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Synthesis of new chiral molecular tweezers with a tris-Tröger's base skeleton

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For the first time, chiral molecular tweezers with a tris-Tröger's base skeleton have been synthesised. Three new compounds 9a, 9b and 9c differ in their stereochemistry.

Tröger's base **1**[1] is a concave chiral molecule, the chirality of which results from the blocked configuration of its stereogenic nitrogen atoms. Tröger's base and its derivatives have been described as 'fascinating molecules',[2] and they provide relatively rigid chiral frameworks for the construction of chelating and biomimetic systems, which were essentially developed by Wilcox and co-workers.[3–7] Tröger's bases show a perpendicular arrangement of the two aromatic rings,[3] as in Kagan's ether, which was used by Harmata and co-authors for the synthesis of molecular tweezers.[8,9] In this context, we have utlilized the Tröger's skeleton as a scaffold for the construction of molecular clips **2**,[10] **3**[11] and **4**[12] (Figure 1). Recently, Klärner and co-workers[13] have described the synthesis of another family of molecular clips **5** with three methylene bridges. These results prompted us to report our preliminary results in the synthesis of chiral molecules with a tris-Tröger's base skeleton.

These tris-Tröger's bases can exist as four stereoisomers: *anti–anti*, *anti–syn*, *syn–anti* and *syn–syn* (Figure 2), the last being the most interesting compound with its cage structure and expected different host properties compared to the other three stereoisomers, which have structures more alike to the bis-Tröger's bases.

We have prepared the tris-Tröger's bases starting from compound **2** (Scheme 1), following a synthetic pathway similar to

Table 1 Aliphatic ^{1}H chemical shifts (δ) of bases **9** in [$^2H_6$]acetone at 500 MHz.

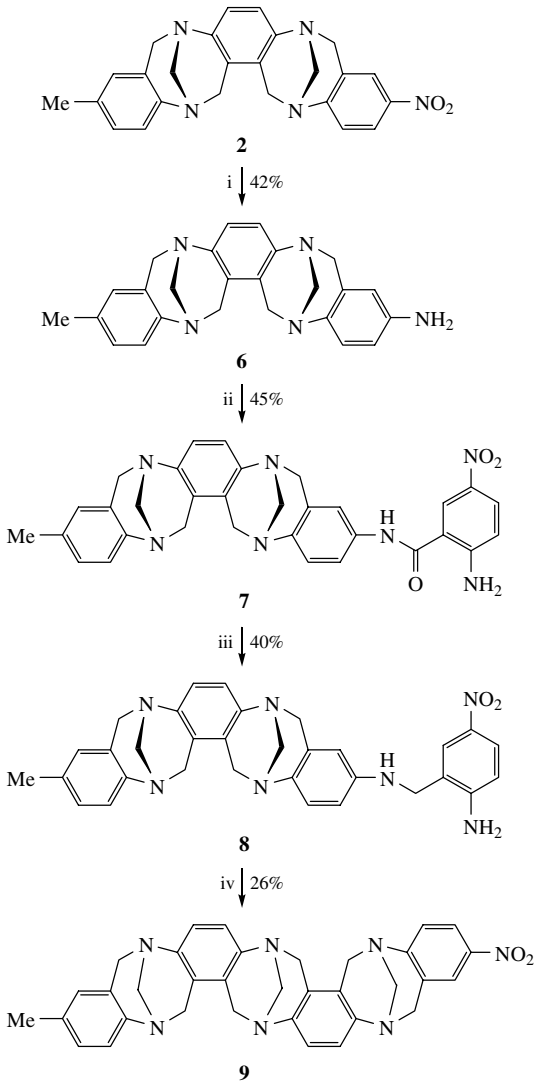
Base	H-6n[a]	H-6x	H-7n	H-7x	H-12n	H-12x	H-18n	H-18x	H-19n	H-19x	H-24n	H-24x	H-25a	H-25b	H-26a	H-26b	H-27a	H-27b
9a	3.80	4.20	3.82	4.27	4.28	4.72	4.21	4.51	3.99	4.31	3.99	4.47	3.93	4.02	4.01	4.01	4.24	4.24
9b	3.96	4.34	3.94	4.30	4.21	4.63	4.02	4.34	3.81	4.30	4.05	4.55	4.12	4.16	3.97	4.03	4.09	4.09
9c	3.88	4.29	3.95	4.31	4.11	4.63	4.14	4.46	4.01	4.32	3.89	4.46	4.04	4.08	4.03	4.03	4.16	4.16

[a]Protons Hn (endo) and Hx (exo) are respectively placed under and aside the methylene bridge.

that used for the synthesis of the last compound.[10] Base **2** was hydrogenated over Pd (10% C) to corresponding amino derivative **6**. The reaction of amine **6** with 2-amino-5-nitrobenzoic acid in the presence of dicyclohexylcarbodiimide (DCC) yielded amide **7**, which was reduced to amine **8** by treatment with a borane–tetrahydrofurane complex. Finally, the reaction of **8** with aqueous formaldehyde and concentrated hydrochloric acid in ethanol afforded a mixture of three tris-Tröger's bases, which were separated by flash chromatography over silica gel. Elution with ethyl acetate/methanol (98/2) yielded successively 11% of **9a**, 7% of **9b** and 8% of **9c**.

New compounds **9a**, **9b** and **9c** were identified by a combination of analytical (HRMS)† and spectroscopic methods (1D and 2D ^{1}H and ^{13}C NMR).[14,15] Tables 1 and 2 show the ^{1}H NMR data of these compounds.

We have previously proved in bis-Tröger's base systems, whose structures were established by X-ray diffraction, that in



Scheme 1 *Reagents and conditions*: i, H_2/Pd (10% C), EtOH, room temperature; ii, 2-amino-5-nitrobenzoic acid, DCC, DMF, room temperature; iii, BH_3–THF, THF, reflux; iv, 37% aq. CH_2O, 36% HCl, 95% EtOH, 90 °C.

† **9a**: mp 280–285 °C, M^+ 569.2549.
9b: mp 265–267 °C, M^+ 569.2531.
9c: mp 250–253 °C, M^+ 569.2540.

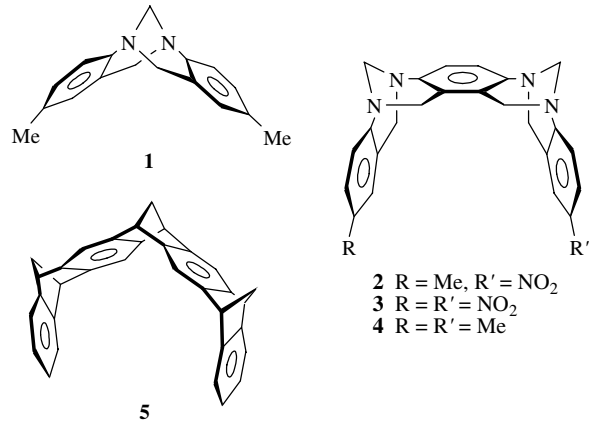


Figure 1

the *syn* arrangement of two consecutive methylene bridges the protons of the external aromatic rings are more shielded than those in the *anti* arrangement.[10,11] The NMR data shown in Table 2 allow us to assign tentatively the stereochemistry *anti–syn* to **9a**, the *syn–anti* to **9b** and the *syn–syn* to **9c**.

In conclusion, we present in this communication a synthesis of new chiral molecular teewzers, one of them, **9c**, with a cage structure and interesting possibilities in host–guest chemistry. Studies towards the isolation of the fourth stereoisomer, *anti–*

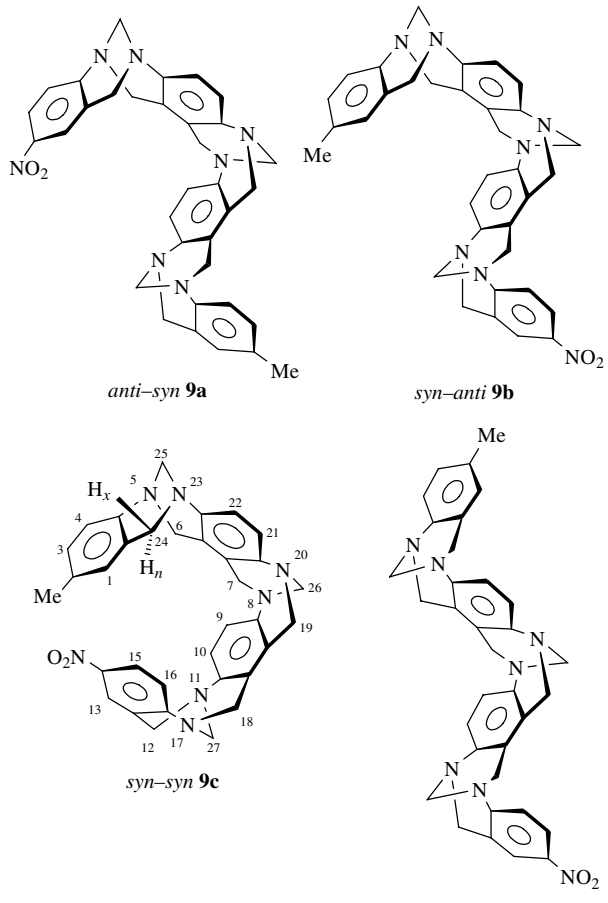


Figure 2

Table 2 Aromatic ^{1}H chemical shifts (δ) of bases **9** in [$^2H_6$]acetone at 500 MHz.

Base	H-1	H-3	H-4	H-9	H-10	H-13	H-15	H-16	H-21	H-22
9a	6.68	6.90	6.92	6.98	6.99	7.83	7.92	7.30	6.81	6.81
9b	6.65	6.86	6.93	6.88	6.85	7.87	7.95	7.30	6.93	6.96
9c	6.45	6.71	6.79	6.91	6.89	7.69	7.81	7.15	6.85	6.85

anti **9d**, to the improvement of the synthetic methodology and to the unequivocally assignation of their stereochemistry are currently under investigation in this laboratory.

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