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Left-Handed Helix of Three-Membered Ring Amino Acid Homopeptide Interrupted by an N−H···Ethereal O-Type Hydrogen Bond

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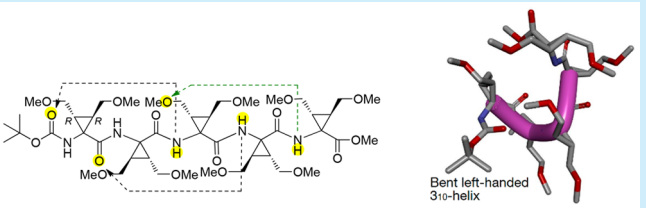
Supporting Information

ABSTRACT: A chiral three-membered ring $C^{\alpha,\alpha}$-disubstituted α-amino acid (*R*,*R*)-Ac_3c^{dMOM}, in which the α-carbon is not a chiral center, but two side chain β-carbons are chiral centers, was synthesized from dimethyl L-(+)-tartrate, and its homopeptides were prepared. X-ray crystallographic analysis of (*R*,*R*)-Ac_3c^{dMOM} pentapeptide showed bent left-handed (*M*) 3_{10}-helical structures with an unusual intramolecular hydrogen bond of the N−H···O (ethereal) type. The left-handedness of the bent helices was exclusively controlled by the side-chain β-carbon chiral centers.



The design of secondary structures of peptides and/or foldamers[1] is attracting marked attention from organic and medicinal chemists because such structures are invaluable for developing chiral catalysts,[2] biological tools,[3] and drug candidates.[4] $C^{\alpha,\alpha}$-Disubstituted α-amino acids (dAAs) are known as one type of building block for the construction of foldamers forming 3_{10}-helix, α-helix, and planar structures.[5] Among dAAs, cyclic dAAs are known to induce helical structures of their peptides.[6]

We previously reported the effect of side-chain chiral centers of cyclic dAAs on their homopeptide conformations. Homopeptides composed of a chiral five-membered ring dAA (*S*,*S*)-Ac_5c^{dOM} with two side chain chiral centers preferentially formed left-handed (*M*) helical structures without an α-chiral center.[7] Contrary to the one-handed helical structure of (*S*,*S*)-Ac_5c^{dOM} homopeptides, the homopeptides composed of a five,six-membered bicyclic ring dAA (*R*,*R*)-$Ab_{5,6=}c$ with two side-chain chiral centers,[8] a four-membered ring dAA (*R*,*R*)-Ac_4c^{3BD} with a chiral acetal moiety,[9] or a six-membered ring dAA (*R*,*R*)-Ac_6c^{35dBu} with two chiral acetal moieties[10] showed uncontrolled right-handed (*P*) and left-handed (*M*) helical-screw structures.

Here, we designed a chiral three-membered ring dAA, (*R*,*R*)-1-amino-2,3-bis(methoxymethyl)cyclopropanecarboxylic acid (Ac_3c^{dMOM}). The Ac_3c^{dMOM} has two methoxymethyl (MOM) substituents at the side-chain β-positions of cyclopropane, and the β-carbons become chiral centers without an α-carbon chiral center. In the Ac_3c^{dMOM} peptide, the distance between side-chain chiral centers and the peptide backbone become shorter than those of five- and six-membered-ring amino acids. Although we reported that similar five-membered ring amino acid (*S*,*S*)-Ac_5c^{dOM} homopeptides with methoxy groups formed left-handed (*M*) 3_{10}- and α-helices without an intramolecular hydrogen bond of the N−H···O (ethereal) type,[7] the Ac_3c^{dMOM} pentapeptide described here shows unprecedentedly left-handed (*M*) 3_{10}-helices interrupted by an N−H···O (ethereal) type intramolecular hydrogen bond. No such bent helical structures bearing the N−H···O (ethereal) type intramolecular hydrogen bond have been reported.

The three-membered ring dAA, (*R*,*R*)-Ac_3c^{dMOM}, was synthesized as follows. At first, dimethyl L-(+)-tartrate was converted into a chiral diol **3** with two MOM substituents according to the reported procedures (Scheme 1).[11] Then the diol **3** was transformed into a cyclic sulfate **4** by treatment with thionyl chloride and subsequent oxidation with $RuCl_3$ and $NaIO_4$ at a quantitative yield.[11] A three-membered ring was constructed by dialkylation of dimethyl malonate with the cyclic sulfate **4**.[12] At the beginning, the cyclization yield of **5** was 19% using K_2CO_3 as a base, and then the yield was improved to 56% using Cs_2CO_3 in DMF. Monohydrolysis of cyclic diester **5**, followed by Curtius rearrangement with diphenylphosphoryl azide (DPPA) and workup with BnOH, gave a benzyloxylcarbonyl (Cbz)-protected (*R*,*R*)-Ac_3c^{dMOM}-OMe **6** at a 71% yield. Hydrogenolysis of **6** using H_2/5% Pd−C gave an *N*-terminal free amine **8** at a quantitative yield, and the reaction in the presence of $(Boc)_2O$ produced a *tert*-butoxylcarbonyl (Boc)-protected Boc-{(*R*,*R*)-Ac_3c^{dMOM}}-OMe **7** at a 72% yield. Hydrolysis of a methyl (Me) ester in **7** in

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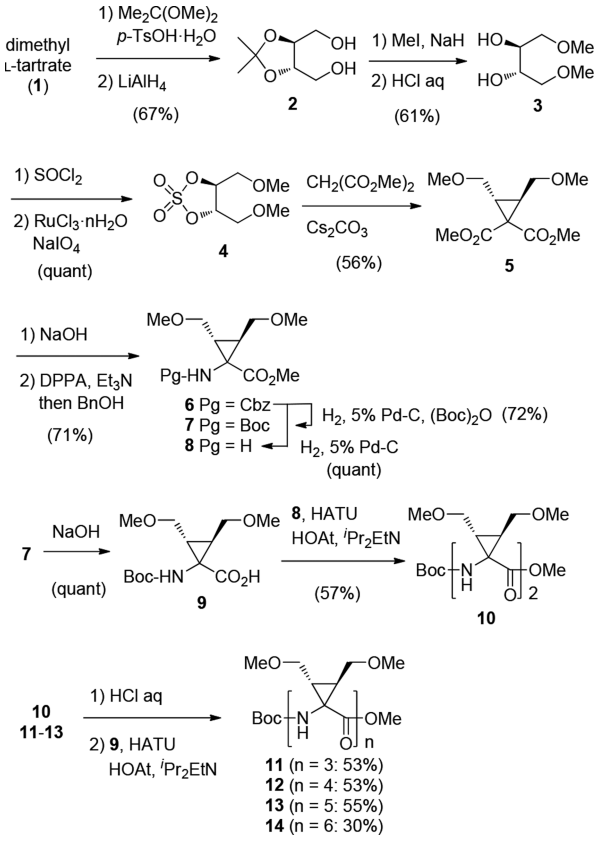
Scheme 1. Synthesis of (R,R)-Ac_3c^{dMOM} and Its Homopeptides



alkaline solution afforded a *C*-terminal free Boc-(R,R)-Ac_3c^{dMOM}-OH **9** at a quantitative yield.

The *N*-terminal free H-{(R,R)-Ac_3c^{dMOM}}-OMe **8** was coupled with C-terminal free Boc-{(R,R)-Ac_3c^{dMOM}}-OH **9** using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAt) to give a (R,R)-Ac_3c^{dMOM} dipeptide **10** at a 57% yield. The peptide chain was elongated in the *C*- to *N*-terminal direction by an iterative sequence of deprotection of a Boc-protecting group and subsequent coupling with **9** using HATU and HOAt up to a hexapeptide.

The FT-IR absorption spectra in the N−H stretching (amide A) region of (R,R)-Ac_3c^{dMOM} homopeptides were measured in $CDCl_3$ solution (Figure S1). Absorptions characteristic of the helical structure at 3420−3430 cm^{-1} (intramolecular hydrogen bond free N−H at the *N*-terminus) and 3320−3370 cm^{-1} (intramolecular hydrogen bond of the N−H···O=C type) were observed.[13] The NOESY NMR spectrum of **13** in $CDCl_3$ solution showed d_{N1N2} and d_{N2N3} correlations but did not show other d_{NN} correlations. The ROESY NMR spectrum of **14** showed d_{N1N2}, d_{N2N3}, and d_{N3N4} but neither d_{N4N5} nor d_{N5N6} (Figure S2). These FT-IR absorption and 2D NMR spectra suggest the formation of a helical secondary structure.

The circular dichroism (CD) spectra of homopeptides (n = 4−6) were measured in 2,2,2-trifluoroethanol solution (0.05 mM) (Figure S3). The CD spectra showed a negative maximum at 222 nm and a positive maximum at 205 nm, but these CD spectra do not yield valuable information for secondary structure analysis because the peptide length may be too short.[14]

The (R,R)-Ac_3c^{dMOM} pentapeptide **13** became crystals suitable for X-ray crystallographic analysis by recrystallization from MeOH/EtOAc/*n*-hexane. The structure was solved in a monoclinic $P2_1$ space group, and two crystallographically independent molecules A and B (both distorted left-handed 3_{10}-helices) together with disordered EtOAc and water molecules existed in the asymmetric unit (Figure 1 and Table S1).[15] The peptide-backbone structures of molecule A and B are well-matched, as shown by superimposition of the structures.

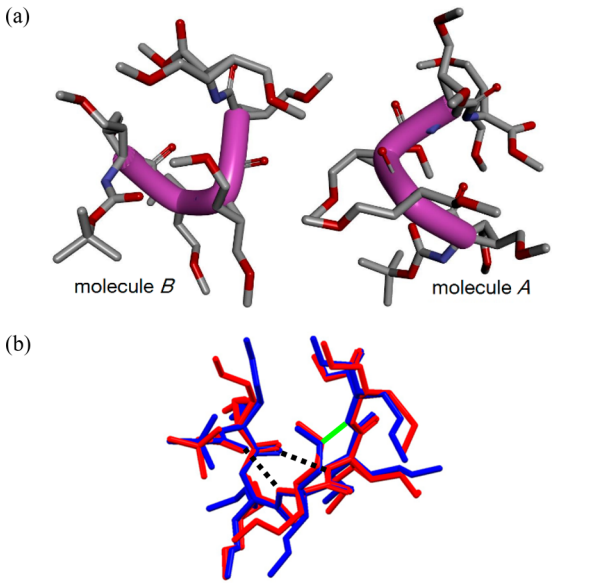


Figure 1. (a) Bent left-handed (M) helices of pentapeptide **13** (solvents and disordered OMe omitted for clarification). (b) Superimposed structure of molecules *A* and *B* with intramolecular hydrogen bonds (H bond of N(5)−H···O (3) (ethereal) type in green).

Two intramolecular hydrogen bonds of the N(i+3)−H···O = C(i) (i = 0 and 1) $i \leftarrow i$+3 type at the *N*-terminal side, corresponding to the 3_{10}-helix,[16,17] existed in molecules A and B. Additionally, one intramolecular hydrogen bond between the N(5)−H of the peptide backbone and the oxygen of the MeO substituent at the side-chain cyclopropane of residue (3) was unprecedentedly observed (Table 1 and Figure 1b). Although intramolecular hydrogen bonds between the oxygen of the side-chain ethereal functional group and the N−H of the peptide backbone of the same amino acid residue or of the adjacent amino acid residue have already been reported,[10,15] no such hydrogen bond between the oxygen of the side-chain ethereal function of the amino acid and the remote N−H of the main chain has been reported.

Table 2 shows the selected torsion angles of (R,R)-Ac_3c^{dMOM} pentapeptide **13**. The average ϕ and ψ torsion angles of amino acid residues (1−3) were +66.2 and +17.2 in molecule A and +65.8 and +16.8 in molecule B, respectively. These values match those of the left-handed (M) 3_{10}-helical conformation.[16] The ψ torsion angles of (R,R)-Ac_3c^{dMOM} residues were smaller than the normal ψ torsion angle of 3_{10}-helix. This may be because the Ac_3c and (R,R)-Ac_3c^{dMOM} residues prefer to form "bridge" region of the conformational map.[17,18] It is noteworthy that the ϕ and ψ torsion angles of (R,R)-Ac_3c^{dMOM} (4) were −94.8 and +17.5 in molecule A and −89.0 and +13.2 in

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Table 1. Intra- and Intermolecular H-Bond Parameters for Boc-{(*R*,*R*)-Ac$_3$c^{dMOM}}$_5$-OMe (13)

peptide	donor D−H	acceptor A	dist (Å) D···A	angle (deg) D−H···A	symmetry operations
mol A	N_3−H	O_0	2.99	161	*x*, *y*, *z*
	N_4−H	O_1	3.03	166	*x*, *y*, *z*
	N_5−H	O_{3MOM}	2.94	154	*x*, *y*, *z*
	$N_{1'}$−H	O_5	2.84	154	1 − *x*, 1/2 + *y*, 1 − *z*
	$N_{2'}$−H	O_6	2.90	136	1 − *x*, 1/2 + *y*, 1 − *z*
	O_w−H	O_4	2.81	178	1 − *x*, 1/2 + *y*, 1 − *z*
mol B	N_3−H	O_0	3.04	160	*x*, *y*, *z*
	N_4−H	O_1	2.89	163	*x*, *y*, *z*
	N_5−H	O_{3MOM}	3.06	150	*x*, *y*, *z*
	$N_{1'}$−H	O_5	2.74	158	−*x*, 1/2 + *y*, 2 − *z*
	$N_{2'}$−H	O_6	3.16	132	−*x*, 1/2 + *y*, 2 − *z*

Table 2. Selected Torsion Angles ω, ϕ, and ψ (deg) for Boc-{(*R*,*R*)-Ac$_3$c^{dMOM}}$_5$-OMe (13), As Determined by X-ray Crystallographic Analysis[16,18]

torsion angle	molecule A	molecule B
θ0	−176.4	−157.8
ω0	−160.8	174.7
ϕ1	73.9	70.7
ψ1	19.6	16.3
ω1	−173.1	−172.6
ϕ2	65.5	63.0
ψ2	9.4	15.6
ω2	−167.9	−169.1
ϕ3	59.2	63.8
ψ3	22.4	18.3
ω3	179.1	177.1
ϕ4	−94.8	−89.0
ψ4	17.5	13.2
ω4	−179.6	179.6
ϕ5	71.0	62.7
ψ5	21.9	28.1
ω5	178.6	179.5

molecule B, respectively, and thus, the peptide-backbone structure was largely bent in this residue (4). The twists of ϕ and ψ torsion angles of the penultimate residue described here have not been reported. These twisted torsion angles might be influenced by the intramolecular hydrogen bond of the N(5)−H···OMe(3) type between the peptide backbone N−H and the side-chain ethereal O atom.[15]

Although the reversal of the *C*-terminal residue ϕ and ψ torsion angles of dAA homopeptides to those of the preceding residues has often been reported[19] and achiral Ac$_3$c homopeptides forming a characteristic *C*-terminal semi-extended conformation (ϕ 90, ψ 180) have also been reported,[18] the *C*-terminal residue of the chiral (*R*,*R*)-Ac$_3$c^{dMOM} pentapeptide formed normal left-handed ϕ and ψ torsion angles (A: ϕ +71.0, ψ +21.9; B: ϕ +62.7, ψ +28.1), but not a semiextended conformation. The exocyclic τ (N−C$^\alpha$−C′) bond angles of achiral three-membered ring amino acid Ac$_3$c residues in peptides have been reported to become larger than that of the regular tetrahedral value.[18] Similarly, the average τ (N−C$^\alpha$−C′) bond angle of the (*R*,*R*)-Ac$_3$c^{dMOM} pentapeptide was 115.7°, which is larger than that of the ideal tetrahedral angle 109.5° (Table S2). In addition, the N−C$^\alpha$ and C$^\alpha$−C′ bond lengths became shorter than those of normal peptides because of the conjugating ability of the three-membered ring (data not shown).[18]

By calculations using MacroModel, 20000 conformations of hexapeptide Cbz-{(*R*,*R*)-Ac$_3$c^{dMOM}}$_6$-OMe were produced with Monte Carlo methods and minimized with the AMBER* (H_2O) force field.[20] The left-handed (*M*) 3_{10}-helix was obtained as a global minimum energy conformation (0 kcal/mol), and the distorted right-handed (*P*) 3_{10}-helix was gained as a local minimum energy conformation (+10.15 kcal/mol) (Figure S4). These results match the left-handed structure determined by X-ray crystallographic analysis, but the calculated left-handed (*M*) 3_{10}-helix was not bent, and no intramolecular hydrogen bond with an N−H···O (ethereal) type was observed.

The secondary structure of (*R*,*R*)-Ac$_3$c^{dMOM} homochiral pentapeptide **13** in the crystalline state was unambiguously determined to be bent left-handed (*M*) 3_{10}-helices. The left-handedness of the helix was exclusively controlled by the chiral centers at the side-chain β-carbons of cyclopropane. These results are in contrast to those of the uncontrolled helical screw direction of (*R*,*R*)-Ac$_4$c^{3BD},[9] (*R*,*R*)-Ab$_{5,6=}$c,[8] and (*R*,*R*)-Ac$_6$c$^{35\ dBu}$ homopeptides[10] but are in accordance with the one-handed helical screw of (*S*,*S*)-Ac$_5$c^{dOM} homopeptides.[7]

Two steric factors could be considered as controlling the helical-screw direction into one-handedness. One is a steric factor, in which the MOM substituent on the side-chain β-carbon directly affects the torsion angles of the same amino acid residue. The cyclopropylcarbonyl parts showed a tendency to form bisected *s-cis* conformations,[21] and the repulsion between the oxygen of C′=O and the γ-carbon of MOM might affect the ψ torsion angles. The other is the steric repulsion between the side-chain MOM substituents of the amino acid residues (*i*) and (*i*+3) in the 3_{10}-helices. The repulsion may be different between right- and left-handed helices. In the case of the chiral (*R*,*R*)-Ac$_3$c^{dPh} (c$_3$diPhe)-containing peptide reported by Toniolo, Cativiela, and co-workers,[22] the steric repulsion between the Ph-substituents of the amino acid residues (*i*) and (*i*+3) was proposed to be one of the important factors controlling the helical-screw sense to one-handedness. However, the MOM substituent of (*R*,*R*)-Ac$_3$c^{dMOM} is smaller than the Ph substituent of (*R*,*R*)-Ac$_3$c^{dPh}, and the effect of this steric repulsion between the MOM of amino acid residues (*i*) and (*i*+3) may be smaller. Thus, the γ-carbon of MOM, and additionally, the methoxy of the MOM substituent on the (*R*,*R*)-Ac$_3$c^{dMOM} residue would directly influence the same amino acid ψ torsion angles, and the helical-screw direction might be controlled as left-handed (Figure 2). Certainly, nonsteric factors such as the hydrophilicity and electronic density of the methoxy group might also affect the secondary structure.

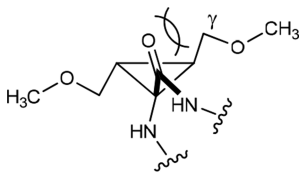

Figure 2. Steric repulsion between the γ-carbon of MOM and oxygen of the C′=O group of the same residue.

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In summary, we synthesized a chiral cyclopropane-based dAA, (*R*,*R*)-Ac_3c^{dMOM} with two MOM-substituents at the β-carbons and prepared its homopeptides up to a hexapeptide. The (*R*,*R*)-Ac_3c^{dMOM} hexapeptide is the longest homopeptide constructed from a chiral three-membered ring dAA. The (*R*,*R*)-Ac_3c^{dMOM} pentapeptide preferentially formed the bent left-handed (*M*) 3_{10}-helical structures that were exclusively controlled by the side-chain chiral centers. The 3_{10}-helical structure of a homopeptide interrupted by an intramolecular hydrogen bond of the N(5)−H···O (3) (ethereal) type has not been reported, and the structure would be useful for designing functional molecules such as chiral peptide catalysts, cell-penetrating peptides, and protein−protein interaction inhibitors.[4]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03331.

Experimental section, spectroscopic data of new compounds, 2D ^{1}H NMR spectra of **13** and **14**, CD spectra of peptides, FT-IR spectra of peptides, ^{1}H and ^{13}C NMR spectra (PDF)

Calculated structure of the (*M*)-3_{10}-helix (PDB)

Calculated structure of the (*P*)-3_{10}-helix (PDB)

Accession Codes

CCDC 1871355 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Dr. Kiyoshi Sakai on the occasion of his 88th birthday.

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