Heteroatom Chemistry
Volume 14, Number 1, 2003

# Diastereospecific Synthesis of (*S,S*)-2-Substituted-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octanes

Gang Zuo, Qihan Zhang, and Jiaxi Xu

*Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China*

*Received 12 December 2001; revised 19 February 2002*

ABSTRACT: *(S,S)-2-Substituted-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octanes were synthesized diastereospecifically from aldehydes and (S)-2-(hydroxydiphenylmethyl)pyrrolidine, which was obtained from* L*-proline, under acid-catalyzed conditions in anhydrous toluene. The stereospecificity of the condensation reaction is discussed.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:42–45, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10064

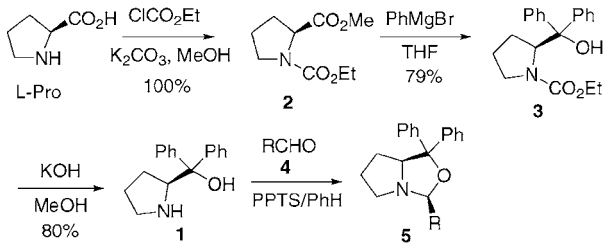
## *INTRODUCTION*

Naturally occurring amino acids constitute an important and inexpensive chiral pool for the synthesis of complex natural products and chiral drugs. During the last decade, pyroglutamic acid, the cyclized form of glutamic acid, has been widely studied for the synthesis of pyrrolidine derivatives [1–4]. Functionalized pyrrolidines are compounds of considerable importance since they are a source of useful synthetic intermediates [5–7], chiral auxiliaries [8,9], and ligands [10–12]. They also occur in a variety of natural products and pharmaceutically active compounds, either as isolated ring systems or embedded in more complex structures, which often possess wide ranging biological activity [1]. The development of the methodology for the preparation of highly functionalized pyrrolidines has attracted considerable interest recently [1–4]. The trans bicyclic derivatives of pyrrolidine, *trans*-3,1-oxazabicyclo[3.3.0]octan-8-one derivatives, can be synthesized mainly from aldehydes and related chiral hydroxymethylpyrrolidinones, which are derived from L-pyroglutamic acid [1–4,13]. Herein we report the preparation of cis bicyclic derivatives of pyrrolidine, chiral *cis*-3,1-oxazabicyclo[3.3.0]octanes, from aldehydes and (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine, which was obtained from L-proline.

## *RESULTS AND DISCUSSION*

(*S*)-2-(Hydroxydiphenylmethyl)pyrrolidine (**1**) was prepared according to the procedure given in Ref. [14]. L-Proline reacted with ethyl chloroformate in the presence of potassium carbonate in anhydrous methanol to produce *N*-carboxyethyl L-proline methyl ester (**2**). The N-protected proline methyl ester **2** was then reacted with phenylmagnesium bromide to yield (*S*)-1-carboxyethyl-2-(hydroxydiphenylmethyl)pyrrolidine (**3**) in anhydrous tetrahydrofuran. After hydrolysis with potassium hydroxide in methanol, (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine (**1**) was obtained in 80% yield. It was refluxed with aldehydes (**4**), in the presence of *p*-toluenesulfonic acid (PPTS) as an acid catalyst, in anhydrous toluene, using a Dean–Stark water separator, and by vigorous

*Correspondence to:* Jiaxi Xu; e-mail: jxxu@chem.pku.edu.cn.
Contract grant sponsor: NSFC.
© 2003 Wiley Periodicals, Inc.




**SCHEME 1** Synthesis of (*S,S*)-2-substituted-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octanes.

stirring in an oil bath to yield (*S,S*)-2-substituted-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octanes **5a–e** and (*S*)-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octane **5f** in satisfactory yields [13] (Scheme 1).

The proposed structures for **5a–f** are based on $^1$H NMR, mass spectral, and elemental analyses (See Tables 1 and 2). According to $^1$H NMR monitoring, only one diastereomer of each of the compounds **5a–e** was found in the reaction mixture. This result could be rationalized as shown in Scheme 2. (*S*)-2-(Hydroxydiphenylmethyl)pyrrolidine (**1**) reacted with aldehydes **4a–e** under acid-catalyzed conditions to first form (E)-iminium intermediates **6**. Then the hydroxy group attacks the iminium group of the intermediates **6**. The attack should occur from the upper side of the iminium bond since it is located over the iminium bond. After the release of a proton, a kind of cis cyclized hemiaminal ether product, (*S,S*)-2-substituted-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octanes **5a–e**, is formed in each case. The stereo-structure of each product in the condensation is also well in agreement with the product of a similar reaction of (*S*)-phenylglycinol with an

**TABLE 1** Physical and Spectral Data

| *Compound* | *R* | *Yield (%)* | *m.p. (°C)* | *$[\alpha]^D_{20}$ (c, acetone)* | *MS/FAB m/z ($MH^+$)* | *$^1$H NMR ($CDCl_3$/TMS) δ (ppm), J (Hz)* |
|---|---|---|---|---|---|---|
| **5a** | Ph | 67 | 139–140 | −84.5 (1.30) | 342 | 7.61–7.17 (15H, m, aromatic), 5.53 (1H, s, NCHO), 4.49 (1H, t, $J = 7.2$, CHN), 3.14–3.03 (1H, m, 1H in $CH_2N$), 2.94–2.81 (1H, m, 1H in $CH_2N$), 1.87–1.60 (4H, m, $CH_2CH_2$) |
| **5b** | *o*-ClPh | 78 | 57–58 | −148 (0.57) | 376 | 7.49–7.17 (14H, m, aromatic), 5.52 (1H, s, NCHO), 4.45 (1H, t, $J = 7.2$, CHN), 3.12 (1H, dt, $J = 11.5, 7.2$, 1H in $CH_2N$), 2.86 (1H, dt, $J = 11.5, 5.5$, 1H in $CH_2N$), 1.87–1.64 (4H, m, $CH_2CH_2$) |
| **5c** | *p*-ClPh | 85 | 126–127 | −101 (0.71) | 376 | 7.85–7.16 (14H, m, aromatic), 5.51 (1H, s, NCHO), 4.45 (1H, t, $J = 7.0$, CHN), 3.17–3.06 (1H, m, 1H in $CH_2N$), 2.89–2.75 (1H, m, 1H in $CH_2N$), 1.85–1.62 (4H, m, $CH_2CH_2$) |
| **5d** | *p*-MeOPh | 61 | 153–154 | −119 (1.05) | 372 | 7.65–7.48 (6H, m, aromatic), 7.38–7.13 (6H, m, aromatic), 6.99–6.92 (2H, m, aromatic), 5.52 (1H, s, NCHO), 4.59 (1H, t, $J = 7.0$, CHN), 3.84 (3H, s, $CH_3O$), 2.58 (1H, dt, $J = 9.2, 7.0$ 1H in $CH_2N$), 2.47 (1H, dt, $J = 2.8, 9.2$, 1H in $CH_2N$), 1.94–1.81 (1H, m, 1H in $CH_2CH_2$), 1.63–1.27 (3H, m, 3H in $CH_2CH_2$) |
| **5e** | *n*-$C_4H_9$ | | Oil | −87.9 (0.84) | 322 | 7.54–7.15 (10H, m, aromatic), 4.67 (1H, t, $J = 5.1$, NCHO), 4.39 (1H, t, $J = 6.4$, CHN), 3.17–3.05 (1H, m, 1H in $CH_2N$), 2.79 (1H, dt, 1H, $J = 7.3, 10.4$, 1H in $CH_2N$), 1.88–0.85 (13H, m, $CH_2CH_2$ and $(CH_2)_3CH_3$) |
| **5f** | H | 81 | 84–85 | −325 (1.10) | 266 | 7.53–7.12 (10H, m, aromatic), 4.50 (1H, d, $J = 6.1$, 1H in $NCH_2O$), 4.44 (1H, dd, $J = 7.2, 14.0$, CHN), 4.28 (1H, d, $J = 6.1$, H in $NCH_2O$), 3.31–2.20 (1H, m, 1H in $CH_2N$), 2.86–2.73 (1H, m, 1H in $CH_2N$), 1.74–1.62 (3H, m, 3H in $CH_2CH_2$), 1.28–1.11 (1H, m, 1H in $CH_2CH_2$) |

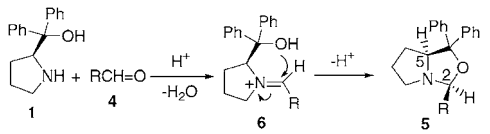
**TABLE 2** Elemental Analysis Data

| | | | *Cald.* | | | *Found* | | |
|---|---|---|---|---|---|---|---|---|
| *Compound* | *Molecular Formula* | *Molecular Weight* | *C* | *H* | *N* | *C* | *H* | *N* |
| **5a** | $C_{24}H_{23}NO$ | 341.45 | 84.42 | 6.79 | 4.10 | 84.16 | 6.59 | 4.07 |
| **5b** | $C_{24}H_{22}ClNO$ | 375.89 | 76.69 | 5.90 | 3.73 | 76.70 | 6.04 | 3.80 |
| **5c** | $C_{24}H_{22}ClNO$ | 375.89 | 76.69 | 5.90 | 3.73 | 76.37 | 5.92 | 3.67 |
| **5d** | $C_{25}H_{25}NO_2$ | 371.47 | 80.83 | 6.78 | 3.77 | 80.89 | 7.00 | 3.89 |
| **5e** | $C_{22}H_{27}NO$ | 321.46 | 82.20 | 8.47 | 4.36 | 82.01 | 8.59 | 4.18 |
| **5f** | $C_{18}H_{19}NO$ | 265.35 | 81.47 | 7.22 | 5.28 | 81.29 | 7.41 | 5.30 |

aldehyde, reported in Ref. [15]. The stereo-chemistry of the products was confirmed by NOE experiments [3]. For example, the NOE difference spectrum of product **5a** shows that the hydrogen atoms located at C2 and C5 have a cis relationship. The newly formed chiral carbon atom C2 can be assigned the (*S*)-configuration based on the known (*S*)-configuration of carbon atom C5 (Scheme 2). Although hydroxymethylpyrrolidinone undergoes this reaction to form *trans* 3,1-oxazabicyclo[3.3.0]octanone derivatives as reported in previous papers [1,3,13], in our case, 2-hydroxymethylpyrrolidine gives *cis* 3,1-oxazabicyclo[3.3.0]octanes. It is a useful method for the synthesis of *cis* 3,1-oxazabicyclo[3.3.0]octane derivatives.

## *EXPERIMENTAL*

Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario EL elemental analyzer. The $^1$H NMR spectra were recorded on a Varian Mercury 200 spectrometer with TMS as an internal standard, in $CDCl_3$. The IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in KBr pellets. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 341LC polarimeter with a thermally jacketed 10 cm cell (concentration *c* given as g/100 ml). TLC separations were performed on silica gel G plates with petroleum ether (60–90°C)/ethyl acetate (10:1) as eluent, and the plates were visualized with UV light. (*S*)-2-(Hydroxydiphenylmethyl)pyrrolidine was prepared according to the procedure given in Ref. [14].




**SCHEME 2** Stereospecificity in condensation reaction.

### *General Procedure for the Synthesis of (S,S)-2-Substituted-4,4-diphenyl-3,1-oxazabicyclo[3.3.0]octanes* **5a–e** *and (S)-4,4-Diphenyl-3,1-oxazabicyclo[3.3.0]-octanes* **5f**

A mixture of (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine (**1**) (200 mg, 0.8 mmol), aldehyde **4** (0.9 mmol), and *p*-toluenesulfonic acid (PPTS) (20 mg, 0.1 mmol) in toluene (20 ml) was refluxed using a Dean–Stark water separator and by vigorous stirring in an oil bath. After 4 h, the collection of water was stopped. The cooled reaction mixture was washed with saturated aqueous sodium bicarbonate solution (2 × 10 ml), saturated sodium bisulfite solution (2 × 10 ml), water, and brine. The organic layer was dried over sodium sulfate and concentrated to afford an oily residue. It was separated on a silica gel column with a mixture of petroleum ether (60–90°C)/ethyl acetate (10:1) as the eluent to give colorless crystals of **5**.

## *REFERENCES*

[1] Beard, M. J.; Bailey, J. H.; Cherry, D. T.; Moloney, M. G.; Shim, S. B.; Statham, K. A.; Bamford, M. J.; Lamont, R. B. Tetrahedron 1996, 52, 3719.
[2] Baldwin, J. E.; Moloney, M. G.; Shim, S. B. Tetrahedron Lett, 1991, 32, 1379.
[3] Bailey, J. H.; Cherry, D. T.; Crapnell, K. M.; Moloney, M. G.; Shim, S. B.; Bamford, M. J.; Lamont, R. B. Tetrahedron 1997, 53, 11731.
[4] Bailey, J. H.; Byfield, A. T. J.; Davis, P. J.; Foster, A. C.; Leech, M.; Moloney, M. G.; Muller, M.; Prout, C. K. J Chem Soc, Perkin Trans 1, 2000, 1977.
[5] Poli, G.; Ciofi, S.; Maccagni, E.; Sardone, N. Tetrahedron Lett 1995, 36, 8669.
[6] Keusenkothen, P. F.; Smith, M. B. Synth Commun 1992, 20, 2935.
[7] Harkin, S. A.; Jones, R. H.; Tapolczay, D. J.; Thomas, E. J. J Chem Soc, Perkin Trans 1, 1989, 489.

[8] Tomioka, K.; Hamada, N.; Suenaga, T.; Koga, K. J Chem Soc, Perkin Trans 1 1990, 426.
[9] Fleming, I.; Kindon, N. D. J Chem Soc, Chem Commun 1987, 1177.
[10] Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. Tetrahedron Lett 1992, 33, 7819.
[11] Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. Tetrahedron 1992, 48, 2143.
[12] Augier, C.; Malara, L.; Lazzeri, V.; Waegell, B. Tetrahedron Lett 1995, 36, 8775.
[13] Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. J Org Chem 1986, 51, 3140.
[14] Kanth, J. V. B.; Periasamy, M. Tetrahedron 1993, 49, 5127.
[15] Panek, J. S.; Masse, C. E. J Org Chem 1998, 63, 2382.