Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1116–1119

A convenient method for the synthesis and resolution of Tröger base

Sakilam Satishkumar and Mariappan Periasamy*

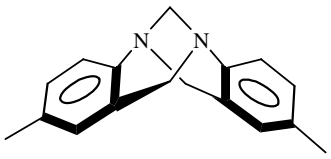
School of Chemistry, University of Hyderabad, Central University PO, Hyderabad 500 046, India

Received 13 March 2006; accepted 5 April 2006
Available online 6 May 2006

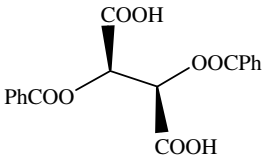
Abstract—Racemic Tröger base **1** can be readily obtained by the condensation of 4-toluidine and paraformaldehyde in the presence of Lewis acids and easily resolved via the preparation of diastereomeric aggregates using chiral dibenzoyl-L-tartaric acid **2**.

1. Introduction

Tröger base **1**,[1] a molecule containing chiral nitrogen centres exists in two enantiomeric forms. Due to its rigid and concave shape, it has attracted a large amount of research over the last several decades.[2] Its chiral nature was first identified by Prelog and Wieland in 1944. These authors separated the two enantiomers through chromatographic resolution on a D-lactose hydrate column followed by fractional crystallization.[3] Most of the hitherto reported methods of resolution of **1** are based on such chromatographic separation techniques.[4] It was thought that the accessibility of the enantiomers of **1** in preparative quantities might lead to substantial increases in the utility of this interesting chiral base for synthetic applications. During our research efforts on the development of new resolution procedures to access important chiral diols,[5] amino alcohols[6] and diamines,[6,7] we herein report a simple and high yielding synthesis and resolution of Tröger base **1** (Fig. 1).



Tröger's base **1**



Dibenzoyl-L-tartaric acid **2**

Figure 1.

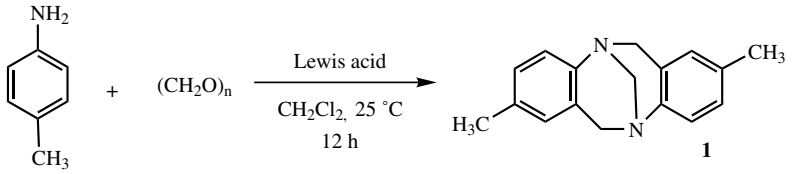
2. Results and discussion

The 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine, Tröger base **1**, was first prepared by Tröger in 1887 and it was structurally characterized by Spielman in 1935. Generally, the Tröger base was prepared by the condensation of 4-toluidine and formaldehyde in dilute aqueous acids.[8] Other synthetic methods have also been developed, but most of them are low yielding and involve tedious extraction procedures.[9] Since the formation of Tröger base goes through an electrophilic substitution reaction, Lewis acids should also promote the reaction. Accordingly, we examined the reaction of 4-toluidine and paraformaldehyde as a methylene group equivalent in the presence of $TiCl_4$. The Tröger base was obtained in 63% yield in this reaction (Scheme 1). The reaction was also carried out using various other Lewis acids and the results are summarized in Table 1.

It has been reported that the resolution of **1** via the formation of diastereomeric salt is not feasible when using chiral acids as it is a weak base.[10] However, we have observed that the Tröger base can be readily resolved via the preparation of hydrogen bonded aggregates by using dibenzoyl-L-tartaric acid (DBTA). We examined the resolution in various solvents such as CH_2Cl_2, ethyl acetate, acetonitrile and THF. In all cases, the partially resolved Tröger base was readily obtained when racemic **1** and resolving agent **2** are used in a 1:2 ratio. Optimum results were obtained in acetone when the racemic Tröger base **1** and dibenzoyl-L-tartaric acid **2** were used in a 1:3 ratio (Scheme 2). After digestion of the precipitate fraction, the (*R*,*R*)-isomer of the Tröger base was obtained in 91% ee while from the filtrate fraction, the (*S*,*S*)-isomer was obtained in 41% ee.

* Corresponding author. Tel.: +91 40 231 34814; fax: +91 40 230 12460; e-mail: mpsc@uohyd.ernet.in

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.04.002



Scheme 1.

Table 1. Synthesis of **1** using various Lewis acids[a]

Entry	Lewis acid	Time (h)	Yield[b] **1** (%)
1	$TiCl_4$	12	63
2	$AlCl_3$	8	73
3	$SnCl_4$	12	58
4	$ZnCl_2$	12	43
5	$ZrCl_4$	36	38

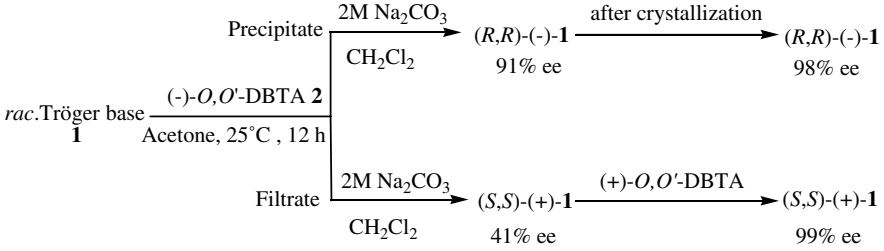
[a] All the reactions were carried out using 4-toluidine (10 mmol), paraformaldehyde (20 mmol) and Lewis acid (10 mmol) in CH_2Cl_2 (40 mL).
[b] The product was identified by spectral data (IR, ^{1}H NMR, ^{13}C NMR); the yields are of isolated products.

The (*R*,*R*)-isomer was obtained in 98% ee by crystallization of the sample of 91% ee. The (*S*,*S*) isomer was easily enriched by repeating the experiment using dibenzoyl-D-tartaric acid. The results are summarized in Table 2.

The precipitated diastereomeric complex **3** [(−)-**1**·(−)-**2**] (Table 2, entry 3) was crystallized from methanol solvent and the X-ray structure analysis was then carried out (Fig. 2).[11] The asymmetric unit of the crystal structure contains one molecule of Tröger base and one molecule of dibenzoyl-L-tartaric acid (1:1). The carboxylic acid moieties of the (−)-DBTA donate the protons to nitrogen acceptors of the Tröger base, making two separate strong O–H···N interactions. The bond lengths of the carboxylic acid groups in the (−)-DBTA–Tröger base complex **3** are C26–O3 = 1.197 Å, C26–O4 = 1.312 Å; C28–O6 = 1.195 Å, and C28–O5 = 1.321 Å, indicating the presence of C=O and C–OH groups in the complex. Hence, it is clear from the X-ray data[11] that the diastereomeric complex formed is not a salt but a hydrogen bonded aggregate (Fig. 3). Thus, the precipitation occurred because of aggregation due to strong O–H···N hydrogen bonding interactions (O4–H4···N1, 2.678(2) Å, 179°; O5–H5··· N2, 2.646(2) Å, 164°) between the Tröger base and the resolving agent. The configuration of (−)-**1** was determined relative to the chiral acid (*R*,*R*)-(−)-**2** used, as (5*R*,11*R*).[12]

3. Conclusion

In conclusion, we have developed a convenient method to readily access racemic Tröger base and devised a method for the resolution of the racemic Tröger base by using the



Scheme 2.

Table 2. Resolution of racemic Tröger base **1** using dibenzoyl-L-tartaric acid **2**

Entry	Tröger base **1** mmol (% ee)	Chiral acid **2** (mmol)	Acetone (mL)	Tröger's base **1** obtained from			
				Precipitate		Filtrate	
				% ee[a]/conf.	Yield[b] (%)	% ee[a]/conf.	Yield[b] (%)
1	2 (00)	4	6	81 (*R*,*R*)	32	28 (*S*,*S*)	64
2	2 (00)	6	6	86 (*R*,*R*)	34	18 (*S*,*S*)	64
3	2 (00)	8	6	>98[c] (*R*,*R*)	31	39 (*S*,*S*)	62
4[d]	2 (39)	8	6	99[c] (*S*,*S*)	42	6 (*R*,*R*)	56
5	5 (00)	15	15	98[c] (*R*,*R*)	39	41 (*S*,*S*)	58
6[d]	5 (41)	15	15	99[c] (*S*,*S*)	62	12 (*R*,*R*)	45

[a] The enantiomeric purities were based on the HPLC analysis by using a CHIRALCEL OJ-H column.[18]
[b] The yields are of isolated products.
[c] These ee's are after one recrystallization from acetone and hexane mixture.
[d] In these experiments, dibenzoyl-D-tartaric acid was used as a resolving agent.

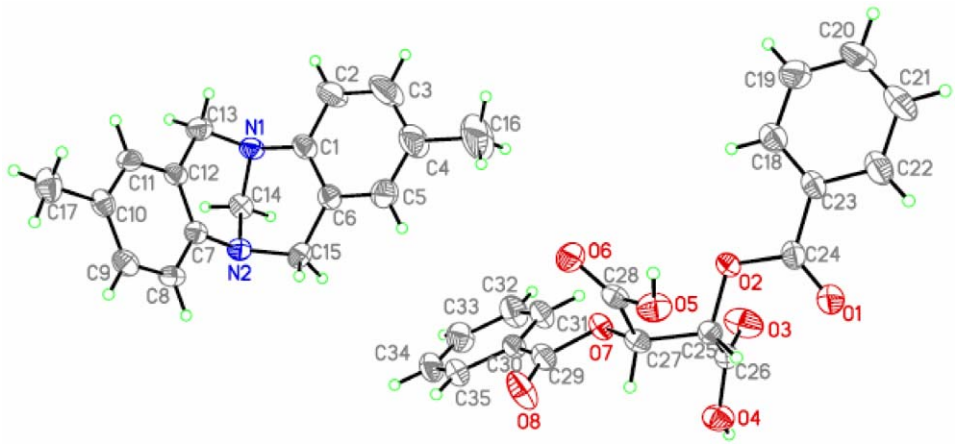


Figure 2. ORTEP representation of the crystal structure of complex **3** [(−)-**1**·(−)-**2**]. (Thermal ellipsoids are drawn at 35% probability and all the hydrogen atoms are unlabelled for clarity.)

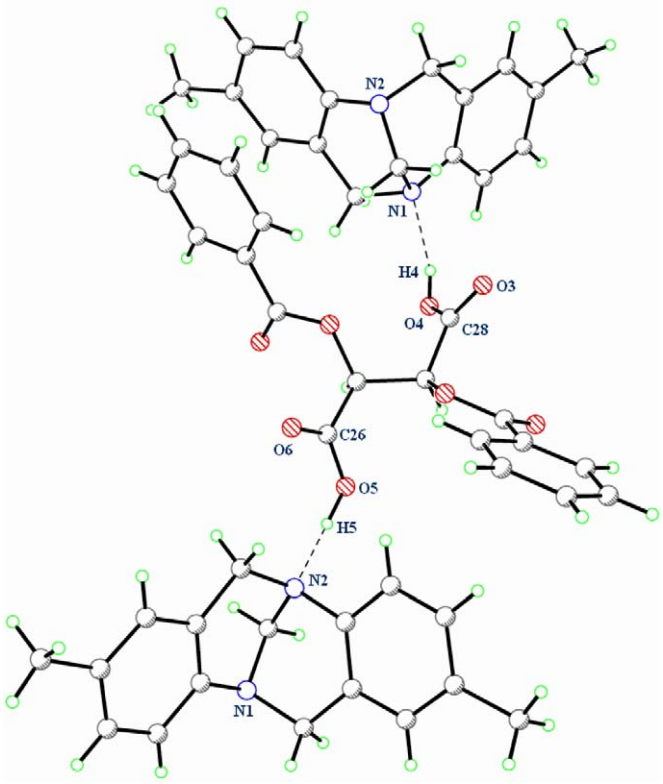


Figure 3. Packing diagram of complex **3** [(−)-**1**·(−)-**2**], indicating the strong O–H···N hydrogen bonding interactions.

readily available and recoverable dibenzoyl-L-tartaric acid. In recent years, this interesting chiral molecule has been used as a ligand in asymmetric catalysis,[13] as a chiral solvating agent[12] and in molecular replication studies.[14] Furthermore, it has been used to design hosts in the molecular recognition phenomenon,[15] biomimetic systems[16] and chiral molecular tweezers.[17] The enantiomers of the Tröger base are commercially available but somewhat expensive. However, the enantiopure Tröger base can now be easily accessed via the method described herein, and has considerable potential for further exploitation.

4. Experimental

4.1. Preparation of racemic Tröger's base 1

To a solution of 4-toluidine (1.07 g, 10 mmol) and paraformaldehyde (0.60 g, 20 mmol) in CH_2Cl_2 (40 mL) was added $TiCl_4$ (10 mmol) under a N_2 atmosphere. The reaction mixture was allowed to stir for 12 h at 25 °C and quenched with saturated K_2CO_3 solution (10 mL). The reaction mixture was extracted in CH_2Cl_2 (50 mL) and the combined organic extracts were successively washed with water, brine solution and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on alumina (basic) column using 10% ethyl acetate in hexane to elute the desired Tröger base **1**, yield: 790 mg (63%); mp 135–137 °C (lit.[8] mp 135–136); IR (KBr): 3150, 1493, 1431, 1325, 1207, 1095, 960, 896, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (d, 2H, $J = 8.2$ Hz), 6.95 (d, 2H, $J = 8.1$ Hz), 6.70 (s, 1H), 4.64 (d, 2H, $J = 16.6$ Hz), 4.30 (s, 2H), 4.10 (d, 2H, $J = 16.6$ Hz), 2.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.4, 133.3, 128.0, 127.4, 127.2, 124.7, 67.0, 58.6, 20.7. A similar experimental procedure was also followed using other Lewis acids (Table 1).

4.2. Resolution of Tröger's base 1 using dibenzoyl-L-tartaric acid

The dibenzoyl-L-(+)-tartaric acid (5.37 g, 15 mmol) and racemic Tröger base **1** (1.25 g, 5 mmol) were taken in acetone (15 mL) and the contents stirred at 25 °C for 12 h. The precipitate was collected and suspended in a mixture of CH_2Cl_2 (20 mL) and 2 M Na_2CO_3 and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated to obtain the product (*R*,*R*)-**1** enantiomer (0.485g, 39% yield, 91% ee). The filtrate was concentrated and the residue was treated as outlined above to obtain the (*S*,*S*)-**1** enantiomer (0.725g, 58% yield, 41% ee). The (*R*,*R*)-**1** isomer (91% ee) was recrystallized from an acetone and hexane mixture to obtain a sample of 98% ee $[\alpha]_D^{25} = -301$

(c 0.22, hexane), lit.[12] $[\alpha]_D^{25} = -307$ (c 0.31, hexane). The (S,S)-**1** isomer with 41% ee was further enriched by repeating the resolution experiment using dibenzoyl-D-tartaric acid to obtain the sample of 99% ee. $[\alpha]_D^{25} = +279$ (c 0.22, hexane), lit.[12] $[\alpha]_D^{25} = +287 \pm 7$ (c 0.281, hexane). The samples were also analyzed by HPLC using a chiral column to assess the enantiomeric purities.[18]

Acknowledgements

We thank the CSIR (New Delhi), for a research fellowship to S.S.K. We also thank the DST for the 400 MHz NMR facility under FIST program and for the National single crystal X-ray difractometer facility. Support of the UGC under the 'University of Potential for Excellence' and the Center for Advanced Study (CAS) programs is gratefully acknowledged.

References

1. Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225–245.
2. Bag, B. G. *Curr. Sci.* **1995**, *68*, 279–288.
3. Prelog, V.; Wieland, P. *Helv. Chim. Acta* **1944**, *27*, 1127–1134.
4. Hesse, G.; Hargel, R. *Liebigs Ann. Chem.* **1976**, 996–1008; Lindner, K. R.; Mannschreck, A. *J. Chromatogr.* **1980**, *193*, 308–310; Saigo, K.; Chen, Y.; Kubota, N.; Tachibana, K.; Yonezawa, N.; Hasegawa, M. *Chem. Lett.* **1986**, 515–518.
5. Periasamy, M.; Venkatraman, L.; Sivakumar, S.; Sampath Kumar, N.; Ramanathan, C. R. *J. Org. Chem.* **1999**, *64*, 7643–7645; Periasamy, M.; Ramanathan, C. R.; Bhanu Prasad, A. S.; Bhaskar Kanth, J. V. *Enantiomer* **1998**, *3*, 3–7; Periasamy, M.; Venkatraman, L.; Thomas, K. R. J. *J. Org. Chem.* **1997**, *62*, 4302–4306; Venkatraman, L.; Periasamy, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2471–2474; Periasamy, M.; Bhanu Prasad, A. S.; Bhaskar Kanth, J. V.; Kishan Reddy, Ch. *Tetrahedron: Asymmetry* **1995**, *6*, 341–344.
6. Periasamy, M.; Sivakumar, S.; Reddy, M. N.; Padmaja, M. *Org. Lett.* **2004**, *6*, 265–268; Periasamy, M.; Reddy, M. N.; Anwar, S. *Tetrahedron: Asymmetry* **2004**, *15*, 1809–1812; Periasamy, M.; Sivakumar, S.; Reddy, M. N. *Synthesis* **2003**, *13*, 965–967; Periasamy, M.; Ramanathan, C. R.; Sampath Kumar, N. *Tetrahedron: Asymmetry* **1999**, *10*, 2307–2310.
7. Padmaja, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2437–2441; Periasamy, M.; Sreenivasaperumal, M.; Padmaja, M.; Rao, V. D. *ARKIVOC* **2004**, *8*, 4–11.
8. Spielman, M. A. *J. Am. Chem. Soc.* **1935**, *57*, 583–585.
9. Li, Z.; Xu, X.; Peng, Y.; Jiang, Z.; Ding, C.; Qian, X. *Synthesis* **2005**, *8*, 1228–1230; Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 98–104.
10. Mason, S. F.; Vane, G. W.; Schofield, K.; Wells, R. J.; Whitehurst, J. S. *J. Chem. Soc. B* **1967**, 553–556; Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge Univ. Press: Cambridge, UK, 1982; p 191.
11. Crystal data: For complex (−)-**1**·(−)-**2** molecular formula: $C_{35}H_{32}N_2O_8$, MW = 608.63, monoclinic, space group: $P2_1$, $a = 8.1272(6)$ Å, $b = 18.1103(14)$ Å, $c = 10.4433$ (8) Å, $\beta = 90.5680(10)°$, $V = 1537.03$ Å^3, $Z = 1$ ($Z = 0$), $\rho_c = 1.315$ mg m^{-3}, $\mu = 0.094$ mm^{-1}, $T = 293(2)$ K. Of the 18,006 reflections collected, 7210 were unique ($R_{int} = 0.0452$). Refinement on all data converged at $R_1 = 0.0438$, $wR_2 = 0.0667$ (Deposition number CCDC 600979).
12. Wilen, S. H.; Qi, J. Z. *J. Org. Chem.* **1991**, *56*, 485–487.
13. Harmata, M.; Kahaman, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2875–2879; Blaser, H. U.; Jalett, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675–12682.
14. Bag, B. G.; Kiedrowski, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 3713–3714.
15. Wilcox, C. S. *Tetrahedron Lett.* **1985**, *26*, 5749–5752; Bailly, C.; Laine, W.; Demeunynck, M.; Lhomme, J. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 681–685; Goswami, S.; Ghosh, K.; Dasgupta, S. *J. Org. Chem.* **2000**, *65*, 1907–1914; Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055–8057; Weber, E.; Muller, U.; Wrosch, D.; Vogtle, F.; Will, G.; Kirfel, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1578–1580.
16. Wilcox, C. S.; Geer, L. M.; Lynch, V. J. *J. Am. Chem. Soc.* **1987**, *109*, 1865–1867.
17. Pardo, C.; Sesmilo, E.; Gutierrez-Puebla, E.; Angeles, M. *J. Org. Chem.* **2001**, *66*, 1607–1611.
18. HPLC analysis of **1** was carried out on a CHIRALCEL OJ-H column using ethanol as mobile phase, flow rate: 0.5 mL/min. Retention times, $t_R = 12.15$ min for (S,S)-isomer and $t_R = 40.78$ min for (R,R)-isomer.