Concave Reagents, 5[1,2]

Bimacrocyclic 1,10-Phenanthroline Cyclophanes

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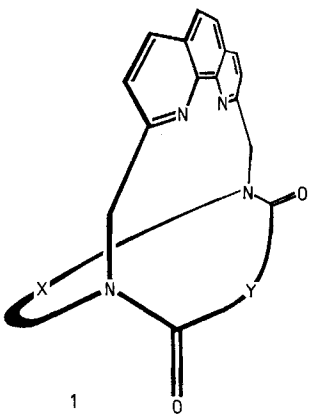
The addition of lithium aryls **3** to 1,10-phenanthroline (**2**), functionalization of the rearomatized bisadduct **8b** to the tetraphenol **8d**, and cyclization of **8d** with two equivalents of an α,ω-ditosylate **9** led to a highly symmetrical, conformer-free bimacrocyclic 1,10-phenanthroline **10a** in which the basic and coordinating region possesses a concave shielding.

One of the reasons for the high selectivity of enzymatic reactions is the concave environment of the active site. If the standard reagents of organic chemistry (acids and bases, reagents for oxidations and reductions) are combined with concave structural elements, the selectivities of these reagents might also increase.

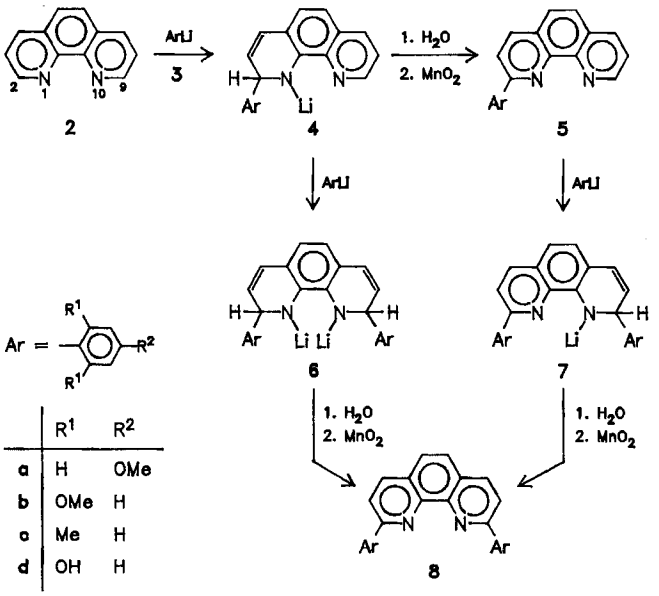
In macrobicyclic 1,10-phenanthroline bislactames[3] **1** and analogous pyridine bislactames[1,4] the reactive centres (basic nitrogen atoms) are imbedded in concave positions. But these reagents are mixtures of conformers, because the amide bridgeheads may exist in (*Z*) and (*E*) conformations[1,3,4]. To solve this problem, new conformer-free, symmetrical and nonbasic bridgehead units have to be found. Trisubstituted benzenes, which have already been incorporated in other macrocycles[5], appear suitable.



(*E,Z*) conformer

When lithium-organic compounds **3** are treated with 1,10-phenanthroline (**2**) aryl (and also alkyl) substituents may be introduced into the 2- and 9-positions of 1,10-phenanthroline (**2**)[6]. Thus 2,9-bis(4′-methoxyphenyl)-1,10-phenanthroline (**8a**) is accessible[6b]. But this strategy could not be applied for the synthesis of 2,9-bis(2′,6′-dimethoxyphenyl)-1,10-phenanthroline (**8b**) without complications: 2,6-dimethoxyphenyllithium (**3b**), prepared from 1,3-dimethoxybenzene and *n*-butyllithium[7], added much slower to the 1,10-phenanthroline unit than unreacted *n*-butyllithium, which still existed in the reaction mixture. Thus, *n*-butyl-substituted 1,10-phenanthrolines were produced.

But when the organolithium compounds **3b** and **3c** were synthesized by treating 1,3-disubstituted 2-bromobenzenes with elementary lithium, they could be added to 1,10-phenanthroline (**2**) without side reactions. Two pathways for the synthesis of **8b** and **8c** were possible: (A) Addition of two equivalents of aryllithium to 1,10-phenanthroline (**2**) formed the tetrahydro-1,10-phenanthroline **6** which could be rearomatized to the tetra-*ortho*-substituted diaryl-1,10-phenanthrolines **8b** and **8c** by MnO_2. (B) The bisaryl-1,10-phenanthrolines **8** could also be prepared in a two-step synthesis via the isolated monoadduct **5**. For **8c**, the first route has an acceptable yield of 56%, whereas the higher yields of **8b** were achieved by the two-step approach (Method A: 20%, method B: 58%).



	R^1	R^2
a	H	OMe
b	OMe	H
c	Me	H
d	OH	H

To build up a bimacrocyclic 1,10-phenanthroline **10a**, the four *ortho* substituents R^1 (Me or OMe) in the diaryl-1,10-phenanthroline **8** have to be functionalized and bridged. For **8c**, halogenation reactions (NBS, NCS, Br_2/hv) only yielded complex product mixtures. However, **8b** could be easily transferred into the tetraphenol **8d** by ether cleavage with BBr_3 (71%). The phenol **8d** then was treated with two equivalents of triethyleneglycol ditosylate[8] (**9**) and sodium hydride in DMF under high-dilution conditions lead-

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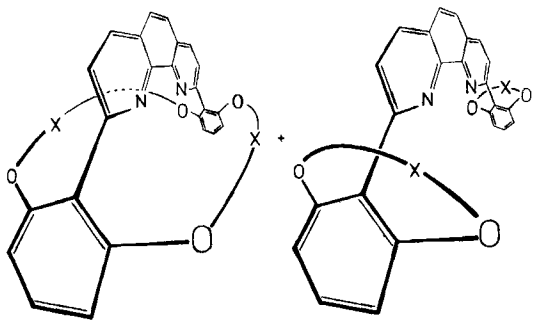
ing to a product **10** where the four phenol functions were bridged by two triethyleneglycol chains.

$$\mathbf{8d} + \mathrm{TosO-X-OTos} \xrightarrow[\mathrm{DMF}]{\mathrm{NaH}} \mathbf{9}$$



10a 10b

X = $CH_2CH_2OCH_2CH_2OCH_2CH_2$

Two isomers of **10** are conceivable: (i) the concave bimacrocycle **10a** and (ii) the bismetacyclophane **10b**. CPK models and NOE-NMR experiments as well as protonation and complexation experiments support structure **10a**.

When **10** was treated with picric acid, not only the 1,10-phenanthroline proton signals were shifted downfield in the ^{1}H-NMR spectrum. Also the signals of the eight hydrogen atoms of the central ethylene groups of the two triethyleneglycol chains were shifted, whereas the signals of the other hydrogen atoms of the X chains were less effected. It follows that the positive charge must be located at the 1,10-phenanthroline nitrogen atoms and that the middle ethylene groups of the triethyleneglycol chains must be close to the 1,10-phenanthroline nitrogen atoms to be influenced by their positive charge.

Similar changes in the ^{1}H-NMR spectrum were found when the 1,10-phenanthroline **10** was mixed with $[Cu^I(CH_3CN)_4][BF_4]$. Again, the largest changes were found for the 1,10-phenanthroline signals and for the multiplets of the eight hydrogen atoms of the middle ethylene groups of the X chains. Thus, structure **10b** can be excluded[9]; the macrobicycle **10** exists as a concave base and ligand **10a**.

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Experimental

General Information: Ref.[1,3,4].

2,9-Bis(2',6'-dimethoxyphenyl)-1,10-phenanthroline (**8b**)

A) *One-Step Synthesis of* **8b**: To a solution of 0.76 g (0.11 mol) of lithium granules in 50 ml of dry diethyl ether, 11.9 g (55.2 mmol) of 2-bromo-1,3-dimethoxybenzene[10], dissolved in 100 ml of dry diethyl ether, was slowly added dropwise under nitrogen. The mixture was then stirred for 2 h and heated to reflux for an additional 3 h.

Then, 2.48 g (13.7 mmol) of 1,10-phenanthroline (**2**), dissolved in 150 ml of dry toluene, was slowly added at 0°C. After 50 h at reflux temp., the deeply red mixture was cooled to 0°C and slowly hydrolyzed by the addition of 100 ml of water yielding a deeply yellow mixture. After separation of the phases, the aqueous layer was extracted five times with 80 ml of dichloromethane. Then, 150 g of MnO_2 was added to the organic phases, and after 15 h of stirring 150 g of $MgSO_4$ was added, and the mixture was stirred for an additional 2 h. After suction filtration through a pad of $MgSO_4$, the solvents were evaporated yielding a viscous, dark brown oil. Chromatography [silica gel; dichloromethane/ethanol (20:1)] yielded, after recrystallization from acetone/dichloromethane, 1.24 g (20%) of analytically pure **8b**, besides which 1.95 g (45%) of the monoadduct **5b** could be isolated.

B) *Two-Step Synthesis of* **8b** *with Isolation of the Monoadduct 2-(2',6'-Dimethoxyphenyl)-1,10-phenanthroline* (**5b**): A solution of 30.0 g (0.14 mol) of 2-bromo-1,3-dimethoxybenzene[10] in 280 ml of dry diethyl ether was added dropwise under argon to a suspension of 2.10 g (0.30 mol) of lithium powder in 50 ml of dry diethyl ether in such a way that the diethyl ether was refluxing gently. After 1 h of reflux, a sample (hydrolyzed, extracted with diethyl ether, dried with Na_2SO_4) was analyzed by GLC and showed 100% conversion. Subsequently, a solution of 5.36 g (29.7 mmol) of 1,10-phenanthroline (**2**) in 240 ml of dry toluene was added during 3.5 h. After 3 h at reflux temp., the mixture was hydrolyzed at room temp. by addition of 250 ml of water. The aqueous phase was extracted three times with 100 ml of dichloromethane, and the combined organic phases were mixed with 50 g (0.57 mol) of MnO_2, and during 26 h water was distilled off azeotropically. Filtration and concentration gave a dark brown oil which was dissolved in a mixture of 200 ml of 6 N HCl and 200 ml of diethyl ether. The aqueous phase was extracted three times with 100 ml of diethyl ether. Then, concd. NaOH was added until the aqueous phase was basic. After extraction with four times 150 ml of dichloromethane, the organic phase was washed twice with 100 ml of water, dried with $MgSO_4$ and concentrated. The resulting semisolid was recrystallized from hot acetone yielding 7.34 g (79%) of 2-(2',6'-dimethoxyphenyl)-1,10-phenanthroline (**5b**) plus 2.30 g of a mixture of the mono- and the bisadduct **5b** and **8b**.

5b: M.p. 189°C. – IR (KBr): $\tilde{\nu}$ = 1612, 1590, 1578, 1465 cm^{-1} (arom.), 1245, 1108 (C–O). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.69 (s, 6H), 6.66 (d, J = 8 Hz, 2H), 7.33 (t, J = 8 Hz, 1H), 7.59 (dd, J = 8 Hz, J = 4.5 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.81 [2 d (AB), J = 8 Hz, 2H], 8.24, 8.27 (dd, d, J = 8 Hz, J = 2 Hz, J = 8 Hz, 2H), 9.17 (dd, J = ca. 4.5 Hz, J = 2 Hz, 1H). – MS (EI, 70 eV): m/z (%) = 315 (88), 255 (100).

$C_{20}H_{16}N_2O_2$ (316.3) Calcd. C 75.93 H 5.09 N 8.85
Found C 75.59 H 5.11 N 8.81

2,6-Dimethoxyphenyllithium (**3b**) was prepared from 8.75 g (40.2 mmol) of 2-bromo-1,3-dimethoxybenzene[10] and 0.40 g (57 mmol) of lithium powder as described above in 150 ml of dry diethyl ether. During 4 h, 5.07 g (16.1 mmol) of **5b** in 250 ml of dry toluene was slowly added at room temp. After workup (see above), 25.0 g (0.28 mol) of MnO_2 was added, and over 4 h water was distilled off azeotropically. The mixture was filtered, and remaining traces of MnO_2 were removed by suction filtration through a pad of $MgSO_4$. The slightly yellow solution was concentrated and the resulting crystals were recrystallized from acetone yielding 5.30 g (73%) of **8b**.

8b: M.p. >250°C. – IR (KBr): $\tilde{\nu}$ = 1590, 1575, 1490, 1460 cm^{-1} (arom.), 1240, 1095 (C–O). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.72 (s, 12H), 6.66 (d, J = 8 Hz, 4H), 7.30 (t, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.81 (s, 2H), 8.24 (d, J = 8 Hz, 2H). – MS (EI, 70 eV): m/z (%) = 452 (92), 451 (100), 434 (46), 433 (39).

$C_{28}H_{24}N_2O_4$ (452.5) Calcd. C 74.32 H 5.34 N 6.19
Found C 74.05 H 5.49 N 6.05

2,9-Bis(2',6'-dimethylphenyl)-1,10-phenanthroline (**8c**): Under N_2 at 0°C, a solution of 17.2 g (92.9 mmol) of 2-bromo-1,3-dimethylbenzene[11] in 80 ml of dry diethyl ether was slowly added dropwise

to 1.11 g (0.16 mol) of lithium granules in 50 ml of dry diethyl ether. After 15 h, a solution of 3.00 g (16.6 mmol) of 1,10-phenanthroline (**2**) in 150 ml of dry toluene was slowly added. The deep red solution was heated to reflux for 4 h, stirred for 16 h, and hydrolyzed with 100 ml of water. After extraction of the aqueous phase with five times 80 ml of dichloromethane, 180 g (2.04 mol) of MnO_2 was added to the combined red organic phases. The mixture was stirred for 14 h, 180 g of $MgSO_4$ was added, and after 2 h the mixture was suction-filtered through a pad of $MgSO_4$. Evaporation of the solvents gave a slightly brown, viscous oil of which 3.70 g (56%) of **8c** could be crystallized from cyclohexane. – M.p. >330°C. – IR (KBr): $\tilde{\nu}$ = 1610, 1598, 1560, 1490 cm^{-1} (arom.). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.15 (s, 12H), 7.05–7.22 (m, 6H), 7.59 (d, *J* = 8 Hz, 2H), 7.88 (s, 2H), 8.30 (d, *J* = 8 Hz, 2H). – MS (EI, 70 eV): *m/z* (%) = 388 (74), 387 (100).

$C_{28}H_{24}N_2$ (388.5) Calcd. C 86.56 H 6.22 N 7.21
Found C 86.82 H 6.36 N 7.28

Besides, 0.49 g (11%) of the monoadduct 2-(2′,6′-dimethylphenyl)-1,10-phenanthroline (**5c**) could be isolated and characterized. – M.p. 129°C. – IR (KBr): $\tilde{\nu}$ = 1610, 1596, 1580, 1480 cm^{-1} (arom.). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 2.12 (s, 6H), 7.09–7.25 (m, 3H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.62 (dd, *J* = 8.2 Hz, *J* = 4.5 Hz, 1H), 7.85 [2 d (AB), *J* = 8.2 Hz, 2H], 8.25 (dd, *J* = 8.2 Hz, *J* = 2 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 9.20 (dd, *J* = 4.5 Hz, *J* = 2 Hz, 1H). – MS (EI, 70 eV): *m/z* (%) = 283 (100), 268 (21), 134 (23).

$C_{20}H_{16}N_2$ (284.4) Calcd. C 84.47 H 5.67 N 9.85
Found C 84.41 H 5.90 N 9.80

2,9-Bis(2′,6′-dihydroxyphenyl)-1,10-phenanthroline (**8d**): 2.50 g (5.5 mmol) of **8b** in 100 ml of dry dichloromethane was cooled to −78°C. During 1.5 h, a solution of 19.0 g (77.0 mmol) of BBr_3 in 40 ml of dry dichloromethane was slowly added. The mixture was allowed to warm up to room temp. during 4.5 h, stirred for additional 48 h, and hydrolyzed by slow addition of 120 ml of concd. $NaHCO_3$ solution. The precipitate was filtered off and the filtrate treated three times as follows: 60 ml of methanol and ca. 100 µl of concd. H_2SO_4 were added and the solvents distilled off. The residue was mixed with 50 ml of concd. $NaHCO_3$ solution and treated in an ultrasound bath for 20 min. After filtration, the residue was washed with water and recrystallized from methanol yielding 1.54 g (71%) of **8d** as a slightly yellow powder. – M.p. >280°C (dec.). – IR (KBr): $\tilde{\nu}$ = 3390 cm^{-1} (very br., OH), 1615, 1600, 1490 (arom.).

$C_{24}H_{16}N_2O_4$ Calcd. 396.11101 Found 396.1099 (MS)

Recrystallization of **8d** from methanol/HCl yielded **8d**·HCl. – M.p. >238°C (dec.). – IR (KBr): $\tilde{\nu}$ = 3100–3300 cm^{-1} (very br., OH), 1600, 1548, 1530, 1490 (arom.). – ^1H NMR ([D$_6$]DMSO, 250 MHz): δ = 6.63 (d, *J* = 9 Hz, 4H), 7.19 (t, *J* = 9 Hz, 2H), 8.16 (s, 2H), 8.72, 8.81 (dd, AB, *J* = 9 Hz, 4H). – MS (EI, 70 eV): *m/z* (%) = 396 (100) [M^+ – HCl], 395 (59).

6,9,12,15,33,36,39,42-Octaoxa-43,46-diazaheptacyclo[18.12.10.4^{22,31}.0^{5,32}.0^{16,21}.0^{25,45}.0^{28,44}]hexatetraconta-1,3,5(32),16,18,20,22,24,26,28,30,43,45-tridecaene (**10a**): To a mixture of 2.20 g (91.0 mmol) of sodium hydride and 4.92 g (15.1 mmol) of Cs_2CO_3 in 600 ml of dry DMF, a solution of 1.49 g (3.78 mmol) of **8d** and 2.98 g (7.56 mmol) of **9** in 280 ml of dry DMF was slowly added dropwise during 8.5 h at 65°C under nitrogen. After additional 2 h at 65°C, the mixture was cooled to room temp., filtered, and the filtrate concentrated. The residue was dissolved in 200 ml of water and 200 ml of dichloromethane. The phases were separated, and the aqueous phase was extracted 4 times with 150 ml of dichloromethane. After drying with $MgSO_4$, the solvents were distilled off yielding 1.51 g of a dark red semisolid which was purified by MPLC [silica gel; dichloromethane/ethanol (20:1)] to yield 0.30 g (13%) of **10a** as a slightly yellow oil. – M.p. 281°C (acetone). – IR (KBr): $\tilde{\nu}$ = 1590, 1460, 1440 cm^{-1} (arom.), 1245, 1095 (C–O). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.17 (s, H_2O), 2.61 (m_c, 4H, $CH_aOCH_2CH_2OAr$), 3.21 (m_c, 4H, $CH_bOCH_2CH_2OAr$), 3.31 (m_c, 4H, CH_aCH_2OAr), 3.78 (m_c, 4H, CH_bCH_2OAr), 4.01 (m_c, 4H, CH_aOAr), 4.11 (m_c, 4H, CH_bOAr), 6.55 (d, *J* = 8 Hz, 4H, *o*-C_6H_3), 7.27 (t, *J* = 8 Hz, 2H, *m*-C_6H_3), 7.56 (d, *J* = 8 Hz, 2H, 3-H, 8-H), 7.85 (s, 2H, 5-H, 6-H), 8.27 (d, *J* = 8 Hz, 2H, 4-H, 7-H). – ^1H NMR ($CDCl_3$, 250 MHz, 3.5 equiv. of picric acid): δ (multiplicity and integration as above) = 2.18, 2.84, 2.94, 3.34, 3.69, 4.02, 4.16, 6.67, 7.45, 8.07, 8.38, 9.03, 9.07 (picric acid). – ^1H NMR ⟨$CDCl_3$/CD_3CN (ca. 1:1), 400 MHz, 1 equiv. of [$Cu^I(CH_3CN)_4$][BF_4]⟩: δ (multiplicity and integration as above) = 2.14, 2.65, 2.77, 3.14, 3.71, 3.90, 3.98, 6.65, 7.40, 7.82, 8.08, 8.59. – NOE: With the exception of an NOE effect between the $ArOCH_2$ hydrogen atoms and the protons being *ortho* to the alkoxy chain substituents of the phenyl rings, no more NOE signals between aromatic and aliphatic hydrogen atoms could be observed. – MS (EI, 70 eV): *m/z* (%) = 624 (74), 536 (100).

$C_{36}H_{36}N_2O_8 \cdot H_2O$ (642.7) Calcd. C 67.27 H 5.96 N 4.36
Found C 66.96 H 6.02 N 3.98

CAS Registry Numbers

2: 66-71-7 / **5b**: 124318-70-3 / **5c**: 124318-72-5 / **8b**: 124318-69-0 / **8c**: 124318-71-4 / **8d**: 124318-73-6 / **8d**·HCl: 124318-74-7 / **9**: 19249-03-7 / **10a**: 124318-75-8 / 2-bromo-1,3-dimethoxybenzene: 16932-45-9 / 2-bromo-1,3-dimethylbenzene: 576-22-7

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[9] A shift of the signals for the central ethylene group of the triethyleneglycol chains in **10b** can only be expected when rotations around the aryl–aryl bond between the 1,10-phenanthroline and the metacyclophane occured in such a way that both X chains would turn towards the positive charge of the copper ion or the proton. But this is not possible for steric reasons especially in the case of the copper(I) complex.

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[355/89]