1, CHOTBS), 4.33 and 4.45 (AB q, J = 12 Hz, 2, C-8 CH_2OBz), 4.50 (m, 1, acetal CH), 7.40–8.06 (m, 5, Ar H); exact mass calcd for $C_{29}H_{41}SiO_6$ [M – C_4H_9]$^+$ 513.2673, found 513.2670.

8β-[(*tert*-Butyldimethylsilyl)oxy]-7α-hydroxy-8β-(hydroxymethyl)-13-methyl-18,19-bisnor-9β-podocarp-13-en-12-one (31). The same procedure described for the preparation of **28** was repeated using 161 mg (0.50 mmol) of **26** and 212 μL (1.1 mmol, 2.2 equiv) of 1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene[26] (**27b**) followed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride and acid-catalyzed hydrolysis to afford, after chromatography on a silica gel plate using 8:1 ethyl acetate–hexane, 169 mg (83%) of **31**: $[\alpha]^{25}_D$ –64.7° (c 1.7 g/100 mL, dichloromethane); mp 215–218 °C; IR (KBr) 3400, 1640, 1240, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.10 (2 s, 6, $SiCH_3$), 0.82 (s, 9, $SiC(CH_3)_3$), 1.01 (s, 3, C-10β CH_3), 1.84 (s, 3, C-13 vinylic CH_3), 2.35–2.80 (m, 3, C-9β CH and C-11 CH_2), 6.46 (s, 1, C-14 vinylic H).

Anal. Calcd for $C_{23}H_{40}SiO_4$: C, 67.60; H, 9.87. Found: C, 67.66; H, 9.92.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-7α-hydroxy-13-methyl-18,19-bisnor-9β-podocarp-13-en-12-one. The procedure described for the preparation of the monobenzoate ester of **28** was repeated using 128 mg (0.31 mmol) of **31**, 90 μL (0.78 mmol) of benzoyl chloride, and 60 mg (0.50 mmol) of 4-(dimethylamino)pyridine to afford, after chromatography on a silica gel plate using 1:1 ethyl acetate–hexane, 143 mg (90%) of the monobenzoate of **31**: $[\alpha]^{25}_D$ –76.8° (c 3.23 g/100 mL, dichloromethane); mp 143–146 °C; IR (TF) 3500, 1725, 1660, 1270, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.09 (2 s, 6, $SiCH_3$), 0.82 (s, 9, $SiC(CH_3)_3$), 1.02 (s, 3, C-10β CH_3), 1.84 (s, 3, C-13 vinylic CH_3), 2.58–2.90 (m, 3, C-9β CH and C-11 CH_2), 3.65–3.78 (m, 2, C-7α OH and C-7 CH), 3.80 (m, 1, C-1 CH), 4.40 (s, 2, C-8 CH_2OBz), 6.37 (s, 1, C-14 vinylic H), 7.36–7.98 (m, 5, Ar H).

Anal. Calcd for $C_{30}H_{44}SiO_5$: C, 70.27; H, 8.65. Found: C, 70.32; H, 8.68.

8β-[(Benzoyloxy)methyl]-7α-[(2-bromo-1-ethoxy)ethoxy]-1β-[(*tert*-butyldimethylsilyl)oxy]-13-methyl-18,19-bisnor-9β-podocarp-13-en-12-one (32). The procedure described for the preparation of **29** was repeated using 140 mg (0.27 mmol) of the monobenzoate ester of **31**, 128 μL (0.96 mmol) of 1,2-dibromoethyl ethyl ether, and 121 μL (0.96 mmol) of *N*,*N*-dimethylaniline to afford, after chromatography on a silica gel plate using 1:3 ethyl acetate–hexane, 166 mg (93%) of **32** as a 1:1 inseparable mixture of diastereomers: $[\alpha]^{25}_D$ –55.9° (c 5.94 g/100 mL, dichloromethane); IR (KBr) 1725, 1665, 1270, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.12 (2 s, 6, $SiCH_3$), 0.82 (s, 9, $SiC(CH_3)_3$), 1.02 and 1.04 (s, 3, diastereomeric C-10β CH_3), 1.1–1.26 (m, 3, CH_2CH_3), 1.78 and 1.80 (s, 3, diastereomeric C-13 vinylic CH_3), 2.58–2.92 (m, 3, C-9β CH and C-11 CH_2), 4.22–4.58 (m, 2, C-8 CH_2OBz), 4.22–4.58 and 4.64–4.70 (m, 1, diastereomeric acetal CH), 6.35 (s, 1, C-14 vinylic H), 7.38–8.00 (m, 5, Ar H); exact mass calcd for $C_{30}H_{42}BrSiO_6$ [M – C_4H_9]$^+$ 605.1937, found 605.1935.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-14α-(formylmethyl)-7α-hydroxy-13-methyl-18,19-bisnor-9β-podocarpan-12-one Ethyl Acetal (33). The procedure described for the preparation of **30** was repeated using 160 mg (0.24 mmol) of **32**, 79 μL (0.390 mmol) of tri-*n*-butyltin hydride, and 4 mg (0.024 mmol) of azobis(isobutyronitrile), which were refluxed for 16 h, to afford, after chromatography on a silica gel plate using 1:3 ethyl acetate–hexane, 115 mg (82%) of **33** as a 3:2 inseparable mixture of diastereomers: $[\alpha]^{25}_D$ –48.0° (c 1.38 × 10^{-1} g/100 mL, toluene); IR (TF) 1725, 1270, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.06 (2 s, 6, $SiCH_3$), 0.79 (s, 9, $SiC(CH_3)_3$), 0.96 and 0.99 (d, J = 6.7 Hz, 3, diastereomeric C-13 vinylic CH_3), 1.03 and 1.04 (s, 3, diastereomeric C-10β CH_3), 1.19 (m, 3, CH_2CH_3), 3.44 and 3.92 (m, 1, diastereomeric CHOTBS), 3.60–3.68 (m, 2, CH_2CH_3), 3.62 and 4.06 (m, 1, diastereomeric C-7 CH), 4.24–4.58 (m, 2, C-8 CH_2OBz), 4.24–4.58 and 4.78–4.84 (m, 1, diastereomeric acetal CH), 7.40–8.10 (m, 5, Ar H); exact mass calcd for $C_{30}H_{43}SiO_6$ [M – C_4H_9]$^+$ 527.2831, found 527.2829.

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Registry No. (±)-**11**, 86863-46-9; (±)-**12**, 95778-38-4; **13**, 111324-60-8; **14**, 111324-61-9; **17**, 111349-22-5; (±)-**19**, 111324-62-0; **24**, 100348-93-4; **24** (1β-OH deriv), 34996-06-0; **24** (1β-OTBS deriv), 111408-46-9; **25**, 111324-63-1; **25** (6β-OH deriv), 111324-72-2; **25** (7-(hydroxymethylene) deriv), 111324-73-3; **26**, 111324-64-2; (*E*)-**27a**, 54125-02-9; (*E*)-**27b**, 72476-03-0; **28**, 111324-65-3; **28** (8-benzoate), 111324-74-4; **29** (isomer 1), 111324-66-4; **29** (isomer 2), 111349-23-6; **30** (isomer 1), 111324-67-5; **30** (isomer 2), 111324-68-6; **31**, 111324-69-7; **31** (8-benzoate), 111324-75-5; **32** (isomer 1), 111324-70-0; **32** (isomer 2), 111324-76-6; **33** (isomer 1), 111324-71-1; **33** (isomer 2), 111324-77-7.

Molecular Armatures. Synthesis and Structure of Tröger's Base Analogues Derived from 4-, 2,4-, 3,4-, and 2,4,5-Substituted Aniline Derivatives[1]

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The preparation of biomimetic systems designed to mimic natural receptor sites and enzymic active sites requires the development of new synthetic strategies for preparing large molecules with predictable and well-defined shapes. In this paper a number of derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocines are prepared. The scope and limitations of the reaction of formaldehyde with aniline derivatives are examined. The molecules prepared have potential value as conformationally restricted armatures for the construction of biomimetic molecular systems. A crystallographic study reveals that the molecules are folded and that the angle formed by the two aryl rings ranges from 88° to 104°. Sulfonamides, bromides, alcohols, and amines can be introduced as side-chain substituents in these systems.

Introduction

Enzymic catalysis and molecular complexation are a sine qua non of life. The study of enzymes and of molecular interactions is based on analytical and abstractive processes.[2] Investigations of enzyme models and biomimetic experiments exemplify the abstractive approach to new knowledge.[3,4] This approach requires the investigator to

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(1) Number 7 in a series on the Chemistry of Synthetic Receptors and Functional Group Arrays.

(2) Nagel, E. *The Structure of Science*; Harcourt, Brace and World: New York, 1961.

0022-3263/88/1953-0098$01.50/0

identify the "important" parts of natural catalysts or receptors, to present a theory that explains the properties of the natural system as a consequence of these parts, and to construct and analyze systems that imitate this proposed mechanism. An essential part of this process of hypothesis and test is the *chemical synthesis* of the target system. This paper addresses issues related to chemical synthetic approaches for the construction of biomimetic systems.

A practical preparative pathway to a synthetic receptor or synthetic enzyme would be simple and easily modified, proceed in high yield, and afford a single stereoisomer of the molecule. The molecule prepared by this "simple" route should be rigid, or at least the dynamic properties of the molecule should be well-understood.[5] If the target is to hold three or more functional groups in a specific (often convergent) relationship, the target is very likely to be a polycyclic system and to have a molecular weight over 700 amu. The speed with which such a target can be prepared is important because that rate is directly proportional to the rate at which new designs can be tested.

Our interests in the chemistry of synthetic receptors and functional group arrays have led us to explore general approaches for constructing new molecular armatures.[6] Derivatives of Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, **6a**) are relatively rigid molecules that have proven useful in our efforts to construct biomimetic systems and specific functional group arrays.[6a-d] The incorporation of Tröger's base derivatives into a macrocyclic molecule can afford water-soluble synthetic receptors more rigid than previously obtained examples.[6b] The methanodibenzodiazocine armature has proven useful as the key component in an approach to chiral molecular clefts and nonmacrocyclic synthetic receptors.[6c] This paper describes an investigation of the chemistry and structure of Tröger's base derivatives.

Results and Discussion

Tröger's Base. Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, **6a**) is a product of the acid-promoted condensation of toluidine (**5a**) and formaldehyde and was first described in 1887.[7] The molecule has an interesting history. It was the first amine proven to have a rate of configurational interconversion so slow as to allow resolution of the synthetic material into its enantiomeric components.[8] The correct structure was established by Spielman in 1935, and the base was first resolved into its enantiomeric forms by Prelog.[9,10] Wagner and co-workers contributed to our understanding of such aromatic amine and formaldehyde condensations, and about 25 years ago Farrar reexamined such reactions and identified several of the byproducts generated in such syntheses.[11,12] Recently, Greenberg examined the mechanism of acid-catalyzed racemization of Tröger's base by nuclear magnetic resonance and ultraviolet spectral techniques.[13] The results of our crystallographic study of this molecule have been previously presented.[6a,d] It is sufficient to point out that, as suggested by molecular modeling calculations, the molecule is sharply folded (comparable to Figure 2) and is well-suited for the preparation of "macrocycles, clathrates, or molecular clefts or helices".[6a]

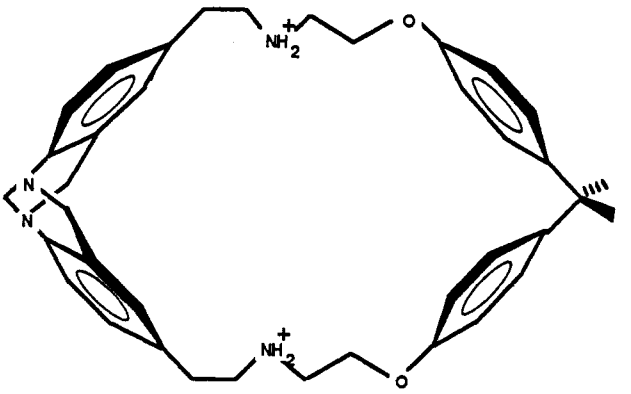
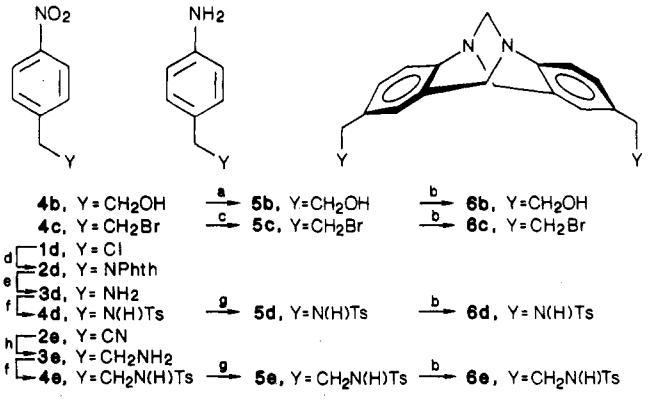


Figure 1. Example of macrocyclic synthetic receptor prepared from **6e**.[6b]

Scheme I[a]



[a] (a) $NaBH_4$, 5% Pd/C; (b) H_2CO/H^+, EtOH; (c) HBr, H_2/PtO_2, MeOH; (d) phthalimide/K_2CO_3, DMF; (e) N_2H_4, THF, EtOH; (f) TsCl/Et_3N, THF; (g) H_2/PtO_2, MeOH; (h) $BF_3/NaBH_4$, THF.

Analogues of Tröger's Base. Macrocyclic molecules that contain the dibenzodiazocine unit can be synthetic receptors. For example, the molecule illustrated in Figure 1 has been reported to form complexes with benzenoid substrates in aqueous solution. To prepare such molecules, it is necessary to have functionalized extensions on both ends of the dibenzodiazocine unit which can serve as

(3) The general area of biomimetic or bioorganic chemistry has enjoyed the attention of gifted chemists for more than 30 years. A short list of references cannot give a fair introduction to this area, but see: Bender, M. L.; Bergeron, R. J.; Komiyama, M. *The Bioorganic Chemistry of Enzymatic Catalysis*: Wiley-Interscience: New York, 1984. For a recent survey of results and goals in this area, see: International Symposium on Bioorganic Chemistry; Breslow, R., Ed.; Annals of the New York Academy of Sciences, Vol. 471; New York Academy of Sciences; New York, 1986.

(4) Breslow, R. *Science (Washington, D.C.)* **1982**, *218*, 532–537.

(5) Control of the conformation of a functional group array would allow more precise interpretations of the properties of the array and would allow the effects of small changes in the array to be predicted with less uncertainty. A disordered array with many degrees of freedom is unlikely to lead to functional group cooperativity.

(6) (a) Wilcox, C, S. *Tetrahedron Lett.* **1985**, *26*, 5749–5752. (b) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563–5566. (c) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865–1867. (d) Larson, S. B.; Wilcox, C. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 224–227. (e) Wilcox, C. S.; Cowart, M. D. *Carbohydr. Res.*, in press. (f) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.*, in press.

(7) Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225–245.

(8) In work contemporary with Spielman's structural determination for Tröger's base, several groups were investigating means to prevent or to slow down amine nitrogen configurational inversion.[10]

(9) Spielman, M. A. *J. Am. Chem. Soc.* **1935**, *57*, 583–585.

(10) Prelog recognized that the structure proposed by Spielman for Tröger's base was chiral and was the first to resolve Tröger's base: Prelog, V.; Wieland, P. *Helv. Chim. Acta.* **1944**, *27*, 1127.

(11) (a) Eisner, A.; Wagner, E. C. *J. Am. Chem. Soc.* **1934**, *56*, 1938. (b) Wagner, E. C. *J. Org. Chem.* **1937**, *2*, 157. (c) Miller, T. R.; Wagner, E. C. *J. Am. Chem. Soc.* **1938**, *60*, 1738. (d) Wagner, E. C.; Miller, T. R. *J. Am. Chem. Soc.* **1941**, *63*, 832. (e) Wagner, E. C. *J. Org. Chem.* **1954**, *19*, 1862.

(12) Farrar, W. V. *J. Appl. Chem.* **1964**, *14*, 389.

(13) Greenberg, A.; Molinaro, N.; Lang, M. *J. Org. Chem.* **1984**, *49*, 1127–1129.

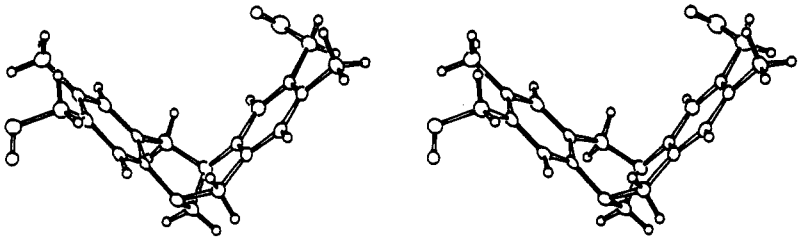


Figure 2. Stereoview of **6h**. Non-H atoms are scaled to the 50% probability level; H atoms are of arbitrary size.

connecting points for attachment of other molecular fragments. A number of experiments were therefore conducted to examine ways to vary the length and type of substituent at positions C-2 and C-8 in the dibenzodiazocine system.

Alcohols and alkyl halides have found frequent use in previous routes to macrocyclic rings, but at the outset of this project, no examples of Tröger's base analogues bearing such functional groups were known. Preparation of the first Tröger's base analogues having such functionalized side chains began with 4-nitrophenethyl alcohol (**4b**) or 4-nitrophenethyl bromide (**4c**). Reduction of these nitroarenes afforded the corresponding amines **5b** and **5c**. Aniline derivatives **5b** and **5c**, when treated with formaldehyde and aqueous acid, gave Tröger's base analogues **6b** and **6c** (Scheme I).

These new examples of Tröger's base type molecules have a two-carbon extension on positions C-2 and C-8. These side chains are functionalized to facilitate macrocycle formation. The functionalized extensions on Tröger's base analogues **6b** and **6c** can be converted to other functional groups to allow for greater ease of macrocycle formation. For example, Tröger's base analogue **6c** has been converted to the corresponding sulfonamide **6e**, which was used successfully in preparing the macrocyclic synthetic receptor shown in Figure 1.[6b]

During the preparation of Tröger's base analogues, the aniline–formaldehyde condensation reaction is usually the step that gives the poorest yields. Due to this circumstance, it is a good strategy to complete most of the (side-chain) synthetic manipulations before this condensation. In consideration of this idea, an improved procedure for preparing **6e** has been developed. Reduction of 4-nitrophenylacetonitrile (**2e**), followed by tosylation of the crude amine **3e** and reduction of the corresponding nitro compound **4e**, gives the aminophenethyl sulfonamide **5e** in 63% overall yield. In the presence of formaldehyde and acid, this aniline affords compound **6e** in 30% yield (Scheme I).

One-carbon side chains at C-2 or C-8 were desired as components of modified synthetic receptors. It was also of interest to determine what functional groups at the para position (if any) could be carried through the formaldehyde condensation step. Treatment of 4-nitrobenzyl chloride (**1d**) with phthalimide and then deprotection of the resulting *N*-benzylphthalimide **2d** with hydrazine afforded the amine **3d**. Tosylation of the crude amine **3d** gave 4-nitrobenzyl sulfonamide **4d** in 65% overall yield from the benzyl chloride. Reduction of the nitro group produced the corresponding amine **5d** in 97% yield, and this aryl amine, when treated with formaldehyde and aqueous acid, gave the benzyl sulfonamide Tröger's base analogue **6d** (Scheme I). This analogue has a one-carbon chain at both ends and can be used for the preparation of smaller macrocycles than might be prepared by using analogue **6e**.

Attempts to use aniline derivatives bearing other functional groups were sometimes unsuccessful. In some cases, the failure can be attributed to the electron-withdrawing (deactivating) effects of the substituents. For example, no dibenzodiazocine products were isolated from reactions of 4-aminobenzoates or 4-chloroaniline. In the case of 4-aminobenzyl alcohol, the failure was most likely due to polymer formation through a cationic mechanism. The presence of a methoxy group at the para position of the aniline derivative gave poor yields in the Tröger's base formation steps.[14] The ethylene thioketal derived from *p*-aminobenzaldehyde gave, under the usual conditions, no dibenzodiazocine product.

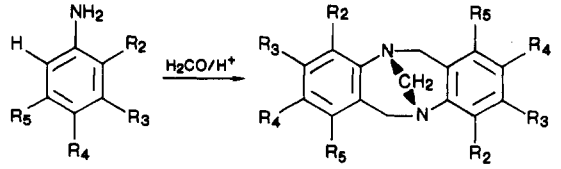
The Question of Additional Side Chains. It was reasoned that if alkyl groups or functional groups could be attached at positions other than C-2 or C-8 in the dibenzodiazocine systems, then several benefits might be realized. First, the presence of simple alkyl groups at positions C-1, C-3, or C-4 (and the corresponding positions C-7, C-9, and C-10) would increase the area of the concave surface and might lead to enhanced binding. A similar effect of added alkyl groups has been observed by Diederich in his investigations of macrocyclic synthetic hosts.[15] Two groups standing at such positions would impose a steric impediment close to the binding site and would contribute to the achievement of diastereoselective complex formation. The unadorned macrocyclic receptor illustrated in Figure 1 is formally chiral, but has a generally cylindrical shape which is not likely to discriminate between chiral substrates. Attachment of alkyl groups at C-4 and C-10 could lead to a more selective receptor. Finally, it was desirable to examine routes to Tröger's base derivatives containing additional side chains because those side chains could be used to support reactive groups or catalytic groups.

When this project began, only a few Tröger's base analogues were known and these were all derived from para-substituted aniline derivatives. No dibenzodiazocines derived from multiply substituted aniline derivatives were known. The formation of Tröger's base must involve an electrophilic substitution reaction. The extent to which the steric and electronic effects of other ring substituents might influence the rate and regiochemistry of this reaction was unknown, and therefore a limited study of the reaction of formaldehyde with di- and trisubstituted aniline derivatives was undertaken.

(14) The methoxy derivative was made in another way in a previous report.

(15) (a) Diederich, F.; Dick, K. *Tetrahedron Lett.* **1982**, *23*, 3167–3170. (b) Diederich, F.; Dick, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 715–716. (c) Diederich, F.; Dick, K. *Angew. Chem. Suppl.* **1983**, 957–972. (d) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8024–8036. (e) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8037–8046. (f) Diederich, F.; Dick, K.; Griebel, D. *Chem. Ber.* **1985**, *118*, 3588–3619. (g) Krieger, C.; Diederich, F. *Chem. Ber.* **1985**, *118*, 3620–3631. (h) Diederich, F.; Dick, K. *Chem. Ber.* **1985**, *118*, 3817–3829. (i) Lutter, H.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1125–1127. (j) Ferguson, S. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1127–11229. (k) Schurmann, G.; Diederich, F. *Tetrahedron Lett.* **1986**, *27*, 4249–4252. (l) Rubin, Y.; Dick, K.; Diederich, F.; Georgiadis, T. M. *J. Org. Chem.* **1986**, *51*, 3270–3278.

Table I



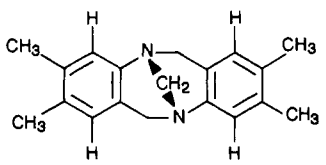
5 6

compd	R_2	R_3	R_4	R_5	time,[a] h	temp,[b] °C	yield of 6, %
5a	H	H	CH_3	H	24	25	60
5b	H	H	CH_2CH_2OH	H	24	25	46
5c	H	H	CH_2CH_2Br	H	18	50	22
5d	H	H	CH_2NHTs	H	24	50	21
5e	H	H	CH_2CH_2NHTs	H	24	50	30
5f	CH_3	H	CH_3	H	24	25	32
5g	CH_3	H	OCH_3	H	24	25	14
5h	H	CH_2OH	CH_3	H	24	25	25
5i	CH_3	H	CH_3	CH_3	24	25	78
5j	H	CH_3	CH_3	H	24	25	80[c]

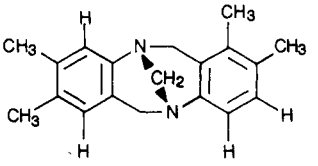
[a] Total reaction time. [b] Reaction temperature. [c] Mixture of two structural isomers **6j–7j**, 7.2:2.8.

Treatment of 2,4-dimethylaniline (**5f**) with formaldehyde and acid afforded a 32% yield of the desired dibenzodiazocine **6f**. The use of 2-methyl-4-methoxyaniline (**5g**) under similar conditions afforded a relatively low yield (14%) of the dibenzodiazocine **6g** (Table I).

The results of two other cases indicate that steric interactions due to methyl groups do not seem to have a negative effect on Tröger's base formation. First, it was observed that when 2,4,5-trimethylaniline (**5i**) is treated with formaldehyde and acid under the usual conditions, the hexamethyl-substituted Tröger's base analogue **6i** can be isolated in good yield. The effect of a methyl group at a site adjacent to the site of electrophilic attack is apparently favorable to the reaction. In the reaction of 3,4-dimethylaniline (**5j**), three isomeric products are possible. Steric hindrance seems to play a role in the extent to which one isomer is formed at the expense of the others. Only two of three possible isomers are observed. The ratio of these isomers is about 7:3, and the less crowded product (**6j**) is the favored product. The structural assignment



6j

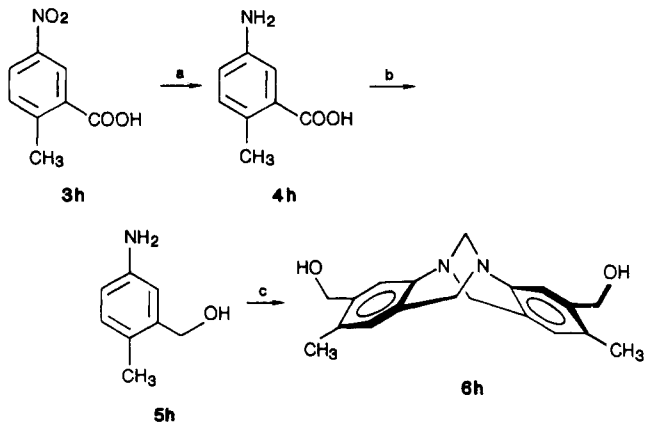


7j

is supported by the X-ray results described below.) It is likely that this is a kinetic result. No interconversion of isomers under the reaction conditions was observed. If the two electrophilic substitution reactions have equal regioselectivities, then the third isomer would make up less than 3% of the mixture.

If Tröger's base analogue were to be used for creating really interesting synthetic receptors and functional group arrays, then side chains more complex than methyl groups would be required at positions ortho and meta to the amine. Attempts to form dibenzodiazocines from aniline derivatives carrying ortho functional groups were not successful. Both 2-amino-5-methylbenzyl alcohol and methyl 2-amino-5-methylbenzoate gave no dibenzodiazocine products. In an effort to obtain a product dibenzodiazocine bearing functionality at C-3 or C-9, the reaction of methyl 5-amino-2-methylbenzoate with formaldehyde and acid was investigated, but again, no success was achieved. The accumulated evidence supported the

Scheme II[a]



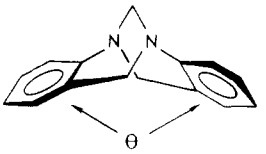
[a] (a) H_2/PtO_2, EtOH; (b) $LiAlH_4$/THF; (c) H_2CO/H^+, EtOH.

reasonable conclusion that in some cases deactivation of the ring by electron-withdrawing groups, and in other cases side reactions due to benzylic cation formation at positions ortho or para to the amine, were preventing Tröger's base formation.

It seemed plausible that a hydroxymethyl group meta to the amine might survive the conditions required for dibenzodiazocine formation. To test this possibility, 5-amino-2-methylbenzyl alcohol (**5h**) was prepared as illustrated in Scheme II. This amine, when treated with formaldehyde and aqueous acid, produced Tröger's base analogue **6h** in 25% yield. The formation of analogue **6h** shows that a one-carbon side chain bearing a functional group can be incorporated into the dibenzodiazocine armature at C-3 or C-9.

To conclude this section, a summary of the results is appropriate. The above observations reveal that sulfonamides, alkyl bromides, and alcohols are compatible with our conditions for Tröger's base formation. Previous results indicate that phthalimides and some esters and aryl nitriles, too, can be carried through the reaction.[6b,c] Not surprisingly, electron-withdrawing groups attached to the aniline ring at any position are not allowable. Also benzylic halides or alcohols ortho or para to the aniline amino group result in very poor yields of the desired dibenzodiazocine. Fortunately, a benzylic alcohol meta to the aniline amine can be carried through to the dibenzodiazocine. Methyl groups do not prevent the reaction and can lead to some selectivity in the site of reactivity. The general success

Table II[a]



compd	θ, deg	compd	θ, deg
6a[b]	92.9 (2)	6f	104.01 (6)
	97.4 (2)	6h	89.71 (7)
6a[c]	102.15 (5)	6j	88.6 (1)
6c	92.73 (10)		

[a] With one exception, all data was obtained for crystalline racemate. [b] There are two types of molecules in each unit cell. [c] Crystals of the (+) enantiomer were generously provided by Prof. A. Dreiding (Zurich).

with alkyl substituents in this reaction indicates that any number of complex side chains might be allowable, provided any functional groups on such side chains are remote from the aryl ring and are stable to acidic ethanol or methanol at room temperature. The ready availability of many of these precursors and products makes these Tröger's base analogues and hybrids of these analogues good starting points for future preparations of enzyme models, synthetic receptors, or functional group arrays.

X-ray Diffraction Studies. Substituents and the Structure of the Armature. In what way do these modifications of Tröger's molecule affect the structure of the basic dibenzodiazocine unit? This queston is important because if these modified dibenzodiazocines are to be used as armatures for biomimetic systems, the structure of the armatures must be known before a rational design can be completed. In addition, the extent to which the parent system changes its shape due to added substituents might be correlated with the flexibility of the methano-bridged dibenzodiazocine system. Finally, in some cases, a means to induce small changes in the fold of the armature would be desirable. For example, if the C-2 and C-8 positions hold catalytic groups, then small changes in the angle of the fold of the armature will cause small changes in the distance between the catalytic groups. A predictable means of changing the angle of the fold would therefore allow the structure of the catalyst to be very subtly controlled and perhaps allow a fine tuning of the catalytic properties.

The phenyl rings of Tröger's base and its analogues are oriented at approximately right angles to each other. In the compounds examined to date, the dihedral angles between phenyl rings range from 88.6 (1)° for **6j** to 104.01 (6)° for **6f** and are listed in Table II. There is a moderate amount of flexibility in the dibenzodiazocine ring system, a fact that may be exploitable in the design of more complex host molecules based on the Tröger's base framework. For example, an almost 10° difference in the dihedral angle is observed for the parent compound, Tröger's base, for which the crystal structures of the racemic mixture and the (+) enantiomer have been determined. The difference can only be due to packing effects associated with the different crystal environments of the molecules. While packing forces do influence the conformation of these molecules, intramolecular steric effects also play a role. The dihedral angle can be influenced by the substitution pattern on the phenyl ring. The largest dihedral angle observed is 104.01 (6)° for **6f**, which has 2,4-dimethyl ring substitution, while the smallest are for **6h** (89.71 (7)°) and **64** (88.6 (1)°), which have 3,4 ring substitution (Figure 2).

Molecules of **6h** form H-bonded dimers in the crystal as shown in Figure 3. The conformation of the dimer is

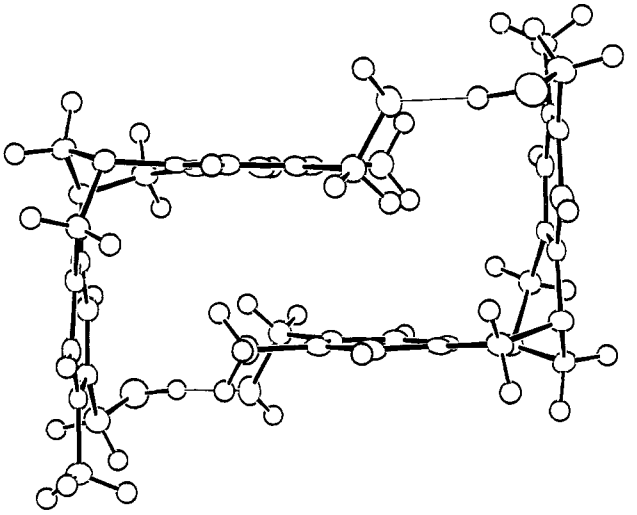


Figure 3. View of the H-bonded dimer of **6h**.

such that a phenyl ring from one molecule stacks on top of a phenyl ring from the second molecule. The plane to plane separation is 3.58 Å. This conformation is of interest to us because it is suggestive of one possible molecular conformation of a synthetic receptor composed of two dibenzodiazocine subunits separated by a flexibile multiatom spacer without the guest molecule situated in the receptor cavity.

Conclusion

This investigation has revealed that a variety of Tröger's base analogues can be prepared by the standard aniline–formaldehyde condensation route. The molecules obtained share the unique property of having rather rigid yet sharply bent conformations. As such, these molecules and their congeners may be applicable to the preparation of new biomimetic synthetic receptors or functional group arrays.

Our experience indicates that within the limits discussed in this paper functionalized Tröger's base analogues can be easily prepared. The shape of such analogues can be changed subtly by changing the substituents adjacent to the diazocine ring. The ready availability of many of these precursors and products and the unique geometry of these molecules persuasively argue for the application of these Tröger's base analogues in future preparations of enzyme models, synthetic receptors, or functional group arrays.

Experimental Section[16]

General Procedure for Synthesis of Tröger's Base Analogues 6a,f,g,i,j. To a mixture of 9.34 mmol of the substituted aniline and 10 mL of 95% ethanol was added 4.5 mL (55.5 mmol) of 37% formalin solution. The stirred mixture was then cooled to 0 °C, 3.8 mL (45.5 mmol) of concentrated HCl was then added, and the solution was stirred at room temperature, under nitrogen, for 24 h. After 24 h at room temperature, the volatile components of the reaction mixture were removed under reduced pressure at 40–50 °C until one-half of the original volume remained. The remaining mixture was poured into a 500-mL separatory funnel containing 130 mL of H_2O and 10 mL of concentrated NH_4OH. The resulting mixture was then extracted three times with 70 mL each of CH_2Cl_2. The organic phases were combined and washed with 200 mL of saturated $NaHCO_3$ solution and with 200 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$

(16) A description of general procedures and experimental details and analytical data dealing with preparations of the precursors to the Tröger's base analogues are contained in the supplementary material.

and filtered. The CH_2Cl_2 was then removed under reduced pressure, and the residual crude material was placed under vacuum overnight.

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6a). The crude product was prepared by the general procedure and purified by flash chromatography (4 × 12 cm column, SiO_2, 10% diethyl ether–CH_2Cl_2) to give 0.70 g (60%) of Tröger's base (**6a**): R_f 0.15 (SiO_2, 10% diethyl ether–CH_2Cl_2); mp 125–128 °C; IR (Nujol) 3150, 1490, 1325, 1300, 1210, 1190, 960, 950, 900, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (d, 2 H, J = 7.9 Hz), 6.94 (br d, 2 H, J = 8.3 Hz), 6.68 (s, 2 H), 4.62 (d, 2 H, J = 16.6 Hz), 4.28 (s, 2 H), 4.09 (d, 2 H, J = 16.6 Hz), 2.20 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.6, 133.2, 128.0, 127.6, 127.2, 124.8, 67.1, 58.7, 20.7; MS calcd for $C_{17}H_{18}N_2$ m/e 250.14699, measured 250.14643.

6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diethanol (6b). To a solution of 9.6 g (70 mmol) of the amino alcohol **5b** in 90 mL of 95% ethanol cooled in an iced bath was added 35 mL (420 mmol) of formalin (37% formaldehyde) followed by (slow addition) 31.5 mL of concentrated HCl. The heterogeneous mixture was stirred under nitrogen at 25 °C for 24 h. The mixture was concentrated under reduced pressure until one-half of the original volume remained, diluted with 500 mL of H_2O, and made basic with excess NH_4OH. The aqueous phase was extracted with 5 × 200 mL each of CH_2Cl_2. The combined organic phases were washed with 200 mL of H_2O and 200 mL of saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent under reduced pressure afforded a foam residue, which was purified by flash chromatography (SiO_2, 10% MeOH–CH_2Cl_2) to give 5.8 g of product, which was crystallized from 15 mL of hot ethanol to afford 4.7 g (38%) of **6b**·C_2H_5OH as straw colored crystals, mp 135–137 °C, unchanged on heating under vacuum for 8 h at 78 °C. An analytical sample was obtained by recrystallizing this material from toluene–chloroform: mp 141–144 °C; R_f 0.26 (SiO_2, 10% MeOH–CH_2Cl_2); IR (Nujol) 3300 (br), 1490, 1350, 1330, 1300, 1210, 1040, 1020, 965, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (s, 4 H), 6.73 (s, 2 H), 4.61 (d, 2 H, J = 16.6), 4.08 (s, 2 H), 3.99 (d, 2 H, J = 16.6), 3.6 (t, 2 H, J = 7 Hz), 2.57 (t, 2 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 146.3, 134.6, 128.1, 127.8, 127.4, 125.2, 66.9, 63.3, 58.6, 38.7.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.54; H, 7.09; N, 9.03. Found: C, 73.61; H, 7.18; N, 8.96.

2,8-Bis(2-bromoethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6c). To 1 g (3.55 mmol) of the hydrobromide **5c** in a 25-mL round-bottom flask under nitrogen were added 5 mL of 95% ethanol and 0.3 mL of H_2O. The stirred mixture was cooled to 0 °C, and 1.8 mL (22.2 mmol) of formalin (37% formaldehyde) was added via syringe followed by 1.6 mL of 8.8 M HBr. The heterogeneous mixture was stirred under nitrogen at 50 °C for 18 h. After 18 h, the reaction mixture was transferred to a 500-mL separatory funnel containing 100 mL of H_2O and 15 mL of concentrated aqueous NH_4OH. The resulting mixture was extracted three times with 100 mL each of CH_2Cl_2. The organic phases were combined and washed with 100 mL of saturated $NaHCO_3$ and with 100 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$ and filtered. Volatile components were then removed under reduced pressure, and the resulting yellow residue was purified by flash chromatography (4 × 15 cm column, SiO_2, 5% diethyl ether–CH_2Cl_2) to give 0.25 g of a white foam. The white foam solidified upon washing with ethanol to afford 0.17 g of **6c** (22%) as a white solid: R_f 0.22 (SiO_2, 5% diethyl ether–CH_2Cl_2); mp (slow decomposition beginning at 120 °C); IR ($CDCl_3$) 3700, 3620, 2910, 1495, 1365, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (d, 2 H, J = 8.1 Hz), 7.00 (d, 2 H, J = 8.1 Hz), 6.74 (s, 2 H), 4.67 (d, 2 H, J = 16.6), 4.28 (s, 2 H), 4.12 (d, 2 H, J = 16.6), 3.47 (t, 4 H, J = 7.5 Hz), 3.02 (t, 4 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 147.0, 134.5, 128.0, 127.6, 126.9, 125.3, 66.9, 58.6, 39.0, 32.5; MS calcd for $C_{19}H_{20}N_2Br_2$ m/e 433.99932, measured 433.99849.

Anal. Calcd for $C_{19}H_{20}N_2Br_2$: C, 52.31; H, 4.58; N, 6.42. Found: C, 52.40; H, 4.66; N, 6.41.

***N*,*N*'-(6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diyldimethylene)bis-*p*-toluenesulfonamide (6d).** To a heterogeneous mixture of 386 mg (1.40 mmol) of the amine **5d** in 1.68 mL of 95% ethanol cooled in an iced bath was added 0.63 mL (8.38 mmol) of 37% formalin followed by (slow addition) 0.58 mL (6.99 mmol) of concentrated HCl. The heterogeneous mixture was stirred under nitrogen at 50 °C for 24 h. The mixture was concentrated under reduced pressure until one-half of the original volume remained. The remaining mixture was diluted with 5 mL of H_2O and made basic with 1.5 M NH_4OH (40 mL). The aqueous phase was extracted with 4 × 30 mL each of CH_2Cl_2. The combined organic phases were washed with 20 mL of H_2O and 50 mL of saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent under reduced pressure afforded a foam residue, which was purified by flash chromatography (SiO_2, 60% diethyl ether–CH_2Cl_2) to give 85.1 mg (21%) of product **6d**, a white powder: decomposed at 180 °C; R_f 0.17 (SiO_2, 50% diethyl ether–CH_2Cl_2); IR (Nujol) 3620, 3060, 1600, 1500, 1330, 1305, 1270, 1205, 1160, 1095, 1065, 960, 890, 840 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.90 (s, 1 H), 7.64 (d, 2 H, J = 7.8 Hz), 7.34 (d, 2 H, J = 7.8 Hz), 6.99 (s, 2 H), 6.74 (s, 1 H), 4.51 (d, 1 H, J = 16.8), 4.16 (s, 1 H), 3.99 (d, 1 H, J = 16.8 Hz), 3.78 (s, 2 H), 3.38 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 147.2, 142.4, 138.0, 132.6, 129.4, 127.6, 126.4, 126.0, 124.4, 66.3, 58.2, 45.8, 20.8; MS calcd for $C_{31}H_{32}N_4O_4S_2$ m/e 558.18650, measured 558.18546.

Anal. Calcd for $C_{31}H_{32}N_4O_4S_2$: C, 63.24; H, 5.48; N, 9.52. Found: C, 63.27; H, 5.49; N, 9.44.

***N*,*N*'-(6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diyldiethylene)bis-*p*-toluenesulfonamide (6e).** To a heterogeneous mixture of 580 mg (2.00 mmol) of the amine **5e** in 2.40 mL of 95% ethanol cooled in an ice bath was added 0.99 mL (12.0 mmol) of 37% formalin followed by (slow addition) 0.83 mL (10 mmol) of concentrated HCl. The reacton mixture was stirred at 50 °C under nitrogen for 24 h. The heterogeneous mixture was concentrated under reduced pressure until one-half of the original volume remained. The remaining mixture was diluted with 5 mL of H_2O, transferred to a separatory funnel with the aid of 100 mL of CH_2Cl_2, and basified with 2.5 M NH_4OH (60 mL). The aqueous phase was separated and extracted with two additional 40-mL portions of CH_2Cl_2. The combined organic phases were washed with 20 mL of H_2O and 30 mL of saturated aqueous $NaHCO_3$ and dried over K_2CO_3. Removal of solvent under reduced pressure afforded a foam residue, which was purified by flash chromatography (SiO_2, 50% diethyl ether–CH_2Cl_2) to give 185 mg (30%) of the product **6e**, a foam: mp 88–95 °C; R_f 0.16 (SiO_2, 50% diethyl ether–CH_2Cl_2); IR (CH_2Cl_2) 3350, 2940, 1920, 1660, 1600, 1490, 1400, 1330, 1200, 1150, 1090, 950, 880, 840, 810, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (d, 2 H, J = 7.9 Hz), 7.24 (d, 2 H, J = 7.9 Hz), 6.99 (d, 1 H, J = 8.3 Hz), 6.84 (d, 1 H, J = 7.6 Hz), 6.58 (s, 1 H), 5.06 (s, 1 H), 4.53 (d, 1 H, J = 13.4 Hz), 4.11 (s, 1 H), 4.01 (d, 1 H, J = 17.0 Hz), 3.05 (m, 2 H), 2.59 (t, 2 H, J = 6.5 Hz), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.7, 143.2, 137.2, 133.4, 129.6, 127.9, 127.6, 127.0, 125.3, 66.7, 58.5, 44.1, 35.3, 21.4; MS calcd for $C_{33}H_{36}N_4O_4S_2$ m/e 616.21780, measured 616.21951.

Anal. Calcd for $C_{33}H_{36}N_4O_4S_2$: C, 64.26; H, 5.88; N, 9.08. Found: C, 64.18; H, 5.93; N, 9.02.

2,4,8,10-Tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6f). The crude product was prepared by the general procedure and purified by flash chromatography (4 × 12 cm column, SiO_2, 10% diethyl ether–CH_2Cl_2) to give 0.757 g of a 7:3 mixture of Tröger's base **6f** and starting material. The mixture was then recrystallized from hot ethanol to afford 0.42 g of **6f** (32%) as a colorless crystalline solid: R_f 0.66 (SiO_2, 10% diethyl ether–CH_2Cl_2); mp 104–106 °C; IR (Nujol) 2750, 1350, 1325, 1300, 1215, 1140, 1125, 980, 915, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84 (s, 2 H), 6.55 (s, 2 H), 4.51 (d, 2 H, J = 16.6 Hz), 4.28 (s, 2 H), 3.91 (s, 2 H, J = 16.6 Hz), 2.35 (s, 6 H), 2.17 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 143.6, 132.9, 132.5, 129.6, 127.7, 124.7, 67.8, 55.1, 20.6, 16.8; MS calcd for $C_{19}H_{22}N_2$ m/e 278.17829, measured 278.17870.

Anal. Calcd for $C_{19}H_{22}N_2$: C, 82.01; H, 7.91; N, 10.07. Found: C, 81.97; H, 7.99; N, 10.02.

2,8-Dimethoxy-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6g). The crude product was prepared by the general procedure and purified by flash chromatography (4 × 12 cm column, SiO_2, 10% diethyl ether–CH_2Cl_2) to give 0.627 g of a 57:43 mixture of starting material and Tröger's base **6g**. The mixture was then recrystallized from hot methanol to give 0.2 g of **6g** (14%) as a colorless crytalline solid: R_f 0.56 (SiO_2, 10% diethyl ether–CH_2Cl_2); mp 127–131 °C; IR (Nujol) 3350, 1590,

1300, 1270, 1180, 1150, 1120, 1040, 950, 900, 850, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (s, 2 H), 6.29 (s, 2 H), 4.53 (d, 2 H, J = 16.6 Hz), 4.29 (s, 2 H), 3.89 (d, 2 H, J = 16.6 Hz), 3.69 (s, 6 H), 2.38 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.8, 139.3, 134.2, 128.9, 115.3, 108.5, 68.0, 55.5, 55.2, 17.1; MS calcd for $C_{19}H_{22}N_2O_2$ m/e 310.16812, measured 310.16868.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.54; H, 7.09; N, 9.03. Found: C, 73.45; H, 7.12; N, 9.01.

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-3,9-dimethanol (6h). To 491 mg (3.6 mmol) of 5-amino-2-methylbenzyl alcohol (**5h**) in 4 mL of 95% ethanol was added 1.8 mL (22.2 mmol) of 37% formalin solution. The mixture was cooled to 0 °C, and 15 mL of concentrated HCl (18.4 mmol) was added. The mixture was stirred at room temperature under nitrogen for 24 h. After 24 h, the reaction mixture was added whole to a 500-mL separatory funnel and worked up with the same quantities of base, CH_2Cl_2, and washes as for the general Tröger's procedure. The vacuum-dried brown solid/foam crude product mixture was combined with a small quantity of CH_2Cl_2 and left for 24 h. At the end of this time a white crystalline solid was deposited, and this was removed by filtration to yield 0.14 g of **6h**, a white solid (25%): mp 230–235 °C dec; IR (Nujol) 3350, 2750, 1320, 1300, 1210, 1170, 920, 720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.02 (s, 2 H), 6.64 (s, 2 H), 4.95 (t, 2 H, J = 5.0 Hz), 4.51 (d, 2 H, J = 16.2 Hz), 4.35 (s, 4 H), 4.16 (s, 2 H), 3.98 (d, 2 H, J = 16.2 Hz), 2.06 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 145.4, 139.0, 129.8, 127.5, 125.7, 122.7, 66.6, 60.8, 57.9, 17.4; MS calcd for $C_{19}H_{22}N_2O_2$ m/e 310.16812, measured 310.16746.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.54; H, 7.09; N, 9.03. Found: C, 73.36; H, 7.15; N, 8.99.

1,2,4,7,8,10-Hexamethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6i). After the workup, the crude product (prepared by the general procedure) was purified by flash chromatography (4 × 12 cm column, SiO_2, 5% diethyl ether–CH_2Cl_2) to give 1.11 g (78%) of Tröger's base **6i**: R_f 0.43 (SiO_2, 5% diethyl ether–CH_2Cl_2); mp 187–190 °C; IR (Nujol) 3150, 2750, 1225, 1210, 975, 945, 870, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (s, 2 H), 4.42 (d, 2 H, J = 16.6 Hz), 4.23 (s, 2 H), 3.95 (d, 2 H, J = 16.9 Hz), 2.38 (s, 6 H), 2.14 (s, 6 H), 1.94 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 144.5, 131.4, 130.8, 130.4, 129.7, 126.3, 66.2, 54.4, 19.5, 16.8, 13.4; MS calcd for $C_{21}H_{26}N_2$ m/e 306.20959, measured 306.21018.

Anal. Calcd for $C_{21}H_{26}N_2$: C, 82.35; H, 8.49; N, 9.15. Found: C, 82.29; H, 8.56; N, 9.12.

2,3,8,9-Tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*]-[1,5]diazocine (6j) and 1,2,8,9-Tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7j). The crude product was prepared by the general procedure and purified by flash chromatography (4 × 12 cm column, SiO_2, 10% diethyl ether–CH_2Cl_2) to give 1.051 g (80%) of a mixture of two structural isomers **6j** and **7j** with a ratio of 72:28, both having R_f 0.18 (SiO_2, 10% diethyl ether–CH_2Cl_2); mp 197–202 °C; IR (Nujol) 2750, 1610, 1550, 1210, 1170, 1100, 1075, 950, 915, 885 cm^{-1}; ^1H NMR ($CDCl_3$) **6j** (major component) δ 6.89 (s, 2 H), 6.64 (s, 2 H), 4.60 (d, 2 H, J = 16.2 Hz), 4.27 (s, 2 H), 4.08 (d, 2 H, J = 16.6 Hz), 2.16 (s, 6 H), 2.11 (s, 6 H); **7j** (minor component) δ 6.96 (d, 1 H, J = 7.9 Hz), 6.91 (d, 1 H, J = 3.9 Hz), 6.89 (s, 1 H, 6.65 (s, 1 H), 4.64–4.49 (m, 2 H), 4.26–4.15 (m, 4 H), 2.18 (s, 3 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.8, 135.5, 132.2, 132.1, 128.6, 127.7, 126.0, 125.9, 125.8, 125.0, 122.3, 67.3, 66.8, 58.4, 58.0, 19.4, 19.0.

Anal. Calcd for $C_{19}H_{22}N_2$: C, 82.01; H, 7.91; N, 10.07. Found: C, 81.95; H, 8.01; N, 10.04.

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Registry No. **2d**, 62133-07-7; **2e**, 555-21-5; **3d**, 7409-30-5; **3e**, 24954-67-4; **3h**, 1975-52-6; **4c**, 5339-26-4; **4d**, 111437-15-1; **4e**, 111437-16-2; **4h**, 2840-04-2; **5a**, 106-49-0; **5b**, 104-10-9; **5c**, 39232-03-6; **5d**, 111437-06-0; **5e**, 111437-08-2; **5f**, 95-68-1; **5g**, 102-50-1; **5h**, 111437-10-6; **5i**, 137-17-7; **5j**, 95-64-7; **6a**, 529-81-7; **6b**, 111437-05-9; **6c**, 101193-83-3; **6d**, 111437-07-1; **6e**, 111554-33-7; **6f**, 98883-82-0; **6g**, 111437-09-3; **6h**, 111437-11-7; **6i**, 111437-12-8; **6j**, 111437-13-9; **7j**, 111437-14-0; 4-$NO_2C_6H_4CH_2Cl$, 100-14-1; 4-$NO_2C_6H_4(CH_2)_2OH$, 100-27-6; formalin, 50-00-0.

Supplementary Material Available: General experimental methods, procedures, and data for the preparation of **2d**, **3d**, **4d**, **4e**, **4h**, **5b–e**, and **5h**, figures showing ORTEP plots and crystal packing diagrams for **6f**, **6h**, and **6j**, and tables of fractional coordinates, isotropic and anisotropic thermal parameters, bond lengths, bond angles, torsion angles, and dihedral angles from X-ray crystallographic analyses (36 pages). Ordering information is given on any current masthead page. Tables of observed and calculated structure factor amplitudes may be obtained from V. Lynch, Department of Chemistry, University of Texas at Austin, Austin, Texas 78712.

Enzymatic Hydrolysis of Alkyl 3,4-Epoxybutyrates. A New Route to (*R*)-(-)-Carnitine Chloride

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The enzyme-catalyzed hydrolysis of alkyl 3,4-epoxybutyrates to the corresponding epoxy acids is reported. By using esterases the reaction occurred with good stereoselectivity leading to optically active unreacted esters of *R* configuration. With proteases the stereoselectivity was reversed, and the *S* enantiomer of the unreacted ester was recovered, albeit in lower enantiomeric excess. Finally, upon preliminary optimization of the reaction conditions, a new synthesis of (*R*)-(-)-carnitine chloride by the successive use of a stereoselective and of a nonstereoselective enzymatic hydrolysis is shown.

The potential of enzymes as catalysts in synthetic organic chemistry has received much attention in recent years.[1] Because enzymes can simultaneously display high chemical, regiochemical, and stereochemical selectivity, their use can be suitable when two or more reactive groups are present in the same substrate as in the case of the enantioselective hydrolysis of epoxy esters. This reaction was reported by Whitesides for the resolution of 2,3-epoxy alcohol carboxylic esters[2] which represents an alternative

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