Rigid Chiral Carbocyclic Clefts as Building Blocks for the Construction of New Supramolecular Hosts

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Abstract : The synthesis and resolution of two chiral carbocyclic cleft molecules containing carbonyl groups on the periphery of the cavity are reported. These compounds are reminiscent of Tröger's base but contain a smaller cleft and additional carbonyl (or alcohol) groups. X-ray crystal structures of the dibromo and dimethyl derivatives show that the dihedral angle between the two aromatic rings is 79° and 85° respectively. The dibromo derivative provides entry into new supramolecular hosts, *via* introduction of additional recognition groups into the cleft molecules. © 1998 Elsevier Science Ltd. All rights reserved.

Organic building blocks, which contain well defined geometries and recognition sites, allow the controlled assembly of synthetic receptors bearing functional group arrays that are complementary to recognition sites of a target substrate.[1] Molecules possessing a rigid backbone and directional functionality along with an element of chirality offer the prospect of constructing assemblies capable of chiral molecular recognition processes. It is the combination of these elements that has led to the incorporation of the diazocine bridge, found in Tröger's base **1**, into numerous macrocyclic host systems.[2-8] The well defined chiral cavity in **1** has allowed the successful development of receptors for biotin and urea derivatives[2] and chiral amines and amino acids.[8]

1   2
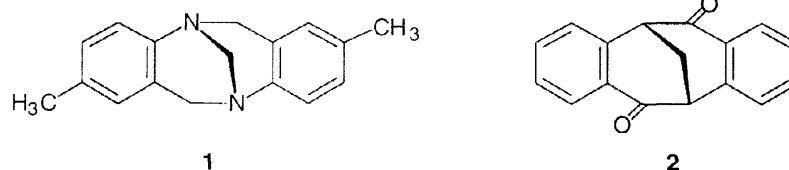
Dibenzobicyclo[b,f][3.3.1]nona-2,6-dien-4,8-dione **2** may be regarded as a carbocyclic analogue of Tröger's base in which each of the tertiary nitrogen atoms have been removed, but which retains the chiral cavity in which the two aromatic rings are rigidly held in essentially the same relative orientation to one another as in **1**. The molecule was first prepared by Tatemitsu *et al* in 1975 as part of a study aimed at establishing the relationship between structure and chiroptical properties of various triptycene derivatives and related compounds.[9] However, in contrast to Tröger's base, which has been widely utilised in the development of a variety of molecular cleft type structures,[2-8] there are relatively few supramolecular systems that have incorporated **2** into their structures.[10]

In this paper we report the synthesis, resolution and X-ray crystal structures of the dibromo and dimethyl derivatives of 2. While the synthesis of Tröger's base systems is restricted to electron donating groups on the primary aromatic amine which is condensed with formaldehyde,[11] both electron donating and withdrawing substituents may be directly incorporated into 2.

Racemic dibromo and dimethyl derivatives, 3 and 4 respectively, were prepared in three steps from commercially available starting materials (Scheme 1). The route is essentially the same procedure reported by Tatemitsu et al for the parent unsubstituted dione 2.[9] Thus, heating nitriles 5 or 6 at 165 °C with diiodomethane in the presence of powdered sodium hydroxide afforded 7 and 9 respectively as dark brown tars. The mixture of diastereomers were hydrolysed (80 °C, 18 h, ethanol/aqueous KOH) to the corresponding diastereomeric mixture of acids 8 and 10 respectively. Heating the crude dicarboxylic acids 8 or 10 with concentrated sulfuric acid at 100 °C promotes a double intramolecular Friedel-Crafts acylation reaction and afforded the doubly bridged compounds 3 and 4 as racemic mixtures.[12]
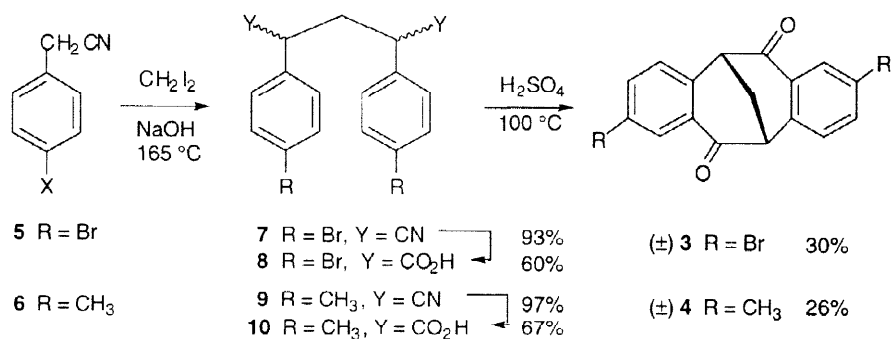
Scheme 1

Diones 3 and 4 were resolved by HPLC on a Pirkle column.[13] The absolute configuration of each of the enantiomers was determined by circular dichroism on comparison with the previously assigned CD data for the parent compound 2.[9] Figure 1 shows the CD spectra of the (+) and (-) enantiomers of 3. Similar features were observed in the spectra of (+) and (-) 4.
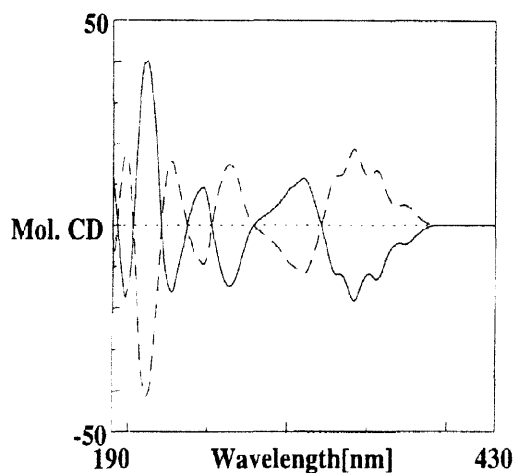

Figure 1 : Circular dichroism spectra (CH₃CN) corrected to enantiomeric purity of (-) 3 (solid line) and (+) 3 (0.4 mM).

X-ray crystallographic analysis[14] of crystals of both the dibromodione 3, and dimethyldione 4, highlights the rigid cleft shape of the molecule and the position of the two carbonyl groups which are oriented downwards (eg., Figure 2). Compared with Tröger's base, the dimensions of the dione cleft are different, notably the separation between the aromatic rings and the dihedral angle that defines the cleft "bite" (Table 1). X-ray crystal structures of a range of substituted Tröger's base systems have shown there is a moderate degree of flexibility in the dibenzodiacine ring system, and the dihedral angle between the two aryl rings varies by up to 12 degrees, depending on the aryl ring substituents.[3] Thus, the shape of the cleft may be subtly changed by substitution and the flexibility present in the bridge is ideal as a breathing mechanism to allow optimal binding of a given substrate. The crystal structures of 3 and 4 also show that the substituents influence the shape of the cleft, with dihedral angles in the two compounds differing by seven degrees.
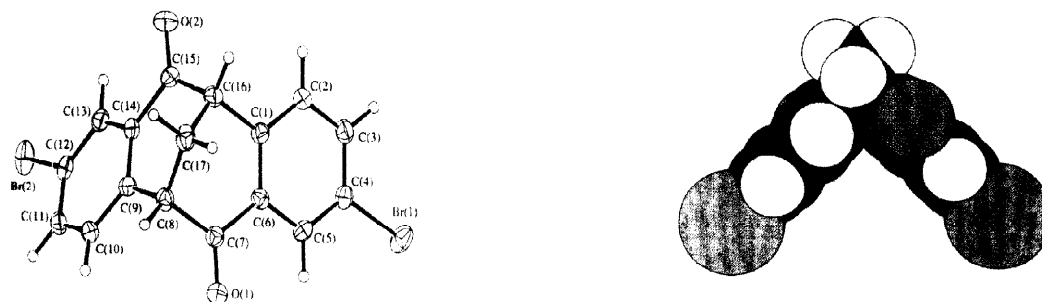
Figure 2 : Two views of dibromodione **3** generated from X-ray coordinates;[14] only one enantiomer shown.

Table 1 : Structural data for diones and comparison with Tröger's Base

R		[α]$_D$	[α]$_D$	distance d C(4) - C(11)	dihedral angle (pqrs)
3	Br	-430	+430 (c 0.13, DCM)	6.7 Å	79
4	CH$_3$	-480	+480 (c 0.62, DCM)	7.3 Å	85
1	Tröger's Base	-280	+280 (c 0.5, hexane)	6.8 Å	74[3]

The presence of the aryl bromide functional groups in dione **3** provides a handle whereby a range of other functionality may be introduced into the system. In addition, the diketone groups also offer further possibilities for elaboration. Indeed these have been utilised (*via* reduction to alcohols) in the construction of chiral crown ether based receptors.[10] Due to the relatively hindered carbonyls, stereoselective reduction of **2** has been reported to give a single diol in which the two hydroxyl groups are pseudo-axial.[9] Thus, similar treatment of dione **3** with lithium aluminium hydride in THF afforded exclusively the diol **11** (Scheme 2, (-)-enantiomer shown). The hydroxyl groups are positioned on the lower face of the cavity in well-defined positions, and thus allow entry into receptors containing hydrogen bonding features different to those present in **2**. Such receptors may be further tailored to recognise a given substrate by introduction of heterocyclic (or other) groups *via* reaction of the aryl bromides.[15]
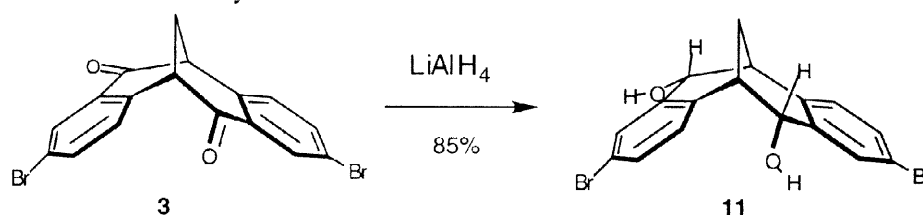
Scheme 2

In conclusion, diones based on **2** provide a complementary chiral building block to Tröger's base for incorporation into the design of molecular clefts and related supramolecular structures. The rigid dibenzo methylene bridge confers similar chirality, but different cleft dimensions to those present in Tröger's base. In addition, the framework allows incorporation of halogen functionality on the rings, which is not possible with Tröger's base systems and thus allows ready access to a range of derivatives, *via* standard metal catalysed cross-coupling reactions.[15] The presence of the two carbonyl groups in **2** (or alcohols after reduction) provide additional recognition sites on the interior of the cavity for recognition of chiral substrates through hydrogen bonding. The development of related cleft systems as well as the incorporation of metal binding sites into these systems is currently under investigation in our laboratories.

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11. While unsymmetrical Tröger's Base systems may be prepared with a halogen (Cl) incorporated on one of the aryl rings), attempts to synthesise the dichloro substituted Tröger's base failed; see T. H. Webb and C. S. Wilcox, *J. Org. Chem.* 1990, **55**, 363.
12. Compound **3** (±)-2,8-dibromodibenzobicyclo[b,f][3.3.1]nona-2,6-dien-4,8-dione, m.p. 259-262°; δ (200 MHz; CDCl₃) 2.97 (2 H, t, J 3.0 Hz), 3.99 (2 H, t, J 3.0 Hz), 7.30 (2 H, d, J 11.1 Hz), 7.64 (2 H, dd, J 11.1 Hz, J 2.3 Hz), 8.08 (2 H, d, J 2.3 Hz); λ_{max} (CHCl₃) 355 (ε 1194), 441 (1549), 327 (sh) (1704), 311 (3827), 302 (sh) (3481), 280 (5846), 248 (13905), 243 (14313), 230 (16150) nm; m/z 406 (100%), 218 (30), 202 (10), 189 (30), 109 (15), 95 (35); Found C 50.3, H 2.6. $C_{17}H_{10}O_2Br_2$ requires C 50.2, H 2.5. Compound **4** (±)-2,8-dimethyldibenzobicyclo[b,f][3.3.1]nona-2,6-dien-4,8-dione, m.p. 183-186 °C; δ (200 MHz; CDCl₃) 2.31 (6 H, s, CH₃), 2.96 (2 H, t, J 3.0 Hz), 3.96 (2 H, t, J 3.0 Hz), 7.32-7.35 (4 H, m), 7.75-7.77 (2 H, m); λ_{max} (CHCl₃) 315 (ε 1458), 341(sh) (2255), 308 (4548), 300 (sh) (4328), 273 (15429), 262 (sh) (20137), 253 (30664), 245 (sh) (29184); Found: C, 82.6; H, 5.8. $C_{19}H_{16}O_2$ requires: C, 82.6; H, 5.8.
13. The enantiomers were resolved on a Pirkle Type 1A chiral column (3.0 mL/min, 1.5% isopropanol/light petroleum); (+)-**3** (99.8% pure), retention time 22 min, (-)-**3**, (93.3% pure) retention time 23.5 min; (+)-**4** (99.4% pure), retention time 20 min. (-)-**4** (97.3% pure) retention time 22 min.
14. X-ray data **3** *Crystal data.-* Formula $C_{17}H_{10}Br_2O_2$; M 406.07, monoclinic, space group P2₁/c, a = 8.579(1), b = 9.670(2), c = 17.781(1) Å, β = 101.406(9), V = 1446.0(3) Å³, Z = 4, D_c = 1.865 g mol⁻¹, μ(CuKα) = 71.27 cm⁻¹, semi-empirical absorption correction (0.976-0.416), λ(CuKα) = 1.54178 Å, F(000) = 584 electrons, θ_{max} = 67.5°, N = 2814, N_0 = 2143 ($I > 3.0$ σ(I)), N_{var} = 191, max shift 0.01σ) R^* = 0.045, R_w = 0.044, GOF = 4.06 and $w = 1/(\sigma^2(F_o))$, $\Delta\rho_{max}$ = 0.83, $\Delta\rho_{min}$ = -0.83 e Å⁻³.
    X-ray data **4** *Crystal data.-* Formula $C_{19}H_{16}O_2$; M 276.33, triclinic, space group P1, a = 2.113(1), b = 2.193(1), c = 0.0945(7) Å, α = 102.113(7), β = 102.563(7), γ = 83.714(7)°, V = 1419.6(2) Å³, Z = 4, D_c = 1.293 g mol⁻¹, μ(CuKα) = 0.66 cm⁻¹, semi-empirical absorption correction (0.976-0.416), λ(CuKα) = 1.5418 Å, F(000) = 584 electrons, θ_{max} = 67.5°, N = 5321, N_0 = 2926 ($I > 2.5$ σ(I)), N_{var} = 508, max shift 0.1σ) R^* = 0.042, R_w = 0.045, GOF = 1.89 and $w = 1/(\sigma^2(F_o))$, $\Delta\rho_{max}$ = 0.15, $\Delta\rho_{min}$ = -0.18 e Å⁻³.
15. For example T. N. Mitchell, *Synthesis* 1992. 803; J. K. Stille, *Angew. Chem., Int. Ed. Engl.* 1986, **25**, 508.