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Preparation of the enantiomers of an *N*-methylpyrrole analogue of Tröger's base

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Abstract—The enantiomers of bis(1-phenylethyl)-4,9-methano-1,6-dimethyl-4,5,9,10-tetrahydro-1*H*,6*H*-dipyrrolo-[3,2-*b*:3′,2′-*f*][1,5]-diazocin-2,7-dicarboxylate were obtained by crystallization-induced asymmetric transformation (CIAT). The CIAT was driven by the absolute configuration of the 1-phenylethyl groups present in their covalent structure. Thus, the first example of CIAT on Tröger's base derivatives in the absence of a resolving agent is reported.

1. Introduction

The Tröger's base[1] (TB) derivatives (methano[1,5]-diazocine derivatives) are compounds containing two nitrogens with fixed tetrahedron arrangement of their moieties. This feature explains the unique V-shape geometry (81–104°) and the inherent chirality of the TB derivatives. These and other characteristics of TB derivatives have attracted the attention of supramolecular chemists, and encouraged them to incorporate TB units into skeletons of various receptors.[2–4] The receptors containing a TB unit have been found to be able to recognize both achiral[5,6] and chiral[7–9] analytes, and DNA.[10–12] The chiral applications are especially promising. Unfortunately, the enantiomerically pure TB derivatives with synthetically exploitable moieties suitable for wider studies of chiral receptors based on the TB chirality are not commercially available. In fact, even their enantioselective preparation on the laboratory scale has not been satisfactorily solved yet. Thus, the question of how to generate enantiomerically pure TB synthons still remains. In general, the enantiomerically pure TB derivatives can be obtained either by the enantioselective formation or by resolution of racemic mixtures.

To the best of our knowledge, only two examples of the enantioselective preparation have been reported. In the first, Webb et al. prepared[8] enantiomerically pure TB cyclophane in 28% yield by a predetermined ring closure of chiral diamine via TB unit formation. This means that only one enantiomer of the TB cyclophane is formed. The formation of other stereoisomers would give acyclic structures, which were not discussed. In the second report, Maitra et al. used[13,14] 7-deoxycholic acid as a particular chiral template for the formation of TB derivatives. Unfortunately, the enantioselectivity of the reactions varied from 0% to 70%.

The resolution of racemic mixtures of TB derivatives has been used more frequently. The first successful resolution of a TB derivative was described[15] by Prelog and Wieland in 1944. They reported a chromatographic separation of Tröger's base **1** on a chiral stationary phase. They also found that the standard procedure of resolution of racemic bases using a chiral acid as the resolving agent was precluded by simultaneous racemization of **1**. On the other hand, a couple of successful enantioseparations of TB derivatives using tartaric acid have been reported.[16–18] Tálas et al. have realized that resolution process can be disabled by the presence of water in the resolving mixture.[18] Wilen et al. have described[19] a very special case of resolving of TB enantiomers. They used either (+)- or (−)-1,1′-binaphthalene-2,2′-diyl hydrogenphosphate as the resolving agent and observed, similarly to Prelog, that the acidic resolving agent caused racemization of **1**, however, this was the case only in the solution. In other words, while the ratio of the enantiomers was nearly 1:1 in solution due to the racemization process, the precipitated diastereomeric salt contained

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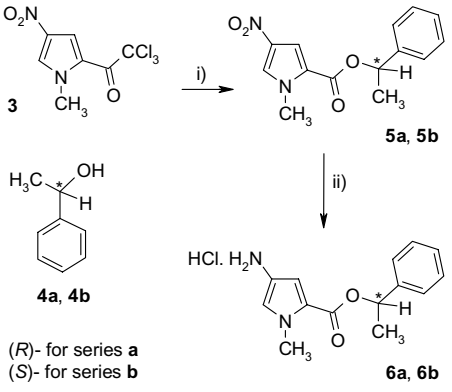
the resolving agent and only one enantiomer. Such a phenomenon is called crystallization-induced asymmetric transformation (CIAT).

Herein, we report the second example of CIAT on TB derivatives. Moreover, in contrast to the described example of CIAT on TB, we report the first example of CIAT of TB derivative in the absence of a resolving agent. Racemization is caused by hydrochloric acid while CIAT is driven by enantiomerically pure (*R*)- or (*S*)-1-phenylethyl groups present in the structure of the TB derivatives.

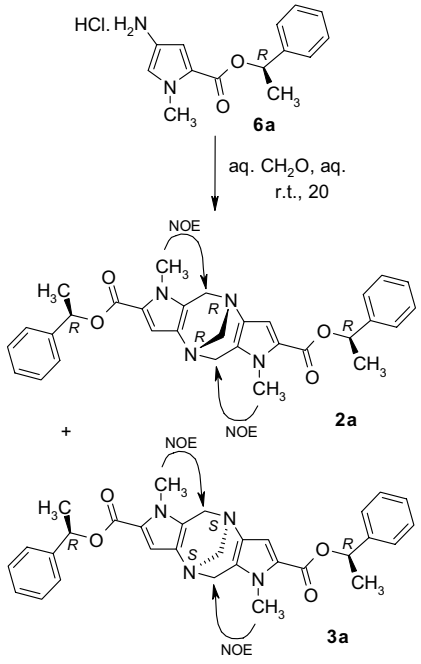
2. Results and discussion

The starting amines **6a** and **6b** were prepared by the reactions shown in Scheme 1. 1-Methyl-4-nitro-2-trichloroacetylpyrrole **3** was prepared as described elsewhere.[20] Subsequent alcoholysis[20] of the trichloroacetyl group of **3** by (*R*)-1-phenylethanol **4a** gave chiral 1-phenylethyl ester **5a**. The following reduction was achieved by nickel boride[21] (Ni_2B) to give amine **6a**. Note, that we did not observe the catalytic reduction of **5a** by $NaBH_4$ in the presence of Ni_2B as described[22] for very similar structure (benzyl instead of 1-phenylethyl). In our case the amount of the formed amine **6a** was equal to the molar amount of applied Ni_2B. The same sequence of reactions was used for the preparation of amine **6b** starting from **3** and (*S*)-1-phenylethanol **4b**.

Amine **6a** [(*R*)-1-phenylethyl] was treated with an aqueous solution of formaldehyde to give the corresponding TB derivative as a mixture of two diastereoisomers **2a** [(4*R*,9*R*) of TB unit] and **3a** [(4*S*,9*S*) of TB unit] in a 1:1 ratio (Scheme 2). The absence of stereoselectivity is not surprising because of the long distances between the stereogenic centers (1-phenylethyls) from the reaction centers (aminopyrrole groups). The crude product was crystallized from diethyl ether to afford pure crystals of **2a**. Subsequent separation of the mother liquor by column chromatography gave an additional portion of pure **2a** and impure **3a**. We found that the purification of **3a** by either chromatographic techniques or crystallization led to **3a** (the best de being 90%). Thus, we



Scheme 1. Reagents and conditions: (i) NaH, THF, **4a** gave 88% **5a**, and **4b** gave 82% **5b**; (ii) Ni_2B, aqueous concd HCl, methanol, 99% **6a**, 97% **6b**.

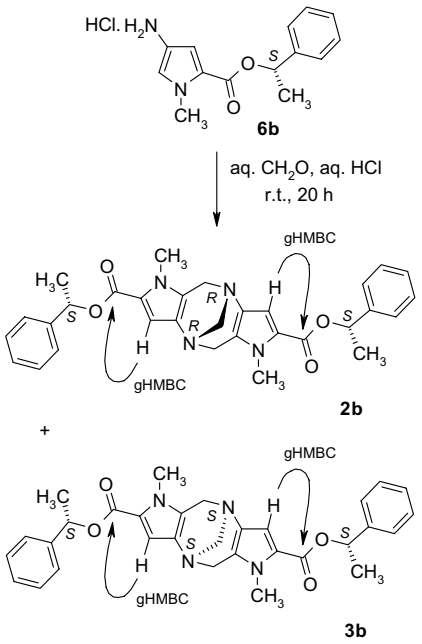


Scheme 2. Prepared TB derivatives with selected observed NOE.

tried to convert **3a** to **2a** by diastereoisomerization, the racemization of the TB unit only. We found that treatment of **3a** in methanol containing a catalytic amount of aqueous HCl led to crystalline **2a** in almost quantitative yield (de ~95%; de >99% after next crystallization from methanol/dichloromethane). This process is known as CIAT (vide supra).

Amine **6b** [(*S*)-1-phenylethyl] was used as the starting compound for the preparation of compounds **2a** and **3a** (Scheme 3). The reaction of amine **6b** with formaldehyde gave the corresponding TB derivative as a mixture of two diastereoisomers **2b** [(4*R*,9*R*) of TB unit] and **3b** [(4*S*,9*S*) of TB unit] in a 1:1 ratio, that is, with no stereoselectivity as expected. In this case we applied CIAT directly on the crude product and obtained pure **3b**.

The TB unit formation can take place at α- or β-position of *N*-methylpyrrole ring of the amine **6**. Thus, three possible regioisomers can be formed as a mixture of one asymmetric (αβ) and two symmetric (αα and ββ) ones. The connectivity structures of all the prepared TB derivatives **2a**,**b**, **3a**, and **3b** were identical and were established by detailed analyses of ^1H, ^{13}C, 1D NOESY, gHSQC, gHMBC, and gCOSY NMR experiments. For example, the NOE between *N*-methyl protons and both CH_2 protons (Scheme 2) and correlation between pyrrole proton and carbonyl carbon in gHMBC (Scheme 3) gave clear evidence that the cyclization (TB derivative formation) took place selectively at α-position of the pyrrole ring. We have no indication of the formation of other TB derivatives. This means that the pyrrole ring is attacked at the α-position exclusively (and not at the less reactive β-position). These findings are in accordance with previously observed total regioselectivity for the benzyl ester of the corresponding TB derivatives.[23]



Scheme 3. Prepared TB derivatives with selected observed correlation in gHMBC.

The absolute configurations of the derivatives **2** and **3** were confirmed by a combination of many experimental results and analyses. The configuration of **2a** was determined by single crystal X-ray structural analysis (Fig. 1). The absolute configurations of 1-phenylethyl groups of **2a** were known to be (*R*) as are in the starting alcohol. The configuration of the TB unit in **2a** was then established as (4*R*,9*R*). In addition, the negative specific rotation of **2a** $[\alpha]_D^{20} = -193$ is consistent with the known[19] specific rotation of (5*R*,11*R*)-isomer of the Tröger's base. The fact that compound **3a** is formed from **6a** together with **2a** (Scheme 2) and the reaction does not affect the configuration of 1-phenylethyl groups leads to the conclusion that the configuration of **3a** differs from the one of **2a** only by the configuration of the TB unit. Thus, the configuration of the TB unit of **3a** is (4*S*,9*S*). The diastereomorphism of **2a** and **3a** was additionally confirmed by acid catalyzed diastereoisomerization, wherein the exclusive racemization of the TB unit takes place, and both **2a** and **3a** give identical 1:1 mixtures of **2a** with **3a**. Compounds **2a** and **3a** have similar but not identical ^{1}H and ^{13}C NMR spectra. Compounds **2b** and **3a** have identical NMR spectra (**2b** is enantiomer of **3a**) and diastereoisomerization of **2b** led to the formation of the mixture of **3b** and **2b** (1:1). Thus, the absolute configuration of the TB unit of **2b** is (4*R*,9*R*). Compound **3b** had an identical NMR spectra as **2a** with a specific rotation $[\alpha]_D^{20} = +192$. This proves that **3b** is enantiomer of **2a**. Thus, the absolute configuration of the TB unit of **3b** is (4*S*,9*S*).

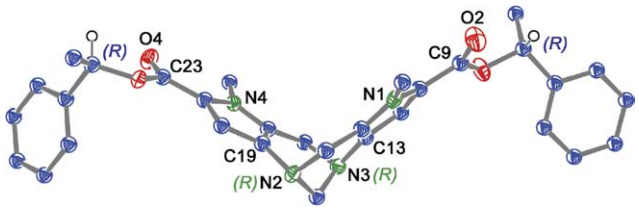


Figure 1. ORTEP plot of the solid-state structure of the compound **2a**. Thermal ellipsoids are drawn at the 50% probability level. Majority of hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: O2–C9 1.211(2), O4–C23 1.208(2); selected distances [Å]: N2–N3 2.47, C13–C19 3.20, N1–N4 5.54, C9–C23 9.00; the angle between pyrrole rings is about 110°.

3. Conclusion

In summary, our results exemplify how the usually undesirable facile racemization of the TB unit can be exploited in the preparation of enantiomerically pure TB derivatives. We have shown that chiral resolving agent is unnecessary while the 'source of chirality' is present in structure of TB derivative. Moreover, our synthetic approach allows the preparation of any of the enantiomers **2a** and **3b** on a large scale with an overall yield >40%. Utilization of **2a** and **3b** as building blocks for the synthesis of compounds containing the enantiomerically pure TB unit with the goal to prepare chiral selective receptors is in progress.

4. Experimental

^{1}H, ^{13}C, 1D NOESY, gHSQC, gHMBC, and gCOSY NMR spectra were obtained with Varian Gemini 300 HC (300.1 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR spectra) at 23 °C in $CDCl_3$ or $(CD_3)_2SO$. The correlation NMR techniques were applied for the assignment of chemical shifts to atoms of the molecules. The chemical shifts are given in ppm relative to $(CH_3)_4Si$. Mass spectra were recorded with a VG Analytical ZAB-EQ spectrometer. Thin-layer chromatography was performed on Merck Silica gel 60 F_{254} TLC plates. For column chromatography, neutral silica gel SiliTech 32–63, 60 Å (ICN Biomedicals) was used. The enantiomeric as well as diastereomeric purity of **2a** and **3b** was determined by HPLC with β-cyclodextrin stationary phase; column ChiraDex (Merck) 250 × 4 mm, 5 μm; mobile phase methanol–water (75:25).

4.1. Preparation of (*R*)-1-phenylethyl 1-methyl-4-nitropyrrole-2-carboxylate 5a

To a stirred solution of (*R*)-1-phenylethanol (6.00 g, 49.2 mmol) in THF (80 mL) at 0 °C ca. 50 mg (2.1 mmol) of NaH was added. Then a solution of 1-methyl-4-nitro-2-trichloroacetylpyrrole **3** (13.5 g, 49.7 mmol) in THF (40 mL) was added in 10 min. The reaction mixture was allowed to warm up to room temperature under stirring. After 20 h the mixture was concentrated to 40 mL in vacuo. The residue was diluted with dichloromethane and washed with aqueous *p*-toluenesulfonic acid. The organic layer was dried over sodium sulfate and evaporated to dryness. The obtained solid was crystallized from MeOH to give **5a** (10.45 g,

78%) as white needles. The mother liquor from crystallization was evaporated and the residue separated by column chromatography (silica, petroleum ether–dichloromethane from 4:6 to 0:1) to give additional portion of **5a** (1.36 g, 10%).

Compound **5a**: Mp 80–82 °C. ^{1}H NMR ($CDCl_3$): δ 1.65 (3H, d, J = 6.6 Hz, CHCH_3), 3.95 (3H, s, NCH_3), 6.03 (1H, q, J = 6.6 Hz, CHCH$_3$), 7.28–7.43 (5H, m, CH–Ph), 7.49 (1H, d, J = 2.2 Hz, CHCCO), 7.58 (1H, d, J = 2.2 Hz, CHNCH$_3$). ^{13}C NMR ($CDCl_3$): δ 22.36 (*C*H$_3$CH), 37.91 (N*C*H$_3$), 73.12 (CH$_3$*C*H), 112.72 (*C*HCCO), 123.11 (*C*CO), 125.91 (*o*-*C*H of Ph), 127.57 (*C*HNCH$_3$), 128.10 (*p*-*C*H of Ph), 128.62 (*m*-*C*H of Ph), 135.20 (*C*NO$_2$), 141.18 (*ipso*-*C* of Ph), 159.36 (*C*O). EA for $C_{14}H_{14}N_2O_4$: calcd C, 61.31; H, 5.14; N, 10.21. Found C, 60.89; H, 5.17; N, 10.22. MS (FAB) *m*/*z*: 275 (M+H)$^+$. $[\alpha]_D^{20} = -117$ (*c* 0.226, $CHCl_3$).

4.2. Preparation of (*S*)-1-phenylethyl 1-methyl-4-nitropyrrole-2-carboxylate 5b

The (*S*)-enantiomer **5b** was prepared by the same synthetic procedure as for **5a**. Reaction of **3** (6.40 g, 23.6 mmol) with (*S*)-1-phenylethanol (2.83 g, 23.2 mmol) gave 5.22 g (82%) of **5b**. Compound **5b** has identical melting point and NMR spectra as **5a**.

4.3. Preparation of hydrochloride of (*R*)-1-phenylethyl 1-methyl-4-aminopyrrole-2-carboxylate 6a

Freshly prepared nickel boride Ni_2B (16.00 g) and **5a** (10.36 g, 37.8 mmol) were added to MeOH (260 mL) and 1 M hydrochloric acid (90 mL). The resulting suspension was stirred at 70 °C until starting **5a** was present in the reaction mixture (followed by TLC). After each hour, 2 mL of concd hydrochloric acid was slowly added to the reaction mixture. The reaction mixture was filtrated, and the filter cake washed with MeOH (3×30 mL). All liquid portions were combined and concentrated in vacuo to 100 mL (mainly to remove MeOH), diluted with water, and extracted by dichloromethane. The organic layer was washed with brine and concentrated to give crude **6a** (10.49 g, 99%), which was used for the preparation of **2a/3a** without further purification.

Compound **6a**: ^{1}H NMR (DMSO-d_6): δ 1.53 (3H, d, J = 6.6 Hz, CHCH_3), 3.82 (3H, s, NCH_3), 5.93 (1H, q, J = 6.4 Hz, CHCH$_3$), 6.85 (1H, dd, J = 2.3 and 1.1 Hz, CHCCO), 7.24 (1H, d, J = 1.5 Hz, CHNCH$_3$), 7.25–7.42 (5H, m, CH–Ph), 10.00–10.20 (3H, br s, $^+$NH_3). ^{13}C NMR (DMSO-d_6): δ 22.26 (*C*H$_3$), 36.56 (*C*H$_3$), 71.65 (*C*H), 111.58 (*C*H), 113.86 (*C*), 120.94 (*C*), 123.89 (*C*H), 125.71 ($2 \times$ *C*H), 127.71 (*C*H). 128.43 ($2 \times$ *C*H), 141.75 (*C*), 158.93 (*C*).

4.4. Preparation of hydrochloride of (*S*)-1-phenylethyl 1-methyl-4-aminopyrrole-2-carboxylate 6b

The (*S*)-enantiomer **6b** was prepared by the same synthetic procedure as **6a**. Reduction of **5b** (4.75 g, 17.3 mmol) by Ni_2B (8.00 g) gave 4.72 g (97%) of **6b**. Compound **6b** has identical NMR spectra with **6a**.

4.5. Preparation of bis(1-phenylethyl)-4,9-methano-1,6-dimethyl-4,5,9,10-tetrahydro-1*H*,6*H*-dipyrrolo-[3,2-*b*:3′,2′-*f*][1,5]diazocin-2,7-dicarboxylate 2a/3a

Hydrochloride amine **6a** (9.50 g, 33.8 mmol) was dissolved in methanol (140 mL), and 36% aqueous formaldehyde (18 mL) at which point concd HCl (18 mL) was added. The reaction mixture was stirred for 20 h at room temperature, then concentrated in vacuo to one half of the original volume (mainly to remove MeOH), diluted with water and alkalized with aqueous ammonia to pH 14 and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was diluted with minimum amount (ca. 50 mL) of diethyl ether, which caused **2a** precipitation as light brown crystals (2.21 g, de ~95%, 25% yield). The mother liquor from crystallization was evaporated and the residue separated by column chromatography (silica, dichloromethane–ethyl acetate 7:3) to give **2a** (0.30 g, de >95%; 3% yield) and **3a** (4.75 g) contaminated by **2a** and side products (purity about 50%). Crude **3a** from chromatography was subjected to crystallization-induced asymmetric transformation by treatment with methanol (50 mL) and concd aqueous HCl (two drops). Pure **2a** was obtained as white crystals (2.72 g). All portions of **2a** were combined and crystallized from dichloromethane/methanol to give colorless crystals of **2a** (4.91 g, de >99%, 55% yield). The part with pure **2a** (370 mg) was dissolved in methanol (15 mL) and concd aqueous HCl (0.6 mL). The solution containing **2a** and **3a** in the ratio 1:1 (HPLC) was neutralized by aqueous ammonia (0.8 mL). This caused precipitation of **2a** (167 mg, de 90%, 45% yield). Diastereoisomer **3a** (184 mg, de 70%, 50% yield) was obtained by diluting the mother liquor with water followed by extraction into dichloromethane, drying over Na_2SO_4, and evaporation to dryness. Subsequent chromatographic separation of **3a** partially improved purity of **3a** (de 90%).

Compound **2a**: Mp 210–214 °C. ^{1}H NMR ($CDCl_3$): δ 1.59 (6H, d, J = 6.6 Hz, CHCH_3), 3.64 (6H, s, NCH_3), 3.95 (2H, d, J = 16.2 Hz, *endo* CHHN), 4.08 (2H, s, NCH_2N), 4.36 (2H, d, J = 16.2 Hz, *exo* CHHN), 6.00 (2H, q, J = 6.6 Hz, CHCH$_3$), 6.81 (2H, s, CHCN), 7.23–7.41 (10H, m, CH–Ph). ^{13}C NMR ($CDCl_3$): δ 22.61 (CH*C*H$_3$), 32.58 (N*C*H$_3$), 52.24 (C*C*H$_2$N), 68.95 (N*C*H$_2$N), 71.47 (*C*HCH$_3$), 110.14 (*C*HCN), 120.13 (*C*CO), 125.75 (*o*-*C*H of Ph), 127.04 (*C*CH$_2$N), 127.62 (*p*-*C*H of Ph), 128.45 (*m*-*C*H of Ph), 131.19 (*C*NCH$_2$), 142.25 (*ipso*-*C* of Ph), 160.39 (*C*O). EA for $C_{31}H_{32}N_4O_4$: calcd C, 70.97; H, 6.15; N, 10.68. Found C, 70.51; H, 6.20; N, 10.71. MS (FAB) *m*/*z*: 525 (M+H)$^+$. $[\alpha]_D^{20} = -193$ (*c* 0.649 g/100 mL CH_2Cl_2). *Single crystal X-ray structure determination of compound* **2a**: $C_{31}H_{32}N_4O_4$, M_r = 524.61, colorless fragment ($0.25 \times 0.38 \times 0.76$ mm^3), monoclinic, $P2_1$ (No. 4), a = 14.8985(2) Å, b = 6.2410(1) Å, c = 15.3275(2) Å, β = 109.2101(5)°, V = 1345.82(3) Å^3, Z = 2, d_{calcd} = 1.295 g cm^{-3}, F_{000} = 556, μ = 0.087 mm^{-1}. Preliminary

examination and data collection were carried out on a κ-CCD device (NONIUS MACH3) with an Oxford Cryosystems cooling system at the window of a rotating anode (NONIUS FR591) with graphite-monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). Data collection was performed at 123 K within the θ range of $1.41° < \theta < 25.37°$. A total of 29,297 reflections were integrated. Raw data were corrected for Lorentz, and polarization, and arising from the scaling procedure, for latent decay and absorption effects. After merging ($R_{int} = 0.037$), 4947 (4777 with $I_o > 2\sigma(I_o)$) independent reflections remained, and all were used to refine 481 parameters. The structure was solved by a combination of direct methods and difference Fourier syntheses. All nonhydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were found and refined with individual isotropic displacement parameters. Full-matrix least-squares refinements were carried out by minimizing $\sum w(F_o^2 - F_c^2)^2$ and converged with $R1 = 0.0274$ ($I_o > 2\sigma(I_o)$), $wR2 = 0.0667$ (all data), GOF = 1.032, and a shift/error of <0.001. The final difference Fourier map shows no striking features ($\Delta e_{min/max} = +0.15/-0.12$ e Å^{-3}). Small extinction effects were corrected with the SHELXL-97 procedure [$\varepsilon = 0.016(1)$]. The correct enantiomer is given by synthesis. All calculations were performed on an Intel Pentium II PC, with the STRUX-V system, including the programs PLATON, SIR92, and SHELXL-97 (Ref. 24). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-269349 **2a**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax (+44) 1223 336 033; e-mail deposit@ccdc.cam.ac.uk.

Compound **3a**: ^{1}H NMR ($CDCl_3$): δ 1.59 (6H, d, $J = 6.6$ Hz, CHCH_3); 3.62 (6H, s, NCH_3); 3.92 (2H, d, $J = 16.2$ Hz, *endo* C*H*HN); 4.09 (2H, s, NCH_2N); 4.36 (2H, d, $J = 16.0$ Hz, *exo* CH*H*N); 5.97 (2H, q, $J = 6.6$ Hz, C*H*CH$_3$); 6.77 (2H, s, C*H*CN); 7.22–7.42 (10H, m, C*H*–Ph). ^{13}C NMR ($CDCl_3$): δ 22.48 (CH*C*H$_3$), 32.59 (N*C*H$_3$), 52.18 (C*C*H$_2$N), 68.96 (N*C*H$_2$N), 71.59 (*C*HCH$_3$), 110.10 (*C*HCN), 120.13 (*C*CO), 125.90 (*o*-*C*H of Ph), 126.97 (*C*CH$_2$N), 127.64 (*p*-*C*H of Ph), 128.43 (*m*-*C*H of Ph), 131.14 (*C*NCH$_2$), 142.14 (*ipso*-*C* of Ph), 160.42 (*C*O).

4.6. Preparation bis(1-phenylethyl)-4,9-methano-1,6-dimethyl-4,5,9,10-tetrahydro-1*H*,6*H*- dipyrrolo-[3,2-*b*:3′,2′-*f*][1,5]diazocin-2,7-dicarboxylate 2b/3b

Compound **3b** was obtained from **6b** (4.70 g, 16.8 mmol), concd HCl (9 mL) and aqueous formaldehyde (9 mL) under similar conditions as **2a**. Unlike **2a**, the crude product was treated with dichloromethane (1 mL), methanol (30 mL), and concd aqueous HCl (three drops) to give crude **3b** (2.80 g), which gave with the next crystallization (dichloromethane/methanol) pure **3b** (2.31 g, de >99%, 53% yield). Diastereoisomerization of **3b** in methanol with HCl gave a 1:1 mixture of **2b** and **3b**.

Compound **3b**: Mp 208–212 °C. EA for $C_{31}H_{32}N_4O_4$: calcd C, 70.97; H, 6.15; N, 10.68. Found C, 70.16; H, 6.11; N, 10.64. MS (FAB) *m*/*z*: 525 $(M+H)^+$. $[\alpha]_D^{20} = +192$ (*c* 1.049, CH_2Cl_2). NMR spectra of **3b** and **2a** were identical as well as NMR spectra of **2b** and **3a**.

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