Organic LETTERS

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Oligomers of N-Substituted β^2-Homoalanines: Peptoids with Backbone Chirality

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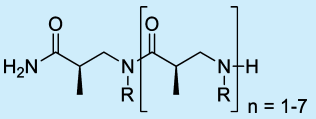
Supporting Information

ABSTRACT: A new class of peptoid-based peptidomimetics composed of oligomers of *N*-substituted β^2-homoalanines is reported. Design, solid-phase synthesis, and preliminary circular dichroism studies of oligomers of *N*-alkylated β^2-homoalanines consisting of up to 8-mers are described.



Development of synthetic oligomers capable of mimicking three-dimensional structures of natural biopolymers such as proteins and oligonucleotides is of significant interest.[1−3] In particular, peptidomimetic foldamers that fold into well-defined conformations and display proteinogenic side chains would be highly valuable alternatives to native peptides in that they may have better proteolytic stability than peptides.[3,4] These peptidomimetic foldamers could serve as functional modulators of biomedically important proteins. Over the last few decades, a great deal of effort has been made to develop such non-natural folding oligomers, which include β- and γ-peptides,[5−9] oligoureas,[10,11] oligotriazoles,[12] oligopyrrolidines,[13] γ-AApeptides,[14] and peptoids.[15−17]

Peptoids, oligomers of *N*-substituted glycines, are a class of peptide-like synthetic oligomers.[18] Peptoids are different from peptides in that the side chains are appended to the nitrogen atoms instead of α-carbon atoms in native peptides. Peptoids can be easily synthesized by a solid-phase submonomer synthesis route.[19] In peptoid synthesis, primary amines are a diversity-generating element. Because a vast number of structurally diverse primary amines are readily available from commercial sources, large peptoid libraries can be constructed.[20,21] Peptoids are resistant to proteolytic degradation like other unnatural peptidomimetics.[22,23] More importantly, peptoids are found to be far more cell-permeable than native peptides.[24−26] Taken together, peptoids are an attractive class of peptidomimetics that possess important advantages as protein capture agents.[27,28]

However, due to the lack of chiral centers and amide hydrogen atoms, peptoids, in general, are relatively flexible and do not form folding structures. As such, approaches to restricting the structural flexibility of peptoids are of great interest (e.g., macrocyclic peptoids[29−39]). Interestingly, it was demonstrated that peptoids are able to form defined secondary structures when they have α-chiral side chains (Figure 1).[40−46] X-ray and NMR studies showed that those peptoids with α-methyl side chains exhibited polyproline-type helical structure. In addition to α-peptoids, β-peptoids with α-chiral side chains (Figure 1) are shown to have helical folding structures as well.[47] Herein, we report a new class of peptoids composed of oligomers of *N*-substituted β^2-homoalanines. Since these molecules have a β-peptoid-like backbone structure with chiral methyl groups at the α-positions of the main chain, we refer to them as α-ABpeptoids (α-*a*lkyl *b*eta-peptoids). This report describes the design, synthesis, and preliminary conformational studies of α-ABpeptoids (Figure 1).

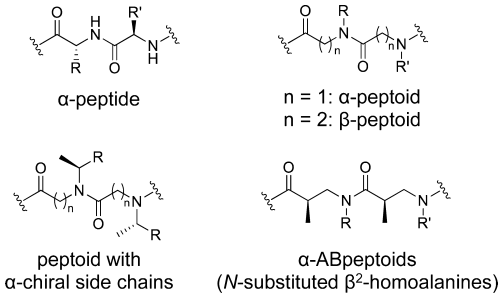


Figure 1. General structures of α-peptides, α- and β-peptoids, peptoids with α-chiral side chains, and α-ABpeptoids.

Inspired by the structures of the peptoids with α-chiral side chains, we designed α-ABpeptoids by incorporating chiral methyl residues at the α-position on the backbone of β-peptoids. We speculated that α-ABpeptoids may adopt folding conformations owing to the chiral methyl groups in the backbone structure like peptoids with α-chiral side chains. To test this idea, we synthesized a series of oligomers of *N*-benzylated β^2-homoalanines as model compounds. First, *N*-benzyl β^2-homoalanine was synthesized as a monomer building block (Scheme 1). Synthesis began with tosylation of (*R*)-methyl 3-

Received: June 14, 2016
Published: July 12, 2016

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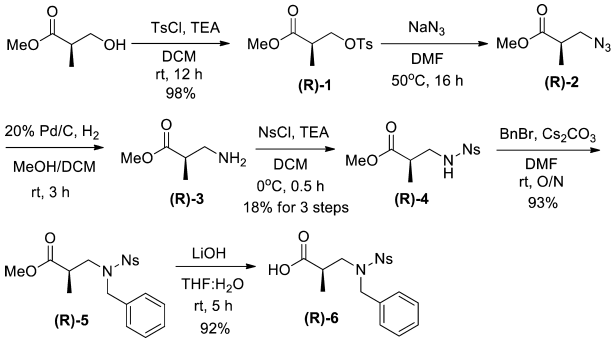
DOI: 10.1021/acs.orglett.6b01726
Org. Lett. 2016, 18, 3678−3681

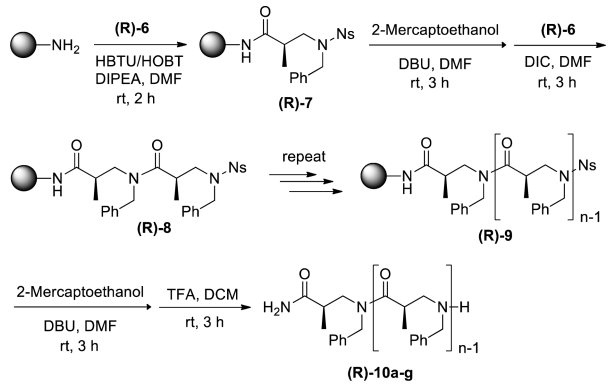
Scheme 1. Synthesis of *N*-Benzyl β^2-Homoalanine (*R*)-6 as a Monomer Building Block



hydroxy-2-methylpropanoate, providing (*R*)-**1** in 98% yield (Scheme 1). Tosylate (*R*)-**1** was treated with sodium azide in DMF to afford (*R*)-**2**. Reduction of the crude azide (*R*)-**2** using hydrogen and palladium on charcoal gave primary amine (*R*)-**3**. The resulting primary amine was protected with a nosyl (Ns) protecting group. *N*-Alkylation was then carried out by treatment with benzyl bromide and cesium carbonate, giving (*R*)-**5**. Finally, methyl ester (*R*)-**5** was hydrolyzed with LiOH to afford (*R*)-3-(*N*-benzyl-4-nitrophenylsulfonamido)-2-methylpropanoic acid (*R*)-**6**. The overall yield was about 15% for six steps. (*S*)-3-(*N*-Benzyl-4-nitrophenylsulfonamido)-2-methylpropanoic acid (*S*)-**6** was also prepared by the same procedure starting from (*S*)-methyl 3-hydroxy-2-methylpropanoate (Scheme 1). The synthetic route described above yielded the products in enantiomerically pure forms without racemization. Their enantiomeric purity was confirmed by comparing the optical rotation of the (*S*)- and (*R*)-forms of the products and their intermediates (Table S1).

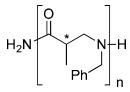
To synthesize oligomers of *N*-benzyl β^2-homoalanines, we developed an efficient solid-phase synthesis method (Scheme 2).

Scheme 2. Solid-Phase Synthesis of Oligomers of *N*-Benzyl β^2-Homoalanine (*R*)-10a−g



First, (*R*)-3-(*N*-benzyl-4-nitrophenylsulfonamido)-2-methylpropanoic acid (*R*)-**6** was loaded on Rink amide MBHA resin under standard peptide coupling conditions using HOBT/HBTU/DIPEA in DMF. The nosyl protecting group was then removed by treatment with 2-mercaptoethanol and 1,8-diazabicycloundec-7-ene (DBU) to yield secondary amine. Compared to the synthesis of regular peptides, solid-phase synthesis of oligomers of *N*-alkylated peptides is generally known to be very difficult.[48] After testing several coupling conditions, we found that use of *N,N′*-diisopropylcarbodiimide (DIC) as a coupling reagent provided the desired dimeric product (*R*)-**8** in nearly quantitative yield, as reported previously.[49] Although DIC was highly efficient, it is known that carbodiimide activation of amino acids with DIC often causes a racemization at the α-carbon position through the formation of an oxazolone intermediate.[50] However, unlike regular amino acids, (*R*)-**6** is unable to form such an oxazolone ring, eliminating the possibility of racemization during the coupling reaction.[51] To validate this, we synthesized all four types of stereoisomers (*RR*, *SS*, *RS*, and *SR*) of dimers under DIC conditions and measured NMR spectra (Figure S1). On the basis of the ^{1}H NMR spectroscopy, expectedly, no racemization at the α-carbon was observed. It is known that tertiary amide bonds have both cis and trans conformations while peptide bonds have a strong preference for the trans conformation. For the dimers, as determined by the ^{1}H NMR spectrum, the cis/trans ratio was approximately 1.0:1.0, which is quite similar to those observed in regular peptoid bonds.[42,45,46,52,53] The desired length of oligomer was achieved via iterative coupling reactions. Using these conditions, we have been able to synthesize oligomers ranging from 2- to 8-mers (*R*)-**10a−g** in reasonably good yield (Table S2 and Figure S2). After a cleavage reaction with 95% TFA, the products were purified to >97% purity by reversed-phase HPLC, and their identity was confirmed by mass analysis (Figure S3). Masses for all the oligomeric products (*R*)-**10a−g** were consistent with the expected masses (Table 1). To explore whether our solid-phase method is generally applicable for the synthesis of α-ABpeptoids of varying sequences, we synthesized homo- and hetero-oligomers substituted with different alkyl groups such as isobutyl and cyclohexyl (Scheme S1). Using the same procedure (Scheme 2), oligomers composed of *N*-cyclohexyl or *N*-isobutyl β^2-homoalanines were also efficiently synthesized (Figures S4 and S5), demonstrating the robustness of the solid-phase method.

Table 1. Synthesized α-ABpeptoid Oligomer Sequence, Purity, and Mass Confirmation



compd no.	chain length	% purity[a]	calcd mass	obsd mass[b]
(*R*)-**10a**	2	97	367.23	368.2 $[M + H]^+$
(*R*)-**10b**	3	99	542.33	543.3 $[M + H]^+$
(*R*)-**10c**	4	99	717.43	718.4 $[M + H]^+$
(*R*)-**10d**	5	99	892.53	893.5 $[M + H]^+$
(*R*)-**10e**	6	99	1067.62	1068.6 $[M + H]^+$
(*R*)-**10f**	7	99	1242.72	1243.7 $[M + H]^+$
(*R*)-**10g**	8	99	1417.82	1418.7 $[M + H]^+$
(*R*)-**10e-Ac**[c]	6	99	1109.64	1110.6 $[M + H]^+$
(*S*)-**10a**	2	99	367.23	368.3 $[M + H]^+$
(*S*)-**10b**	3	99	542.33	543.3 $[M + H]^+$
(*S*)-**10c**	4	99	717.43	718.4 $[M + H]^+$
(*S*)-**10d**	5	99	892.53	893.5 $[M + H]^+$
(*S*)-**10e**	6	99	1067.62	1068.5 $[M + H]^+$
(*S*)-**10f**	7	99	1242.72	1243.6 $[M + H]^+$
(*S*)-**10g**	8	99	1417.82	1418.8 $[M + H]^+$
(*S*)-**10e-Ac**[c]	6	95	1109.64	1110.6 $[M + H]^+$

[a]Determined by analytical reversed-phase HPLC of purified products. [b]Mass spectrometry data were acquired using ESI techniques. [c]*N*-Terminal was acetylated.

We utilized circular dichroism (CD) spectroscopy to investigate whether the synthesized oligomers adopt ordered

DOI: 10.1021/acs.orglett.6b01726
Org. Lett. 2016, 18, 3678−3681

folding conformations. The CD spectra of α-ABpeptoids of varying length were obtained in acetonitrile at 20 °C in the far UV area (190−260 nm), which corresponds to a region of absorbance of amide bonds. CD values were expressed as mean residue ellipticity (MRE). As shown in Figure 2a, trimer **(*R*)-10b**

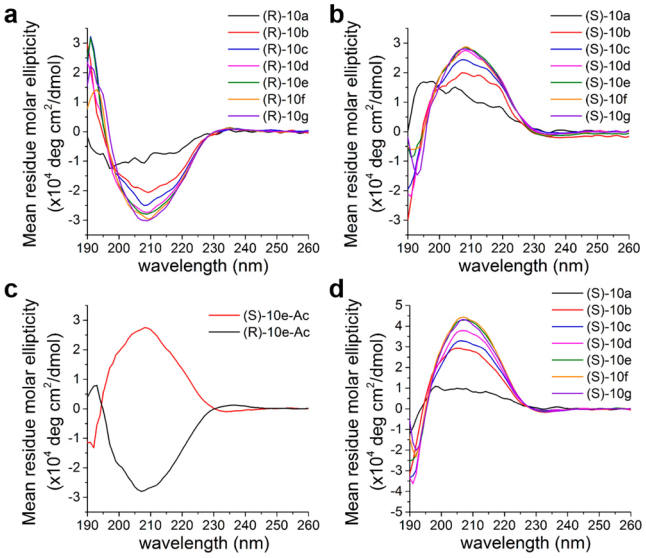


Figure 2. CD data. (A) CD spectra of (*R*)-form of α-ABpeptoids **(*R*)-10a−g** (2-mer to 8-mer) in acetonitrile (60 μM). (B) CD spectra of (*S*)-form of α-ABpeptoids **(*S*)-10a-g** (2-mer to 8-mer) in acetonitrile (60 μM). (C) CD spectra of (*S*)- and (*R*)-forms of *N*-acetylated α-ABpeptoids in acetonitrile (60 μM). (D) CD spectra of (*S*)-form of α-ABpeptoids **(*R*)-10a−g** (2-mer to 8-mer) in trifluoroethanol (60 μM).

displayed a characteristic CD spectral feature with intense minima at near 208 nm and maxima at near 230 nm, while dimer **(*R*)-10a** did not show apparent CD signals. The CD intensity was gradually increased as the residues were added, and oligomers with more than five residues showed nearly identical CD spectra. The CD spectra of the oligomers are reminiscent of those of polyproline type II (PPII) helices (with a strong minimum at 200−210 nm and a weak maximum at 220−230 nm), which are not stabilized by intramolecular hydrogen bonds like peptoid foldamers.[54,55] Similar CD features were observed in α-ABpeptoids substituted with *N*-cyclohexyl and *N*-isobutyl side chains (Figure S6). These observations indicate that α-ABpeptoids are able to adopt ordered structures. This was supported by nuclear Overhauser effect (NOE) experiments. We investigated the increase in the number of NOEs in the trimer **(*R*)-10b** compared to dimer **(*R*)-10a** since ordered conformations normally induce additional NOEs, which are not observed in unstructured conformations. As shown in Figure S7, the numbers of NOEs in the NOESY spectrum of trimer **(*R*)-10b** were significantly increased compared to that of dimer **(*R*)-10a**. Moreover, some of the NOE peaks were totally missing in the dimer spectrum, suggesting that α-ABpeptoids of longer than dimer are able to adopt ordered structures.

Next, we investigated the CD spectra of the oligomers with opposite chirality. (*S*)-Forms of oligomers ranging in size from 2- to 8-mers **(*S*)-10a−g** were prepared using (*S*)-3-(*N*-benzyl-4-nitrophenylsulfonamido)-2-methylpropanoic acid **(*S*)-6** as a monomer building block by the same solid-phase synthetic route (Scheme 2). Not surprisingly, (*S*)-form oligomers gave rise to mirror image CD spectra compared to (*R*)-form oligomers (Figure 2B). These results suggest that the oligomers of α-ABpeptoids with opposite chirality adopt identical conformations of opposing handedness, and the formation of ordered conformations is attributed to the presence of chiral methyl groups on the backbone of the oligomers.

There is a possibility that the protonated *N*-terminus could influence the conformation of the oligomers presumably through intramolecular hydrogen bonds. To test this, we chose hexamers because they contain the minimum sequence showing the saturated CD signal intensity. Both (*S*)- and (*R*)-forms of *N*-acetylated hexamers **(*S*)-10e-Ac** and **(*R*)-10e-Ac** were synthesized by treatment with acetic anhydride and purified (Scheme S2, Figure S3, and Table 1), and the CD spectra for them were recorded under the same conditions. The spectral shape and intensity of the acetylated hexamers were nearly identical to those of **(*S*)-10e** and **(*R*)-10e** (Figure 2C), indicating that the *N*-terminal amine is not important for the formation of the conformation.

We then examined the influence of oligomer concentrations on CD spectra. There was no significant change in the CD signature of hexamer **(*R*)-10e** between 7 and 100 μM in acetonitrile (Figure S8), implying that the characteristic CD signals of the oligomers do not arise from intermolecular association or aggregation. Next, we investigated temperature dependence. The CD spectra of heptamer **(*R*)-10f** at different temperatures from 5 to 70 °C in acetonitrile were obtained to assess thermal stability of the ordered structure. The heptamer **(*R*)-10f** maintained the spectral shape, and the intensity of the minimum at 210 nm was slightly decreased over the temperature range (Figure S9). These results show that the ordered structures of the oligomers are thermally stable like helical conformations adopted by peptoids with chiral side chains. Lastly, we tested solvent effects on the conformations of oligomers. The CD spectra of oligomers of different chain lengths (**(*S*)-10a−g**) were recorded in polar protic solvents such as MeOH and trifluoroethanol (TFE) (Figure 2D and Figure S10). The oligomers exhibited nearly identical CD spectra to those observed in acetonitrile, suggesting that steric interactions between side chains would be a major driving force to form the ordered conformation, like peptoids with α-chiral side chains.[40−42,45,47,56,57]

In summary, we have introduced a new class of peptoids with backbone chirality, called α-ABpeptoids, which are composed of oligomers of *N*-substituted β^2-homoalanines. These oligomers displayed a characteristic CD spectral feature resembling of PPII helices, suggesting that they adopt ordered folding conformations. It should be noted that the observed CD spectra for α-ABpeptoids might arise from ensembles of different secondary conformations.[58] Thus, further structural studies such as X-ray study and NMR study would be needed to determine the detailed folding structures. We have also developed an efficient solid-phase synthetic method that allows for convenient preparation of α-ABpeptoid oligomers. It is worth noting that a library of α-ABpeptoids with a large chemical diversity can be generated by incorporating structurally diverse alkyl halides at the side-chain positions, while chemical diversity in peptoids with α-chiral side chains is limited by the shortage of chemically diverse α-chiral methyl-containing primary amines. Taken together, given their potential as foldamers, ease of synthesis, and structural diversity, α-ABpeptoids represent an interesting new class of peptoids that may be highly useful in biomedical applications and material sciences.

DOI: 10.1021/acs.orglett.6b01726
Org. Lett. 2016, 18, 3678−3681

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01726.

Experimental details, synthesis, and characterization data of all new compounds, NMR spectra, CD spectra, and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Samsung Research Funding Center of Samsung Electronics (SRTF-BA1402-13).

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DOI: 10.1021/acs.orglett.6b01726
Org. Lett. 2016, 18, 3678−3681