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Synthesis of Chiral Cyclic Nitrones *via* a Nitrosoketene Intermediate and Their Use for the Complete EPC Synthesis of Nonproteinogenic Amino Acids

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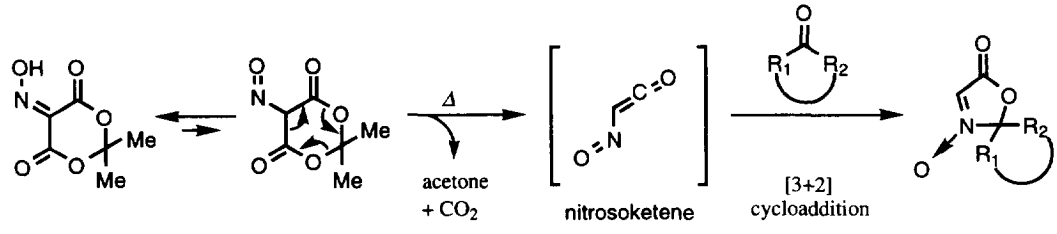
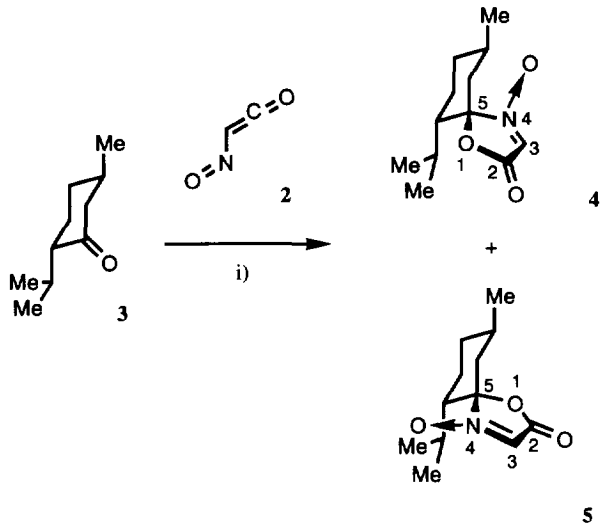
Abstract: New cyclic chiral nitrones constituting two diastereomers were synthesized by the reaction of isonitroso Meldrum's acid with *l*-menthone *via* a nitrosoketene intermediate. Both nitrones reacted with allyltrimethylsilane diastereoselectively to give the corresponding isoxazolidine derivatives as sole products, which were converted to (*S*)- and (*R*)- allylglycines in *ca.* 100% ee, respectively.

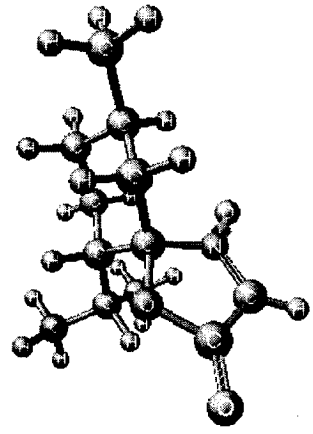
Recently, we have reported the reaction of isonitroso Meldrum's acid (**A**= **1**) with ketones under reflux in toluene to give cyclic nitrones (**C**).[1] It can be considered that the reaction would proceed *via* [3+2] cycloadditions of ketones with nitrosoketene (**B**= **2**) generated by thermolysis of **1**.[2] The nitrones thus obtained underwent 1,3-dipolar cycloaddition with electron-rich olefins to form the corresponding isoxazolidine derivatives stereoselectively, which could be converted to amino acids.[3] In this paper, we report the synthesis of new chiral cyclic nitrones from a chiral ketone and their use for the complete EPC (enantiomerically pure compound) synthesis of nonproteinogenic amino acids, (*S*)- and (*R*)-allylglycines (**9**, **13**)[4,5], the former of which has the same configuration as the natural product isolated from the *Amanita* mushroom.



Scheme 1

When **1** (1 equiv.) was allowed to react with *l*-menthone (**3**) (2 equiv.) under reflux in toluene, two cyclic nitrones (**4**[6] and **5**[7]) were obtained in 26 and 28% yields, respectively.[8] The two compounds were chromatographically separable from each other. Since the structure of **4** was determined by X-ray crystallographic analysis[9] as shown in Scheme 2, the structure of **5** coincided with the configuration of 5*S* (Scheme 2).



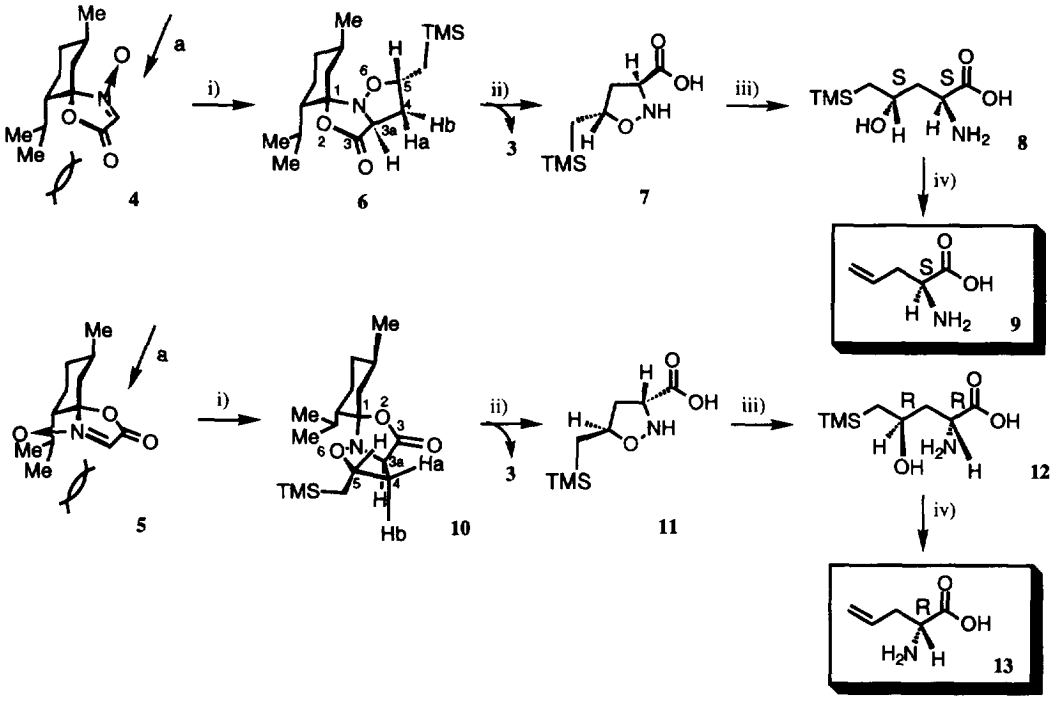


Scheme 2. Reagents and conditions: i) isonitroso Meldrum's acid, toluene, reflux.

X-Ray Structure of **4**

The 1,3-dipolar cycloaddition of **4** with allyltrimethylsilane was carried out under high pressure (800 MPa) in dichloromethane at 40 °C to give the adduct **6**[10] as a single isomer in 90% yield. The reaction also proceeded in the presence of BF_3-Et_2O in dichloromethane at room temperature to give the same compound **6** in quantitative yield. The structure of **6** was determined to be (1*R*, 3a*S*, 5*S*) by careful NOE experiment as shown in Table 1. Therefore, allyltrimethylsilane approached from the less hindered side (a-side) of **4** with *exo*-transition state to form **6** as a single isomer. Treatment of **6** 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) (**7**)[11] in almost quantitative yield, concomitant with the quantitative recovery of *l*- menthone. Under this condition, the *cis* isomer of **7** was not detected, which might be formed by inversion under an alkaline condition. Hydrogenolysis of **7** with Pd-C gave (2*S*, 4*S*)-2-amino-4-hydroxy-5-(trimethylsilyl) pentanoic acid (**8**)[12] in 88% yield, whose optical purity was determined to be *ca.* 100% ee by HPLC analysis using chiral column (CROWNPAK-CR). Next, we examined the olefination of **8** under various conditions. Desilylating reagents such as KF and n-Bu_4NF were inactive for the reaction. We found that BF_3-Et_2O was the best reagent for the olefination of **8** without epimerization. Thus, **8** was treated with BF_3-Et_2O in acetonitrile at room temperature for 3 h to give (*S*)-allylglycine[13] (**9**) in quantitative yield. Though hydrochloric acid also catalyzed the reaction in 93% 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 (7%). The optical purity of **9** was also determined to be *ca.* 100% ee by comparison of the HPLC analysis of its racemic allylglycine prepared by another route.[15]

Employing the same procedure, the EPC synthesis of (*R*)-allylglycine (**12**) 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 (**10**)[16] as a sole product (Table 2).



Scheme 3. Reagents and conditions: i) allyltrimethylsilane, 800 MPa, toluene, 40 °C (or allyltrimethylsilane, BF_3-Et_2O, CH_3CN, r.t.); ii) 0.15 M aqueous NaOH, r.t.; iii) H_2/ Pd-C, MeOH, r.t.; iv) BF_3-Et_2O, CH_3CN, r.t.

Table 1
NOE Experiment of Compound **6**

Irradiated Protons	Increase in Integration (%)	
3a-H	4-Hb	7.1
4-Ha	3a-H	1.4
4-Ha	5-H	2.6
4-Hb	3a-H	6.8
4-Hb	5-H	1.3
5-H	4-Ha	5.4

Table 2
NOE Experiment of Compound **10**

Irradiated Protons	Increase in Integration (%)	
3a-H	4-Hb	8.0
3a-H	4-Ha	2.3
4-Ha	5-H	5.3
4-Ha	3a-H	1.4
4-Hb	3a-H	7.1
4-Hb	5-H	1.3
5-H	4-Ha	5.3
5-H	4-Hb	1.6

In conclusion, we have achieved the synthesis of new chiral nitrones *via* a nitrosoketene intermediate. We have applied the nitrones for the complete EPC synthesis of α-amino acids. This method should also be applicable for EPC synthesis of naturally occurring nonproteinogenic amino acids such as cyclopentenyl- and cyclohexenylglycines, which are interesting amino acids from the viewpoint of biosynthesis[16]. Study on the synthesis of these amino acids is also in progress and the results will be reported in due course.

Acknowledgment: This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (No. 06225205, C. K.) and by a Grant-in-Aid for Scientific Research (No. 06672230, N. K.) from the Ministry of Education, Science and Culture, Japan. We are also grateful to Prof. Kuninobu Kabuto (Faculty of Science, Tohoku University) for his helpful discussion concerning the determination of optical purity of our compounds.

References and Notes

1. Katagiri, N.; Kurimoto, A.; Yamada, A.; Sato, H.; Katsuhara, T.; Takagi, K.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1994**, 281.
2. Two reaction pathways could be considered for the formation of nitrones (**C**), a [4+2] cycloaddition followed by a 1,2-migration, or a direct [3+2] cycloaddition. Quite recently, Birney and his co-worker proposed on the basis of the *ab* initio study that the reaction should proceed *via* the direct [3+2] cycloaddition. Ham S.; Birney D. M. *Tetrahedron Lett.* **1994**, *44*, 8113.
3. Katagiri, N.; Sato, H.; Kurimoto, A.; Okada, M.; Yamada, A.; Kaneko, C. *J. Org. Chem.* **1994**, *59*, 8101.
4. For recent papers dealing with the synthesis of optically active allylglycines, see: (a) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta.* **1994**, *77*, 2363; (b) Rose, J. E.; Leeson, P. D.; Gani, D. *J. Chem. Soc. Perkin Trans. 1.* **1995**, 157. In these references, the amino acids were synthesized by the allylation of chiral glycine derivatives in the presence of butyl lithium followed by appropriate manipulation.
5. For a recent review dealing with the stereoselective synthesis of α-amino acids, see: Duthaler, R. O. *Tetrahedron*, **1994**, *50*, 1539.
6. Compound **4**: mp 102-103 °C, $[\alpha]_D^{20}$+88.8° (*c*= 0.5, $CHCl_3$).
7. Compound **5**: oil, $[\alpha]_D^{20}$-35.6° (*c*= 0.5, $CHCl_3$).
8. In this reaction, the other isomer was also obtained in 14% yield, which would be formed by the reaction of nitrosoketene with isomenthone being contained as an impurity.
9. Full details of the X-ray data are to be deposited at the Cambridge Crystallographic Data Centre.
10. Compound **6**: mp 88-90 °C, $[\alpha]_D^{21}$+18.6° (*c*= 2.9, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (1H, ddd, *J*= 12.5, 11.5, 8.8 Hz, 4-Hb), 2.67 (1H, dd, *J*= 12.5, 3.8 Hz, 4-Ha), 3.84-3.92 (1H, m, 5-H), 4.14 (1H, d, *J*= 8.8 Hz, 3a-H).
11. Compound **7**: amorphous solid, $[\alpha]_D^{20}$-28.9° (*c*= 12.5, MeOH). ^{1}H-NMR (CD_3OD) δ: 0.84 (1H, dd, *J*= 14.0, 8.7 Hz, C*H*H'TMS), 1.04 (1H, dd, *J*= 14.0, 5.5 Hz, CH*H*'TMS), 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).
12. Compound **8**: mp 174-175 °C (MeOH-Et_2O), $[\alpha]_D^{28}$-21.6° (*c*= 1, MeOH). ^{1}H-NMR (CD_3OD) δ: 0.88 (1H, dd, *J*= 14.5, 7.0 Hz, C*H*H'TMS), 0.97 (1H, dd, *J*= 14.5, 7.0 Hz, CH*H*'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).
13. mp 248-249°C, $[\alpha]_D^{24}$-32.40° (*c*= 1, H_2O) [*lit.*[14] $[\alpha]_D^{24}$-37.1° (*c*= 4, H_2O)].
14. Black, S.; Wright, N. G. *J. Biol. Chem.* **1955**, *213*, 39.
15. Racemic allylglycine was obtained from the reaction of *rel*-(2*R*,4*S*)-2-amino-4-hydroxy-5-(trimethylsilyl) pentanoic acid[3] with BF_3-Et_2O.
16. Compound **10**: oil, $[\alpha]_D^{22}$-37.4° (*c*= 2.9, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.13 (1H, ddd, *J*= 12.2, 11.1, 8.7 Hz, 4-Hb), 2.63 (1H, dd, *J*= 12.2, 4.0 Hz, 4-Ha), 3.73-3.86 (1H, m, 5-H), 4.17 (1H, d, *J*= 8.7 Hz, 3a-H).
17. Cramer, U.; Rehfeldt, A. G.; Spener, F. *Biochemistry*, **1980**, *19*, 3074.

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