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Synthesis of Ethano-Tröger's Base, Configurationally Stable Substitute of Tröger's Base

Yasumasa Hamada[a]*and **Shiho Mukai**[b]

[a] Faculty of Pharmaceutical Sciences, Chiba University

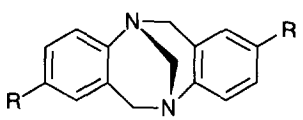
Yayoi-cho, Inage-ku, Chiba 263, Japan

[b] Faculty of Pharmaceutical Sciences, Nagoya City University

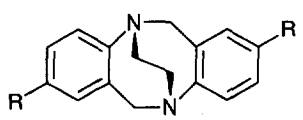
Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Abstract: Optically active ethano Tröger's base with configurationally stable stereogenic nitrogens and an ethylene bridge was synthesized by reaction with 1,2-dibromoethane and subsequent resolution using (-)- and (+)-di-*p*-toluoyl-D-tartaric acids from commercially available (±)-Tröger's base in one step.

Nitrogen-containing chiral compounds constitute a class of chiral auxiliaries for asymmetric synthesis and have been widely used for obtaining a variety of optically active compounds.[1] Among them, chiral amines bearing both stereogenic nitrogen and stereogenic carbon(s), such as cinchona alkaloids, are quite useful for catalytic asymmetric synthesis. Sharpless asymmetric dihydroxylation[2] and asymmetric phase transfer reactions[3] are typical transformations. However, to our knowledge, chiral amines with only stereogenic nitrogen(s) are only a few and remain to be developed. Tröger's base[4,5] **1** and its enantiomer are such amines with two stereogenic nitrogen atoms without any stereogenic carbons and are now commercially available. However, the use of these chiral amines **1** has been limited in the area of design and construction of molecular receptors[6,7] and no application of **1** to asymmetric synthesis has been reported.[8] In addition the racemization under acidic media through the iminium cation has been known.[9] As part of our efforts to search for a new chiral amine for asymmetric synthesis, we describe here a facile synthesis of ethano Tröger's base (-)-(*R,R*)-**2a** and (+)-(*S,S*)-**2a**, configurationally stable analogues of Tröger's base **1**, both in enantiopure form from commercially available (±)-**1**.

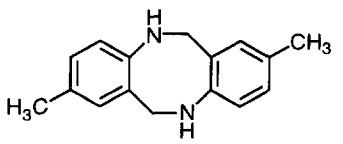


1a : R = CH_3 Tröger's base
b : R = OCH_3



2a : R = CH_3 ethanoTröger's base
b : R = OCH_3

First, we attempted to prepare (±)-**2a** by alkylation of the secondary diamine **3a** derived from **1** according to the literature.[6a] However, alkylation of **3a** with 1,2-dibromoethane in the presence of lithium carbonate in dimethyl formamide (DMF) failed to afford **2a** even at high temperature (150°C, DMF) or high pressure (ca. 10 kbar, 50°C) conditions. Next, we turned our attention to direct alkylation of the tertiary amine **1a** with 1,2-dibromoethane. The alkylation should take place through the ammonium ion **5** and the dibromide **6** from **1a** and give the homologated product **2a** along with dibromomethane. After considerable trials, we found that treatment of commercially available (±)-**1a** with 1,2-dibromoethane in the presence of lithium carbonate in DMF at 105°C for 12 h afforded the desired ethano Tröger's base (±)-**2a** in 76 % yield. Incidentally, high-pressure reaction of (±)-**1a** with 1,2-dibromoethane at 10kbar and 50°C for 38 h resulted in incomplete alkylation to give after workup the monoalkylated product **4** in moderate yield. The methoxy derivative (±)-**2b** was also obtained from (±)-**1b** under the similar conditions in 72 % yield.



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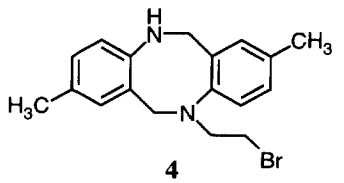
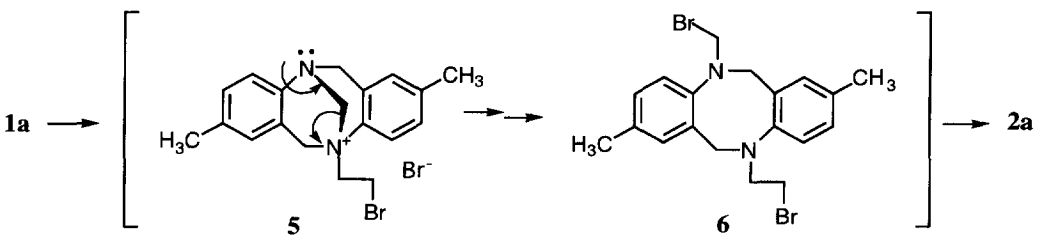


4



5 **6**

Resolution of (±)-**2a** was carried out by salt formation with (-)-di-*p*-toluoyl-D-tartaric acid ((-)-DTTA). Treatment of (±)-**2a** with (-)-DTTA (0.6eq) in acetone gave the (-)-**2a**•(-)-DTTA as colorless crystals. After one recrystallization of the crystals and base treatment of the obtained salt, the pure (-)-**2a** (100 %ee) was obtained in 36 % yield based on (±)-**2a**. The enantiomeric excess was clearly determined by a chiral column using HPLC. The above mother liquor was treated with base and thus obtained (+)-**2a** enriched material (80 %ee) was crystallized after addition of (+)-di-*p*-toluoyl-L-tartaric acid((+)-DTTA) to give the enantiomerically pure salt (+)-**2a**•(+)-DTTA. The salt afforded the pure (+)-**2a** (100 %ee) in 37 % yield from (±)-**2a**. The absolute configurations of both enantiomers (-)-**2a** and (+)-**2a** were determined to be (*R, R*)- and (*S, S*)-isomers by comparisons of their CD spectra[10] with the ones of (-)-(*R,R*)-**1a** and (+)-(*S,S*)-**1a**, respectively. Unfortunately, the attempts of resolution of the methoxy derivative **2b** by use of several optically active acids failed on the crystallization or the salt formation.

In summary we have accomplished preparation and characterization of optically active ethano Tröger's

bases, (-)-(*R,R*)-**2a** and (+)-(*S,S*)-**2a**, with configurationally stable stereogenic nitrogens. The applications of thus obtained (-)-(*R,R*)-**2a** and its enantiomer (+)-(*S,S*)-**2a** are under investigation.

Experimental Section

(±)-2,8-Dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine (±)-2a

To a stirred solution of commercially available (±)-**1** (50 g, 0.2 mol) in DMF (200 ml) was added Li_2CO_3 (66.4 g, 0.9 mol) and 1,2-dibromoethane (34.4 ml, 0.4 mol). The mixture was warmed to 105°C and stirred for 12 h. After cooling, the reaction mixture was diluted with EtOAc-benzene (4:1, 300 ml) and filtered through a celite pad. The filtrate was diluted with EtOAc-benzene (4:1, 1 l) and washed with water (300 ml x 2). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography and then recrystallization from benzene gave (±)-**2a** (40.2 g, 76%): mp 142-144°C ; IR ν_{max}(KBr): 1509, 1458 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ 2.17 (6H, s), 3.57 (4H, m), 4.47 (4H, ABq J=17.16Hz), 6.71 (2H, s), 6.86 (2H, d, J=8.25Hz), 6.99 (2H, d, J=7.92Hz). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 82.17; H, 7.75; N, 10.54.

(±)-2,8-Dimethoxy-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine (±)-2b

The same procedure as described above was applied to (±)-**1b** (282 mg, 1 mmol). The (±)-**2b** (214 mg, 72%) was obtained by column chromatography (silica gel BW-820MH, hexane:EtOAc=2:1~1:1) and then recrystallization from MeOH as pale orange crystals: mp 186-189°C; IR ν_{max}(KBr): 1044, 1024 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ 3.56 (4H, m), 3.68 (6H, s), 4.45 (4H, ABq, J=17.16Hz), 6.43 (2H, d, J=2.97Hz, ArH), 6.61 (2H, dd, J=7.42, 2.97Hz), 7.03 (2H, d, J=8.57Hz). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.84; H, 6.73; N, 9.50.

Resolution of (±)-2a

The (±)-**2a** (14.18 g, 53.64 mmol) and (-)-di-*p*-toluoyl-L-tartaric acid (12.4 g, 32.2 mmol, (-)-DTTA) were dissolved in hot acetone (200 ml). The mixture was stood at room temperature until crystallization, and the precipitates were recrystallized from acetone to give [2(-)-**2a**•(-)-DTTA] (9.27 g) as colorless crystals: mp 100-102°C; $[\alpha]^{24}_D$ = -116.5 (c 1.02, $CHCl_3$); IR ν_{max}(KBr): 1725, 1711, 1260 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ 2.09 (12H, s), 2.39 (6H, s), 3.61 (2H, m), 3.61 (8H, ABq, J=10.23Hz), 4.37 (8H, ABq, J=17.15Hz), 6.23 (2H, s), 6.46 (4H, s), 6.74 (4H, d, J=7.92Hz), 7.03 (4H, d, J=8.25Hz), 7.22 (2H, s), 8.15 (4H, d, J=7.91Hz), 12.08 (2H, brs, disappeared with D_2O). Anal. Calcd for $2C_{18}H_{20}N_2$•$C_{20}H_{18}O_8$: C, 73.50; H, 6.39; N, 6.12. Found: C, 73.49; H, 6.58; N, 5.88.

Thus obtained [2(-)-**2a**•(-)-DTTA] (9.27 g) was treated with saturated aqueous $NaHCO_3$ in CH_2Cl_2. The mixture was extracted with CH_2Cl_2 (100 ml x 3) and washed with brine (50 ml). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give (-)-**2a** (5.04 g, 36%, 100%ee) as colorless needles, which was recrystallized from MeOH: mp 118-119°C; $[\alpha]^{24}_D$ = -411 (c 1.02, $CHCl_3$); IR ν_{max}(KBr): 1497, 1493, 1175, 830 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ 2.17 (6H, s), 3.57 (4H, m), 4.47 (4H, ABq J=17.16Hz), 6.71 (2H, s), 6.86 (2H, d, J=8.25Hz), 6.99 (2H, d, J=7.92Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 54.8, 59.1, 127.6, 127.8, 129.2, 134.1, 136.5, 147.5. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.73; H, 7.71; N, 10.57.

The mother liquor from the above described separation of (-)-**2a** was concentrated and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give (+)-**2a** (7.75 g, 80.4%ee) as pale yellow solids. The solid and (+)-di-*p*-toluoyl-D-tartaric acid monohydrate (7.11 g, 17.6 mmol, (+)-DTTA•H_2O) were dissolved in hot acetone (100 ml). The mixture was stood at room temperature until crystallization to give [2(+)-**2a**•(+)-DTTA•$2H_2O$] (10.2 g) as colorless crystals: mp 98-100°C ; $[\alpha]^{24}_D$ = +126.9 (c 1.26, $CHCl_3$); IR ν_{max}(KBr): 1719, 1711, 1260 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ 2.10 (12H, s), 2.39 (6H, s), 3.61 (2H, m), 3.61 (8H, ABq, J=10.23Hz), 4.38 (8H, ABq J=17.16Hz), 6.21 (2H, s), 6.48 (4H, s), 6.75 (4H, d, J=7.92Hz), 7.03 (4H, d, J=7.92Hz), 7.22 (2H, s), 7.64 (2H, brs, disappeared with D_2O), 8.14 (4H, d, J=8.24Hz). Anal. Calcd for $2C_{18}H_{20}N_2$•$C_{20}H_{18}O_8$•$2H_2O$: C, 70.72; H, 6.57; N, 5.89. Found: C, 70.73; H, 6.64; N, 5.43.

The same procedure as described for (-)-**2a** was applied to [2(+)-**2a**•(+)-DTTA•$2H_2O$] (10.2 g) to give

(+)-**2a** (5.22 g, 37%, 100%ee) as colorless needles, which was recrystallized from MeOH: mp 118-119°C ; $[\alpha]^{24}_D$ = +415.8 (c 1.03, $CHCl_3$); IR ν_{max}(KBr): 1497, 1493, 1175, 830 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ 2.17 (6H, s), 3.57 (4H, m), 4.47 (4H, ABq J=17.16Hz), 6.71 (2H, s), 6.86 (2H, d, J=8.25Hz), 6.99 (2H, d, J=8.25Hz); ^{13}C NMR ($CDCl_3$) δ 20.721, 54.862, 59.157, 127.655, 127.871, 129.236, 134.124, 136.514, 147.547. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.91; H, 7.97; N, 10.55. MS m/z: 264 (M+), 132.

The enantiomeric excess of (+)-**2a** and (-)-**2a** was determined by HPLC analysis according to the following conditions. Column: CHIRALPAK OP(+) (0.46 φ x 25 cm, Daicel); solvent: MeOH; flow rate: 0.5 ml/min; detector: UV (254 nm); retention time: (+)-**2a**, 9.93 min; (-)-**2a**, 12.81 min.

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