The first enantiomerically pure synthesis of (2*S*,1′*S*)-(cyclopent-2-enyl)glycine by boron trifluoride mediated asymmetric 1,3-dipolar cycloaddition

Nobuya Katagiri,*† Makoto Okada, Yoshihiro Morishita and Chikara Kaneko

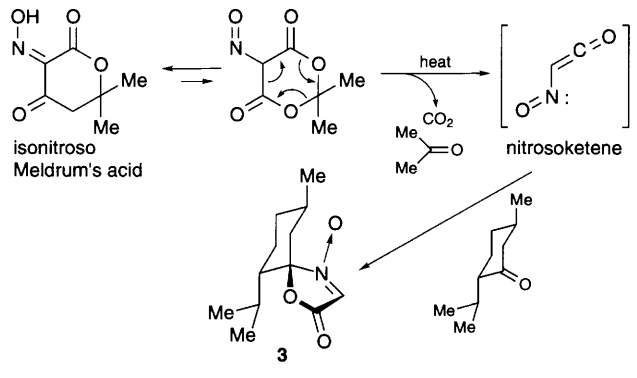
Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980-77, Japan

Chiral spiro nitrone 3, treated with (3-trimethylsilyl)cyclopent-1-ene in the presence of BF_3·Et_2O, gives the 1,3-dipolar cycloadduct 4 as a single isomer, which is converted to (2*S*,1′*S*)-(cyclopent-2-enyl)glycine (2*S*,1′*S*)-7 by alkaline hydrolysis, catalytic reduction and BF_3 mediated alkene formation.

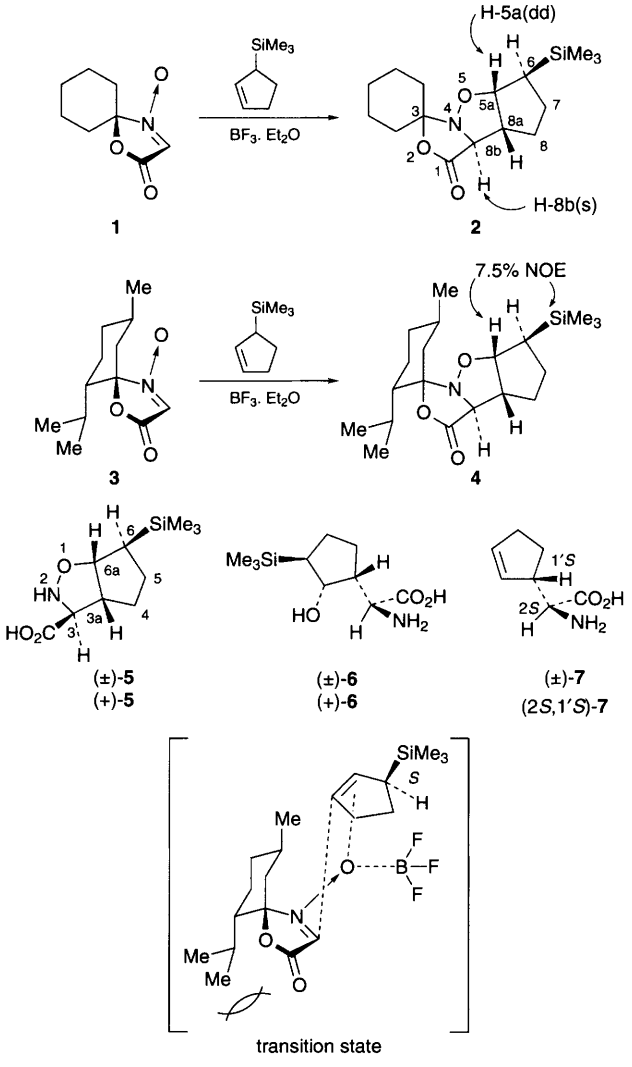
(2*S*,1′*S*)-(Cyclopent-2-enyl)glycine, (2*S*,1′*S*)-**7**, is a naturally occurring nonproteinogenic amino acid which has been isolated from the seeds of *Hydnocarpus anthelminthica* and the leaves of *Caloncoba echinata*.[1] Racemic (cyclopent-2-enyl)glycine has been shown to be a potent growth inhibitor of *Escherichia coli*[2] as well as a biogenic precursor of unusual cyclopentenyl fatty acids.[3] The asymmetric synthesis of (cyclopent-2-enyl)glycine was first carried out by Williams and co-workers, who obtained an optically active (cyclopent-2-enyl)glycine as a 1 : 1 mixture of epimers at the cyclopentene methine.[4] However, the enantiomerically pure synthesis of (cyclopent-2-enyl)glycine has not been achieved so far. We now report the first enantiomerically pure synthesis of (2*S*,1′*S*)-(cyclopent-2-enyl)-glycine, (2*S*,1′*S*)-**7**, from the chiral spiro cyclic nitrone **3**, which was synthesized by our group from the reaction of isonitroso Meldrum's acid and *l*-menthone *via* a nitrosoketene intermediate.[7]

Before investigating the chiral synthesis of (2*S*,1′*S*)-**7**, we studied the racemic synthesis starting with an achiral nitrone **1**.[5,6] When the nitrone **1** was treated with 3-(trimethylsilyl)-cyclopent-1-ene in the presence of BF_3·Et_2O (1 equiv.) in acetonitrile at room temperature for 14 h, the adduct **2**‡ was obtained as a single isomer in almost quantitative yield. The structure of **2** was determined by ^{1}H NMR spectroscopy. Thus, the proton at the 8b-position shows a singlet signal at δ 3.845 whereas the signal due to the H-5a was observed as a doublet of doublets at δ 4.427 (*J* 7.5 and 5.3 Hz). These data show that the reaction proceeds with the *exo* transition state and with complete regioselectivity to form the adduct **2** exclusively. Adduct **2** was treated with aq. sodium hydrogen carbonate (2 equiv.) at room temperature for 24 h followed by Amberlite IRC-50S to give the isoxazolidine derivative (±)-**5** [δ 3.437 (d, *J* 5.3 Hz, H-3) and 4.402 (dd, *J* 7.0 and 2.2 Hz, H-6a)] as an amorphous solid in 84% yield, concomitant with the quantitative recovery of cyclohexanone. Compound (±)-**5** was then catalytically hydrogenated using 5% Pd–C in methanol under standard atmospheric pressure for 32 h to give the cyclopentylglycine derivative (±)-**6** (mp 175–178 °C) as colourless needles in 83% yield. Treatment of compound (±)-**6** with BF_3·Et_2O in acetonitrile with ice-cooling for 1 h followed by DOWEX 50W-X4 gave racemic (cyclopent-2-enyl)glycine (±)-**7** [mp 260 °C (dec.)] in 84% yield.

According to this synthetic pathway, we next carried out the EPC synthesis of (2*S*,1′*S*)-(cyclopent-2-enyl)glycine, (2*S*,1′*S*)-**7**, from the chiral nitrone **3**. Asymmetric 1,3-dipolar cycloaddition of **3** with 3-(trimethylsilyl)cyclopent-1-ene (2.4 equiv.) in the presence of BF_3·Et_2O (1 equiv.) in acetonitrile at room temperature for 91 h afforded the cycloadduct **4** [mp



Scheme 1



Scheme 2

118–120 °C, $[\alpha]_D^{23}$ +87.99 (*c* 1.05, $CHCl_3$)} as sole product in 69% yield. As for **2**, the stereochemistry of **4** was determined by ^{1}H NMR spectroscopy [δ 3.876 (s, H-8b) and 4.310 (dd, *J* 6.5 and 4.5, H-5a)]. Especially, 7.5% NOE effect was observed between H-5a and the Me_3Si group. Removal of the chiral auxiliary of **4** was carried out by treatment with sodium hydrogen carbonate (2 equiv.) in a 1 : 1 mixture of water and THF to give (+)-**5** {$[\alpha]_D^{21}$ +39.6 (*c* 0.5, MeOH)} in 76% yield, together with 83% recovery of menthone. Transformation of (+)-**5** to the final product (2*S*,1′*S*)-**7**, {mp 243–246 °C (dec.), $[\alpha]_D^{21}$ −121 (*c* 0.32, H_2O)} was carried out according to the racemic series *via* (+)-**6** {mp 169–170 °C (dec.), $[\alpha]_D^{24}$ +13.47 (*c* 0.95, MeOH)}. The ee of (+)-**6** and (2*S*,1′*S*)-**7** was determined to be more than 98% by HPLC analysis using CROWNPAC-CR(+) [solvent: $HClO_4/H_2O$–MeOH (1 : 1), pH 1.0, and $HClO_4$–H_2O, pH 1.0, respectively], compared with that of the corresponding racemic series.

We have synthesised enantiomerically pure (2*S*,1′*S*)-(cyclopent-2-enyl)glycine, (2*S*,1′*S*)-**7**, using the asymmetric 1,3-dipolar cycloaddition of chiral cyclic nitrone **3** with 3-(trimethylsilyl)cyclopent-1-ene with complete regio- and stereo-control. Since this reaction does not proceed without the catalyst, BF_3 chelates with the oxide of the nitrone to give 1,3-dipolar transition state,[8] to which 3-(trimethylsilyl)-cyclopent-1-ene approaches from the less hindered side *via* the *exo* transition state as shown in Scheme 2. It is noteworthy that, although the starting 3-(trimethylsilyl)cyclopent-1-ene is racemic, only the *S*-isomer reacts with **3** to give the adduct **4** exclusively. This would be due to the sterical factor between the $SiMe_3$ group and BF_3 and only the *S*-isomer of racemic (3-trimethylsilyl)cyclopent-1-ene matches this transition state to form the adduct **4** as sole product. Therefore, a novel kinetical resolution of the dipolarophile is involved in the asymmetric 1,3-dipolar cycloaddition step.

This research was supported in part by a Grant-in-Aid for Scientific Research (No. 0867405 to N. K.) from the Ministry of Education, Science, Sports, and Culture, Japan.

Footnotes

† E-Mail: nobu@phi.pharm.tohoku.ac.jp

‡ All new compounds gave satisfactory analytical and/or spectral data. *Selected data* for **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.223 (1 H, dt, *J* 15.0, 7.5 Hz), 3.845 (1 H, s), 4.427 (1 H, dd, *J* 7.5, 5.3 Hz). For **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.862 (3 H, d, *J* 6.5 Hz), 0.892 (3 H, d, *J* 6.5 Hz), 0.898 (3 H, d, *J* 6.5 Hz), 3.163 (1 H, dt, *J* 15.0, 7.5 Hz), 3.876 (1 H, s), 4.310 (1 H, dd, *J* 6.5, 4.5 Hz); IR ($CHCl_3$) ν_{max}/cm^{-1} 1782. For (±)-**5** and (+)-**5**: ^{1}H NMR (300 MHz, CD_3OD) δ 1.160–2.063 (5 H, m), 2.838–2.957 (1 H, m), 3.437 (1 H, d, *J* 5.3 Hz), 4.402 (1 H, dd, *J* 7.0, 2.2 Hz). For (±)-**6** and (+)-**6**: ^{1}H NMR (300 MHz, CD_3OD) δ 1.102 (1 H, dt, *J* 9.0, 3.5 Hz), 1.232–2.102 (4 H, m), 2.110 (1 H, dq, *J* 12.5, 6.0 Hz), 3.708 (1 H, d, *J* 6.0 Hz), 4.178 (1 H, dd, *J* 5.5, 3.5 Hz). For (±)-**7** and (2*S*, 1′*S*)-**7**: ^{1}H NMR (300 MHz, CD_3OD) δ 1.460–2.510 (5 H, m), 3.471 (1 H, d, *J* 4.8 Hz), 5.582–5.646 (1 H, m), 5.900–5.960 (1 H, m).

References

1 V. Cramer, A. G. Rehfeldt and F. Spener, *Biochemistry*, 1980, **19**, 3074.
2 R. L. Dennis, W. J. Plent, C. G. Skinner, G. L. Sutherland and W. Shire, *J. Am. Chem. Soc.*, 1995, **77**, 2362.
3 V. Cramer and F. Spener, *Eur. J. Biochem.*, 1977, **74**, 495.
4 R. M. Williams, P. J. Sinclair, D. Zhai and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547.
5 N. Katagiri, A. Kurimoto, A. Yamada, H. Sato, T. Katsuhara, Y. Takagi and C. Kaneko, *J. Chem. Soc., Chem. Commun.*, 1994, 281.
6 N. Katagiri, H. Sato, A. Kurimoto, M. Okada, A. Yamada and C. Kaneko, *J. Org. Chem.*, 1994, **59**, 8101.
7 N. Katagiri, M. Okada, C. Kaneko and T. Furuya, *Tetrahedron Lett.*, 1996, **39**, 1801.
8 Recent papers dealing with the 1,3-dipolar cycloaddition of nitrones in the presence of Lewis acid catalyst: S.-I. Murahashi, Y. Imada, M. Kohno and T. Kawakami, *Synlett*, 1993, 395; K. V. Gothelf and K. A. Jorgenson, *J. Org. Chem.*, 1994, **59**, 5687; S. Kanemasa, T. Tsuruoka and H. Yamamoto, *Tetrahedron Lett.*, 1995, **36**, 5019; J.-P. G. Seerden, M. M. M. Kuypers and H. W. Scheeren, *Tetrahedron: Asymmetry*, 1995, **6**, 1441.

Received, 25th June 1996; Com. 6/04409C