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Robust *trans*-Amide Helical Structure of Oligomers of Bicyclic Mimics of *β*-Proline: Impact of Positional Switching of Bridgehead Substituent on Amide *cis*−*trans* Equilibrium

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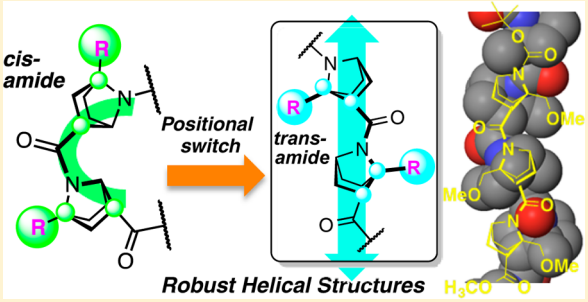
Supporting Information

ABSTRACT: Because homooligomers of 7-azabicyclo[2.2.1]-heptane-2-*endo*-carboxylic acid, a bridged *β*-proline analogue with a substituent installed at the remote C4-bridgehead position, completely biased the amide *cis*−*trans* equilibrium to the *cis*-amide structure, we expected that introduction of a substituent at the C1-bridgehead position adjacent to the carboxylic acid moiety, rather than the remote C4-bridgehead position, would tip the *cis*−*trans* amide equilibrium toward *trans*-amide structure without the aid of hydrogen bonding. Thus, in this work we established an efficient synthetic route to an optically active bicyclic analogue of 1,1-disubstituted *β*-proline, bearing a substituent at the C1-bridgehead position. Crystallographic, spectroscopic, and computational studies showed that indeed oligomers of this analogue take a consistent helical structure involving all-*trans*-amide linkages, independently of the number of residues, from the dimer up to the octamer. Oligomers composed of (*R*)-*β*-amino acid units form an extended left-handed helix with about 2.7 residues per turn and an approximately 4.0 Å rise per residue, characterized by complete lack of main-chain hydrogen bonding. This unique helical structure shows some similarity in shape to the *trans*-amide-based polyproline II (PPII) helix. The present helix was stable in various kinds of solvents such as alcohols. The present work provided a fundamental structural basis for future applications.



INTRODUCTION

Understanding the relationships between ordered structures of peptides/proteins and their functions, including their interactions with proteins, is crucial for molecular biology, chemical biology, and medicinal chemistry. However, this is still a challenging issue, partly because of the dynamic nature of peptide and protein structures in solution and the occurrence of interaction-induced changes in structures, as exemplified by induced fit and pre-existing equilibria of conformers.[1] Structural fluctuations are likely to be present even in ordered structures, as shown by the broad distributions of torsional angles (ϕ and ψ) in Ramachandran-type plots.[2] Artificial oligopeptides mimicking secondary structures of natural *α*-peptides and proteins could help to uncover structure−function relationships.

The polyproline II (PPII) helix,[3] which is frequently observed in proline-rich domains of natural proteins[4] and in short non-proline sequences in denatured proteins,[5] has been recognized as a *trans*-amide-based rigid helical structure. It is characterized by a complete lack of main-chain hydrogen bonding. Indeed, *α*-proline oligomers have been used as linkers with defined lengths in design of chemical probes to study protein−surface interactions and also have been used as molecular rulers.[6,7] However, while the PPII helix is stable in water, it is fragile in methanol, in which it is transformed into the *cis*-amide-based polyproline I (PPI) helix.[8]

Robust helical structures that are relatively independent of environmental changes and interaction with other molecules are therefore important 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. Inspired by the polyproline helix, researchers have intensively studied tertiary amide-linked *α*-peptides,[9] such as substituted *α*-proline[10] or peptoid.[11] Nevertheless, generation of well-defined helical structures from tertiary amide-linked *β*-amino acid derivatives has been little explored,[12] even though *β*-peptides have physicochemical advantages such as stability to enzymatic degradation.[13] Oligomers of *β*-proline have been synthesized and structurally investigated.[14] However, it was difficult to fully evaluate the structures, probably because of structural flexibility arising from both amide *trans*−*cis* (*E*−*Z*) isomerization and ring puckering. Thus, control of *cis*−*trans* isomerization of the amide linkage is crucial for the robustness of these ordered structures, and several recent studies have focused

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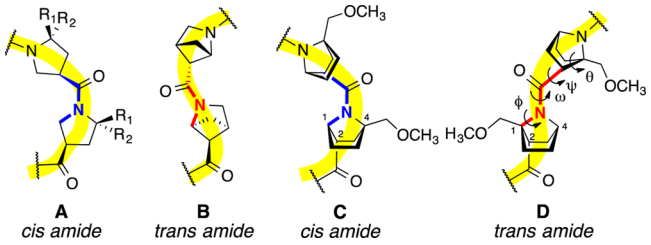

Figure 1. Conformationally constrained β-proline oligomers.

on conformationally constrained β-proline analogues, such as 2,2-disubstituted-β-proline (Figure 1, **A**)[15] and (1*S*,4*R*,5*R*)-5-*syn*-carboxy-2-azabicyclo[2.1.1]hexane, a methano-bridged pyrrolidine-β-carboxylic acid (Figure 1, **B**).[16] These studies showed that a *cis*-amide structure along the main chain is preferred in the former case (**A**), while an ordered secondary structure with all-*trans* amide bonds is preferred in the latter case (**B**).

We have also reported the synthesis and structural analysis of homooligomers of 7-azabicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, a bridged β-proline analogue.[17] Our further study of bicyclic oligomers with a substituent installed at the remote C4-bridgehead position (Figure 1, **C**) revealed that a bridgehead methoxymethyl substituent completely biased the amide *cis*–*trans* equilibrium to the *cis*-amide structure.[14] These helical structures were generated independently of the number of residues and irrespective of the solvent. This complete selectivity is assumed at least partially to stem from steric repulsion between the bridgehead substituent and the neighboring residue. Thus, we expected that introduction of a substituent at the C1-bridgehead position adjacent to the carboxylic acid moiety, rather than the remote C4-bridgehead position (Figure 1, **D**), would tip the *cis*–*trans* amide equilibrium toward *trans*-amide structure without the aid of hydrogen bonding.

In this study, we focused on creation of stable helical structure with all *trans*-amide linkages by means of substitution at the alternative bridgehead position of the present bicyclic β-proline mimic (**D**). We established a synthetic method for 7-azabicyclo-[2.2.1]heptane-2-*endo*-carboxylic acid bearing a C1-bridgehead substituent (**1**) and its homooligomers (**2**, **3**, **4**, **6**, and **8**) (Figure 2a).

We studied the secondary structures of these oligomers (**2**, **3**, **4**, **6**, and **8**) in solution and in the solid state and found that the homooligomers take stable helical structures with all-*trans* amide linkage, from the dimer through to the octamer. These helical molecules show some overall similarity of shape to the PPII helix, presumably because both assume a *trans*-amide structure. The structure was stable in various solvents and under heating. These results indicate that positional switching of the bridgehead substituent in the present bicyclic system is an effective strategy to completely control the amide *cis*–*trans* equilibrium.

RESULTS AND DISCUSSION

Design and Synthesis of C1-Bridgehead Methoxymethyl-Substituted Bicyclic β-Amino Acids and Their Homooligomers. We anticipated that bicyclic β-amino acids ((*R*)-**1** and (*S*)-**1**) bearing a substituent at the C1-bridgehead position would be *trans*-amide structure-inducing (Figure 2a). A methoxymethyl group was chosen as the substituent because it was shown to increase water solubility in the case of *cis*-amide based oligomers.[18] DFT calculations of both *cis*- and *trans*-rotamers of dimer (*R*)-**2** showed that the *trans* rotamer is more stable than the *cis* rotamer by 5.4 kcal/mol (Figure 2b). This result supports the idea that a substituent at the C1-bridgehead

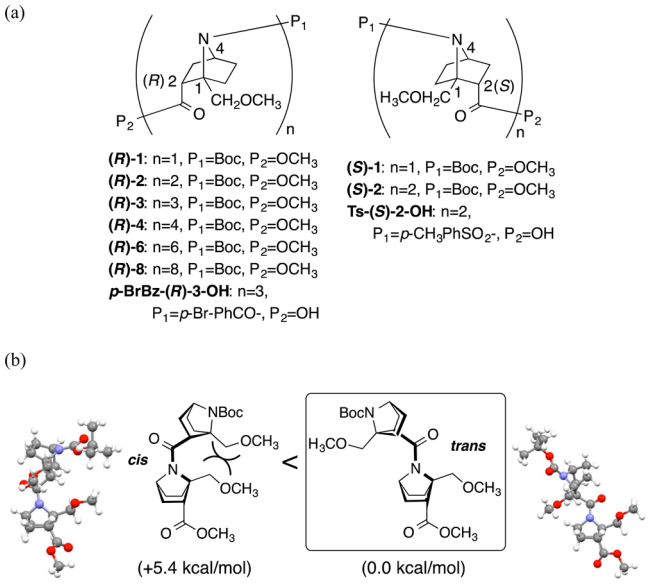

Figure 2. (a) Bicyclic amide oligomers with a substituent at the C1 position synthesized in this study. (b) DFT-calculated structures and energy difference between *cis* and *trans* rotamers of dimer (*R*)-**2**.

position will tip the *cis*–*trans* equilibrium toward the *trans* amide and result in generation of robust helical structures. Therefore, we set out to synthesize this β-amino acid unit ((*R*)-**1** and (*S*)-**1**) and its homooligomers (Figure 2a).

β-Amino Acid Synthesis. We established a new synthetic route of the present β-amino acid unit ((*R*)-**1** and (*S*)-**1**) (Scheme 1): two diastereoisomers of α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester (1*R*,2*R*,4*S*,2′*S*)-**18** and (1*S*,2*S*,4*R*,2′*R*)-**18**[19] 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*)-**18** in the solid state was confirmed by X-ray crystallographic analysis (Figure S1 in Supporting Information). Diol **19** was obtained from ester **18** by reduction, and the primary alcohol was selectively protected with a TBDMS group. Oxidation of this secondary alcohol **20** gave ketone **21**, followed by Wittig reaction to give *exo*-olefin **22**. The silyl group was deprotected with Amberlyst-15, followed by methyl etherification to give **24**. Hydroboration–oxidation reaction of exo-methylene **24** was performed with a combination of BH_3·THF and 2,3-dimethyl-2-butene to afford alcohol **25**. 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 **25** was subjected to oxidation. Swern oxidation and then Pinnick oxidation gave first the corresponding aldehyde **26** and then the carboxylic acid **27**, which was transformed to the 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**. The (2*S*)-enantiomer ((*S*)-**1**) was similarly synthesized.

Homooligomer Synthesis. With the building block in hand, sterically congested homooligomers, dimers (*S*)-**2** and (*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) (Scheme 2). The hexamer (*R*)-**6** was synthesized by coupling the amine of the dimer (*R*)-**2** to the carboxylic acid of the tetramer (*R*)-**4**. The octamer (*R*)-**8** was

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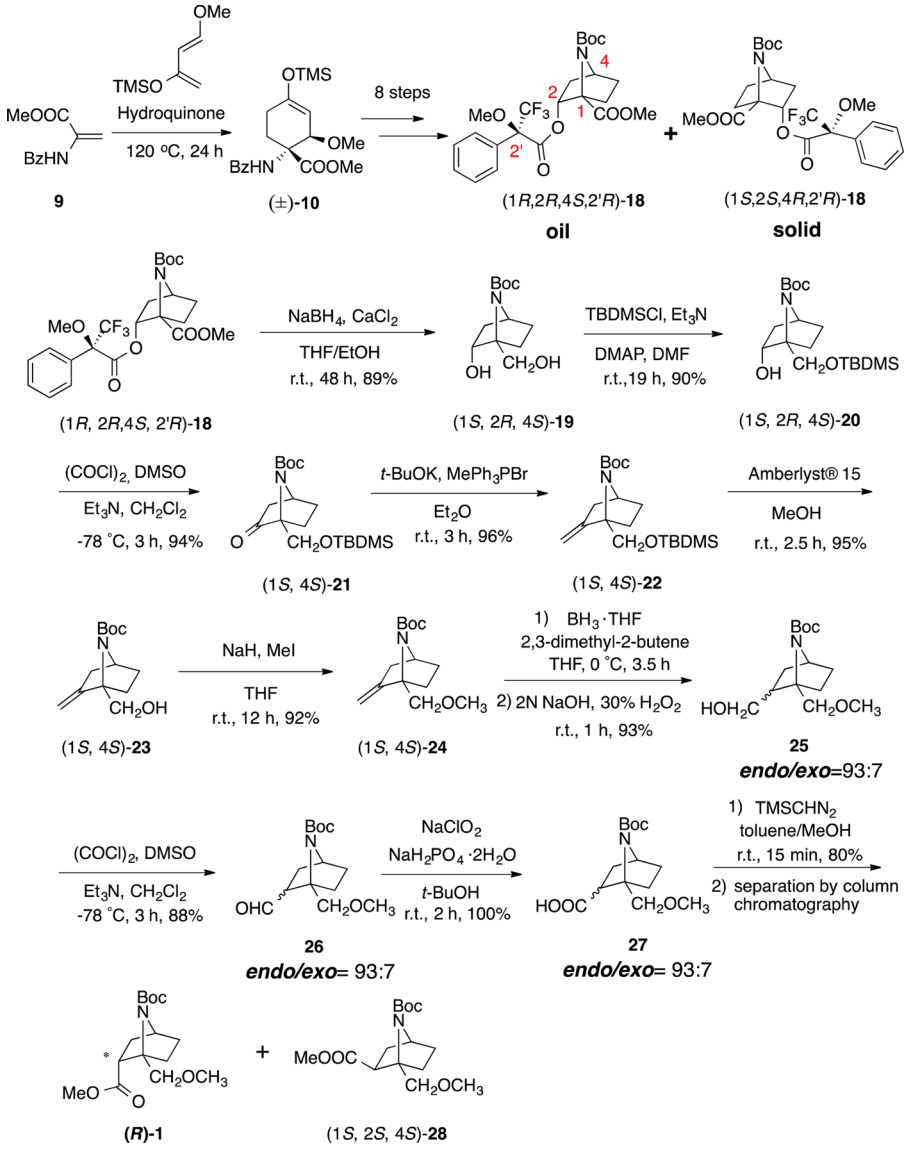
Scheme 1. Synthesis of Bridgehead-Substituted Bicyclic β-Amino Acid



synthesized by coupling the amine of (*R*)-**6** to the carboxylic acid of (*R*)-**2**. All oligomers were obtained in good to moderate yields.

Structural Analysis of the β-Amino Acid Oligomers. *Crystallographic Analyses.* Single-crystal structures of optically pure, protected monomeric β-amino acid (*R*)-**1** (Figure S2 in Supporting Information) and diastereoisomeric dimers (*R*)-**2** (Figure 3a) and (*S*)-**2** (Figure S3 in Supporting Information) were obtained (see crystallographic data, Table S1 in Supporting Information1). The crystal structure of (*R*)-**2** was consistent with the calculated *trans* structure of (*R*)-**2** ($\omega_2 = 172.3°$, $\phi_1 = 158.0°$, $\phi_2 = 154.8$, $\theta_1 = 158.3°$, $\theta_2 = 157.9°$, $\psi_1 = 88.7°$) (Figure 2b). To obtain other single crystals suitable for X-ray crystallographic analysis, we changed the N-terminal group from N-Boc to N-Ts and N-*p*-Br-Bz. Solid-state structures of *N*-tosyl-protected dimer carboxylic acid Ts-(*S*)-**2**-OH and the *N*-*p*-bromobenzoyl-protected trimer carboxylic acid ***p*-BrBz-(*R*)-3-OH** were determined (Figure 3b,c). Intermolecular water bridges involving two water molecules were detected in the crystal structure of *p*-BrBz-(*R*)-**3**-OH, which was recrystallized from water and methanol. This indicates that the carbonyl oxygen atoms of the amide in the present oligomer are directed outward and can work as hydrogen-bonding acceptors.[20]

The main-chain torsional angles of the optically pure oligomers are summarized in Table 1. In the solid state, the dimers and trimer all take *trans*-amide structures, i.e., the values of ω are close to ±180°. Furthermore, all of the torsion angles (ω, ϕ, θ, ψ) along the main chain converged to consistent values (Table 1): the absolute value of ϕ is in the range of 132.8−162.9°, that of θ is in the range of 153.8−168.7°, and that of ψ is in the range of 75.5−93.8°. These narrow distributions of structural parameters suggest the existence of homogeneous ordered structure even in the dimer.

NMR Spectroscopy. 1D-^{1}H, 1D-^{13}C, and 2D-NMR (COSY, TOCSY, and NOESY/ROESY) analyses were conducted for the dimer (*R*)-**2**, trimer (*R*)-**3**, tetramer (*R*)-**4**, hexamer (*R*)-**6**, and octamer (*R*)-**8** in various solvents including chloroform-*d*, methanol-d_4, and DMSO-d_6. The results showed that all of the oligomers take an all-*trans* amide structure that is heat-stable and independent of the solvent: diagnostic inter-residual NOEs between β_i-H and $\alpha'_{(i+1)}$-H were observed in the 2D-NOESY spectra of (*R*)-**2**, (*R*)-**3** (Figure 4),[21] and (*R*)-**4** (Figure S4 in

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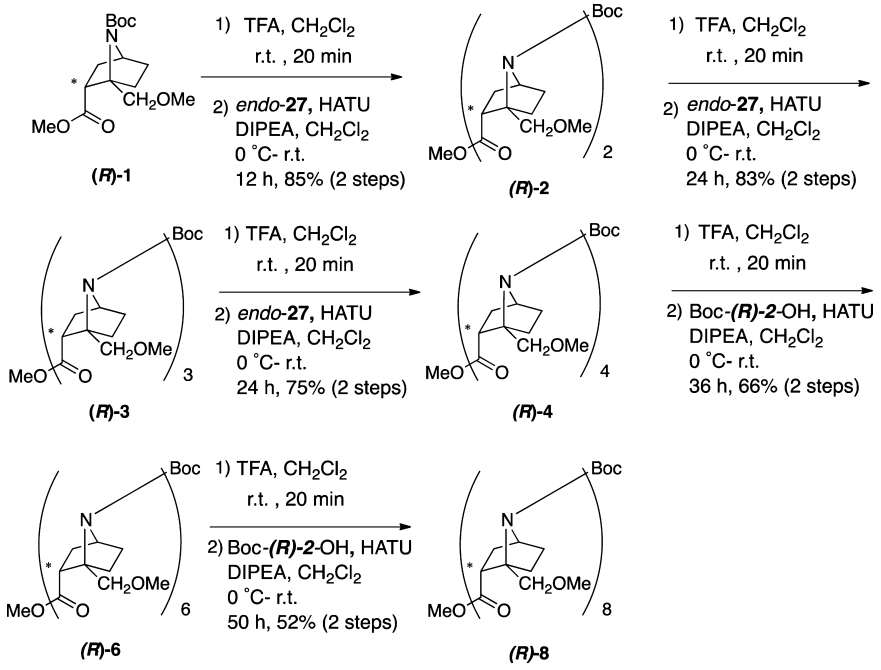
Scheme 2. Synthesis of Homooligomers (*R*)-2, (*R*)-3, (*R*)-4, (*R*)-6, and (*R*)-8



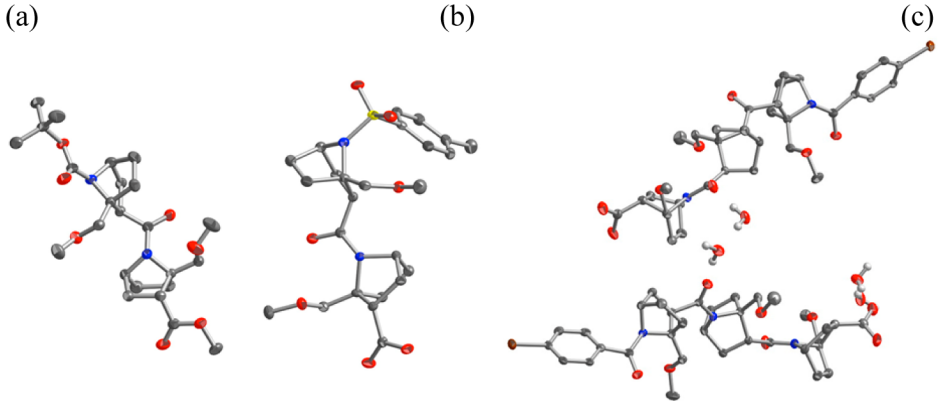


Figure 3. ORTEP drawings (50% probability) of the crystal structures of (a) (*R*)-**2**, (b) Ts-(*S*)-**2**-OH, and (c) *p*-BrBz-(*R*)-**3**-OH. Hydrogen atoms except for those of water molecules are omitted.

Table 1. Main-Chain Torsional Angles in the Crystal Structures[a,b]

compound	residue	ω (deg)	ϕ (deg)	θ (deg)	ψ (deg)
(*R*)-**2**	1	(163.3)	(165.9)	159.6	75.5
	2	174.6	162.1	156.7	(72.2)
(*S*)-**2**	1	(−162.8)	(−166.7)	−160.1	−75.0
	2	−172.7	−162.9	−157.4	(−74.2)
Ts-(*S*)-**2**-OH	1		(−89.8)	−153.8	−88.8
	2	−162.4	−153.4	−164.6	(153.5)
p-BrBz-(*R*)-**3**-OH	1	176.7	155.1	163.4	85.2
	2	179.7	151.2	155.2	93.8
	3	179.5	132.8	168.7	(−82.5)

[a]The torsional angles (ω, ϕ, θ, ψ) are defined in Figure 1, **D**. [b]The values excluding amide linkage are shown in parentheses.

Supporting Information) in chloroform-d and in methanol-d_4 (Figures S5−S7 in Supporting Information). The NOESY spectrum of (*R*)-**2** in a mixture of methanol-d_4 and D_2O (1:1, v/v) also showed that (*R*)-**2** took a single *trans*-amide conformer (Figure S8 in Supporting Information), which indicates that the *trans*-amide structure is stable even in the presence of water.

The NOESY spectrum of (*R*)-**6** and ROESY spectrum of octamer (*R*)-**8** were also obtained in $CDCl_3$ (Figures S9 and S10 in Supporting Information). Although some peaks were overlapped, both spectra showed the diagnostic NOEs/ROEs of an all-*trans* amide structure and no other cross-peaks were detected, excluding the contribution of equilibrating *cis*-amide conformers.

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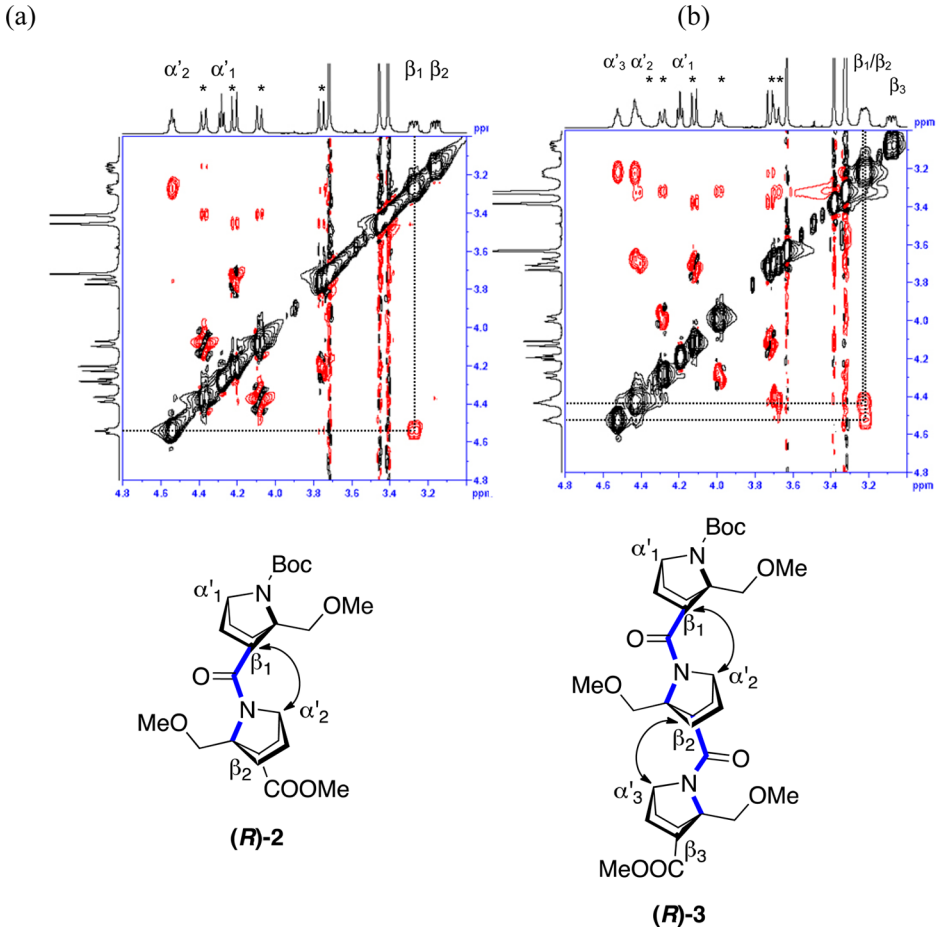

Figure 4. Diagnostic inter-residue NOE signals of (a) (*R*)-**2** and (b) (*R*)-**3** in $CDCl_3$ at 25 °C. Asterisks denote methylene proton signals of the bridgehead substituents.

The ^1H and ^{13}C NMR data at various temperatures showed the presence of a single *trans* conformer, and practically no *cis* conformer could be detected in the solution phase. When the temperature was gradually increased from 20 to 50 °C, there were only slight changes of the shapes and chemical shifts of the peaks (Figure S11 in Supporting Information).

Circular Dichroism. The CD spectra of (*R*)-**2**, (*R*)-**3**, (*R*)-**4**, (*R*)-**6**, and (*R*)-**8** were obtained at the concentration of 100 μM in methanol at 20 °C (Figure 5a). Intensities of the spectra were normalized in terms of the concentration and the number of residues. The spectra showed strong negative signals at around 215 nm and weaker positive signals at around 240 nm, different from those of *cis*-amide oligomers (strong positive signal at around 195 nm and strong negative signal at around 220 nm) (**C**, Figure 1).[18] While the shape of the CD spectrum of the dimer is a little different at short wavelength, the overall shapes of the signals and intensities per residue were similar throughout the range of oligomers, which is consistent with an idea that homogeneous ordered structures are formed. The CD spectrum of the dimer of the *S*-enantiomer ((*S*)-**2**) was a mirror image of the spectrum of the dimer of (*R*)-**2** with respect to the wavelength (*x*-axis) (Figure S12 in Supporting Information). Furthermore, the shapes of the signals of the present *trans*-amide oligomers resemble to those of other *trans*-amide-based helical molecules such as the PPII helix of α-proline in water[3c,5a,d] and oligomers of methano-bridged pyrrolidine-β-carboxylic acid (**B**, Figure 1)[16] but are different from those of *cis*-amide -based helix molecules such as 2,2-disubstituted-β-proline (**A**, Figure 1)[15] and the PPI helix of α-proline.[3c,5a,d]

The CD spectrum did not show significant solvent dependency. The CD spectra of (*R*)-oligomers in 2,2,2-trifluoroethanol (TFE) (Figure S13 in Supporting Information) were similar to those in methanol. The CD spectra for octamer (*R*)-**8** showed little change in mixtures of methanol and water at varying ratios, suggesting that water has little effect on the conformation of the octamer (Figure 5b). These results indicate that the present helix is stable in alcohols. This is in sharp contract to the observation that while the PPII helix is stable in water, it is fragile in methanol, being transformed into a *cis*-amide-based polyproline I (PPI) helix.[7] Further, the CD spectra of tetramer (*R*)-**4** in methanol in the concentration range of 50−1000 μM showed almost no change (Figure S14 in Supporting Information), which indicates that aggregation did not occur. Also, the CD spectra of octamer (*R*)-**8** (100 μM in methanol) did not change even after 2 months at rt, which indicates that time-dependent conformational change can be excluded. The CD spectra of hexamer (*R*)-**6** and octamer (*R*)-**8** in methanol did not change significantly as the temperature was raised to 50 °C (Figure S15 in Supporting Information).

Calculated Structure. The energy-minimized structure of the octamer (*R*)-**8** was obtained by Monte Carlo conformation search[22] followed by DFT geometry optimization in simulated water.[23,24] The energy-minimized structure bears all-*trans* amides and takes a left-handed helical structure. The helix has about 2.7 residues per turn and 4.2 Å rise per residue. These parameters are different, but not much, from the case of PPII (3 residues per

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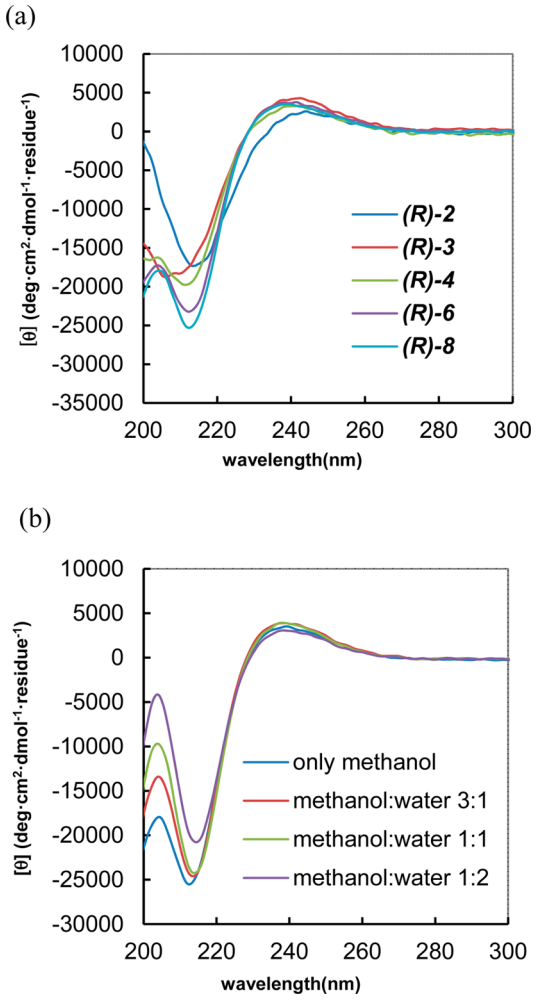

Figure 5. (a) CD spectra of (***R***)-**2**, (***R***)-**3**, (***R***)-**4**, (***R***)-**6**, and (***R***)-**8** at 100 μM in methanol at 20 °C. (b) CD spectra of (***R***)-**8** at 100 μM in mixed solutions of methanol and water at 20 °C.

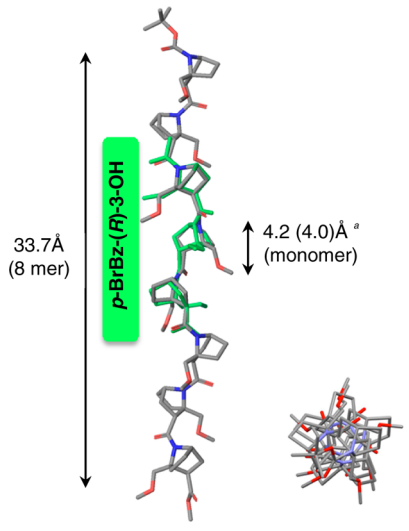

Figure 6. Side view and top view of the DFT-optimized structure of octamer (***R***)-**8** in water, superimposed on the crystal structure of trimer ***p*-BrBz-(*R*)-3-OH** (light green, the *p*-bromobenzoyl group is substituted with an acetyl group). Hydrogen atoms are omitted for clarity. [a]Mean-residue terminal-to-terminal distance between the nitrogen atom and the carbonyl carbon atom. The value in parentheses is the value calculated from the crystal structure.

turn and 3.1 Å per residue). The calculated structure of the octamer (***R***)-**8** coincided well with the crystal structure of *p*-BrBz-(***R***)-**3**-OH (4.0 Å rise per residue) along the main chain (Figure 6). This is also different from the structure of the *cis*-amide-type oligomer substituted at the C4-bridgehead position (**C**, Figure 1); the (*S*)-oligomer takes a left-handed *cis*-amide helix with about 4 residues per turn and a 2.2 Å rise per residue.[18]

The crystal structures of both dimers (***R***)-**2** and (***S***)-**2** also have a 4.0 Å rise per residue. These results indicate that the present oligomers have a highly organized structure with little fluctuation in terminal-to-terminal distance from the dimer to longer oligomers.

The crystal structure of trimer *p*-BrBz-(***R***)-**3**-OH and α-proline tetramer model with an idealized PPII structure are shown in Figure 7. These two oligomers have different chain

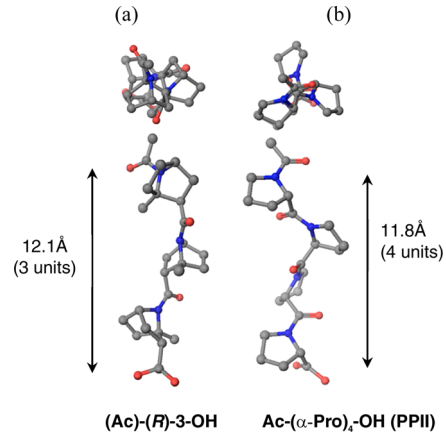

Figure 7. Top view and side views of (a) the crystal structure of trimer *p*-BrBz-(***R***)-**3**-OH (the methoxy groups of side chains are omitted and the *p*-bromobenzoyl group is changed to an acetyl group) and (b) Ac-α-Pro_4-OH (tetramer model) with typical PPII structure. Hydrogen atoms are omitted for clarity.

lengths, that is, the former has 3 units and the latter has 4 units, but both have similar values of terminal-to-terminal distances. Because the numbers of main-chain carbon atoms are different in the cases of α-proline and the β-amino acid, the helix pitch and main-chain torsion angles are different. The trimer *p*-BrBz-(***R***)-**3**-OH tends to take a more extended PPII-like helix. Nevertheless, the present helix and PPII helix show some degree of similarity.

■ CONCLUSIONS

We established a synthetic route to bridgehead-substituted 7-azabicyclo[2.2.1]heptane ester as a building block for oligomer formation. Sterically congested homooligomers were also obtained in good yields by a solution coupling procedure, using HATU as a coupling reagent. We found that the homooligomers take a robust helical structure with all-*trans* amide linkages. Furthermore, the all-*trans* amide structure was heat-stable and was also stable in both hydrophobic and hydrophilic solvents. Crystal structural analysis of the dimers and the trimer showed that the conformation of each monomeric unit is highly pre-organized, indicating that the oligomers take a consistent helical structure from the dimer to the octamer. This well-defined helix constitutes a new addition to the category of *trans*-amide helices, which was characterized by complete lack of main-chain hydrogen bonding. The present work has also demonstrated that positional switching of the bridgehead substituent in this bicyclic system is an efficient strategy to bias the amide *cis*–*trans*

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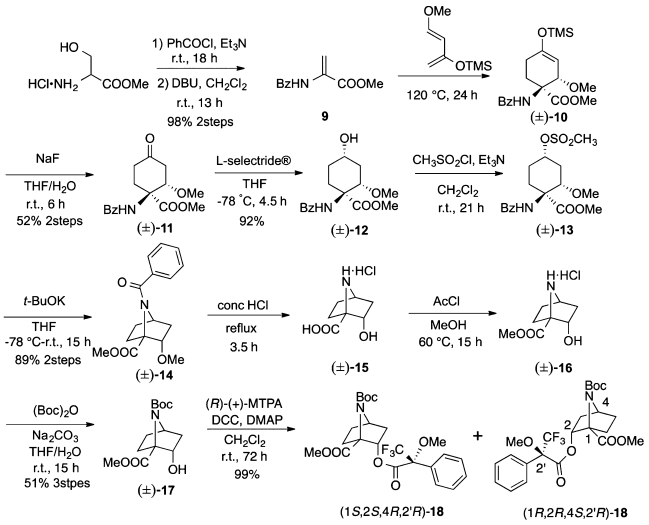
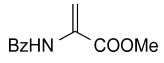
equilibrium. Two types of tertiary-amide oligomers with the same β-amino acid skeleton individually afforded *cis*-amide helix and *trans*-amide helix. We believe these oligomers will be useful as scaffolds for functional helical molecules with a range of potential biochemical applications, e.g., as modulators of protein−protein interactions and reliable spacers with well-defined lengths, upon installing various functional groups at the bridgehead positions. The present work provided a fundamental structural basis for future applications.

EXPERIMENTAL SECTIONS

General Procedures. Open column chromatography was carried out on silica gel (silica gel 60N (100−210 μm)). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) experiments were recorded on a NMR spectrometer at 25−50 °C. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) are shown in ppm. Coupling constants are given in hertz. Mass spectra were recorded on a micrOTOF-05. All of the melting points were measured with a Yanaco Micro Melting Point Apparatus without correction. The combustion analyses were carried out in the microanalytical laboratory of this department. All CD spectra were recorded on a spectropolarimeter in a 1 mm quartz cell. A series of synthetic procedures were repeated several times to synthesize all of the oligomers shown in the manuscript. Here we show the detailed procedure that afforded the product in highest yield.

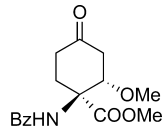


Compound ***9***.



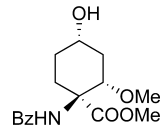
To a solution of serine methyl ester hydrochloride (8.0000 g, 51.42 mmol) in CH_2Cl_2 (150 mL) were added Et_3N (17.1706 g, 169.68 mmol) and benzoyl chloride (16.6246 g, 118.28 mmol) in portions at 0 °C. The mixture was stirred for 18 h at room temperature under argon atmosphere. Then the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give the residue (18.0217 g) as a yellow oil. The crude material was dissolved in CH_2Cl_2 (150 mL), and DBU (7.8282 g, 51.42 mmol) was added dropwise at 0 °C. The mixture was stirred for 13 h at room temperature. Another portion of DBU (2 mL) was added until the starting material disappeared. Then the reaction mixture was washed with water and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give 13.8034 g of a brown oil, which was column chromatographed just before the Diels−Alder reaction. Eluting with *n*-hexane/EtOAc (5/1 v/v) gave a colorless oil (10.3409 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.531 (brs, 1H), 7.838−7.817 (m, 2H), 7.549−7.462 (m, 3H), 6.800 (s, 1H), 6.000 (s, 1H), 3.895 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 164.8, 134.3, 132.1, 131.1, 128.8, 127.0, 108.9, 53.1.

*Compound (±)-**11**.*



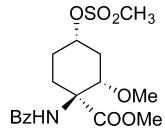
Compound **9** (4.5000 g, 21.93 mmol) was added to Danishefsky's diene (11.3356 g, 65.79 mmol) and hydroquinone (1.2079 g, 10.97 mmol). The reaction mixture was stirred at 120 °C for 24 h. This reaction mixture (containing **10**) was dissolved in a mixture of THF/H_2O (4/1 v/v) solution, and then NaF (1.2892 g, 30.70 mmol) was added to the mixture. After stirring for 6 h, the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give 7.2314 g of the residue, which was column chromatographed (solvent system: *n*-hexane/EtOAc = 2/1−1/1 v/v) to give (±)-**11** (3.3479 g, 52%) as a white solid. Mp: 128.0−129.0 °C (colorless crystal, recrystallized from *n*-hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.800−7.776 (m, 2H), 7.562−7.522 (m, 1H), 7.479−7.439 (m, 2H), 6.850 (brs, 1H), 4.336−4.306 (m, 1H), 3.840 (s, 3H), 3.358 (s, 3H), 2.782−2.723 (m, 3H), 2.643−2.542 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 172.0, 167.6, 134.0, 132.1, 128.7, 127.1, 80.0, 62.1, 57.7, 52.9, 41.3, 37.0, 26.7. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{16}H_{19}NO_5Na$: 328.1161, found 328.1151. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H,6.27; N, 4.59. Found: C, 62.79; H, 6.28; N, 4.59.

*Compound (±)-**12**.*



To a solution of compound (±)-**11** (8.5000 g, 27.84 mmol) in anhydrous THF (250 mL) was added L-Selectride (1.0 M in THF, 50.12 mL, 50.12 mmol) dropwise at −78 °C under Ar atmosphere. The mixture was stirred at −78 °C for 4.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was allowed to warm and was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give a yellow oil, which was column chromatographed (solvent system: *n*-hexane/EtOAc = 1/4 v/v) to give (±)-**12** (7.8719 g, 92%) as a white solid. Mp: 155.0−157.0 °C (white solid, recrystallized from *n*-hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.769−7.744 (m, 2H), 7.538−7.498 (m, 1H), 7.460−7.419 (m, 2H), 6.664 (brs, 1H), 4.113−4.086 (m, 1H), 3.957−3.828 (m, 1H), 3.828 (s, 3H), 3.404 (s, 3H), 2.514−2.483 (m, 1H), 2.342−2.308 (m, 1H), 2.116−1.991 (m, 1H), 1.931−1.900 (m, 3H), 1.811−1.777 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 166.9, 134.4, 131.9, 128.7, 126.9, 79.3, 66.6, 62.5, 58.4, 52.7, 32.4, 29.6, 23.3. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{16}H_{21}NO_5Na$: 330.1317, found 330.1316.

*Compound (±)-**13**.*



To a solution of compound (±)-**12** (6.3540 g, 20.67 mmol) in anhydrous CH_2Cl_2 (160 mL) were added Et_3N (5.2279 g, 51.68 mmol) and methanesulfonyl chloride (3.5522 g, 31.01 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 21 h at room temperature. Then the mixture was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated to give compound (±)-**13** (7.9669 g) as a pale orange amorphous solid, which was used for the next reaction without further purification except for a small portion of the crude product that was chromatographed on a silica gel column, eluting with *n*-hexane/EtOAc (1/3 v/v), and gave compound (±)-**13** as a white solid. Mp: 139.0−141.0 °C (white solid, recrystallized from *n*-hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.793−7.768 (m, 2H), 7.522−7.500 (m, 1H), 7.467−7.426 (m, 2H), 7.302 (brs, 1H), 4.884−4.832 (m, 1H), 4.357−4.317 (m, 1H), 3.866 (s, 3H), 3.359 (s, 3H), 3.046 (s, 3H), 2.725−2.689 (m, 1H), 2.500−2.465 (m, 1H), 2.240−2.139 (m, 3H),

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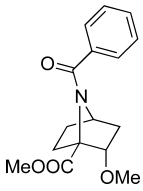
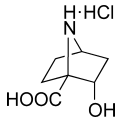
2.106−2.035 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 166.9, 134.8, 131.8, 128.7, 126.9, 63.4, 58.3, 53.1, 38.7, 33.2, 28.6, 26.6. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{17}H_{23}NO_7SNa$: 408.1087, found 408.1062. Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.98; H,6.02; N, 3.63. Found: C, 52.76; H, 5.88; N, 3.61.

*Compound (±)-**14**.*



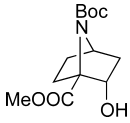
To a solution of compound (±)-**13** (3.7810 g, 7.94 mmol) in anhydrous THF (80 mL) was added a THF solution of *t*-BuOK (1.0692 g, 9.53 mmol) at −78 °C under Ar atmosphere. After stirring for 30 mi at −78 °C, the reaction mixture was warmed to room temperature and stirred for 15 h. Then the reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was stirred for 15 min. THF was evaporated, and the resultant mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to give 5.0178 g of yellow oil, which was column chromatographed (solvent system: *n*-hexane/EtOAc = 2/1−1/2 v/v) to give compound (±)-**14** (2.0445 g, 89% yield) as a white solid. Mp: 50.0−52.0 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.650−7.626 (m, 2H), 7.497−7.457 (m, 1H), 7.416−7.375 (m, 2H), 4.369−4.332 (m, 1H), 4.207−4.182 (m, 1H), 3.840 (s, 3H), 3.344 (s, 3H), 2.435−2.363 (m, 2H), 2.268−2.253 (m, 1H), 1.777−1.738 (m, 1H), 1.648−1.584 (m, 1H), 1.321−1.282 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 171.2, 134.2, 131.7, 128.7, 128.5, 82.9, 70.4, 62.3, 58.2, 52.7, 37.9, 30.9, 22.4. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{16}H_{19}NO_4Na$: 312.1212, found 312.1235. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H,6.62; N, 4.84. Found: C, 66.14; H, 6.57; N, 4.79.

*Compound (±)-**15**.*



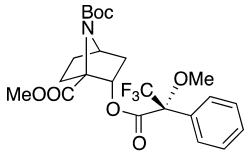
Compound (±)-**14** (800.0 mg, 2.77 mmol) was suspended in 12 N HCl (15 mL), and the mixture was heated to 120 °C under microwave heating for 3.5 h. Then the solvent was evaporated to give a residue, which was dissolved in water and washed with Et_2O. The aqueous layer was evaporated and then coevaporated with toluene to give compound (±)-**15** (560.4 mg) as a pale brown solid.

*Compound (±)-**17**.*



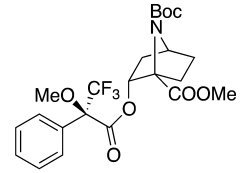
Acetyl chloride (5.7533 g, 73.29 mmol) was added dropwise to anhydrous MeOH (150 mL) at 0 °C, and the mixture was stirred for 10 min. To the solution was added compound (±)-**15**, and the solution was stirred at 60 °C for 15 h. The solution was concentrated in vacuo to give the residual oil, which was suspended in Et_2O, and the solvent was evaporated. This process was repeated twice more to give methyl ester hydrochloride (5.3924 g) as a pale brown solid. The hydrochloride salt was dissolved in water (40 mL), and Na_2CO_3 (5.1787 g, 48.86 mmol) was added to it. To the solution was added $(Boc)_2O$ (7.9989 g, 36.65 mmol) in THF(160 mL) at 0 °C. The mixture was stirred for 15 h at room temperature. Then brine was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give a residue, which was column chromatographed (solvent system: *n*-hexane/EtOAc = 2/1−1/1 v/v) to give (±)-**17** (3.3805 g, 51% from compound (±)-**14**) as a white solid. Mp: 84.0−86.0 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.611−4.571 (m, 1H), 4.219−4.195 (m, 1H), 3.814 (s, 3H), 2.540−2.487 (m, 1H), 2.368−2.326 (m, 1H), 2.296 (brs, 1H), 2.003−1.932 (m, 2H), 1.624−1.573 (m, 1H), 1.414 (s, 9H), 1.275−1.233 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 156.4, 81.1, 73.1, 71.4, 59.9, 52.4, 37.8, 29.6, 28.2, 25.8. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{13}H_{21}NO_5Na$: 294.1317, found 294.1329. Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.33; H, 7.55; N, 5.09.

*Compound **18**.* To a solution of alcohol (±)-**17** (3.1725 g, 11.70 mmol), DCC (3.1383 g, 15.21 mmol), and DMAP (100.2 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C was slowly added a solution of (*R*)-(+)-MTPA (3.5618 g, 15.21 mmol) in anhydrous CH_2Cl_2 (40 mL). The mixture was stirred at 0 °C for 1 h and the reaction was warmed to ambient temperature and stirred at room temperature for 72 h. The resulting suspension was filtered to remove the *N*,*N*′-dicyclohexylurea. The filtrate was concentrated in vacuo to give a white slurry, and the solvent was evaporated. The residue was purified by column chromatography, eluting with *n*-hexane/EtOAc (7/3 v/v), to give the mixture of (1*S*,2*S*,4*R*,2′*R*)-**18** and (1*R*,2*R*,4*S*,2′*R*)-**18** (5.6464 g, 99%). The diasteroisomers were separated by crystallization from *n*-octane to give (1*S*,2*S*,4*R*,2′*R*)-**18** as a white solid. The mother liquor containing (1*R*,2*R*,4*S*,2′*R*)-**18** was purified by column chromatography, using *n*-hexane/EtOAc (10/1 v/v) as eluent, to give (1*R*,2*R*,4*S*,2′*R*)-**18** as a colorless oil.



(1*S*,2*S*,4*R*,2′*R*)-**18**

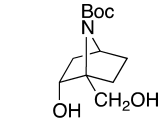
Mp: 94.0−94.2 °C (recrystallized from *n*-octane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.516−7.492 (m, 2H), 7.429−7.402 (m, 3H), 5.608−5.571 (m, 1H), 4.338−4.313 (m, 1H), 3.771 (s, 3H), 3.521−3.518 (m, 3H), 2.536−2.523 (m, 1H), 2.182−1.936 (m, 3H), 1.600−1.498 (m, 1H), 1.419 (s, 9H), 1.378−1.337 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 165.9, 155.6, 131.9, 129.8, 128.5, 127.5, 124.7, 121.9, 84.9, 84.6, 81.6, 76.1, 70.2, 59.6, 55.4, 52.5, 37.2, 28.6, 28.1, 26.4. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{23}H_{28}NF_3O_7Na$: 510.1716, found 510.1724. Anal. Calcd for $C_{23}H_{28}NF_3O_7$: C, 56.67; H, 5.79; N, 2.87. Found: C, 56.80; H, 5.76; N, 2.83.



(1*R*,2*R*,4*S*,2′*R*)-**18**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.524−7.500 (m, 2H), 7.417−7.400 (m, 3H), 5.577−5.540 (m, 1H), 4.307−4.282 (m, 1H), 3.807 (s, 3H), 3.524−3.522 (m, 3H), 2.558−2.479 (m, 1H), 2.240−2.174 (m, 1H), 2.116−2.037 (m, 1H), 1.978−1.898 (m, 1H), 1.469−1.372 (m, 1H), 1.420 (s, 9H), 1.272−1.233 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 166.0, 155.8, 132.1, 129.9, 128.6, 127.8, 124.9, 122.0, 84.9, 84.7, 81.8, 76.3, 70.4, 59.7, 55.5, 52.6, 37.4, 28.8, 28.2, 26.6. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{23}H_{28}NF_3O_7Na$: 510.1716, found 510.1707. Anal. Calcd for $C_{23}H_{28}NF_3O_7$: C, 56.67; H, 5.79; N, 2.87. Found: C, 56.38; H, 5.72; N, 2.84.

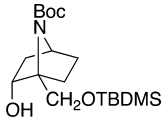
*Compound (1S,2R,4S)-**19**.*



dx.doi.org/10.1021/jo500916j | J. Org. Chem. 2014, 79, 5287−5300

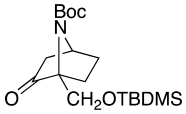
To a suspension of compound (1*S*,2*S*,4*R*,2′*R*)-**18** (831.2 mg, 3.06 mmol) and $CaCl_2$ (679.2 mg, 7.38 mmol) in EtOH (24 mL)/THF (16 mL) at 0 °C was added $NaBH_4$ (463.1 mg, 12.24 mmol). The suspension was stirred at room temperature for 48 h. The mixture was diluted with EtOAc and extracted with 5% aqueous K_2CO_3, 0.5 N HCl, and brine. The organic layer was dried, filtered, and evaporated to give 853.4 mg of the diol as a white solid. Column chromatography (solvent system: *n*-hexane/EtOAc = 1/1−1/2 v/v) gave the compound (1*S*,2*R*,4*S*)-**19** (420.1 mg, 89%) as a white solid. Mp: 137.0−138.0 °C (recrystallized from *n*-hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.333−4.293 (m, 1H), 4.160−4.134 (m, 1H), 3.997 (d, J = 12.8 Hz, 1H), 3.855 (d, J = 12.8 Hz, 1H), 3.760 (brs, 2H), 2.224−2.112 (m, 2H), 1.781−1.732 (m, 1H), 1.590−1.474 (m, 2H), 1.438 (s, 9H), 1.179−1.138 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 80.6, 71.5, 70.1, 60.2, 58.6, 38.2, 29.8, 28.5, 23.7. HRMS (ESI-TOF, [M + Na]$^+$) calcd for $C_{12}H_{21}NO_4Na$: 266.1368, found 266.1373. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.99; H, 8.48; N, 5.74.

*Compound (1S,2R,4S)-**20**.*



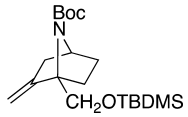
Compound (1*S*,2*R*,4*S*)-**19** (389.3 mg, 1.60 mmol) was dissolved in anhydrous DMF (20 mL), and then TBDMSCl (277.3 mg, 1.84 mmol), Et_3N (0.27 mL, 1.92 mmol), and DMAP (47.0 mg, 0.38 mmol) were added. The mixture was stirred at room temperature for 19 h. The mixture was extracted with water and CH_2Cl_2, and the organic layer was dried over Na_2SO_4 and evaporated to give a residue, which was column chromatographed (solvent system: *n*-hexane/EtOAc = 20/1−15/1 v/v) to give compound (1*S*,2*R*,4*S*)-**20** (380.0 mg, 90%) as a white solid. Mp: 40.0−41.0 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.329 (s, 2H), 4.328−4.172 (m, 1H), 4.159−4.146 (m, 1H), 3.081 (s, 1H), 2.599−2.200 (m, 1H), 2.195−2.143 (m, 1H), 1.828−1.785 (m, 1H), 1.618−1.554 (m, 1H), 1.424 (s, 9H), 1.046 (dd, J = 6.0 Hz, 3.6 Hz, 1H), 0.903 (s, 9H), 0.902−0.873 (m, 1H), 0.108 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 79.9, 76.9, 68.5, 68.4, 58.7, 37.0, 29.9, 28.4, 26.0, 18.2, −5.45, −5.48. HRMS (ESI-TOF, [M + Na]$^+$) calcd for $C_{18}H_{35}NO_4SiNa$: 380.2233, found 380.2220. Anal. Calcd for $C_{18}H_{35}NO_4Si$: C, 60.46; H, 9.87; N, 3.92. Found: C, 60.24; H, 9.92; N, 3.87.

*Compund (1S,4S)-**21**.*



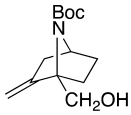
To a mixture of oxalyl chloride (269.1 mg, 2.12 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise a solution of DMSO (248.5 mg, 3.18 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C, and the mixture was stirred for 20 min at −78 °C. Then a solution of compound (1*S*,2*R*,4*S*)-**20** (377.4 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −78 °C, and the mixture was stirred for 40 min at −78 °C. Then Et_3N (643.6 mg, 6.36 mmol) was added to the solution in one portion at −78 °C, and the mixture was stirred for 15 min at −78 °C and then for 1 h at ambient temperature. Saturated aqueous NH_4Cl was added to the mixture, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give a residue, which was column chromatographed (solvent system: *n*-hexane/EtOAc = 20/1−15/1 v/v) to give ketone (1*S*,4*S*)-**21** (326.1 mg, 94%) as a colorless needle crystal. Mp: 41.5−42.5 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.590−4.565 (m, 1H), 4.312−4.234 (m, 2H), 2.478−2.415 (m, 1H), 2.093−1.940 (m, 3H), 1.573−1.522 (m, 2H), 1.450 (s, 9H), 0.880 (s, 9H), 0.087 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.4, 155.2, 80.6, 73.8, 59.4, 56.6, 44.6, 28.2, 27.2, 27.0, 25.8, 18.3, −5.4, −5.5. HRMS (ESI-TOF, [M + Na]$^+$) calcd for $C_{18}H_{33}NO_4SiNa$: 378.2077, found 378.2067. Anal. Calcd for $C_{18}H_{33}NO_4Si$: C, 60.81; H, 9.36; N, 3.94. Found: C, 61.02; H, 9.09; N, 3.97.

*Compund (1S,4S)-**22**.*



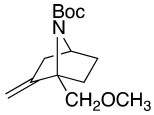
To a solution of *t*-BuOK (183.8 mg, 1.64 mmol) in anhydrous Et_2O (12 mL) was added methyltriphenylphosphonium bromide (650.2 mg, 1.82 mmol) at 0 °C. The reaction mixture was heated at reflux with stirring for 1 h, and then the whole was cooled to room temperature. A solution of compound (1*S*,4*S*)-**21** (321.1 mg, 0.91 mmol) in Et_2O was added to the above mixture at room temperature, and the reaction mixture was stirred for additional 3 h at room temperature. The reaction mixture was quenched by the additional of water, and the whole was extracted with Et_2O. The combined organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. Column chromatography (solvent system: *n*-hexane/EtOAc = 20/1 v/v) gave compound (1*S*,4*S*)-**22** (300.5 mg, 96% yield) as a colorless needle crystal. Mp: 40.5−41.5 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.159−5.147 (m, 1H), 4.781−4.772 (m, 1H), 4.358 (d, J = 10.4 Hz, 1H), 4.279 (t, J = 4.8 Hz, 1H), 4.230 (d, J = 10.0 Hz, 1H), 2.506−2.455 (m, 1H), 2.176−2.137 (m, 1H), 1.994−1.903 (m, 1H), 1.858−1.782 (m, 1H), 1.775−1.715 (m, 1H), 1.417 (s, 9H), 1.395−1.333 (m, 1H), 0.896 (s, 9H), 0.090 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 151.3, 103.4, 79.8, 70.7, 64.3, 58.5, 39.1, 34.4, 28.5, 27.5, 26.0, 18.3, −5.3, −5.4. HRMS (ESI-TOF, [M + Na]$^+$) calcd for $C_{19}H_{35}NO_3SiNa$: 376.2284. Found: 376.2262. Anal. Calcd for $C_{19}H_{35}NO_3Si$: C, 64.54; H, 9.98; N, 3.96. Found: C, 64.29; H, 9.69; N, 3.85.

*Compound (1S,4S)-**23**.*



To a solution of compound (1*S*,4*S*)-**22** (450.4 mg, 1.27 mmol) in MeOH (15 mL) was added Amberlyst 15 (2.2836 g) at 0 °C, and the reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was filtered through a Celite, washed with EtOAc. Evaporation of the solvent gave the crude product as a brown oil. Column chromatography (solvent system: *n*-hexane/EtOAc = 6/1 v/v) gave compound (1*S*,4*S*)-**23** (289.6 mg, 95% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.872−4.851 (m, 1H), 4.846−4.840 (m, 1H), 4.320−4.296 (m, 1H), 4.189 (d, J = 13.0 Hz, 1H), 4.063 (d, J = 13.0 Hz, 1H), 2.513−2.455 (m, 1H), 2.193−2.144 (m, 1H), 2.052−1.986 (m, 1H), 1.885−1.800 (m, 1H), 1.497−1.398 (m, 2H), 1.408 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 149.5, 103.4, 80.5, 71.8, 60.0, 57.1, 39.0, 32.7, 28.40, 28.37. HRMS (ESI-TOF, [M + Na]$^+$) calcd for $C_{13}H_{21}NO_3Na$: 262.1419. Found: 262.1398. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.85; N, 5.85. Found: C, 65.04; H, 9.06; N, 5.83.

*Compound (1S,4S)-**24**.*



To a solution of compound (1*S*,4*S*)-**23** in THF (20 mL) was added NaH (145.2 mg, 3.63 mmol) at 0 °C. Ten minutes later, MeI (1.0305 g, 7.26 mmol) was added dropwise at 0 °C. Then the ice bath was withdrawn, and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water. The mixture was extracted with Et_2O. The combined organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. Column chromatography (solvent system: *n*-hexane/EtOAc = 10/1 v/v) gave compound (1*S*,4*S*)-**24** (282.6 mg, 92% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.938−4.926 (m, 1H), 4.804−4.794 (m, 1H), 4.323 (m, 1H), 4.112 (d, J = 10.0 Hz, 1H), 4.072 (d, J = 10.0 Hz, 1H), 3.454 (s, 3H), 2.523−2.472 (m, 1H), 2.175−2.127 (m, 1H), 2.059−1.987 (m, 1H), 1.886−1.836 (m, 1H), 1.610−1.547 (m, 1H), 1.434 (s, 9H), 1.417−1.364 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6,

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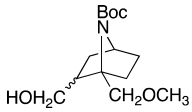
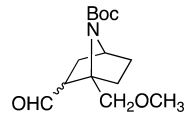
150.7, 103.0, 79.8, 72.1, 69.9, 59.4, 58.1, 38.5, 33.6, 28.4, 27.5. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{14}H_{23}NO_3Na$: 276.1576. Found: 276.1565. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.17; H, 8.94; N, 5.41.

Compound endo/exo ***25***.



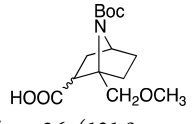
To a solution of BH_3·THF (1.0 M in THF, 55.0 mL, 2.64 mmol) at 0 °C was added 2,3-dimethylbut-2-ene (1.0 M in THF, 55.0 mL, 2.64 mmol), and the reaction mixture was stirred for 1 h. To the reaction mixture was added dropwise a solution of (1*S*,4*S*)- **24** (4.6007 g, 18.16 mmol) in THF (50 mL) at 0 °C, and the mixture was stirred for 2.5 h at this temperature. After that to the reaction solution were added 2 N NaOH solution (21.6 mL) and 30% H_2O_2 (14.5 mL) at 0 °C, and then the mixture was allowed to warm to ambient temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. Column chromatography (solvent system: *n*-hexane/EtOAc = 4/1−2/1 v/v) gave compound *endo/exo* **25** (4.5800 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.277−4.248 (m, 1H), 4.232−4.220 (m, 0.1H), 4.176−4.085 (m, 2H), 4.028 (d, J = 9.2 Hz, 1H), 3.968 (d, J = 10.0 Hz, 0.07H), 3.682−3.614 (m, 1H), 3.590−3.532 (m, 0.07H), 3.490−3.340 (m, 1H), 3.442 (s, 3H), 3.319−3.264 (m, 0.07H), 3.107−3.080 (m, 0.05H), 2.330−2.287 (m, 1H), 2.106−2.026 (m, 2.3H), 1.825−1.746 (m, 1.1H), 1.649−1.563 (m, 1.2H), 1.437 (s, 8.4H), 1.430 (s, 0.6H), 1.289−1.224 (m, 1.3H), 0.827−0.783 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 79.9, 76.0, 69.2, 59.4, 57.8, 48.5, 34.2, 28.7, 28.32, 28.29. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{14}H_{25}NO_4Na$: 294.1681, found 294.1673. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.77; H, 9.29; N, 5.10.

Compound endo/exo ***26***.



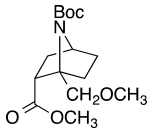
To a solution of oxalyl chloride (143.5 mg, 1.13 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DMSO (131.3 mg, 1.68 mmol) at −78 °C. The reaction mixture was stirred for 20 min, and a solution of *endo/exo* **25** (153.0 mg, 0.56 mmol) in anhydrous CH_2Cl_2 (8.0 mL) was added at −78 °C. The reaction mixture was stirred for 40 min at −78 °C, and then Et_3N (340.0 mg, 3.36 mmol) was added. The solution was allowed to warm to room temperature. After 1 h of stirring, the reaction mixture was quenched by the addition of water. The mixture was extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. Column chromatography (solvent system: *n*-hexane/EtOAc = 8/1 v/v) gave compound *endo/exo* **26** (132.8 mg, 88% yield) as a colorless oil. During the column chromatography process, we obtained some pure compound *endo* **26**, so the pure *endo* compound was used to determine the ^{1}H NMR and ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.780 (s, 1H), 4.278−4.255 (m, 1H), 4.238 (d, J = 10.0 Hz, 1H), 4.048 (d, J = 10.0 Hz, 1H), 3.411 (s, 3H), 3.059−3.009 (m, 1H), 1.900−1.736 (m, 4H), 1.681−1.661 (m, 1H), 1.411 (s, 9H), 1.431−1.398 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 155.0, 80.2, 74.9, 69.6, 59.5, 59.2, 57.6, 30.3, 30.1, 28.4, 28.3. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{14}H_{23}NO_4Na$: 292.1525, found 292.1544.

Compound endo/exo ***27***.



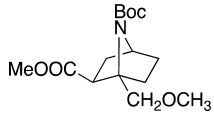
To a solution of *endo/exo* **26** (131.0 mg, 0.49 mmol) in *t*-BuOH (12 mL) were added 2-methyl-2-butene (702.8 mg, 10.02 mmol) and a solution of $NaClO_2$ (412.4 mg, 4.56 mmol) and NaH_2PO_4·$2H_2O$ (542.9 mg, 3.48 mmol) in H_2O (6 mL) at room temperature, and the reaction mixture was stirred for 2 h at room temperature. *t*-BuOH was evaporated, and the aqueous residue was poured into a 5% aqueous solution of $KHSO_4$ and extracted with EtOAc. The combined organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated to give compound *endo/exo* **27** (160.1 mg, 100% yield) as a white solid. Pure *endo* compound could be obtained by recrystallization, so the characterization data of the *endo* compound are shown. Mp: 88.0−89.0 °C (recrystallized from *n*-hexane/Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.390 (d, J = 10.0 Hz, 1H), 4.278−4.256 (m, 1H), 4.169 (d, J = 10.0 Hz, 1H), 3.539 (s, 3H), 3.147−3.101 (m, 1H), 2.094−2.059 (m, 2H), 1.956−1.825 (m, 2H), 1.731−1.663 (m, 1H), 1.557−1.494 (m, 1H), 1.444 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 155.1, 80.4, 74.4, 68.5, 59.5, 58.6, 50.3, 33.9, 30.4, 28.3, 28.1. HRMS (ESI-TOF, $[M - H]^-$) calcd for $C_{14}H_{22}NO_5$: 284.1498, found 284.1520. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.78; H, 7.94; N, 4.93.

(R)-1.



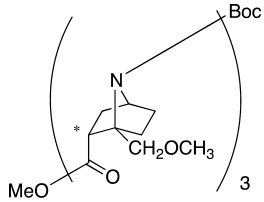
To a solution of compound *endo* **27** (80.0 mg, 0.28 mmol) in toluene/MeOH (3 mL/1 mL) was added $TMSCHN_2$ (0.28 mL, 0.56 mmol) at 0 °C. The reaction mixture was stirred for 15 min at room temperature under Ar atmosphere, and the solvent was evaporated. Column chromatography (solvent system: *n*-hexane/EtOAc = 10/1−5/1 v/v) gave compound (***R***)-**1** (52.4 mg) as a colorless oil and **28** (3.0 mg) as a colorless oil (80% in total yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.289−4.264 (m, 1H), 4.095 (d, J = 10.0 Hz, 1H), 4.019 (d, J = 10.0 Hz, 1H), 3.697 (s, 3H), 3..422 (s, 3H), 3.099−3.052 (m, 1H), 2.069−1.996 (m, 1H), 1.990−1.812 (m, 3H), 1.589−1.501 (m, 2H), 1.488 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 155.2, 80.0, 72.1, 70.2, 59.2, 59.1, 51.8, 48.0, 33.1, 28.5, 28.3, 28.2. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{15}H_{25}NO_5Na$: 322.1630, found 322.1618. Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.03; H, 8.24; N, 4.57. Optical rotation $[\alpha]_D$ = −32.5 (20 °C, *c* 1.0, chloroform)

*Compound (1S,2S,4S)-****28***.



^{1}H NMR (400 MHz, $CDCl_3$): δ 4.359−4.336 (m, 1H), 3.944−3.897 (m, 2H), 3.647 (s, 3H), 3..352 (s, 3H), 2.771−2.735 (m, 1H), 2.168−2.105 (m, 1H), 1.865−1.706 (m, 2H), 1.690−1.629 (m, 2H), 1.418 (s, 9H), 1.355−1.329 (m, 1H). HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{15}H_{25}NO_5Na$: 322.1630, found 322.1615.

(R)-2.

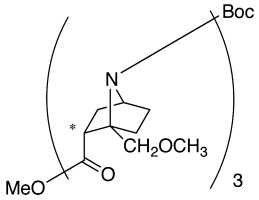


To a solution of (***R***)-**1** (598.8 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (10.0 mL) was added TFA (1.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% Na_2CO_3 aqueous solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. To a solution of *endo*-**27** (542.1 mg, 1.90 mmol) in anhydrous CH_2Cl_2 were added HATU (950.6 mg, 2.50 mmol) and DIPEA (0.9 mL, 5.00 mmol) at 0 °C, and the reaction mixture was allowed to warm to ambiente temperature for 12 h under Ar atmosphere. The reaction mixture was washed with water and extracted with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated. Column chromatography (solvent system: *n*-hexane/EtOAc = 10/1−2/1 v/v) gave compound (***R***)-**2** (753.5 mg, 85%) as a white solid. Mp: 93.5−94.5 °C (recrystallized from *n*-hexane). ^{1}H NMR (400 MHz,

dx.doi.org/10.1021/jo500916j | *J. Org. Chem.* 2014, 79, 5287−5300

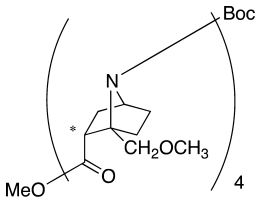
$CDCl_3$): δ 4.530−4.506 (m, 1H), 4.363 (d, J = 10.0 Hz, 1H), 4.269−4.244 (m, 1H), 4.202 (d, J = 10.0 Hz, 1H), 4.072 (d, J = 10.0 Hz, 1H), 3.749 (d, J = 10.0 Hz, 1H), 3.693 (s, 3H), 3.430 (s, 3H), 3.385 (s, 3H), 3.273−3.228 (m, 1H), 3.160−3.113 (m, 1H), 2.102−1.953 (m, 3H), 1.904−1.583 (m, 8H), 1.481−1.398 (m, 1H), 1.445 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 170.8, 155.2, 79.7, 72.6, 71.3, 70.9, 70.8, 59.3, 59.1, 58.9, 58.8, 51.8, 47.7, 46.3, 33.5, 32.8, 30.2, 28.9, 27.9, 27.2. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{24}H_{38}N_2O_7Na$: 489.2577, found 489.2581. Anal. Calcd for $C_{24}H_{38}N_2O_7$: C, 61.78; H, 8.21; N, 6.00. Found: C, 61.49; H, 8.06; N, 5.78. Optical rotation $[\alpha]_D$ = −46.4 (20 °C, c 1.0, chloroform)

(R)-3.



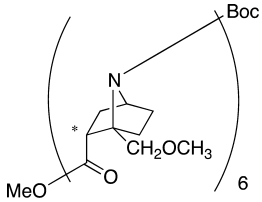
To a solution of (***R***)-**2** (145.1 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added TFA (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% Na_2CO_3 aqueous solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. To a solution of *endo*-**27** (79.9 mg, 0.28 mmol) in anhydrous CH_2Cl_2 were added HATU (136.9 mg, 0.36 mmol) and DIPEA (129.3 μL, 0.72 mmol) at 0 °C, and the reaction mixture was allowed to increase to ambiente temperature for 24 h under Ar atmosphere. The reaction mixture was washed with water and extracted with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated. Column chromatography (solvent system: n-hexane/EtOAc = 4/1−2/1 v/v) gave compound (***R***)-**3** (147.3 mg, 83%) as a white solid. Mp: 137.0−138.0 °C (recrystallized from n-hexane/Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.605−4.560 (m, 1H), 4.500−4.458 (m, 2H), 4.366 (d, J = 10.0 Hz, 1H), 4.276−4.247 (m, 1H), 4.198 (d, J = 10.0 Hz, 1H), 4.071 (d, J = 10.0 Hz, 1H), 3.798 (d, J = 10.0 Hz, 1H), 3.765 (d, J = 10.0 Hz, 1H), 3.698 (s, 3H), 3.450 (s, 3H), 3.393 (s, 3H), 3.386 (s, 3H), 3.290−3.280 (m, 2H), 3.163−3.125 (m, 1H), 2.063−1.601 (m, 16H), 1.496−1.395 (m, 2H), 1.449 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 170.8, 170.0, 155.2, 79.5, 72.5, 71.3, 70.8, 59.2, 59.1, 59.0, 58.74, 58.73, 58.5, 51.7, 47.6, 46.3, 45.9, 33.2, 32.3, 30.5, 30.2, 28.7, 28.3, 27.7, 27.1, 26.5. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{33}H_{51}N_3O_9Na$: 656.3523, found 656.3520. Anal. Calcd for $C_{33}H_{51}N_3O_9$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.26; H, 7.91; N, 6.61.

(R)-4.



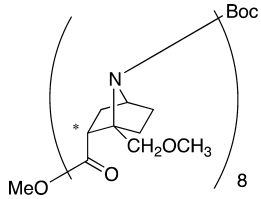
To a solution of (***R***)-**3** (29.0 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added TFA (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% aqueous Na_2CO_3 solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. To a solution of *endo*-**27** (31.4 mg, 0.11 mmol) in anhydrous CH_2Cl_2 were added HATU (53.3 mg, 0.14 mmol) and DIPEA (50.3 μL, 0.28 mmol) at 0 °C, and the reaction mixture was allowed to warm to ambiente temperature for 24 h under Ar atmosphere. The reaction mixture was washed with water and extracted with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated. Column chromatography (solvent system: n-hexane/EtOAc = 3/2−1/2 v/v) gave compound (***R***)-**4** (66.1 mg, 75%) as a white solid. Mp: 197.5−198.5 °C (white powder, recrystallized from n-hexane/DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.584−4.574 (m, 2H), 4.505−4.490 (m, 3H), 4.366 (d, J = 10.0 Hz, 1H), 4.266−4.242 (m, 1H), 4.185 (d, J = 10.0 Hz, 1H), 4.061 (d, J = 10.0 Hz, 1H), 3.801−3.728 (m, 3H), 3.694 (s, 3H), 3.446 (s, 3H), 3.400 (s, 3H), 3.384 (s, 3H), 3.382 (s, 3H), 3.332−3.297 (m, 3H), 3.163−3.125 (m, 1H), 2.049−1.593 (m, 21H), 1.466−1.394 (m, 3H), 1.444 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 171.1, 170.3, 170.2, 155.3, 79.6, 71.42, 71.35, 70.9, 59.3, 59.2, 59.1, 58.8, 58.6, 58.5, 51.8, 47.7, 46.5, 46.0, 33.3, 33.2, 32.7, 32.2, 30.6, 30.3, 28.8, 28.4, 27.8, 27.2, 26.5. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{42}H_{64}N_4O_{11}Na$: 823.4469, found 823.4489. Anal. Calcd for $C_{42}H_{64}N_4O_{11}$: C, 62.98; H, 8.05; N, 6.99. Found: C, 62.73; H, 7.83; N, 6.92.

(R)-6.



To a solution of (***R***)-**4** (45.6 mg, 0.06 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added TFA (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% aqueous Na_2CO_3 solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. To a solution of Boc-(***R***)-**2**-OH (24.0 mg, 0.05 mmol) in anhydrous CH_2Cl_2 were added HATU (24.8 mg, 0.07 mmol) and DIPEA (25.2 μL, 0.14 mmol) at 0 °C, and the reaction mixture was allowed to warm to ambiente temperature for 36 h under Ar atmosphere. The reaction mixture was washed with water and extracted with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated. Column chromatography (solvent system: EtOAc only) gave compound (***R***)-**6** (37.5 mg, 66%) as a white solid. Mp: 180.0−182.0 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.572−4.494 (m, 8H), 4.374 (d, J = 10.0 Hz, 1H), 4.272−4.248 (m, 1H), 4.189 (d, J = 10.0 Hz, 1H), 4.067 (d, J = 10.4 Hz, 1H), 3.812−3.757 (m, 6H), 3.701 (s, 3H), 3.453 (s, 3H), 3.405 (s, 3H), 3.393 (s, 3H), 3.389 (s, 3H × 2, overlap), 3.374 (s, 3H), 3.319−3.281 (m, 5H), 3.173−3.133 (m, 1H), 1.979−1.589 (m, 31H), 1.482−1.412 (m, 5H), 1.451 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 173.3, 171.4, 170.9, 170.7, 170.6, 155.4, 79.6, 71.72, 71.69, 71.6, 71.3, 71.13, 71.11, 59.6, 59.4, 59.1, 58.9, 58.7, 58.59, 58.57., 51.7, 47.9, 46.7, 46.32, 46.29, 46.2, 33.5, 33.0, 32.8, 30.6, 30.4, 28.9, 28.5, 28.0, 26.7. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{60}H_{90}N_6O_{15}Na$: 1157.6362, found 1157.6346.

(R)-8.



To a solution of (***R***)-**6** (46.9 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added TFA (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% Na_2CO_3 aqueous solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. To a solution of Boc-(***R***)-**2**-OH (20.8 mg, 0.05 mmol) in anhydrous CH_2Cl_2 were added HATU (19.8 mg, 0.05 mmol) and DIPEA (18.0 μL, 0.10 mmol) were at 0 °C, and the reaction mixture was allowed to warm to ambiente temperature for 50 h under Ar atmosphere. The reaction mixture was washed with water and extracted with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated. Column chromatography (solvent system: EtOAc only) gave compound (***R***)-**8** (29.0 mg, 52%) as a white solid. Mp: 190.0−191.5 °C (after column chromatography). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.605−4.541 (m, 6H), 4.541−4.450 (m, 6H), 4.365 (d, J = 10.0 Hz, 1H), 4.262−4.238 (m, 1H), 4.178 (d, J = 9.6 Hz, 1H), 4.065 (d, J = 10.0 Hz, 1H), 3.801−3.721 (m, 8H), 3.691 (s, 3H), 3.443 (s, 3H),

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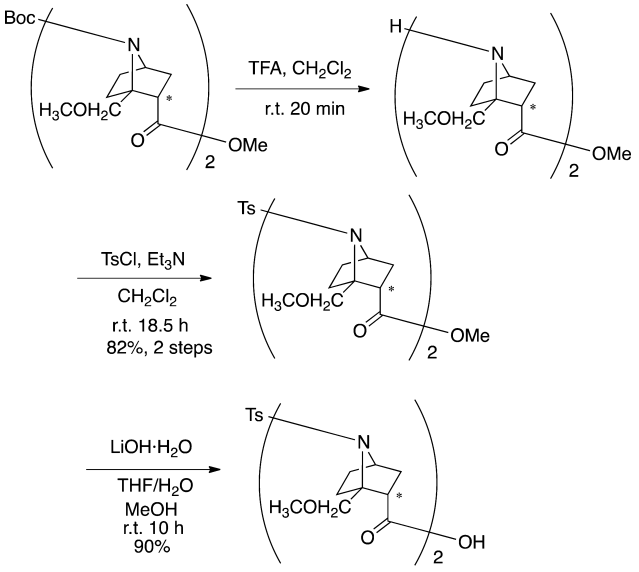
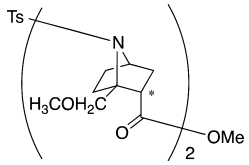
3.396 (s, 3H × 7, overlap), 3.379−3.300 (m, 7H), 3.162−3.124 (m, 1H), 2.045−1.596 (m, 42H), 1.402−1.393 (m, 6H), 1.441 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 173.3, 171.4, 170.8, 170.7, 170.6, 155.3, 79.5, 72.6, 71.7, 71.6, 71.3, 71.08, 71.06, 59.6, 59.4, 59.0, 58.9, 58.8, 58.6, 58.54, 58.52, 51.7, 47.8, 46.7, 46.3, 46.2, 33.5, 33.0, 32.9, 32.8, 30.6, 30.3, 28.9, 28.5, 28.0, 27.4, 26.7. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{78}H_{116}N_8O_{19}Na$: 1491.8254, found 1491.8279.



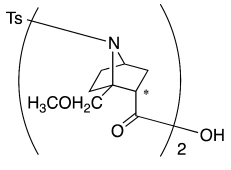
Synthesis of **Ts-(*S*)-2-OH**

*Ts-**(S)**-**2**-OMe.*

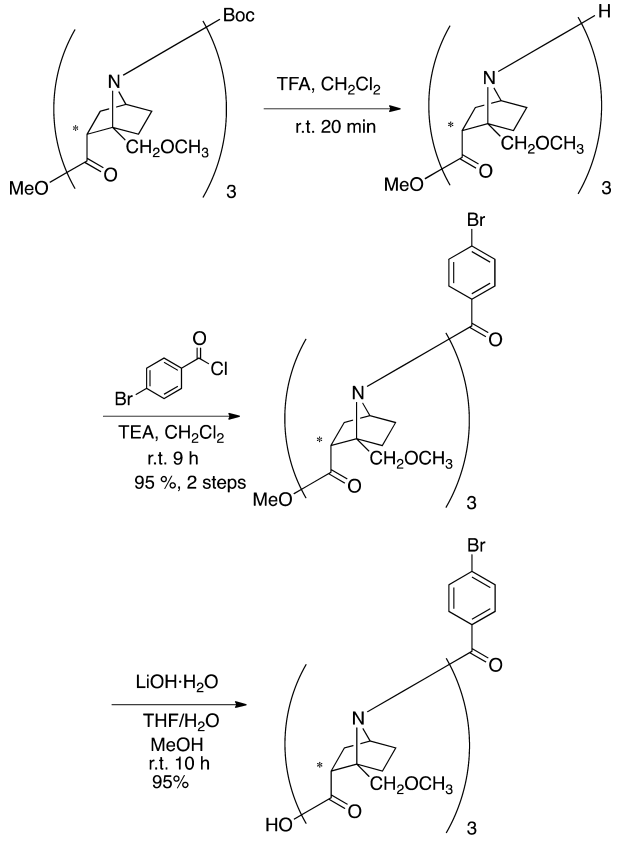


To a solution of (*S*)-**2** (49.0 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added TFA (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% Na_2CO_3 aqueous solution and extracted with EtOAc. Evaporation of the solvent gave the crude product. Anhydrous CH_2Cl_2 (1.5 mL) was added to the crude product, and then *p*-bromobenzyl chloride (24.8 mg, 0.13 mmol) and Et_3N (80 μL, 0.55 mmol) were added at 0 °C. Twenty minutes later the ice bath was removed, and the reaction mixture was stirred at room temperature for 18.5 h under Ar atmosphere. The solvent was evaporated, and column chromatography (solvent system: *n*-hexane/EtOAc = 3/1−2/1 v/v) gave compound Ts-(*S*)-**2**-OMe (46.7 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.825 (d, J = 8.4 Hz, 2H), 7.265 (d, J = 8.4 Hz, 2H), 4.364−4.340 (m, 1H), 4.319−4.314 (m, 1H), 4.301−4.289 (m, 1H), 4.011 (d, J = 10.0 Hz, 1H), 3.877 (d, J = 10.8 Hz, 1H), 3.669 (s, 3H), 3.639 (d, J = 10.8 Hz, 1H), 3.349 (s, 3H), 3.268−3.214 (m, 1H), 3.113−3.044 (m, 1H), 3.099 (s, 3H), 2.393 (s, 3H), 2.084−2.039 (m, 1H), 1.961−1.741 (m, 6H), 1.662−1.538 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 173.2, 170.3, 143.2, 138.8, 129.1, 127.7, 74.5, 72.3, 70.9, 69.9, 62.1, 59.1, 58.8, 58.3, 51.9, 47.5, 46.1, 33.8, 33.3, 30.2, 29.5, 28.5, 27.1, 21.5. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{26}H_{36}N_2O_7NaS$: 543.2141, found 543.2111.

*Ts-**(S)**-**2**-OH.*

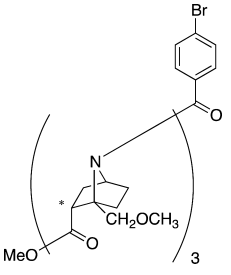


To a solution of Ts-(***S***)-**2**-OMe (46.7 mg, 0.09 mmol) in THF (5.0 mL) was added a solution of $LiOH·H_2O$ (7.5 mg, 0.18 mmol) in water (2.5 mL). Two drops of methanol were added into the mixture. The whole mixture was stirred at room temperature for 10 h, and 5% $KHSO_4$ aqueous solution was added. The mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4, and then the solvent was evaporated. A white solid (41.0 mg, 90%) was obtained after recrystallization. Mp: 181.5−182.5 °C (recrystallized from *n*-hexane/Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.847 (d, J = 8.4 Hz, 2H), 7.297 (d, J = 8.4 Hz, 2H), 4.495 (d, J = 10.0 Hz, 1H), 4.418 (d, J = 10.0 Hz, 1H), 4.380−4.330 (m, 2H), 3.915 (d, J = 10.8 Hz, 1H), 3.615 (d, J = 10.4 Hz, 1H), 3.563 (s, 3H), 3.268−3.240 (m, 1H), 3.131−3.096 (m, 1H), 3.105 (s, 3H), 2.424 (s, 3H), 2.238−2.197 (m, 1H), 2.062−1.926 (m, 5H), 1.767−1.554 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ173.0, 170.6, 143.4, 138.7, 129.3, 127.8, 74.8, 74.5, 70.0, 69.6, 62.1, 59.6, 58.4, 58.2, 50.4, 46.0, 34.3, 34.1, 29.7, 29.5, 28.6, 21.6. HRMS (ESI-TOF, $[M - H]^-$) calcd for $C_{25}H_{33}N_2O_7S$: 505.2008, found 505.2011.



Synthesis of ***p*-BrBz-(*R*)-3-OH**

*p-BrBz-**(R)**-**3**-OMe.*

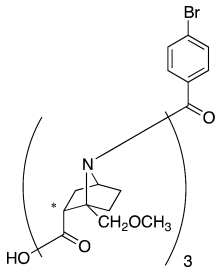


To a solution of (***R***)-**3** (41.2 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added TFA (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction mixture was evaporated. The residue was washed with 10% Na_2CO_3 aqueous solution and extracted with EtOAc. Evaporation of the solvent gave the crude product. Anhydrous CH_2Cl_2 was added to the crude product, and then *p*-bromobenzyl chloride (17.6 mg, 0.08 mmol) and Et_3N (20 μL,

dx.doi.org/10.1021/jo500916j | J. Org. Chem. 2014, 79, 5287−5300

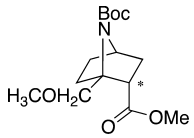
0.15 mmol) were added at 0 °C. Twenty minutes later the ice bath was removed, and the reaction mixture was stirred at room temperature for 9 h under Ar atmosphere. The solvent was evaporated, and column chromatography (solvent system: *n*-hexane/EtOAc = 2/1 v/v) gave compound *p*-BrBz-(***R***)-**3**-OMe (51.1 mg, 95%) as a white solid. Mp: 189.0−190.0 °C (recrystallized from *n*-hexane/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.537 (d, J = 8.8 Hz, 2H), 7.457 (d, J = 8.4 Hz, 2H), 4.623−4.600 (m, 1H), 4.582−4.559 (m, 1H), 4.516 (d, J = 10.4 Hz, 1H), 4.469 (d, J = 10.0 Hz, 1H), 4.387 (d, J = 10.4 Hz, 1H), 4.086−4.072 (m, 1H), 4.072 (d, J = 10.4 Hz, 1H), 3.976 (d, J = 10.0 Hz, 1H), 3.763 (d, J = 10.4 Hz, 1H), 3.706 (s, 3H), 3.506−3.467 (m, 1H), 3.427 (s, 3H), 3.406 (s, 3H), 3.396 (s, 3H), 3.346−3.306 (m, 1H), 3.183−3.144 (m, 1H), 2.133−1.599 (m, 17H), 1.485−1.415 (s, 1H). HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{35}H_{46}N_3O_8BrNa$: 738.2366, found 738.2358.

p-BrBz-(R)-3-OH.



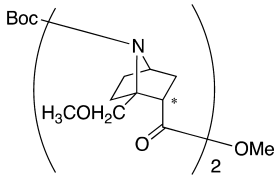
To a solution of *p*-BrBz-(***R***)-**3**-OMe (20.0 mg, 0.03 mmol) in THF (3.0 mL) was added a solution of LiOH·H_2O (10.0 mg, 0.24 mmol) in water (1.5 mL). Two drops of methanol were added into the mixture. The whole mixture was stirred at room temperature for 10 h. 5% $KHSO_4$ aqueous solution was added. The mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4, then the solvent was evaporated. A white solid was obtained (20.1 mg 95%) after recrystallization. Mp: 144.0−146.0 °C (recrystallized from MeOH/H_2O 9/1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.537 (d, J = 8.4 Hz, 2H), 7.451 (d, J = 8.4 Hz, 2H), 4.635−4.578 (m, 2H), 4.531−4.399 (m, 4H), 4.112−4.070 (m, 1H), 3.961 (d, J = 10.0 Hz, 1H), 3.735 (d, J = 10.0 Hz, 1H), 3.559 (s, 3H), 3.501−3.460 (m, 1H), 3.426 (s, 3H), 3.410 (s, 3H), 3.349−3.311 (m, 1H), 3.185−3.147 (m, 1H), 2.240−2.198 (m, 1H), 2.138−1.930 (m, 7H), 1.861−1.429 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ172.8, 170.5, 170.3, 169.7, 135.8, 131.6, 129.6, 125.2, 71.6, 71.5, 69.6, 62.1, 59.7, 59.0, 58.8, 58.3, 46.1, 46.0, 34.3, 33.4, 29.9, 29.7, 29.6, 27.0. HRMS (ESI-TOF, $[M - H]^-$) calcd for $C_{34}H_{43}N_3O_8Br$: 700.2234, found 700.2209.

(S)-1.



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.261−4.236 (m, 1H), 4.067 (d, J = 10.0 Hz, 1H), 3.991 (d, J = 10.0 Hz, 1H), 3.671 (s, 3H), 3.395 (s, 3H), 3.073−3.026 (m, 1H), 2.041−1.962 (m, 1H), 1.822−1.739 (m, 3H), 1.687−1.505 (m, 2H), 1.422 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 155.2, 80.0, 72.1, 70.2, 59.2, 59.1, 51.8, 48.0, 33.1, 28.5, 28.3, 28.2. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{15}H_{25}NO_5Na$: 322.1630, found 322.1635.

(S)-2.



White solid. Mp: 93.5−94.5 °C (recrystallized from *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.518−4.495 (m, 1H), 4.348 (d, J = 10.0 Hz, 1H), 4.254−4.229 (m, 1H), 4.187 (d, J = 10.0 Hz, 1H), 4.057 (d, J = 10.0 Hz, 1H), 3.728 (d, J = 10.0 Hz, 1H), 3.678 (s, 3H), 3.417 (s, 3H), 3.369 (s, 3H), 3.260−3.216 (m, 1H), 3.144−3.098 (m, 1H), 2.078−1.547 (m, 11H), 1.484−1.379 (m, 1H), 1.429 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 170.8, 155.2, 79.7, 72.7, 71.4, 70.88, 70.86, 59.3, 59.1, 58.9, 58.8, 51.9, 47.8, 46.3, 33.5, 32.9, 30.2, 29.0, 27.9, 27.3. HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{24}H_{38}N_2O_7Na$: 489.2577, found 489.2568. Anal. Calcd for $C_{24}H_{38}N_2O_7$: C, 61.78; H, 8.21; N, 6.00. Found: C, 61.70; H, 7.94; N, 6.06.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supplementary figures and tables and supplementary NMR spectral spectra, CD spectra, X-ray crystallographic data, and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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