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Enantioseparations of non-benzenoid and oligo-Tröger's bases by HPLC on Whelk O1 column

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ABSTRACT

The separation of enantiomers of several 'bis- and tris-Tröger's bases' by HPLC on commercially available chiral stationary phase Whelk O1 is described for the first time. The observed structure–enantioselectivity relationships are in agreement with the previously established molecular recognition model. For all 'bis- and tris-Tröger's bases' studied, satisfactory to excellent enantioselectivities were observed.

1. Introduction

Tröger's base, (±)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (Fig. 1), was first synthesized in 1887 by the condensation of 4-methylaniline with formaldehyde.[1] Tröger's base is chiral due to the two stereogenic bridgehead nitrogen atoms. The unique set of structural features (C_2-symmetry and a rigid V-shape geometry with the two aromatic rings nearly perpendicular to each other) makes derivatives of Tröger's base very attractive as nanometer-sized molecular scaffolds for supramolecular chemistry and molecular recognition.[2–4] However, many of these applications only explore the geometry of the Tröger's base skeleton, and deal with racemates. Thus, the advantages of the chirality of Tröger's base remain largely unexploited.

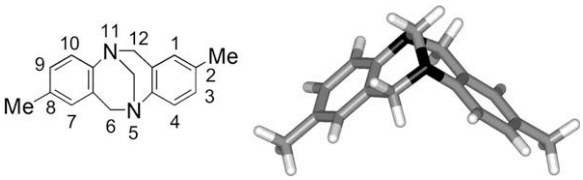

Figure 1. Tröger's base: structural formula (left) and optimized geometry of the (*S*,*S*)-enantiomer (right).

The common resolution of chiral amines via the formation of diastereoisomeric salts with enantiomerically pure chiral acids, was for a long time considered unfeasible for Tröger's base analogues due to the acid-promoted racemization.[5,6] In the light of some recent publications,[7,8] resolution in such a way does not appear impossible, but it certainly requires a careful choice of resolving agents and experimental conditions on a case-to-case basis, and therefore lacks generality. A number of other approaches toward the enantioseparation of Tröger's base analogues were described, including spontaneous resolution[9,10] and crystallization-induced asymmetric transformations.[11] It is however noteworthy that as early as 1944, Prelog and Wieland separated the enantiomers of Tröger's base by column chromatography on lactose followed by repeated crystallization.[5] Recently, high performance liquid chromatography (HPLC) on both commercial and tailor-made chiral stationary phases (CSP) has become increasingly popular as a method for the enantioseparation of functionalized analogues of Tröger's base.[9,12,13]

In recent years, a great deal of attention has been given to the synthesis of 'bis- and tris-Tröger's bases', that is, molecules comprising two or three methanodibenzodiazocine units fused in such a way, that a benzene ring of one methanodibenzodiazocine unit constitutes a part of a neighboring one (see review[3]). At the same time, there are no reports on the enantioseparation of such 'bis- and tris-Tröger's bases'. Since 'bis- and tris-Tröger's bases' are of particular interest as molecular tweezers or cavitands,[3,14] their preparation in enantiomerically pure form is of obvious interest for applications in chiral molecular recognition. Herein, we report the first study on the analytical enantioseparation of several 'bis- and tris-Tröger's bases' by HPLC on commercial CSP Whelk O1 column.

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2. Results and discussion

The structures of molecules used in this study are shown in Figure 2. For the two families of 'bis-Tröger's bases' (±)-**1a**–**c** and (±)-**2a**–**e**, which differ in the substitution pattern of the central benzene ring, only the *anti*-diastereoisomers were studied. Although the corresponding *syn*-isomers are always obtained in the synthesis, they are C_s-symmetrical molecules and can be viewed as achiral *meso*-forms, while the *anti*-diastereoisomers are C_2-symmetrical and represent pairs of enantiomers. On the other hand, the two diastereoisomeric 'tris-Tröger's bases'[14] (±)-*throne*-**4** (C_1-symmetry) and (±)-*calix*-**4** (C_3-symmetry) are both chiral. We have also included in this study the corresponding 'monomeric' analogues of Tröger's base (±)-**3a**–**g**. The interest for this extension of the analyte set is twofold. Firstly, we would like to compare the chromatographic behavior of derivatives comprising one methanodibenzodiazocine unit and those comprising two or three, yet derived from one and the same aromatic amine [e.g., (±)-**1a–3a** as well as (±)-*throne*-**4** and (±)-*calix*-**4** are all obtained from 4-methoxyaniline]. Secondly, there are, to the best of our knowledge, no litera-

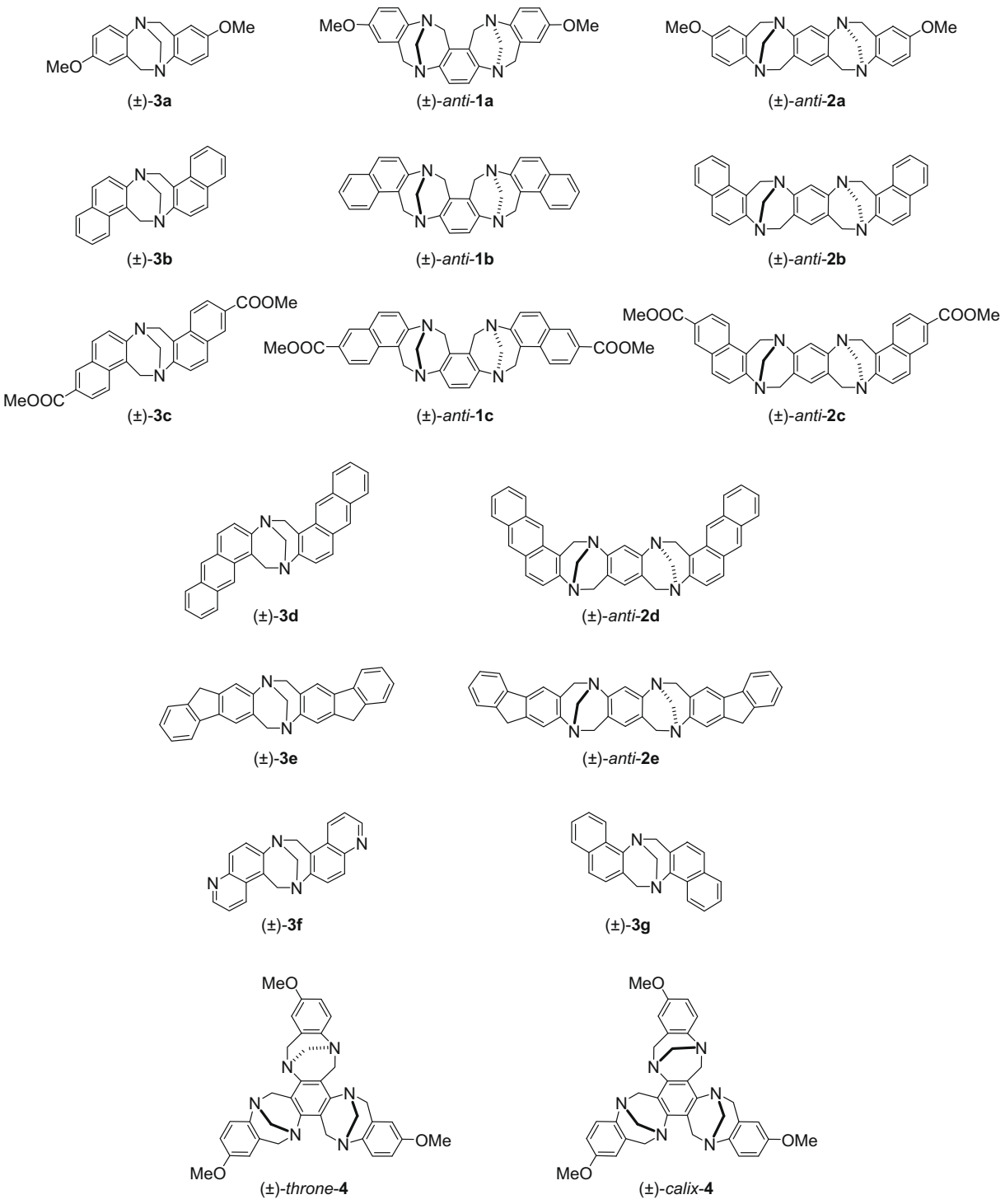
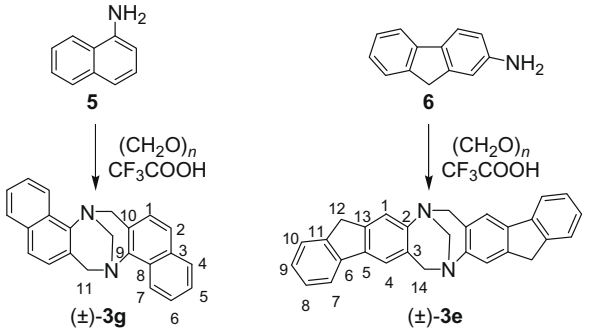


Figure 2. Structural formula of the Tröger's base analogues used in the present study.

ture reports on the enantioseparation by chromatography of Tröger's base analogues comprising non-benzenoid aromatic systems.

Most of the molecules shown in Figure 2 were previously reported by us or by other groups and were synthesized according to the published procedures (see references in Section 4). The exceptions are fluorene derivative (±)-**3e** and naphthalene derivative (±)-**3g**, the synthesis of which is depicted in Scheme 1.



Scheme 1. Synthesis of (±)-**3e** and (±)-**3g**; numbering of atoms is arbitrary and given for the assignment of chemical shifts in the NMR spectra, see Section 4.

Previously, it was reported that (±)-**3g** is inaccessible via condensation of 1-aminonaphthalene **5** with formaldehyde.[15] This finding was in striking contrast with the high-yielding synthesis of its isomer (±)-**3b** from 2-aminonaphthalene[7] and can be explained by the lower reactivity of the β-position in naphthalene compared to the α-position. However, in recent years a protocol based on the use of paraformaldehyde as a source of reactive formaldehyde and of CF_3COOH as a reaction medium has manifested itself as the method of choice for the synthesis of Tröger's base analogues from relatively unreactive, electron-deficient anilines (see Refs.[13,16,17] for examples and Refs.[13,16] for a possible rationalization of the different reactivity in CF_3COOH).

We therefore attempted the condensation of 1-aminonaphthalene **5** with paraformaldehyde in CF_3COOH and succeeded in the isolation of the corresponding Tröger's base analogue (±)-**3g**, albeit in modest yield (26%). The structure of (±)-**3g** was unambiguously confirmed by single crystal X-ray diffraction (see Fig. 3). The molecule of (±)-**3g** features a typical V-shaped geometry with the dihedral angle between the planes of the aromatic rings amounting to 99.13°, which falls into the usual range (between ca. 85° and ca. 105°) observed for the Tröger's base analogues.[3] It is however interesting that while (±)-**3b** forms conglomerates in the chiral space group $P2_12_12_1$,[10] and thus represents one of a very few Tröger's base analogues for which a spontaneous resolution was reported,[9] the isomer (±)-**3g** prepared by us forms racemic crystals in the centrosymmetric space group $P\bar{1}$.

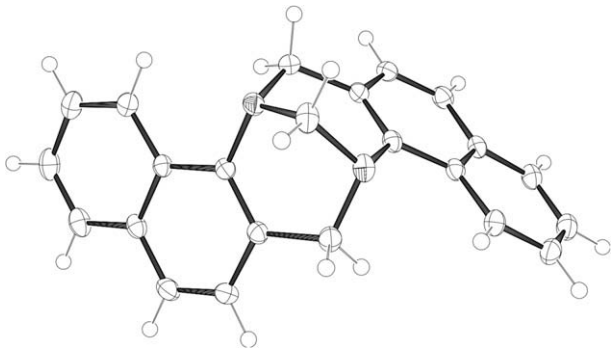


Figure 3. ORTEP-style plot of (±)-**3g** with thermal ellipsoids drawn at 50% probability level.

The fluorene derivative (±)-**3e** was prepared from 2-amino-9*H*-fluorene **6** by the same method. Amine **6** can yield a Tröger's base derivative by reacting at the 1- or 3-position (see Scheme 1). Analogously to the regioselectivity observed in the preparation of (±)-*anti*-**2e**,[18] we have isolated the expected symmetrical isomer (±)-**3e,** resulting from attack at the 3-positions. The structure of (±)-**3e** was elucidated based on the HMBC and NOESY NMR correlation spectra, as well as on the similarity of the ^{13}C NMR chemical shifts of (±)-**3e** with those of (±)-*anti*-**2e**. The molecular structure of the latter was unambiguously confirmed by single crystal XRD analysis (Fig. 4).

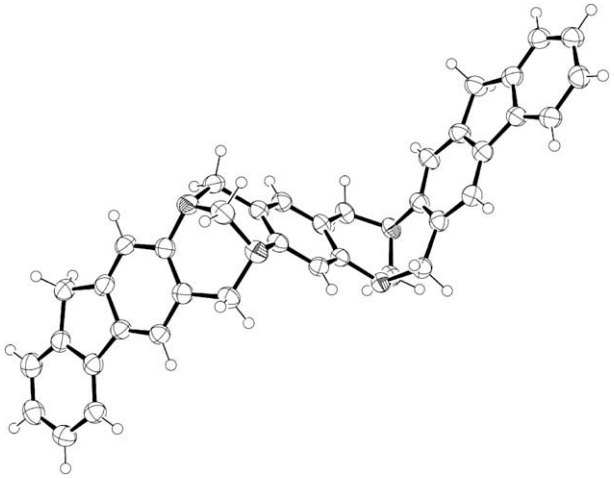


Figure 4. ORTEP-style plot of (±)-*anti*-**2e** with thermal ellipsoids drawn at 50% probability level.

The chromatographic separation of enantiomers was performed on the commercial chiral stationary phase (CSP) Whelk O1, with a covalently bound chiral selector derived from 3,4-disubstituted 1,2,3,4-tetrahydrophenanthrene (Fig. 5). Originally developed by Pirkle et al.[19] for the separation of naproxene and other non-steroidal anti-inflammatory drugs (NSAIDS), this CSP has later become increasingly popular due to its broad versatility.

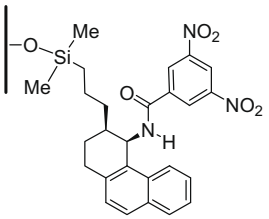


Figure 5. Chemical structure of CSP (3*S*,4*R*)-Whelk O1 used in this study. This CSP is marketed by Regis Technologies, Inc. under the name (*R*,*R*)-Whelk O1. The absolute configuration of the chiral selector is thus incorrectly designated, but this should not lead to confusion. What is important is the relative stereochemistry of the two stereogenic carbon atoms (*cis*) and the correct designation of the absolute configuration of C(4). The incorrect designation of the absolute configuration of C(3) results from the fact that the original version of this CSP had an 11-carbon linker, but substitution of it by the three-carbon linker results in the inversion of Cahn-Ingold-Prelog priorities at C(3).[20]

Due to the conformational preferences of the saturated ring in 1,2,3,4-tetrahydrophenanthrene (half-chair with the pseudoaxial amide group), the Whelk O1 chiral selector has a cleft-like shape. The preferential binding of the more-retained enantiomer of a chiral analyte in the cleft is provided through simultaneous

face-to-face π–π interactions with the π-acidic 3,5-dinitrobenzoyl moiety, face-to-edge CH–π binding with the π-basic naphthalene system, and H-bonding with the hydrogen of the amide group. The less-retained enantiomer is incapable of all these interactions without inducing a deviation from the lowest-energy conformation. This model is supported by systematic separations of various analytes, as well as by co-crystallization of homo- and heterochiral complexes of the chiral selector and an analyte, by analysis of ^{1}H NMR spectra of homo- and heterochiral complexes, and by computational studies.[21] Therefore, a typical good analyte for Whelk O1 CSP is an aromatic system with an additional H-bond acceptor in the proximity of the stereogenic center.

In a recent study published by some of us,[13] we demonstrated that CSP Whelk O1 is rather versatile for the separation of Tröger's base analogues, in which the stereogenic center itself (stereogenic N-atom) serves as an H-bond acceptor. Moreover, the systematic separation of a library of simple Tröger's base analogues allowed us to build a predictive model which is based on simple mechanistic considerations. Major factors influencing the enantioselectivity were established. Firstly, the face-to-face π–π binding between the electron-poor dinitrobenzoyl aromatic ring of the chiral selector and the aromatic ring of the analyte is greatly affected by the electronic nature of the substituents: it is favored by electron-donating and disfavored by electron-withdrawing groups. Secondly, achiral retention is increased if highly polar functional groups are present. Thirdly, steric hindrance plays an important role. By taking all these factors into account, we can conclude that: (1) electron-withdrawing substituents are detrimental to enantioseparation, (2) strongly electron-donating substituents are tolerated, but increase retention; (3) even rather bulky substituents at the 2- and 8-positions (see Fig. 1 for numbering) do not affect the separation while substituents at the 4- and 10-positions greatly decrease the enantioselectivity due to steric constraints; and (4) the best substrates are hence derivatives of Tröger's base bearing only modestly electron-donating substituents (such as alkyl groups) at the 2- and 8-positions.

We concluded that on the basis of this mechanistic model, a prediction could be made whether or not the enantioseparation of a given, perhaps yet unknown derivative of Tröger's base will be feasible with the aid of chromatography on Whelk O1. One of the objectives of the present study was the evaluation of the predictive capacity of this model on more complex Tröger's base analogues. Hence, we decided to also explore it for the separation of 'bis- and tris-Tröger's bases' and the corresponding 'monomeric' analogues (±)-**3a–g** as reference molecules. Experimental data are summarized in Table 1 as the retention factors of the two enantiomers k_1, k_2, the separation factors $\alpha = k_2/k_1$, and the baseline resolutions R_s. As long as it was practical, we used hexane/*i*-PrOH (50:50) as a mobile phase, for the purpose of better direct comparison between different analytes.

The chromatographic behavior of non-benzenoid Tröger's base analogues (±)-**3a–g** was in good agreement with the predictions based on the rationalization described earlier. Thus, two isomeric electron-rich naphthalene analogues (±)-**3b** and (±)-**3g** demonstrated excellent enantioselectivity, as did electron-rich anthracene and fluorene derivatives (±)-**3d** and (±)-**3e**. In sharp contrast, installing a strongly electron-withdrawing ester group on the naphthalene ring (derivative (±)-**3c**) dramatically reduced enantioselectivity. Quinoline derivative (±)-**3f** showed very low enantioselectivity but rather high retention compared to naphthalene derivatives (±)-**3b** and (±)-**3g.** This is likely due to the basic character of the N-atom of the quinoline moiety, which contributes to the achiral retention and may also compete with the stereogenic N-atom in the formation of H-bonds with the amido group of the chiral selector.

The behavior of 'bis-Tröger's bases' (±)-**1a**–**c** and (±)-**2a**–**e** was somewhat more complex but largely in line with the model established above. For structurally similar molecules, electron-rich derivatives showed better selectivity. Thus, electron-rich derivatives (±)-**1b** and (±)-**2b**,**d**,**e** showed better separation than (±)-**1c** and (±)-**2c**, which bear electron-withdrawing ester groups. Without exception, all 'bis-Tröger's bases' (±)-**1a–c** and (±)-**2a–e** demonstrated higher retention than the corresponding 'monomeric' analogues (±)-**3a–e**. This is probably due to the stronger achiral retention because of the larger number of highly polar amino functions per molecule.

In general, the comparison between 'bis-Tröger's bases' possessing identical peripheral aromatic systems but featuring a different substitution pattern of the central benzene ring shows better selectivity for (±)-**1a–c** versus the corresponding analogues (±)-**2a–c**. For instance, 'monomeric' Tröger's base analogue (±)-**3a** and 'bis-Tröger's base' (±)-**2a** showed modest enantioselectivity, while 'bis-Tröger's base' (±)-**1a** separates very well. A possible reason for this might be the difference in the substitution pattern of the central ring, which impacts the molecular recognition. Apparently, in the case of (±)-**1a**, all stereogenic N-atoms connected to both the peripheral rings, as well as the central one, are efficiently recognized by the chiral selector of CSP, while in the case of (±)-**2a**, only the stereogenic N-atoms connected to the peripheral ring efficiently participate in the chiral molecular recognition. The chiral recognition of the central ring in (±)–**2a** possibly hampered by steric factors.

Table 1
Enantioseparation of Tröger's base analogues on Whelk O1 with hexane/*i*-PrOH 50 : 50 (v/v) as a mobile phase

Tröger's base analogue	k_1	k_2	α	R_s
(±)-*anti*-**1a**	5.75	13.2	2.30	3.5
(±)-*anti*-**2a**	5.44	7.07	1.30	1.2
(±)-**3a**	2.07	2.73	1.32	1.25
(±)-*anti*-**1b**	6.97	21.0	3.01	5.7
(±)-*anti*-**2b**	4.71	7.20	1.53	2.1
(±)-**3b**	2.15	5.91	2.75	5.0
(±)-*anti*-**1c**[a]	21.9	41.6	1.90	2.6
(±)-*anti*-**2c**	21.2	30.1	1.42	1.9
(±)-**3c**	12.0	16.7	1.39	2.2
(±)-*anti*-**2d**	13.4	22.2	1.66	2.9
(±)-**3d**	8.11	19.1	2.35	5.9
(±)-*anti*-**2e**	10.27	17.7	1.72	2.9
(±)-**3e**	6.34	19.6	3.09	9.1
(±)-**3f**	13.8	16.0	1.16	0.6
(±)-**3g**	1.81	6.03	3.33	7.7
(±)-*throne*-**4**	11.3	14.7	1.30	0.9
(±)-*calix*-**4**	5.85	15.4	2.63	4.3

[a] *i*-PrOH as the mobile phase.

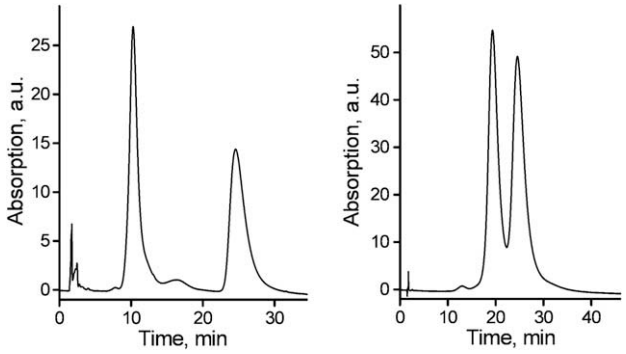


Figure 6. Chromatograms of (±)-*calix*-**4** (left) and (±)-*throne*-**4** (right) on Whelk O1, mobile phase hexane/*i*-PrOH (50:50).

The behavior of the two diastereoisomers of 'tris-Tröger's base' **4** was also very different. While (±)-*throne*-**4** showed rather poor enantioselectivity, excellent separation was achieved for (±)-*calix*-**4** (Fig. 6). This can be interpreted in the following way: the two enantiomers of *calix*-**4** have (all-*S*) and (all-*R*) configurations, and in this case, for the more-retained enantiomer all the three stereogenic N-atoms connected to the peripheral benzene rings are recognized equally well by the CSP. The two enantiomers of *throne*-**4** have (*R*,*R*,*R*,*R*,*S*,*S*)- and (*S*,*S*,*S*,*S*,*R*,*R*)-configurations: this means that only two stereogenic N-atoms are favorably recognized for the more-retained enantiomer, while still one N-atom is preferably recognized for the less-retained one. In other words, the enantioseparation of (±)-*throne*-**4** is due to the preferable recognition of effectively only one third of the stereogenic N-atoms connected to the peripheral rings. Hence, the enantioselectivity for (±)-*calix*-**4** is expected to be much higher than that for (±)-*throne*-**4**.

In addition, a quantitative estimation of the expected differences in enantioselectivities between (±)-*throne*-**4** and (±)-*calix*-**4** can also be made. Indeed, the apparent enantioselectivity α on an enantiomerically impure CSP can be related to the enantiomeric excess of the CSP (ee) and the enantioselectivity on the enantiomerically pure CSP (α_0) by the following equation:[22]

$$\alpha = \frac{\alpha_0(1+\mathrm{ee}) + (1-\mathrm{ee})}{\alpha_0(1-\mathrm{ee}) + (1+\mathrm{ee})} \quad (1)$$

One can now reciprocally apply the same notion to the analyte, considering the more-retained enantiomer of (±)-*calix*-**4** as 'inherently enantiopure' and the more-retained enantiomer of (±)-*throne*-**4** as possessing 2:1 'inherent enantiomeric composition'. Then, with ee = 1/3, Eq. 1 can be modified to Eq. 2:

$$\alpha_{throne} = \frac{2\alpha_{calix} + 1}{\alpha_{calix} + 2} \quad (2)$$

From the experimentally observed enantioselectivity for *calix*-**4** in hexane/*i*-PrOH 50:50 ($\alpha = 2.63$) one would expect from Eq. 2 $\alpha_{calc} = 1.35$ for *throne*-**4**, which is in good agreement with the experimental data in the same eluent ($\alpha = 1.30$, Table 1).

The rather high enantioselectivity observed for (±)-*calix*-**4** is particularly encouraging: *calix*-**4** can be viewed as an entry to a new family of C_3-symmetrical chiral cavitands, which are of obvious interest for enantioselective encapsulation of small chiral molecules. Chromatography on CSP Whelk O1 offers easy access to this class of molecules in enantiomerically pure form.

Finally, we attempted to improve the separation parameters of selected derivatives that showed modest enantioselectivity in hexane/*i*-PrOH (50:50) by variation of the mobile phase. The results are summarized in Table 2. Lowering polarity of eluents only marginally improved the enantioselectivity for (±)-*anti*-**2a** and (±)-**3a**. For the purpose of comparison we also performed an analysis of (±)-**3e** and (±)-**3g** with eluents of varied polarity. For the two latter compounds, a considerable increase in selectivity was observed with a decrease in polarity. Thus, for naphthalene derivative (±)-**3g**, α grew from 3.33 to 5.20 upon a decrease of *i*-PrOH content in the mobile phase from 50% to 2%. However, for all the compounds studied, the retention times became impractically high in the mobile phases with a low content of *i*-PrOH. It was concluded that the mobile phase hexane/*i*-PrOH (50:50) represents a good compromise between the selectivity and the retention times for all the molecules studied and should probably be chosen as an initial system for the future studies of similar molecules.

Table 2
Enantioseparation of Tröger's base analogues upon variation of the composition of mobile phase

Tröger's base analogue	Mobile phase (hexane/*i*-PrOH, v/v)	k_1	k_2	α	R_s
(±)-*anti*-**2a**	50/50	5.44	7.07	1.30	1.2
(±)-*anti*-**2a**	80/20	12.4	16.1	1.30	1.2
(±)-*anti*-**2a**	90/10	20.1	26.9	1.34	1.25
(±)-**3a**	50/50	2.07	2.73	1.32	1.25
(±)-**3a**	90/10	5.37	7.62	1.42	1.6
(±)-**3a**	95/5	7.61	11.4	1.50	1.9
(±)-**3e**	50/50	6.34	19.6	3.09	9.1
(±)-**3e**	80/20	8.50	33.3	3.91	9.1
(±)-**3e**	90/10	11.5	51.4	4.41	10.3
(±)-**3g**	50/50	1.81	6.03	3.33	7.7
(±)-**3g**	90/10	3.20	13.9	4.35	8.5
(±)-**3g**	98/2	4.82	24.5	5.10	10.4

3. Conclusion

For the first time, we have reported a method for the enantioseparation of 'bis- and tris-Tröger's bases' with the aid of chromatography on the commercially available CSP Whelk O1. The previously established simple mechanistic model for the enantioselective recognition of Tröger's base derivatives on the CSP Whelk O1 appears to be also valid for the more complex non-benzenoid analogues, as well as for 'bis- and tris-Tröger's bases'. It should be mentioned that this model should be used with some caution, since it does not take into account the entropic contributions to the enantioselective molecular recognition. For all 'bis- and tris-Tröger's bases' studied, satisfactory to excellent enantioselectivity was observed. Although we did not perform the separation of enantiomers on a preparative scale, the method transfer from analytical to preparative chromatography on Whelk O1 is straightforward, as was already demonstrated by us on simpler Tröger's base analogues. Hence, chromatography on Whelk O1 grants access to preparative amounts of these unprecedented molecules in enantiopure form. This should considerably facilitate new applications of these molecules that take full advantage of their chirality.

4. Experimental

4.1. General

All chemicals were purchased from Aldrich, Acros, or TCI Europe and used without further purification. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra: chemical shifts (δ) are given in ppm relative to Me_4Si (internal standard). The following derivatives were synthesized according to previously published procedures: (±)-*anti*-**1a**,[23] (±)-*anti*-**1b**,**c**,[24] (±)-*anti*-**2a**,**b**,[25] (±)-*anti*-**2c**,[26] (±)-*anti*-**2d**,[18] (±)-**3a**,[13] (±)-**3b**,[7] (±)-**3c**,[24] (±)-**3d**,[18] (±)-**3f**,[27] (±)-*throne*-**4**[14], and (±)-*calix*-**4**.[14]

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 734608 (±)-**3g** and 733466 (±)-*anti*-**2e**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

The HPLC separations were performed at ambient temperature on an Agilent 1100 instrument equipped with the Rheodyne 7725 manual loop injector. The solvents were of HPLC grade. The column (*R*,*R*)-Whelk-O1 (250 × 4.6 mm) was purchased from Regis Technologies (USA). Injection: 20 μL of analyte solution in CH_2Cl_2, ca. 1 mg mL^{-1}; mobile phase: hexane/*i*-PrOH, nominal flow rate 2.0 mL min^{-1}; detection: UV at fixed wavelength 254 nm. Separation parameters were calculated as follows: $k_1 = (t_1 - t_0)/t_0$, $k_2 = (t_2 - t_0)/t_0$, $\alpha = k_2/k_1$, $R_s = 2(t_2 - t_1)/(w_2 + w_1)$, where t_1 and t_2 are the retention times of the first and the second eluted

enantiomers, t_0 is the void time (retention time of 1,3,5-tri-*tert*-butylbenzene), k_1 and k_2 are the retention factors of the two enantiomers, α is the separation factor, w_1 and w_2 are the widths of peaks at the base line, and R_s is the resolution at the base line.

4.1.1. 5,13,19,23-Tetrahydro-8*H*,10*H*-7,22:11,20-dimethano difluoreno[2,3-*f*:2,3-*f*′]benzo[1,2-*b*:5,4-*b*′]bis[1,5]diazocine (±)-*anti*-2e

This compound was prepared as previously described.[18] Slow evaporation of a solution of (±)-*anti*-**2e** in acetone/CH_2Cl_2 gave a crystal suitable for XRD analysis: found formula $C_{38}H_{30}N_4{\cdot}0.5CH_2Cl_2$, space group $P2_1/n$, unit cell parameters: a = 14.1420(2) Å, b = 16.1620(2) Å, c = 24.8480(3) Å, β = 91.8723(11), for more details see data deposited as CCDC 733466.

4.1.2. 6,9,15,18-Tetrahydro-7,16-methanodifluoreno[2,3-*b*:2′,3′-*f*][1,5]diazocine (±)-3e

2-Amino-9*H*-fluorene **6** (300 mg, 1.66 mmol) was dissolved in 30 mL of CF_3COOH and paraformaldehyde (358 mg, 11.9 mmol of 'CH_2O') was added at room temperature. The resulting mixture was stirred for 24 h, then slowly added to a stirred mixture of ice and 30% aqueous NH_3 (50 mL). Extraction with CH_2Cl_2 (3 × 150 mL), drying of the organic layer over $MgSO_4$, and removal of the solvent in vacuo gave a crude product, which was purified by preparative TLC (20 × 20 × 0.2 with pre-concentration zone, CH_3OH/CH_2Cl_2 3:97) to give (±)-**3e** (94 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.78 (d, $^2J_{H,H}$ = 21.7 Hz, 2H, H–C(12)), 3.89 (d, $^2J_{H,H}$ = 21.7 Hz, 2H, H–C(12)), 4.39 (d, $^2J_{H,H}$ = 16.4 Hz, 2H, H^{endo}–C(14)), 4.48 (s, 2H, NCH_2N), 4.89 (d, $^2J_{H,H}$ = 16.4 Hz, 2H, H^{exo}–C(14)), 7.22 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, H–C(8)), 7.29 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, H–C(9)), 7.39 (s, 2H, H–C(1)), 7.33 (s, 2H, H–C(4)), 7.47 (d, $^3J_{H,H}$ = 7.3 Hz, 2H, H–C(10)), 7.61 (d, $^3J_{H,H}$ = 7.5 Hz, 2H, H–C(7)); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 36.5 (C(12)), 59.3 (C(14)), 67.1 (NCH_2N), 117.8 (C(4)), 119.3 (C(7)), 121.4 (C(1)), 124.8 (C(10)), 126.10 (C(3)), 126.11 (C(9)), 126.6 (C(8)), 137.9 (C(5)), 141.2 (C(6)), 142.5 (C(13)), 143.0 (C(11)), 146.9 (C(2)); HRMS (ESI^+): m/z calcd for $C_{29}H_{23}N_2$ ($[M+H]^+$) 399.1861; found 399.1868.

4.1.3. 7*H*,15*H*-8,16-Methanodinaphtho[1,2-*b*:1′,2′-f][1,5]diazocine (±)-3g

1-Aminonaphthalene **5** (716 mg, 5 mmol) followed by paraformaldehyde (300 mg, 10 mmol of 'CH_2O') was added in portions under vigorous stirring to CF_3COOH (10 mL) at −15 °C. The resulting mixture was allowed to reach room temperature and stirred for 24 h, then slowly added to a stirred mixture of ice and 30% aqueous NH_3 (17 mL). Extraction with CH_2Cl_2 (3 × 50 mL), drying of the organic layer over $MgSO_4$, and removal of the solvent in vacuo gave a crude product, which was purified by column chromatography on SiO_2 (CH_2Cl_2 as eluent) to give (±)-**3g** (214 mg, 26%) as an off-white solid; mp 209.7–211.3 °C; R_f 0.25 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.41 (d, $^2J_{H,H}$ = 17.0 Hz, 2H, H^{endo}–C(11)), 4.91 (d, $^2J_{H,H}$ = 17.0 Hz, 2H, H^{exo}–C(11)), 4.59 (s, 2H, NCH_2N), 6.90 (d, $^3J_{H,H}$ = 8.4 Hz, 2H, H–C(1)), 7.43–7.48 (m, 4H, H–C(5), H–C(6)), 7.55–7.61 (m, 2H, H–C(4)), 7.74 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, H–C(7)), 8.37 (2H, d, $^3J_{H,H}$ = 8.4 Hz, 2H, H–C(2)); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 56.1 (C(11)), 67.6 (NCH_2N), 122.5 (C(2)), 124.3 (C(7)), 124.4 (C(10)), 124.7 (C(5)), 125.5 (C(6)), 126.0 (C(1)), 128.3 (C(4)), 129.1 (C(8)), 133.3 (C(3)), 142.5 (C(9)); HRMS (ESI^+): m/z: calcd for $C_{23}H_{19}N_2$ ($[M+H]^+$) 323.1548; found 323.1588. Slow evaporation of a solution of (±)-**3g** in CH_2Cl_2 gave a crystal suitable for XRD analysis: found formula $C_{23}H_{18}N_2$, space group $P\bar{1}$, unit cell parameters: a = 7.902(1) Å, b = 10.413(1) Å, c = 11.093(1) Å, α = 103.385(8)°, β = 98.365(7)°, γ = 110.022(2)°, for more details see data deposited as CCDC 734608.

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