A New Synthesis of Highly Functional Nitrones through a Nitrosoketene Intermediate and Their Use for the Stereoselective Synthesis of Amino Acids

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Reaction of 5-isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione with various ketones under reflux in toluene gives 3-oxazolin-5-one 3-oxides (cyclic nitrones) *via* a nitrosoketene intermediate generated from the isonitroso derivative. The cyclic nitrones can be used for the stereoselective [3 + 2] dipolar cycloaddition to electron-rich olefins under high pressure to produce fused isoxazolidines. These isoxazolidines, in turn, are versatile intermediates for the stereoselective preparation of substituted α-amino acids.

Introduction

The 1,3-dipolar cycloaddition of a nitrone to a C–C double bond is a useful reaction in organic synthesis because the isoxazolidine thus obtained is a versatile precursor for the synthesis of natural products.[1] Most nitrones have so far been synthesized by the condensation reaction of hydroxylamines with aldehydes or ketones.[2] In this paper, we report a novel synthesis of cyclic nitrones from the reaction of 5-isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (isonitroso Meldrum's acid) (**2**) with ketones.[3] Subsequent 1,3-dipolar cycloaddition of electron-rich olefins to the resulting cyclic nitrones then provides an efficient route to the synthesis of α-amino acids.

In 1961, Eistert and Geiss[4] and Zavyalov[5] reported the nitrosation of 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**: Meldrum's acid) to give 5-isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (**2**) (Scheme 1). Since compound **2** corresponds to an isostere of 5-(hydroxymethylene)-1,3-dioxane-4,6-dione (**6**), which is a useful reagent in organic synthesis, it could also be a potentially valuable reagent. However, to the best of our knowledge, only two references besides our recent report[6] dealing with its behavior as a dienophile are available concerning **2**. One describes its catalytic reduction to the corresponding amine[4] and the other the thermolysis of its *O*-alkylated derivatives.[7]

Previously, we reported that formylketene (**7**) generated by heating 5-(hydroxymethylene)-1,3-dioxane-4,6-dione (**6**: formyl Meldrum's acid) underwenty [4 + 2] cycloaddition to ketones to produce 1,3-dioxin-4-ones **8** which are versatile reagents in organic synthesis.[8] If isonitroso Meldrum's acid (**2**) is used instead of **6** for this reaction, we could formally expect its thermolysis to generate nitrosoketene (**3**)[9] which could then form 1,3,4-dioxazin-6-ones **5** after the [4 + 2] cycloaddition of ketones. Actual experiments, however, revealed that the products were 3-oxazolin-5-one 3-oxides (cyclic nitrones) **4** instead of **5**.

Results and Discussion

Synthesis of 3-Oxazolin-5-one 3-Oxides (Cyclic Nitrones). When **2** was refluxed in toluene with 4 equiv of cyclohexanone (**9b**), the nitrone **4b** was obtained in 60% yield. On the basis of spectral data, the product **4b** was identified as the cyclic nitrone, 4-aza-2-oxo-1-oxaspiro-[5.4]dec-3-ene 4-oxide (**4b**). To confirm the structure of **4b**, it was reduced with $LiAlH_4$ and the products were acetylated to give the diacetates **10** and **11**.

Cyclopentanone (**9a**) was also reacted with **2** to give the nitrone **4a**. Similar treatment of **2** with acyclic ketones such as acetone (**9c**) or 2-pentanone (**9d**) resulted in the formation of the nitrones **4c** and **4d** in low yields. The low yield of **4c** may partly be due to the low boiling point of acetone. The reaction of *para*-substituted phenyl methyl ketones **9e–h** with **2** showed the interesting phenomenon that, under the same reaction conditions (see Experimental Section), the yield of nitrones **4e–h** increased with increasing electron-donating ability of the *para*-substituents as tabulated in Scheme 2.

We propose the following mechanism for the formation of nitrones **4e–h**. Nitrosoketene (**3**) undergoes [4 + 2] cycloaddition with ketones **9e–h** to yield 1,3,4-dioxazin-6-ones **5**, which spontaneously are transformed to nitrones **4e–h** by 1,2-rearrangement. This mechanism is supported by the facile ring contraction of 5,6-dihydro-1,2-oxazin-4-ones to 1-pyrrolin-3-one 1-oxides under simi-

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(1) (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Confalone, P. N.; Huie, E. M. *Organic Reactions*; John Wiley and Sons, Inc.: New York, 1988; Vol. 36, p 1. (c) DeShong, P.; Lander, S. W., Jr.; Leginus, J. M.; Dicken, C. M. *Advances in Cycloaddition*, Curran, D. P., Ed.; JAI Press: Greenwich and London, 1988; Vol. 1, p 87. (d) Breuer, E. *Nitrones, Nitronates and Nitroxides*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons Ltd.: New York, 1989; p 139. (e) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*; VCH: Weinheim, 1991; p 77.

(2) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.

(3) A preliminary account of a portion of this work has been published: Katagiri, N.; Kurimoto, A.; Yamada, A.; Sato, H.; Katsuhara, T.; Takagi, K.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1994**, 281.

(4) Eistert, B.; Geiss, F. *Chem. Ber.* **1961**, *94*, 929.

(5) Zavyalov, S. I. *Izv. Akad. Nauk. SSSR. Otdel. Khim. Nauk.* **1961**, 2042 [*Chem. Abstr.* **1962**, *57*, 12344i].

(6) Katagiri, N.; Nochi, H.; Kurimoto, A.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 1251.

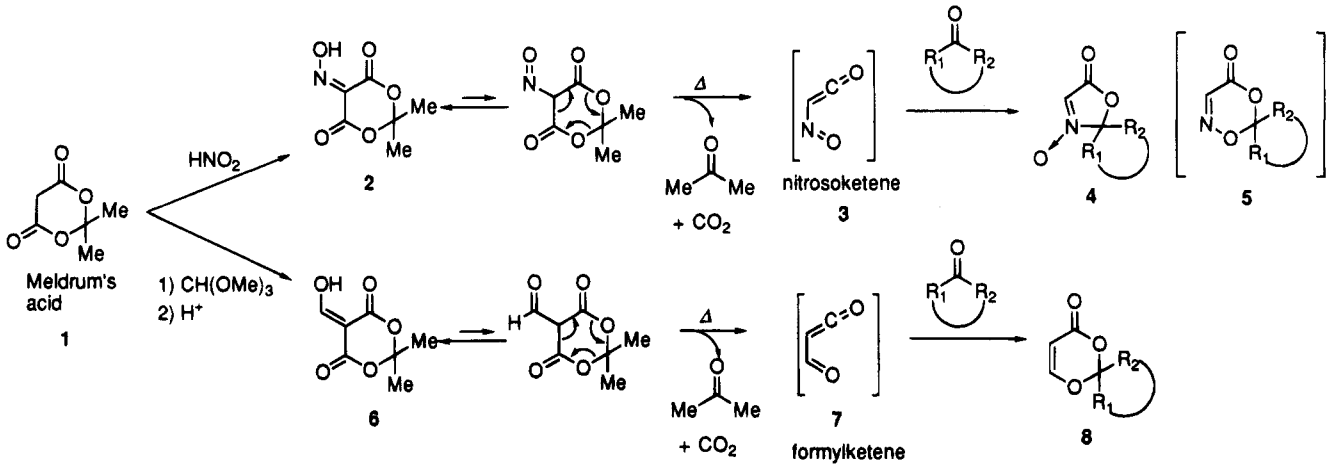
(7) Briehl, H.; Likosch, A.; Wentrup, C. *J. Org. Chem.* **1984**, *49*, 2772.

(8) Sato, M.; Sekiguchi, K.; Ogasawara, H.; Kaneko, C. *Synthesis* **1985**, 224.

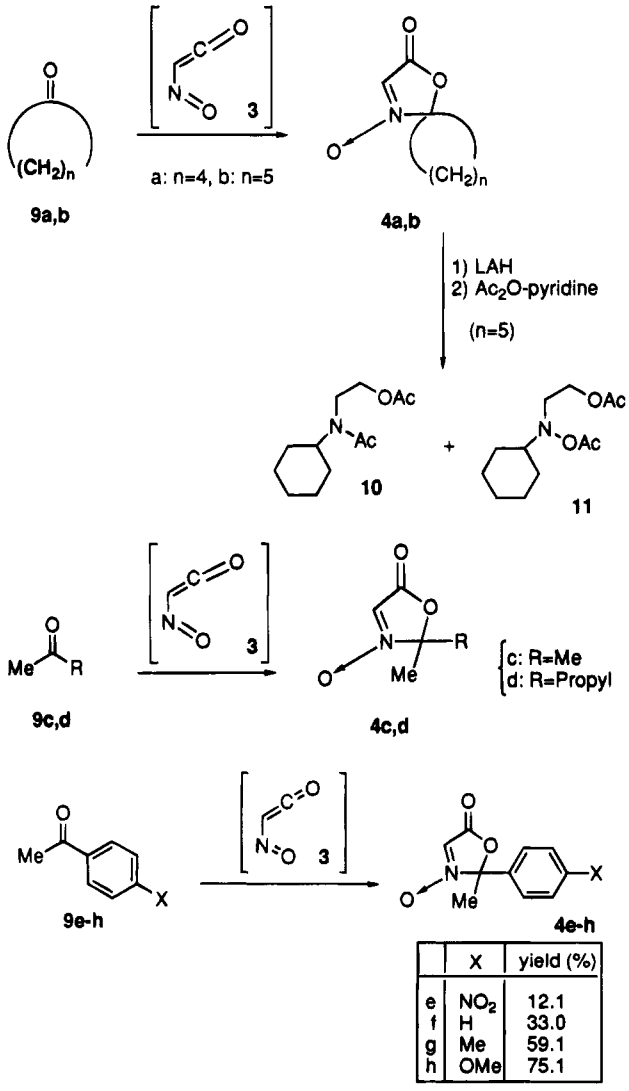
(9) (a) Although numerous papers have dealt with the chemistry of ketene intermediates, to the best of our knowledge, none has described cycloadditions involving nitrosoketene as a reactive intermediate: Ward, R. S. *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; p 223. (b) Quite recently, Tidwell and co-workers have calculated at the HF/6-31G*//HF-6-31G* level the structure and energy of nitrosoketene and have predicted that the ketene will have reasonable thermodynamic stability, although it might be quite reactive in a kinetic sense: McAllister, M. A.; Tidwell, T. T. *J. Org. Chem.* **1994**, *59*, 4506.

0022-3263/94/1959-8101$04.50/0

Scheme 1



Scheme 2



	X	yield (%)
e	NO_2	12.1
f	H	33.0
g	Me	59.1
h	OMe	75.1

lar conditions.[10] However, we cannot rigorously exclude the possibility[11] of direct [3 + 2] cycloaddition to **3**.

The results using the series of acetophenones (**9e–h**) tabulated in Scheme 2 show clearly that the reactions are facilitated by interaction between the LUMO of the π-system of **3** and the HOMO of that of the ketones **9e–h** (upper part of Scheme 3) rather than the reverse. The energy level of the former **3** is much higher than that of the latter. Considering the energy gaps of)s, it is more likely that the reaction proceeds by the [4 + 2] cycloaddition rather than by [3 + 2] cycloaddition.[12] This view is supported by our finding that the electron-deficient ketones are poorer reactants than the electron-rich ketones. Two other ketones **9i** and **9j** shown in Scheme 3 were reacted with **2** to produce the corresponding nitrones **4i** and **4j**. In accord with the above arguments, the yield of **4i** was higher than that of **4j**.

1,3-Dipolar Cycloaddition of Nitrones to Electron-Rich Olefins and Conversion of the Cycloadducts to Amino Acids. Cycloaddition reactions so far reported with nitrones bearing electron-withdrawing substituents on the 1,3-dipole are inverse electron demand reactions.[13] We therefore examined the behavior of our newly synthesized cyclic nitrones in cycloadditions to electron-rich olefins (Scheme 4). We found that **4b** did not react with ethyl vinyl ether at 1 atm. However, under 8 kbar without solvent, the isoxazolidine **12** was obtained in a quantitative yield. Compound **12** could not be purified by either silica gel column chromatography or recrystallization,[14] but the ^{1}H NMR spectrum of crude **12** clearly showed the isoxazolidine structure (see Experimental Section).

The stereochemistry of **12** was verified converting it

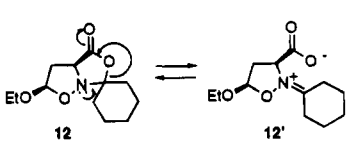
(10) Deshayers, C.; Gelin, S. *Tetrahedron Lett.* **1981**, *22*, 2557.

(11) The direct formation of five-membered cyclic nitrones *via* vinyl nitroso cycloadditions which do not involve six-membered ring intermediates (1,3-oxazines) has been reported: (a) Mackay, D.; Watson, K. N. *J. Chem. Soc., Chem. Commun.* **1982**, 775. (b) Davies, D. E.; Gilchrist, T. L.; Robertes, T. G. *J. Chem. Soc., Perkin Trans. 1*, 1983, 1275. (c) Davies, D. E.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1479.

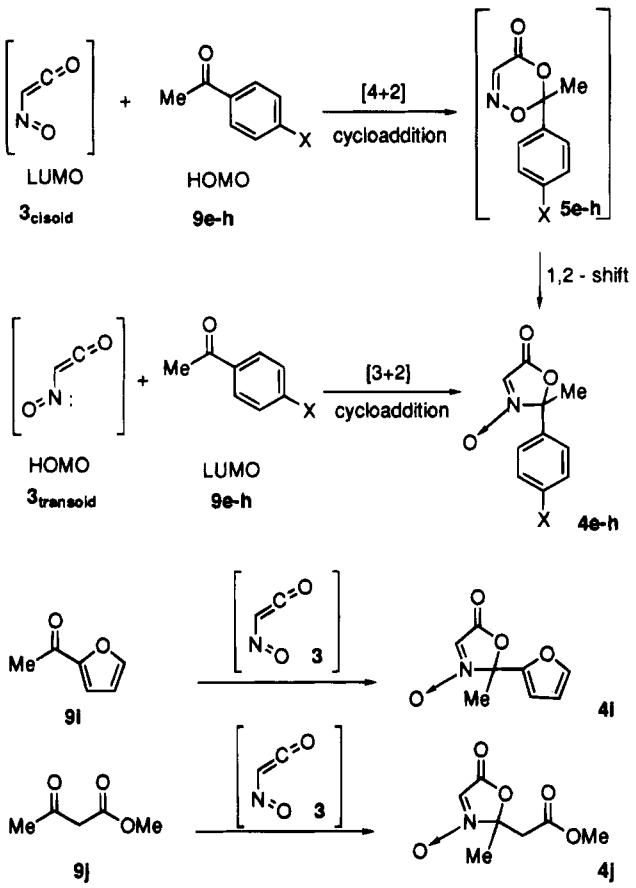
(12) More strictly, the nitrogen lone pair would be the HOMO of **3** and hence becomes the most nucleophilic site. In this case, the [3 + 2] cycloaddition should be facilitated by using acetophenones having an electron-withdrawing *para*-substituent. However, the experimental data show that acetophenones having such an electron-donating group facilitate the reaction. Therefore, if one considers that the [3 + 2] cycloaddition proceeds either in a stepwise or pseudopericyclic manner, this process is not in accordance with the data shown in Scheme 2. For pseudopericyclic reactions, see: Birney, D. M.; Wagenseller, P. E. *J. Am. Chem. Soc.* **1994**, *116*, 6262.

(13) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990; p 298.

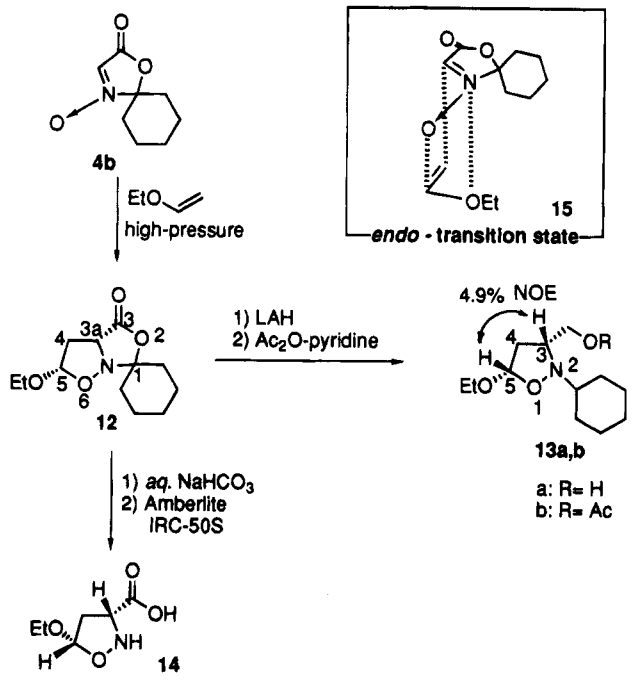
(14) The contribution of zwitterion (**12'**) might account for our failure to isolate **12** in pure form by column chromatography or crystallization.



Scheme 3

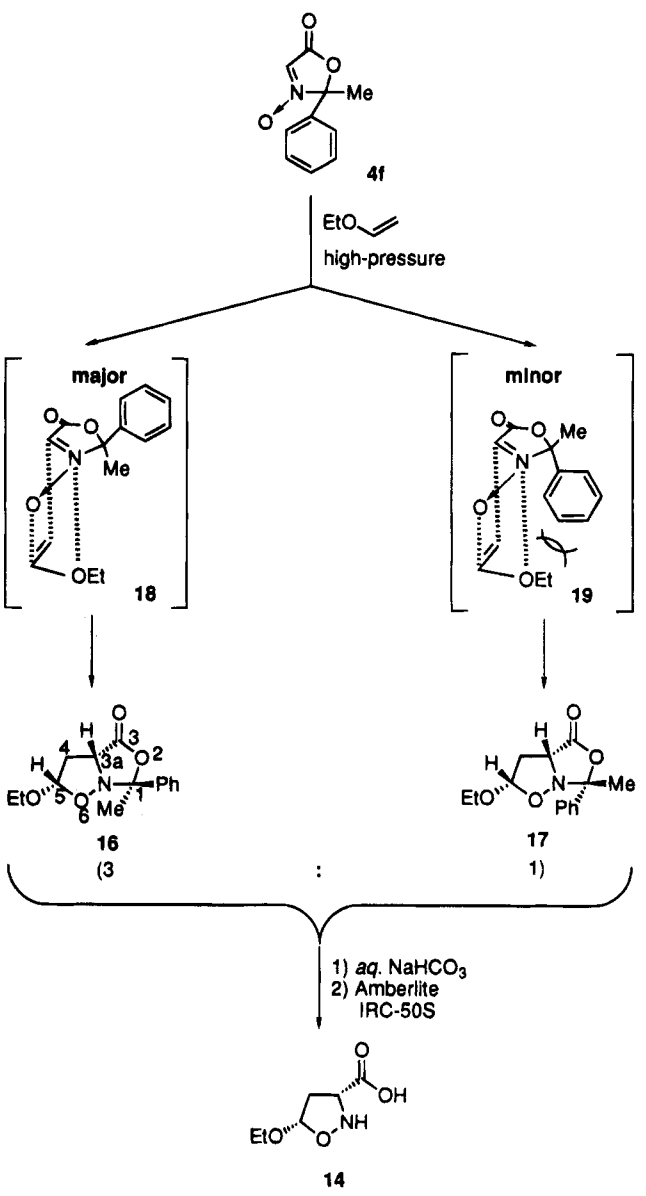


Scheme 4



to the stable derivative **13** by reduction with $LiAlH_4$ and acetylation. Since 4.9% NOE (nuclear Overhouser effect) was observed between 3-H and 5-H in the ^1H NMR spectrum of **13**, the configuration of **13** (and hence **12**) must be 3,5-*cis*. Most likely the addition proceeded *via* the *endo*-transition state **15**.[15] The high selectivity of the reaction may be attributable to the interaction of the positively charged nitrone with the oxygen of ethyl vinyl ether.

Scheme 5

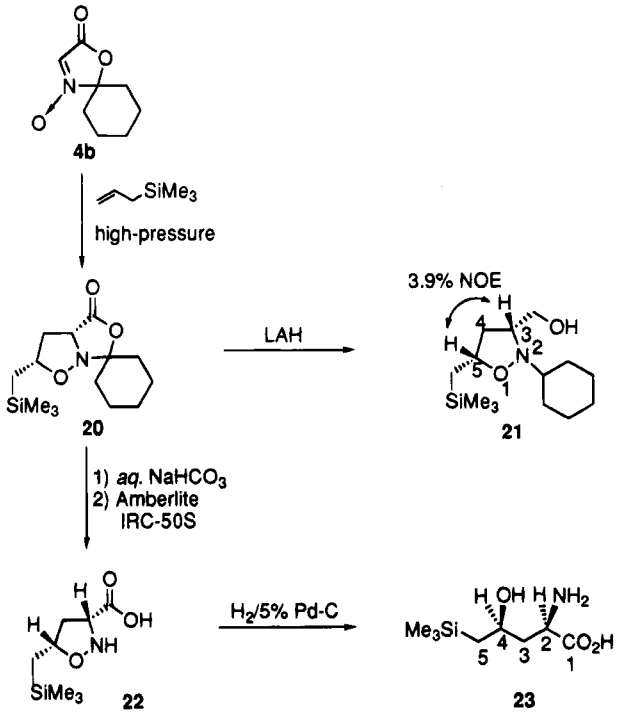


In order to obtain an amino acid from **12**, compound **12** was subjected to hydrogenolysis with Pd–C in methanol. However, the reaction gave a complex mixture. On the other hand, alkaline hydrolysis of **12** directly obtained from the reaction mixture by evaporation of an excess of ethyl vinyl ether followed by neutralization with Amberlite IRC-50S gave the cyclic amino acid **14** in 92% overall yield from **4b** (Scheme 4).

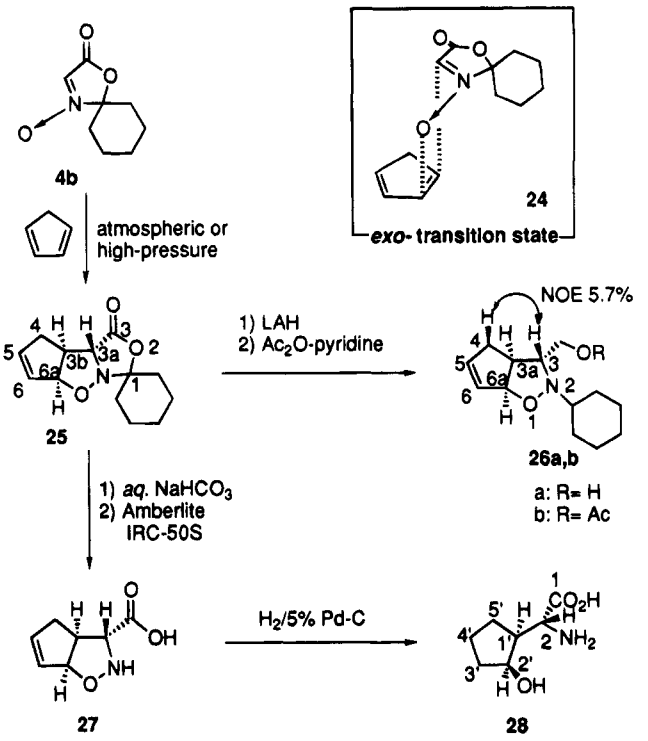
The reaction of nitrone **4f** with ethyl vinyl ether resulted in the formation of the two diastereomers, **16** and **17**, in a ratio of 3:1, which were chromatographically inseparable. However, when the mixture was treated with sodium bicarbonate followed by Amberlite IRC-50S, the sole product was again **14** in the 3,5-*cis* configuration (Scheme 5).

(15) It should be noted that, in reactions with cyclic nitrones, *endo* transition states are not favored because of steric interactions between the substituents on the dipolarophile and the ring of the 1,3-dipoles. However, secondary orbital interactions, which favor the *endo* transition state, are more important here than steric effects. Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1263.

Scheme 6



Scheme 7



These observations mean that the 1,3-dipolar cycloaddition of **4f** to ethyl vinyl ether proceeds *via* the *endo*-transition states **18** and **19** to form the product **16** and **17**, respectively. Because of steric hindrance between the ethoxy and phenyl groups, the adduct **17** is formed in less amounts than **16**. The relative yields of **16** and **17** were deduced from the ^{1}H NMR spectra, and the 3a-H signal of **16** suffers a shielding effect from the phenyl ring and is therefore observed at higher field than that of **17**.

Reaction of **4b** with allyltrimethylsilane under the same conditions also proceeded with regio- and stereoselectivity *via* the corresponding *endo*-transition state to give the adduct **20** as the sole product (Scheme 6). Since **20** was again an unisolable product in a pure form, it was converted to the stable 2,3,5-trisubstituted isoxazolidine **21** by reduction with $LiAlH_4$. The NOE observed with **21** confirmed that the configuration was 3,5-*cis*. Alkaline hydrolysis of **20** and subsequent treatment of the crude product with Amberlite IRC-50S gave the cyclic α-amino acid **22**. Compound **22** was subjected to catalytic hydrogenation with Pd–C to give 2-amino-4-hydroxy-5-(trimethylsilyl)pentanoic acid (**23**).

Cyclopentadiene reacted with **4b** under high pressure or at atmospheric pressure to give exclusively the adduct **25**. We suggest that in this reaction, due to the steric hindrance of the cyclopentadiene ring, the reaction occurs through the *exo*-transition state **24** (Scheme 7). Thus, the ^{1}H NMR spectrum of **25** shows the proton at 3a-position as a singlet, indicating the *trans* relationship between the 3a- and 3b-protons (see Experimental Section). The configuration of **25** was confirmed by reduction with $LiAlH_4$ followed by acetylation to give **26**. The product **26** gave a 5.7% NOE between 3-H and 4-H, indicating *cis* relationship. Alkaline hydrolysis of **25** with sodium bicarbonate followed by treatment with Amberlite IRC-50S again gave a cyclic α-amino acid **27**, which when catalytically reduced gave stereoselectively the α-cyclopentyl α-amino acid **28**.

Conclusions

We have developed a new synthetic method for preparing cyclic nitrones *via* a novel nitrosoketene intermediate (**3**). The intermediate **3** should also serve as an active precursor for the synthesis of many other functional heterocyclic compounds because of its ability to react with a variety of $_\pi$2 components. We have used the cyclic nitrones for the stereoselective synthesis of α-amino acids having various functional groups. Because a chiral nitrone has already been synthesized by reaction of (+)-nopinone with **2**,[3] this method should also be applicable to the enantioselective synthesis of α-amino acids.

Experimental Section

General Methods. Descriptions of instruments, general procedures, and chromatographic procedures have been published previously.[6]

General Procedure for the Preparation of 3-Oxazolin-5-one 3-Oxide Derivatives 4a–j. A solution of 1 mol equiv of **2** and 4 mol equiv of ketone **9a–j** in 3 mL of toluene was heated under reflux for 3 h. Evaporation of the solvent gave an oily residue, which was subjected to silica gel column chromatography. Elution with hexane–EtOAc (5:1) gave the 3-oxazolin-5-one 3-oxide derivatives **4a–j**. If the products were crystalline substances, they were purified by recrystallization from ether–hexane.

4-Aza-2-oxo-1-oxaspiro[4.4]non-3-ene 4-oxide (4a) (22%): colorless oil; IR ($CHCl_3$) 1791, 1564 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.7–2.8 (8H, m), 7.16 (1H, s); HRMS *m/z* calcd for $C_7H_9NO_3$ 155.0582, found 155.0572.

4-Aza-2-oxo-1-oxaspiro[5.4]dec-3-ene 4-oxide (4b) (60%): colorless needles, mp 87–88 °C; IR ($CHCl_3$) 1776, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3–2.5 (10H, m), 7.04 (1H, s). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.88; H, 6.72; N, 8.26.

2,2-Dimethyl-3-oxazolin-5-one 3-oxide (4c) (trace): colorless oil; IR ($CHCl_3$) 1784, 1568 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78 (6H, s), 6.96 (1H, s); HRMS *m/z* calcd for $C_5H_7NO_3$ 129.0425, found 129.0400.

2-Methyl-2-propyl-3-oxazolin-5-one 3-oxide (4d) (39%): colorless oil; IR ($CHCl_3$) 1789, 1568 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 0.7–1.62 (5H, m), 1.75 (3H, s), 1.83–2.22 (2H, m), 7.08 (1H, s); HRMS *m/z* calcd for $C_7H_{11}NO_3$ 157.0739, found 157.0730.

2-Methyl-2-(*p*-nitrophenyl)-3-oxazolin-5-one 3-oxide (4e) (12%): colorless needles, mp 83–85 °C; IR ($CHCl_3$) 1795, 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (3H, s), 7.03 (1H, s), 7.87 (2H, d, *J* = 9 Hz), 8.30 (2H, d, *J* = 9 Hz). Anal. Calcd for $C_{10}H_8N_2O_5$: C, 50.85; H, 3.41; N, 11.86. Found: C, 50.89; H, 3.44; N, 11.96.

2-Methyl-2-phenyl-3-oxazolin-5-one 3-oxide (4f) (33%): colorless oil; IR ($CHCl_3$) 1781, 1566 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (3H, s), 7.16 (1H, s), 7.47 (5H, m); HRMS *m/z* calcd for $C_{10}H_9NO_3$ 191.0582, found 191.0598.

2-Methyl-2-*p*-tolyl-3-oxazolin-5-one 3-oxide (4g) (59%): colorless needles, mp 60–61 °C; IR ($CHCl_3$) 1783, 1569 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (3H, s), 2.38 (3H, s), 7.00 (1H, s), 7.23 (2H, d, *J* = 9 Hz), 7.52 (2H, d, *J* = 9 Hz). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.27; H, 5.50; N, 6.84.

2-*p*-Anisyl-2-methyl-3-oxazolin-5-one 3-oxide (4h) (75%): colorless needles, mp 81–82 °C; IR ($CHCl_3$) 1785, 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (3H, s), 3.83 (3H, s), 6.93 (2H, d, *J* = 9 Hz), 7.00 (1H, s), 7.53 (2H, d, *J* = 9 Hz). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.75; H, 5.14; N, 6.30.

2-Furyl-2-methyl-3-oxazolin-5-one 3-oxide (4i) (52%): colorless needles, mp 99–100 °C; IR ($CHCl_3$) 1792, 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (3H, s), 6.37–6.63 (1H, m), 6.67–6.83 (1H, m), 7.13 (1H, s), 7.46–7.67 (1H, m). Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 52.77; H, 3.79; N, 7.70.

2-[(Methoxycarbonyl)methyl]-2-methyl-3-oxazolin-5-one 3-oxide (4j) (4%): colorless oil; IR ($CHCl_3$) 1795, 1740, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (3H, s), 2.94 (1H, d, *J* = 8.5 Hz), 3.25 (1H, d, *J* = 8.5 Hz), 3.70 (3H, s), 7.13 (1H, s); HRMS *m/z* calcd for $C_7H_9NO_5$ 187.0480, found 187.0489.

Reduction of 4b with $LiAlH_4$. A mixture of 507 mg (3 mmol) of **4b** and 228 mg (6 mmol) of $LiAlH_4$ in 15 mL of THF was heated under reflux with stirring for 1 h. Aqueous ether was added to the reaction mixture under ice-cooling. The mixture was filtered using Celite, and the filtrate was condensed *in vacuo*. The residue was treated with a mixture of 2 mL of acetic anhydride and 0.1 mL of pyridine for 1 h. The mixture was concentrated *in vacuo* to give an oily substance, which was subjected to 20 g of silica gel column chromatography. Elution with hexane–EtOAc (1:2) gave 248 mg (34%) of *N*-acetyl-*N*-(acetoxyethyl)cyclohexylamine (**10**) and 48 mg (7%) of *N*-acetoxy-*N*-(acetoxyethyl)cyclohexylamine (**11**) as colorless oil, successively.

10: HRMS *m/z* calcd for $C_{12}H_{21}NO_3$ 227.1517, found 227.1521; IR ($CHCl_3$) 1756, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (3H, s), 2.13 (3H, s), 3.47 (2H, t, *J* = 6 Hz), 4.18 (2H, t, *J* = 6 Hz).

11: HRMS *m/z* calcd for $C_{12}H_{21}NO_4$ 243.1440, found 243.1470; IR ($CHCl_3$) 1765, 1744 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.05 (6H, s), 2.75 (1H, m), 3.17 (2H, t, *J* = 6 Hz), 4.23 (2H, t, *J* = 6 Hz).

***rel*-(3a*R*,5*S*)-5-Ethoxy-3-oxo-3,3a,4,5-tetrahydroisoxazolo[2,3-*c*]oxazole-1,1′-spirocyclohexane (12).** A solution of 169 mg (1 mmol) of **4b** in 4 mL of ethyl vinyl ether was placed in a Teflon tube (4 mL) with a Teflon stopper. The tube was placed in a high-pressure reactor and pressurized to 8 kbar for 19 h at room temperature. The pressure was released and the reaction mixture was concentrated under reduced pressure to give 240 mg (99%) of **12** as a pale yellow oil; IR ($CHCl_3$) 2950, 1778 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–2.23 (10H, m), 1.18 (3H, t, *J* = 7 Hz), 2.23–4.03 (4H, m), 4.27 (1H, dd, *J* = 9 and 2 Hz), 5.18 (1H, dd, *J* = 6 and 2 Hz); HRMS *m/z* calcd for $C_{12}H_{19}NO_4$ 241.1314, found 241.1324.

12, without further purification, was used for the preparation of **13** and **14**.

***rel*-(3*R*,5*S*)-2-Cyclohexyl-3-(hydroxymethyl)-5-ethoxyisoxazolidine (13a).** A mixture of 241 mg (1 mmol) of **12** and 78.7 mg (2 mmol) of $LiAlH_4$ in 10 mL of THF was heated under reflux in nitrogen atmosphere for 2 h. Aqueous ether was added to the reaction mixture with ice-cooling. The mixture was filtered using Celite, and the filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography on 8 g of silica gel. Elution with hexane–EtOAc (1:1) gave 130 mg (57%) of **13** as a colorless oil: IR ($CHCl_3$) 3484 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.195 (3H, t, *J* = 7 Hz), 2.193 (1H, ddd, *J* = 13, 8, and 2 Hz), 2.336 (1H, m), 2.945 (1H, m), 3.405 (1H, m), 3.505 (2H, q, *J* = 7 Hz), 3.638 (1H, m), 3.801 (1H, ddd, *J* = 16, 7, and 7 Hz), 5.150 (1H, dd, *J* = 8 and 2 Hz); HRMS *m/z* calcd for $C_{12}H_{23}NO_3$ 229.1678, found 229.1694.

***rel*-(3*R*,5*S*)-3-(Acetoxymethyl)-2-cyclohexyl-5-ethoxyisoxazolidine (13b).** A solution of 30 mg (0.13 mmol) of **13a**, 1 mL of acetic anhydride, and 0.5 mL of pyridine was allowed to stand at room temperature for 1 h. The mixture was concentrated *in vacuo*, and the residue was subjected to silica gel column chromatography. Elution with hexane–EtOAc (3:1) gave 35 mg (100%) of **13b** as a colorless oil: IR ($CHCl_3$) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.630 (3H, t, *J* = 7 Hz), 2.029 (3H, s), 2.175 (1H, m), 2.396 (1H, ddd, *J* = 13, 8, and 2 Hz), 2.847 (1H, m), 3.488 (1H, ddd, *J* = 16, 7, and 7 Hz), 3.787 (2H, q, *J* = 7 Hz), 3.897 (1H, dd, *J* = 11 and 7 Hz), 4.058 (1H, dd, *J* = 11 and 7 Hz), 5.125 (1H, dd, *J* = 6 and 2 Hz); HRMS *m/z* calcd for $C_{14}H_{25}NO_4$ 271.1784, found 271.1767.

***rel*-(3*R*,5*S*)-5-Ethoxyisoxazolidine-3-carboxylic Acid (14).** A mixture of 1 mmol of **12** or a mixture of **16** and **17** in 10 mL of saturated aqueous $NaHCO_3$ was stirred at room temperature for 24 h. The mixture was extracted with ether to remove the ketone, and the aqueous layer was passed through ion-exchange resin column (IRC-50S) to give 148 mg (92%) as an amorphous solid: ^1H NMR (CD_3OD) δ 1.19 (3H, t, *J* = 7 Hz), 2.41 (1H, ddd, *J* = 13.5, 9, and 1.2 Hz), 2.58 (1H, dt, *J* = 13.5 and 5.3 Hz), 3.48 (1H, dq, *J* = 9.5 and 7 Hz), 3.71 (1H, dq, *J* = 9.5 and 7 Hz), 4.12 (1H, dd, *J* = 9 and 5.3 Hz), 5.30 (1H, d, *J* = 5.3 Hz). Anal. Calcd for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.68; H, 6.90; N, 8.50.

1,3-Dipolar Cycloaddition of 4f with Ethyl Vinyl Ether. Following the procedure given for the preparation of **12**, reaction of 191 mg (1 mmol) of **4f** with 4 mL of ethyl vinyl ether under high-pressure (8 kbar) gave 262 mg (99%) of a mixture of *rel*-(1*S*,4*R*,6*S*)-5-ethoxy-1-methyl-3-oxo-1-phenyl-3,3a,4,5-tetrahydroisoxazolo[2,3-*c*]oxazole (**16**) and *rel*-(1*R*,4*R*,6*S*)-5-ethoxy-1-methyl-3-oxo-1-phenyl-3,3a,4,5-tetrahydroisoxazolo[2,3-*c*]oxazole (**17**) (3:1): IR ($CHCl_3$) 1783 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H × 1/4, t, *J* = 6.9 Hz, OCH_2CH_3), 1.29 (3H × 3/4, t, *J* = 6.9 Hz, OCH_2CH_3), 1.82 (3H × 1/4, s, CH_3), 1.91 (3H × 3/4, s, CH_3), 2.49 (1H × 3/4, ddd, *J* = 13.8, 9.0, and 2.2 Hz, 4-H), 2.63 (1H × 1/4, ddd, *J* = 13.2, 9.0, and 1.8 Hz, 4-H), 2.93 (1H × 3/4, ddd, *J* = 13.8, 6.6, and 1.5 Hz, 4-H), 2.97 (1H × 1/4, ddd, *J* = 13.2, 6.3, 1.5 Hz, 4-H), 3.3–3.7 (5/4H, m, OCH_2CH_3), 3.8–4.0 (3/4H, m, OCH_2CH_3), 3.86 (3/4H, dd, *J* = 9.0 and 1.5 Hz, 3a-H), 4.45 (1/4H, dd, *J* = 9.0 and 1.5 Hz, 3a-H), 5.06 (1/4H, dd, *J* = 6.3 and 1.8 Hz, 5-H), 5.27 (3/4H, dd, *J* = 6.6 and 2.2 Hz, 5-H).

***rel*-(3a*R*,5*S*)-3-Oxo-5-[(trimethylsilyl)methyl]-3,3a,4,5-tetrahydroisoxazolo[2,3-*c*]oxazole-1,1′-spirocyclohexane (20).** Following the procedure given for the preparation of **12**, high-pressure mediated reaction of 169 mg (1 mmol) of **4b** with 1.30 g (11.3 mmol) of allyltrimethylsilane in CH_2Cl_2 (2 mL) gave 280 mg (quant) of **20** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.30 (9H, s), 0.86 (1H, dd, *J* = 14.0 and 6.5 Hz), 1.03 (1H, dd, *J* = 14.0 and 7.5 Hz), 1.40–1.82 (10H, m), 2.04–2.27 (1H, m), 2.70 (1H, dd, *J* = 12.0 and 4.5 Hz), 3.96–4.09 (1H, m), 4.25 (1H, d, *J* = 8.0 Hz). **20**, without further purification, was used for the preparation of **21** and **22**.

***rel*-(3*R*,5*S*)-3-(Hydroxymethyl)-2-cyclohexyl-5-[(trimethylsilyl)methyl]isoxazolidine (21).** Following the procedure given for the preparation of **13a**, reaction of 280 mg (1 mmol) of **20** with 76 mg (2 mmol) of $LiAlH_4$ gave 143 mg (53%) of **21** as a colorless oil: IR ($CHCl_3$) 3484 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.038 (9H, s, $SiMe_3$), 0.804 (1H, dd, *J* = 14.0 and 8.0 Hz, $CHH'SiMe_3$), 1.106 (1H, dd, *J* = 14.0 and 6.0 Hz, $CHH'SiMe_3$), 2.106 (2H, ddd, *J* = 11.0, 6.0, and 2.0 Hz, 4-H × 2), 2.640 (1H, m, cyclohexyl 1-H), 3.376 (1H, m, 5-H), 3.484 (2H, m, CH_2OH), 4.079 (1H, m, 3-H); HRMS *m/z* calcd for $C_{14}H_{29}NO_2Si$ 271.1968, found 271.1957.

***rel*-(3*R*,5*S*)-5-[(Trimethylsilyl)methyl]isoxazolidine-3-carboxylic Acid (22).** Following the procedure given for the preparation of **14**, 281 mg (1 mmol) of **20** was treated with 10

mL of saturated aqueous $NaHCO_3$ to give 120 mg (59%) of **22** as an amorphous solid: ^1H NMR (CD_3OD) δ 0.80 (1H, dd, J = 14.0 and 8.5 Hz, C*H*H'SiMe$_3$), 1.01 (1H, dd, J = 14.0 and 5.8 Hz, CH*H*'SiMe$_3$), 1.99 (1H, dt, J = 11.5 and 10.0 Hz, 4-H), 2.31 (1H, ddd, J = 12.0, 6.0 and 4.5 Hz, 4-H), 3.75 (1H, dd, J = 10.0 and 4.5 Hz, 3-H), 3.85–3.98 (1H, m, 5-H). Anal. Calcd for $C_8H_{17}NO_3Si$: C, 47.26; H, 8.43; N, 6.89. Found: C, 47.20; H, 8.45; N, 6.70. IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (1H, dddd, J = 7.5, 7.0, 2.0, 1.0 Hz, 3b-H), 3.89 (1H, s, 3a-H), 5.26 (1H, brd, J = 7.5 Hz, 3b-H), 5.69 (1H, m, 5-H or 6-H), 6.04 (1H, m, 6-H or 5-H).

***rel*-(2*R*,4*S*)-2-Amino-4-hydroxy-5-(trimethylsilyl)-pentanoic Acid (23).** A mixture of 102 mg (0.5 mmol) of **22** and 20 mg of 5% Pd–C in 10 mL of MeOH was shaken in hydrogen atmosphere under atmospheric pressure at room temperature for 12 h. The catalyst was filtered off using Celite. The filtrate was concentrated *in vacuo* to give a crystalline substance, which was purified by recrystallization from MeOH–EtOAc to afford 55 mg (54%) of **23** as colorless amorphisms: mp 181–183 °C; ^1H NMR (CD_3OD) δ 0.870 (1H, dd, J = 14.0 and 7.0 Hz), 0.955 (1H, dd, J = 14.0 and 7.0 Hz), 1.90 (1H, ddd, J = 14.0, 9.5, and 4.5 Hz), 2.01 (1H, ddd, J = 14.0, 7.0, and 3.1 Hz), 3.74 (1H, dd, J = 7.0 and 4.0 Hz), 4.01 (1H, m). Anal. Calcd for $C_8H_{19}NO_3Si$: C, 46.80; H, 9.33; N, 6.82. Found: C, 46.70; H, 9.35; N, 6.65.

***rel*-(3a*R*,3b*S*,6a*S*)-5,6-Dehydro-3-oxo-3,3a,3b,6a-tetrahydrocyclopent[*f*]isoxazolo[2,3-*c*]oxazole-1,1'-spirocyclohexane (25).** (a) Following the procedure given for the preparation of **12**, high-pressure mediated reaction of 169 mg (1 mmol) of **4b** with 1.65 g (25 mmol) of cyclopentadiene in 2 mL of CH_2Cl_2 gave 235 mg (quant.) of **25** as a pale yellow viscous oil: (b) A solution of 845 mg (5 mmol) of **4b** in 1.65 g (25 mmol) of cyclopentadiene was allowed to stand at room temperature for 3 d. The starting material **4b** was not detected on the TLC plate. Excess of cyclopentadiene was evaporated off *in vacuo* to give **25** in quantitative yield. **25**, without further purification, was used for the preparation of **26** and **27**.

***rel*-(3*R*,3a*S*,6a*S*)-2-Cyclohexyl-3-(hydroxymethyl)-5,6-dehydro-2,3,3a,6a-tetrahydrocyclopent[*d*]isoxazole (26a).** Following the procedure given for the preparation of **13a**, reaction of 235 mg (1 mmol) of **25** with 76 mg (2 mmol) of $LiAlH_4$ gave 123 mg (55%) of **26a** as a colorless oil (hexane–EtOAc = 3:1): IR ($CHCl_3$) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (2H, d, J = 13 Hz), 5.16 (1H, m), 5.92 (2H, m); HRMS *m/z* calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1584.

***rel*-(3*R*,3a*S*,6a*S*)-3-(Acetoxymethyl)-2-cyclohexyl-5,6-dehydro-2,3,3a,6a-tetrahydrocyclopent[*d*]isoxazole (26b).** To a solution of 123 mg (0.55 mmol) of **26a** in 2 mL of acetic anhydride was added 0.5 mL of pyridine. After being kept at room temperature for 1 h, the mixture was concentrated *in vacuo*. The residue was subjected to silica gel (30 g) column chromatography. Elution with hexane–EtOAc (7:1) gave 120 mg (82%) of **26b** as a colorless oil: IR ($CHCl_3$) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.068 (3H, s), 2.480 (1H, m), 2.719 (1H, m), 2.802 (1H, m), 2.957 (1H, m, 3a-H), 3.345 (1H, m, 3-H), 4.059 (1H, dd, J = 14 and 10 Hz), 4.107 (1H, dd, J = 14 and 8 Hz), 5.110 (1H, m), 5.835 (1H, m), 5.928 (1H, m); HRMS *m/z* calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1678.

***rel*-(3*R*,3a*S*,6a*S*)-5,6-Dehydro-2,3,3a,6a-tetrahydrocyclopent[*d*]isoxazole-3-carboxylic Acid (27).** Following the procedure given for the preparation of **14**, 235 mg (1 mmol) of **25** was treated with 10 mL of saturated aqueous $NaHCO_3$ to give 76 mg (49%) of **27** as an amorphous solid: ^1H NMR ($CDCl_3$) δ 2.47 (1H, dt, J = 17.8 and 1.9 Hz), 2.74 (1H, ddd, J = 17.8, 8.5, and 1.2 Hz), 3.42–3.52 (1H, m), 3.70 (1H, d, J = 3.2 Hz), 5.30 (1H, d, J = 7.2 Hz), 5.60 (1H, m), 6.10 (1H, m). Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.01; H, 5.88; N, 8.89.

***rel*-(2*R*,1'*S*,2'*S*)-2-Amino-2-(2'-hydroxycyclopentyl)-acetic Acid (28).** A mixture of 62 mg (0.4 mmol) of **27** and 20 mg of 5% Pd–C in 10 mL of MeOH was shaken in hydrogen atmosphere under atmospheric pressure at room temperature for 12 h. The catalyst was filtered off using Celite. The filtrate was concentrated *in vacuo* to give a crystalline substance, which was purified by recrystallization from MeOH–ether to afford 40 mg (63%) of **28** as colorless amorphisms: mp 227–229 °C; ^1H NMR ($CDCl_3$) δ 1.60–1.95 (6H, m), 2.30 (1H, m), 3.75 (1H, d, J = 6 Hz), 4.33 (1H, dt, J = 7 and 2 Hz). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.95; H, 8.29; N, 8.76.

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Supplementary Material Available: ^1H NMR spectra of compounds **4a**,**c**,**d**,**f**,**j**,**10**,**12**,**13a**,**13b** (COSY), **21** (COSY), **26a**, and **26b** (COSY) (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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