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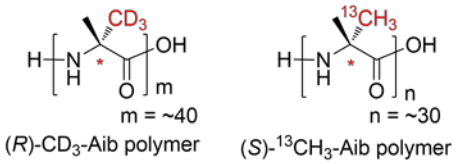

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Helical structures of homo-chiral isotope-labeled α-aminoisobutyric acid peptides

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The chiral deuterium- and ^{13}C-isotope-labeled α-aminoisobutyric acids CD_3-Aib and $^{13}CH_3$-Aib were enantioselectively synthesized from L-Ala aldimine using simplified Maruoka chiral phase-transfer catalysts. Homo-chiral (*S*)-CD_3-Aib homopeptides, up to decamers, were prepared. A (*R*)-CD_3-Aib polymer and (*S*)-$^{13}CH_3$-Aib polymer were also prepared. Conformational studies on homopeptides using CD spectra and an X-ray crystallographic analysis revealed that the preferred conformations were 3_{10}-helical structures comprising equal amounts of right-handed (*P*) and left-handed (*M*) helical-screw structures. The α-carbon chiral centers induced by the D- or ^{13}C-isotope substitution of Aib were incapable of controlling the helical-screw directions of their oligopeptides and short polymers.

1. Introduction

α-Aminoisobutyric acid (Aib; α-methylalanine, α,α-dimethylglycine) is an achiral α,α-disubstituted α-amino acid, in which the α-hydrogen atom of alanine is replaced with a methyl substituent.[1] Aib peptides preferentially form 3_{10}-helical structures,[2] and Aib is often used to design conformational-freedom restricted peptides in the fields of medicinal and organic chemistry.[3] Aib is achiral as are its homopeptides; therefore, these helical structures of Aib homopeptides exist as enantiomeric right-handed (*P*) and left-handed (*M*) helical-screw conformers in a ratio of 1 to 1.[4] Incidentally, if the isotope of an atom is taken into consideration in Aib, for example, the ^{13}C-isotope of a methyl substituent at the α-carbon atom accounts for approximately 2% in nature, then approximately 2% of Aib exists as the racemic chiral $^{13}CH_3$-Aib.

Regarding the relationship between deuterium D(^{2}H) isotope-induced chirality and the polymer helical-screw direction, Green and co-workers reported that the side-chain chirality of isocyanate caused by the replacement of H with the D isotope was capable of controlling its isocyanate polymer (chiral pseudo-peptoid polymer) helical-screw direction.[5] However, a relationship between an α-carbon chiral center induced by a replacement with an isotope (D or ^{13}C) and the helical-screw direction of its peptides has not yet been reported. Thus, we synthesized chiral Aib; CD_3-Aib and $^{13}CH_3$-Aib, by replacing a methyl substituent of Aib with CD_3[6] or $^{13}CH_3$,[7] and examined the effects of the isotopes (D and ^{13}C) on their homopeptide helical-screw directions (Fig. 1).

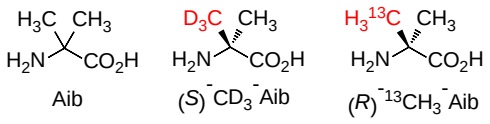

Fig.1. Chemical structures of Aib, CD_3-Aib, and $^{13}CH_3$-Aib.

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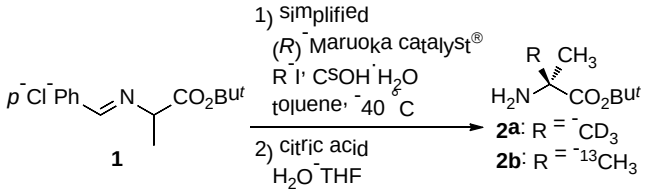
2. Results and Discussion

2.1. Enantioselective synthesis of optically active CD_3-Aib and $^{13}CH_3$-Aib

We synthesized both enantiomers of optically active (*S*)- and (*R*)-CD_3-Aib using (*R*)- and (*S*)-simplified Maruoka catalysts®[8], respectively, as the chiral phase-transfer catalyst (Scheme 1). According to Maruoka's procedure, the alkylation of the aldimine Schiff base **1**, derived from an L-alanine *tert*-butyl (Bu^t) ester, with CD_3I (2.1 equiv) and $CsOH·H_2O$ (5 equiv) in toluene in the presence of 0.5 mol % (*R*)-simplified Maruoka catalyst® {(*R*)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphto[7,6,1,2-cde]azepinium bromide} at −40 °C, and a work-up with acidic aqueous citric acid, gave (*S*)-CD_3-Aib-OBu^t (*S*)-**2a** in a quantitative yield. In contrast, the reaction of **1** using the (*S*)-simplified Maruoka catalyst® produced enantiomeric (*R*)-**2a** in a quantitative yield. We attempted to examine the % ee of **2a** using chiral HPLC; however, the separation of enantiomers did not work well. The % ee of **2a** was established as 90% ee, after the conversion of (*S*)-**2a** into a (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) amide and by measuring the ^1H NMR spectrum.[9]

Both enantiomers of $^{13}CH_3$-Aib were subsequently synthesized in a similar manner to those of CD_3-Aib. The alkylation of **1** with $^{13}CH_3I$ (1.2 equiv) and $CsOH·H_2O$ (5 equiv) in toluene in the presence of 0.5 mol % (*R*)-simplified Maruoka catalyst® at −40 °C and a work-up under acidic conditions gave (*R*)-$^{13}CH_3$-Aib-OBu^t **2b** in a quantitative yield.[10] While, the reaction using (*S*)-simplified Maruoka catalyst® produced enantiomeric (*S*)-**2b** in quantitative yield. The % ee of (*R*)-**2b** was established after the conversion of **2b** into (*R*)-MTPA amide and by ^1H NMR measurements. The enantiomeric excess of (*R*)-**2b** was *ca.* 82% ee.[9]

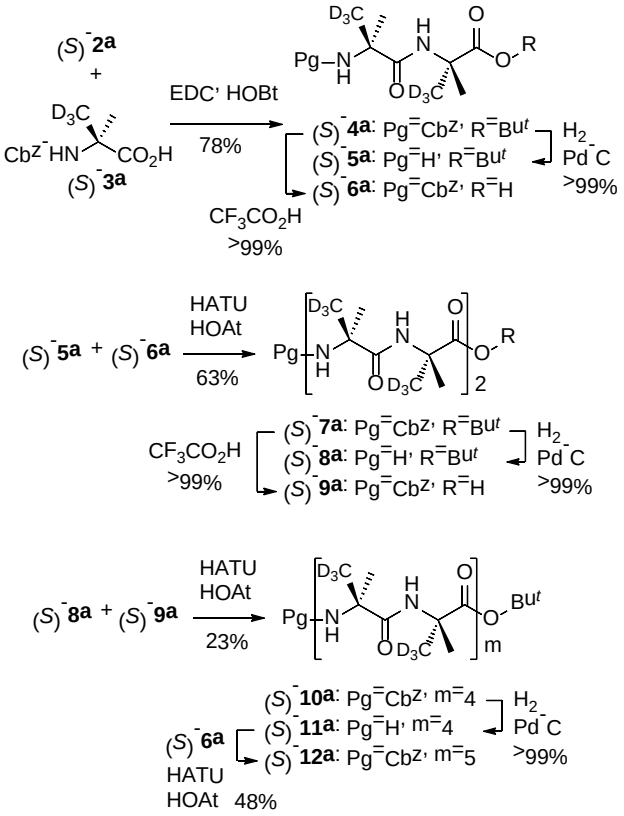


Scheme 1. Enantioselective syntheses of (*S*)-CD_3-Aib and (*R*)-$^{13}CH_3$-Aib. Abbreviations: *p*-chlorophenyl (*p*-Cl-Ph); tetrahydrofuran (THF).

2.2. Preparation of homo-chiral CD_3-Aib homopeptides

We prepared homopeptides, up to the (*S*)-CD_3-Aib decapeptide and (*R*)-CD_3-Aib octapeptide, using solution-phase methods, as follows (Scheme 2). The N-terminal-protected Cbz-(*S*)-CD_3-Aib-OH **3a** was synthesized from (*S*)-**2a** by benzyloxycarbonyl (Cbz) protection and C-terminal deprotection in 77% yield. The coupling between (*S*)-**2a** and (*S*)-**3a** using 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) gave the dipeptide (*S*)-**4a** in 78% yield. The removal of the protecting groups at the N terminus and C terminus produced the dipeptide amine (*S*)-**5a** and dipeptide carboxylic acid (*S*)-**6a**, respectively. Fragment coupling between (*S*)-**5a** and (*S*)-**6a** using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAt) gave the tetrapeptide (*S*)-**7a** in 63% yield. The octapeptide (*S*)-**10a** (23%) was prepared from the tetrapeptide amine **8a** and tetrapeptide carboxylic acid **9a** in a similar manner to that of (*S*)-**7a**. Furthermore, the decapeptide (*S*)-**12a** was prepared by coupling between the octapeptide amine (*S*)-**11a** and dipeptide carboxylic acid (*S*)-**6a** in 48% yield.

Enantiomeric (*R*)-CD_3-Aib homopeptides were prepared in a similar method as that described for (*S*)-CD_3-Aib homopeptides.



Scheme 2. Preparation of homo-chiral (*S*)-CD_3-Aib homopeptides.

2.3. Conformational analysis of homo-chiral (*S*)-CD_3-Aib homopeptides

The (*S*)-CD_3-Aib tetrapeptide **7a** and octapeptide **10a** provided crystals suitable for an X-ray crystallographic analysis following slow evaporation of the solvent (MeOH/H_2O) at room temperature.

An X-ray crystallographic analysis is incapable of discriminating between isotopes D and H because X-ray diffraction is caused by electrons, and the D and H atoms both have the same electron. The bond lengths of C–H and C–D are slightly different because zero-point energy differs for the C–H and C–D bonds.[11] However, the difference in the two bond lengths is markedly smaller than X-ray analysis precision. Therefore, even if the X-ray crystallographic analysis exclusively showed a one-handed helical structure for (*S*)-CD_3-Aib peptides in the crystal state, we cannot establish the right-handedness or left-handedness of the helix. However, if the crystal structure was solved in the chiral space group and only a one-handed helical structure existed, the helical-screw sense may be controlled by chiral centers at the α-carbon atoms to one-handedness, although its right-handedness or left-handedness cannot be clarified.

The crystal and diffraction parameters of (*S*)-**7a** and (*S*)-**10a** are summarized in Table S1.[9] Their molecular structures are given in Figures 2 and 3. The relevant backbone and side-chain torsion angles as well as the intra- and intermolecular hydrogen-bond parameters are listed in Tables 1 and 2.[12,13]

Table 1. Selected torsion angles of homo-chiral (*S*)-CD_3-Aib homopeptides **7a** and **10a**.[a]

Torsion Angle	(*S*)-CD_3-Aib tetramer **7a**	(*S*)- CD_3-Aib octamer **10a**			
		A	*B*	*C*	*D*
ω0	175.7	−170.0	−176.1	176.9	167.0
ϕ1	−56.9	−59.5	−59.1	54.3	64.0
ψ1	−36.2	−33.3	−32.0	34.0	24.7
ω1	−174.5	−178.4	−179.7	176.2	176.8
ϕ2	−55.6	−46.2	−51.1	55.5	54.8
ψ2	−31.2	−36.3	−35.0	30.5	36.4
ω2	−176.3	−175.4	−176.1	178.6	175.3
ϕ3	−59.8	−61.0	−56.0	56.1	54.2
ψ3	−31.0	−19.7	−23.4	27.9	26.1
ω3	−172.4	176.1	179.8	180.0	−178.9

ϕ4	50.9	−52.5	−56.9	53.3	50.5
ψ4	41.7	−31.7	−24.4	22.4	25.0
ω4	177.0	179.9	173.6	−174.7	177.9
ϕ5	---	−51.4	−50.9	47.9	57.0
ψ5	---	−26.3	−23.9	35.3	25.8
ω5	---	178.1	−177.0	176.2	180.0
ϕ6	---	−51.5	−53.4	45.2	52.1
ψ6	---	−28.7	−35.5	41.9	28.0
ω6	---	−179.2	−170.8	169.6	178.8
ϕ7	---	−54.3	−69.0	61.6	56.9
ψ7	---	−28.0	−15.6	19.9	26.7
ω7	---	−176.3	175.1	179.3	170.6
ϕ8	---	54.0	56.0	−51.9	−51.0
ψ8	---	42.2	40.1	−44.2	−42.7
ω8	---	174.0	167.8	−167.9	−176.3

[a] The number of amino acid residues begins at the *N* terminus of the peptide chain.

Table 2. Intra- and intermolecular H-bond parameters for (*S*)-CD_3-Aib peptides **7a** and **10a**.

Peptide	Donor D–H	Acceptor A	Distance [Å] D···A	Angle [°] D–H···A	Symmetry operations
Cbz-{(*S*)-CD_3-Aib}$_4$-OBu^t (**7a**)					
	N_3-H	O_0	3.04	153	x,y,z
	N_4-H	O_1	2.99	159	x,y,z
	N_1-H	$O_{M'}$	2.83	140	2−x,1−y, −z
	N_2-H	$O_{4'}$	3.03	121	−1/2+x, 3/2−y, −1/2+z
	O_M-H	$O_{2'}$	2.72	175	3/2−x, −1/2+y, 1/2−z
Cbz-{(*S*)-CD_3-Aib}$_8$-OBu^t (**10a**)					
A (*P*)	N_{3a}-H	O_{0a}	3.15	157	x,y,z
	N_{4a}-H	O_{1a}	3.01	160	x,y,z
	N_{5a}-H	O_{2a}	3.04	164	x,y,z
	N_{6a}-H	O_{3a}	2.92	165	x,y,z
	N_{7a}-H	O_{4a}	3.05	165	x,y,z
	N_{8a}-H	O_{5a}	3.00	166	x,y,z
B (*P*)	N_{3b}-H	O_{0b}	2.93	151	x,y,z
	N_{4b}-H	O_{1b}	2.95	162	x,y,z
	N_{5b}-H	O_{2b}	3.03	164	x,y,z
	N_{6b}-H	O_{3b}	2.90	167	x,y,z
	N_{7b}-H	O_{4b}	3.10	164	x,y,z
	N_{8b}-H	O_{5b}	3.02	161	x,y,z
C (*M*)	N_{3c}-H	O_{0c}	2.95	155	x,y,z
	N_{4c}-H	O_{1c}	2.92	159	x,y,z
	N_{5c}-H	O_{2c}	2.98	165	x,y,z
	N_{6c}-H	O_{3c}	2.86	163	x,y,z
	N_{7c}-H	O_{4c}	3.03	162	x,y,z
	N_{8c}-H	O_{5c}	3.07	163	x,y,z
D (*M*)	N_{3d}-H	O_{0d}	3.10	154	x,y,z
	N_{4d}-H	O_{1d}	2.88	161	x,y,z
	N_{5d}-H	O_{2d}	2.98	170	x,y,z
	N_{6d}-H	O_{3d}	2.99	165	x,y,z
	N_{7d}-H	O_{4d}	2.92	167	x,y,z
	N_{8d}-H	O_{5d}	2.96	171	x,y,z
	N_{1a}-H	$O_{7a'}$	2.90	160	x, −1+y,z

N_{1b}-H	$O_{7b'}$	2.81	176	x, −1+y,z
N_{1c}-H	$O_{7c'}$	2.80	173	x, 1+y,z
N_{1d}-H	$O_{7d'}$	2.87	163	x, 1+y,z
O_{M4}-H[a]	O_{4c}	3.02	176	x,y,z
O_{M1}-H[a]	$O_{4b'}$	2.86	177	x,y,1+z
O_{M2}-H[a]	O_{M1}	2.87	153	x,y,z

[a] O_M: O atom of MeOH.

The (*S*)-CD_3-Aib tetrapeptide **7a** was solved in the space group $P2_1/n$ to form a 3_{10}-helical structure in the asymmetric unit. The space group $P2_1/n$ is centrosymmetric; and therefore, right-handed (*P*) and left-handed (*M*) helical enantiomers existed in the crystal. Figure 2 shows a right-handed (*P*) 3_{10}-helical structure, in which reversal of the C-terminal torsion angles occurred, *i.e.*, the signs of the ϕ and ψ torsion angles of the C-terminal residue (residue 4) were opposite to those of the preceding residues (1–3). This phenomenon is frequently observed in 3_{10}-helical Aib and related peptides.[14] The average values of the torsion angles ϕ and ψ of residues (1–3) were −57.4°, −32.9°. The intramolecular hydrogen bonds of the $i \leftarrow i+3$ type (3_{10}-helix) were found between H–N(3) and the C(0)=O(0) oxygen atom of the Cbz-group, and between H–N(4) and the C(1)=O(1). In the packing mode, the (*P*) conformer is connected to the symmetry-related (−1/2+x, 3/2−y, −1/2+z) (*M*) conformer by one intermolecular hydrogen bond [H–N(2)···O(4')].

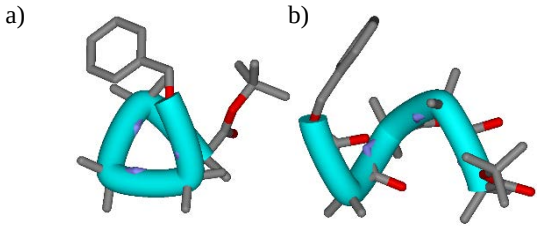
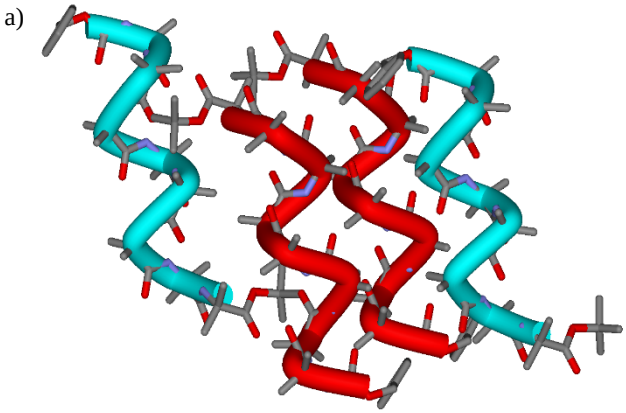


Fig. 2. A right-handed (*P*) 3_{10}-helical structure of the (*S*)-CD_3-Aib tetrapeptide **7a** by an X-ray crystallographic analysis. An enantiomeric left-handed (*M*) 3_{10}-helix also existed. Views (a) along the helical axis, and (b) perpendicular to the helical axis.

The structure of the (*S*)-octapeptide **10a** was solved in the space group *P1*. Two right-handed (*P*) 3_{10}-helices and two left-handed (*M*) 3_{10}-helices existed in the asymmetric unit, along with methanol molecules. The space group *P1* is chiral and non-centrosymmetric; therefore, the right-handed (*P*) helices and left-handed (*M*) helices are not enantiomeric, but diastereomeric. This result may be due to solvent molecules disturbing the symmetry of the helical molecule arrangement. Reversal of the C-terminal torsion angles occurred in conformers *A*–*D*, *i.e.*, the signs of the ϕ and ψ torsion angles of the C-terminal residue (residue 8) were opposite to those of the preceding residues (1–7). The average values of the torsion angles ϕ and ψ of residues (1–7) were *A*: −53.8°, −29.1°; *B*: −56.6°, −27.1°; *C*: 53.4°, 30.3°; *D*: 55.6°, 27.5°. Conformers *A*–*D* showed six intramolecular hydrogen bonds of the $i \leftarrow i+3$ type (3_{10}-helix) between H–N(3) and the C(0)=O(0) oxygen atom of the Cbz-group, between H–N(4) and C(1)=O(1), between H–N(5) and C(2)=O(2), between H–N(6) and C(3)=O(3), between H–N(7) and C(4)=O(4), and between H–N(8) and C(5)=O(5). In the packing mode, an intermolecular hydrogen bond formed between the H-N(1) peptide donor and C7'=O7' of a symmetry-related conformer (*A* and *B*: x, −1+y, z) or (*C* and *D*: x, 1+y, z). Thus, the chains of intermolecularly hydrogen-bonded right-handed (*P*) 3_{10}-helices; ···*A*···*A*···*A*··· and ···*B*···*B*···*B*···, and left-handed (*M*) 3_{10}-helices; ···*C*···*C*···*C*··· and ···*D*···*D*···*D*···, were formed in a head-to-tail alignment.



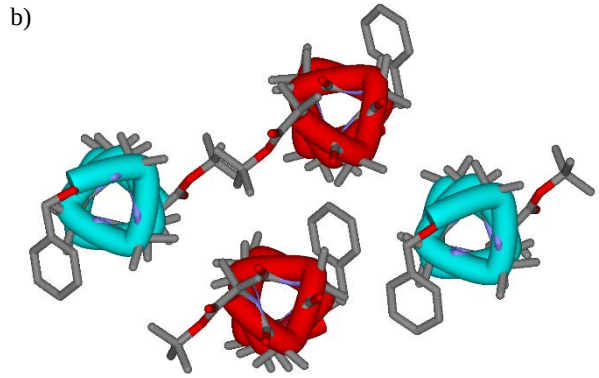


Fig 3. Right-handed (*P*) and left-handed (*M*) 3_{10}-helical structures of the (*S*)-CD_3-Aib octapeptide **10a** by an X-ray crystallographic analysis. Views (a) perpendicular to the helical axes, and (b) along the helical axes.

The X-ray crystallographic structure of the achiral Aib octapeptide *p*-BrBz-$(Aib)_8$-OBu^t (*p*-BrBz: *p*-bromobenzoyl) has already been solved in the centrosymmetric space group *P-1*, and enantiomeric (*P*) and (*M*) 3_{10}-helices existed, together with three methanol molecules.[4e] These differences in the X-ray crystallographic results between the achiral Aib octapeptide[4e] and our chiral CD_3-Aib octapeptide **10a** may be attributed to the difference in the N-terminal protecting groups of peptides, but not to the effects of CD_3-induced chiral centers. These X-ray crystallographic results suggest that chiral centers at the α-carbons of (*S*)-CD_3-Aib peptides are incapable of controlling their helical-screw sense to one-handedness up to an octapeptide length.

The FT-IR absorption spectra of Cbz-{(*S*)-CD_3-Aib}$_n$-OBu^t {n = 4 (**7a**), 8 (**10a**), 10 (**12a**)} showed weak bands in the 3420–3440 cm^{-1} region, which were assigned to solvated free peptide NH groups, and strong bands at the 3350–3370 cm^{-1} region to peptide NH groups with N–H···O=C intramolecular hydrogen bonds of different strengths.[9] These FT-IR spectra are almost the same as those of the reported Aib homopeptides, which formed 3_{10}-helices.[4] The CD spectra of the (*S*)-CD_3-Aib octa- and decapeptides **10a** and **12a** in 2,2,2-trifluoroethanol (TFE) solution (0.10 mM) did not show maxima (208 and 222 nm) for the one-handed helical structure (Fig. 4). These results also suggest that right-handed (*P*) and left-handed (*M*) 3_{10}-helices exist in equal amounts.[15]

Toniolo and coauthors reported that right-handed and left-handed helices of achiral Aib homopeptides rapidly interconverted in solution at room temperature.[16] Therefore, the right-handed and left-handed helices of chiral (*S*)-CD_3-Aib homopeptides also might rapidly interconvert in solution at room temperature.

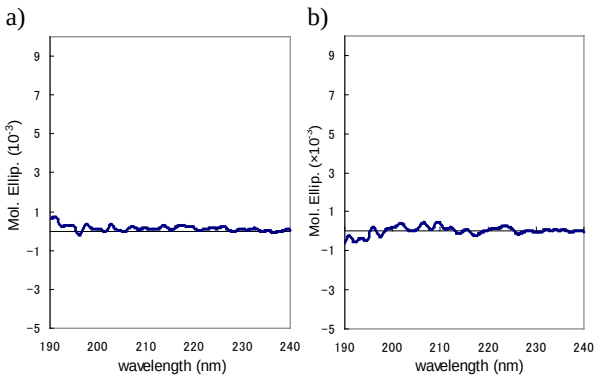


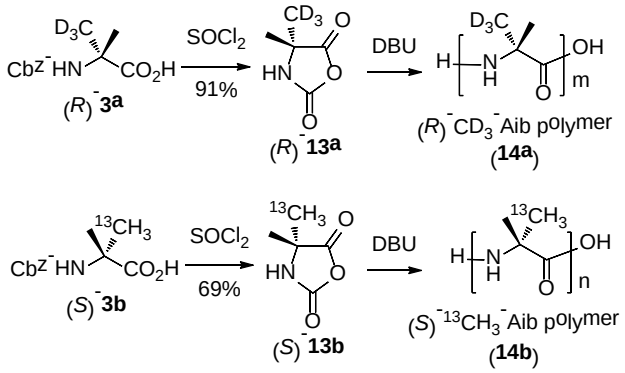
Fig. 4. CD spectra of (*S*)-CD_3-Aib homopeptides Cbz-{(*S*)-CD_3-Aib}$_n$-OBu^t {(a) n = 8 (**10a**), (b) n = 10 (**12a**)} in TFE solution (0.10 mM).

2.4. (*R*)-CD_3-Aib and (*S*)-$^{13}CH_3$-Aib polymer syntheses based on *N*-carboxy anhydride methods and their CD spectra

We attempted to prepare a (*R*)-CD_3-Aib polymer and (*S*)-$^{13}CH_3$-Aib polymer based on *N*-carboxy anhydride method. According to Deming's procedure,[17] the Cbz-protected CD_3-Aib (*R*)-**3a** was converted to the *N*-carboxy anhydride (*R*)-**13a** in 91% yield by a treatment with $SOCl_2$ in THF at 65 °C. Furthermore, the Cbz-protected $^{13}CH_3$-Aib (*S*)-**3b**, which was prepared from (*S*)-**2b**, was similarly converted to the *N*-carboxy anhydride (*S*)-**13b** in 69% yield.

Initiators for polymerization: *n*-hexyl amine, triethylamine (Et_3N), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were examined using the achiral Aib *N*-carboxy anhydride **13**.[18,19] The MALDI-ToF-MS spectra of products showed molecular ion peaks of *m/z* 1230

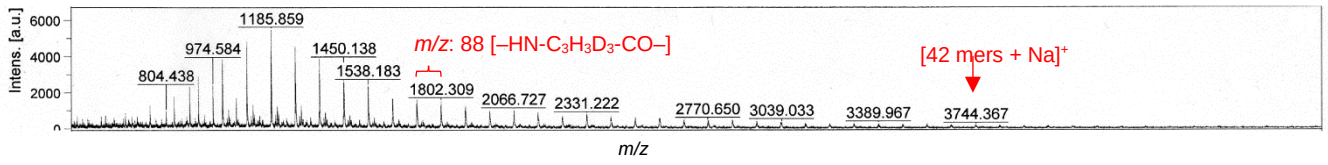
(14 mers) by *n*-hexyl amine, *m/z* 2594 (30 mers) by Et_3N, and *m/z* 3443 (40 mers) by DBU. The use of the strongest base DBU as an initiator in *N*,*N*-dimethylformamide (DMF) gave the highest polymerization degree. Thus, we polymerized the isotope-labeled chiral Aib *N*-carboxy anhydrides **13a**,**b** under these reaction conditions.



Scheme 3. Preparation of (*R*)-CD_3-Aib and (*S*)-$^{13}CH_3$-Aib *N*-carboxy anhydrides and their polymerization.

The MALDI-ToF-MS spectrum of the (*R*)-CD_3-Aib polymer **14a** showed larger molecular ion peaks than 42 mers {3744.3: $(M+Na)^+$}, and these peaks appeared at regular intervals of *m/z* 88, which corresponded to the monomer unit of –HN-$C_3H_3D_3$-CO–. On the other hand, the MALDI-ToF-MS spectrum of the (*S*)-$^{13}CH_3$-Aib polymer **14b** showed larger molecular ion peaks than 30 mers {2635.5: $(M+K)^+$}, and the interval of these peaks was *m/z* 86, corresponding to the monomer unit of –HN-$^{13}CC_2H_6$-CO– (Fig. 5).

a)



b)

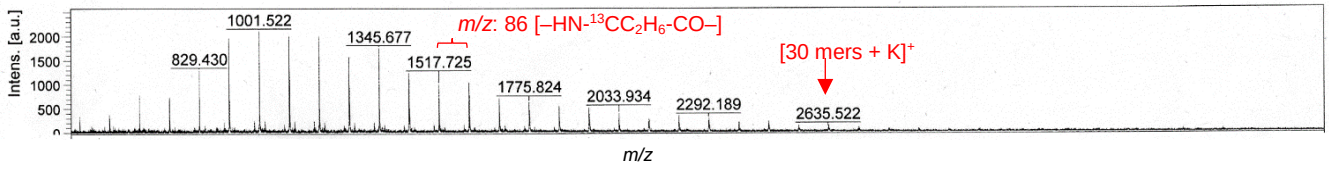


Fig. 5. MALDI-ToF-MS spectra of (a) the (*R*)-CD_3-Aib polymer and (b) (*S*)-$^{13}CH_3$-Aib polymer.

The CD spectra of the (*R*)-CD_3-Aib polymer **14a** and (*S*)-$^{13}CH_3$-Aib polymer **14b** in TFE solution did not show any positive or negative maxima for the one-handed helical structure. These CD spectra suggest that these polymers form right-handed and left-handed helical structures in almost equal amounts, and the control of the helical-screw sense of polymers is not possible at these polymer lengths (Fig. 6).

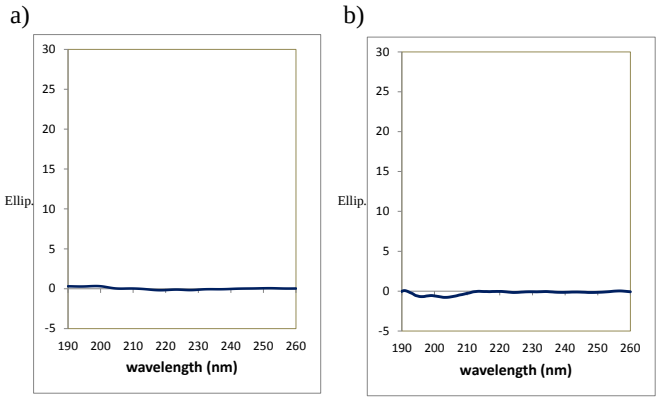


Fig. 6. CD spectra of (a) the (*R*)-CD_3-Aib polymer **14a** (0.3 mg in TFE 1.0 mL) and (b) (*S*)-$^{13}CH_3$-Aib polymer **14b** (0.4 mg in TFE 1.0 mL).

Helical-screw control by chiral centers due to isotope substitutions were different between Green's pseudo-peptoid polymers and our Aib oligomers. In Green's study,[5] isocyanate polymers showed an excess of one-handed helical-screw structures in the CD spectra. In our study, neither (*R*)-CD_3-Aib peptides nor (*S*)-$^{13}CH_3$-Aib peptides had a bias for the one-handed helical-screw direction detected in the CD spectra; however, they had right-handed and left-handed helical-screw directions in equal amounts. The most prominent difference between isocyanate polymers and Aib polymers is molecular weight, and thus, the numbers of existing chiral centers. The average molecular weight (M_w) of Green's isocyanate polymers was 870,000; therefore, *ca.* 6,800 unit polymers and nearly 6,800 chiral centers existed. However, our Aib polymers were 30-50 mers, with only 30-50 chiral centers existing.

3. Conclusion

Optically active isotope-labeled Aib **2a** and **2b** were synthesized using simplified Maruoka catalysts®. The (*S*)-CD_3-Aib homopeptides, up to decamers, were prepared by peptide-fragment coupling using a solution-phase method. Homo-chiral CD_3-Aib and $^{13}CH_3$-Aib polymers, up to ca. 30-40 mers, were also prepared by the polymerization of *N*-carboxy anhydrides. The conformational analysis of these peptides demonstrated that right-handed and left-handed helical structures existed in equal amounts, and 30-40 chiral centers caused by D and ^{13}C isotope substitutions were incapable of affecting the helical-screw directions of their oligopeptides. Isotope-labeled drugs have recently attracted the attention of medicinal chemists.[20] Therefore, these results demonstrate that isotope-labeled drugs have negligible effects on conformational changes.

4. Experimental Section

4.1. General

Optical rotations $[\alpha]_D$ were measured using a 1.0-dm cell. Circular dichroism spectra (CD) were measured using a 1.0-mm path length cell. Infrared spectra (IR) were recorded for conventional measurements (neat or KBr), and the solution ($CDCl_3$) method was performed using the 0.1-mm path length of a NaCl cell. ^1H NMR spectra were determined at 400 MHz at room temperature. EI(MS) and HRMS(FAB) spectra were taken in the dual-focusing sector field mode, while HRMS(ESI), HRMS(DART), and MALDI-MS spectra were measured in the ToF mode.

4.2. Synthesis of isotope-labeled amino acids

4.2.1. tert-*Butyl 2-(4-Chlorobenzylideneamino)propionate (**1**).*[21] A mixture of H-Ala-OBu^t·HCl (30.0 g, 165 mmol), $NaHCO_3$ (10 g) in H_2O (200 mL), and CH_2Cl_2 (200 mL) was stirred at room temperature for 2 h. The organic layer was separated, *p*-chlorobenzaldehyde (13.3 g, 14.6 mmol) and anhydrous $MgSO_4$ (16 g) were then added, and the whole mixture was stirred at room temperature for 4 days. After filtration, the filtrate was evaporated and diluted with diethyl ether. The ethereal solution was washed with brine and H_2O, and then dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from *n*-pentane to give the imine **1** (20.1 g, 79%) as colorless crystals: mp 25–27 ºC; IR (neat) ν 2982, 1732, 1645, 1217, 1155, 1090, 770, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.26 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 4.04 (q, *J* = 6.8 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.47 (s, 9H); HRMS(DART): $[M+H]^+$, found 268.1111. $C_{14}H_{19}ClNO_2$ requires 268.1104.

4.2.2. tert-*Butyl (*S*)-2-Amino-2-(trideuteriomethyl)propionate [H-(S)-CD_3-Aib-OBu^t; (S)-**2a**]*. CD_3-I (2.00 mL, 32.0 mmol) was added dropwise to a stirred solution of **1** (4.00 g, 14.9 mmol), (*R*)-simplified Maruoka catalyst® (0.5 mol %, 56 mg, 0.075 mmol), and CsOH·H_2O (12.5 g, 74.7 mmol) in toluene (80 mL) at −40 ºC, and the solution was stirred for 24 h. The solution was diluted with water, and extracted with $CHCl_3$. Evaporation of the solvent afforded the oily residue, which was dissolved in THF (250 mL) and 0.5 M aqueous citric acid

solution (250 mL), and the solution was stirred for 4 h. After removal of THF, the residual solution was washed with *n*-hexane, basified with Na_2CO_3 (*ca*. 44 g), extracted with diethyl ether, and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was distilled under reduced pressure using Kugelrohr apparatus to leave **2a** (2.45 g, quantitative) as a colorless oil: bp 100–110 ºC/300 mbar (oil bath temp.); $[\alpha]^{30}_D$ ±0.0 (*c* 1.31, $CHCl_3$); IR (neat) ν 3422 (br), 2980, 2878, 1717, 1636, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (br s, 2H), 1.46 (s, 9H), 1.29 (s, 3H); HRMS(DART): $[M+H]^+$, found 163.1532. $C_8H_{15}D_3NO_2$ requires 163.1526. Enantiomeric (*R*)-**2a** was synthesized using (*S*)-simplified Maruoka catalyst®, and racemic (±)-**2a** was synthesized using tetrabutyl ammonium iodide instead of Maruoka catalyst®.

*4.2.3. Determination of enantiomeric excess of **2a***. A mixture of amine **4a** (9 mg, 0.057 mmol), (*R*)-MTPA (16 mg, 0.068 mmol), and EDC (13.6 mg, 0.071 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 50 ºC for 4 days. After removal of the solvent, the residue was purified by short column chromatography on silica gel to give an MTPA amide. Enantiomeric excess of **2a** was determined by the ^1H NMR spectrum of the corresponding MTPA amide.[9]

4.2.4. tert-*Butyl (R)-2-Amino-2-(*^{13}*C-methyl)propionate [H-(*R*)-*$^{13}CH_3$*-Aib-OBu*^{t}*; (*R*)-**2b**]*.[7] $^{13}CH_3$-I (56 μL, 0.90 mmol) was added dropwise to a stirred solution of **1** (200 mg, 0.75 mmol), (*R*)-simplified Maruoka catalyst® (0.5 mol %, 4.2 mg, 0.006 mmol), and $CsOH·H_2O$ (66 mg, 4.40 mmol) in toluene (4 mL) at −40 ºC, and the solution was stirred for 24 h. The solution was diluted with water, and extracted with $CHCl_3$. Evaporation of the solvent afforded the oily residue, which was dissolved in THF (13 mL) and 0.5 M aqueous citric acid solution (13 mL), and the solution was stirred for 4 h. After removal of THF, the residual solution was washed with *n*-hexane, basified with Na_2CO_3, extracted with ether, and then dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was distilled under reduced pressure using Kugelrohr apparatus to leave (*R*)-**2b** (120 mg, quantitative) as a colorless oil: bp 100–110 ºC/380 mbar (oil bath temp.); $[\alpha]^{29}_D$ ±0.0 (*c* 1.10, $CHCl_3$); IR (neat) ν 3372 (br), 1724, 1369, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (br s, 2H), 1.46 (s, 9H), 1.30 (d, $^4J_{CH}$ = 4.4 Hz, 3H), 1.29 (d, $^1J_{CH}$ = 128 Hz, 3H); HRMS(DART): $[M+H]^+$, found 161.1329. $C_7{}^{13}CH_{18}NO_2$ requires 161.1371. Enantiomeric (*S*)-**2b** was synthesized using (*S*)-simplified Maruoka catalyst®, and racemic (±)-**2b** was synthesized using tetrabutyl ammonium iodide instead of Maruoka catalyst®.

*4.2.5. Determination of enantiomeric excess of **2b***. A mixture of amine **4b** (9 mg, 0.057 mmol), (*R*)-MTPA (16 mg, 0.068 mmol), and EDC (13.6 mg, 0.071 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 50 ºC for 4 days. After removal of the solvent, the residue was purified by column chromatography on silica gel to give an MTPA amide. Enantiomeric excess of **2b** was determined by the ^1H NMR spectrum of the corresponding MTPA amide.[9]

4.3. Preparation of (*S*)-CD_3-Aib homopeptides

*4.3.1. (*S*)-2-(Benzyloxycarbonyl)amino-2-(trideuteriomethyl)propionic acid [Cbz-{(*S*)-CD_3-Aib}-OH; (*S*)-**3a**]*. A mixture of (*S*)-**2a** (2.00 g, 12.3 mmol), Na_2CO_3 (1.57 g, 14.8 mmol), and benzyloxycarbonyl chloride (Cbz-Cl; 2.60 mL, 18.4 mmol) in acetone-water (1 : 1; 50 mL) was stirred at room temperature for 4 days. After removal of acetone, the aqueous solution was extracted with ethyl acetate (EtOAc), and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% EtOAc in *n*-hexane) to give Cbz-protected amino ester (3.00 g, 83%) as colorless crystals. Cbz-{(*S*)-CD_3-Aib}-OBu^t: mp 60–62 ºC; $[\alpha]^{20}_D$ ±0.0 (*c* 0.99, $CHCl_3$); IR (KBr) ν 3372 (br), 2976, 1711 (br), 1518, 1302, 1260, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.36 (m, 5H), 5.46 (br s, 1H), 5.08 (s, 2H), 1.51 (s, 3H), 1.43 (s, 9H); HRMS(DART): $[M+H]^+$, found 297.1913. $C_{16}H_{21}D_3NO_4$ requires 297.1894. A mixture of Cbz-{(*S*)-CD_3-Aib}-OBu^t (1.38 g, 4.66 mmol) and anisole (0.9 mL, 8.30 mmol) in 2,2,2-trifluoroacetic acid (TFA; 9.2 mL) was stirred at room temperature for 3 h. Removal of the solvent afforded a solid, which was purified by short column chromatography on silica gel (20% EtOAc in *n*-hexane) to give (*S*)-**3a** (1.11 g, 99%) as colorless crystals: mp 70–71 ºC; $[\alpha]^{28}_D$ ±0.0 (*c* 1.00, $CHCl_3$); IR (KBr) ν 3333 (br), 2988, 2945, 2907, 1750 (br), 1653, 1543, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 7.30–7.40 (m, 5H), 5.39 (br s, 1H), 5.10 (s, 2H), 1.57 (s, 3H); HRMS(DART): $[M+H]^+$, found 241.1251. $C_{12}H_{13}D_3NO_4$ requires 241.1268.

*4.3.2. Cbz-[(*S*)-CD_3-Aib]$_2$-OBu*^{t} *[(*S*)-**4a**]*. A mixture of amine (*S*)-**2a** (353 mg, 2.17 mmol), carboxylic acid (*S*)-**3a** (447 mg, 1.86 mmol), EDC (432 mg, 2.25 mmol), and HOBt (308 mg, 2.28 mmol) was stirred at 60 ºC for 3 days. After removal of the solvent, the residue was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and then dried over Na_2SO_4. After removal of the solvent, the white solid was purified by column chromatography on silica gel (20% EtOAc in *n*-hexane) to produce a terminally-protected dipeptide (*S*)-**4a** (558 mg, 78%) as colorless crystals: mp 136–137 ºC; $[\alpha]^{31}_D$ ±0.0 (*c* 1.00, $CHCl_3$); IR (KBr) ν 3406, 3294 (br), 2978, 1721, 1659, 1535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.36 (m, 5H), 6.91 (br s, 1H), 5.36 (br s, 1H), 5.09 (s, 2H), 1.52 (s, 3H), 1.49 (s, 3H), 1.45 (s, 9H); HRMS(DART): $[M+H]^+$, found 385.2626. $C_{20}H_{25}D_6N_2O_5$ requires 385.2610.

*4.3.3. H-[(*S*)-CD_3-Aib]$_2$-OBu*^{t} *[(S)-**5a**]*. A mixture of (*S*)-**4a** (951 mg, 2.47 mmol), and 10% Pd-C (760 mg) in MeOH (70 mL) was rigorously stirred under a H_2 atmosphere at room temperature for 13 h. After filtration, the filtrate was evaporated to give a crude amine (*S*)-**5a** (619 mg, quantitative), which was used for the next reaction without purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 1.73 (br s, 2H), 1.51 (s, 3H), 1.45 (s, 9H), 1.34 (s, 3H); HRMS(DART): $[M+H]^+$, found 251.2256. $C_{12}H_{19}D_6N_2O_3$ requires 251.2242.

*4.3.4. Cbz-[(*S*)-CD_3-Aib]$_2$-OH [(S)-**6a**]*. A mixture of (*S*)-**4a** (113 mg, 0.294 mmol) and anisole (60 μL) in trifluoroacetic acid (0.6 mL) was stirred at room temperature for 4 h. Removal of the solvent afforded a white solid, which was used without purification.

*4.3.5. Cbz-[(*S*)-CD_3-Aib]$_4$-OBu*^{t} *[(S)-**7a**]*. A mixture of (*S*)-**5a** (242 mg, 0.968 mmol), (*S*)-**6a** (273 mg, 0.832 mmol), HATU (597 mg, 1.57 mmol), HOAt (217 mg, 1.59 mmol), and diisopropylethylamine (^{i}Pr$_2$EtN) (0.40 mL) in MeCN (5 mL) was stirred at 50 ºC for 5 days under an Ar atmosphere. After removal of the solvent, the residue was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and then dried over Na_2SO_4. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (40% EtOAc in *n*-hexane) to produce a terminally-protected tetrapeptide (*S*)-**7a** (293 mg, 63%) as colorless crystals: mp 184–185 ºC; $[\alpha]^{26}_D$ ±0.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$): ν 3426, 3358 (br), 2982, 1717, 1674, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–

7.40 (m, 6H), 7.24 (br s, 1H), 6.59 (br s, 1H), 5.51 (br s, 1H), 5.09 (s, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 1.43 (s, 9H), 1.39 (s, 3H), 1.26 (s, 3H); HRMS(DART): $[M+H]^+$, found 561.4002. $C_{28}H_{33}D_{12}N_4O_7$ requires 561.4041.

*4.3.6. H-[(S)-CD₃-Aib]₄-OBu^t [(S)-**8a**]*. Amine (*S*)-**8a** was prepared from (*S*)-**7a** in a manner similar to that described for the preparation of (*S*)-**5a**, and used for the next reaction without purification.

*4.3.7. Cbz-[(S)-CD₃-Aib]₄-OH [(S)-**9a**]*. Carboxylic acid (*S*)-**9a** was prepared from (*S*)-**7a** in a manner similar to that described for the preparation of (*S*)-**6a**, and used for the next reaction without purification.

*4.3.8. Cbz-[(S)-CD₃-Aib]₈-OBu^t [(S)-**10a**]*. Terminally-protected octapeptide (*S*)-**10a** was prepared by coupling between (*S*)-**8a** and (*S*)-**9a** in a manner similar to that described for the preparation of (*S*)-**7a**. 23%; colorless crystals; mp 241–243 ºC; $[\alpha]^{22}_D$ ±0.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3316 (br), 2984, 1713, 1661, 1530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.66–7.67 (br s, 2H), 7.58 (br s, 1H), 7.52 (br s, 1H), 7.44 (br s, 1H), 7.28–7.42 (m, 5H), 6.64 (br s, 1H), 5.58 (s, 1H), 5.11 (s, 2H), 1.48 (s, 3H), 1.46 (s, 6H), 1.45 (s, 15H), 1.44 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H); HRMS(FAB): $[M]^+$, found 912.6824. $C_{44}H_{48}D_{24}N_8O_{11}$ requires 912.6827.

*4.3.9. H-[(S)-CD₃-Aib]₈-OBu^t [(S)-**11a**]*. Amine (*S*)-**11a** was prepared from (*S*)-**10a** in a manner similar to that described for the preparation of (*S*)-**5a**, and used for the next reaction without purification.

*4.3.10. Cbz-[(S)-CD₃-Aib]₁₀-OBu^t [(S)-**12a**]*. Terminally-protected decapeptide (*S*)-**12a** was prepared by coupling between (*S*)-**11a** and (*S*)-**6a** in a manner similar to that described for the preparation of (*S*)-**7a**. 48%; colorless crystals; mp >250 ºC; $[\alpha]^{23}_D$ ±0.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) ν 3321 (br), 2984, 1715, 1661, 1530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.66 (br s, 1H), 7.65 (br s, 1H), 7.64 (br s, 1H), 7.61 (br s,1H), 7.53 (br s, 1H), 7.39 (br s, 2H), 7.35–7.38 (m, 5H), 6.43 (br s, 1H), 5.63 (br s, 1H), 5.12 (s, 2H), 1.53 (s, 3H), 1.47–1.48 (m, 21H), 1.44 (s, 12H), 1.31 (s, 3H); HRMS(FAB): $[M]^+$, found 1088.8254. $C_{52}H_{56}D_{30}N_{10}O_{13}$ requires 1088.8259.

4.4. Synthesis of *N*-carboxy anhydrides of chiral CD_3-Aib and $^{13}CH_3$-Aib

*4.4.1. (R)-4-trideuteriomethyl-4-methyloxazoline-2,5-dione [(R)-**13a**]*. Thionyl chloride ($SOCl_2$; 40 μL, 0.55 mmol) was added to the stirred solution of (*R*)-**3a** (32.0 mg, 0.133 mmol) in THF (1 mL) at 65 ºC under an Ar atmosphere. After being stirred for 6 h, the solution was evaporated, and the residue was recrystallized from *n*-hexane/EtOAc (5/1) to give (*R*)-**13a** (16.0 mg, 91%) as colorless crystals: mp 95–96 ºC; $[\alpha]^{28}_D$ ±0.0 (*c* 0.50, MeOH); IR (KBr) ν 3568 (br), 2974, 2862, 1856, 1782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (br, 1H), 1.58 (s, 3H); MS(EI): *m/z* 132 $[M]^+$.

*4.4.2. (S)-2-(Benzyloxycarbonyl)amino-2-(¹³C-methyl)propionic acid [Cbz-{(S)-¹³CH₃-Aib}-OH; (S)-**3b**]*. A mixture of (*S*)-**2b** (107 mg, 0.670 mmol), Na_2CO_3 (87 mg, 0.82 mmol), and benzyloxycarbonyl chloride (Cbz-Cl; 142 μL, 1.0 mmol) in acetone-water (1 : 1; 50 mL) was stirred at room temperature for 2 days. After removal of acetone, the aqueous solution was extracted with EtOAc, and the extract was dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (20 % EtOAc in *n*-hexane) to give Cbz-protected amino ester (159 mg, 80%) as colorless crystals. Cbz-{(*S*)-$^{13}CH_3$-Aib}-OBu^t: mp 58–59 ºC; $[\alpha]^{31}_D$ ±0.0 (*c* 1.00, $CHCl_3$); IR (KBr) ν 3372 (br), 2976, 1711 (br), 1520, 1306, 1260, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5H), 5.46 (br s, 1H), 5.08 (s, 2H), 1.51 (d, $^1J_{CH}$ = 129 Hz, 3H), 1.51 (d, $^4J_{CH}$ = 4.4 Hz, 3H), 1.43 (s, 9H); HRMS(DART): $[M+H]^+$, found 295.1739. $C_{15}{}^{13}CH_{24}N_1O_4$ requires 295.1739. A mixture of Cbz-{(*S*)-$^{13}CH_3$-Aib}-OBu^t (137 mg, 0.466 mmol) and anisole (0.1 mL, 9.2 mmol) in TFA (1 mL) was stirred at room temperature for 4 h. Removal of the solvent afforded a white solid, which was purified by short column chromatography on silica gel (20% EtOAc in *n*-hexane) to give (*S*)-**3b** (87.5 mg, 79%) as colorless crystals: mp 64–65 ºC; $[\alpha]^{29}_D$ ±0.0 (*c* 0.71, $CHCl_3$); IR (KBr) ν 3333 (br), , 2990 (br), 1724, 1694, 1535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.38 (m, 5H), 5.32 (br s, 1H), 5.11 (s, 2H), 3.10 (br, 1H), 1.59 (d, $^1J_{CH}$ = 130 Hz, 3H), 1.59 (d, $^4J_{CH}$ = 4.2 Hz, 3H); HRMS(DART): $[M+H]^+$, found 239.1128. $C_{11}{}^{13}CH_{16}N_1O_4$ requires 239.1112.

*4.4.3. (S)-4-¹³C-methyl-4-methyloxazoline-2,5-dione [(R)-**13b**]*. Thionyl chloride ($SOCl_2$; 40 μL, 0.55 mmol) was added to the stirred solution of (*S*)-**3b** (32.0 mg, 0.134 mmol) in THF (1 mL) at 65 ºC under an Ar atmosphere. After being stirred for 7 h, the solution was evaporated, and the residue was recrystallized from *n*-hexane/EtOAc (5/1) to give (*S*)-**13b** (12.0 mg, 69%) as colorless crystals: mp 95–96 ºC; $[\alpha]^{28}_D$ ±0.0 (*c* 0.24, MeOH); IR (KBr) ν 3356 (br), 3175 (br), 2978, 2870, 1855, 1786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (br s, 1H), 1.58 (d, $^1J_{CH}$ = 131 Hz, 3H), 1.58 (d, $^4J_{CH}$ = 4.1 Hz, 3H); MS(EI): *m/z* 130 $[M]^+$.

4.5. Polymerization Procedure of *N*-carboxy anhydrides

4.5.1. A solution of the chiral Aib *N*-carboxy anhydride (*S*)-**13** (0.160 mmol) and DBU (1.14 μL) in DMF (1 mL) was stirred at room temperature overnight under an Ar atmosphere. Evaporation and concentration *in vacuo* gave a polymer.

Acknowledgments

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Supplementary data

Supplementary data (crystal and diffraction parameters, ^1H NMR spectra of (*R*)-MTPA amides, and FT-IR absorption spectra) associated with this manuscript may be found in the online version, at xxxxxxxxx.

References and notes

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9. See supplementary data.
10. The priority rule of the CIP nomenclature is N > ^{13}C > ^{12}C, and, thus, *R*/*S* descriptors are different between CD_3-Aib and $^{13}CH_3$-Aib. The absolute configurations of products were assumed based on the reaction mechanisms of the simplified Maruoka catalyst®.
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13. CCDC-1482529 (**7a**) and 1482530 (**10a**) contain the supplementary crystallographic data for this manuscript. These data may be obtained free of charge from The Cambridge Crystallographic Data Centre via: www.ccdc.cam.ac.uk/data_request/cif.
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