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디하이드로 아미노산 유도체의 라디칼에 의한 분자 내 고리형성반응에 관한 연구

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Intramolecular Radical Cyclizations of Dehydroamino Acid Derivatives

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요 약. 디하이드록시 아미노산을 포함하는 다이펩타이드를 합성하고 여러 실험조건에서의 라디칼에 의한 고리형성 반응을 시켜보았다. 할로겐 기를 라디칼 선구물질로 하여 AIBN, Bu_3SnH, 70 ℃ 조건에서 반응시킨 결과 고리 형 치환기를 갖는 아미노산을 높은 수율로 얻을 수 있었으나 새로 생성되는 키랄성 탄소의 입체 선택성은 발견되지 않았다. 같은 반응을 Et_3B, Bu_3SnH, −20 ℃ 조건에서 반응 시킨 결과 개선된 입체선택성을 얻을 수 있었다. 또한, 이중결합 인근에 키랄성 OH기를 갖는 디하이드록시 아미노산을 합성하고 AIBN, Bu_3SnH, 70 ℃ 조건에서 고리형성을 시켜본 결과 높은 수율과 개선된 입체선택성을 얻을 수 있었다.

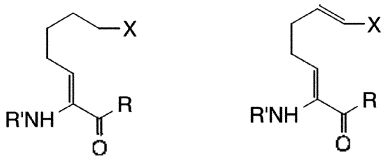
주제어: 디하이드로 아미노산, 라디칼, Et_3B, 고리형성반응

ABSTRACT. Intramolecular radical cyclizations of dehydroamino acid dipeptide derivatives were performed with various radical initiation methods and precursors. When the radical precursor was iodine, the reaction under the radical initiation condition with AIBN, Bu_3SnH, and heating gave the cyclized product with high yield. However, the stereoselectivity of new forming stereocenter which was suppose to be controlled by the chiral auxiliary on the adjacent amino acid was low. In case of radical initiation with Et_3B and Bu_3SnH at −20 ℃, much enhanced stereoselectivity was found with similar yield. The intramolecular radical cyclization of dehydroamino acid methyl ester which has a chiral center next to the double bond was also checked. High yield and affordable stereoselectivity was found but still unsatisfactory under the reaction condition with AIBN, Bu_3SnH at 70 ℃.

Keywords: Dehydroamino Acid, Radical, Et_3B, Intramolecular Cyclization

INTRODUCTION

Free radicals are reactive intermediates of considerable importance in organic chemistry. Over the past years, detailed studies of the reactivity, selectivity, and stability of many types of organic radicals have been reported.[1] Recently, stereochemical control in cyclic and acyclic radical reactions has shown great promise, and a general understanding of this problem is becoming clear.[2] The most popular method for this purpose is attaching a chiral auxiliary near the reaction center,[3] and the incorporation of a Lewis acid for chelation control was published.[4] Finding a general rule and making a prediction possible are still important issues. Steric hindrance is considered a main factor again.[2a] The preferred conformations of intermediates based on steric hindrance are postulated to explain many



1 2

R, R' : amino acid
X : radical precursor

Fig. 1.

experimental results, but still there are exceptions.

Ring construction by intramolecular free radical cyclization has proved to be particularly useful. The regio and stereochemistry of cyclization has been widely studied and a general understanding and prediction of stereoselectivity becomes possible.[5] Steric effects have proved to be the most important factors controlling the stereochemistry.[2e,f] This methodology has been extended to various synthetic processes.[2d]

If there is a protein that contains dehydroaminoacids like **1** or **2** (*Fig.* 1) in its polypeptide chain, intramolecular radical cyclization of these would generate a new stereocenter at the α-carbon. A stereospecific structural change might be able to trigger a specific alteration in the tertiary structure of the protein. Thus, such an internal trigger which might induce structural changes can provide a bioactive peptide with a certain activation or deactivation signal which can turn on or off specific enzymatic transformations. Our initial purpose in studying the intramolecular radical cyclization of dehydroamino acid dipeptides was: a) to establish the reaction conditions necessary to effect the transformation, including the compatibility with a fully functionalized protein; b) to determine the stereoselectivity (if any) in solution or in the solid phase for small optically pure peptides.

Not many examples of intramolecular cyclization of dehydroamino acids have been reported. This is a little surprising because many examples of the amenability of various derivatives of side chain functionalized amino acids by radical methods have been demonstrated by several groups.[6] Intermolecular radical additions to dehydroamino acid derivatives were reported by D. Crich and Davis.[7]

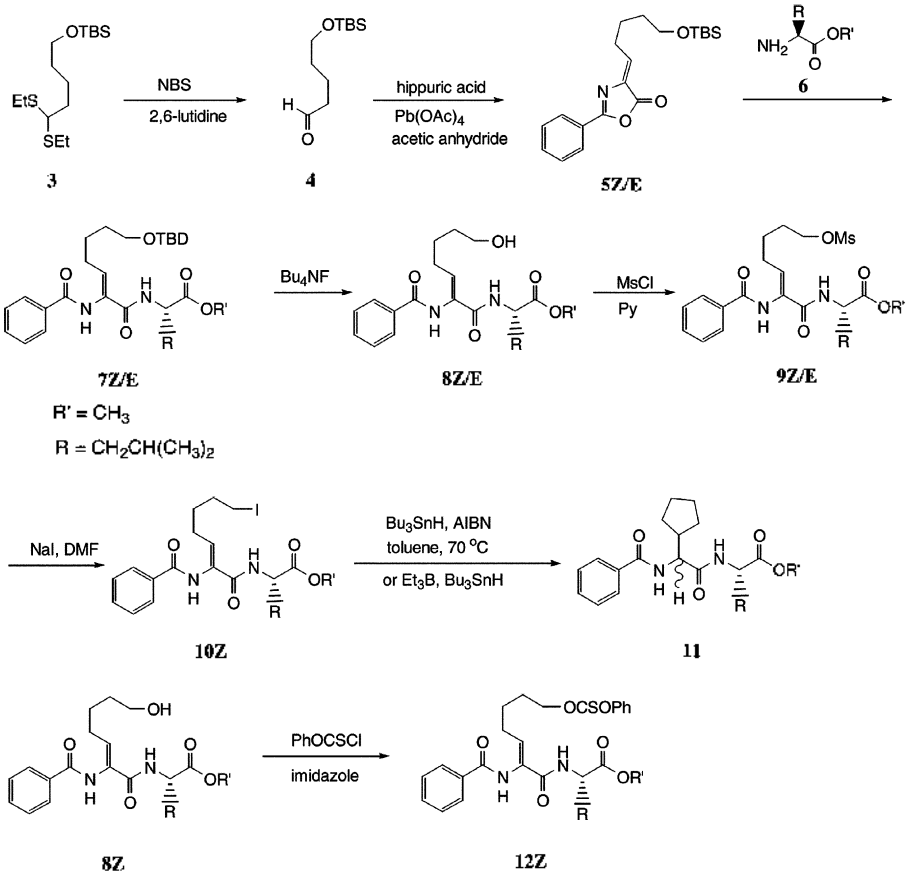
RESULT AND DISCUSSION

Intramolecular cyclization to cyclopentylamino acid dipeptide was examined. As a radical precursor, iodinated dehydroamino acid dipeptide **10*Z*** was chosen (*Scheme* 1).

Phenyl thiocarbamate **12*Z*** was considered, too. However, this precursor has been reported to have a limitation. Tin hydride meditated free radical generation via xanthate esters and related thiocarbamates has been developed by Barton and McCombie, and it's often the method of choice for deoxygenation of secondary alcohols in synthesis.[8] Relatively few examples of use of this radical precursor for intramolecular cyclization were reported, and most of them were with secondary radicals.[9]

The synthesis of the dehydroamino acid dipeptide is shown in *Schemes* 1. Compound **3**[10] was easily converted into aldehyde **4** with NBS and 2,6-lutidine in acetone/water (9:1) solvent. Because **4** was not stable enough to be separated with silica gel, the removal of excess 2,6-lutidine was carried out under vacuum for 5 hours, and the remaining crude oil was used for next step without purification. The Erlenmeyer azlactone synthesis gave **5*Z*/*E*** in good yield (84%) and the ***Z*:*E*** ratio was 5:1. To the ***Z*** and ***E*** mixture of azlactones was added *S*-leucine methyl ester (**6**) to yield dipeptie **7*Z*/*E***. The TBS protecting group of **7*Z*/*E*** was taken off with tetrabutyl ammonium fluoride. Direct conversion of hydroxyl group in **8*Z*/*E*** to bromide with trioctylphosphine and carbon tetrabromide was not satisfactory. The reaction proceeded too slowly with low yield. However, mesylation of **8*Z*/*E*** followed by substitution reaction with NaI in DMF produced the target radical precursor **10*Z*/*E*** in 87% yield.

For the final cyclization, the traditional method, tributyltin hydride and AIBN (azoisobutyronitrile) with heating was tried. The removal of oxygen by bubbling dry argon through the solvent for 30 minutes before adding Bu_3SnH was necessary. After heating at 70 °C for 12 hours under the Ar atmo-



Schemes 1.

sphere, high yield conversions into **11** were performed starting from pure ***Z*** isomer of **10**. However, no diastereoselectivity was found.

Recently, several new techniques have been developed for asymmetric radical reactions. The most common method is lowering the temperature with a different radical initiator instead of AIBN and heating. One of them is triethylborane that has proved to be an effective radical initiator in the presence of trace amounts of oxygen.[11] Several examples of use of the Et_3B have been reported in the reduction of alkyl, alkenyl, and aryl halides.[12] This methodology is attractive for the following reasons: 1) It is mild enough not to perturb other functional groups (carbonyl, ether, hydroxyl). 2) The reaction temperature can be lowered to -78 °C. Especially, K. Oshima reported interesting reactions of α-halo ketones and aldehydes with Ph_3SnH and Et_3B at room temperature.[13] The important two roles of Et_3B in this reaction were both initiation of radical reaction to generate α-carbonyl radical and trapping this radical as boron enolate. He also extended this to the three component coupling reaction of alkyl iodide, α, β-unsaturated ketone, and aldehyde.

Et_3B methodology was attractive for our purpose of enhancing diastereoselectivity by lowering the reaction temperature. Additionally, if boron enolate was forming as an intermediate, an intramolecular chelation of boron enolate could exist, and it might have a positive effect to improve the diastereoselectivity.

Pure ***Z*** isomer of **10** was dissolved in toluene and O_2 was removed by bubbling dry argon through the reaction mixture. Et_3B (1.3 equiv.) in THF and

Bu_3SnH (1.3 equiv.) was added, and the reaction was stirred at -78 °C, -50 °C, -20 °C, and 0 °C. At -78 °C and -50 °C, no product formation was found, and starting material was recovered. It might be because of the low solubility of the reagents at low temperature. Actually, a white precipitate in the reaction flask was found during the reaction. At -20 °C, reaction was finished in 5 hours, and a 2:1 mixture of two diastereomers (**11**) was obtained in 74% yield. The amounts of added Et_3B was essential. With less than 1 equivalent, reaction was not complete, but with more than 1.5 equivalents, side products were formed. This result suggests that Et_3B is not just a radical initiator, but also participates in forming an intermediate, which seems to be a boron enolate.

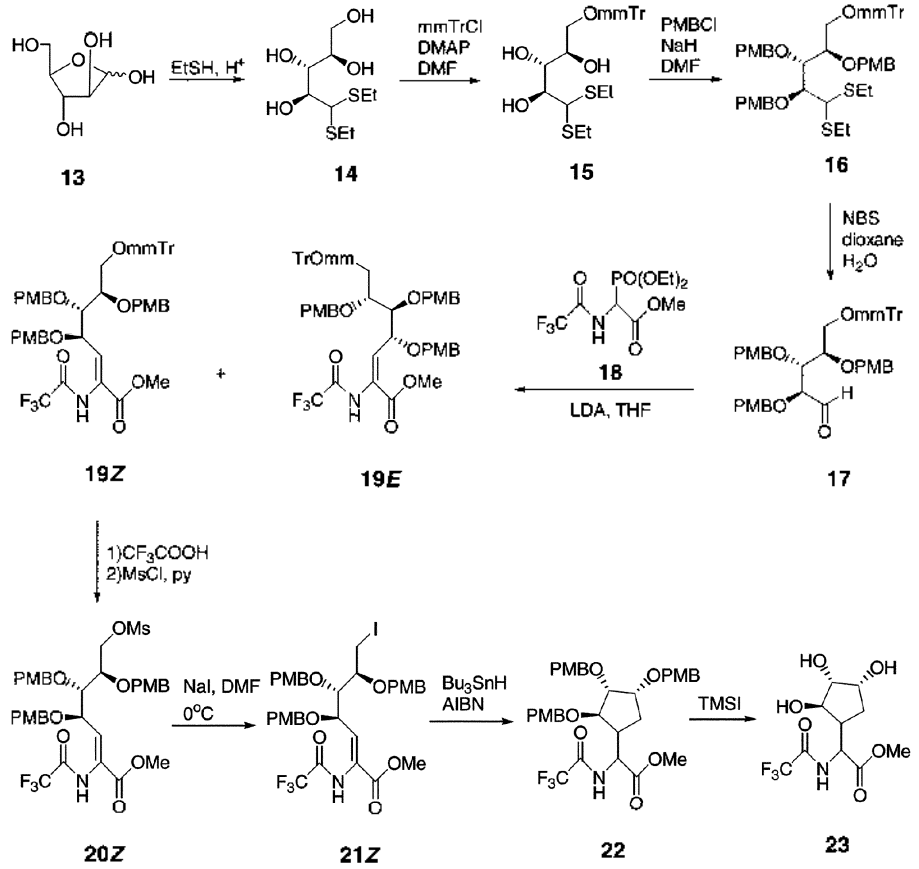
Diastereoselectivity is induced by the asymmetric H-abstraction of boron enloate which might depend marginally on the stereochemistry of adjacent amino acid side chain (R). The exact mechanism is still unclear and studies to figure out the absolute stereochemistry of major diastereomer of **11** are going on. At 0 °C, reaction was completed within 30 minutes, and slightly lower diastereoselectivity (3:2 ratio of two diastereomers) with similar yield was obtained.

Our dipeptide was designed using adjacent amino acid groups as the chiral auxiliary. However, for this purpose, O=C-N and C-C=O bond rotations in the peptide bond should be considered carefully. For the best stereoselectivity, the orientation of these two bonds must be fixed. In the field of stereoselective alkylation of enolates and enamines, several techniques have been developed to restrict these two bond rotations. Especially, for O=C-N bond fixing, the C2 symmetry strategy[14], chelation[15], H-bonding, dipole-dipole control[16],and steric control techniques have been reported. In the radical chemistry field, some chiral amide auxiliaries - dimethylpyrrolidine[4a-c], Oppolzer camphorsultam[2a], and oxazolidines[4d] - have been applied successfully for this purpose. In our dipeptide, although the orientation of C-C=O bond rotation might be fixed by forming boron enolate, the steric hindrance from chiral auxiliary in adjacent amino acid was proved to have little effect. However, If we do same radical cyclization of dehydroamino acid included in a longer peptide chain, we carefully expect better diastereoselectivity, because the tertiary structure of the long peptide chain might be rigid enough not to allow the free rotation of individual peptide bonds, and the adjacent amino acids will be used as effective chiral auxiliaries.

For better diastereocontrol, intramolecular cyclization of a dehydroamino acid **21*Z*** (*Scheme* 2) which has a chiral carbon next to double bond was tried. In this case, two stereocenters are generated by asymmetric intramolecular cycloaddition and subsequent H-abstraction. Different from the previous dipeptide, the stereocontrol on cycloaddition was designed to be performed by a chiral group attached next to the double bond, and the newly formed chiral cyclopentyl moiety controlled the direction of H-abstraction of α-carbon.

The radical precursor **21*Z*** was easily synthesized from **20*Z***.[17] Mesyl compound **20*Z*** was converted into **21*Z*** by refluxing with NaI in DMF for 8 hours. Fot the cyclization, **21*Z*** was dissolved in dry toluene, and O_2 was removed before adding Bu_3SnH and AIBN. After heating at 70 °C for 8 hours, cyclized product **22** was separated by column chromatography with silica gel. The yield was 90%, but **22** was inseparable mixtures of four diastereomers in 9:3:3:1 ratio. Deprotection of three PMB (*p*-methoxybenzyl) groups of **22** with TMSI (tetramethylsilyl iodide) gave **23** which was separated as mixtures of two diastereomers (3:1). Because of the failure of purification, there were difficulties in assigning the configurations of two new forming stereocenters in the major isomer. However, the configuration of the β-carbon in the major isomer could be barely figured out by an NOE experiment. Its result is in *Fig.* 2. Transannular NOE between H-1 and H-3, and H-4 is evidence supporting H-1, H-3 and H-4 have a *syn* configuration. Therefore, the configuration of the β-carbon on the major diastereomer of **23** could be assigned as *R*.

Low diastereoselectivity can be enhanced when the reaction is carried out at lower temperature with irradiation or using the Et_3B initiator, and we hope to report its result near future.



Schemes 2.

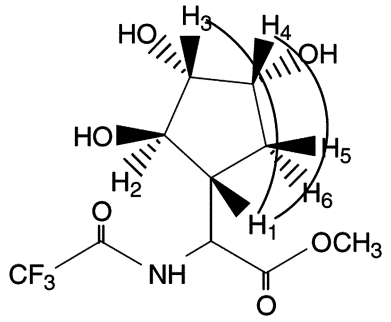


Fig. 2.

EXPERIMENT

4-[5-(*t*-Butyldimethylsilyloxy)-pentylidene]-2-phenyl-5(4H)-oxazolone 5*Z*/*E*. To 12 g (0.037 mol) of 5-*t*-butyldimethylsilyloxy-1,1-dithioethylpentanal (**3**) in 200 mL of acetone/water mixture (10:1) was added 17.3 mL (0.149 mol, 4 equiv.) of 2,6-lutidine, and 13.2 g (0.074 mol, 2 equiv.) of *N*-bromosuccinimide (NBS) was titrated into the reaction mixture with stirring at rt (room temperature) until the yellow color remained. After stirring for 15 min, the reaction mixture was transferred into a 1 M sodium sulfite aqueous solution. Extractions were carried out with hexane/CH_2Cl_2 (4:1) three times. The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The remaining clear oil was dried by toluene azeotropic distillation, and excess 2,6-lutidine was also removed by evaporation. Without further purification, crude aldehyde was dissolved in 100 mL dry toluene and transferred into a mixture of 10 g (0.0555 mol, 1.5 equiv.) of hippuric acid, 13.7 mL (0.233 mol, 4 equiv.) of acetic anhydride, and 5 g (0.0112 mol, 1.2 equiv.) of $Pb(OAc)_4$ in 200 mL dry toluene under nitrogen atmosphere.

The reaction mixture was heated for 12 hr at 80 °C, and the color became yellow. Cooling the reaction flask in ice bath, 50 mL of 0.1 M $NaHSO_4$ aqueous solution was added slowly, and an extraction was carried out with three portions of toluene. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The remaining yellow oil was purified by column chromatography with florisil to yield 11.3 g (84%) of **5*Z*** and **5*E*** mixture (*Z*:*E*=5:1). For analytical purpose, **5*Z*** was isolated.

5*Z*: IR (neat, cm^{-1}) 2928, 2856, 1810, 1654, 1602, 1580, 1522, 1472, 1324, 1293, 1179, 1091, 836, 777, 710; ^1H NMR (360 MHz, $CDCl_3$) δ 8.07 (d, J =7.17 Hz, 2H, Ar**H**), 7.56 (m, 1H, Ar**H**), 7.42 (m, 2H, Ar**H**), 6.69 (dd, J=7.98, 7.98 Hz, 1H, vinyl-**H**), 3.65 (dd, J=5.97, 5.97 Hz, 2H, C**H**$_2$OTBS), 2.69 (ddd, J=7.63, 7.63, 7.63 Hz, 2H, allylic-C**H**$_2$), 1.53 (m, 4H, C**H**$_2$), 0.90 (s, 9H, (C**H**$_3$)$_3$C), 0.05 (s, 6H, Si(C**H**$_3$)$_2$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.0, 162.7, 139.6, 136.3, 133.1, 128.8, 128.1, 125.7, 62.6, 32.3, 28.5, 25.9, 24.9, 18.3, -5.4.

N*-(1*S*-methoxycarbonyl-3-methylbutyl)-7-(*t*-butyldimethylsilyloxy)-2-phenacylamino-2-heptenamide 7*Z*/*E*.** To 10 g of L-leucine methyl ester hydrochloride (**6**) in 300 mL of dry CH_2Cl_2 was added NH_3 gas by bubbling into the reaction mixture for 2 hr. The reaction was stirred for 6 hr at rt. A white precipitate of NH_4Cl was removed by filtering, and the CH_2Cl_2 was removed at reduced pressure. The remaining clear oil was distilled in vacuum (25 mmHg) to yield leucine methylester as a clear oil. 1.5 g (4.18 mmol) of **5*Z*/*E (*Z*:*E*=5:1) and 1.1 g (8.36 mmol, 2 equiv.) of leucine methyl ester were dissolved in 10 mL dry THF. After refluxing 12 hr, the solvent was removed at reduced pressure, and the remaining yellow oil was purified by column chromatography with silica gel to yield 1.89 g (90%) of a **7*Z*/*E*** mixture (5:1). For analytical purpose, a pure sample of **7*Z*** was obtained.

7*Z*: IR (neat, cm^{-1}) 3258, 3045, 2954, 2857, 1751, 1636, 1558, 1522, 1486, 1472, 1435, 1361, 1255, 1198, 1157, 1101, 836, 775; ^1H NMR (360 MHz, $CDCl_3$) δ 8.08 (s, 1H, N**H**), 7.86 (d, J=7.35 Hz, 2H, Ar**H**), 7.49 (m, 1H, Ar**H**), 7.40 (m, 2H, Ar**H**), 6.83 (d, J=8.06 Hz, 1H, N**H**), 6.39 (dd, J=7.15, 7.15 Hz, 1H, vinyl-**H**), 4.62 (m, 1H, NC**H**CO), 3.64 (s, 3H, OC**H**$_3$), 3.54 (dd, J=5.68, 5.68 Hz, 2H, C**H**$_2$OTBS), 2.15 (m, 2H, allylic-C**H**$_2$), 1.62 (m, 4H, C**H**$_2$), 1.48 (m, 3H, C**H**$_2$, C**H**), 0.88 (m, 6H, C**H**$_3$), 0.83 (s, 9H, (C**H**$_3$)$_3$C), 0.01 (s, 6H, (C**H**$_3$)$_2$Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7, 173.6, 165.1, 133.7, 133.4, 131.9, 128.7, 128.5, 127.5, 62.6, 52.1, 51.0, 41.6, 36.1, 32.4, 28.1, 25.8, 24.7, 22.7, 21.8, 18.2, -5.4.

N*-(1*S*-methoxycarbonyl-3-methylbutyl)-7-hydroxy-2-phenacylamino-2-hepenamide 8*Z*/*E*.** To 1.50 g (2.97 mmol) of **7*Z*/*E (*Z*:*E*=5:1) dissolved in 100 mL of dry THF, was added 3.56 mL (3.56 mmol, 1.2 equiv.) of tetrabutylanunonium fluoride (1 M solution in THF). After stirring 2 hr, the reaction mixture was transferred into 50 mL saturated aqueous NH_4Cl solution. Extraction was carried out with three portions of ethylacetate, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The remaining oil was purified by column chromatography over silica gel to yield 1.07 g (92%) of **8*Z*/*E*** (*Z*:*E*=5:1).

8*Z*: IR (neat, cm^{-1}) 3288, 2954, 2869, 1736, 1648, 1522, 1482, 1438, 1369, 1276, 1207, 1158, 1058, 709; ^1H NMR (360 MHz, $CDCl_3$) δ 8.20 (s, 1H, NH), 7.88 (m, 2H, Ar**H**), 7.53 (m, 1H, Ar**H**), 7.45 (m, 2H, Ar**H**), 6.77 (d, J=8.21 Hz, 1H, N**H**), 6.41 (dd, J=7.36, 7.36 Hz, 1H, vinyl-**H**), 4.65 (m, 1H, NC**H**CO), 3.65 (s, 3H, OC**H**$_3$), 3.61 (m, 2H, C**H**$_2$OH), 2.22 (m, 2H, allylic-**H**$_2$), 1.62 (m, 7H, C**H**$_2$, C**H**), 0.92 (m, 6H, C**H**$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7, 165.0, 133.5, 133.2, 132.1, 128.9, 128.6, 128.4, 127.5, 62.4, 52.3, 51.1, 41.5, 31.7, 27.9, 24.8, 24.7, 22.8, 21.9.

N*-(1*S*-methoxycarbonyl-3-methylbutyl)-7-(methanesulfonyloxy)-2-phenacylamino-2-heptenamide 9*Z*/*E*.** To 1.03 g (2.64 mmol) of **8*Z*/*E (*Z*:*E*=5:1) dissolved in 50 mL of dry CH_2Cl_2 were added 0.63 mL (7.92 mmol, 3 equiv.) of pyridine and 0.61 L (7.92 mmol, 3 equiv.) of methanesulfonyl chloride, and the reaction was stirred for 12 hr at rt. The reaction mixture was transferred into 20 mL of a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent

was removed at reduced pressure, and the remaining oil was separated by column chromatography with silica gel to yield 1.10 g (89 %) of **9*Z*/*E*** (***Z*:*E*** =5:1). For analytical purpose, a pure sample of **9*Z*** was obtained.

9*Z*: IR (neat, cm^{-1}) 3270, 2956, 2870, 1744, 1647, 1522, 1479, 1438, 1351, 1277, 1200, 1173, 975, 937, 832, 710; ^1H NMR (360 MHz, $CDCl_3$) 8.25 (s, 1H, N**H**), 7.88 (m, 2H, Ar**H**), 7.50 (m, 1H, Ar**H**), 7.41 (m, 2H, Ar**H**), 7.00 (d, J=8.05 Hz, 1H, N**H**), 6.40 (dd, J=7.20, 7.20 Hz, 1H, vinyl-**H**), 4.60 (m, 1H, NC**H**CO), 4.17 (dd, J=6.21, 6.21 Hz, 2H, C**H**$_2$OMs), 3.63 (s, 3H, OC**H**$_3$), 2.95 (s, 3H, OC**H**$_3$), 2.20 (ddd, J=7.35, 7.35, 7.35 Hz, 2H, allylic-C**H**$_2$), 1.70 (m, 4H, C**H**$_2$), 1.58 (m, 3H, C**H**$_2$, C**H**), 0.91 (m, 6H, C**H**$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7, 173.6, 164.9, 133.3, 132.8, 132.0, 129.2, 128.5, 127.5, 69.6, 52.2, 51.1, 41.1, 37.2, 28.6, 27.5, 24.7, 24.0, 22.7, 21.8.

N*-(1*S*-methoxycarbonyl-3-methylbutyl)-7-iodo-2-phenylacylamino-2-heptenamide 10*Z*/*E*.** To 1.05 g (2.24 mmol) of **9*Z*/*E (***Z*:*E***=5:1) dissolved in 50 mL dry DMF was added 0.50 g (3.36 mmol, 1.5 equiv.) of NaI, and the reaction was heated at 70 °C for 12 hr under nitrogen atmosphere. The DMF solvent was concentrated at reduced pressure, and the remaining yellow solid was purified by column chromatography with silica gel to yield 0.97 g (87%) of **10*Z*/*E*** (***Z*:*E***=5:1). Approximately 200 mg of the **10*Z*/*E*** mixture was repurified by preparative TLC and 110 mg of pure **10*Z*** was isolated.

10*Z*: IR (neat, cm^{-1}) 3055, 2956, 2867, 1749, 1634, 1556, 1524, 1458, 1434, 1367, 1296, 1201, 1159, 1028, 984, 692; ^1H NMR (360 MHz, $CDCl_3$) δ 8.04 (s, 1H, N**H**), 7.86 (m, 2H, Ar**H**), 7.52 (m, 1H, Ar**H**), 7.44 (m, 2H, Ar**H**), 6.74 (d, J=8.07 Hz, 1H, N**H**), 6.36 (dd, J=7.12, 7.12 Hz, vinyl-**H**), 4.65 (m, 1H, NC**H**CO), 3.68 (s, 3H, OC**H**$_3$), 3.15 (dd, J =6.91, 6.91 Hz, 2H, C**H**$_2$I), 2.21 (ddd, J=7.49, 7.49, 7.49 Hz, 2H, allylic-C**H**$_2$), 1.79 (m, 2H, C**H**$_2$), 1.61 (m, 5H, C**H**$_2$, C**H**), 0.93 (d, J=5.99 Hz, 3H, C**H**$_3$), 0.91 (d, J=5.99 Hz, 3H, C**H**$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.6, 164.9, 133.4, 132.1, 128.9, 128.4, 127.5, 52.3, 52.1, 41.4, 32.9, 29.1, 27.4, 24.8, 22.8, 21.9, 6.5.

(*N*-phenylacyl-2-cyclopentylglycyl)-(*S*)-leucine methyl ester 11. A) Bu_3SnH/ AIBN method: To 60 mg (0.120 mmol) of **10*Z*** dissolved in 50 mL of dry toluene was added a catalytic amount of azoisobutyronitrile (AIBN). Dry argon was bubbled through the reaction mixture for 30 min, then 41.9 μL (0.144 mmol, 1.2 equiv.) of Bu_3SnH was injected via syringe and the reaction was heated at 75 °C under an argon atmosphere for 12 hr. The reaction mixture was transferred into a saturated aqueous NH_4Cl solution and extracted with toluene three times. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The remaining yellow oil was purified by column chromatography with silica gel to yield 39.5 mg (88%) of **11** (1:1 mixture of two diastereomers).

B) Et_3B/Bu_3SnH method: To 20 mg (0.040 mmol) of **10*Z*** in dry toluene degassed with dry argon was added 52.0 μL (1.3 equiv.) of Et_3B 1.0 M solution in THF and 15.1 μL (0.052 mmol, 1.3 equiv.) of Bu_3SnH at -20 °C. After stirring 5 hours, small water was added, and extractions were carried out with three portions of toluene. Combined organic layers was dried over anhydrous $MgSO_4$, filtered, and concentrated. The resultant oil was purified by column chromatography with silica gel to yield 11.0 mg (74%) of **11** (2:1 mixture of two diastereomers).

11 (a mixture of two diastereomers): IR (neat, cm^{-1}) 3068, 2955, 2870, 1750, 1633, 1579, 1539, 1490, 1436, 1386, 1328, 1259, 1203, 1171, 1152, 1027, 692; ^1H NMR (360 MHz, $CDCl_3$) δ 7.79 (m, 4H, Ar**H**), 7.45 (m, 6H, Ar**H**), 6.86 (dd, J=6.00, 6.00 Hz, 2H, N**H**), 6.76 (d, J=8.20 Hz, 1H, N**H**), 6.67 (d, J=7.93 Hz, 1H, N**H**), 4.59 (m, 4H, NHC**H**CO), 3.73 (s, 3H, OC**H**$_3$), 3.66 (s, 3H, OC**H**$_3$), 2.39 (m, 2H, C**H**), 1.79 (m, 4H, C**H**$_2$), 1.60 (m, 10H, C**H**$_2$), 1.39 (m, 8H, C**H**$_2$, C**H**), 0.94 (d, J=6.05 Hz, 3H, C**H**$_3$), 0.92 (d, J=5.85 Hz, 3H, C**H**$_3$), 0.89 (d, J=6.16 Hz, 3H, C**H**$_3$), 0.87 (d, J=5.96 Hz, 3H, C**H**$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.0, 172.9, 171.7, 167.5, 167.4, 134.0, 133.9, 131.7, 128.5, 128.4, 127.1, 127.0, 77.4, 77.0, 76.6, 57.1, 52.2, 50.8, 42.7, 42.5, 41.2, 41.0, 29.5, 29.4, 28.9, 28.8, 26.8, 26.6, 25.3, 25.1, 25.0, 24.9, 24.7, 22.8, 21.7, 21.7; HRMS (FAB) $[MH]^+$ calculated for $C_{21}H_{30}O_4N_2$ 375.2284, found 375.2285.

Methyl (*Z*)-7-iodo-4*R*,5*S*,6*S*-tris(*p*-methoxybenzyloxy)-2-trifluoroacetyl-2-heptenoate 21*Z*. To 195.5 mg (0.25 mmol) of **20*Z*** in DMF (15 mL) was added 74.9 mg (0.50 mmol, 2 equiv.) of NaI. The reaction mixture was stirred at 70 °C for 12 hr, and the solvent was removed at reduced pressure. The remaining oil and excess NaI were separated by column chromatography with silica gel to yield 140 mg (71%) of **21*Z***: IR (neat, cm^{-1}) 3309, 3001, 2954, 2837, 1735, 1655, 1612, 1586, 1515, 1465, 1437, 1303, 1250, 1210, 1174, 1034, 910, 822, 760; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.68 (s, 1H, N**H**), 7.20 (m, 4H, Ar**H**), 7.10 (m, 1H, Ar**H**), 6.82 (m, 6H, Ar**H**), 6.43 (d, J=6.72 Hz, 1H, vinyl-**H**), 4.71 (d, J=10.48 Hz, 1H, OC**H**$_2$Ar), 4.50 (d, J=10.48 Hz, 2H, OC**H**$_2$Ar), 4.43 (d, J=11.17 Hz, 1H, OC**H**$_2$Ar), 4.37 (dd, J=6.80, 2.53 Hz, 1H, C**H**OPMB), 4.23 (d, J=10.72 Hz, 1H, OC**H**$_2$Ar), 4.19 (d, J=11.24 Hz, 1H, OC**H**$_2$Ar), 3.83 (s, 3H, ArOC**H**$_3$), 3.80 (s, 3H, ArOC**H**$_3$), 3.79 (s, 3H, ArOC**H**$_3$), 3.76 (s, 3H, COC**H**$_3$), 3.70 (dd, J=6.58, 2.54 Hz, 1H, C**H**OPMB), 3.56 (dd, J=4.13, 4.13 Hz, 2H, C**H**$_2$I), 3.50 (m, 1H, C**H**OPMB); ^{13}C NMR (90 MHz, $CDCl_3$) δ 162.9, 159.7, 159.5, 159.4, 155.0 (ddd, J=37.8, 37.8, 37.8 Hz, CF_3**C**O), 130.7, 130.2, 129.8, 129.7,129.2, 128.8, 128.7, 128.2, 113.9, 113.8, 81.5, 76.1, 75.2, 74.4, 71.3, 71.2, 55.2, 55.1, 52.8, 8.8; HRMS (FAB) $[MNa]^+$ calculated for $C_{34}H_{37}F_3INO_9$ 810.1364, found 810.1367.

Methyl *N*-trifluoroacetyl-2-[2*R*,3*R*,4*R*-tris(*p*-methoxybenzyloxy)-cyclopentyl]-glycinate 22. To 100 mg (0.13 mmol) of **21*Z*** dissolved in dry toluene was added a catalytic amount (5 mg) of AIBN. Dry argon was bubbled through the reaction mixture for 30 min, then 45.5 μL (0.17 mmol, 1.3 equiv.) of Bu_3SnH was added via syringe and the reaction mixture was heated to 75 °C for 12 hr. Toluene was removed at reduced pressure, and the remaining oil was purified by column chromatography with silica gel to yield 77 mg (90%) of **23** as an inseparable mixture of four diastereomers (9:3:3:1).

Major diastereomer. (in a mixture of diastereomers): IR (neat, cm^{-1}), 3268, 3074, 3000, 2952, 2909, 2837, 1724, 1612, 1586, 1550, 1515, 1464, 1442, 1361, 1302, 1250, 1210, 1174, 1111, 1034, 821, 728; 1H NMR (360 MHz, $CDCl_3$) δ 8.12 (d, J =5.56 Hz, 1H, N**H**), 7.25 (m, 4H, Ar**H**), 7.14 (m, 2H, Ar**H**), 6.88 (m, 6H, Ar**H**), 4.39 (dd, 1H, NC**H**CO), 3.95 (m, 2H, C**H**OPMB), 3.86 (m, 1H, C**H**OPMB), 3.85 (s, 3H, ArOC**H**$_3$), 3.82 (s, 3H, ArOC**H**$_3$), 3.81 (s, 3H, ArOC**H**$_3$), 3.64 (s, 3H, COOC**H**$_3$), 2.58 (m, 1H, C**H**), 2.13 (m, 1H, C**H**$_2$), 1.70 (m, 1H, C**H**$_2$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.9, 159.4, 159.3, 159.2, 157.8 (ddd, J=37.5, 37.5, 37.5 Hz, CF_3**C**O), 129.7, 129.6, 129.5, 129.4, 129.3, 115.6 (ddd, J=285.9, 285.9, 285.9 Hz, **C**F$_3$), 113.8, 113.7, 113.6, 82.6, 81.9, 75.8, 72.0, 71.9, 71.2, 55.2, 54.8, 52.4, 41.7, 29.3; HMRS (FAB) $[MH]^+$ calculated for $C_{34}H_{38}F_3NO_9$ 660.2420, found 660.2426.

Methyl *N*-trifluoroacetyl-2-(2*R*,3*R*,4*R*-trihydroxy-cyclopentyl)-glycinate 23. To 55 mg (0.083 mmol) of **22** (mixture of four diastereomers) in 5 mL dry CH_2Cl_2 at 0 °C was added 63.2 μL (0.44 mmol, 5 equiv.) of TMSI portionwise for 2 hr under nitrogen atmosphere. Stirring was continued until all starting material disappeared at 0 °C, and the aqueous CH_3OH was added to quench excess TMSI. After stirring 1 hr, the solvent was removed at reduced pressure. The remaining oil was transferred into a saturated aqueous NH_4Cl solution, and extraction was carried out with three portions of EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The remaining dark brown oil was purified by column chromatography with silica gel to yield 21.5 mg (86%) of an inseparable mixture (9:3:3:1) of diastereomers **23**. Small amount of **23** were repurified with preparative TLC, but still a mixture of two diastereomers (3:1) was obtained.

Major diastereomer. (in a mixture of two diastereomers): IR (neat, cm^{-1}) 3342, 3084, 2927, 1716, 1565, 1440, 1220, 1182, 1069, 1037, 975, 878, 729; ^{1}H NMR (360 MHz, CD_3COCD_3) δ 9.08 (brd, 1H, N**H**), 4.28 (dd, J=6.00, 6.00 Hz, 1H, NC**H**CO), 4.11 (m, 1H, C**H**OH), 4.00 (dd, J=4.70, 10.19 Hz, 1H, C**H**OH), 3.77 (dd, J=4.50, 9.43 Hz, 1H, C**H**OH), 3.69 (s, 3H, OC**H**$_3$), 2.45 (m,1H, C**H**), 2.25 (m, 1H, C**H**$_2$), 1.56 (m, 1H, C**H**$_2$); ^{13}C NMR (90 MHz, CD3CN) δ 170.9, 158.2 (ddd, J=36.8, 36.8, 36.8 Hz, CF3**C**O), 115.0 (ddd, J=285.1, 285.1, 285.1 Hz, **C**F$_3$), 79.9, 77.3, 72.0, 56.3, 52.8, 43.7, 32.1; HRMS (FAB)

$[MNH_4]^-$ calculated for $C_{10}H_{14}F_3NO_6$ 319.1117, found 319.1115.

CONCLUSION

Various intramolecular radical cyclizations of dehydroamino acid derivatives were studied. The 5-exo radical cyclization of dehydroamino acid derivative in which adjacent amino acid was used as a chiral auxiliary was performed with high yield but with poor stereoselectivity. In low temperature reaction, enhanced stereo selectivity was found, but it was still unsatisfactory. However, a 5-exo radical cyclization of a dehydroamino acid in which chiral carbons were located around the double bond gave promising results. Two new stereocenters were generated at the same time, and even at high temperature reaction condition, affordable stereoselectivity was found. It is expected that the changing reaction condition at low temperature with Et_3B initiator can improved the stereoselectivity. We believe intramolecular radical cyclization of dehydroamino acids must be a useful methodology for the synthesis of amino acids that have a cyclic side chain.

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