

# Synthesis and configuration determination of enantiomerically pure 4,10-di-substituted Tröger's base derivatives

Zhong Jin,<sup>a,\*</sup> Su-Xian Guo,<sup>a</sup> Xiao-Peng Gu,<sup>a</sup> Ling-Ling Qiu,<sup>a</sup> Gui-Ping Wu,<sup>a</sup> and Jian-Xin Fang<sup>a,b</sup>

<sup>a</sup> Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

<sup>b</sup> State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

E-mail: [zjin@nankai.edu.cn](mailto:zjin@nankai.edu.cn)

---

## Abstract

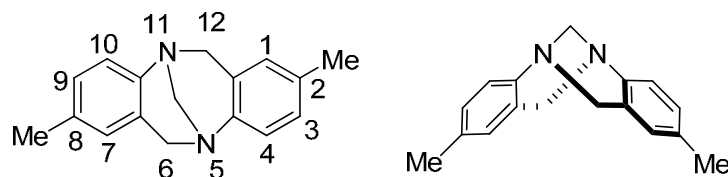
A practical and scalable method for synthesis and resolution of 4,10-di-substituted Tröger's base derivatives is described. By combination of circular dichroism (CD) spectra and X-ray diffraction (XRD) analysis method, the absolute configuration on two stereogenic nitrogen atoms of the crucial intermediate (–)-diastereomer is assigned as 5*S*,11*S*.

**Keywords:** Tröger's base, stereogenic nitrogen atom, resolution, absolute configuration

---

## Introduction

Tröger's base **1**, (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine), first synthesized by Julius Tröger in 1887,<sup>1</sup> is a rigid, *C*<sub>2</sub>-symmetric chiral molecule with a V-shape concave due to stereogenic pyramidal geometry on two nitrogen atoms (Scheme 1). As the first chiral tertiary amine molecule, **1** had been resolved by Prelog and Wieland in 1944.<sup>2</sup> The unique structural features, including *C*<sub>2</sub>-symmetry, high rigidity, and a folded geometry with two aromatic ring planes almost perpendicular to each other, have made **1** and its analogues very intriguing for the application<sup>3,4</sup> as chiral solvating agents,<sup>5,6</sup> artificial receptors in molecular recognition,<sup>7,8</sup> DNA molecular probes,<sup>9-11</sup> chiral tethers for the regio- and stereoselective tether-directed remote functionalization of fullerenes,<sup>12-14</sup> and chiral ligands for asymmetric catalysis.<sup>15-17</sup>



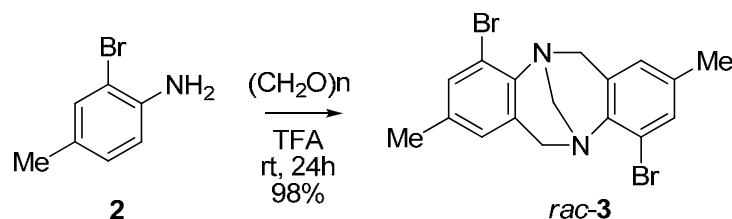
**Scheme 1.** The structure of Tröger's base **1**.

Due to ready racemization via the formation of an iminium intermediate under the acidic condition,<sup>18</sup> the resolution of Tröger's base derivatives using chiral acids as the resolving agents, by fractional crystallization of diastereomeric salts, was considered as unfeasible for a long period. However, Tröger's base **1** has been resolved successfully in 1991 by formation of a diastereomeric salt of (+)-**1** and (–)-1,1'-bi-naphthyl phosphoric acid via a crystallization-induced asymmetric transformation (CIAT),<sup>6</sup> which revealed considerable controversy in this issue. Recently, through diastereomeric salt formation of racemic **1** and (–)-di-*O,O'*-*p*-benzoyl tartaric acid (DBTA), both enantiomers of Tröger's base were readily available on a multigram scale.<sup>19</sup> In addition, a few successful examples, including application of enantiomerically pure DBTA or di-*O,O'*-*p*-toluoyl tartaric acid (DTTA) in diastereomeric salt formations of an acridine-substituted analogue of Tröger's base,<sup>9</sup> an 5,11-ethano-bridged derivative,<sup>20</sup> and a naphthyl-substituted derivative,<sup>21</sup> have been reported on the resolution of functionalized analogues of Tröger's base. On the other hand, other solvating methods, such as preparative chromatographic methods,<sup>22</sup> conglomerate crystallization of bis-*ortho*-methyl derivatives of Tröger's base,<sup>23</sup> and crystallization-induced asymmetric transformation (CIAT) of an *N*-methylpyrrole analogue of Tröger's base in the absence of a chiral solvating agent,<sup>24</sup> have been devised to produce the enantiomerically pure Tröger's base derivatives.

Although several types of difunctionalized derivatives of Tröger's base, have been obtained for their enantiomerically pure forms by preparative or semi-preparative chromatography methods,<sup>12-14, 25-27</sup> the availability of enantiomerically pure Tröger's base derivatives on the synthetically useful scale is still limited, which encumbered largely their practical utility. We herein reported an efficient and practical method for synthesis and resolution of 4,10-di-substituted Tröger's base derivatives. In addition, based on the circular dichroism spectra (CD) and X-ray diffraction analysis method (XRD), the absolute configuration on the stereomeric *N*-atom centers of these compounds was assigned.

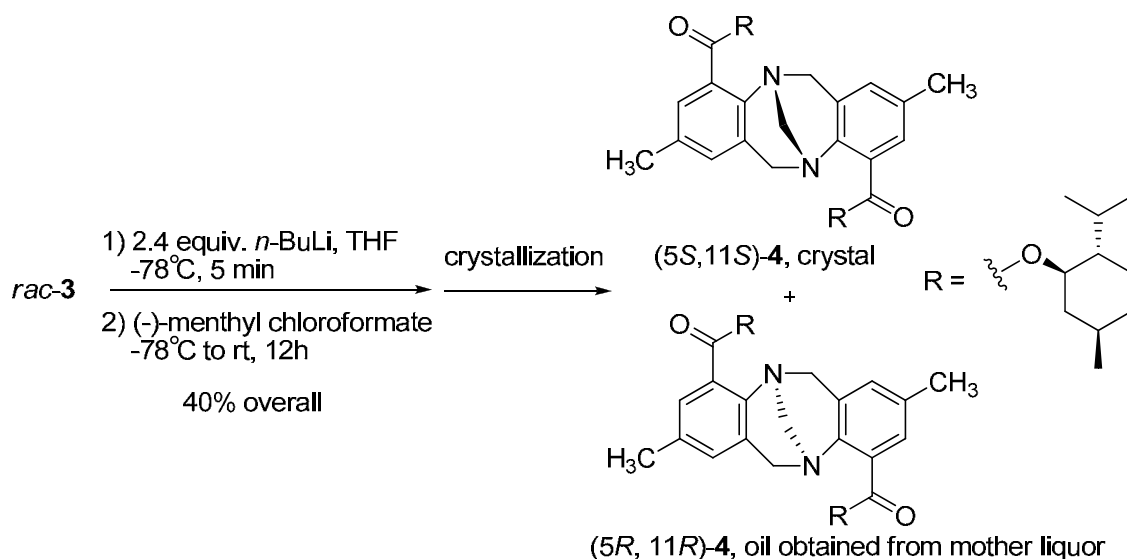
## Results and Discussion

Starting from 2-bromo-4-methylaniline **2** which was prepared from *p*-toluidine, *rac*-(±)-**3** was synthesized in nearly quantitative yield by condensation of **2** with paraformaldehyde in trifluoroacetic acid (TFA) according to the procedure described by Wärnmark (Scheme 2).<sup>28</sup>



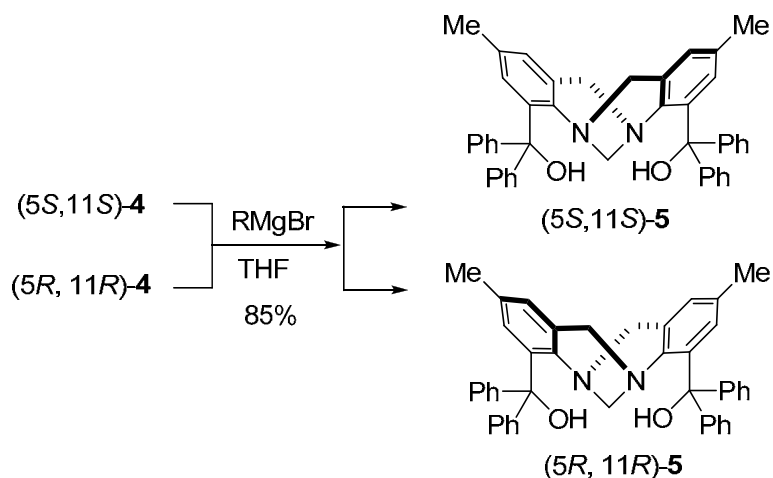
**Scheme 2.** Synthesis of *rac*-3.

Initially, our attempt to optical resolution of *rac*-3 using several chiral acids has proven to be unsuccessful. We hypothesized that the bulkiness of two bis-*ortho* bromine atoms neighboring *N*-atoms should be responsible for this. Alternatively, by application of general protocols developed by Wärnmark,<sup>29</sup> double bromine-lithium exchanges of *rac*-3 were accomplished over 5 minutes using 2.4 equivalent *n*-butyllithium at  $-78^\circ\text{C}$  to afford the corresponding dilithiated intermediate, which was trapped with (–)-menthyl chloroformate to give a 1:1 mixture of two diastereomers (5*S*,11*S*)-4 and (5*R*,11*R*)-4 in modest yield (Scheme 3). To our delight, the two diastereoisomers (5*S*,11*S*)-4 and (5*R*,11*R*)-4 were readily separable by silica gel column chromatography. Furthermore, it is noteworthy that, fractional crystallization of the mixture of two diastereomers from diethyl ether gave only the single diastereomer (5*S*,11*S*)-2 as a colorless crystal, while optical pure (5*R*,11*R*)-2 can be obtained as a pale yellow oil from the mother liquor after simple silica gel column chromatography.



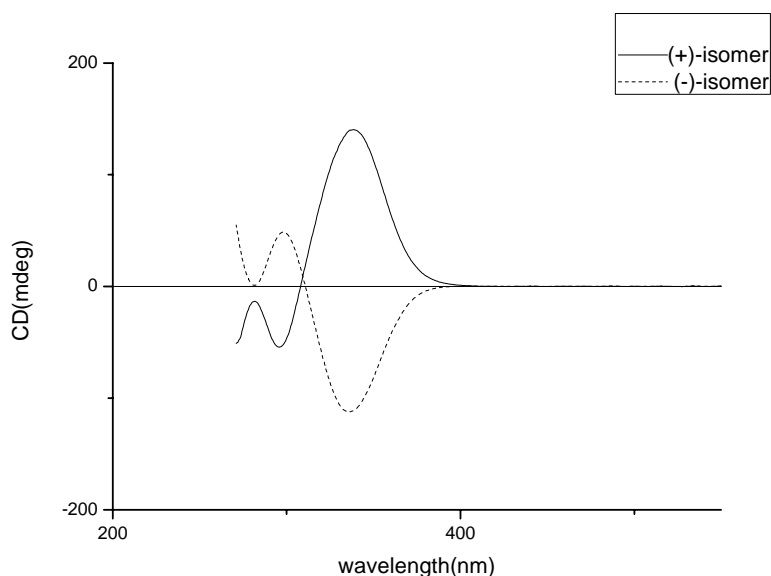
**Scheme 3.** Synthesis and separation of (5*S*,11*S*)-4 and (5*R*,11*R*)-4.

Enantiomerically pure esters 4, as the versatile intermediates, are suitable for further transformation into other optically pure Tröger's base derivatives such as another ester by exchange, the corresponding carboxylic acid, reduction to the corresponding primary alcohol, etc. For example, treatment of (5*S*,11*S*)-4 and (5*R*,11*R*)-4 with Grignard's reagent (PhMgBr) in THF smoothly produced enantiopure (5*S*,11*S*)-5 and (5*R*,11*R*)-5 in satisfying yields (Scheme 4).

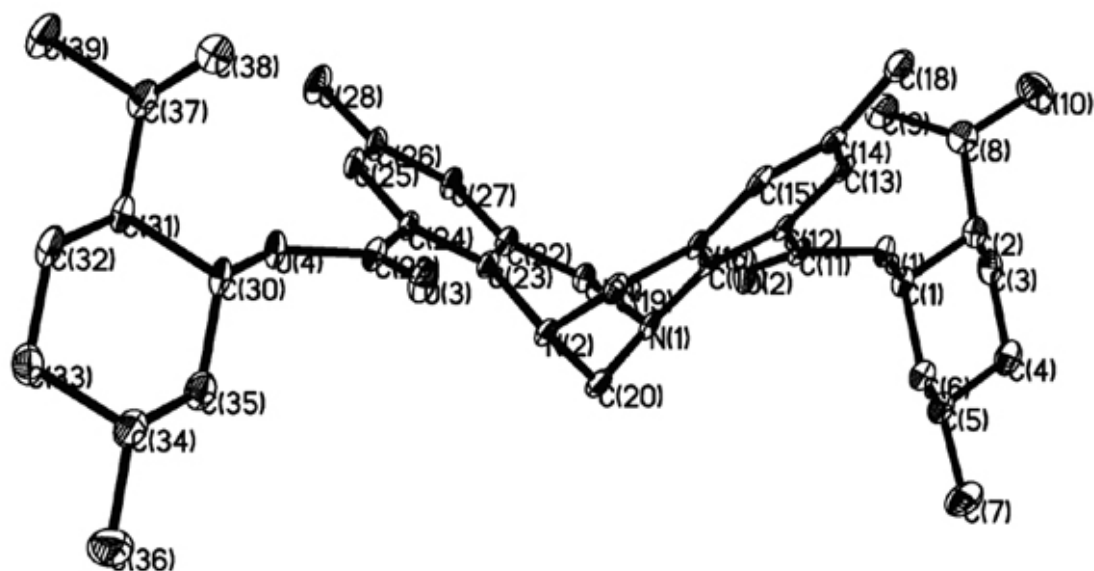


**Scheme 4.** Synthesis of  $(5S,11S)\text{-5}$  and  $(5R,11R)\text{-5}$ .

Historically, the absolute configuration of  $(+)\text{-1}$  was wrongly assigned to  $5R,11R$  by the circular dichroism (CD) and optical rotatory dispersion spectra.<sup>30-32</sup> Subsequently, X-ray diffraction (XRD) analysis,<sup>6</sup> vibrational CD and optical rotatory calculation,<sup>33-35</sup> and DFT computational studies<sup>36</sup> finally revised the absolute configuration of  $(+)\text{-1}$  to be  $5S,11S$ . Firstly, The absolute configuration of  $(-)\text{-4}$  was assigned tentatively as  $(5S,11S)$  based on the close similarity of its CD spectrum with that of  $(+)\text{-(5S,11S)-1}$  (Figure 1).<sup>13,14</sup> The absolute configuration of the latter was undoubtedly determined previously by X-ray diffraction analysis. Subsequently, a suitable single crystal for XRD analysis of  $(-)\text{-4}$  was obtained from ether solution. Finally, the crystal structure of  $(-)\text{-4}$  provides the clear evidence for our abovementioned configuration assignment of  $(-)\text{-(5S,11S)-4}$  (Figure 2).



**Figure 1.** The CD spectra of  $(+)\text{-}$  and  $(-)\text{-4}$  at 293K (Jasco 715 spectrometer) in  $\text{CH}_2\text{Cl}_2$ .



**Figure 2.** The crystal structure of (–)-**4** (All hydrogen atoms are omitted for clarity).

## Conclusions

In conclusion, we have developed an expeditious and efficient approach to the enantiomerically pure 4,10-di-substituted Tröger's base derivatives. The absolute configuration of key intermediate (–)-**4** was assigned as *5S,11S* based on the circular dichroism (CD) spectra and XRD analyses. We believed that the present method is applicable for synthesis of enantiomerically pure derivatives of Tröger's base which may be used as chiral molecular recognition, chiral supramolecular construction, and chiral ligands for asymmetrical synthesis.

## Experimental Section

**General Procedures.** Unless otherwise indicated, all reactions were carried out under nitrogen. THF and ether were freshly distilled from sodium benzophenone ketyl. Toluene were freshly distilled from sodium. Dichloromethane and hexane were freshly distilled from  $\text{CaH}_2$ . Methanol was distilled from magnesium and  $\text{CaH}_2$ . Reactions were monitored by thin-layer chromatography (TLC) analysis. Optical rotations were measured with a Perkin–Elmer 241MC polarimeter or a Perkin–Elmer 341 polarimeter. HR-ESI-MS were obtained on a Varian QFT-ESI spectrometer. NMR spectra were run on a Bruker AM-300 or 400 spectrometer with TMS as internal standard. Elemental analyses were performed after crystallization at the test center in Nankai university, China. Column chromatographic separations were carried out by using Silica Gel H60 (200–300 mesh, Qingdao Haiyang Chemical Group Corporation, People's Republic of

China), HSGF254 silica gel TLC plates (Yantai Chemical Industrial Institute, People's Republic of China) were used for analytical TLC.

### Synthesis of (+)- and (-)-4

To a stirred solution of *rac*-**3** (12.2 g, 30 mmol) in THF (100 mL) cooled in  $-78^{\circ}\text{C}$  was added dropwise a solution of *n*-BuLi (2.5 M, 30 mL, 75 mmol) in *n*-hexane in 5 min by a syringe. During the procedure of addition, the temperature of reaction mixture was always keep under  $-75^{\circ}\text{C}$ . After completion of addition, reaction mixture was stirred for another 5 min at that temperature. Then, a solution of (-)-menthyl chloroformate (16.4 g, 75 mmol) in THF (20 mL) was added in one portion by the syringe. The cooling bath was removed off and reaction mixture was warmed to room temperature and stirred overnight. Water (20 mL) was added to quench the reaction and most volatile was removed under vacuum. The residue was extracted with dichloromethane (50 mL  $\times$  3), organic phase combined was washed with water (40 mL) and saturated brine (40 mL) once, respectively. Organic phase was ultimately dried over anhydrous  $\text{MgSO}_4$ . After removal of organic solvent, residue was crystallized from diethyl ether (20 mL). More polar (-)-**4**, (3.2 g, 17 % yield), was isolated from the mother liquor by suction filtration as the colorless crystal. M.p.  $248\text{--}250^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}}^{20} = -230.0$  ( $c = 0.5$ ,  $\text{CH}_2\text{Cl}_2$ ), IR (KBr)  $\nu$  2954 (s), 2926 (m), 2868 (m), 1720 (vs), 1458 (s), 1295 (s), 1197 (vs), 1103 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (*d*- $\text{CHCl}_3$ )  $\delta$  7.48 (s, 2H), 6.88 (s, 2H), 4.99 (t,  $J = 10.5$  Hz, 2H), 4.68 (d,  $J = 17.3$  Hz, 2H), 4.38 (d,  $J = 19.0$  Hz, 2H), 4.35 (m, 2H), 2.26 (s, 6H), 2.22 (m, 2H), 2.08 (m, 2H), 1.75 (m, 4H), 1.58 (m, 4H), 1.15 (m, 4H), 0.96 (m, 14H), 0.88 (m, 6H);  $^{13}\text{C}$  NMR (*d*- $\text{CHCl}_3$ )  $\delta$  165.9 (s), 145.7 (s), 132.9 (s), 131.4 (d), 129.9 (d), 129.5 (s), 126.4 (s), 74.6 (d), 67.4 (t), 57.9 (t), 47.3 (d), 41.0 (t), 34.4 (t), 31.6 (q), 26.4 (d), 23.4 (t), 22.1 (d), 21.0 (q), 20.8 (q), 16.4 (q); HR-ESIMS:  $m/z$ : calcd. for  $\text{C}_{39}\text{H}_{54}\text{N}_2\text{O}_4$ : 615.4156 ( $\text{M}+\text{H}$ ) $^{+}$ ; found 615.4159 ( $\text{M}+\text{H}$ ) $^{+}$ . Anal. Calcd for  $\text{C}_{39}\text{H}_{54}\text{N}_2\text{O}_4$ : C, 76.18; H, 8.85; N, 4.56. Found: C, 76.29; H, 8.88; N, 4.52.

The filtrate was concentrated and subjected to column chromatography with 5% ethyl acetate in petroleum ether as an eluent. Another part of (-)-**4** (0.5 g) was obtained. Additionally, less polar (+)-**4** was separated as pale yellow oil (3.8 g, 20.6 % yield).  $[\alpha]_{\text{D}}^{20} = +210.0$  ( $c = 0.5$ ,  $\text{CH}_2\text{Cl}_2$ ), IR (KBr)  $\nu$  2953 (s), 2925 (m), 2866 (m), 1719 (vs), 1459 (s), 1294 (s), 1196 (vs), 1102 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (*d*- $\text{CHCl}_3$ )  $\delta$  7.45 (s, 2H), 6.88 (s, 2H), 4.98 (t,  $J = 11.2$  Hz, 2H), 4.68 (d,  $J = 17.9$  Hz, 2H), 4.37 (d,  $J = 10.4$  Hz, 2H), 4.36 (m, 2H), 2.25 (s, 6H), 2.21 (m, 2H), 2.06 (m, 2H), 1.74 (m, 4H), 1.57 (m, 4H), 1.14 (m, 4H), 0.95 (m, 14H), 0.87 (m, 6H);  $^{13}\text{C}$  NMR (*d*- $\text{CHCl}_3$ )  $\delta$  166.0 (s), 145.9 (s), 133.2 (s), 131.1 (d), 129.7 (d), 129.5 (s), 126.9 (s), 74.9 (d), 71.6 (t), 57.7 (t), 50.1 (d), 47.2 (d), 45.1 (t), 41.0 (t), 34.5 (t), 34.4 (t), 31.6 (q), 31.5 (q), 26.2 (d), 25.9 (d), 23.5 (t), 23.2 (t), 22.2 (d), 22.1 (d), 21.1 (q), 20.9 (q), 16.5 (q), 16.1 (q). HR-ESIMS:  $m/z$ : calcd. for  $\text{C}_{39}\text{H}_{54}\text{N}_2\text{O}_4$ : 615.4156 ( $\text{M}+\text{H}$ ) $^{+}$ ; found 615.4146 ( $\text{M}+\text{H}$ ) $^{+}$ . Anal. Calcd for  $\text{C}_{39}\text{H}_{54}\text{N}_2\text{O}_4$ : C, 76.18; H, 8.85; N, 4.56. Found: C, 76.19; H, 8.90; N, 4.50.

### Synthesis of 4,10-bis-*ortho*-substituted Tröger's base derivatives **5**

To a stirred solution of Grignard's reagent  $\text{PhMgBr}$  ( $c = 0.85 \text{ M}$ ,  $2.2 \text{ mL}$ ,  $105 \text{ mmol}$ ) in THF was added dropwise a solution of (–)-**4** ( $642 \text{ mg}$ ,  $1.05 \text{ mmol}$ ) in THF ( $5 \text{ mL}$ ) at  $-60^\circ\text{C}$ . After completion of addition, the mixture was stirred for  $6 \text{ h}$  at that temperature and then heated to reflux for  $1 \text{ h}$  and finally cooled to room temperature with ice-bath. Saturated solution of ammonium chloride was carefully added dropwise to quench the reaction. The stirring was not ceased until all solid was resolved. Organic layer was removed and water layer was extracted twice ( $10 \text{ mL}$ ) by diethyl ether. Organic phase combined was dried over anhydrous  $\text{MgSO}_4$ . After removal of organic solvent, the residue was subjected to column chromatography to produce (–)-**5** as a colorless solid,  $550 \text{ mg}$  ( $85.3\%$  yield,  $100\%$  ee). M.p.  $>300^\circ\text{C}$  (dec.),  $[\alpha]_{\text{D}}^{20} = -448.3$  ( $c = 1.0$ ,  $\text{CH}_2\text{Cl}_2$ ), IR (KBr)  $\nu$   $3159$  (br),  $3055$  (m),  $2305$  (w),  $1599$  (w),  $1447$  (s),  $1265$  (s),  $748$  (vs),  $702$  (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $d\text{-CHCl}_3$ )  $\delta$   $9.30$  (s, 2H),  $7.54$  (m, 4H),  $7.40$  (m, 6H),  $7.25$  (m, 10H),  $6.35$  (s, 2H),  $6.01$  (s, 2H),  $4.35$  (s, 2H),  $3.88$  (d,  $J = 17.7 \text{ Hz}$ , 2H),  $3.00$  (d,  $J = 17.7 \text{ Hz}$ , 2H),  $2.04$  (s, 6H);  $^{13}\text{C}$  NMR ( $d\text{-CHCl}_3$ )  $\delta$   $147.5$  (s),  $147.3$  (s),  $141.6$  (s),  $141.2$  (s),  $134.0$  (s),  $131.1$  (d),  $128.8$  (d),  $128.4$  (s),  $128.1$  (d),  $127.8$  (d),  $127.6$  (d),  $127.2$  (d),  $127.1$  (d),  $126.2$  (d),  $83.3$  (s),  $65.7$  (t),  $54.3$  (t),  $21.0$  (q). HR-ESIMS:  $m/z$ : calcd. for  $\text{C}_{43}\text{H}_{38}\text{N}_2\text{O}_2$ :  $615.3006$  ( $\text{M}+\text{H}^+$ ); found  $615.3000$  ( $\text{M}+\text{H}^+$ ). Anal. Calcd for  $\text{C}_{43}\text{H}_{38}\text{N}_2\text{O}_2$ : C,  $84.01$ ; H,  $6.23$ ; N,  $4.56$ . Found: C,  $84.10$ ; H,  $6.25$ ; N,  $4.59$ .

In a similar manner, (+)-**5** was prepared from (+)-**4** as a colorless solid with  $82\%$  yield ( $100\%$  ee). M.p.  $>300^\circ\text{C}$  (dec.),  $[\alpha]_{\text{D}}^{20} = +442.6$  ( $c = 1.0$ ,  $\text{CH}_2\text{Cl}_2$ ), IR (KBr)  $\nu$   $3632$  (br),  $3186$  (br),  $2952$  (m),  $1720$  (w),  $1447$  (s),  $1211$  (w),  $1105$  (m),  $701$  (vs)  $\text{cm}^{-1}$ ; HR-ESIMS:  $m/z$ : calcd. for  $\text{C}_{43}\text{H}_{38}\text{N}_2\text{O}_2$ :  $615.3006$  ( $\text{M}+\text{H}^+$ ); found  $615.3008$  ( $\text{M}+\text{H}^+$ ). Anal. Calcd for  $\text{C}_{43}\text{H}_{38}\text{N}_2\text{O}_2$ : C,  $84.01$ ; H,  $6.23$ ; N,  $4.56$ . Found: C,  $84.08$ ; H,  $6.23$ ; N,  $4.52$ . The enantiomeric purity of (+)- and (–)-**5** was analyzed by HPLC using a Chiral column and a sample of *rac*-**5** was prepared directly from *rac*-**3** by double bromine-lithium exchanges and subsequent quench with benzophenone. HPLC analysis of (+)- and (–)-**5** was carried out on a CHIRALCEL OD-H column using a mixture of *n*-hexan : *i*-propanol ( $93 : 7$ ) as mobile phase, flow rate:  $1 \text{ mL/min}$ . Retention times:  $t_{\text{R}} = 8.15 \text{ min}$  for (5*R*,11*R*)-isomer and  $t_{\text{R}} = 13.93 \text{ min}$  for (5*S*,11*S*)-isomer.

### Crystal structure determination of (–)-**4**

X-ray crystallographic analysis of (–)-(5*S*,11*S*)-**4**: Data were collected on a Bruker CCD diffractometer by using monochromated  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Programs used: Data collection: *CrystalClear*; cell refinement: *CrystalClear*; data reduction: *CrystalClear*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on carbon atoms were placed in calculated positions and refined isotropically by using a riding model. For some details of the crystallographic data of (–)-**4**, see Table 1. CCDC 704334 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

**Table 1.** Crystallographic data for (–)-(5*S*,11*S*)-**4**

	(–)-(5 <i>S</i> ,11 <i>S</i> )- <b>4</b>
formula	C <sub>39</sub> H <sub>54</sub> N <sub>2</sub> O <sub>4</sub>
<i>M<sub>r</sub></i>	614.84
<i>T</i> [K]	113 (2)
crystal system	monoclinic
space group	<i>P</i> 2(1)
crystal dimensions [mm]	0.24 × 0.20 × 0.16
<i>a</i> [Å], <i>α</i> [°]	13.373 (3), 0
<i>b</i> [Å], <i>β</i> [°]	8.5570 (17), 97.90 (3)
<i>c</i> [Å], <i>γ</i> [°]	15.912 (3), 0
<i>V</i> [Å <sup>3</sup> ]	1803.5 (6)
<i>Z</i> , <i>ρ</i> [mg m <sup>3</sup> ]	2, 1.132
<i>μ</i> [mm <sup>–1</sup> ]	0.07
<i>θ</i> range [°]	1.87–25.01
reflns measured	12198
reflns ( <i>R</i> <sub>int</sub> )	0.062
data/restraints/parameters	5900/1/415
final <i>R</i> indices	<i>R</i> <sub>1</sub> = 0.0617,
[ <i>I</i> > 2σ ( <i>I</i> )]	<i>wR</i> <sub>2</sub> = 0.1397
<i>R</i> indices (all data)	<i>R</i> <sub>1</sub> = 0.0745,
	<i>wR</i> <sub>2</sub> = 0.1516
absolute structure parameter <i>x</i>	–3.5 (14)

## Acknowledgements

Financial support from the National Natural Science Foundation of China (NNSFC) (Contract No. 20502012) and the Tianjin Commission of Science and Technology was gratefully acknowledged.

## References and Notes

1. Tröger, J. *J. Prakt. Chem.* **1887**, 36, 225–245.
2. Prelog, V.; Wieland, P. *Helv. Chim. Acta* **1944**, 27, 1127–1134.
3. (a) Demeunynck, M.; Tatibouët, A. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Gilchrist, T. L., Eds. Pergamon: Oxford, UK, 1999; pp. 1–20. (b) Dolensky, B.; Elguero, J.; Kral, V.; Pardo, C.; Valik, M. *Adv. Heterocycl. Chem.* **2007**, 93, 1.
4. Valik, M.; Strongin, R. M.; Kral, V. *Supramol. Chem.* **2005**, 17, 347.



5. Weber, E.; Müller, U.; Worsch, D.; Vögtle, F.; Will, G.; Kirfel, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1578.
6. Wilen, S. H.; Qi, J. Z.; Willard, P. G. *J. Org. Chem.* **1991**, 56, 485.
7. Goswami, S.; Ghosh, K. *Tetrahedron Lett.* **1997**, 38, 4503.
8. Goswami, S.; Ghosh, K.; Dasgupta, S. *J. Org. Chem.* **2000**, 65, 1907.
9. Tatibouët, A.; Demeunynck, M.; Andraud, C.; Collet, A.; Lhomme, J. *Chem. Commun.* **1999**, 161.
10. Bailly, C.; Laine, W.; Demeunynck, M.; Lhomme, J. *Biochem. Biophys. Res. Commun.* **2000**, 273, 681.
11. Baldeyrou, B.; Tardy, C.; bailly, C.; Colson, P.; Houssier, C.; Charmantray, F.; Demeunynck, M. *Eur. J. Med. Chem.* **2002**, 37, 315.
12. Sergeyev, S.; Diederich, F. *Angew. Chem. Int. Ed.* **2004**, 43, 1738.
13. Sergeyev, S.; Schär, M.; Seiler, P.; Lukyanova, O.; Echegoyen, L.; Diederich, F. *Chem. Eur. J.* **2005**, 11, 2284.
14. Wong, W. W. H.; Diederich, F. *Chem. Eur. J.* **2006**, 12, 3463.
15. Blaser, H. U.; Jalett, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, 122, 12675.
16. Harmata, M.; Kahraman, M. *Tetrahedron: Asymmetry* **2000**, 11, 2875.
17. Harmata, M.; Rayanil, K.; Barnes, C. L. *Surpramol. Chem.* **2006**, 18, 581.
18. Greenberg, A.; Molinaro, N.; Lang, M. *J. Org. Chem.* **1984**, 49, 1127.
19. Satishkumar, S.; Periasamy, M. *Tetrahedron: Asymmetry* **2006**, 17, 1116.
20. Harmada, Y.; Mukai, S. *Tetrahedron: Asymmetry* **1996**, 7, 2671.
21. Talas, E.; Margitfalvi, J.; Machytka, D.; Czugler, M. *Tetrahedron: Asymmetry* **1998**, 9, 4151.
22. For recent example see: Amanullah, M.; Mazzotti, M. *J. Chromatogr. A* **2006**, 1107, 36. For other more chromatographic separation methods for tröger's base **1**, see ref. 3 and 4.
23. Lenev, D. A.; Lyssenko, K. A.; Golovanov, D. G.; Malyshev, O. R.; Levkin, P. A.; Kotstyanovsky, R. G. *Tetrahedron Lett.* **2006**, 47, 319.
24. Valik, M.; Dolensky, B.; Herdtweck, E.; Kral, V. *Tetrahedron: Asymmetry* **2005**, 16, 1969.
25. Didier, D.; Tylleman, B.; Lambert, N.; Vande Velde, C. M. L.; Blockhuys, F.; Collas, A.; Sergeyev, S. *Tetrahedron* **2008**, 64, 6252.
26. Sergeyev, S.; Diederich, F. *Chirality* **2006**, 18, 707.
27. Kiehne, U.; Bruhn, T.; Schnakenburk, G.; Frohlich, R.; Bringmann, G.; Lutzen, A. *Chem. Eur. J.* **2008**, 14, 4246.
28. Jensen, J.; Warnmark, K. *Synthesis* **2001**, 1873.
29. Jensen, J.; Tejler, J.; Wärmarm, K. *J. Org. Chem.* **2002**, 67, 6008.
30. Cervinka, O.; Fabryova, A.; Novak, V. *Tetrahedron Lett.* **1966**, 5375.
31. Mason, S. F.; Schofield, K.; Wells, R. J.; Whitehurst, J. S.; Vane, G. W. *Tetrahedron Lett.* **1967**, 137.
32. Mason, S. F.; Vane, G. W.; Schofield, K.; Wells, R. J.; Whitehurst, J. S. *J. Chem. Soc. (B)* **1967**, 553.
33. Aamouche, A.; Devlin, F. J.; Stephens, P. J. *Chem. Commun.* **1999**, 361.

34. Aamouche, A.; Devlin, F. J.; Stephens, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 2346.
35. Giorgio, E.; Viglione, R. G.; Zanasi, R.; Rosini, C. *J. Am. Chem. Soc.* **2004**, *126*, 12968.
36. Pardo, C.; Alkorta, I.; Elguero, J. *Tetrahedron: Asymmetry* **2006**, *17*, 191.