論文の内容の要旨

論文題目　Generation of Robust *trans*-Amide Helix by Using Bicyclic *β*-Proline Oligomers
（二環性β−プロリンオリゴマーによる剛直なトランスアミドヘリックスの創製）

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Introduction

It has been shown that non-natural *β*-amino acids can form regular structures such as helices. Development of robust helical structures that are relatively independent of environmental changes and interaction with short *β*-peptides is a challenging goal in the area of peptide engineering. To this aim, it is necessary to control amide *cis*-*trans* equilibrium as well as main chain conformation, because unbiased rotamers are present in the case of tertiary amides. It was reported that *β*-amino acid of bicyclic 7-azabicyclo[2.2.1]heptane derivatives bearing with a C4-bridgehead methoxymethyl group sides with the *cis*-amide completely (**Figure 1(a)**)[1]. Thus I expected that introduction of a substituent at the C1-bridgehead position can bias the equilibrium to the *trans*-amide conformation. In this work I show substitution at the bridgehead position C1 close to the carboxylic functionality can indeed shift the amide equilibrium to *trans* amide (**Figure 1(b)**). Thus a method for synthesis of *β*-proline mimics, bridgehead-substituted 7-azabicyclo[2.2.1]heptane-*endo*-carboxylic acid and the homooligomers ((***R*)-2, 3, 4, 6, 8,** (***S*)-2^{h}** and (***S*)-3^{h}**) was established and their structures were investigated (**Figure 1(c)**).

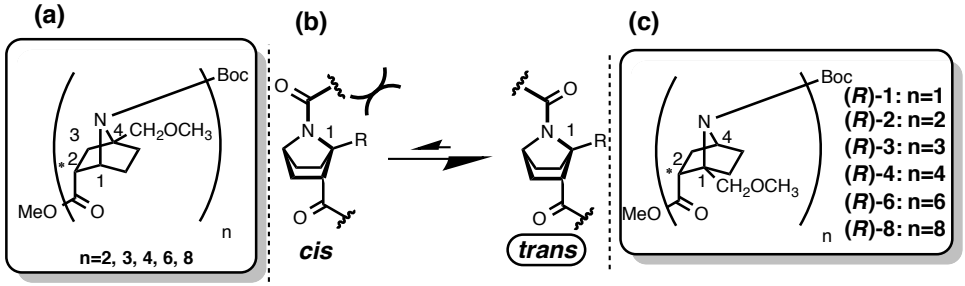
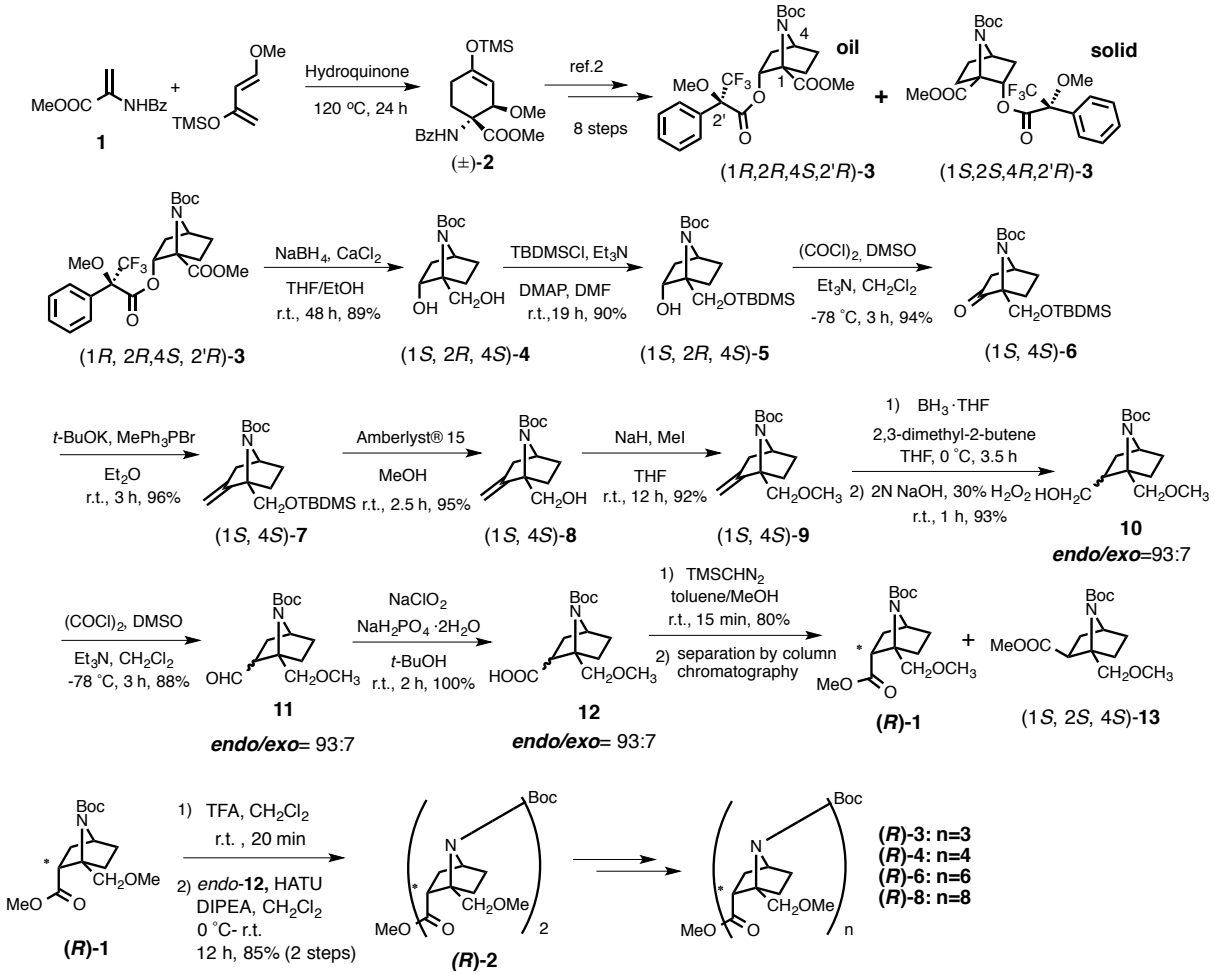


Figure 1. (a) *cis*-Amide homooligomers. (b) Controlling amide *cis*-*trans* equilibrium by steric hindrance. (c) Target *trans*-amide homooligomers.

Results and Discussion

1. Synthesis of monomers and homooligomers

A synthetic route of *β*-amino acid unit ((***R*)-1**) is established for the first time **(Scheme 1)**:

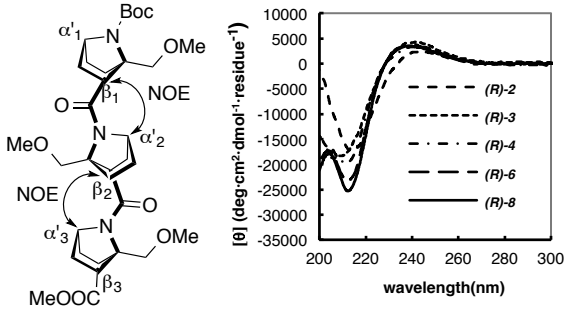


Scheme 1. Synthesis of homooligomers with bridgehead-substituted bicyclic *β*-amino acid.

the two diastereoisomers of *α*-methoxy-*α*-(trifluoromethyl)phenylacetyl (MTPA) ester (1*R*,2*R*,4*S*,2'*R*)-**3** and (1*S*,2*S*,4*R*,2'*R*)-**3**[2] were separated by recrystallization from *n*-octane to afford two optically pure diastereoisomers. The stereochemical structure of (1*S*,2*S*,4*R*,2'*R*)-**3** in the solid state was confirmed by X-ray crystallographic analysis. Diol **4** was obtained from ester **3** by reduction, and the primary alcohol was selectively protected with a TBDMS group. Oxidation of this secondary alcohol **5** gave ketone **6**, followed by Wittig reaction to give *exo*-olefin **7**. The silyl group was deprotected with Amberlyst®-15, followed by methyl etherification to give **9**. Hydroboration-oxidation reaction of *exo*-methylene **9** was performed with a combination of BH_3·THF and 2,3-dimethyl-2-butene to afford alcohol **10**. The bulky 2,3-dimethylbutan-2-ylborane (thexyl borane) improved the facial selectivity, affording an *endo/exo* ratio of 93:7. The resulting mixture of alcohols **10** was subjected to sequential oxidation reactions; Swern oxidation, and following Pinnick oxidation gave the corresponding aldehyde **11** first and the carboxylic acid **12**, which was transformed to methyl ester by the action of (trimethylsilyl)diazomethane ($TMSCHN_2$). At this stage, the *endo/exo* isomers of the methyl ester were separated by column chromatography on silica gel to give **(*R*)-1**.

With the building block in hand, sterically congested homooligomers, dimer **(*R*)-2**, trimer **(*R*)-3**, tetramer **(*R*)-4**, hexamer **(*R*)-6** and octamer **(*R*)-8**, were successfully synthesized by means of a solution-phase coupling procedure using O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and *N,N*-diisopropylethylamine (DIPEA). All oligomers were obtained in moderate to good yields (52-85%).

2. Structural Analysis of Homooligomers



(a) **(b)**

Figure 2. (a) Diagnostic inter-residue NOE of **(*R*)-3**. (b) CD spectra of **(*R*)-2**, **(*R*)-3**, **(*R*)-4**, **(*R*)- 6**, and **(*R*)-8** at 100 μM in methanol.

With the homooligomers in hand, structural studies of the homooligomers in solution and solid states were performed. I investigated the solution conformation of the oligomers by 2D-NMR in various kinds of protic and aprotic solvents. The observed NOE signals in all of the solvents are consistent with the postulate that the oligomers take *trans* amide conformation (**Figure 2(a)**), while the *cis* conformer is practically not detected. Single crystal structure analyses of the optical pure **(*R*)-2** and *p*-BrBz-**(*R*)-3**-OH were successfully conducted. Both the **(*R*)-2** and *p*-BrBz-**(*R*)-3**-OH take *trans* amide conformation, which is consistent with the 2D-NMR results. And main chain conformation is well regulated. The energy-minimized structure of the octamer **(*R*)-8** was obtained by Monte Carlo conformation search followed by DFT geometry optimization. The energy-minimized structure bears all-*trans* amide and takes a left-handed helical structure, which coincided well with the crystal structure of *p*-BrBz-**(*R*)-3**-OH. In addition to the NMR spectra, circular dichroism (CD) spectra also highlighted a similar consistent folding property of these series of compounds (**Figure 2(b)**). The overall shapes of the signals and intensities per residue were similar throughout the range of oligomers.

3. Effect of Hydrogen Bonding on Oligomer Structures

The effect of intra-residual hydrogen bonding on the ordered structure was also studies.

Conclusion

I established a synthetic route to bridgehead-substituted 7-azabicyclo[2.2.1]heptane ester as a building block for oligomer formation.[3] Sterically congested homooligomers were also obtained in good yields by a solution coupling procedure, using HATU as a coupling reagent. I found that the homooligomers take robust helical structure with all-*trans* amide linkages. Crystal structural analysis of the dimers and the trimer showed that the conformation of each monomeric unit is highly preorganized, indicating that the oligomers take consistent helical structure from the dimer to the octamer. I believe these oligomers will be useful as scaffolds for functional helical molecules with a range of potential biochemical applications, e.g., as modulators of protein-protein interactions and reliable spacers with well-defined lengths, upon installing various functional groups at the bridgehead positions.

Reference: (1) M. Hosoya; Y. Otani; M. Kawahata; K. Yamaguchi; T. Ohwada. *J. Am. Chem. Soc.* **2010**, *132*, 14780-14789. (2) A. Avenoza; J. I. Barriobero; J. H. Busto; C. Cativiela, J. M. Peregrina. *Tetrahedron Asymm.* **2002**, *13*, 625-632. (3) S. Y. Wang; Y. Otani; X. Liu; M. Kawahata; K. Yamaguchi; T. Ohwada. *J. Org. Chem.* **2014**, *79*, 5287-5300.