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Stabilized α-Helix-Catalyzed Enantioselective Epoxidation of α,β-Unsaturated Ketones

Masanobu Nagano,[†,⊥] Mitsunobu Doi,[‡] Masaaki Kurihara,[§] Hiroshi Suemune,[†] and Masakazu Tanaka*[,†,||]

Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan, Division of Organic Chemistry, National Institute of Health Sciences, Tokyo 158-8501, Japan, Osaka University of Pharmaceutical Sciences, Osaka 569-1094, Japan, and Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

matanaka@nagasaki-u.ac.jp

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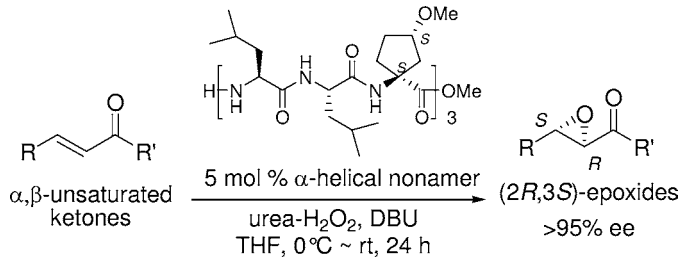
ABSTRACT



Chiral cyclic α-amino acid containing oligopeptide catalyzed highly enantioselective epoxidation of α,β-unsaturated ketones and the α-helical secondary structure of the peptide catalyst were revealed by X-ray crystallographic analysis.

Poly L-α-amino acid catalyzed epoxidation of chalcone is known as the Juliá−Colonna asymmetric reaction.[1] Many research endeavors of chemists have been devoted to disclosing the reaction mechanisms, overcoming substrate limitations, and developing a more efficient asymmetric reaction.[2] In the reaction, poly L-α-amino acids might form α-helical structures, and at their α-helical N-terminal, three or four NH protons of amide are important for asymmetric induction. To stabilize the α-helical structure of the oligomer catalyst, polyethyleneglycol and resin-attached L-Leu oligomers have been developed, and thus the high molecular weight and insolubility of catalysts were in part overcome.[2,3] Also, α,α-disubstituted amino acids (dAAs) were used to induce a helical structure, but dAA-containing oligomers formed 3_{10}-helices, which did not give an epoxide of high enantiomeric excess.[2d,4] On the basis of our studies of dAA peptides,[5] we reasoned that cyclic amino acid containing L-Leu-based peptides would form elaborate α-helical structures[5d] and would catalyze the asymmetric epoxidation of (*E*)-chalcone. Here we demonstrate the

[†] Kyushu University.
[‡] Osaka University of Pharmaceutical Sciences.
[§] National Institute of Health Sciences.
[||] Nagasaki University.
[⊥] Research Fellow of the Japan Society for the Promotion of Science.

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enantioselective epoxidation of α,β-unsaturated ketones and the relationship between the secondary structure of catalysts and the enantiomeric excesses of epoxides.

We synthesized chiral cyclic dAA-containing oligomers Boc-{L-Leu-L-Leu-dAA}$_n$-OMe {n = 2 (**1**), 3 (**2**), and 4 (**3**); dAA = Aib (**a**), (*R*,*R*)-Ac$_5$c^{dOM} (**b**), (*S*,*S*)-Ac$_5$c^{dOM} (**c**), (1*R*,3*S*)-Ac$_5$c^{OM} (**d**), (1*S*,3*S*)-Ac$_5$c^{OM} (**e**)} using solution-phase methods (Figure 1).

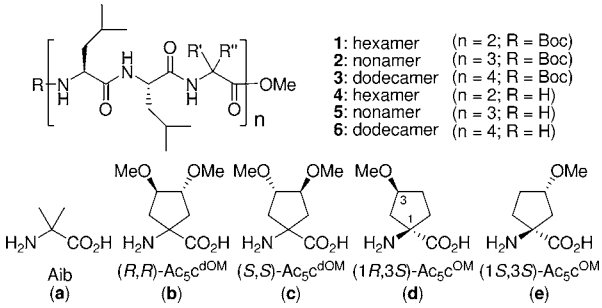
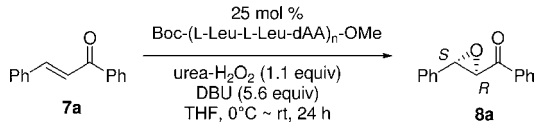


Figure 1. Structures of α,α-disubstituted amino acids and their peptides.

First, asymmetric epoxidation of (*E*)-chalcone **7a** using 25 mol % of oligomer was examined under conditions of urea−H_2O_2 (1.1 equiv) and DBU (5.6 equiv) in THF at 0 °C to room temperature for 24 h.[2,4a] Selected results are shown in Table 1. Although the reactions by hexamers **1a**−**e** afforded epoxide **8a** of low enantiomeric excesses (7−11% ee) in 77−91% conversion yield (not shown), elongation of the peptide chain improved enantiomeric excesses, except for Aib-containing peptides. It should be noted that side-chain chiral centers affected enantiomeric excesses, and those by (1*S*,3*S*)-Ac$_5$c^{OM}-containing nonamer **2e** and dodecamer **3e** were 82−83% ee, which are in contrast to other cases.

Table 1. Asymmetric Epoxidation of (*E*)-Chalcone **7a** Using Boc-Protected Oligomer[a]



entry	Boc-protected peptide	conversion %	ee of **8a** %
1	**2a**: Aib nonamer	91	6
2	**2b**: (*R*,*R*)-Ac$_5$c^{dOM} nonamer	86	20
3	**2c**: (*S*,*S*)-Ac$_5$c^{dOM} nonamer	86	12
4	**2d**: (1*R*,3*S*)-Ac$_5$c^{OM} nonamer	76	16
5	**2e**: (1*S*,3*S*)-Ac$_5$c^{OM} nonamer	98	82
6	**3a**: Aib dodecamer	84	6
7	**3b**: (*R*,*R*)-Ac$_5$c^{dOM} dodecamer	96	24
8	**3c**: (*S*,*S*)-Ac$_5$c^{dOM} dodecamer	99	40
9	**3d**: (1*R*,3*S*)-Ac$_5$c^{OM} dodecamer	92	28
10	**3e**: (1*S*,3*S*)-Ac$_5$c^{OM} dodecamer	99	83

[a] Epoxidation proceeded to give a racemic epoxide **8a** in 50% conversion yield without oligopeptides.

X-ray crystallographic analysis revealed that the (1*S*,3*S*)-Ac$_5$c^{OM} hexamer **1e** assumed a mixture of (*P*) 3_{10}-/α-helix, where intramolecular hydrogen bonds of i←i+3-type are formed on the N-terminal side (i = 0, 1) and those of i←i+4-type are formed on the C-terminal side (i = 1, 2). Three crystallographic independent conformers, which are similar in the peptide backbone, exist in asymmetric units. Contrary to the 3_{10}-/α-helix of **1e**, the (1*S*,3*S*)-nonamer **2e** formed fully developed right-handed α-helices, where i←i+4-type hydrogen bonds were observed (Figure 2). Judging from the *R* value (maxima: $\theta_{222}/\theta_{208}$) of the CD spectra in 2,2,2-trifluoroethanol solution, Aib hexamer and nonamer (R = 0.4) form (*P*) 3_{10}-helices, whereas the cyclic dAA-containing nonamer and dodecamer (R = >0.7) assume (*P*) α-helices.[6]

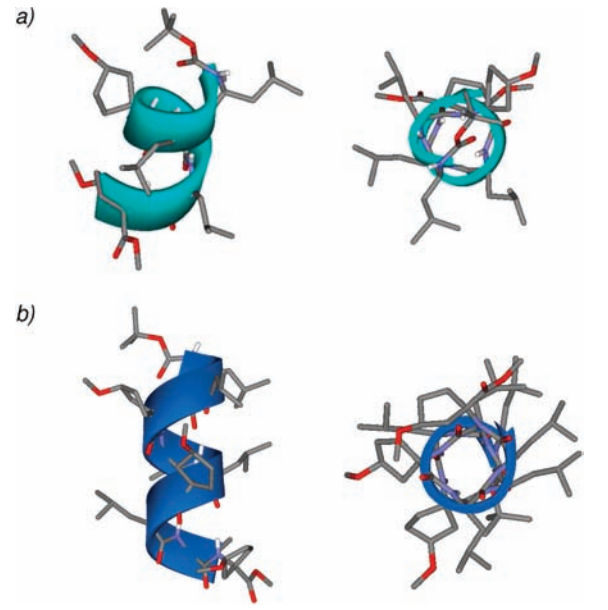


Figure 2. 3_{10}-/α-helical structure of **1e** (a) and α-helical structure of **2e** (b) by X-ray crystallographic analysis.

In Boc-protected 3_{10}-helical peptides, intramolecular hydrogen bonds of i←i+3-type are formed, and the two N-terminal NH protons are not involved in intramolecular hydrogen bonding. On the other hand, in α-helical peptides, intramolecular hydrogen bonds of i←i+4-type are formed, and the first three N-terminal NH protons are free of intramolecular hydrogen bonding. According to Roberts' model,[2b,c,7b] the three N-terminal N(2)H, N(3)H, and N(4)H

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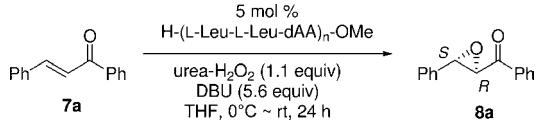
(6) See the Supporting Information.

protons are crucial for asymmetric induction, and the N(1)H proton is less important.[7] In Boc-protected α-helical peptides, the N(4)H proton forms an intramolecular hydrogen bond with the C═O of the protecting group, and thus, the N(4)H proton may not be available for interaction with the chalcone intermediate. Thus, we deprotected the Boc-protecting group to remove the intramolecular hydrogen bond of N(4)H and examined epoxidation using reduced 5 mol % of oligomers **4**−**6**. The results are summarized in Table 2.

Table 2. Asymmetric Epoxidation of (*E*)-Chalcone **7a** Using N-Terminal Free Oligomers **4**−**6**



entry	N-terminal free peptide	conversion %	ee of **8a** %
1	**4a**: Aib hexamer	80	5
2	**4b**: (*R*,*R*)-Ac$_5$c^{dOM} hexamer	86	27
3	**4c**: (*S*,*S*)-Ac$_5$c^{dOM} hexamer	86	31
4	**4d**: (1*R*,3*S*)-Ac$_5$c^{OM} hexamer	85	15
5	**4e**: (1*S*,3*S*)-Ac$_5$c^{OM} hexamer	92	61
6	**5a**: Aib nonamer	91	29
7	**5b**: (*R*,*R*)-Ac$_5$c^{dOM} nonamer	96	93
8	**5c**: (*S*,*S*)-Ac$_5$c^{dOM} nonamer	96	95
9	**5d**: (1*R*,3*S*)-Ac$_5$c^{OM} nonamer	97	72
10	**5e**: (1*S*,3*S*)-Ac$_5$c^{OM} nonamer	99	98
11	**6a**: Aib dodecamer	97	58
12	**6b**: (*R*,*R*)-Ac$_5$c^{dOM} dodecamer	99	96
13	**6c**: (*S*,*S*)-Ac$_5$c^{dOM} dodecamer	98	97
14	**6d**: (1*R*,3*S*)-Ac$_5$c^{OM} dodecamer	99	93
15	**6e**: (1*S*,3*S*)-Ac$_5$c^{OM} dodecamer	99	98

Except for hexamers having Aib and (*R*,*R*)-Ac$_5$c^{dOM}, N-terminal free peptides gave better enantiomeric excesses than Boc-protected ones. In particular, the reaction by (*S*,*S*)-Ac$_5$c^{dOM} and (1*S*,3*S*)-Ac$_5$c^{OM} containing nonamers **5c**,**e** and dodecamers **6c**,**e** afforded epoxides of >95% ee in good yield. X-ray crystallographic analysis of (*S*,*S*)-Ac$_5$c^{dOM} dodecamer **6c** shows an α-helical structure, along with disordered DMF molecules (Figure 3). The disordered DMF molecules connect to N(1)H and N(3)H protons by hydrogen bonds.[7] The chalcone might bind to amide NH protons of the helical peptide instead of DMF in the initial stage of the reaction.

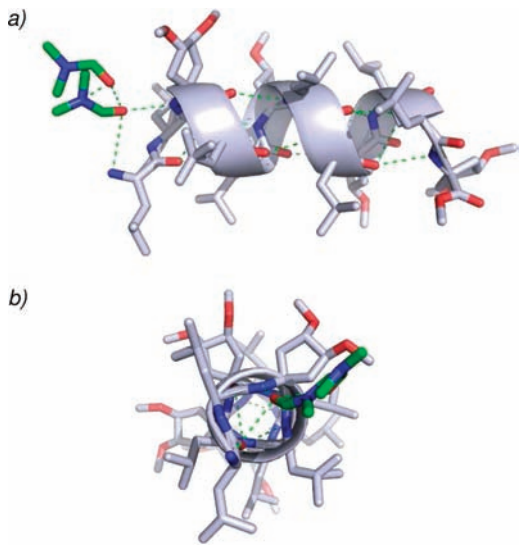
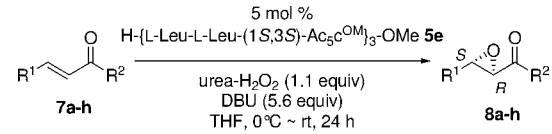


Figure 3. X-ray crystallographic analysis of H-{L-Leu-L-Leu-(*S*,*S*)-Ac$_5$c^{dOM}}$_4$-OMe **6c**. (a) View perpendicular to the α-helical axis and (b) along the α-helical axis.

The generality of asymmetric epoxidation of α,β-unsaturated ketones **7a**−**h** was examined using 5 mol % of α-helical nonamer **5e** (Table 3). Acyclic (*E*)-α,β-unsaturated ketones were suitable as substrates, and all substrates in Table 3 were converted to epoxides of excellent enantiomeric excesses (>95% ee), although the yields of **8b**−**d** having an alkyl substituent as R^2 were moderate.

Table 3. Asymmetric Epoxidation of α,β-Unsaturated Ketones Using N-Terminal Free Nonamer **5e**[2a,c]



entry	substrate	conversion %	ee of **8** %
1	**7a**: R^1 = Ph, R^2 = Ph	99	**8a**: 98
2	**7b**: R^1 = Ph, R^2 = Me	43	**8b**: 96
3	**7c**: R^1 = Ph, R^2 = *i*-Pr	52	**8c**: 97
4	**7d**: R^1 = Ph, R^2 = *t*-Bu	67	**8d**: 97
5	**7e**: R^1 = Ph, R^2 = 2-furanyl	99	**8e**: 98
6	**7f**: R^1 = Me, R^2 = Ph	99	**8f**: 97
7	**7g**: R^1 = 4-Cl-Ph, R^2 = Ph	96	**8g**: 96
8	**7h**: R^1 = 4-MeO-Ph, R^2 = Ph	94	**8h**: 97

In summary, we synthesized chiral cyclic amino acid containing peptide catalysts for asymmetric epoxidation, revealed the relationship between the helical structures and enantiomeric excesses, and remodeled the peptide catalyst by taking the hydrogen bonding pattern of helices into consideration. Using 5 mol % of the N-terminal free (1*S*,3*S*)-Ac$_5$c^{OM} nonamer **5e**, highly enantioselective epoxidation of α,β-unsaturated ketones has been completed. Other cyclic amino acid containing oligomer-catalyzed asymmetric reactions are currently underway in our group.[8]

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Supporting Information Available: Experimental section, spectroscopic data of new compounds, and crystallographic details (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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