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Synthesis of Chiral Spiro 3-Oxazolin-5-one 3-Oxides (Chiral Nitrones) via a Nitrosoketene Intermediate and Their Asymmetric 1,3-Dipolar Cycloaddition Reactions Leading to the EPC Synthesis of Modified Amino Acids.

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Abstract: Cycloaddition of chiral cyclic ketones such as (-)-menthone, (+)-nopinone, and (+)camphenilone to nitrosoketene generated by thermolysis of 5-hydroxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione gave the corresponding chiral spiro 3-oxazolin-5-one 3-oxides (chiral cyclic nitrones). These nitrones underwent asymmetric 1,3-dipolar cycloaddition reactions with electron rich olefins to give the corresponding oxazolidine derivatives with high diastereoselectivity, which were converted to optically pure amino acids. © 1997 Elsevier Science Ltd.

Introduction

Recently, Tidwell and coworkers have calculated at the HF/ $6-31G^{*}//$ HF- $6-31G^{*}$ level the structure and energy of nitrosoketene (2) and have predicted that the ketene will have reasonable thermodynamic stability, although it might be quite reactive in a kinetic sense.^{1,2} However, although numerous papers dealt with the chemistry of ketene intermediates, ³ none describes the reaction involving 2 as a reactive intermediate, and the detection of 2 by spectroscopy. Quite recently, we have reported a new synthesis of cyclic nitrones B (3oxazolin-5-one 3-oxides) from the reaction of 5-hydroxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (1: isonitroso Meldrum's acid) with ketones. This reaction can be considered to involve the cycloaddition of ketones with 2⁴ generated by thermolysis of 1, and there are two pathways for the formation of B: one is that the *cisoid* nitrosoketene initially undergoes [4+2] cycloaddition with ketones to form the dioxazines A which are then transformed to the nitrones B; another is that the *transoid* nitrosoketene directly undergoes [3+2] cycloaddition with ketones to give the nitrones B.^{5,6} Later, Birney and his coworker were interested in our reaction, and proposed using the *ab initio* calculation of the energy on [4+2] or [3+2] transition state that the reaction proceeded with [3+2] cycloaddition to form the cyclic nitrones B.⁷

As an extension of our nitrosoketene chemistry, we report here the synthesis of chiral spiro nitrones via 2 and their asymmetric 1,3-dipolar cycloaddition reactions leading to the EPC (enantiomerically pure compound) synthesis of amino acids.⁸ A part of this work has already appeared as communications.^{9,10}



Scheme 1

Results and Discussion

Synthesis of Chiral Spiro 3-Oxazolin-5-one 3-Oxides

According to the reaction conditions previously reported in the synthesis of achiral cyclic nitrones,⁶ (-)menthone (3) was heated with 1 in toluene to give two nitrones 4 and 5 in 26% and 28% yields,¹¹ respectively, which were chromatographically separable from each other. Since the structure of the less polar nitrone 4 was determined to be 5*R* by X-ray crystallographic analysis,⁹ the structure of more polar nitrone 5 coincided with the configuration of 5*S*. In a similar manner, (+)-nopinone (6) and (+)-camphenilone (8) also reacted with 1 to form chiral nitrones 7 and 9 as sole products in 62% and 51% yields, respectively. In these reactions, the corresponding diastereomers 7' and 9' were not detected. The structure of 7 was again determined to be 5*R* by X-ray crystallographic analysis.⁵ The reaction of 3 with 2 produced two isomers because both attack-sides of 2 to the carbonyl group of 3 would be sterically equal. On the contrary, only compound 7 was formed by the attack of 2 from the less hindered side of 6 as shown in Scheme 2. In a similar fashion, 2 approached from the less hindered side (convex face) of 8 to form 9 exclusively. Therefore, the structure of 9 should be the 5*S* configuration.



Scheme 2

Asymmetric 1,3-Dipolar Cycloaddition Reactions of Chiral Nitrones to Electron Rich Olefins and Conversion of Their Adducts to Enantiomerically Pure Amino Acids.

Previously, we reported the 1,3-dipolar cycloaddition of ethyl vinyl ether or allyltrimethylsilane with the achiral nitrone (10) obtained from the reaction of 1 with cyclohexanone to give the endo adduct C exclusively.⁶ This is because the product **D** derived from **C** by LiAlH₄ reduction was assigned to be 3,5-cis by the NOE experiment as shown in Scheme 3.12 We reinvestigated the reaction and concluded on the basis of the NOE experiment of the adducts 11a,b themselves that the products were not the endo adducts C but the exo 11a,b. Though the adducts 11a,b could not be purified by silica gel column chromatography as reported previously, the NOE experiments of both crude compounds 11a,b revealed that the adducts 11a,b definitely were the exo adducts.¹⁴ Thus, as shown in Scheme 3, the NOE effect between 7-Hb and 7a-H or 6-H and 7-Ha of 11a,b was observed showing the exo adduct. Therefore, the isoxazolidine derivatives (\pm) -12b obtained by mild alkaline hydrolysis of 11b should be 3,5-trans. Catalytic hydrogenation of (\pm) -12b gave a γ -hydroxy- α -amino acid (±)-13. Next, in oder to transform (±)-13 to racemic allylglycine (±)-14, we examined the olefination of (±)-13 under various conditions. Desilylating reagents such as KF and n-Bu₄NF were inactive for the reaction. We found that BF_3 -Et₂O was the best reagent for the olefination of (±)-13. Thus, (±)-13 was treated with BF₃-Et₂O in acetonitrile at room temperature for 3 h to give allylglycine (\pm) -14 in quantitative yield. Though hydrochloric acid also catalyzed the reaction in high yield, a longer reaction time was required (hydrochloric acid-MeOH at room temperature for 6 days) and γ -trimethylsilylmethyl- α -amino- γ -lactone was formed as a by-product.





According to this procedure, we intended to synthesize the enantiomerically pure allylglycine (+)-14 from the chiral nitrone 4. The chiral nitrone 4 underwent 1,3-dipolar cycloaddition with allyltrimethylsilane under high pressure or in the presence of BF₃-Et₂O to give the adduct 15 as a single isomer in 90% yield. The reaction proceeded with the *exo* transition state as the same in the case of the reaction of 10 with allyltrimethylsilane. Therefore, allyltrimethylsilane approached from the less hindered side of 4 as shown in Scheme 4 to give 15 selectively. The structure of 15 was determined to be (3*R*, 7a*S*, 6*S*) by NOE experiment. Thus, 5.4% and 7.1% increase in integration of 7-Ha and 7-Hb were observed by irradiation of 6-H and 7a-H, respectively (Scheme 4). Treatment of 15 with 0.15 M aqueous sodium hydroxide solution at room temperature for 4 h followed by treatment with ion exchange resin (Amberlite IRC-50, acid form) gave the cyclic amino acid (isoxazolidine derivative) (-)-12b in almost quantitative yield, concomitant with the quantitative recovery of 3. Hydrogenolysis of (-)-12b with Pd-C gave (2*S*, 4*S*)-2-amino-4-hydroxy-5-(trimethylsilyl)pentanoic acid [(-)-13] in 88% yield, whose optical purity was determined to be *ca*. 100% *ee* by HPLC analysis using chiral column (CROWNPAK-CR). As the same in the case of racemic series, (-)-13 was treated with BF₃-Et₂O in CH₃CN to give the desired enantiomerically pure (*S*)-allylglycine [(-)-14].¹⁵ The optical purity of (-)-14 was also determined to be *ca*. 100% *ee* by comparison of the HPLC analysis of racemic allylglycine [(±)-14].





Employing the same procedure, the EPC synthesis of (R)-allylglycine ((+)-14) from the nitrone 5 was also achieved. As in the case of the reaction with 4, allyltrimethylsilane would approach from the a-side of 5 to give the adduct 16 as a sole product. The NOE effects were observed between 6-H and 7-Ha, and between 7-Hb and 7a-H, respectively (Scheme 5). Transformation of 16 to (+)-14 (via (+)-12b and (+)-13) was accomplished by similar procedure given for the synthesis of (-)-14 from 15.

On the contrary, the chiral nitrone 7 reacted with allyltrimethylsilane under the same conditions to give the *exo* adduct 17, whose ¹H-NMR spectrum showed 17 to be a mixture of two diastereomers with 60% dewhich were chromatographically inseparable. The adduct 17 was also converted to (S)-allylglycine [(-)-14] with 60% *ee*. The *ee* was reflected on the diastereoselectivity in the formation of the adduct 17.

Reaction of the chiral nitrone 9 with allyltrimethylsilane also took place under high pressure (800 MPa) to give 18 and its diastereomer 19 in 62% and 8% yields, respectively. Both compounds were again formed by the *exo* transition state, and their structures were determined by NOE experiment. The adduct 18 should serve as a precursor of (R)-allylglycine [(+)-14].

No endo adduct was detected in all 1,3-dipolar cycloadditions of the chiral nitrones 4, 5, 7, and 9 with allyltrimethylsilane. This would be probably due to the steric interaction between the corresponding chiral auxiliaries and the dipolarophile.



Scheme 5

To apply the EPC synthetic method of allylglycine to the asymmetric synthesis of naturally occurring cyclopentenyl amino acid (2S, 1'S)-28 being a potent growth inhibitor of *Escherichia coli* ¹⁶ as well as a biogenic precursor of unusual cyclopentenyl fatty acids,¹⁷ we examined the asymmetric 1,3-dipolar cycloaddition of chiral nitrone 4 with 3-trimethylsilylcyclopent-1-ene. Before investigating the asymmetric

reaction, we tried the reaction of achiral nitrone 10 with 3-trimethylsilylcyclopent-1-ene as a preliminary experiment. When the nitrone 10 was allowed to react with 3-trimethylsilylcyclopent-1-ene in CH₂Cl₂ under high pressure, three products 20, 21, and 22 were obtained in 70%, 13%, and 13% yields, respectively. These compounds were not separated by chromatography, and therefore these yields were determined by 300 MHz ¹H-NMR data. All products were determined to be the *exo* adducts because the ¹H-NMR spectra showed a singlet signal due to 8b-H of all adducts 20-22. On the basis of ¹H-NMR spectra analysis as shown in Experimental section, it was determined that the minor product 21 corresponded to the stereoisomer of the major product 20 in the 6-position, and compound 22 was a regioisomer of 20 because in the ¹H-NMR spectra of 20 and 21 5a-H was observed as a signal of double of doublet (dd) and triplet (t), respectively, whereas that of 22 showed the peak of double of triplet (dt).

In a similar fashion, the asymmetric reaction of chiral nitrone 4 with 3-trimethylsilylcyclopent-1-ene gave three products 23-25 in 55%, 20%, and 24% yield, respectively, which were chromatographically separable from one another. The stereo- and regio-chemistry of compounds 23-25 completely coincided with those of racemic series 20-22, respectively. The structures of 23 and 25 were eventually confirmed by NOE experiment as shown in Scheme 6 and Table 1.





Scheme 6

radiated rotons	Increase in Integration (%)	Irradiated Protons	Increase in Integration (%)	
8a-H 8a-H 5a-H 5a-H TMS TMS	5a-H 10.0 TMS 0.0 8a-H 8.8 TMS 0.6 8a-H 1.4 5a-H 7.5	8a-H 8a-H 8-H 5a-H 5a-H 5a-H TMS TMS	8-H 5a-H 8a-H 5a-H 8a-H 8-H 8-H 5a-H	0.7 6.7 1.3 0.0 8.1 0.0 3.9 0.0
		TMS	8a-H	6.7

Table 1. NOE Experiments of Compounds 23 and 25.

Since the 1,3-dipolar cycloaddition of nitrones 10 and 4 with 3-trimethylsilylcyclopent-1-ene did not proceed with high regio- and stereo-selectivity, these reactions were not versatile from viewpoint of synthetic chemistry. Therefore, in order to improve the regio- and stereo-selectivity, we examined Lewis acid mediated 1,3-dipolar cycloaddition of nitrones 10 and 4 with 3-trimethylsilylcyclopent-1-ene. When the nitrone 10 was treated with 3-trimethylsilylcyclopent-1-ene in the presence of one equivalent of BF3-Et2O at room temperature, the adduct 20 was obtained as a single isomer in 96% yields. Asymmetric 1,3-dipolar reaction of 4 with 3trimethylsilylcyclopent-1-ene under the same conditions also proceeded with very high diastereoselectivity to give the adduct 23 as a sole product in 69% yields. These remarkably selective reaction was due to the coordination of BF3 with the oxygen atom of nitrones 10 and 4 as shown in Scheme 7. Thus, the coordination increased the reactivity of the nitrones by decrease of LUMO energy of 1,3-dipolar, and caused the steric hindrance in the transition state to improve the diastereoselectivity. Therefore, in the asymmetric 1,3-dipolar cycloaddition, the nitrone coodinated with BF3 recognized exclusively only one enantiomer (3S-isomer) of 3trimethylsilylcyclopent-1-ene to form 23 as a single isomer. This means that a novel kinetic resolution of the dipolarophile is involved in the asymmetric 1,3-dipolar cycloaddition.¹⁸ The adduct 20 was then subjected to alkaline hydrolysis with aqueous NaHCO₃, hydrogenolysis with Pd-C, and olefination with BF₃-Et₂O, successively, to give racemic cyclopentenylglycine (\pm)-28. Employing the similar procedure, chiral adduct 23 was also converted to the chiral amino acid, (2S, 1'S)-cyclopentenylglycine (2S, 1'S)-28 as an enantiomerically pure compound (EPC), which has the same configuration as the natural product isolated from Hydnocarpus anthelminthica and Caloncoba echinata.²⁰ The asymmetric synthesis of cyclopentenylglycine (2S,1'S)-28 has been first carried out by Williams and his coworkers, who have obtained a optically active cyclopentenylglycine as a 1:1 mixture of epimers at the cyclopentene methine.²¹ We have achieved the first EPC synthesis of cyclopentenylglycine (2S,1'S)-28.10



Previously, we reported the reaction of 10 with cyclopentadiene without solvent at atmospheric pressure or in dichloromethane under high pressure to give the exo adduct E selectively, which was converted to the cyclopentylglycine (\pm) -32 in two steps.⁶ In oder not only to clarify if cyclopentene being less active than 3trimethylsilylcyclopent-1-ene or cyclopentadiene behaves as a dipolarophile of nitrones 4 or 10 but also to synthesize chiral (-)-32, we examined the 1,3-dipolar cycloaddition of 4 or 10 with cyclopentene under various conditions. The nitrone 10 did not react with cyclopentene in an organic solvent at room temperature or on heating. Although BF₃-Et₂O also catalyzed the reaction of 10 with cyclopentene in CH₃CN to give the *exo* adduct 29 in 32% yield, the reaction without the catalyst and solvent gave a better yield (73%) of 29. The quantitative yield of 29 was obtained under high pressure without solvent at room temperature. Therefore, high pressure was also applied for the asymmetric 1,3-dipolar addition of 4 with cyclopentene. The adduct 30 was obtained as a single product in quantitative yield. Transformation of the adducts 29 and 30 to the isoxazolidine derivatives (\pm)-31 and (+)-31 by alkaline hydrolysis was unsuccessful. However, we found that treatment of both compounds with dioxane-H₂O at room temperature afforded (\pm)-31 and (+)-31 in good yield,

respectively. Finally, catalytic hydrogenation of (\pm) -31 and (+)-31 gave cyclopentylglycine (\pm) -32 and (+)-32, respectively.



Scheme 8

The nitrones 10 and 4 reacted with norbornadiene at room temperature to form the *exo* adducts 33 and 34 as single isomers. Although the reactions were also accelerated by BF₃-Et₂O, the reactions without solvent afforded the best results, whose yields were almost quantitative. Hydrolysis of 33 and 34 was achieved by treatment with SiO₂ in dioxane-H₂O to form cyclic amino acids (\pm)-35 and chiral-35, which were then subjected to catalytic reduction using Pd-C to give norbornylglycines (\pm)-36 and (-)-36, respectively. The optical purity of (-)-36 was again determined by HPLC to be more than 98 % *ee*.

In conclusion, we have developed a new synthetic method of chiral spiro nitrones via nitrosoketene (2), which serves as new chiral 1,3-dipolars. We have found that the 1,3-dipolar cycloaddition of nitrones thus obtained with olefins proceeds with the exo transition state irrespective to dipolarophiles and the reaction conditions to form diastereoselectively the isoxazolidine derivatives. We have also found that BF₃ is a powerful Lewis acid catalyst for the diastereoselective 1,3-dipolar cycloaddition using the cyclic nitrones, and have achieved the EPC synthesis of nonproteinogenic amino acids. The chiral nitrones synthesized in the present work would be versatile synthons not only for the EPC synthesis of amino acids but also for the chiral synthesis of biologically active substances such as nucleoside analogs containing an amino acid residue. Study on the synthesis of these products is also in progress and the results will be reported in due course.



Experimental Section

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. IR spectra were measured on a JASCO-102 spectrophotometer and optical rotations were measured with a JASCO DIP-340 digital polarimeter. ¹H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI, Hitachi R-3000, Varian Gemini-300L or JEOL GX-500 spectrometer with tetramethylsilane as an internal standard. Most ¹H-NMR spectra were shown as selected data. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 or JMS-AX-500 spectrometer. Enantiomeric excesses (*ees*) were determined by HPLC (high-performance liquid chromatography) analyses using a chiral column (CROWNPAK-CR). HPLC analyses were carried out on a Water Associates instrument (M 6000 pump: U6K injector) using a 220 or 254 nm UV or RI detector. Wakogel (C-200) and Merck Kiesel-gel 60F 254 were employed for silica gel column and thin layer chromatography (TLC), respectively. The ratios of solvent mixtures for chromatography are shown as volume / volume. High pressure reactions were carried out by using a piston-cylinder apparatus equipped with a PK. 15. B pump (Hikari Koatsu Kiki Ltd., Co.).

Reaction of (-)-Menthone (3) with 5-Hydroxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (1)

A solution of 1 (1.73 g, 10 mmol) and 3 (6.16 g, 40 mmol) in toluene (30 ml) was heated under reflux for 2 h. After evaporation of the solvent, the residue was subjected to silica gel (100 g) column chromatography. Elution with hexane-ethyl acetate (10:1) gave 4 (0.59 g, 26%) as colorless needles, mp 102-103 °C (pentane), 5 (0.63 g, 28%) as colorless oil, and the most polar compound (0.31 g, 14%) as colorless oil, successively. (5R, 6S, 9R)-6-Isopropyl-9-methyl-2-oxo-4-aza-1-oxaspiro[5.4]dec-3-ene 4-Oxide (4): $[\alpha]_D^{20} + 88.8$ ° (c = 0.50, CHCl₃). IR (CHCl₃): 1780, 1557 cm⁻¹. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.73 (3H, d, J = 6.8 Hz, CH₃), 0.94 (3H, d, J = 6.8 Hz, CH₃), 0. 97 (3H, d, J = 6.8 Hz, CH₃), 7.00 (1H, s, N=CH). Anal. Calcd for C₁₂H₁₉NO₃: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.97; H, 8.56; N, 6.16.

[5S, 6S, 9R]-6-Isopropyl-9-methyl-2-oxo-4-aza-1-oxaspiro[5.4]dec-3-ene 4-oxide (5): $[\alpha]_D^{20}$ -35.6 ° (c = 0.50, CHCl₃). IR (CHCl₃): 1777, 1560 cm⁻¹. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.83 (3H, d, J = 7.5 Hz, CH₃), 0.92 (3H, d, J = 7.5 Hz, CH₃), 0.98 (3H, d, J = 5.8 Hz, CH₃), 7.05 (1H, s, N=CH). Highresolution MS m/z Calcd for C₁₂H₁₉NO₃ (M⁺): 225.1365. Found: 225.1378.

The most polar compound: $[\alpha]_D^{20}$ -9.6 ° (c = 0.50, CHCl₃). IR (CHCl₃): 1772, 1561 cm⁻¹. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.87 (3H, d, J = 7.0 Hz, CH₃), 0.92 (3H, d, J = 7.0 Hz, CH₃), 1.15 (3H, d, J = 7.5 Hz, CH₃), 7.07 (1H, s, N=CH). High-resolution MS m/z Calcd for C₁₂H₁₉NO₃ (M⁺): 225.1365. Found: 225.1371.

(5R,6R,8S)-7,7-Dimethyl-2-oxo-6,8-methano-4-aza-1-oxaspiro[5.4]dec-3-ene 4-Oxide (7)

A solution of 1 (173 mg, 1 mmol) and 6 (552 mg, 4 mmol) in toluene (5 ml) was heated under reflux for 2 h. After evaporation of the solvent, the residue was subjected to silica gel (10 g) column chromatography. Elution with hexane-ethyl acetate (10:1) gave 7 (130 mg, 62 %) as colorless prisms, mp 77-78 °C (hexane). $[\alpha]_D^{22}$ -136.4° (c = 1.00, CHCl₃). IR (CHCl₃): 1779, 1565 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.09 (3H, s, CH₃), 1.32 (3H, s, CH₃), 6.98 (1H, s, N=CH). Anal. Calcd for C₁₁H₁₅NO₃: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.98; H, 7.23; N, 6.65.

(55,7R,10S)-6,6-Dimethyl-2-0x0-7,10-methano-4-aza-1-oxaspiro[5.4]dec-3-ene 4-Oxide (9)

A mixture of 1 (0.865 g, 5 mmol) and 8 (2.760 g, 20 mmol) in toluene (20 ml) was heated under reflux for 2 h. After evaporation of the solvent, the residue was subjected to silica gel (50 g) column chromatography. Elution with hexane-ethyl acetate (10:1) gave 9 (0.533 g, 51%) as a colorless oil. $[\alpha]_D^{15}+11.3^\circ$ (c = 1.60, CHCl₃). ¹H-NMR (CDCl₃, 300 MHz) δ : 1.06 (3H, s, CH₃), 1.15 (3H, s, CH₃), 1.40 (1H, br dt, J = 11.0, 1.1 Hz, 11-H), 1.43-1.95 (4H, m), 1.97 (1H, br d, J = 2.0 Hz, 7-H), 2.49 (1H, br d, J = 2.8 Hz, 10-H), 2.66 (1H, br dt, J = 11.0, 2.0 Hz, 11-H'), 6.90 (1H, s, N=CH). High-resolution MS *m/z* Calcd for C₁₁H₁₅NO₃ (M⁺): 209.1052. Found: 209.1032.

rel-(6*S*,7*aS*)-6-Ethoxy-1-oxo-1,6,7,7*a*-tetrahydroisoxazolo[2,3-*c*]oxazole-3-spiro-1'cyclohexane (11a)

According to the procedure previously reported,⁶ 11a was prepared by the reaction of 10 with ethyl vinyl ether. IR (CHCl₃): 2950, 1778 cm⁻¹. ¹H-NMR (CDCl₃, 500 MHz) δ : 1.21 (3H, t, J = 7.0 Hz, OCH₂CH₃), 1.4-1.9 (8H, m, cyclohexyl H), 2.05 (2H, t, J = 6.2, cyclohexyl H), 2.54 (1H, ddd, J = 13.6, 9.5, 1.8 Hz, 7-Hb), 2.88 (1H, ddd, J = 13.6, 6.2, 1.8 Hz, 7-Ha), 3.47 (1H, dq, J = 9.9, 7.0 Hz, OCHH'CH₃), 3.78 (1H, dq, J = 9.9, 7.0 Hz, OCHH'CH₃), 4.23 (1H, dd, J = 9.5, 1.8 Hz, 7a-H), 5.15 (1H, dd, J = 6.2, 1.8 Hz, 6-H). High-resolution MS *m*/z Calcd for C₁₂H₁₉NO₄ (M⁺): 241.1314. Found: 241.1324. The NOE experiment was carried out by using 500 MHz ¹H-NMR spectrometer. The results were shown in Scheme 3.

rel-(6*S*,7*aS*)-6-[(Trimethylsilyl)methyl]-1-oxo-1,6,7,7*a*-tetrahydroisoxazolo[2,3-*c*]oxazole-3-spiro-1'-cyclohexane (11b) According to the procedure previously reported,⁶ 11b was prepared by the reaction of 10 with allyltrimethylsilane. High-resolution MS m/z Calcd for C₁₄H₂₅NO₃Si (M⁺): 283.1604. Found: 283.1624. ¹H-NMR (CDCl₃, 500 MHz) δ : 0.30 (9H, s, TMS), 0.84 (1H, dd, J = 14.29, 6.59 Hz, CHHTMS), 1.01 (1H, dd, J = 14.3, 7.7 Hz, CHHTMS), 1.40-1.82 (10H, m, cyclohexyl H), 2.14 (1H, ddd, J = 12.5, 9.9, 8.1 Hz, 7-Hb), 2.70 (1H, dd, J = 12.5, 4.8 Hz, 7-Ha), 3.96-4.09 (1H, m, 6-H), 4.25 (1H, d, J = 8.1 Hz, 7a-H). The NOE experiment was carried out by using 500 MHz ¹H-NMR spectrometer. The results were shown in Scheme 3.

(\pm) -Allylglycine $[(\pm)-14]$

To a solution of (\pm) -13⁶ (103 mg, 0.5 mmol) in CH₃CN (14 ml) was added BF₃-Et₂O (284 mg, 2 mmol) in argon atmosphere under ice-cooling. After stirring under ice-cooling for 1 h, the solvent was evaporated off *in vacuo*. The residue was dissolved in water (2 ml), and the solution was passed through ion exchange resin (Dowex 50W-X4). The eluate was condensed *in vacuo* to give (\pm) -14 (46 mg, 80%) as colorless needles, mp 155-157 °C (MeOH)(*lit.*²², 158-159 °C). ¹H-NMR (D₂O, 300 MHz) δ : 2.55-2.77 (2H, m, 3-H), 3.74 (1H, dd, J = 7.3, 4.8 Hz, 2-H), 5.23-5.37 (2H, m, 5-H), 5.81 (1H, ddt, J = 17.1, 10.0, 7.1 Hz, 4-H).

(3R,6S,7aS,1'R,4'S)-1-Oxo-6-[(trimethylsilyl)methyl]-1,6,7,7a-tetrahydroisoxazolo[2,3c]oxazole-3-spiro-3'-menthane (15)

1) A solution of the nitrone 4 (225 mg, 1 mmol) in CH₂Cl₂ (2 ml) and allyltrimethylsilane (1.30 g, 11.4 mmol) were placed in Teflon tube (4 ml) with a Teflon stopper. The tube was placed in a high pressure reactor and pressurized to 800 MPa at 40 °C for 2 d (or at room temperature for 5 d). The pressure was released after the reaction. After evaporation of the solvent and excess allyltrimethylsilane, the residue was subjected to silica gel (50 g) column chromatography. Elution with hexane-ethyl acetate (6:1) gave 15 (308 mg, 91%) as colorless needles, mp 89-91 °C (pentane). $[\alpha]_D^{21}$ +18.6 ° (c = 2.93, CHCl₃). ¹H-NMR (CDCl₃, 500 MHz) δ : 0.90 (3H, d, J = 6.7 Hz, 8'-CH₃), 0.91 (3H, d, J = 6.7 Hz, 8'-CH₃), 0.95 (3H, d, J = 6.3 Hz, 1'-CH₃), 2.16 (1H, ddd, J = 12.5, 11.5, 8.8 Hz, 7-Hb), 2.67 (1H, dd, J = 12.5, 3.8 Hz, 7-Ha), 3.84-3.92 (1H, m, 6-H), 4.14 (1H, d, J = 8.8 Hz, 7a-H). High-resolution MS m/z Calcd for C₁₈H₃₃NO₃Si (M⁺): 339.2230. Found: 339.2231. Anal . Calcd for C₁₈H₃₃NO₃Si: C, 63.67; H, 9.80; N, 4.13. Found: C, 63.48; H, 9.85; N, 4.07.

2) To a solution of the nitrone 4 (225 mg, 1 mmol) in CH₃CN (1 ml) was added BF₃-Et₂O (142 mg, 1 mmol) under ice-cooling in argon atmosphere. After stirring under ice-cooling for 15 min, allyltrimethylsilane (137 mg, 1.2 mmol) was added to the solution. The mixture was stirred for 2 d at room temperature. The reaction mixture was diluted with CH₂Cl₂ (10 ml), and washed with aq. sodium bicarbonate. The organic layer was dried over Na₂SO₄. After evaporation of the solvent and excess of allyltrimethylsilane, the residue was subjected to silica gel (50 g) column chromatography. Elution with hexane-ethyl acetate (6:1) gave (+)-15 (305 mg, 90%) of colorless needles (pentane).

(3S,5S)-5-[(Trimethylsilyl)methyl]isoxazolidine-3-carboxylic Acid [(-)-12b]

1) A suspension of 15 (339 mg, 1 mmol) and sodium hydroxide (80 mg, 2 mmol) in water (2 ml) was stirred for 24 h. (-)-Menthone (3) (154 mg, 100 %) was extracted with ether, and the aqueous layer was passed through ion exchange resin (IRC-50S) and the solution was condensed *in vacuo* to give the amino acid (-)-12b

(191 mg, 94%). $[\alpha]_D^{20}$ -28.9 ° (c = 12.70, MeOH). ¹H-NMR (CD₃OD, 300 MHz) δ : 0.84 (1H, dd, J = 14.0, 8.7 Hz, CHHTMS), 1.04 (1H, dd, J = 14.0, 5.5 Hz, CHHTMS), 2.03 (1H, dt, J = 12.0, 10.0 Hz, 4-H), 2.35 (1H, ddd, J = 12.0, 6.0, 4.5 Hz, 4-H), 3.79 (1H, dd, J = 10.0, 4.5 Hz, 3-H), 3.89- 4.02 (1H, m, 5-H).

2) In a similar manner, (-)-12b was also obtained from the adduct 17 using sodium bicarbonate (2 equiv.) instead of sodium hydroxide in 70% yield (from 7). $[\alpha]_D^{20}$ -16.5 ° (c = 12.70, MeOH).

(2S,4S)-2-Amino-4-hydroxy-5-(trimethylsilyl)pentanoic Acid [(-)-13]

1) A suspension of (-)-12b (102 mg, 0.5 mmol) and 5% Pd-C (20 mg) in MeOH (10 ml) was shaken in hydrogen atmosphere under atmospheric pressure at room temperature for 12 h. After removal of the catalyst by Celite filtration, the filtrate was condensed *in vacuo* to give a residue, which was subjected to silica gel (50 g) column chromatography. Elution with EtOAc-acetone-MeOH-H₂O (8:1:1:1) gave (-)-13 (90 mg, 88%) of colorless needles (MeOH-EtOAc), mp 174-175 °C. The *ee* of (-)-13 was determined to be 100% by HPLC analysis using CROWNPAK-CR (solvent: pH 2.0 HClO₄ - H₂O / MeOH = 85 / 15). $[\alpha]_D^{28}$ -21.6 ° (*c* = 1.00, MeOH), ¹H-NMR (CD₃OD, 300 MHz) δ : 0.07 (9H, s, TMS), 0.88 (1H, dd, *J* = 14.5, 7.0 Hz, CHH'TMS), 0.97 (1H, dd, *J* = 14.5, 7.0 Hz, CHH'TMS), 1.91 (1H, ddd, *J* = 15.0, 9.3, 4.2 Hz, 3-H), 2.03 (1H, ddd, *J* = 15.0, 6.7, 3.0 Hz, 3-H), 3.75 (1H, dd, *J* = 6.7, 4.2 Hz, 2-H), 3.97-4.09 (1H, m, 4-H). High-resolution MS *m*/z Calcd for C5H9NO₂ (M⁺-TMSOH): 115.0633. Found: 115.0599.

2) In a similar manner, (-)-13 was also obtained from (-)-12b derived from the adduct 17 in 79% yield. $[\alpha]_D^{28}$ -13.6 ° (c = 1.00, MeOH), 60% ee, mp 155-170 °C.

(S)-Allylglycine [(-)-14]

1) According to the procedure given for the preparation of (\pm) -14, (-)-13 (103 mg, 0.5 mmol) was treated with BF₃-Et₂O (284 mg, 2 mmol) to give (-)-14 (46 mg, 80%) of colorless needles, mp 248-249°C. [α]D²⁶-32.4 ° (c = 1.00, H₂O) [*lit.*²⁰ [α]D²⁴-37.1 ° (c = 4.00, H₂O)]. The *ee* was determined to be more than 99% by HPLC analysis using CROWNPAK-CR (solvent: pH 1.0 *aq.* HClO₄). The ¹H-NMR spectrum of (-)-14 was identical with that of (\pm)-14.

2) Similarly, (-)-14 was obtained from (-)-13 derived from the adduct 17 with two steps in 87% yield. $[\alpha]_D^{26}$ -21.4 ° (c = 1.00, H₂O), 60% ee.

(3S,6R,7aR,1'R,4'S)-1-Oxo-6-[(trimethylsilyl)methyl]-1,6,7,7a-tetrahydroisoxazolo[2,3c]oxazole-3-spiro-3'-menthane (16)

1) According to the procedure given for the preparation of 15, the nitrone 5 (225 mg, 1 mmol) was reacted with allyltrimethylsilane (1.30 g, 11.3 mmol) under high pressure at 40 °C for 2 d (or at room temperature for 5 d) to give 16 (312 mg, 92 %) as a colorless oil. $[\alpha]_D^{22}$ -37.4 ° (c = 2.93, CHCl₃). ¹H-NMR (CDCl₃, 300MHz) δ : 0.73 (3H, d, J = 6.8 Hz, 8'-CH₃), 0.91 (3H, d, J = 6.8 Hz, 8'-CH₃), 0.95 (3H, d, J = 6.2 Hz, 1'-CH₃), 2.13 (1H, ddd, J = 12.2, 11.1, 8.7 Hz, 7-Hb), 2.63 (1H, dd, J = 12.2, 4.0 Hz, 7-Ha), 3.73-3.86 (1H, m, 6-H), 4.17 (1H, d, J = 8.7 Hz, 7a-H). High-resolution MS *m*/z Calcd for C₁₈H₃₄NO₃Si (M⁺+1): 340.2308. Found: 340.2318.

2) According to the procedure given for the preparation of 15, the nitrone 5 (225 mg, 1 mmol) was reacted with allyltrimethylsilane (137 mg, 1.2 mmol) in the presence of BF₃-Et₂O (142 mg, 1 mmol) at room temperature for 2 d to give 16 (305 mg, 90%) as a colorless oil.

(3R,5R)-5-[(Trimethylsilyl)methyl]isoxazolidine-3-carboxylic Acid [(+)-12b]

According to the procedure given for the preparation of (-)-12b, 16 (339 mg, 1 mmol) was treated with *aq.* sodium hydroxide to give the amino acid (+)-12b (190 mg, 93 %) and (-)-menthone (154 mg, 100%). $[\alpha]_D^{20}$ +29.0 ° (*c* =12.50, MeOH).

(2R,4R)-2-Amino-4-hydroxy-5-(trimethylsilyl)pentanoic Acid [(+)-13]

According to the procedure given for the preparation of (-)-13, (+)-12b (102 mg, 0.5 mmol) was subjected to hydrogenolysis using 5% Pd-C (20 mg) in MeOH (10 ml) to give (+)-13 (90 mg, 88%) as colorless needles (MeOH-EtOAc), mp 174-175 °C. $[\alpha]_D^{28}$ +21.6 ° (c = 1.00, MeOH). The ¹H-NMR spectrum of (+)-13 was identical with that of (-)-13.

(R)-Allylglycine [(+)-14]

According to the procedure given for the preparation of (-)-14, (+)-13 (103 mg, 0.5 mmol) was treated with BF₃-Et₂O (284 mg, 2 mmol) to give (+)-14 (46 mg, 80%) as colorless needles. $[\alpha]_D^{24}$ + 33.5 ° (c = 1.00, H₂O). The *ee* was determined to be more than 99% by HPLC analysis using CROWNPAK-CR (solvent: pH 1.0 *aq.* HClO₄).

(3R,6S,7aS,1'R,5'S)-1-Oxo-6-[(trimethylsilyl)methyl]-1,6,7,7a-tetrahydroisoxazolo[2,3c]oxazole-3-spiro-2'-(6',6'-dimethylbicyclo[3.1.1]heptane) (17)

According to the procedure given for the preparation of 16, 7 (209 mg, 1 mmol) was reacted with allyltrimethylsilane (1.30 g, 11.3 mmol) in CH₂Cl₂ (2 ml) at 800 MPa for 17 h to give 17 (323 mg, quant.), which was used for the preparation of (-)-12b without further purification. ¹H-NMR (CDCl₃, 300MHz) δ : 4.02 (4/5 H, d, J = 8.1 Hz, 7a-H), 4.12 (1/5 H, d, J = 8.2 Hz, 7a-H).

(3S,6R,7aR,1'R,4'S)-1-Oxo-6-[(trimethylsilyl)methyl]-1,6,7,7a-tetrahydroisoxazolo[2,3c]oxazole-3-spiro-3'-(2',2'-dimethylbicyclo[2.2.1]heptane) (18)

According to the procedure given for the preparation of 16, the nitrone 9 (209 mg, 1 mmol) was reacted with allyltrimethylsilane (1.30 g, 11.3 mmol) in CH_2Cl_2 (2 ml) under 800 MPa at 40 °C for 69 h to give 18 (200 mg, 62%) and 19 (26 mg, 8%), respectively. These products were purified by silica gel (50 g) column chromatography using hexane-ethyl acetate (6:1).

More polar (18): $[\alpha]_D^{18} + 10.2^{\circ}$ (c = 1.9, CHCl₃). High-resolution MS m/z Calcd for C₁₇H₂₉NO₃Si (M⁺): 323.1917. Found: 323.1955. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.03 (9H, s, TMS), 0.80 (1H, dd, J = 14.3, 6.8 Hz, CHH'TMS), 0.90 (3H, s, 2'-CH₃), 1.09 (1H, dd, J = 14.3, 7.4 Hz, CHH'TMS), 1.11 (3H, s, 2'-CH₃), 1.21-2.08 (7H, m), 2.14 (1H, dt, J = 12.2, 8.3 Hz, 7-Hb), 2.69 (1H, dd, J = 12.2, 5.4 Hz, 7-Ha), 2.97 (1H, br d, J = 3.3 Hz, 4'-H), 3.97 (1H, br d, J = 7.2 Hz, 7a-H), 4.03-4.12 (1H, m, 6-H).

Less polar (19): High-resolution MS m/z Calcd for C₁₇H₂₉NO₃Si (M⁺): 323.1917. Found: 323.1936. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.01 (9H, s, TMS), 0.87 (1H, dd, J = 14.2, 6.2 Hz, CHHTMS), 0.94 (3H, s, 2'-CH₃), 1.00 (1H, dd, J = 14.2, 7.3 Hz, CHHTMS), 1.06 (3H, s, 2'-CH₃), 1.21-2.08 (7H, m), 2.16 (1H, dt, J = 12.3, 8.2 Hz, 7-Hb), 2.59 (1H, br d, J = 3.0 Hz, 4'-H), 2.72 (1H, dd, J = 12.3, 5.3 Hz, 7-Ha), 3.92-4.05 (1H, m, 7a-H), 4.11 (1H, ddd, J = 14.2, 7.3, 6.9 Hz, 6-H).

Reaction of the Nitrone 10 with 3-Trimethylsilylcyclopent-1-ene

1) under high pressure

Following the procedure given for the preparation of 11a, high pressure mediated reaction of 10 (169 mg, 1 mmol) with 3-trimethylsilylcyclopent-1-ene (720 mg, 5 mmol) in CH₂Cl₂ (2 ml) for 24 h at room temperature gave 20, 21, and 22 which were chromatographically inseparable. The ratio of these compounds were determined to be 20: 21: 22 = 70: 13: 13 by ¹H-NMR spectroscopy.

rel-(5aS,6S,8aR,8bS)-1-Oxo-6-[(trimethyl)silyl]-1,5a,8a,8b-tetrahydrocyclopent[*f*]isoxazolo[2,3-*c*]oxazole-3-spiro-1'-cyclohexane (20): ¹H-NMR (CDCl₃, 300 Mz) δ : 3.22 (1H, dt, *J* = 15.0, 7.5 Hz, 8a-H), 3.85 (1H, s, 8b-H), 4.43 (1H, dd, *J* = 7.5, 5.3 Hz, 5a-H).

rel-(5aS,6R,8aR,8bS)-1-Oxo-6-[(trimethyl)silyl]-1,5a,8a,8b-tetrahydrocyclopent[*f*]isoxazolo[2,3-*c*]oxazole-3-spiro-1'-cyclohexane (21): ¹H-NMR (CDCl₃, 300 Mz) δ : 0.04 (9H, s, TMS), 3.38 (1H, br t, J = 6.7 Hz, 8a-H), 3.81 (1H, s, 8b-H), 4.71 (1H, t, J = 6.1 Hz, 5a-H).

rel-(5aS,8R,8aR,8bS)-1-Oxo-8-[(trimethyl)silyl]-1,5a,8a,8b-tetrahydrocyclopent[f]isoxazolo[2,3-c]oxazole-3-spiro-1'-cyclohexane (22): ¹H-NMR (CDCl₃, 300 Mz) δ : 0.03 (9H, s, TMS), 3.05 (1H, t, J = 8.3 Hz, 8a-H), 3.75 (1H, s, 8b-H), 4.56 (1H, dt, J = 6.2, 6.2 Hz, 5a-H).

2) in the presence of BF₃-Et₂O

According to the procedure given for the preparation of 15, 10 (169 mg, 1 mmol) was allowed to react with 3-trimethylsilylcyclopent-1-ene (168 mg, 1.2 mmol) in the presence of BF₃-Et₂O (142 mg, 1 mmol) for 14 h at room temperature to give 20 (295 mg, 96%) as a pale yellow oil. IR (CHCl₃): 1784 cm⁻¹. ¹H-NMR (CDCl₃, 300 Mz) δ : 3.22 (1H, dt, J = 15.0, 7.5 Hz, 8a-H), 3.85 (1H, s, 8b-H), 4.43 (1H, dd, J = 7.5, 5.3 Hz, 5a-H). High-resolution MS *m/z* Calcd for C₁₆H₂₇NO₃Si (M⁺): 309.1760. Found: 309.1755.

Reaction of the Nitrone 4 with 3-Trimethylsilylcyclopent-1-ene

1) under high pressure

Following the procedure given for the preparation of **11a**, high pressure mediated reaction of **4** (112.5 mg, 0.5 mmol) with 3-trimethylsilylcyclopent-1-ene (140 mg, 1 mmol) under 800 MPa at 40 °C for 48 h gave a mixture of **23**, **24**, and **25** in almost quantitative total yield. The ratio of these compounds were determined to be **23**: **24**: **25** = 55: 20: 24 by 300 MHz ¹H-NMR spectroscopy.

(3R, 5aS, 6S, 8aR, 8bS, 1'R, 4'S)-1-Oxo-6-[(trimethyl)silyl]-1,5a,8a,8b-tetrahydrocyclopent[f]isoxazolo[2,3-c]oxazole-3-spiro-3'-menthane (23): mp 118-120 °C (pentane). [α]_D²³ +88.0 ° (c = 1.05, CHCl₃). IR (CHCl₃): 1782 cm⁻¹. ¹H-NMR (CDCl₃, 300 Mz) & 0.86 (3H, d, J = 6.5 Hz, 8'-CH₃), 0.89 (3H, d, J = 6.5 Hz, 8'-CH₃), 0.90 (3H, d, J = 6.5 Hz, 1'-CH₃), 3.16 (1H, dt, J = 15.0, 7.5 Hz, 8a-H), 3.88 (1H, s, 8b-H), 4.31 (1H, dd, J = 6.5, 4.5 Hz, 5a-H). High-resolution MS *m*/z Calcd for C₂₀H₃₅NO₃Si (M⁺): 365.2384. Found: 365.2361. *Anal*. Calcd for C₂₀H₃₅NO₃Si: C, 65.71; H, 9.65; N, 3.83. Found: C, 65.90; H, 9.33; N, 3.72.

(3R,5aS,6R,8aR,8bS,1'R,4'S)-1-Oxo-6-[(trimethyl)silyl]-1,5a,8a,8b-tetrahydrocyclopent[f]isoxazolo[2,3-c]oxazole-3-spiro-3'-menthane (24): ¹H-NMR (CDCl₃, 300 Mz) δ : 0.05 (9H, s, TMS), 3.31 (1H, dt, J = 7.5, 5.2 Hz, 8a-H), 3.82 (1H, s, 8b-H), 4.61 (1H, t, J = 5.5 Hz, 5a-H).

(3R,5aS,8R,8aR,8bS,1'R,4'S)-1-Oxo-8-[(trimethyl)silyl]-1,5a,8a,8b-tetrahydrocyclopent[f]isoxazolo[2,3-c]oxazole-3-spiro-3'-menthane (25): ¹H-NMR (CDCl₃, 300 Mz) δ: 0.04 (9H, s, TMS), 0.80-2.41 (14H, m), 0.86 (3H, d, J = 6.9 Hz, 8'-CH₃), 0.89 (3H, d, J = 6.9 Hz, 8'-CH₃), 0.91 (3H, d, J = 6.3 Hz, 1'-CH₃), 3.00 (1H, dd, J = 9.6, 5.8 Hz, 8a-H), 3.83 (1H, s, 8b-H), 4.43 (1H, dt, J = 5.0, 3.3 Hz, 5a-H).

2) in the presence of BF3-Et2O

According to the procedure given for the preparation of 15, 4 (225 mg, 1 mmol) was allowed to react with 3-trimethylsilylcyclopent-1-ene (336 mg, 2.4 mmol) in CH₃CN (1 ml) in the presence of BF₃-Et₂O (142 mg, 1 mmol) at room temperature for 91 h to give 23 (252 mg, 69%) as colorless needles (pentane). mp 118-120 °C. Hexane- ethyl acetate (5:1) was used for silica gel (50 g) column chromatography.

rel-(3S,3aR,6aS,6S)-6-Trimethylsilyl-2,3,3a,6a-tetrahydrocyclopent[*d*]isoxazole-3carboxylic Acid [(<u>+</u>)-26]

A suspension of **20** (309 mg, 1 mmol) and NaHCO₃ (168 mg, 2 mmol) in H₂O (2 ml) was stirred at room temperature for 24 h. The mixture was extracted with ether to remove cyclohexanone. The aqueous layer was passed through ion exchange resin (IRC-50S). The resulting solution was condensed *in vacuo* to give (\pm)-**26** (192 mg, 84 %). ¹H-NMR (CD₃OD, 300 Mz) δ : 1.16-2.06 (5H, m), 2.84-2.96 (1H, m, 3a-H), 3.44 (1H, d, J = 5.3 Hz, 3-H), 4.40 (1H, dd, J = 7.0, 2.2 Hz, 6a-H).

rel-(2S, 1'R, 2'S, 3'S)-2-Amino-2-[2'-hydroxy-3'-(trimethylsilyl)cyclopentyl]acetic Acid [(\pm)-27]

A suspension of (\pm) -26 (115 mg, 0.5 mmol) and 5% Pd-C (20 mg) in methanol (10 ml) was shaken in H₂ atmosphere at room temperature for 32 h. After removal of the catalyst by Celite filtration, the solvent was evaporated off to give a residue, which was subjected to silica gel (50 g) column chromatography. Elution with EtOAc-acetone-MeOH-H₂O (7: 1: 1: 1) gave (\pm)-27 (96 mg, 83%) as colorless needles, mp 175-178 °C (MeOH-EtOAc). ¹H-NMR (CD₃OD, 300 Mz) δ : 1.10(1H, dt, J = 9.0, 3.5 Hz, CHTMS), 1.23-2.10 (5H, m), 2.11 (1H, dq, J = 12.5, 6.0 Hz, 1'-H), 3.71 (1H, d, J = 6.0 Hz, 2-H), 4.18 (1H, dd, J = 5.5, 3.5 Hz, 2'-H). High-resolution MS m/z Calcd for C₁₀H₂₁NO₃Si (M⁺): 231.1291. Found: 231.1287.

rel-(25,1'5)-2-Amino-2-(2'-cyclopentenyl)acetic Acid [(+)-28: cyclopentenylglycine]

To a solution of (\pm) -27 (116 mg, 0.5 mmol) in CH₃CN (14 ml) added BF₃-Et₂O (284 mg, 2 mmol) under Ar atmosphere with ice-cooling. The mixture was stirred with ice-cooling for 1 h. After removal of the solvent *in vacuo*, the residue was dissolved in water (5 ml), and the solution was passed through ion exchange resin (Dowex 50W-X4). The solution was condensed *in vacuo* to give (\pm) -28 (59 mg, 84%) of mp 260 °C (dec.) as colorless needles. ¹H-NMR (CD₃OD, 300 MHz) δ : 1.46-2.51 (5H, m), 3.47 (1H, d, J = 4.8 Hz, 2-H), 5.58-5.65 (1H, m, olefinic H), 5.90-5.96 (1H, m, olefinic H'). High-resolution MS *m/z* Calcd for C₇H₁₂NO₂ (M⁺+1): 142.0868; C₇H₁₁NO₂ (M⁺): 141.0790. Found: 142.0901; 141.0779.

(3S,3aR,6aS,6S)-6-Trimethylsilyl-2,3,3a,6a-tetrahydrocyclopent[d]isoxazole-3-carboxylic Acid [(+)-26]

A solution of 23 (437 mg, 1.2 mmol) and NaHCO₃ (202 mg, 2.4 mmol) in THF (15 ml)-H₂O (15 ml) was stirred at room temperature for 32 h. After evaporation of THF, the residue was extracted with

ether to recover menthone (152 mg, 0.99 mmol, 83%). The aqueous layer was passed through ion exchange resin (IRC-50S). The resulting solution was condensed *in vacuo* to give (+)-26 (209 mg, 0.91 mmol, 76%). $[\alpha]D^{21}$ +39.6° (c = 0.50, MeOH). The ¹H-NMR spectrum of (+)-26 was identical with that of (±)-26.

(2S,1'R,2'S,3'S)-2-Amino-2-[2'-hydroxy-3'-(trimethylsilyl)cyclopentyl]acetic Acid [(+)-27]

According to the procedure given for the preparation of (\pm) -27, (+)-26 (115 mg, 0.5 mmol) was subjected to catalytic reduction using 5% Pd-C to give (+)-27 (87 mg, 75%). mp 170-171 °C (dec.). $[\alpha]_D^{24}$ +13.5° (c = 0.95, MeOH). The *ee* was determined to be more than 99% by HPLC analysis using CROWNPAK-CR (+) (solvent: pH 1.0 HClO₄-H₂O / MeOH = 99:1). The ¹H-NMR spectrum of 27 was identical with that of (\pm) -27.

(2S,1'S)-2-Amino-2-(2'-cyclopentenyl)acetic Acid [(2S, 1'S)-28: (2S, 1'S)-cyclopentenylglycine]

According to the procedure given for the preparation of (\pm) -28, (+)-27 (46 mg, 0.2 mmol) was treated with BF₃-Et₂O (113 mg, 0.8 mmol) in CH₃CN (5 ml) for 1.5 h to give (2*S*, 1'*S*)-28 (23 mg, 80%). mp 243-246 °C (dec.). $[\alpha]_D^{21}$ -121.3 ° (c = 0.32, H₂O). The *ee* was determined to be more than 98% by HPLC analysis using CROWNPAK-CR (+) (solvent: pH 1.0 HClO₄-H₂O). The ¹H-NMR spectrum of (2*S*, 1'*S*)-28 was identical with that of (\pm)-28.

rel-(5aS,8aR,8bS)-1-Oxo-1,5a,8a,8b-tetrahydrocyclopent[f]isoxazolo[2,3-c]oxazole-3-spiro-1'-cyclohexane (29)

According to the procedure given for the preparation of 15, 10 (845 mg, 5 mmol) was reacted with cyclopentene (9 ml) without solvent at 800 MPa at 30 °C for 48 h to give 29 (913 mg, quant.), which was used for the preparation of (\pm)-31 without further purification. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.37-2.06 (16H, m), 3.31-3.39 (1H, m, 8a-H), 3.84 (1H, s, 8b-H), 4.64 (1H, t, J = 6.2 Hz, 5a-H). High-resolution MS *m*/z Calcd for C₁₃H₁₉NO₃ (M⁺): 237.1365. Found: 237.1356.

rel-(3S,3aR,6aR)-2,3,3a,6a-Tetrahydrocyclopent[d]isoxazole-3-carboxylic Acid [(±)-31]

A solution of **29** (913 mg, crude) in dioxane (25 ml) and H₂O (5 ml) was stirred at room temperature for 48 h. To the reaction mixture was added Et₂O (40 ml) and H₂O (40 ml). The resulting mixture was shaken in a separating funnel, and the aqueous layer was condensed *in vacuo* to give (\pm)-**31** (468 mg, 60% from **10**) as a pale yellow oil. ¹H-NMR (CD₃OD, 300 MHz) δ : 1.54-1.93 (6H, m), 3.04-3.16 (1H, m), 3.56 (1H, d, J = 6.6 Hz, 3-H), 4.65 (1H, dt, J = 5.7, 1.6 Hz, 6a-H). High-resolution MS *m*/z Calcd for C₇H₁₁NO₃ (M⁺): 157.0739. Found: 157.0737.

rel-(2S,1'R,2'R)-2-Amino-2-(2'-hydroxycyclopentyl)acetic Acid [(±)-32]

A suspension of (\pm) -31(314 mg) and 5% Pd-C (60 mg) in MeOH (3 ml) was stirred in hydrogen atmosphere at room temperature for 24 h. The catalyst was filtered off by using Celite, and the filtrate was subjected to silica gel (10 g) column chromatography. Elution with AcOEt-MeOH-acetone-H₂O (5:1:1:1) gave (\pm) -32 (283 mg, 53% from 29) of mp 227-229 °C as colorless needles (MeOH), which was identical in every respect with the authentic sample.⁶ ¹H-NMR (CD₃OD, 300 MHz) δ : 1.55-1.95 (6H, m), 2.22-2.36 (1H, m, 1'-H), 3.76 (1H, d, J = 6.0 Hz, 2-H), 4.33 (1H, dt, J = 7.0, 2.0 Hz, 2'-H).

(3R, 5aR, 8aR, 8bS, 1'R, 4'S)-1-Oxo-1, 5a, 8a, 8b-tetrahydrocyclopent[f] isoxazolo[2, 3-c]-oxazole-3-spiro-3'-menthane (30)

According to the procedure given for the preparation of **15**, a solution of **4** (675 mg, 3 mmol) in cyclopentene (9 ml) was pressurized at 800 MPa at 30 °C for 72 h. After removal of excess cyclopentene *in vacuo*, a crystalline substance (880 mg, quant.) was obtained, which was purified by recrystallization from Et₂O-hexane to give **30** (609 mg, 69%) of mp 114-115 °C as colorless needles. $[\alpha]_D^{24}$ +64.3° (*c* =1.10, CHCl₃). IR (CHCl₃): 1765 cm⁻¹. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.87 (3H, d, *J* = 6.6 Hz, Me), 0.92 (3H, d, *J* = 6.6 Hz, Me), 0.93 (3H, d, *J* = 6.6 Hz, Me), 1.30 (1H, t, *J* = 12.6 Hz), 1.50-1.95 (13 H, m), 2.390 (1H, dt, *J* = 12.6, 2.6 Hz), 3.25-3.35 (1H, m, 8a-H), 3.82 (1H, s, 8b-H), 4.55 (1H, t, *J* = 5.4 Hz, 5-H). ¹³C-NMR (CDCl₃, 75 MHz) δ : 18.07, 21.91, 22.95, 23.67, 24.37, 24.87, 29.75, 32.21, 32.88, 34.21, 41.89, 51.17, 51.47, 72.00, 82.47, 108.43, 175.97. *Anal.* Calcd for C₁₇H₂₇NO₃: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.20; H, 9.05; N, 4.58.

(3S,3aR,6aR)-2,3,3a,6a-Tetrahydrocyclopent[d]isoxazole-3-carboxylic Acid [(+)-31]

A solution of **30** (586 mg) in dioxane (10 ml) and H₂O (2 ml) was stirred at room temperature for 48 h. To the reaction mixture was added Et₂O (30 ml) and H₂O (30 ml). The resulting mixture was shaken in a separating funnel, and the aqueous layer was condensed *in vacuo* to give (+)-**31** (263 mg, 84%) of mp 105-108 °C (dec.) as colorless needles (MeOH-AcOEt). $[\alpha]_D^{22}$ +60.2° (c = 2.10, MeOH). The ¹H-NMR spectrum was identical with that of (±)-**31**.

(2S,1'R,2'R)-Amino-2-(2'-hydroxycyclopentyl)acetic Acid [(-)-32]

A suspension of (+)-31 (152 mg, 0.97 mmol) and 5% Pd-C (30 mg) was stirred in hydrogen atmosphere at room temperature for 24 h. After removal of the catalyst by using Celite filtration, the filtrate was subjected to silica gel (10 g) column chromatography. Elution with AcOEt-MeOH-acetone-H₂O (5:1:1:1) gave (-)-32 (145 mg, 95%) as colorless needles, mp 213-216 °C (dec.) (MeOH-AcOEt). $[\alpha]_D^{24}$ -53.0° (c = 0.40, MeOH). The optical purity was determined to be more than 99% by HPLC using CROWNPAK-CR (+) (solvent: pH 2.0, HClO4-H₂O). The ¹H-NMR spectrum was identical with that of the racemic (±)-32.

rel-(5a*R*,6*R*,9*S*,9a*R*,9b*S*)-7,8-Dehydro-6,9-methano-1-oxo-1,5a,9a,9b-tetrahydrocyclohex[*f*]isoxazolo[2,3-*c*]oxazole-3-spiro-1'-cyclohexane (33)

A solution of **10** (169 mg, 1mmol) and norbornadiene (4 mmol) was kept at room temperature for 9 h. After evaporation of excess norbornadiene *in vacuo*, **33** (260 mg) was obtained in quantitative yield, which was used without further purification for the preparation of (\pm)-**35**. ¹H-NMR (CDCl₃, 300 MHz) &: 1.39-2.37 (12H, m), 2.89 (1H, s, 6- or 9-H), 2.93 (1H, s, 6- or 9-H), 3.06 (1H, d, J = 6.5 Hz, 9a-H), 3.89 (1H, s, 9b-H), 4.28 (1H, d, J = 7 Hz, 5a-H), 6.03 (1H, dd, J = 5.5, 3.0 Hz, 7- or 8-H), 6.25 (1H, dd, J = 5.5, 4.0 Hz, 7- or 8-H). High-resolution MS *m*/z Calcd for C₁₅H₁₉NO₃ (M⁺): 261.1365. Found: 261.1405.

rel-(3S,3aR,4S,7R,7aR)-5,6-Dehydro-4,7-methano-2,3,3a,7a-tetrahydrocyclohex[d]isoxazole-3-carboxylic Acid [(±)-35]

A suspension of **33** (260 mg) and silica gel (500 mg) in dioxane-H₂O (3:1, 5 ml) was stirred for 30 h at room temperature. Silica gel was filtered off, and the silica gel was washed with MeOH (10 ml). The combined solution of the filtrate and washings was condensed *in vacuo* to give a residue, to which were added ether (10 ml) and H₂O (10 ml). The mixture was shaken in a separating funnel. The aqueous layer was condensed *in vacuo* to give (\pm)-**35** (160 mg, 89 %). Due to its instability, (\pm)-**35** was used for the preparation of (\pm)-**36** without further purification. ¹H-NMR (CD₃OD, 300 MHz) δ : 1.74 (1H, d, J = 9.3 Hz, 8-H), 2.00 (1H, d, J =9.3 Hz, 8-H), 2.73 (1H, t, J = 6.9 Hz, 3a-H), 2.84 (1H, br s, 4- or 7-H), 2.90 (1H, br s, 4- or 7-H), 3.56 (1H, d, J = 7.2 Hz, 3-H), 4.42 (1H, d, J = 6.6Hz, 7a-H), 6.11 (1H, dd, J = 3.2, 5.6 Hz, olefinic H), 6.37 (1H, dd, J = 3.2, 5.9 Hz, olefinic H). High-resolution MS *m*/z Calcd for C₉H₁₁NO₂ (M⁺-16): 165.0790. Found: 165.0812.

rel-(2S,1'R,2'R,3'R,4'S)-2-Amino-2-(3'-hydroxy-2'-norbornyl)acetic Acid [(±)-36: (±)-norbornylglycine]

To a solution of (\pm) -35 (160 mg) in MeOH (10 ml) was added 5% Pd-C (30 mg). The mixture was stirred in hydrogen atmosphere for 36 h at room temperature. The catalyst was filtered off by using Celite, and the filtrate was condensed *in vacuo*. The residue was subjected to silica gel (10 g) column chromatography using AcOEt-MeOH-acetone-H₂O (8:1:1:1) as eluent to give (\pm)-36 (74 mg). ¹H-NMR (CD₃OD, 300 MHz) δ : 1.00–2.05 (7H, m), 2.20 (1H, br s, 1'- or 4'-H), 2.52 (1H, br s, 1'- or 4'-H), 3.58 (1H, d, J = 9.6 Hz, 2-H), 3.90 (1H, d, J = 6.9 Hz, 3'-H). High-resolution MS *m*/z Calcd for C₉H₁₃NO₂ (M⁺-18): 167.0946. Found: 167.0969.

(3R,5aR,6R,9S,9aR,9bS,1'R,4'S)-7,8-Dehydro-6,9-methano-1-oxo-1,5a,9a,9b-tetrahydrocyclohex[f]isoxazolo[2,3-c]oxazole-3-spiro-3'-menthane (34)

A solution of 4 (225mg, 1mmol) in norbornadiene (2 ml) was stirred for 21 h at room temperature. The reaction mixture was condensed *in vacuo* to give a pale yellow crystalline substance **34** (317 mg, 99%). mp 115-117 °C (dec.) (ether-hexane). $[\alpha]_D^{25}$ +68.9 ° (c = 1.00, CHCl₃). IR (CHCl₃): 1770 cm⁻¹. ¹H-NMR (CDCl₃, 300 MHz) δ : 0.85 (3H, d, J = 6.9 Hz, 1'-Me), 0.92 (3H, d, J = 6.6 Hz, 8'-Me), 0.93 (3H, d, J = 6.6 Hz, 8'-Me), 1.27 (1H, t, J = 12.6 Hz, 2'-H_{ax}), 1.50-1.95 (8H, m), 2.18 (1H, d, J = 9.2 Hz, 10-H), 2.49 (1H, dt, J = 12.8, 2.6 Hz, 4'-H), 2.87 (1H, br s, 9-H), 2.91 (1H, br s, 6-H), 3.08 (1H, d, J = 6.2 Hz, 9a-H), 3.79 (1H, s, 9b-H), 4.26 (1H, d, J = 6.2 Hz, 5a-H), 6.03 (1H, dd, J = 5.8, 3.0 Hz, olefinic H). High-resolution MS *m*/z Calcd for C₁₉H₂₇NO₃ (M⁺): 317.1991. Found: 317.2009. *Anal*. Calcd for C₁₉H₂₇NO₃: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.39; H, 8.70; N, 4.30.

(2S,1'R,2'R,3'R,4'S)-2-Amino-2-(3'-hydroxy-2'-norbornyl) acetic Acid [(-)-36: (-)-norbornylglycine]

A suspension of **34** (317 mg) and silica gel (500 mg) in dioxane-H₂O (3:1, 5 ml) was stirred for 30 h at room temperature. Silica gel was filtered off, and the silica gel was washed with MeOH (10 ml). To the combined solution of the filtrate and washings was added 5% Pd-C (30 mg). The mixture was stirred in hydrogen atmosphere for 36 h at room temperature. The catalyst was filter off by using Celite, and the filtrate

was condensed *in vacuo*. The residue was subjected to silica gel (10 g) column chromatography using AcOEt-MeOH-acetone-H₂O (8:1:1:1) as eluent to give (-)-36 (74 mg, 40% from 34). $[\alpha]_D^{26}$ -22.8 ° (c = 0.71, MeOH). The ¹H-NMR spectrum was identical with that of (\pm)-36. The *ee* was determined to be more than 98% by HPLC analysis using CROWNPAK-CR (+) (solvent: pH 1.0, HClO₄-H₂O).

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