctions formed both diastereomeric right-handed and left-handed helices (Figure 1).[10] We also reported helical structures of two series of diastereomeric homochiral homopeptides composed of chiral five-membered ring amino acids with one methoxy group at the cyclopentane side chain, and the helical-screw control was dependent on the length of their peptides.[11]

Here, we designed and synthesized a chiral five-membered ring amino acid with two azido functional groups at the side chain, (3*R*,4*R*)-1-amino-3,4-(diazido)cyclopentanecarboxylic acid $\{(R,R)$-Ac$_5$c$^{dN3}\}$ (Figure 1).[12] The azido functional group is known to preferentially form a *gauche* conformation (azido *gauche* effect), like the fluoro *gauche* effect (Figure 2).[13,14] Thus, the cyclopentane ring envelope conformation may be different from that of (S,S)-Ac$_5$c^{dOM} with a dimethoxy group, and cyclopentane conformational differences may affect the secondary structure of its peptides. We reasoned that the azido functional group in the cyclic amino acid is capable of converting into several 1,2,3-triazole groups by the Huisgen 1,3-dipolar cycloaddition reaction.[15] Thus, we envisaged that the cyclic amino acid (R,R)-Ac$_5$c^{dN3} could be not only a helical conformational controlling moiety but also a versatile functionalizable site. We also demonstrated that the (R,R)-Ac$_5$c^{dN3} homochiral homohexapeptide preferentially formed a one-handed helical secondary structure, and the "click conversion" of 12 azido functional groups of the (R,R)-Ac$_5$c^{dN3} hexapeptide into 12 triazole groups was possible. Furthermore, we incorporated the (R,R)-Ac$_5$c^{dN3} into L-Leu-based peptides, demonstrated the conversion of the azido functions of (R,R)-Ac$_5$c^{dN3} residues into triazole groups, and studied the preferred secondary structures of their peptides

Received: July 7, 2014
Published: September 2, 2014

   dx.doi.org/10.1021/jo501493x | *J. Org. Chem.* 2014, 79, 9125−9140

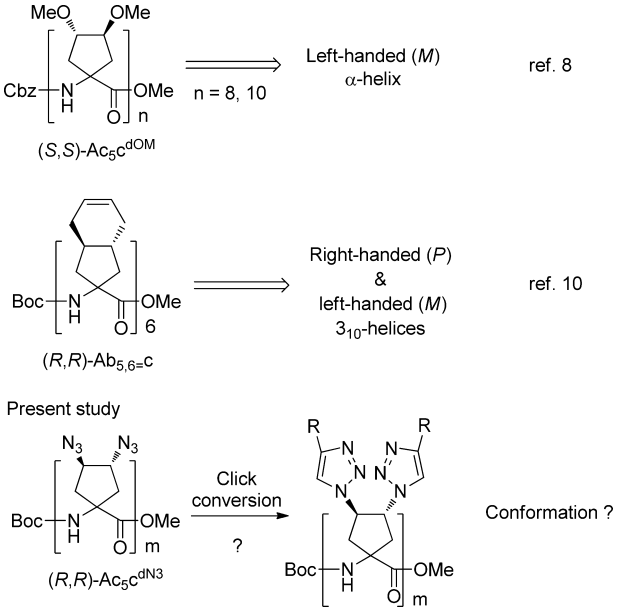


Figure 1. Chiral cyclic amino acid containing peptides and their conformation.

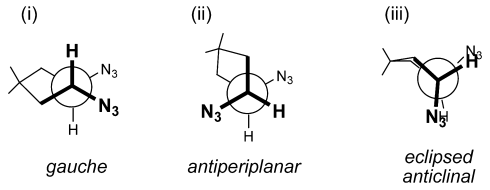


Figure 2. Newman projection of a cyclopentane ring in amino acid residue (*R*,*R*)-Ac$_5$c^{dN3}.

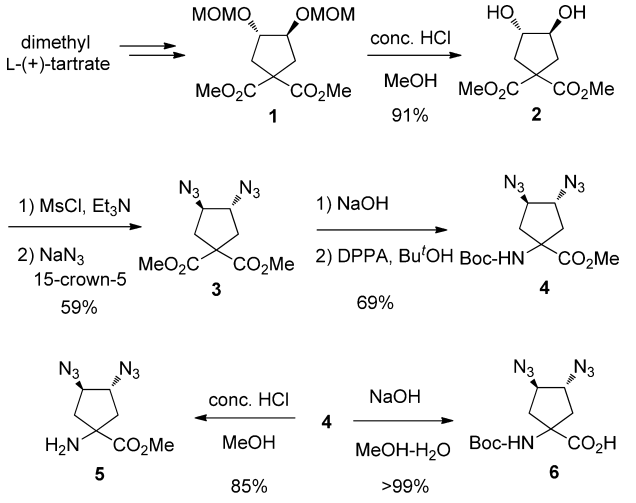
using FT-IR absorption, CD, ^{1}H NMR, and X-ray crystallographic analyses.

RESULTS AND DISCUSSION

Synthesis of a Chiral Five-Membered Ring Amino Acid with Two Azido Functional Groups, Its Homochiral Homopeptides, and Its L-Leu-Based Heteropeptides. A chiral cyclic amino acid (*R*,*R*)-Ac$_5$c^{dN3} was synthesized starting from dimethyl L-tartrate, as follows: First, dimethyl L-tartrate was converted into a cyclic diester **1** by previously reported procedures.[8] Deprotection of methoxymethyl (MOM) ether in **1** gave a diol **2**, which was converted into a diazido compound **3** at a 59% yield by mesylation and subsequent substitution with sodium azide. Monohydrolysis of diester **3**, followed by Curtius rearrangement with diphenylphosphoryl azide (DPPA)[16] in *t*-BuOH produced a cyclic amino acid Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}-OMe **4** at a 69% yield. Deprotection of the N-terminal Boc-protecting group under acidic conditions gave an N-terminal free H-{(*R*,*R*)-Ac$_5$c^{dN3}}-OMe **5** at an 85% yield, and alkaline hydrolysis of ester produced a C-terminal free Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}-OH **6** at a quantitative yield (Scheme 1).

(*R*,*R*)-Ac$_5$c^{dN3} homochiral homopeptides were prepared by solution-phase methods as follows: Dipeptide Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_2$-OMe **7** was prepared by the coupling of amine **5** and carboxylic acid **6** at an 85% yield using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) hydrochloride, 1-hydroxybenzotriazole (HOBt), and Et$_3$N in CH$_3$CN at room temperature. Alkaline hydrolysis of dipeptide **7** with aqueous NaOH gave a C-terminal free dipeptide Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_2$-OH **8** in quantitative yield, and deprotection of the Boc-protecting group produced an N-terminal free dipeptide H-{(*R*,*R*)-Ac$_5$c^{dN3}}$_2$-OMe **9** at an 85% yield. Coupling between the dipeptide acid **8** and the amine **9** gave a tetrapeptide **10** at a low yield (25%) because 2,5-dioxopiperazine **11** was obtained as a byproduct at a 44% yield. Such 2,5-dioxopiperazine formation was already observed when we attempted to synthesize a tetrapeptide composed of a cyclic amino acid with a monomethoxy group.[11] Thus, dipeptide **7** was elongated to tripeptide **12** at a 52% yield by coupling of the dipeptide acid **8** and the amine **5**. Tripeptide acid **13** and amine **14** were prepared in a manner similar to those described for the preparation of **8** and **9**, and the coupling between them gave a homochiral homohexapeptide, Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_6$-OMe **15**, at a 48% yield. The five-membered ring of the cyclic amino acid does not strongly hamper the coupling reaction like *α*-ethylated amino acids, in which the ethyl substituents severely hinder the coupling reaction; the coupling reaction of ethylated amino acid requires very severe reaction conditions.[7] Also, we prepared (*R*,*R*)-Ac$_5$c^{dN3}-containing heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe (**16**: *n* = 1; **17**: *n* = 2; **18**: *n* = 3; **19**: *n* = 4) by tripeptide-fragment condensation using solution-phase methods. The spectroscopic data of all synthetic compounds supported the proposed chemical structures (Scheme 2).

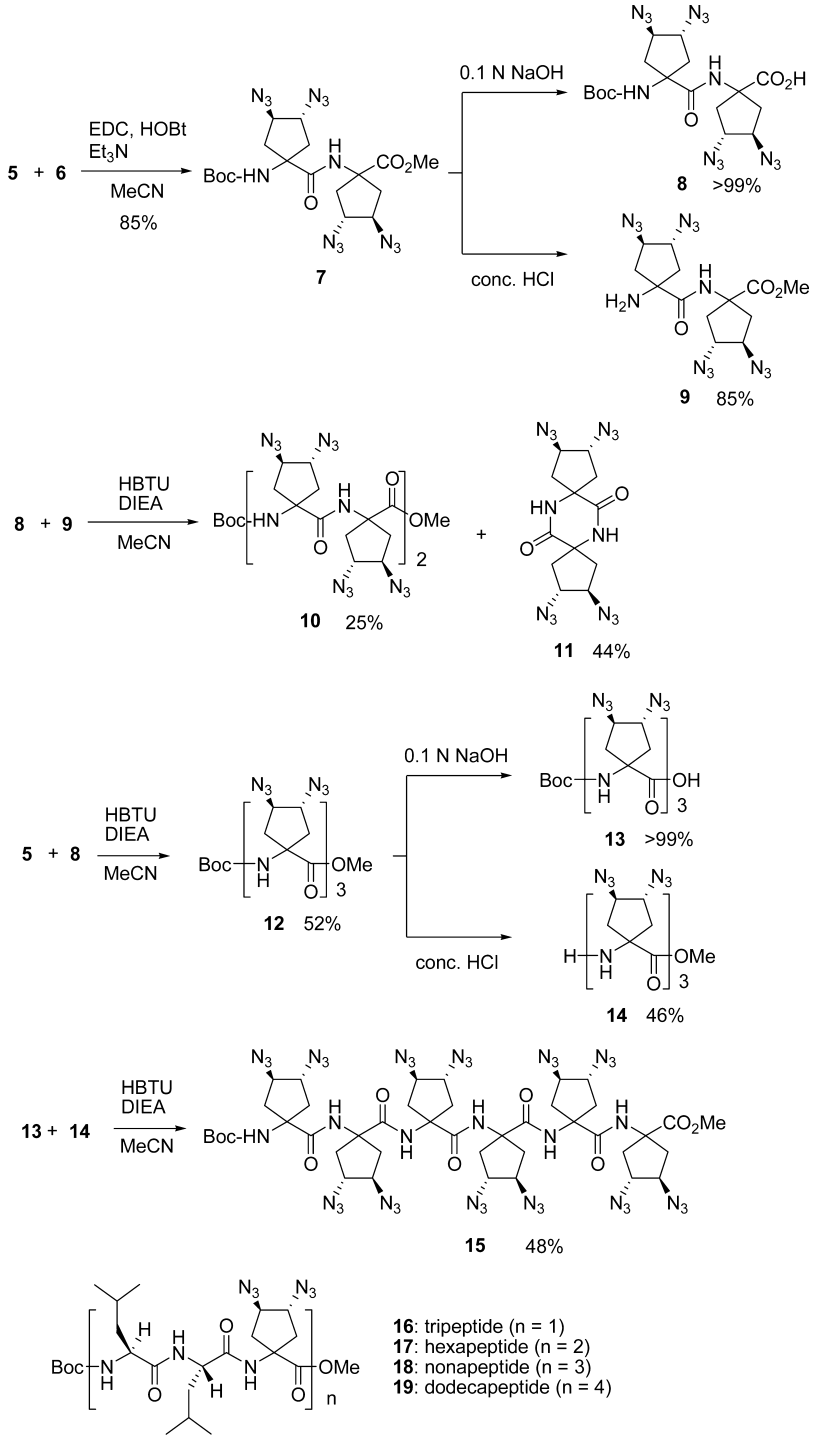
Scheme 1



"Click Reaction" of a Side-Chain Azido Functional Group into Triazole Functional Group. The cyclic amino acid Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}-OMe **4** was subjected to "click reaction" conditions to convert the side-chain azido functional groups into 1,2,3-triazole functional groups. That is to say, cyclic amino acid **4** was treated with various alkynes (6−10 equiv) in the presence of CuSO$_4$ and sodium ascorbate in *t*-BuOH/H$_2$O (2:1) solution.[15] The results are summarized in Table 1. All alkynes in Table 1 were suitable for the 1,3-dipole cycloaddition reaction, although the reaction of *tert*-butylethyne with a bulky *t*-Bu substituent (in entry 2) did not proceed at room temperature, but did proceed at 110 °C to give di(triazole) product **20b** at an 84% yield. In the IR spectra of products **20a**−**e**, the absorption of the azido functional group at around 2100 cm^{-1} disappeared, and in the ^{1}H NMR spectra, the methine proton signals derived from triazole appeared at *δ* 7.20−8.23 (each s, 2H) and the methine proton signals at *γ*- and *δ*-carbons bearing the triazole appeared at *δ* 5.47−5.94 (m,

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

Scheme 2



2H). In addition, the molecular ion peak ($M^+ + H$) in the MS spectra supported the triazole structures. The isolated products were di(1,2,3-triazole) products but not (monotriazole)-(monoazido) products. These results may be attributed to the fact that an intermediate, a monotriazole−Cu−alkyne complex, intramolecularly reacted with another azido group of a monotriazole intermediate, as Finn and co-workers reported.[15b] The nuclear Overhauser and exchange spectroscopy (NOESY) ^{1}H NMR spectra of triazole products **20b**,**c**,**e** showed correlations between the triazole methine proton and the proton signals at β- and ϵ-carbons of the cyclopentane side chain, suggesting that the regiochemistry of products is of 1,4-substituted adducts, but not 1,5-substituted adducts.[17] The regioselectivity of 1,4-substituted triazole adduct formation may be due to steric repulsion between the alkyne substituent and the cyclopentane skeleton arising if an intermediate corresponding to 1,5-adduct formation occurs.

Next, we examined the "click reaction" of the azido group in peptides. The (*R*,*R*)-Ac$_5$c^{dN3} homopeptides **7**, **10**, and **15** and heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe (n = 2 and 3) **17** and **18** were treated with *tert*-butyl propiolate (or methyl propiolate) in the presence of $CuSO_4$ and sodium

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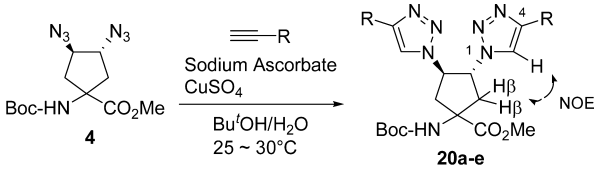
Table 1. "Click Conversion" of Side-Chain Azido Functions of a Cyclic Amino Acid



entry[a]	R =	reaction time (h)	yield (%)
1	Ph	24	**20a**: quantitative
2	*t*-Bu	48	**20b**: 84[b]
3	CO_2CH_3	40	**20c**: 74
4	$COCH_3$	24	**20d**: 83
5	CO_2-*t*-Bu	24	**20e**: 85

[a]Amino acid **4** (1.0 equiv), substituted alkyne (6−10 equiv), sodium ascorbate (0.5 equiv), and $CuSO_4$ (0.5 equiv) in *t*-BuOH/H_2O were reacted. [b]Reaction was performed at 110 °C.

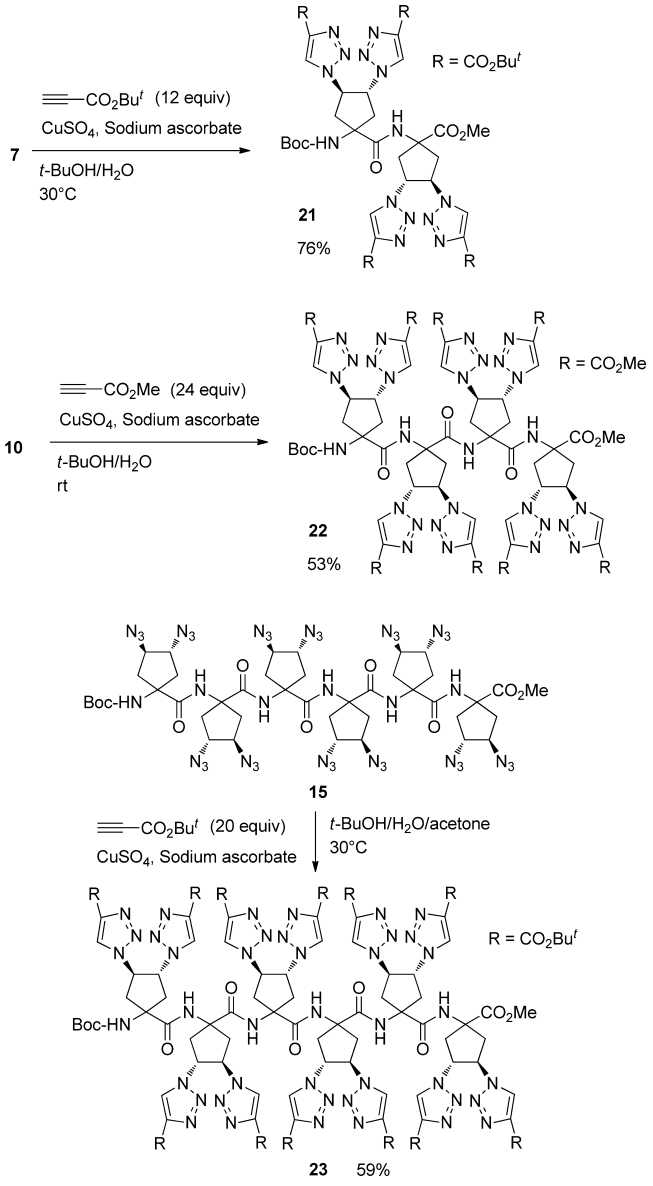
ascorbate. All azido functional groups in the five peptides were converted into triazole groups under these reaction conditions, and the products Boc-{(*R*,*R*)-$Ac_5c^{d\text{-triazole}}$}$_n$-OMe ($n$ = 2, 4 and 6) **21** (76%), **22** (53%), and **23** (59%) and Boc-[L-Leu-L-Leu-{(*R*,*R*)-$Ac_5c^{d\text{-triazole}}$}]$_n$-OMe ($n$ = 2 and 3) **24** (quantitative) and **25** (75%) were isolated, respectively (Schemes 3 and 4).

The ^{1}H NMR spectra of dipeptide **21** in $CDCl_3$, tetrapeptide **22** in acetone-d_6, and hexapeptide **23** in CD_3CN showed triazole methine proton signals and the corresponding side-chain ester proton signals, although the ^{1}H NMR spectra of **22** and **23** measured in $CDCl_3$ gave broadened proton signals. The IR spectra of **21**−**23** indicated the disappearance of azido absorption at around 2100 cm^{-1}. Also, the molecular ion peaks m/z 1023.5 (M^+ + H) in **21**, 1577.5 (M^+ + H) in **22**, and 2827.3 (M^+ + H + Na) in **23** in the MS spectra supported the respective triazole structures. It is noteworthy that 12 azido functional groups in (*R*,*R*)-Ac_5c^{dN3} homochiral hexapeptide **15** were converted into 12 triazole groups in hexapeptide **23** by the "click reaction" with *tert*-butyl propiolate. The (*R*,*R*)-Ac_5c^{dN3} hexapeptide **15** formed a 3_{10}-helical structure, in which azido groups are located at the lateral surface of the helix (vide infra), so the azido groups are not sterically hindered and can react with alkyne. The chemical structures of heteropeptides **24** and **25** with triazole functions were determined by the occurrence of triazole methine protons at δ 8.00−8.70 (m, 4H in **24**, and 6H in **25**) in the ^{1}H NMR spectra, disappearance of the azido absorption at around 2100 cm^{-1} in the IR spectra, and molecular ion peaks m/z 1497.8 (M^+ + Na) in **24** and 2169.1 (M^+ + Na) in **25** in the MS spectra. Wennemers reported that 4-azidoproline could be efficiently converted into triazole−proline in the peptide state by the "click reaction".[13a−c] On the other hand, we demonstrated here that two azido groups in the cyclic amino acid residue in peptides could be converted into two triazole groups and that azido groups in cyclic amino acid homohexapeptide could be changed into triazole functional groups in a one-pot reaction.

Conformational Analyses of Homopeptides and L-Leu-Based Heteropeptides in Solution. First, the preferred secondary structures of homo- and heteropeptides were studied by FT-IR absorption spectra. Figure 3 and Figure S2 (Supporting Information)[17] show the IR absorption spectra of (*R*,*R*)-Ac_5c^{dN3} homo- and heteropeptides Boc-{(*R*,*R*)-Ac_5c^{dN3}}$_n$-OMe [n = 1 (**4**), 2 (**7**), 3 (**12**), 4 (**10**), 6 (**15**)] and Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac_5c^{dN3}}]$_n$-OMe [n = 1 (**16**), 2 (**17**), 3 (**18**), 4 (**19**)] and also (*R*,*R*)-$Ac_5c^{d\text{-triazole}}$ homohexa- and heteropeptides Boc-{(*R*,*R*)-$Ac_5c^{d\text{-triazole}}$}$_6$-OMe **23** and Boc-[L-Leu-L-Leu-{(*R*,*R*)-$Ac_5c^{d\text{-triazole}}$}]$_n$-OMe [$n$ = 2 (**24**), 3 (**25**)] in the 3500−3250 cm^{-1} (N−H stretching) region. The IR absorption spectra were measured at a peptide concentration of 5.0 mM in $CDCl_3$ solution, except for homopeptide Boc-{(*R*,*R*)-$Ac_5c^{d\text{-triazole}}$}$_6$-OMe **23**, which was measured in CD_3CN solution because the solubility of the peptide in $CDCl_3$ was poor.

In the IR absorption spectra of (*R*,*R*)-Ac_5c^{dN3} homopeptides (Figure 3a), the weak bands at 3420−3440 cm^{-1} region are assigned to free (solvated) peptide NH groups. The strong band (peptide NH groups with N−H···O=C intramolecular hydrogen bonds) observed at the 3350 cm^{-1} region in tripeptide **12** shifts to slightly lower wavenumbers (3320 cm^{-1} in **15**) as the peptide-chain length increases, and the relative intensity of the bands at 3320−3350 cm^{-1} gradually increases. These IR absorption spectra are very similar to those of helical α-aminoisobutyric acid (Aib) homopeptides[18] and cyclopentanecarboxylic acid (Ac_5c) homopeptides[19] but are

Scheme 3



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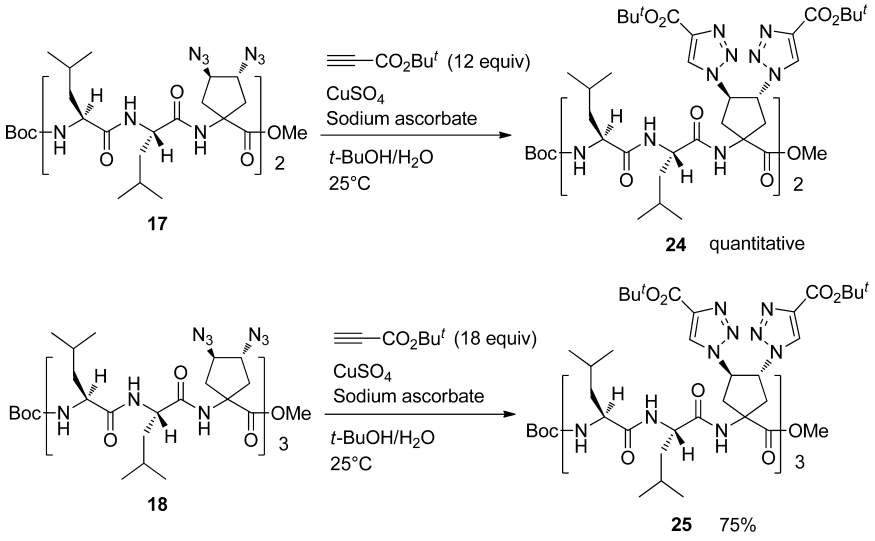
Scheme 4



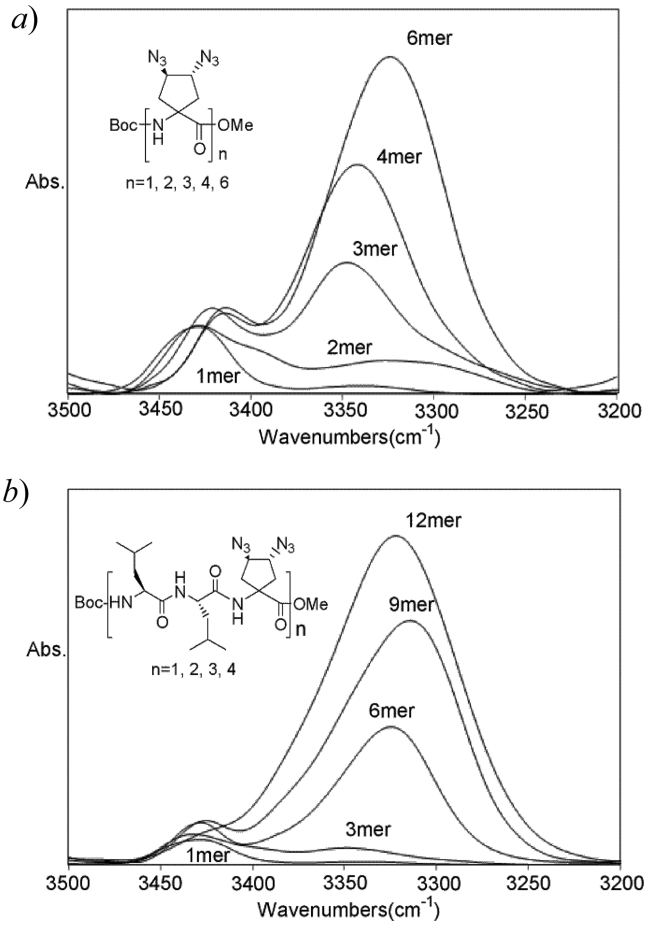


Figure 3. Infrared (IR) absorption spectra in the N−H stretching region: (a) Boc-{(*R*,*R*)-Ac_5c^{dN3}}$_n$-OMe, [**4** (*n* = 1), **7** (2), **12** (3), **10** (4), **15** (6)] in $CDCl_3$; (b) Boc-(*R*,*R*)-Ac_5c^{dN3}-OMe and Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac_5c^{dN3}}]$_n$-OMe [**16** (*n* = 1), **17** (2), **18** (3), **19** (4)] in $CDCl_3$. Peptide concentration: 5.0 mM.

different from those of fully extended planar diethylglycine (Deg) homopeptides[7] and (*S*)-butylethylglycine (Beg) peptides.[7c,d] Also, the IR absorption spectra of L-Leu-based heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac_5c^{dN3}}]$_n$-OMe (*n* = 1−4) are very similar to those of helical peptides (Figure 3b). The IR absorption spectra of homohexapeptides **15** and **23** in CD_3CN before and after the "click reaction" are shown in Figure S2a (Supporting Information).[17] These FT-IR absorption spectra are similar, suggesting helical conformations. The weak band in the 3420−3440 cm^{-1} region in $CDCl_3$ disappeared in CD_3CN solution. This result may be due to a (solvent) CN···H−N (peptide) hydrogen bond interaction.[20] The bands at 3320−3325 cm^{-1} in Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac_5c^{dN3}}]$_n$-OMe (*n* = 2, 3) **17** and **18** shifted slightly to lower wavenumbers in Boc-[L-Leu-L-Leu-{(*R*,*R*)-$Ac_5c^{d\text{-triazole}}$}]$_n$-OMe (*n* = 2, 3) **24** and **25** (Figure S2b and S2c, Supporting Information).[17] The FT-IR absorption spectra of (*R*,*R*)-Ac_5c^{dN3} and (*R*,*R*)-$Ac_5c^{d\text{-triazole}}$ heteropeptides showed a similar shape and thus suggested a helical conformation.

In the ^1H NMR measurements, solvent perturbation experiments by the addition of a strong H-bond acceptor solvent DMSO-d_6 (0−10% (v/v)) or the paramagnetic free radical 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO; 0−5 × 10^{-2} % (w/v)) were performed for the (*R*,*R*)-Ac_5c^{dN3} hexapeptide **15** in $CDCl_3$ solution (Figure 4).[18a,b] In the ^1H NMR spectrum of **15**, the N(1)H signal at the N-terminus

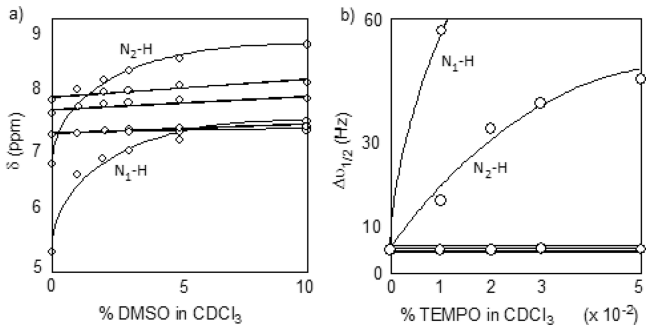


Figure 4. Plots of N−H chemical shifts and bandwidth of the N−H protons in the ^1H NMR spectra of homochiral (*R*,*R*)-Ac_5c^{dN3} hexapeptide **15**. (a) Plots of N−H chemical shifts as a function of an increasing percentage of DMSO-d_6 (v/v) added to the $CDCl_3$ solution. (b) Plots of bandwidth of the N−H protons as a function of increasing percentage of TEMPO (w/v) added to the $CDCl_3$ solution. Peptide concentration: 1.0 mM.

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

could be unambiguously determined by its high-field positions at δ 5.48, due to its urethane structure,[21] but the remaining five NH protons could not be assigned at this stage (see text). Two NH chemical shifts of **15** were sensitive (solvent-exposed NH group) to the addition of perturbing reagent DMSO-d_6, and also the bandwidth of two NH proton signals broadened by the addition of a TEMPO radical. These results mean that the two NH protons are solvent-exposed, suggesting that they are not intramolecularly hydrogen-bonded and are in accord with a 3_{10}-helical structure, where two NH groups at the N-terminus of the peptide are solvated (not intramolecularly hydrogen-bonded).

The NOESY and/or the rotating frame nuclear Overhauser and exchange spectroscopy (ROESY) ^{1}H NMR spectra of (*R*,*R*)-Ac$_5$c^{dN3} homochiral tetrapeptide **10**, hexapeptide **15**, and heteropeptides having (*R*,*R*)-Ac$_5$c^{dN3} **17**, **18**, and **19** were measured in $CDCl_3$ solution. Generally, sequential NH dipolar interactions [d_{NN} ($i \rightarrow i + 1$)] are used to diagnose helical structures. To discriminate between a 3_{10}- and an α-helical conformation, the NOE constraint [$d_{\alpha N}$ ($i \rightarrow i + 2$)] is characteristic of the 3_{10}-helical structure, and the NOE constraint [$d_{\alpha N}$ ($i \rightarrow i + 4$)] is characteristic of α-helical structure, respectively.[22] The NOESY ^{1}H NMR spectrum of (*R*,*R*)-Ac$_5$c^{dN3} homochiral tetrapeptide **10** showed a complete series of sequential NH dipolar interactions [d_{NN} ($i \rightarrow i + 1$)] from the N-terminal N(1)H to the N(4)H (Figure S3, Supporting Information).[17] The ROESY ^{1}H NMR spectrum of hexapeptide **15** showed a series of sequential NH dipolar interactions [d_{NN} ($i \rightarrow i + 1$)] from the N-terminal N(1)H to the N(5)H. Although the interaction d_{NN} (5→ 6) was not seen, the series of sequential NOE cross peaks suggest the helical structure of **15** (Figure 5). In the (*R*,*R*)-Ac$_5$c^{dN3} homopeptides **10** and **15**, there was no hydrogen at the α-carbon atom, so we could not discriminate between a 3_{10}- or an α-helical conformation.

The ROESY ^{1}H NMR spectra of (*R*,*R*)-Ac$_5$c^{dN3} heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe (n = 2,3,4)

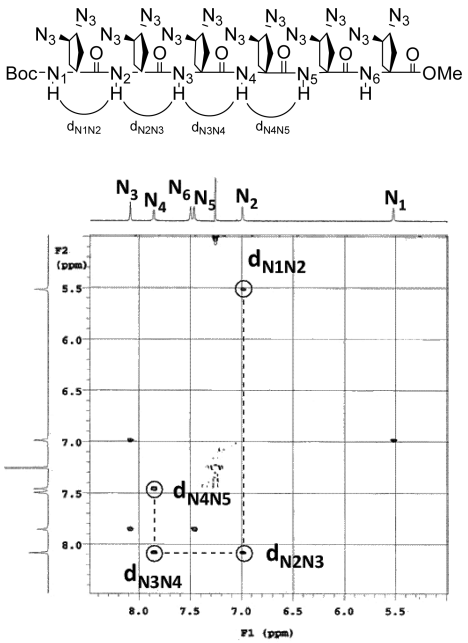


Figure 5. ROESY ^{1}H NMR spectrum of (*R*,*R*)-Ac$_5$c^{dN3} hexapeptide **15**.

17−**19**, from hexapeptide to dodecapeptide, showed a complete series of sequential dipolar interactions [d_{NN} NH ($i \rightarrow i + 1$)] from the N-terminal NH to the C-terminal NH, suggesting helical secondary structures in the $CDCl_3$ solution (Figure S4, Supporting Information,[17] and Figure 6). In hexapeptide **17**, two NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 2$); i = 2 and 4] were observed, and these results suggest the existence of a 3_{10}-helical conformation. Also, two NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 2$); i = 1 and 4] were found in the nonapeptide **18**, suggesting the existence of a partial 3_{10}-helical conformation.[17] The ROESY ^{1}H NMR spectrum of dodecapeptide **19** showed five NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 2$); i = 1, 2, 5, 7, and 10] characteristic of the 3_{10}-helical structure and also three NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 4$); i = 2, 5, and 8] characteristic of the α-helical structure.[22] These results suggested that the (*R*,*R*)-Ac$_5$c^{dN3} dodecapeptide **19** formed a mixture of 3_{10}- and α-helical conformation segments in $CDCl_3$ solution (Figure 6).

The ROESY ^{1}H NMR spectrum of the (*R*,*R*)-Ac$_5$c$^{d\text{-triazole-Me}}$ homochiral tetrapeptide **22** in acetone-d_6 solution showed a series of sequential NH dipolar interactions [d_{NN} ($i \rightarrow i + 1$)] from the *N*-terminal N(1)H to the *C*-terminal N(4)H, suggesting a helical conformation (Figure S5, Supporting Information).[17] Thus, the preferred conformation of homochiral tetrapeptides before and after "click conversion" may be similar to wholly helical structures of the peptide backbone, although small conformational changes cannot be excluded. The 2D ^{1}H NMR spectra of (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ hexapeptide **23** in $CDCl_3$, CD_3CN, or in acetone-d_6 solution did not give good NOE correlations because overlap of NH signals with triazole methine proton signals occurred, and broadening of signals was also observed.

The ROESY ^{1}H NMR spectra of (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ heteropeptides **24** and **25** with triazole functional groups in $CDCl_3$ solution are shown in Figure S6 (Supporting Information)[17] and Figure 7. The ROESY ^{1}H NMR spectrum of the (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ hexapeptide **24** showed partial dipolar interactions [d_{NN} ($i \rightarrow i + 1$); i = 4 and 5] but did not show dipolar interactions [d_{NN} ($i \rightarrow i + 1$); i = 1−3]. Furthermore, the ROESY spectrum showed two NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 2$); i = 2 and 4], suggesting the existence of a partial 3_{10}-helical conformation (Figure S6, Supporting Information).[17] The ROESY ^{1}H NMR spectrum of (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ heterononapeptide **25** showed a complete series of sequential dipolar interactions [d_{NN} NH ($i \rightarrow i + 1$)] from the N-terminal NH to the C-terminal NH, suggesting a helical secondary structure in the $CDCl_3$ solution, although NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 2$) or $d_{\alpha N}$ ($i \rightarrow i + 4$)] could not be analyzed due to the overlap of the proton signals (Figure 7).

The CD spectra of (*R*,*R*)-Ac$_5$c^{dN3} and/or (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ homochiral homopeptides, and heteropeptides were measured in 2,2,2-trifluoroethanol (TFE) solution. Neither (*R*,*R*)-Ac$_5$c^{dN3} homochiral hexapeptide **15** nor (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ hexapeptide **23** showed characteristic maxima of a one-handed helical-screw structure (Figure S8, Supporting Information).[17] These results may be attributed to the fact that the peptide lengths are not enough for one-handed helices or the interference of azido and triazole functional groups.[17] On the other hand, (*R*,*R*)-Ac$_5$c^{dN3} heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe, hexa-, nona-, and dodecapeptides **17**−**19** showed characteristic negative maxima of right-handed (*P*) helical structures, although hexapeptide **17** showed a blue-shift with a weak negative maximum at 205 nm. Tripeptide **16** did not show characteristic maxima for helical structures. Judging from the *R*

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

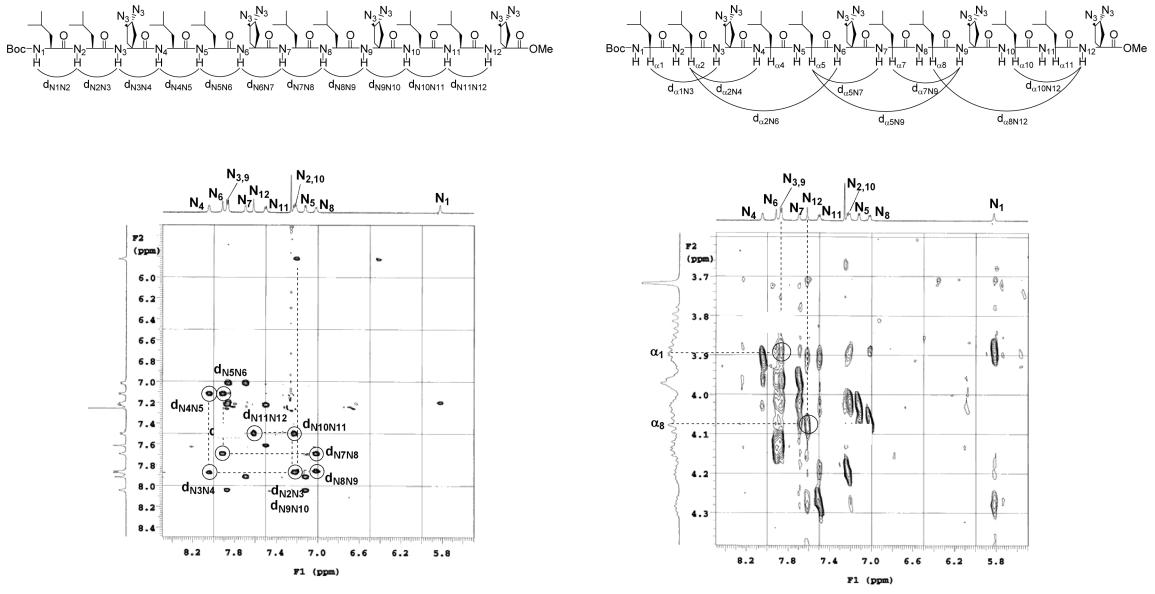


Figure 6. ROESY ^{1}H NMR spectrum of (*R*,*R*)-Ac$_5$c^{dN3} heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_4$-OMe (**19**).

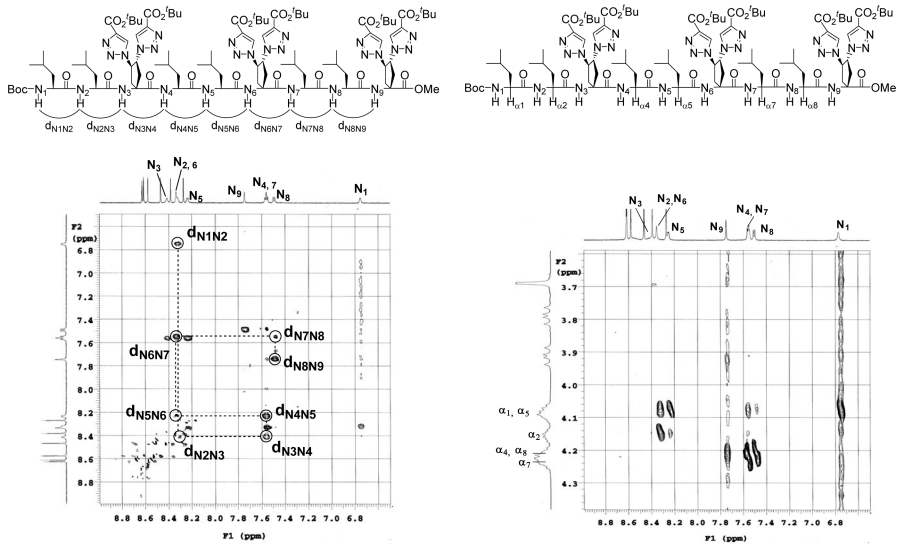


Figure 7. ROESY ^{1}H NMR spectrum of the (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ heteropeptide Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$}]$_3$-OMe (**25**).

values, hexapeptide **17** seemed to partially form a 3_{10}-helix (ratio of maxima: $\theta_{222}/\ \theta_{205}$; 0.28), and nona- and dodecapeptides **18** and **19** form α-helices (ratio of maxima: $\theta_{222}/\ \theta_{208}$; 0.83 for **18** and 0.96 for **19**) in TFE solution (Figure 8).[23] The length of hexapeptide **17** may be not long enough to perfectly control the peptide-backbone helix to one-handedness in solution. The right-handed (*P*) helical-screw sense of heteropeptides **18** and **19** may be controlled by the chiral centers of L-Leu residues because these heteropeptides have 66% L-Leu content in the sequences, and the helical screw bias of side-chain chiral centers is not as strong as those of the α-carbon chiral centers.[24] Two NOE constraints [$d_{\alpha N}$ ($i \rightarrow i + 2$)] of nonapeptide **18** in the ROESY ^{1}H NMR spectrum indicated the existence of a 3_{10}-helical conformation, but the *R* value of **18** in the CD spectrum suggested an α-helical conformation in the whole structure. These differences may be attributed to the fact that the solvents used for the CD measurement (TFE) and ^{1}H NMR measurement ($CDCl_3$) were different. In general, it is believed that TFE is a helix inductive solvent, and peptides

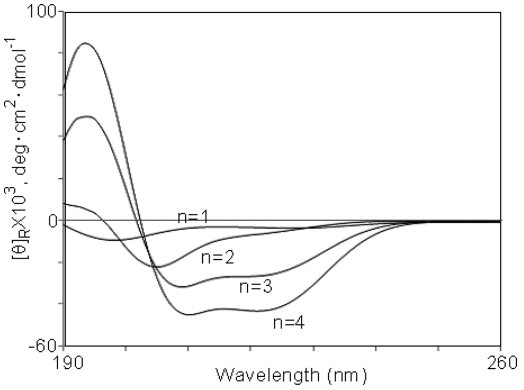


Figure 8. CD spectra of Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe [*n* = 1 (**16**), 2 (**17**), 3 (**18**), 4 (**19**)] in TFE solution. Peptide concentration 0.1 mM.

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

become more α-helical in a more polar TFE solution than in $CDCl_3$ solution.

Figure 9 shows the CD spectra of heteropeptides before and after the "click reaction", that is to say, (*R*,*R*)-Ac$_5$c^{dN3} and

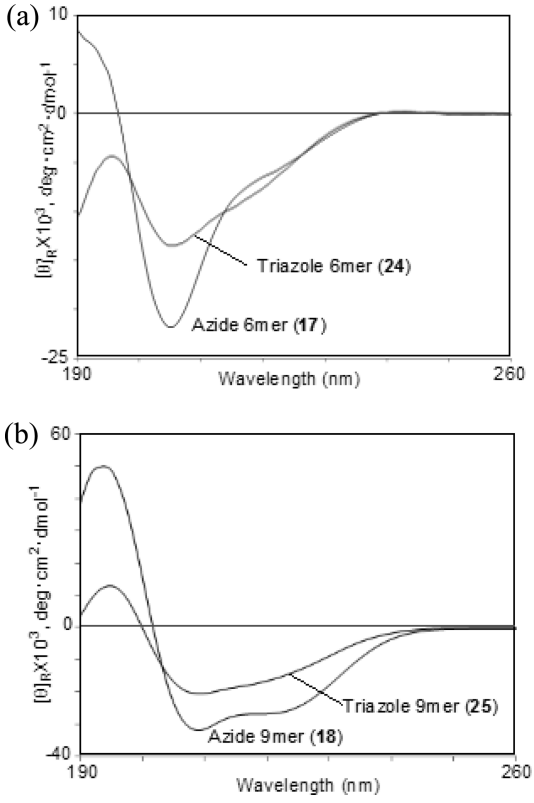


Figure 9. CD spectra of heteropeptides before and after the "click reaction": (a) Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_2$-OMe **17** and Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$}]$_2$-OMe **24**; (b) Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_3$-OMe **18** and Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$}]$_3$-OMe **25**. Peptide concentration 0.1 mM in TFE.

(*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ heteropeptides Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe [n = 2 (a) and 3 (b)]. Conversion of the azido functional group into a triazole group weakened the intensity of negative maxima both in the hexapeptide and nonapeptide. In particular, the CD spectra suggested that the content of the right-handed α-helicity percentage decreased following the change of (*R*,*R*)-Ac$_5$c^{dN3} into (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ in nonapeptide **25**, although the chromophore of the azido and triazole functional groups may directly affect the CD spectra of their peptides.[17]

Structures of the (*R*,*R*)-Ac$_5$c^{dN3} Homochiral Hexapeptide and (*R*,*R*)-Ac$_5$c^{dN3} Heteropeptides in the Crystal State. X-ray crystallographic analyses unambiguously revealed the molecular structures and conformations of the terminally protected (*R*,*R*)-Ac$_5$c^{dN3}-containing oligomers in the crystal state. The (*R*,*R*)-Ac$_5$c^{dN3} homochiral hexapeptide **15**, and the (*R*,*R*)-Ac$_5$c^{dN3} heteropeptides **17**, **18**, and **19** provided crystals suitable for X-ray crystallographic analysis following slow evaporation of the solvent at room temperature (**15**, **18**, and **19** from MeOH-acetone, and **17** from MeOH). Crystal and diffraction parameters of **15**, **17**, **18**, and **19** are summarized in Table S1 (Supporting Information).[17,25,26] The molecular structures are given in Figures 10 and 11. Relevant backbone and side-chain torsion angles and the intra- and intermolecular

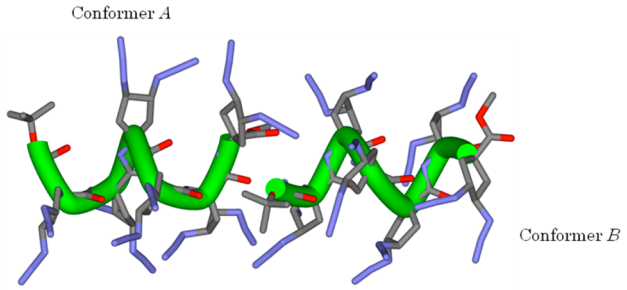


Figure 10. 3$_{10}$-Helical secondary structures of Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_6$-OMe (**15**) determined by X-ray crystallographic analysis.

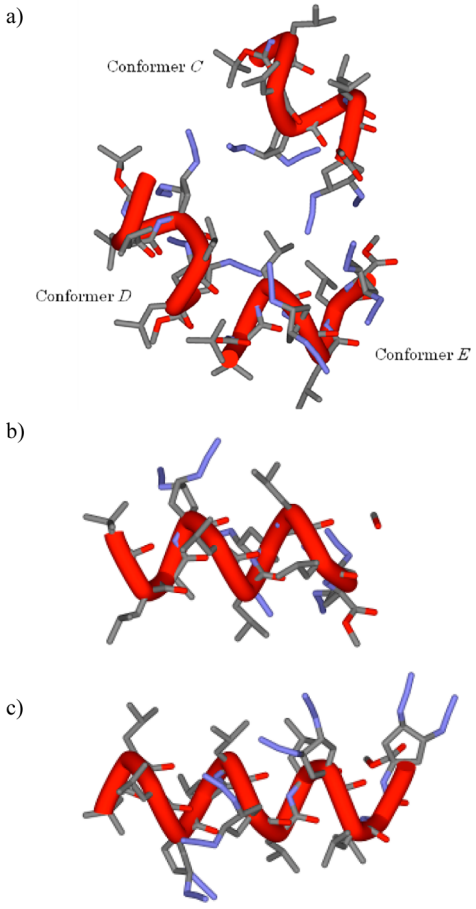


Figure 11. Helical secondary structures of Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_n$-OMe (**17**–**19**), determined by X-ray crystallographic analysis: (a) hexapeptide (**17**), (b) nonapeptide (**18**), (c) dodecapeptide (**19**).

hydrogen-bond parameters are listed in Tables 2 and 3. Unfortunately, we could not obtain good crystals of (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ peptides for X-ray crystallographic analysis by recrystallization of purified samples from several solvents.

In the asymmetric unit of homochiral hexapeptide Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_6$-OMe (**15**), two crystallographically independent conformers *A* and *B* occurred (Figure 10). Both conformers *A* and *B* were right-handed (*P*) 3$_{10}$-helical structures, showing negative signs for the ϕ and ψ torsion angles at each amino acid residue, except for the C-terminal residue. The signs of the C-terminal residue (6) ϕ and ψ torsion angles (51.4°, 45.0° for *A*, and 51.9°, 43.1° for *B*) were opposite (positive) to those of the preceding residues (1–5; negative). This phenomenon is

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125–9140

Table 2. Selected Torsion Angles ω, ϕ, and ψ (deg) for 15, 17, 18, and 19, As Determined by X-ray Crystallographic Analysis

	15		17				
torsion angle	*A*	*B*	*C*	*D*	*E*	**18**	**19**
$\theta 0$	164.4	151.8	−179.3	−168.9	−176.0	159.0	148.0
ω_0	−168.9	−175.8	−175.7	179.8	−173.8	−178.5	−172.2
ϕ_1	−67.7	−58.5	−54.3	−67.8	−64.5	−76.4	−57.9
ψ_1	−28.3	−40.5	−38.1	−13.7	−24.1	−38.9	−48.8
ω_1	−175.5	−169.1	−173.9	171.9	175.7	−178.7	−174.5
ϕ_2	−63.4	−61.0	−63.1	−56.8	−58.6	−72.3	−65.7
ψ_2	−14.5	−25.7	−30.5	−33.3	−29.9	−40.3	−37.1
ω_2	172.5	179.8	175.2	−179.4	−178.9	176.3	179.1
ϕ_3	−53.8	−51.8	−55.8	−59.0	−56.7	−51.7	−59.5
ψ_3	−26.2	−39.3	−44.2	−36.5	−41.2	−53.0	−52.3
ω_3	−178.0	−171.6	−177.4	−179.5	−179.1	−176.6	−177.4
ϕ_4	−56.0	−61.0	−73.3	−79.5	−79.5	−61.6	−64.9
ψ_4	−24.5	−21.3	−38.1	−47.0	−39.6	−41.5	−39.4
ω_4	−178.7	179.0	−179.5	−179.2	−179.2	−179.9	−179.1
ϕ_5	−56.1	−56.4	−60.9	−59.8	−61.6	−62.8	−63.3
ψ_5	−30.5	−33.2	−41.1	−49.4	−54.6	−42.4	−43.4
ω_5	179.0	177.3	176.1	174.4	174.9	−179.5	178.0
ϕ_6	51.4	51.9	55.7	48.0	46.5	−56.1	−56.4
ψ_6	45.0	43.1	38.1	48.5	45.6	−41.1	−49.0
ω_6	175.0	−177.3	179.4	−178.6	−178.2	−178.8	−176.4
ϕ_7						−71.4	−64.6
ψ_7						−47.7	−47.7
ω_7						−173.1	−179.0
ϕ_8						−72.4	−56.5
ψ_8						−45.5	−44.0
ω_8						173.2	−177.0
ϕ_9						56.2	−57.2
ψ_9						42.8	−41.8
ω_9						162.1	−173.1
ϕ_{10}							−85.5
ψ_{10}							−18.1
ω_{10}							−179.7
ϕ_{11}							−95.3
ψ_{11}							−30.5
ω_{11}							−167.3
ϕ_{12}							63.9
ψ_{12}							26.9
ω_{12}							−173.1

frequently observed in the 3_{10}-helical peptide esters of α-aminoisobutyric acid (Aib) and related residues.[27] The average values of torsion angles ϕ and ψ of amino acid residues (1−5) were −59.4°, −24.8° in conformer *A*, and −57.7°, −32.0° in conformer *B*. These torsion angles are in good agreement with the ideal torsion angles (−60°, −30°) of the (*P*) 3_{10}-helical structure.[28] The two conformers *A* and *B* had generally similar peptide-backbone structures, but showed differences in the conformation of the cyclopentyl side chain and azido groups (Figure S9, Supporting Information).[17]

Four consecutive intramolecular hydrogen bonds of $i \leftarrow i + 3$ type (i = 0−3), which correspond to the 3_{10}-helical structure, were found in each conformer. Conformer *A* showed four intramolecular hydrogen bonds between the H−N(3a) and C(0a)═O(0a) O atom of the Boc-group, between the H−N(4a) and C(1a)═O(1a), between the H−N(5a) and C(2a)═O(2a), and between the H−N(6a) and C(3a)═O(3a). Similarly, conformer *B* showed four intramolecular hydrogen bonds between the H−N(3b) and C(0b)═O(0b), between the H−N(4b) and C(1b)═O(1b), between the H−N(5b) and C(2b)═O(2b), and between the H−N(6b) and C(3b)═O(3b).[17]

The crystal structure of heteropeptide Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac_5c^{dN3}}]$_2$-OMe (**17**) was solved in the space group *P*1 (Figure 11a). Three crystallographically independent conformers *C*, *D*, and *E* occurred in the asymmetric unit. All conformers were folded into right-handed (*P*) helical structures. All three conformers showed negative signs for the ϕ and ψ torsion angles at each amino acid residue, except for the C-terminal residue [(*R*,*R*)-Ac_5c^{dN3} (6) positive ϕ, ψ: 55.7°, 38.1° for *C*, 48.0°, 48.5° for *D*, and 46.5°, 45.6° for *E*)]. The average values of torsion angles ϕ and ψ of amino acid residues (1−5) were −61.5°, −38.4° in conformer *C*, −64.6°, −36.0° in conformer *D*, and −64.2°, −37.9° in conformer *E*, respectively. The three molecules showed similar peptide-backbone conformation, but small differences in isobutyl Leu side chain and azido functional groups (Figure S10, Supporting Information).[17]

Two intramolecular hydrogen bonds of the $i \leftarrow i + 3$ type, which correspond to the 3_{10}-helical structure, were shown

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

Table 3. Intra- and Intermolecular H-Bond Parameters for 15, 17, 18, and 19

peptide	donor D−H	acceptor A	distance (Å) D···A	angle (deg) D−H···A	symmetry operations
Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_6$-OMe (**15**)[a]					
A (*P*)	N_{3a}−H	O_{0a}	3.14	164	*x*, *y*, *z*
	N_{4a}−H	O_{1a}	2.97	169	*x*, *y*, *z*
	N_{5a}−H	O_{2a}	2.92	164	*x*, *y*, *z*
	N_{6a}−H	O_{3a}	2.99	155	*x*, *y*, *z*
B (*P*)	N_{3b}−H	O_{0b}	3.15	147	*x*, *y*, *z*
	N_{4b}−H	O_{1b}	2.97	151	*x*, *y*, *z*
	N_{5b}−H	O_{2b}	3.02	155	*x*, *y*, *z*
	N_{6b}−H	O_{3b}	3.05	151	*x*, *y*, *z*
	$N_{1a'}$−H	O_{5b}	2.92	170	3/2−*x*, 1−*y*, −1/2+*z*
	$N_{2a'}$−H	O_{6b}	3.09	137	3/2−*x*, 1−*y*, −1/2+*z*
	N_{1b}−H	O_{5a}	2.86	171	*x*, *y*, *z*
	N_{2b}−H	O_{6a}	3.28	150	*x*, *y*, *z*
Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_2$-OMe (**17**)					
C (*P*)	N_{3c}−H	O_{0c}	3.13	136	*x*, *y*, *z*
	N_{4c}−H	O_{1c}	2.94	123	*x*, *y*, *z*
	N_{5c}−H	O_{1c}	2.92	160	*x*, *y*, *z*
	N_{6c}−H	O_{2c}	3.05	164	*x*, *y*, *z*
D (*P*)	N_{3d}−H	O_{0d}	3.04	155	*x*, *y*, *z*
	N_{4d}−H	O_{1d}	2.96	131	*x*, *y*, *z*
	N_{5d}−H	O_{1d}	2.94	174	*x*, *y*, *z*
	N_{6d}−H	O_{2d}	2.89	163	*x*, *y*, *z*
E (*P*)	N_{3e}−H	O_{0e}	3.00	148	*x*, *y*, *z*
	N_{4e}−H	O_{1e}	2.98	131	*x*, *y*, *z*
	N_{5e}−H	O_{1e}	3.04	166	*x*, *y*, *z*
	N_{6e}−H	O_{2e}	2.89	159	*x*, *y*, *z*
	N_{1d}−H	$O_{5c'}$	2.85	151	*x*−1, *y*+1, *z*
	N_{2d}−H	$O_{4c'}$	3.12	158	*x*−1, *y*+1, *z*
	N_{1c}−H	$O_{5e'}$	2.92	165	*x*, *y*, *z*−1
	N_{2c}−H	$O_{4e'}$	3.02	177	*x*, *y*, *z*−1
	N_{1e}−H	O_{5d}	2.86	169	*x*, *y*, *z*
	N_{2e}−H	O_{4d}	2.97	167	*x*, *y*, *z*
Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_3$-OMe (**18**)[b]					
(*P*)	N_5−H	O_1	2.99	155	*x*, *y*, *z*
	N_6−H	O_2	2.92	165	*x*, *y*, *z*
	N_7−H	O_3	3.20	153	*x*, *y*, *z*
	N_8−H	O_4	2.97	164	*x*, *y*, *z*
	N_9−H	O_5	2.81	159	*x*, *y*, *z*
	N_1−H	$O_{8'}$	2.80	139	*x*, *y*, *z*−1
	$N_{3'}$−H	O′ (MeOH)	2.92	159	*x*, *y*, *z*+1
	MeO−H	O_7	2.88	130	*x*, *y*, *z*
Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_4$-OMe (**19**)[c]					
(*P*)	N_4−H	O_0	3.14	173	*x*, *y*, *z*
	N_5−H	O_1	2.87	160	*x*, *y*, *z*
	N_6−H	O_2	3.05	166	*x*, *y*, *z*
	N_7−H	O_3	3.14	164	*x*, *y*, *z*
	N_8−H	O_4	2.84	170	*x*, *y*, *z*
	N_9−H	O_5	2.98	161	*x*, *y*, *z*
	N_{11}−H	O_7	2.93	133	*x*, *y*, *z*
	N_{12}−H	O_8	2.98	143	*x*, *y*, *z*
	N_1−H	$O_{10'}$	2.90	160	−*x*+1, −1/2+*y*, 1/2−*z*
	N_2−H	$O_{11'}$	2.91	159	−*x*+1, −1/2+*y*, 1/2−*z*

[a]Distance of N_{2b}-H···O_{6a} (3.28 Å) in **15** is slightly too long for an intermolecular hydrogen bond. [b]Distance of N_4−H···O_0 (3.37 Å) in **18** is too long for an intramolecular hydrogen bond.[5a,29] [c]Distance of N_{10}-H···O_6 (3.32 Å) in **19** is too long for an intramolecular hydrogen bond. The N_3−H in **19** does not participate in any hydrogen bonding interaction.[5a,29]

between the H−N(3) and C(0)═O(0) (*c*, *d*, *e*), and between the H−N(4) and C(1)═O(1) (*c*, *d*, *e*). In addition, two intramolecular hydrogen bonds of the $i \leftarrow i + 4$ type, which correspond to the α-helical structure, were observed between the H−N(5) and C(1)═O(1) (*c*, *d*, *e*) and between the H−N(6) and C(2)═O(2) (*c*, *d*, *e*). The O atom of C(1)═O(1) acted as a double-acceptor of hydrogen bonds from the H−N(4) and H−N(5) groups. These results mean that the N-

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

Table 4. Side-Chain Azido N−C−C−N Torsion Angles (deg) for 15, 17, 18, and 19, As Determined by X-ray Crystallographic Analysis

	15		17				
N−C−C−N torsion angle	*A*	*B*	*C*	*D*	*E*	**18**	**19**
residue 1	−77.3	−122.4					
residue 2	−73.5	−166.2					
residue 3	−78.1	−74.9	−159.0	−112.0	−153.0	−168.0	−108.2
residue 4	−81.2	−116.6					
residue 5	−163.3	−163.8					
residue 6	−75.0	−69.0	−73.0	−69.2	−75.0	−101.0	−80.0
residue 9						−70.0	−81.6
residue 12							−99.0

terminus forms a 3_{10}-helical structure and the C-terminus forms an α-helical structure. These results are slightly different from those of the ROESY ^{1}H NMR spectrum (3_{10}-helix) and the CD spectrum (not perfect right-handed helix). This is because the single crystals for X-ray analysis were obtained by recrystallization from MeOH, and the ^{1}H NMR and CD spectra were measured in $CDCl_3$ and TFE, respectively.[30] The right-handed (*P*) 3_{10}- and α-helical conformer in the crystal state was slightly different from the α-helices of Cbz-[L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_2$-OMe having dimethoxy groups in the crystal state, where the N-terminal hydrogen bonds of the $i \leftarrow i + 3$ type were not observed or were weak.[24] The different results may be attributed to the fact that the recrystallizing solvents (MeOH vs MeOH/H_2O),[30] the stereochemistry of side-chain chiral centers (*RR* vs *SS*), and the substituents ($-N_3$ vs −OMe) were different between hexapeptide **17** and the (*S*,*S*)-Ac$_5$c^{dOM}-containing L-Leu-based hexapeptide.

The nonapeptide Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_3$-OMe (**18**) was folded into one right-handed (*P*) α-helical structure, along with a methanol molecule in an asymmetric unit (Figure 11b). Disorder of the azido functional group at residue (*R*,*R*)-Ac$_5$c^{dN3} (3) was observed. The molecule showed negative signs of the ϕ and ψ torsion angles from residue L-Leu (1) to L-Leu (8). The C-terminal (*R*,*R*)-Ac$_5$c^{dN3} (9) residue (ϕ, ψ = 56.2°, 42.8°) showed positive signs for ϕ and ψ torsion angles, which are opposite those of the preceding residues (1−8). The mean values of the ϕ and ψ torsion angles of the amino acid residues (1−8) were −65.6° and −43.8°, close to the ideal right-handed (*P*) α-helix (−60° and −45°).[28] Five intramolecular hydrogen bonds, in which each hydrogen bond formed a 13-membered (atoms) pseudoring of the $i \leftarrow i + 4$ type corresponding to the α-helical conformation, existed in the crystal state. That is to say, five successive intramolecular hydrogen bonds between H−N(5) and C(1)═O(1), between H−N(6) and C(2)═O(2), between H−N(7) and C(3)═O(3), between H−N(8) and C(4)═O(4), and between H−N(9) and C(5)═O(3) were observed. However, the distance of H−N(4)···O(0) (3.37 Å) was too long for an intramolecular hydrogen bond.[29,17]

The dodecapeptide Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_4$-OMe (**19**) was solved in space group $P2_12_12_1$ to give a right-handed (*P*) α-helical structure (Figure 11c). Disorders of the side-chain isobutyl groups at residues L-Leu (8), L-Leu (10), and L-Leu (11) were observed. The signs for the ϕ and ψ torsion angles from residues L-Leu (1) to L-Leu (11) were negative, but the signs of the torsion angles at the C-terminal (*R*,*R*)-Ac$_5$c^{dN3} (12) residue were positive. The average values of the ϕ and ψ torsion angles of amino acid residues (1−11) were −66.0° and −41.1°, close to the ideal right-handed (*P*) α-helix (−60° and −45°).[28] Eight intramolecular hydrogen bonds of $i \leftarrow i + 4$ type, corresponding to the α-helical conformation, were observed. That is to say, six consecutive intramolecular hydrogen bonds between H−N(4) and C(0)═O(0), between H−N(5) and C(1)═O(1), between H−N(6) and C(2)═O(2), between H−N(7) and C(3)═O(3), between H−N(8) and C(4)═O(4), and between H−N(9) and C(5)═O(1) were observed. The distance of N(10)···O(6) (3.32 Å) was too long for an intramolecular hydrogen bond.[5a,29] In addition, intramolecular hydrogen bonds between H−N(11) and C(7)═O(7) and between H−N(12) and C(8)═O(8) were observed.[17]

The right-handed (*P*) α-helices of **18** and **19** in the crystal state are in accordance with the results of the CD spectra but are different from those of the ROESY ^{1}H NMR spectra, which suggested a mixture of 3_{10}- and α-helical segment conformation. These results may also be attributed to the fact that the solvents used for analyses were different. The (*R*,*R*)-Ac$_5$c^{dN3}-containing L-Leu-based peptides preferentially formed a (*P*) α-helix and/or a mixture of (*P*) $3_{10}/\alpha$-helix segment conformation. Thus, the α-helix-induced property of the cyclic amino acid (*R*,*R*)-Ac$_5$c^{dN3} was similar to that of the cyclic amino acid Ac$_5$c^{dOM}, but different from that of Aib (at least from what we know so far), which induces a 3_{10}-helix.

Wennemers reported that the azido group in the pyrrolidine ring could be used as a conformation-directing element by the "azido *gauche* effect" (Figure 2).[13a] Thus, we were interested in the "azido *gauche* effect" and conformation of the cyclopentane ring. Table 4 shows the N−C−C−N torsion angles of the (*R*,*R*)-Ac$_5$c^{dN3} residues in peptides **15**, **17**, **18**, and **19** determined by X-ray crystallographic analysis. Of the 25 (*R*,*R*)-Ac$_5$c^{dN3} amino acid residues, 13 N−C−C−N torsion angles showed *gauche*, *synclinal* (−30° ∼ −90°) conformations. This result may be attributed to the "azido *gauche* effect" because the corresponding O−C−C−O torsion angles of (*S*,*S*)-Ac$_5$c^{dOM} peptides did not preferentially form *gauche* conformations (Table S2, Supporting Information).[17] However, six N−C−C−N torsion angles of (*R*,*R*)-Ac$_5$c^{dN3} showed *antiperiplanar* (−150° to −180°) conformations, and interestingly, the other six N−C−C−N torsion angles did not become *staggered* conformation, but rather *eclipsed anticlinal* (−90° to −150°) conformations. In the *eclipsed anticlinal* conformation, the quaternary Cα carbon became the flap of the envelope cyclopentane conformation, and this quaternary Cα carbon at the envelope flap may prefer to form the *eclipsed anticlinal* conformation. These results are in accordance with the O−C−C−O torsion angles of the (*S*,*S*)-Ac$_5$c^{dOM} residue, in which *eclipsed anticlinal* conformations were preferred.[17] No apparent correlation between the N−C−C−N (−) *synclinal* conformation and ring puckering was observed.

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

CONCLUSION

We synthesized a chiral five-membered ring α,α-disubstituted α-amino acid (*R*,*R*)-Ac_5c^{dN3} with two azido groups and prepared (*R*,*R*)-Ac_5c^{dN3}-containing oligopeptides. The cyclic amino acid (*R*,*R*)-Ac_5c^{dN3} could be converted to several cyclic amino acids (*R*,*R*)-$Ac_5c^{d\text{-}triazole}$ with two 1,2,3-triazole groups by the "click reaction". Also, the "click conversion" of (*R*,*R*)-Ac_5c^{dN3} homopeptides and (*R*,*R*)-Ac_5c^{dN3}-containing L-Leu-based heteropeptides was demonstrated. X-ray crystallographic analyses unambiguously confirmed the "azido *gauche* effect" and revealed 3_{10}- and α-helical structures of peptide foldamers with poly azido functional groups. In addition, it was revealed that the property of (*R*,*R*)-Ac_5c^{dN3} was to form α-helix over 3_{10}-helix, like the cyclic amino acid (*R*,*R*)-Ac_5c^{dOM} α-helix-forming property, although an α- or a 3_{10}-helix depends on the peptide main-chain length. Therefore, the cyclic amino acid (*R*,*R*)-Ac_5c^{dN3} in peptides acted as not only a helix-inducing moiety but also a versatile functionalizable site. No such peptide foldamers have been found previously, and helical organocatalysts based on cyclic amino acids are currently being designed by our group.[31]

EXPERIMENTAL SECTION

General Methods. Methyl (3*S*,4*S*)-3,4-bis(methoxymethoxy)-1-(methoxycarbonyl)cyclopentanecarboxylate (**1**) was prepared from dimethyl L-(+)-tartrate according to the previously reported methods.[8] Optical rotations $[\alpha]_D$ were measured using a 1.0 dm cell. Circular dichroism spectra (CD) were measured using a 1.0 mm path length cell. Infrared spectra (IR) were recorded for conventional measurement (KBr), and the solution ($CDCl_3$) method using 0.1 mm path length of an NaCl cell. ^{1}H NMR spectra were determined at 400 or 500 MHz. HRMS(FAB) spectra were taken in dual-focusing sector field mode, and HRMS(ESI) spectra were measured in TOF mode.

Methyl (3*S*,4*S*)-3,4-Dihydroxy-1-(methoxycarbonyl)cyclopentanecarboxylate (2). Concentrated aqueous HCl (2 mL) was added to the stirred solution of diester **1** (2.00 g, 6.53 mmol) in MeOH (25 mL) at room temperature, and the solution was stirred at 60 °C for 5 h. Then, the solution was neutralized with 5% aqueous $NaHCO_3$ and MeOH was evaporated. The aqueous residue was extracted with EtOAc and dried over $MgSO_4$. Removal of the solvent gave crude diol **2** (1.30 g, 91%), which was used in the next reaction without purification: colorless oil; IR (neat) ν 3408 (br), 2956, 1732, 1436, 1271, 1204, 1173, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (m, 2H), 3.76 (s, 6H), 2.63 (dd, *J* = 4.8, 14.8 Hz, 2H), 2.34 (dd, *J* = 1.9, 14.8 Hz, 2H), 2.21 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.5, 53.2, 56.8, 77.8, 173.2; HRMS(FAB) *m*/*z* [M + H]$^+$ calcd for $C_9H_{15}O_6$ 219.0869, found 219.0876.

Methyl (3*S*,4*S*)-3,4-Bis(methanesulfonyloxy)-1-(methoxycarbonyl)cyclopentanecarboxylate. Methanesulfonyl chloride (MsCl, 3.20 mL, 41.2 mmol) was dropwise added to the stirred solution of **2** (1.30 g, 5.96 mmol) and Et_3N (5.7 mL) in CH_2Cl_2 (20 mL) at 0 °C, and the solution was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (60% EtOAc in *n*-hexane) to give a bismesylate (1.91 g, 86%): colorless oil; $[\alpha]^{23}_D$ −1.75 (*c* 1.04, $CHCl_3$); IR (neat) ν 3017, 2957, 1739, 1357, 1282, 1170, 929 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (m, 2H), 3.78 (s, 6H), 3.08 (s, 6H), 3.00 (dd, *J* = 6.4, 16.0 Hz, 2H), 2.51 (dd, *J* = 3.8, 16.0 Hz, 2H); FAB-MS *m*/*z* 374.0 [M$^+$]; HRMS(ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}O_{10}S_2Na$ 397.0234, found 397.0240.

Methyl (3*R*,4*R*)-3,4-Diazido-1-(methoxycarbonyl)cyclopentanecarboxylate (3). A solution of bismesylate (6.40 g, 17.1 mmol), 15-crown-5 (100 mg), and NaN_3 (5.60 g, 85.5 mmol) in DMF (50 mL) was stirred at 85 °C for 6 h. Then, the solution was diluted with water, extracted with ether, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% EtOAc in *n*-hexane) to give **3** (3.15 g, 68%) as a colorless oil: $[\alpha]^{23}_D$ +7.11 (*c* 1.07, $CHCl_3$); IR (neat) ν 2956, 2112, 1736, 1436, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (m, 2H), 3.77 (s, 6H), 2.80 (dd, *J* = 6.7, 14.1 Hz, 2H), 2.20 (dd, *J* = 7.7, 14.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 53.3, 56.1, 65.6, 171.2; HRMS(FAB) *m*/*z* [M + H]$^+$ calcd for $C_9H_{13}O_4N_6$ 269.0998, found 269.1036.

(3*R*,4*R*)-3,4-Diazido-1-(*tert*-butoxycarbonylamino)cyclopentanecarboxylic Acid Methyl Ester [Boc-{(*R*,*R*)-Ac_5c^{dN3}}-OMe; 4]. A solution of diester **3** (1.41 g, 5.28 mmol) in MeOH (40 mL) and 0.1 M NaOH (53 mL) was stirred overnight at room temperature. Then, the solution was neutralized with citric acid and MeOH was evaporated. The aqueous solution was extracted with EtOAc and dried over $MgSO_4$. Removal of the solvent afforded a crude acid (1.26 g, 94%), which was used in the next reaction without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 3.85−3.89 (m, 2H), 3.80 (s, 3H), 2.78−2.87 (m, 2H), 2.23−2.29 (m, 2H). A mixture of the crude acid (1.26 g, 4.96 mmol), Et_3N (1.04 mL) and diphenylphosphoryl azide (DPPA, 1.60 mL, 7.44 mmol) in *t*-BuOH (20 mL) was heated at 95 °C for 12 h. After evaporation, the residue was diluted with EtOAc, washed with 1 M aqueous HCl, brine, 5% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Removal of the solvent afforded a residue, which was purified by column chromatography on silica gel. The fraction eluted with 10% EtOAc in *n*-hexane gave cyclic amino acid **4** (1.15 g, 71%) as colorless crystals: mp 58−60 °C; $[\alpha]^{23}_D$ −8.79 (*c* 1.10, $CHCl_3$); IR (KBr) ν 3286 (br), 2979, 2116, 1738, 1667, 1531 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (br s, 1H), 4.12 (br m, 1H), 3.92 (q, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 2.59 (dd, *J* = 7.9, 13.8 Hz, 1H), 2.43 (m, 1H), 2.25 (dd, *J* = 9.6, 13.8 Hz, 1H), 2.12 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 40.3, 40.6, 53.2, 61.3, 65.4, 65.9, 80.6, 154.1, 173.6; HRMS(FAB) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}O_4N_7$ 326.1577, found 326.1534.

(3*R*,4*R*)-1-Amino-3,4-(diazido)cyclopentanecarboxylic Acid Methyl Ester [{(*R*,*R*)-Ac_5c^{dN3}}-OMe; 5]. Concentrated HCl (16.6 mL) was added to the stirred solution of **4** (1.00 g, 3.07 mmol) in MeOH (10 mL) at 0 °C. Then the solution was stirred at room temperature for 6 h. The solution was neutralized with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by short column chromatography on silica gel (50% EtOAc in *n*-hexane) to give **5** (590 mg, 85%) as a colorless oil: $[\alpha]^{21}_D$ = −58.1 (*c* = 0.70 in $CHCl_3$); IR (neat) ν 3372 (br), 2953, 2108, 1732, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.3 Hz, 1H), 3.85 (q, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 2.66 (dd, *J* = 8.8, 14.0 Hz, 1H), 2.14 (dd, *J* = 9.5, 13.0 Hz, 1H), 2.07 (dd, *J* = 7.1, 14.0 Hz, 1H), 1.78 (br s, 2H), 1.66 (dd, *J* = 7.1, 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.1, 42.5, 52.8, 61.0, 66.00, 66.05, 176.2; HRMS(ESI) *m*/*z* [M + H]$^+$ calcd for $C_7H_{12}N_7O_2$ 226.1052, found 226.1057.

(3*R*,4*R*)-3,4-Diazido-1-(*tert*-butoxycarbonylamino)cyclopentanecarboxylic Acid [Boc-{(*R*,*R*)-Ac_5c^{dN3}}-OH; 6]. A solution of **4** (200 mg, 0.615 mmol) in MeOH (10 mL) and 0.1 M aqueous NaOH (12 mL) was stirred at room temperature for 12 h. After acidification with 1 M aqueous HCl, MeOH was evaporated. The aqueous solution was extracted with EtOAc and dried over Na_2SO_4. Removal of the solvent afforded crude carboxylic acid **6** (192 mg, quantitative), which was used in the next reaction without purification: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (br s, 1H), 4.13 (q, *J* = 7.3 Hz, 1H), 4.08 (br s, 1H), 3.95 (q, *J* = 7.3 Hz, 1H), 2.70 (m 1H), 2.45 (m, 1H), 2.32 (dd, *J* = 9.6, 14.0 Hz, 1H), 2.10 (m, 1H), 1.45 (s, 9H); HRMS(FAB) *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{18}O_4N_7$ 312.1420, found 312.1424.

Boc-{(*R*,*R*)-Ac_5c^{dN3}}$_2$-OMe (7, Dipeptide). A solution of amine **5** (284 mg, 1.26 mmol), crude acid **6** (505 mg, 1.52 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC; 290 mg, 1.52 mmol), 1-hydroxybenzotriazole (HOBt; 205 mg, 1.52 mmol), and Et_3N (206 μL, 1.52 mmol) in MeCN (33 mL) was stirred at room temperature for 4 days. After evaporation of the solvent, the residue was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent afforded a residue,

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

which was purified by column chromatography on silica gel. The fraction eluted with 35% EtOAc in *n*-hexane gave dipeptide **7** (548 mg, 84%) as colorless crystals: mp 139−141 °C; $[\alpha]^{23}_{D}$ −23.8 (*c* 1.01, $CHCl_3$); IR (KBr) ν 3317, 2979, 2116, 2098, 1730, 1680, 1509, 1255, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (br s, 1H), 5.09 (br s, 1H), 4.19 (q, *J* = 8.7 Hz, 1H), 3.89−3.96 (m, 3H), 3.79 (s, 3H), 2.84 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.48−2.54 (m, 2H), 2.24−2.35 (m, 3H), 2.17 (dd, *J* = 8.4, 14.0 Hz, 1H), 1.84 (dd, *J* = 6.6, 14.0 Hz, 1H), 1.46 (s, 9H); HRMS(FAB) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{27}O_5N_{14}$ 519.2289, found 519.2332.

Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_2$-OH (8, Dipeptide Acid). A solution of dipeptide **7** (550 mg, 1.06 mmol) in MeOH (30 mL) and 0.1 M aqueous NaOH (20 mL) was stirred at room temperature for 20 h. After acidification with 1 M aqueous HCl, MeOH was evaporated. Then the aqueous solution was extracted with EtOAc and dried over Na_2SO_4. Removal of the solvent produced crude carboxylic acid **8** (550 mg, quantitative), which was used in the next reaction without purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 5.40 (br, 1H), 5.22 (br s, 1H), 4.09 (m, 1H), 3.91−3.98 (m, 3H), 2.85 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.71 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.51 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.35−2.45 (m, 3H), 2.10 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.88 (m, 1H), 1.47 (s, 9H); HRMS(FAB) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}O_5N_{14}$ 505.2133, found 505.2136.

H-{(*R*,*R*)-Ac$_5$c^{dN3}}$_2$-OMe (9, Dipeptide Amine). A solution of **7** (650 mg, 1.25 mmol) in MeOH (20 mL) and concentrated HCl (6.7 mL) was stirred at room temperature for 20 h. After neutralization with 5% aqueous $NaHCO_3$, MeOH was evaporated. Then, the solution was extracted with EtOAc and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by short column chromatography on silica gel (50% EtOAc in *n*-hexane) to give crude **9** (447 mg, 85%) as a colorless oil: $[\alpha]^{23}_{D}$ = −145.5 (*c* = 0.25 in $CHCl_3$); IR ($CHCl_3$) ν 2110, 1706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 4.17 (m, 1H), 3.93−4.03 (m, 3H), 3.80 (s, 3H), 2.68 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.61 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.45 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.41 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.28 (dd, *J* = 14.0, 8.8 Hz, 1H), 2.18 (dd, *J* = 15.2, 8.8 Hz, 1H), 1.99 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.75 (br s, 2H), 1.58 (dd, *J* = 14.0, 8.0 Hz, 1H); HRMS(FAB) *m*/*z* $[M + H + Na]^+$ Calcd for $C_{13}H_{19}O_3N_{14}Na$ 442.1662, found 442.1658.

Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_4$-OMe (10, Tetrapeptide). A solution of crude acid **8** (446 mg, 0.885 mmol), crude amine **9** (370 mg, 0.885 mmol), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU, 403 mg, 1.06 mmol), and $^iPr_2EtN$ (308 μL, 1.77 mmol) in MeCN (30 mL) was stirred at room temperature for 7 days. After evaporation of the solvent, the residue was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel. The fraction eluted with 33% EtOAc in *n*-hexane afforded tetrapeptide **10** (201 mg, 25%) as colorless crystals. The fraction eluted with 50% EtOAc in *n*-hexane afforded diketopiperazine **11** (150 mg, 44%) as colorless crystals. **10**: mp 176−178 °C; $[\alpha]^{23}_{D}$ −24.9 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3342, 2932, 2110, 1742, 1684, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.45 (br s, 1H), 6.92 (br s, 1H), 5.55 (br s, 1H), 3.69−4.06 (m, 8H), 3.75 (s, 3H), 2.84−2.91 (m, 4H), 2.11−2.61 (m, 9H), 1.98 (dd, *J* = 7.7, 14.6 Hz, 1H), 1.79−1.87 (m, 2H), 1.52 (s, 9H); HRMS(FAB) *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{41}O_7N_{28}$ 905.3713, found 905.3720.

11: mp >220 °C; $[\alpha]^{23}_{D}$ = −11.3 (*c* = 0.14 in MeOH); IR ($CHCl_3$) ν 2110 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 2H), 4.02 (q, *J* = 9.3 Hz, 2H), 3.91 (q, *J* = 8.1 Hz, 2H), 2.57 (dd, *J* = 7.5, 13.1 Hz, 2H), 2.15−2.30 (m, 4H), 1.75 (dd, *J* = 10.7, 13.1 Hz, 2H); HRMS(FAB) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{15}O_2N_{14}$ 387.1502, found 387.1510.

Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_3$-OMe (12, Tripeptide). A solution of crude acid **8** (130 mg, 0.258 mmol), crude amine **5** (58.0 mg, 0.258 mmol), HBTU (117 mg, 0.309 mmol), and $^iPr_2EtN$ (89 μL, 0.520 mmol) in MeCN (23 mL) was stirred at room temperature for 4 days. After evaporation of the solvent, the residue was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (50% EtOAc in *n*-hexane) to give tripeptide **12** (95.0 mg, 52%) as colorless crystals: mp 152−154 °C; $[\alpha]^{23}_{D}$ −39.1 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3414 (br), 3348 (br), 2110, 1734, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 6.72 (br s, 1H), 5.35 (br s, 1H), 3.98−4.04 (m, 4H), 3.80−3.91 (m, 2H), 3.74 (s, 3H), 2.87 (dd, *J* = 8.2, 14.3 Hz, 1H), 2.79 (dd, *J* = 7.5, 14.3 Hz, 1H), 2.75 (dd, *J* = 6.8, 14.3 Hz, 1H), 2.48−2.58 (m, 3H), 2.17−2.36 (m, 3H), 2.11 (dd, *J* = 8.4, 14.3 Hz, 1H), 1.74−1.83 (m, 2H), 1.50 (s, 9H); HRMS(ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{33}N_{21}O_6Na$ 734.2815, found 734.2788. Anal. Calcd for $C_{24}H_{33}O_6N_{21}$: C, 40.51; H, 4.67; N, 41.33. Found: C, 40.58; H, 4.74; N, 41.09.

Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_3$-OH (13, Tripeptide Acid). A solution of tripeptide **12** (84 mg, 0.12 mmol) in MeOH (8 mL) and 0.1 M aqueous NaOH (3 mL) was stirred at room temperature for 24 h. After acidification with 1 M aqueous HCl, MeOH was evaporated. Then, the aqueous solution was extracted with EtOAc and dried over Na_2SO_4. Removal of the solvent produced crude carboxylic acid **13** (82 mg, quantitative), which was used in the next reaction without purification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 6.99 (br s, 1H), 5.60 (br s, 1H), 3.98−4.02 (m, 3H), 3.87−3.93 (m, 3H), 2.10−2.95 (m, 10H), 1.79−1.84 (m, 2H), 1.50 (s, 9H); HRMS(ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{31}N_{21}O_6Na$ 720.2664, found 720.2631.

H-{(*R*,*R*)-Ac$_5$c^{dN3}}$_3$-OMe (14, Tripeptide Amine). A solution of **12** (176 mg, 0.247 mmol) in MeOH (6 mL) and concentrated HCl (2 mL) was stirred at room temperature for 24 h. After neutralization with 5% aqueous $NaHCO_3$, the solution was extracted with EtOAc and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by short column chromatography on silica gel (EtOAc) to give crude **14** (70.1 mg, 46%) as a colorless oil. $[\alpha]^{22}_{D}$ = −83.7 (*c* = 0.49 in $CHCl_3$); IR ($CHCl_3$) ν 3333 (br), 2110, 1743, 1681, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.83 (br s, 1H), 4.19 (q, *J* = 8.6 Hz, 1H), 3.88−4.09 (m, 5H), 3.79 (s, 3H), 2.86 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.73 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.38−2.56 (m, 5H), 2.16−2.25 (m, 2H), 1.99−2.05 (m, 2H), 1.69 (br s, 2H), 1.62 (dd, *J* = 5.7, 14.3 Hz, 1H); HRMS(FAB) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}O_4N_{21}$ 612.2477, found 612.2483.

Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}$_6$-OMe (15, Hexapeptide). A mixture of crude acid **13** (80.0 mg, 0.115 mmol), HBTU (52.2 mg, 0.140 mmol), and $^iPr_2EtN$ (40 μL, 0.23 mmol) in MeCN (20 mL) was stirred at room temperature for 1 h. Then, the amine **14** (70.1 mg, 0.115 mmol) in MeCN (3 mL) was added to the solution, and the whole was stirred at room temperature for 3 days. After removal of the solvent, the residue was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave a solid, which was purified by column chromatography on silica gel (50% EtOAc in *n*-hexane) to afford hexapeptide **15** (71.0 mg, 48%) as colorless crystals: mp 215−217 °C dec; $[\alpha]^{23}_{D}$ +15.1 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3325 (br), 2930, 2112, 1735, 1667, 1526 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.85 (br s, 1H), 7.49 (br s, 1H), 7.46 (br s, 1H), 6.97 (br s, 1H), 5.48 (br s, 1H), 3.82−4.12 (m, 12H), 3.75 (s, 3H), 1.90−3.20 (m, 24H), 1.55 (s, 9H); FAB-MS *m*/*z* 1291.0 $[M^+]$; HRMS(FAB) *m*/*z* $[M + Na + H]^+$ Calcd for $C_{42}H_{55}O_9N_{42}Na$ 1314.5035, found 1314.5068.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]-OMe (16). A mixture of amine **5** (500 mg, 2.22 mmol), Boc-(L-Leu)$_2$-OH (920 mg, 2.67 mmol),[8] EDC (509 mg, 2.67 mmol), and HOBt (360 mg, 2.67 mmol) in MeCN (50 mL) was stirred at room temperature for 24 h. After removal of the solvent, the residue was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent afforded a solid, which was purified by column chromatography on silica gel. The fraction eluted with 33% EtOAc in *n*-hexane gave tripeptide **16** (1.10 g, 91%) as colorless crystals: mp 105−107 °C; $[\alpha]^{23}_{D}$ −67.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3431 (br), 2962, 2111, 1741, 1698, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 4.79 (br m, 1H), 4.37 (m, 1H), 4.04−4.10 (m, 2H), 3.89 (q, *J* = 8.0 Hz, 1H), 3.76 (s, 3H), 2.58 (dd, *J* = 7.6, 14.0 Hz, 1H), 2.49 (dd, *J* = 8.0, 14.4 Hz, 1H), 2.30 (dd, *J* = 8.8, 14.4 Hz, 1H), 2.15 (dd, *J* = 8.6, 14.0 Hz, 1H), 1.48−1.74 (m, 6H),

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

1.46 (s, 9H), 0.90−0.97 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.8, 24.6, 24.7, 28.2, 39.7, 39.8, 40.0, 40.5, 51.6, 53.1, 53.5, 61.0, 65.2, 65.7, 80.5, 155.9, 171.7, 172.8, 173.0; HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{24}H_{42}O_6N_9$ 552.3258, found 552.3293.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_2$-OMe (17). Hexapeptide **17** was prepared in 73% yield by the coupling between tripeptide acid and tripeptide amine: colorless crystals; mp 170−172 °C; $[\alpha]^{23}_D$ −4.98 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3325 (br), 2961, 2111, 1734, 1668, 1527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.40 (d, *J* = 6.2 Hz, 1H), 7.32 (br s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 4.4 Hz, 1H), 5.02 (br m, 1H), 4.33 (m, 1H), 4.19 (m, 1H), 3.80−4.05 (m, 6H), 3.73 (s, 3H), 3.31 (dd, *J* = 8.0, 14.3 Hz, 1H), 2.82 (dd, *J* = 8.0, 14.3 Hz, 1H), 2.55−2.65 (m, 2H), 2.35 (dd, *J* = 9.8, 14.3 Hz, 1H), 2.17 (dd, *J* = 8.5 14.3 Hz, 1H), 1.96 (dd, *J* = 9.9, 14.3 Hz, 1H), 1.50−1.90 (m, 13H), 1.54 (s, 9H), 0.86−1.02 (m, 24H); HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{42}H_{71}O_9N_{18}$ 971.5651, found 971.5660. Anal. Calcd for $C_{42}H_{70}O_9N_{18}$: C, 51.95; H, 7.27; N, 25.96. Found: C, 51.91; H, 7.35; N, 25.75.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_3$-OMe (18). Nonapeptide **18** was prepared in 63% by the coupling between hexapeptide acid and tripeptide amine: colorless crystals; mp 211−213 °C; $[\alpha]^{23}_D$ −1.99 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3313 (br), 2961, 2109, 1736, 1659, 1531 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.74 (br s, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.40 (br s, 2H), 7.30 (d, *J* = 6.2 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.62 (br s, 1H), 5.19 (br s, 1H), 4.33 (m, 1H), 4.20 (m, 1H), 3.80−4.06 (m, 10H), 3.72 (s, 3H), 3.34 (dd, *J* = 8.9, 14.8 Hz, 1H), 3.30 (dd, *J* = 7.3, 14.4 Hz, 1H), 2.87 (dd, *J* = 8.0, 14.2 Hz, 1H), 2.82 (dd, *J* = 6.9, 13.7 Hz, 1H), 2.68 (dd, *J* = 6.0, 14.2 Hz, 1H), 2.63 (dd, *J* = 7.6, 14.2 Hz, 1H), 2.31 (dd, *J* = 9.9, 14.2 Hz, 1H), 2.14 (dd, *J* = 9.6, 14.2 Hz, 1H), 1.63−2.00 (m, 22H), 1.56 (s, 9H), 0.90−1.03 (m, 36H); HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{60}H_{100}O_{12}N_{27}$ 1390.8045, found 1390.8035.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dN3}}]$_4$-OMe (19). Dodecapeptide **19** was prepared in 72% by the coupling between hexapeptide acid and hexapeptide amine: colorless crystals; 228 °C dec; $[\alpha]^{23}_D$ −1.13 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3321 (br), 2960, 2108, 1737, 1661, 1534 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.92 (br s, 1H), 7.87 (br d, *J* = 6.4 Hz, 2H), 7.69 (br s, 1H), 7.62 (br s, 1H), 7.50 (br d, *J* = 6.6 Hz, 1H), 7.20−7.23 (m, 2H), 7.11 (br d, *J* = 5.0 Hz, 1H), 7.00 (br d, *J* = 6.4 Hz, 1H), 5.82 (br s, 1H), 4.29 (m, 1H), 4.20 (m, 1H), 3.79−4.15 (m, 14H), 3.71 (s, 3H), 3.42 (dd, *J* = 9.0, 14.9 Hz, 1H), 3.28−3.35 (m, 2H), 2.70−2.90 (m, 4H), 2.60 (dd, *J* = 8.0, 14.2 Hz, 1H), 2.31 (dd, *J* = 10.3, 14.2 Hz, 1H), 2.17 (t, *J* = 12.6 Hz, 1H), 1.63−2.01 (m, 30H), 1.56 (s, 9H), 0.85−1.10 (m, 48H); HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{78}H_{129}O_{15}N_{36}$ 1810.0438, found 1810.0436. Anal. Calcd for $C_{78}H_{128}O_{15}$ N_{36}: C, 51.76; H, 7.13; N, 27.86. Found: C, 51.76; H, 7.15; N, 27.61.

General Method of "Click Conversion" of Boc-{(*R*,*R*)-Ac$_5$c^{dN3}}-OMe 4. A mixture of amino acid **4** (50.0 mg, 0.154 mmol), substituted alkyne (0.92 mmol), sodium ascorbate (15.3 mg, 0.077 mmol), and $CuSO_4$ (12.3 mg, 0.077 mmol) in *t*-BuOH (4 mL) and H_2O (2 mL) was stirred at room temperature for 24 h. After evaporation of solvent, the residue was diluted with water, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent gave the residue, which was purified by column chromatography on silica gel to give triazole.

20a: quantitative; colorless crystals; mp 179−180 °C; $[\alpha]^{23}_D$ −68.5 (*c* 1.01, $CHCl_3$); IR (neat) ν 3367 (br), 3141, 3017, 2981, 1740, 1708, 1485, 1216, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.77−7.79 (m, 5H), 7.38−7.42 (m, 4H), 7.30−7.34 (m, 2H), 5.93 (br s, 1H), 5.70−5.78 (br s, 2H), 3.90 (s, 3H), 3.21 (m, 1H), 3.03−3.05 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 40.9, 41.4, 53.4, 61.7, 64.1, 65.0, 81.0, 120.1, 120.3, 125.7, 128.4, 128.8, 123.0, 148.0, 154.8, 173.1; FAB-MS m/z 530.0 (M$^+$ + H); HRMS(ESI) m/z [M + Na]$^+$ calcd for $C_{28}H_{31}O_4N_7Na$ 552.2335, found 552.2345.

20b: 84%; colorless crystals; mp 175−177 °C; $[\alpha]^{23}_D$ −86.5 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3426 (br), 2967, 1742, 1709, 1648 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.16 (s, 1H), 5.98 (br s, 1H), 5.54 (m, 1H), 5.46 (n, 1H), 3.84 (s, 3H), 3.11 (t, *J* = 12 Hz, 1H), 2.90−3.00 (m, 3H), 1.46 (s, 9H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 30.2, 30.7, 41.0, 53.2, 61.8, 63.8, 64.9, 80.6, 119.0, 119.5, 154.8, 157.8, 157.9, 173.0; HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{24}H_{40}O_4N_7$ 490.3142, found 490.3158.

20c: 74%; colorless crystals; mp 89−91 °C; $[\alpha]^{23}_D$ −70.3 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3421 (br), 3019, 1741, 1552, 1493 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.08 (s, 1H), 5.80−5.92 (m, 2H), 5.72 (q, *J* = 9.2 Hz, 1H), 3.930 (s, 3H), 3.928 (s, 3H), 3.90 (s, 3H), 3.14 (dd, *J* = 10.5, 13.7 Hz, 1H), 2.95−3.06 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 40.9, 41.3, 52.2, 53.4, 61.4, 64.4, 64.8, 80.8, 127.9, 128.1, 140.0, 140.0, 154.8, 160.6, 160.7, 172.9; HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{20}H_{28}O_8N_7$ 494.1999, found 494.1998.

20d: 83%; colorless crystals; 170 °C dec; $[\alpha]^{23}_D$ −61.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 1749, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.10 (s, 1H), 5.85−5.89 (m, 2H), 5.74 (q, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 3.12 (dd, *J* = 10.6, 13.9 Hz, 1H), 2.97−3.05 (m, 3H), 2.66 (s, 6H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 28.2, 40.9, 41.4, 53.5, 61.23, 64.4, 64.7, 81.0, 125.7, 125.9, 147.98, 148.02, 154.7, 172.9, 192.38, 192.40; HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{20}H_{28}O_6N_7$ 462.2101, found 462.2085.

20e: 85%; colorless crystals; mp 124−126 °C; $[\alpha]^{23}_D$ −53.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 2981, 1740, 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.97 (s, 1H), 5.78−5.83 (m, 2H), 5.72 (q, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 3.10 (dd, *J* = 10.8, 13.7 Hz, 1H), 2.95−3.00 (m, 3H), 1.58 (s, 18H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 41.1, 41.5, 53.5, 61.3, 64.3, 64.8, 81.0, 82.6, 82.6, 127.4, 127.5, 141.6, 141.7, 154.7, 159.4, 159.4, 172.9; HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{26}H_{40}O_8N_7$ 578.2938, found 578.2969.

"Click Conversion" of (*R*,*R*)-Ac$_5$c^{dN3} Dipeptide 7 into (*R*,*R*)-Ac$_5$c$^{d\text{-}triazole}$ Dipeptide (21). A mixture of dipeptide **7** (30.0 mg, 0.0578 mmol), *tert*-butyl propiolate (96 μL, 0.70 mmol), sodium ascorbate (5.7 mg, 0.029 mmol), and $CuSO_4$ (4.6 mg, 0.029 mmol) in *t*-BuOH (3 mL) and H_2O (1 mL) was stirred at 30 °C for 24 h. After evaporation of solvent, the residue was diluted with water, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (50% EtOAc in *n*-hexane) to afford triazole **21** (45.0 mg, 76%) as colorless crystals: mp 218−220 °C; $[\alpha]^{23}_D$ −52.5 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 2983, 1740, 1716 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.10 (s, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 6.33 (s, 1H), 5.65−5.85 (m, 4H), 3.89 (s, 3H), 3.41 (dd, *J* = 14.0, 8.7 Hz, 1H), 3.22 (dd, *J* = 8.0, 13.7 Hz, 1H), 3.00−3.18 (m, 5H), 2.70 (m, 1H), 1.59 (s, 9H), 1.580 (s, 18H), 1.578 (s, 9H), 1.26 (s, 9H); HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{46}H_{67}O_{13}N_{14}$ 1023.5012, found 1023.5007.

"Click Conversion" of (*R*,*R*)-Ac$_5$c^{dN3} Tetrapeptide 10 into (*R*,*R*)-Ac$_5$c$^{d\text{-}triazole\text{-}Me}$ Tetrapeptide (22). A mixture of tetrapeptide **10** (40.0 mg, 0.0442 mmol), methyl propiolate (88 μL, 1.06 mmol), sodium ascorbate (4.4 mg, 0.022 mmol), and $CuSO_4$ (3.5 mg, 0.022 mmol) in *t*-BuOH (4 mL) and H_2O (1 mL) was stirred at room temperature for 48 h. After evaporation of solvent, the residue was diluted with water, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to afford triazole **22** (37.0 mg, 53%) as colorless crystals: mp 230 °C dec; $[\alpha]^{23}_D$ −64.7 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3324 (br), 2954, 1734, 1675 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.65 (s, 1H), 8.82 (s, 1H), 8.79 (s, 1H), 8.75 (s, 1H), 8.72 (s, 1H), 8.58 (s, 1H), 8.56 (s, 1H), 8.51 (s, 1H), 8.32 (s, 1H), 8.30 (s, 1H), 7.95 (s, 1H), 6.38 (m, 1H), 5.66−6.03 (m, 8H), 3.77−3.85 (m, 27H), 2.90−3.75 (m, 16H), 1.43 (s, 9H); HRMS(FAB) m/z [M + H]$^+$ calcd for $C_{62}H_{73}O_{23}N_{28}$ 1577.5403, found 1577.5413.

"Click Conversion" of (*R*,*R*)-Ac$_5$c^{dN3} Hexapeptide 15 into (*R*,*R*)-Ac$_5$c$^{d\text{-}triazole}$ Hexapeptide (23). A mixture of hexapeptide **15** (32.0 mg, 0.0450 mmol), *tert*-butyl propiolate (123 μL, 0.90 mmol), sodium ascorbate (2.5 mg, 0.012 mmol), and $CuSO_4$ (2.0 mg, 0.012 mmol) in *t*-BuOH (2 mL), acetone (2 mL), and H_2O (1 mL) was stirred at 30 °C for 48 h. After evaporation of solvent, the residue was diluted with water, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column

dx.doi.org/10.1021/jo501493x | J. Org. Chem. 2014, 79, 9125−9140

chromatography on silica gel (50% acetone in *n*-hexane) to give triazole **23** (41.7 mg, 59%) as a white solid: mp 265 °C dec; $[\alpha]^{23}_{D}$ −43.8 (*c* 1.00, CH_3CN); IR (CD_3CN) ν 3323, 3140, 2984, 1732, 1715, 1683, 1528 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.85 (br s, 1H), 8.68 (br s, 1H), 8.55 (br s, 1H), 8.20−8.40 (m, 12H), 8.02 (br s, 1H), 6.90 (br s, 1H), 5.95−6.10 (m, 2H), 5.50−5.90 (m, 11H), 3.77 (s, 3H), 2.70−3.90 (m, 24H), 1.35−1.65 (m, 117H); HRMS(FAB) *m*/*z* $[M + H + Na]^+$ calcd for $C_{126}H_{175}O_{33}N_{42}Na$ 2827.3204, found 2827.3208.

"Click Conversion" of (*R*,*R*)-Ac$_5$c^{dN3} Heterohexapeptide 17 into (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ Heterohexapeptide (24). A mixture of heteropeptide **17** (30.0 mg, 0.0310 mmol), *tert*-butyl propiolate (51 μL, 0.370 mmol), sodium ascorbate (3.0 mg, 0.015 mmol), and $CuSO_4$ (2.5 mg, 0.015 mmol) in *t*-BuOH (1 mL) and H_2O (1 mL) was stirred at 25 °C for 48 h. After evaporation of solvent, the residue was diluted with water, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (66% EtOAc in *n*-hexane) to give triazole **24** (52.0 mg, quantitative) as colorless crystals: mp 174−176 °C; $[\alpha]^{23}_{D}$ −36.7 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3317 (br), 2962, 1732, 1710, 1667, 1531 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 7.65 (d, *J* = 5.5 Hz, 1H), 7.54 (s, 1H), 7.26 (br s, 1H), 7.18 (br s, 1H), 6.12 (m, 1H), 5.78 (q, *J* = 9.4 Hz, 1H), 5.62−5.72 (m, 2H), 5.37 (br s, 1H), 4.30 (m, 1H), 4.18 (m, 1H), 4.01 (m, 1H), 3.86−3.94 (m, 2H), 3.77 (s, 3H), 3.20 (dd, *J* = 8.5, 14.0 Hz, 1H), 3.10−2.98 (m, 3H), 2.76 (m, 1H), 2.61 (m, 1H), 1.89 (m, 1H), 1.80−1.60 (m, 12H), 1.60 (s, 9H), 1.56 (s, 9H), 1.55 (s, 9H), 1.51 (s, 9H), 1.32 (s, 9H), 1.00−0.89 (m, 24H); HRMS(FAB) *m*/*z* $[M + Na]^+$ calcd for $C_{70}H_{110}O_{17}N_{18}Na$ 1497.8194, found 1497.8179.

"Click Conversion" of (*R*,*R*)-Ac$_5$c^{dN3} Heterononapeptide 18 into (*R*,*R*)-Ac$_5$c$^{d\text{-triazole}}$ Heterononapeptide (25). A mixture of nonapeptide **18** (30.0 mg, 0.0220 mmol), *tert*-butyl propiolate (53 μL, 0.39 mmol), sodium ascorbate (2.1 mg, 0.011 mmol), and $CuSO_4$ (1.7 mg, 0.011 mmol) in *t*-BuOH (4 mL) and H_2O (2 mL) was stirred at 25 °C for 72 h. After evaporation of solvent, the residue was diluted with brine, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (50% acetone in *n*-hexane) to give triazole **25** (35.0 mg, 75%) as colorless crystals: mp 270 °C dec; $[\alpha]^{23}_{D}$ −34.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3422 (br), 3307 (br), 2961, 1735, 1718, 1654, 1533 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.63 (br s, 1H), 8.62 (s, 1H), 8.59 (s, 1H), 8.48 (s, 1H), 8.43 (br s, 1H), 8.39 (s, 1H), 8.34 (m, 2H), 8.28 (s, 1H), 8.24 (br s, 1H), 7.75 (s, 1H), 7.57 (br m, 2H), 7.49 (br d, *J* = 6.8 Hz, 1H), 6.77 (br s, 1H), 6.20 (m, 1H), 6.03 (m, 1H), 5.95 (m, 1H), 5.70 (q, *J* = 9.7 Hz, 1H), 5.61 (q, *J* = 9.2 Hz, 1H), 5.51 (m, 1H), 4.08−4.22 (m, 6H), 3.92 (dd, *J* = 14.8, 10.8 Hz, 1H), 3.79 (dd, *J* = 14.8, 9.6 Hz, 1H), 3.69 (s, 3H), 3.39 (m, 1H), 3.20−3.28 (m, 3H), 2.95−3.11 (m, 3H), 2.86 (m, 1H), 2.65−2.72 (m, 2H), 1.65−2.05 (m, 18H), 1.54 (s, 9H), 1.51 (s, 18H), 1.50 (s, 9H), 1.48 (s, 18H), 1.37 (s, 9H), 0.85−1.03 (m, 36H); HRMS(FAB) *m*/*z* $[M + Na]^+$ calcd for $C_{102}H_{159}O_{24}N_{27}Na$ 2169.1949, found 2169.1943.

■ ASSOCIATED CONTENT

Supporting Information

NOESY ^1H NMR spectrum of **20e**, FT-IR absorption spectra of peptides before and after the click reaction, NOESY or ROESY ^1H NMR spectra of **10**, **17**, **18**, **22**, and **24**, CD spectra of amino acids **4** and **20e** and hexapeptides **15** and **23**, superimposed structures of **15** and **17**, X-ray crystallographic parameters, the O−C−C−O torsion angles of (*S*,*S*)-Ac$_5$c^{dOM} homopeptides, structural analyses in packing mode, ^1H and ^{13}C NMR chart, and crystallographic details (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: matanaka@nagasaki-u.ac.jp.

Notes

The authors declare no competing financial interest.

Caution: Poly azido compounds are in general known to be explosive at high temperature or by stimulation. We examined the stability of azido compounds using differential scanning calorimetry (DSC). DSC analyses indicated that compounds **3**, **4**, and **7** are relatively stable under 200 °C, but above 200 °C the compounds are explosive. Diester **3**: T_{DSC} 207.4 °C; T_{peak} 234.7 °C; ΔH −1098 mJ/mg, amino acid **4**: T_{DSC} 204.8 °C; T_{peak} 233.3 °C; ΔH −1321 mJ/mg, dipeptide **7**: T_{DSC} 207.2 °C; T_{peak} 227.8 °C; ΔH −1252 mJ/mg.

■ ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Young Scientists (A) (25713008) from JSPS, a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (26105745) from MEXT, and a Grant from the Naito Foundation.

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