Stereoselective synthesis of configurationally stable functionalized *ethano*-bridged Tröger bases†

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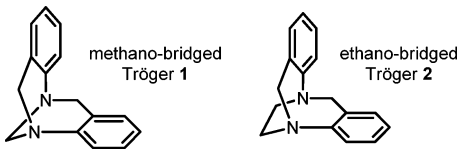
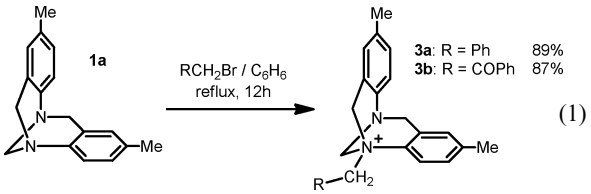
New functionalized *ethano*-bridged Tröger bases are readily prepared using a simple alkylation/rearrangement sequence which affords configurationally stable derivatives as single stereoisomers (de > 96%).

Tröger bases of type **1**, which are the classical products from condensation reactions of aromatic amines with formaldehyde, have been extensively studied for their properties and reactivities.[1–4] A large array of Tröger bases has been prepared thanks to modular synthetic routes to the tricyclic core,[5,6] and this for a variety of applications such as molecular recognition,[7] DNA-interacting probes,[8] biomimetic systems,[9] and self-assembled structures.[10,11] In the field of organic stereochemistry, Tröger bases hold a special place, being the first compounds with stereogenic nitrogen atoms to be resolved.[12] Regrettably, reactions using compounds **1** as enantiopure ligands, auxiliaries or catalysts are rare.[6] This situation is possibly due to the relatively facile racemization of compounds **1** in acidic media (barrier of inversion *ca.* 101 kJ mol^{-1}).[13,14] A few solutions to this problem have been brought forward,[3,11,13] including the interesting transformation of *methano*-Tröger bases into *ethano*-derivatives (**2**).[15,16] The presence of the *ethano* bridge in **2** avoids the conventional racemization pathway *via* an achiral iminium intermediate. Herein, we report a novel two-step sequence for the preparation of *ethano*-Tröger bases *via* the synthesis of quaternary ammonium salts and an unprecedented ring-expansion Stevens-like rearrangement. This simple-to-run protocol yields configurationally stable functionalized derivatives as single stereoisomers.



Previously, our group has studied quaternary ammonium salts for their conformational, configurational and host–guest properties.[17] [1,2]-Stevens rearrangements, which are spontaneous transformations of quaternary ammonium ions into tertiary amines under basic conditions,[18] have also been investigated for their interesting mechanism and synthetic utility.[19] In the course of these studies, we noticed that a [1,2]-Stevens rearrangement of Tröger derivatives had never been reported. This was somewhat surprising as several quaternary ammonium salts of compounds **1** had been described[14,15,20] and all the more interesting as such a rearrangement had the potential to create novel interesting framework(s).[18]



(1)

To test the feasibility of the transformation, salt [**3a**][Br] was prepared following reported conditions (eqn (1), R = Ph).[14] However, in line with previous reports,[20,21] we observed only starting material and/or demethylenated product **4a** (up to 93%, Scheme 1) with no trace of rearrangement adduct(s) in our many attempts.[22] This exclusive formation of **4a** was explained by a preferred reactivity of the added bases with the bridge-methylene carbon of **3a** (Scheme 1, path *a*). To upset the situation, we considered that the deprotonation of the side-chain protons to form a necessary ylide should be enforced (Scheme 1, path *b*). This should be achieved by the introduction of more acidic hydrogen atoms and that of $ArCOCH_2$ side-chains in particular. A search of the literature indicated that these protons should indeed be more acidic than the previously-used benzylic ones (pK_a 14.6 and 31.9 for $PhCOCH_2N^+Me_3$ and $PhCH_2N^+Me_3$, respectively).[23] Salt [**3b**][Br] was then prepared by treatment of Tröger base **1a** with α-bromoacetophenone at reflux in benzene (87%, eqn (1)).

Experiments on the rearrangement of [**3b**][Br] were initially disappointing using regular conditions for the Stevens rearrangement (NaOH, KOH, *t*-BuOK as bases). Only dihydrodibenzodiazocine adduct **4b** was observed in the ^{1}H NMR spectra of the crude reaction mixtures. However, with other bases (CsOH, Cs_2CO_3, NaOMe, NaOAc), a trace amount of a new compound was noticed. Using organic amines (Table 1, entries 1–4), reactions were slow. After 10 h, starting material was still present but an isolable amount of this novel species was afforded (5–18%) which was characterized as novel rearrangement product **5b**. Yet, diazocine **4b** was still a major component even in the reactions

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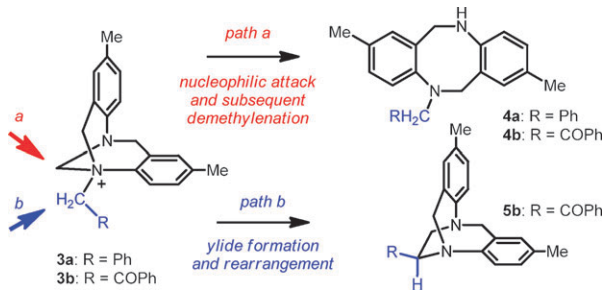


Scheme 1 Possible reactivity pathways of quaternary ammonium salts of cations of type **3** in the presence of bases.

of hindered bases such as *i*-Pr_2NEt (entry 4). Looking then for essentially non-nucleophilic conditions, basic alumina (Brockman activity I, pH 9.5 ± 0.5, entries 5–6) was used. To our delight, *ethano*-bridged Tröger **5b** was now isolated in much higher yields than before (up to 85%).

While it was clear by NMR spectroscopy that compound **5b** was a single stereoisomer (diastereomeric ratio, dr > 98 : 2), the configuration of the new sp^3 center relative to the stereogenic N-atoms could not be determined with certainty. X-Ray diffraction analysis of a monocrystal of racemic **5b**, obtained by slow evaporation of an Et_2O solution, was performed and revealed (5*S*,11*S*,14*R*)/(5*R*,11*R*,14*S*) configurations for the tricyclic moiety (Fig. 1).[24] Interestingly, the folded geometry of classical Tröger bases remains with the *ethano* bridge and the extra substituent. The planes of the tolyl rings are almost perpendicular to each other (83° *vs. ca.* 90° for compounds **1**).

With the optimized conditions in hand, the scope of the rearrangement was studied (Table 2). Salts [**3c**][Br] to [**3f**][PF_6] bearing different substituents on the aromatic nucleus of the side-chain were used. As expected, these compounds afforded the rearranged products with excellent stereoselectivity, albeit lower yields (34–65%, entries 1–5). Better yields seem to be obtained with electron-poor rather than strongly electron-donating substituents on the migrating group. From the NMR spectra, one can conclude that the relative configuration of the corresponding compounds **5** remains the same. Looking for a possible influence of substituents on the Tröger core itself, *rac*-2,3,8,9-tetramethoxy-Tröger was prepared[25] and reacted with α-bromoacetophenone to afford the ammonium salt [**3g**][Br] (57% yield). Treatment of [**3g**][Br] with basic alumina led to rearranged product **5g** (35% yield); the lower yield being probably due to a noticeable instability of the starting salt.

With *rac*-**5b** in hand, we turned our attention to its enantiomeric resolution and configurational stability. Preparative

Table 1 Rearrangement of [**3b**][Br], base influence

Entry	Salt	Base	Equiv.	**5b** : **4b**[a]	Yield[b]
1[c]	[**3b**][Br]	DABCO	5.0	34 : 64	10%
2[c]	[**3b**][Br]	Et_3N	5.0	43 : 57	8%
3[c]	[**3b**][Br]	Proton sponge	5.0	27 : 73	5%
4[c]	[**3b**][Br]	Hünig's base	5.0	60 : 40	18%
5[d]	[**3b**][Br]	Al_2O_3 (pH = 9.5 ± 0.5)	20×	94 : 6	45%
6[d]	[**3b**][Br]	Al_2O_3 (pH = 9.5 ± 0.5)	40×	89 : 11	85%

[a] Determined by ^1H NMR (400 MHz) spectroscopy on the crude reaction mixture. [b] Isolated yields. [c] [**3b**][Br], Base, $CHCl_3$, 10 h, 25 °C. [d] [**3b**][Br], Al_2O_3, $CHCl_3$, 2.5 h, 25 °C. Mass equivalents are used.

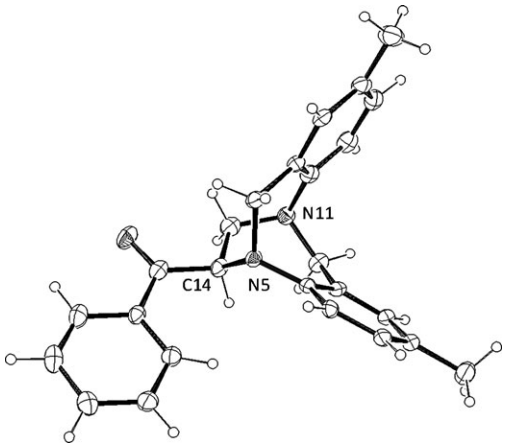
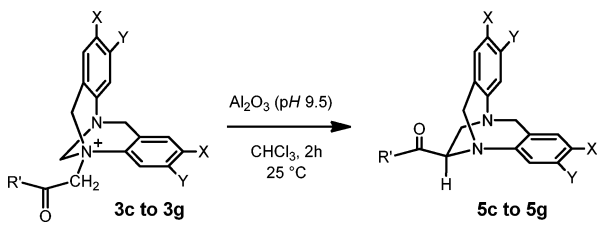


Fig. 1 ORTEP view of the crystal structure of *rac*-**5b**. Only the (5*S*,11*S*,14*R*) enantiomer is shown. Ellipsoids are represented at 30%.

chromatographic resolution on chiral stationary phases is now recognized as a very powerful and general method to separate and isolate enantiomers of racemic compounds in good yield and high optical purity.[26] This approach was applied to *rac*-**5b** and the two enantiomers were obtained on a preparative scale using cellulose-based phase Chiralcel OJ and a mixture of *n*-heptane : ethanol 90 : 10. From a batch of 190 mg of racemic **5b**, two separated fractions were afforded, 53 mg (ee > 99%, 28%) and 60 mg (ee > 99%, 32%) for the first and second eluted fractions.[27] These fractions correspond to (+)-**5b** and (−)-**5b**, respectively. Solutions in MeOH or $CHCl_3$ of each enantiomer were then stirred for 2 h at 25 and at 60 °C with no visible loss of enantiomeric purity even in the presence of a strong acid such as (+)-camphorsulfonic acid (2 equiv.). Only under more forcing conditions (DMF, 100 °C, 2 h, 2 equiv. of camphorsulfonic acid) was a drop of enantiomeric purity observed (from >99% to 88%, HPLC monitoring).[28]

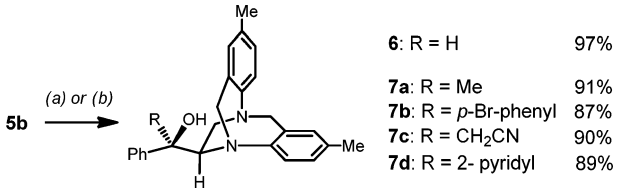
Finally, ketone **5b** was treated with $NaBH_4$ (MeOH, 0 °C) and the corresponding amino-alcohol **6** was afforded in good yield (97%) and excellent diastereoselectivity (dr > 49 : 1, Scheme 2). This excellent result prompted us to study the reactivity of **5b** with a few other nucleophiles (MeLi, *p*-Br-PhLi, $LiCH_2CN$, 2-LiPy) and, in all cases, the corresponding tertiary

Table 2 Rearrangement of ammoniums **3c** to **3g**, side-chain influence[a]



Entry	Salt	X, Y	R′	Yield[b]	dr[c]
1	[**3c**][Br]	Me, H	C_6H_4-*p*-Me	51%	>98 : 2
2	[**3d**][Br]	Me, H	C_6H_4-*p*-OMe	34%	>98 : 2
3	[**3e**][Br]	Me, H	C_6H_4-*p*-F	65%	>98 : 2
4	[**3f**][PF_6]	Me, H	C_6H_4-*o*-Br	40%	>98 : 2
5	[**3g**][Br]	OMe, OMe	Ph	35%	>98 : 2

[a] Ammonium salt, Al_2O_3 (pH 9.5 ± 0.5), $CHCl_3$, 2 h, 25 °C. [b] Isolated yields. [c] Determined by ^1H NMR (400 MHz) spectroscopy.



Scheme 2 Reaction conditions: (a) $NaBH_4$ (3 equiv.), MeOH, 0 °C, 97%; (b) RLi (1.5 equiv.), THF, −78 °C, 2 h, 87–91% yield.

alcohols **7a** to **7d** were isolated in excellent yield (87–91%) and diastereoselectivity (dr > 49 : 1, ^{1}H NMR). So far, all spectral data indicate a classical Felkin–Anh trajectory for the nucleophile approach.

In conclusion, this paper reports that a novel [1,2]-Stevens like rearrangement of quaternary ammonium ions of Tröger bases affords, in only two steps, functionalized configurationally stable *ethano*-bridged Tröger derivatives that can themselves be easily transformed highly selectively. Efforts are currently directed towards applications of these novel moieties and the understanding of the underlying chemistry.

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24 *Crystallographic data for* ***rac*-5b**: $(C_{25}H_{24}N_2O)$; M_r = 368.5, tetragonal, $P42_1c$, a = 23.9934(10), c = 6.8262(3) Å, U = 3929.7(3) Å^3; Z = 8, μ = 0.076 mm^{-1}, d_x = 1.246 g cm^{-3}, Mo-Kα radiation (λ = 0.71073 Å); 22 803 reflections measured at 150 K on a STOE IPDS diffractometer, 3854 unique reflections of which 2304 with $|Fo| > 2\sigma(Fo)$. The structure was solved by direct methods (SIR97). All calculations were performed with the XTAL system. Full-matrix least-squares refinement based on F using weights of $1/(\sigma^2(Fo) + 0.0002(Fo^2))$ gave final values R = 0.034, wR = 0.023 (ωR_{all} = 0.034) and S_{all} = 1.05(2).
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27 Retention times were 7.54 and 10.25 min for these two fractions using an analytical Chiralcel OJ–H (0.46 × 25 cm) and a mixture of *n*-heptane : ethanol 90 : 10 as eluent. Flow 1 ml min^{-1}. UV 210 nm. The electronic circular dichroism (ECD) spectra of the separated enantiomers are reported in the ESI†.
28 The reason for this surprising loss is still under evaluation.

