Deracemization of a Macrocyclic 1,1′-Biisoquinoline

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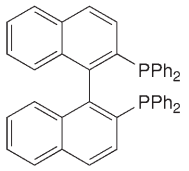
The macrocyclic biisoquinoline **14** was synthesized in just four preparative steps starting from the simple biscarboxaldehyde **8**. The interaction with camphorsulfonic acid induces an acid-catalyzed partial deracemization.

Introduction. – Atropchiral ligands such as BINAP (**1**) [1] and BINOL (**2**) [2] are of tremendous value for enantioselective transition metal catalysis [3]. In complexes of the related isoquinolinyl ligands QUINAP (**3**) [4] and its β-naphthol-substituted congener **4** [5] the transition metal is bound more closely to the stereogenic axes, a fact that might have positive influence on the enantioselectivity of catalyzed processes. On the other hand, one might anticipate that racemization of the ligand is favored in two ways: it should be relatively easy for the isoquinoline nitrogen to pass sterically the *peri*-H-atom of the naphthyl substituent, and secondly, cyclic six-membered complexes should diminish the activation energy for the two *peri*-H-atoms passing each other, in analogy to the configurational lability of six-membered binaphthyllactones of type **5** [6], which were utilized for dynamic kinetic resolutions by the 'lactone approach' to chiral biaryls according to *Bringmann et al.* [7].



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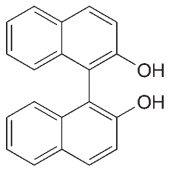

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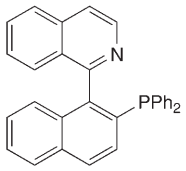

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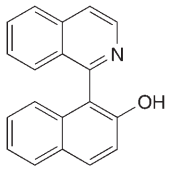

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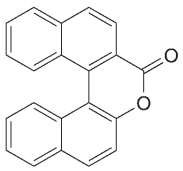

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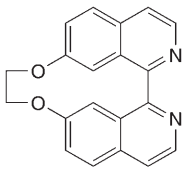

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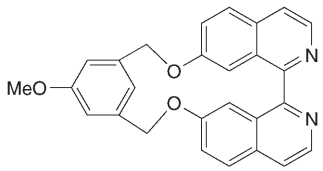

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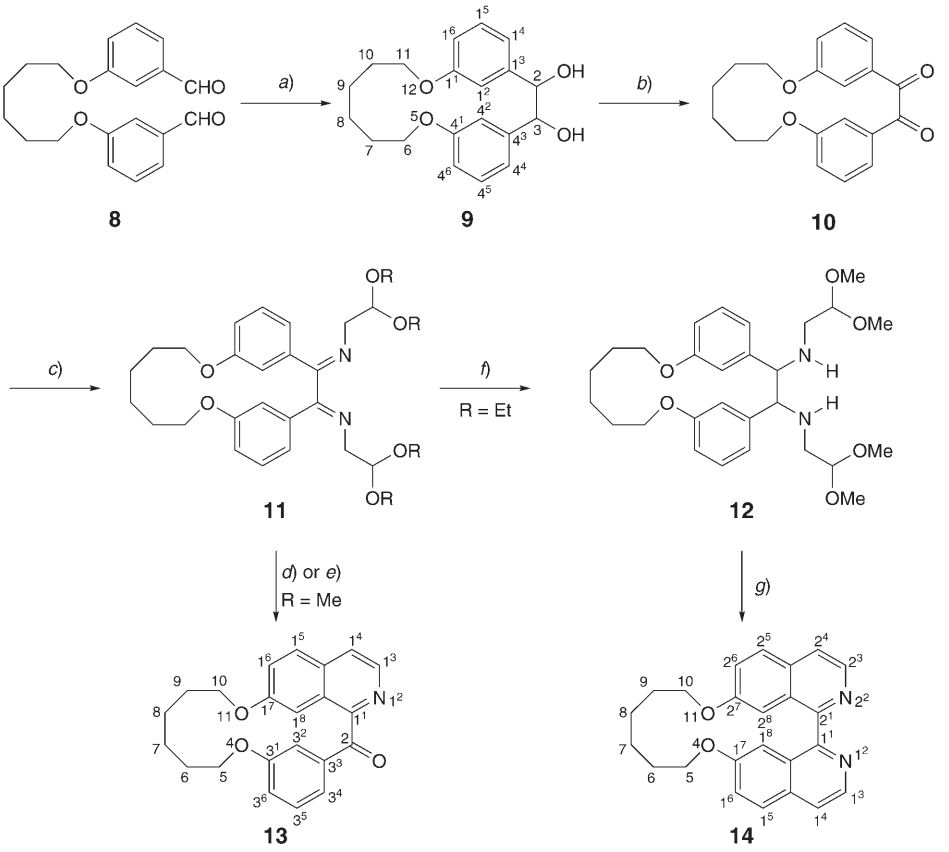
We became interested in the configurational stability of macrocyclic 1,1′-biisoquinolines as precursors for chiral bis-*N*-oxides [8]. The dioxa-bridged examples **6** and **7** have been synthesized by *Yamamoto et al. via* intramolecular *Ullmann* coupling reactions [9] and turned out to differ significantly in terms of configurational stability. While **6** with a rather short bridge racemized with a half-life period of 64 min in refluxing EtOH (translated to a $\Delta G^{\ddagger}$ of *ca.* 109 kJ/mol), even a Rh-complex of its more rigid congener **7** was configurationally stable. We envisioned an alternative synthetic route starting from biscarboxylate **8** *via* the macrocyclic diol **9** [10] (*Scheme*).

Scheme. *Synthesis of the Conformationally Stabilized Biisoquinoline* **14**



a) Zn, $TiCl_4$, THF, $-5°$, 10 h; 93%. *b*) *Swern* oxidation, DMSO, TFAA; 95%. *c*) Aminoacetaldehyde diethylacetal, molecular sieves, 70°, 3 h; 67%. *d*) 73% H_2SO_4, 22°, 2.5 d; 1.7% of **13**. *e*) 1. Ethyl chloroformate; 2. trimethyl phosphite; 3. $TiCl_4$, CH_2Cl_2, reflux, 2 d; yield: 7% of **13** and 18% of **14** (yields of one-pot procedure starting from **10**). *f*) 10% Pd/C (20 mol-%), 2 bar H_2, MeOH, 3 d; quant. yield. *g*) 1. TsCl, pyridine, CH_2Cl_2, reflux, 18 h; crude **12** directly transformed; 2. MsOH, CH_2Cl_2, reflux, 3 d; yield: 2% of **14**.

Results and Discussion. – The macrocyclization of the dicarbaldehyde **8** by a pinacol coupling reaction with $TiCl_4$ and Zn as reducing reagents succeeds with an astonishing 93% yield as reported earlier [10]. The subsequent double *Swern* oxidation to the 1,2-dione **10** followed by the condensation with aminoacetaldehyde diethyl acetal represents a straight forward route to the bisimine **11** as the central isoquinoline precursor. Established conditions for the *Pomeranz – Fritsch* isoquinoline synthesis [11] with H_2SO_4 as catalyst led only to the mono-cyclization product **13** in no more than 1.7% yield. In analogy to *Watanabe* [12] and *Shannon* [13], we then tried a three-step procedure with catalytic hydrogenation of **11**, followed by *N*-tosylation and acid-driven cyclocondensation, giving the target biisoquinoline **14** for the first time, albeit in a totally unsatisfactory yield of 2%. Far better was the result with *Hendrickson*'s method [14], although somewhat surprising, because a sterically overcrowded double carbamate-phosphonate had to be formed as an intermediate in this one-pot procedure. Nevertheless, we obtained 18% yield of the biisoquinoline **14**, besides 7% of the monocyclization product **13**. Single crystals of biisoquinoline **14** were obtained by slow diffusion of petroleum ether into a solution of **14** in AcOEt. A dihedral angle of 63° was found between the two planar isoquinoline subunits by X-ray crystal structure analysis (*Fig. 1*).

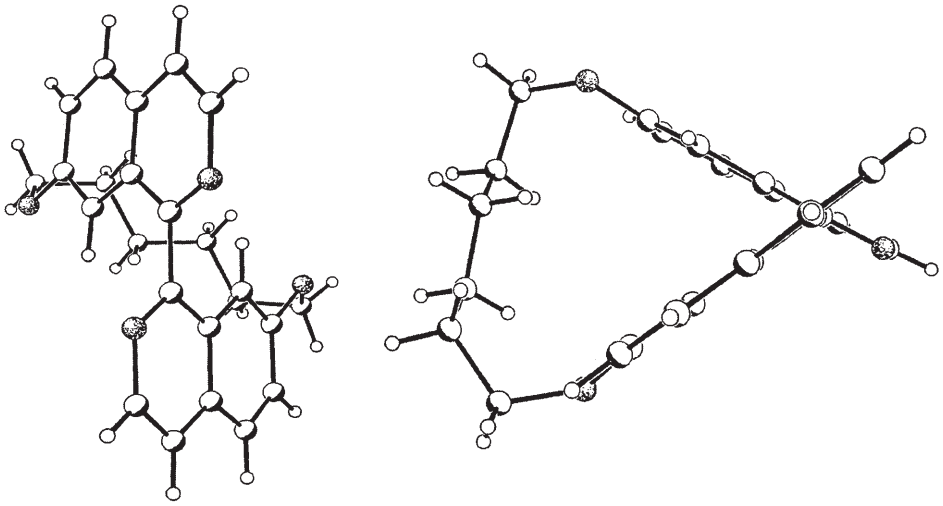


Fig. 1. *Perspectives of the structure of biisoquinoline* **14** *in the crystal*

Density functional theory (DFT) computations at B3PW91/cc-pVDZ level (see *Exper. Part* for details of the computations) give a slightly smaller dihedral angle of 56°; this agreement is excellent because the torsional potential is rather flat around the minimum and packing effects are taken into consideration in the computations (*Fig. 2*). We computed a barrier for the atropisomeric transition structure of $\Delta H_0^{\ddagger} = +26.2$ kcal/mol, which is not much different from the parent case (*Fig. 3*, $\Delta H_0^{\ddagger} = +29.4$ kcal/mol) that we computed for comparison and evaluation of the effects of the tether. Mono-

protonation diminishes the dihedral angle to 32° while substantially increasing the partial double bond character between C(1^1) and C(2^1) (from 1.504 Å in **14** to 1.486 Å in the protonated form). As a consequence, the epimerization barrier is significantly reduced to $\Delta H_0^{\ddagger} = +18.8$ kcal/mol (for H–C(1^8) and H–C(2^8) passing each other; this distance also diminishes from 2.647 Å in **14** to 2.411 Å in the protonated species). The protonated transition structure **TSH**$^+$ benefits from maximizing the internal H-bond to the unprotonated N-atom: the distance is only 1.663 Å. The same trend is not observed in the parent system (*Fig. 3*), for which the protonated barrier is about the same ($\Delta H_0^{\ddagger} = +17.0$ kcal/mol). The tether equalizes the torsional difference between the protonated and non-protonated forms. These results also indicate that it should be possible to design tethers that restrict the torsions in a way that the biisoquinoline moiety becomes configurationally stable even when protonated.

These computational findings are in accord with our observations upon trying to separate the enantiomers of **14** by crystallization of the diastereoisomeric salts with (–)-camphor-10-sulfonic acid: to our surprise, we found always the same enantiomer enriched, both in the crystallized salt *and* in the mother liquor. In a typical control experiment, we observed the specific rotation of a 1:1 mixture of *rac*-**14** and (–)-camphor-10-sulfonic acid in CH_2Cl_2 at room temperature, increasing from $[\alpha]_D^{22} = -16$ to constant -5 within 30 min, obviously reaching an equilibrium. After treatment with 5% aqueous NaOH solution, the resulting free base was analyzed by analytical HPLC on a chiral stationary phase (*DAICEL Chiralpak OT*(+), MeOH) revealing an enantiomeric excess of 17.2% in favor of (+)-**14**. When (+)-camphor-10-sulfonic acid was used, (–)-**14** was enriched, although the reproducibility of the enantiomeric excess seemed to be sensitive towards the dryness of the sample. Nevertheless, our observations clearly prove a partial deracemization [15] catalyzed by a chiral acid, regarded as a special case of a dynamic kinetic resolution [16]. With HPLC on semipreparative scale, we obtained enantiomerically pure samples (f.i. $[\alpha]_D^{22} = -614.4°$ in EtOH), suitable to determine the absolute configuration [17] by CD spectra using the exciton-chirality method [18] and by comparison with related compounds [19], thus identifying (+)-(*S*)-**14** and (–)-(*R*)-**14**.

The configurational stability was tested in various solvents, measuring the time dependence of the optical rotation (assuming proportionality with enantiomeric excess) [20]. At room temperature, in the rather unpolar solvent toluene, **14** racemizes rather slowly. At 78° a half-life period of 110 min and a free activation enthalpy of *ca.* 115 kJ/mol were ascertained (slightly more stable than a derivative of **4** tested in benzene) [21]. In EtOH as polar and protic solvent, the half-life period of **14** drops to 5.6 min at 75°. Obviously, **14** with its flexible hexanediyl chain racemizes faster than **6** with a more rigid ethanediyl chain (see *Introduction*).

To test whether H-bonds of EtOH to the N-atoms of **14** or the polarity of EtOH as solvent (1.7 D) is responsible for the accelerated racemization, we chose benzonitrile as an aprotic, but more polar solvent for comparison (4.0 D) [22]. In benzonitrile – again at 75° – a half-life period of 11.3 min was found: about 10 times shorter compared to toluene, but twice as long as in EtOH, illustrating that both the polarity of the solvent and H-bonds are important factors in the racemization process. Finally, we proved that 0.01 equiv. of F_3CCOOH in toluene at 75° indeed catalyze the racemization ($t_{1/2} =$ 21 min).

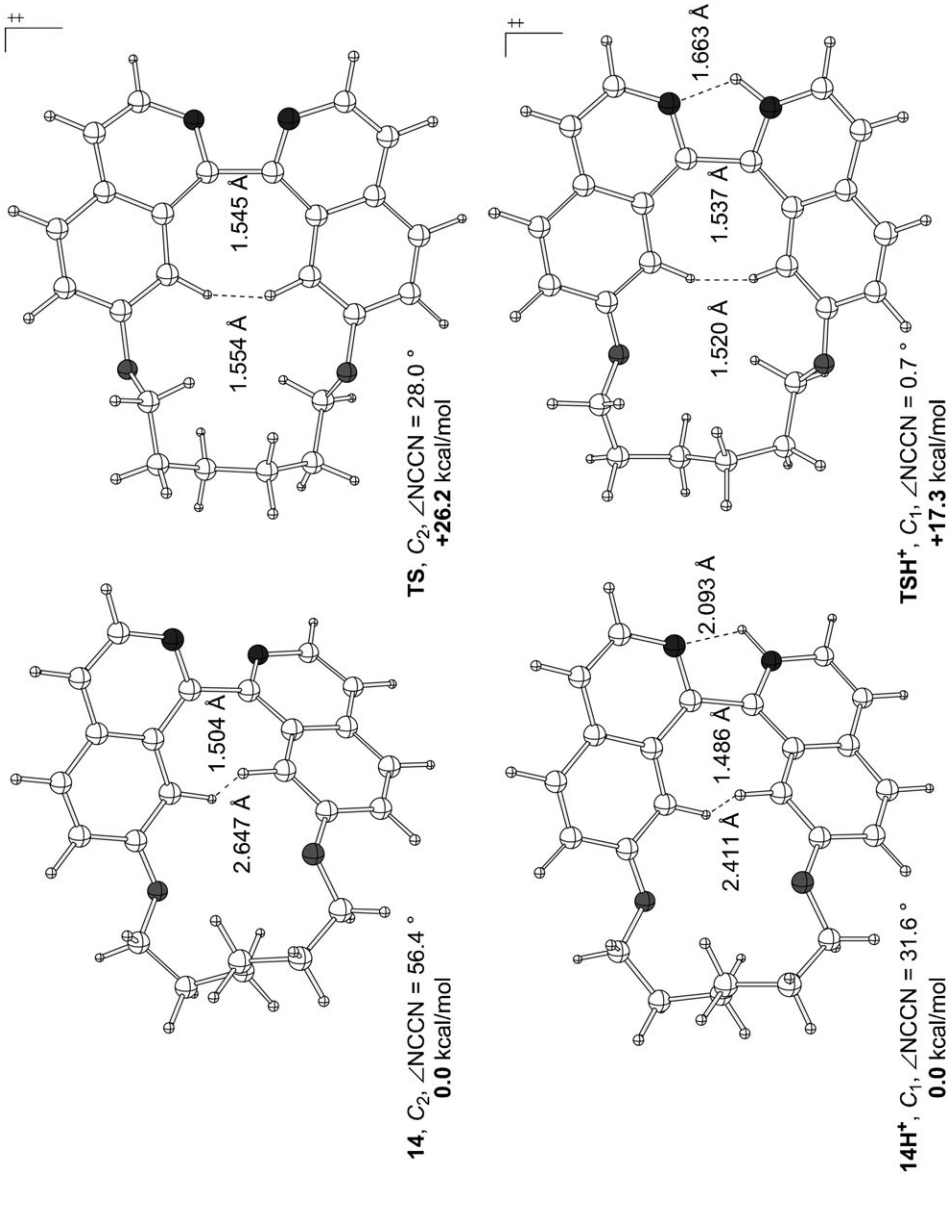


Fig. 2. *B3PW91/cc-pVDZ Optimized geometries of* **14** *as well as of its protonated form* **14H**$^+$ *and their respective atropisomeric transition structures* **TS** *and* **TSH**$^+$ *with their associated barriers* ($\Delta H_0^{\ddagger}$). Selected bond lengths and angles are given for comparison with the experimental data.

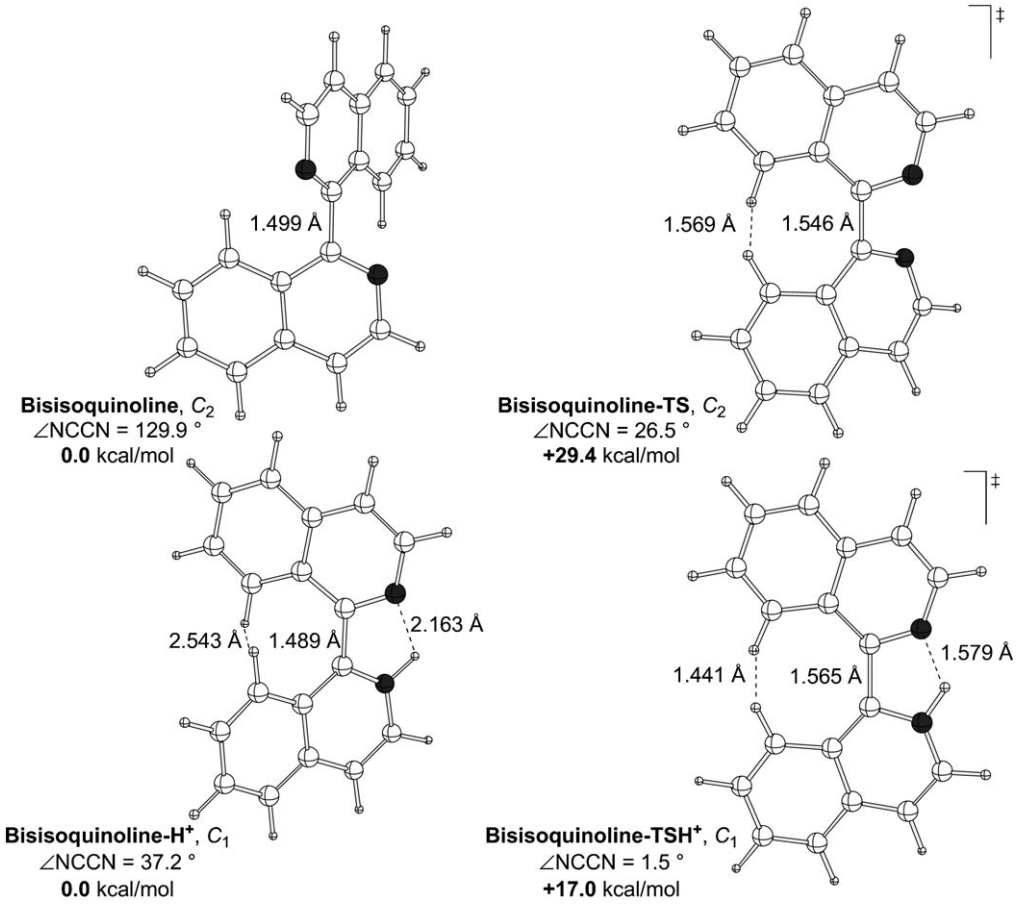


Fig. 3. *B3PW91/cc-pVDZ Optimized geometries of the parent biisoquinoline system as well as of its protonated form and their respective atropisomeric transition structures with their associated barriers* ($\Delta H_0^{\ddagger}$)

Conclusions. – In a case of dynamic kinetic resolution, the target biisoquinoline **14** is partially deracemized by treatment with a chiral acid. Since rapid racemization takes place in polar, especially protic solvents, and naturally under acidic conditions, applications as chiral base or as chiral ligand for transition metal catalysis are ruled out. Therefore, future work should concentrate on the corresponding bis-*N*-oxides as configurationally stable chiral catalysts [23].

This work was supported by the *Fonds der Chemischen Industrie*. We are indepted to *A. Deege* and *H. Hinrichs* from the *Max Planck Institute of Coal Research* for the preparative HPLC separation of the enantiomers of **14**.

Experimental Part

General. For anal. TLC, precoated plastic sheets '*POLYGRAM SIL G/UV254*' from *Macherey-Nagel* were used. M.p. [°], uncorrected values, were determined with a *Reichert Thermovar*. UV/VIS:

Perkin-Elmer Lambda-40 apparatus; λ in nm. IR: *Perkin-Elmer 983* instrument. ^{1}H- and ^{13}C-NMR: *Bruker DRX-500*, $CDCl_3$ as solvent and TMS as the internal standard. MS: *Varian MAT 311A ITD* (70 eV). Elemental analyses were determined with an *Euro Elemental Analyzer 3000*.

1,4(1,3)-Dibenzena-5,12-dioxacyclododecaphane-2,3-dione (**10**). To a mixture of dry DMSO (1.74 ml, 1.91 g, 24.5 mmol) and dry CH_2Cl_2 (100 ml) at $-60°$ under Ar was added trifluoroacetic acid anhydride (TFAA) (3.10 ml, 4.70 g, 22.3 mmol). After 10 min of stirring, diol **9** (2.57 g, 7.80 mmol) dissolved in dry CH_2Cl_2 (40 ml) was added dropwise over 45 min. Stirring was continued for 90 min at $-60°$, dry Et_3N (7.2 ml, 5.3 g, 52 mmol) was added, and the mixture was warmed to r.t. within 90 min. After hydrolyzation with 50 ml of 2M HCl, the aq. phase was extracted three times with 50 ml CH_2Cl_2. The combined org. phases were dried by adsorptive filtration through a pad of silica and concentrated. The residue was purified by flash chromatography (*t*-BuOMe/hexane 1:1) to give 2.42 g (95%) of **10**. Colorless solid. M.p. 117.5–118.5°. UV (MeCN): 196 (4.31, sh), 218 (4.49), 262 (4.16), 320 (3.68). IR (KBr): 3060*w*, 2966*w*, 2936*m*, 2890*w*, 2860*w*, 1685v*s*, 1672v*s*, 1592*s*, 1487*m*, 1437*m*, 1332*m*, 1308*m*, 1280*m*, 1260*w*, 1225*m*, 1203*s*, 1176*m*, 1159*m*, 1089*w*, 1028*m*, 986*w*, 975*w*, 858*w*, 809*w*, 787*w*, 766*m*, 728*m*, 688*w*, 682*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.24–1.26 (*m*, $CH_2(8)$, $CH_2(9)$); 1.51–1.53 (*m*, $CH_2(7)$, $CH_2(10)$); 4.14 (*t*, J = 6.8, $CH_2(6)$, $CH_2(11)$); 7.16–7.18 (*m*, 4 arom. H); 7.40 ('*t*', 'J' = 7.6, 2 arom. H); 7.60 (*dt*, J = 7.6, 1.3, 2 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.2 (*t*, C(8), C(9)); 27.9 (*t*, C(7), C(10)); 67.5 (*t*, C(6), C(11)); 115.1 (*d*); 121.2 (*d*); 124.2 (*d*); 130.5 (*d*); 134.6 (*s*, C(1^1), C(4^1)); 158.9 (*s*, C(1^3), C(4^3)); 196.3 (*s*, C(2), C(3)). EI-MS: 325 (15), 324 (86, M^+), 242 (20), 241 (15), 214 (30), 213 (10), 197 (17), 139 (10), 121 (69), 93 (13), 83 (40), 82 (39), 76 (16), 67 (22), 65 (10), 55 (100). Anal. calc. for $C_{20}H_{20}O_4$ (324.38): C 74.06, H 6.21; found: C 73.84, H 6.24.

N,N′*-(1,4(1,3)-Dibenzena-5,12-dioxacyclododecaphane-2,3-diylidene)bis(2,2-diethoxyethanamine)* (**11**, R = Et). A mixture of diketone **10** (0.65 g, 2.0 mmol), 4-Å molecular sieves (1.0 g), and aminoacetaldehyde diethyl acetal (0.69 ml, 0.67 g, 5.0 mmol) was heated for 3 h at 70° without solvent. Et_2O (100 ml) was added, and the molecular sieves were filtered off. After evaporation of the solvent, the residue was purified by flash chromatography (Et_2O/hexane 1:1) to give 0.74 g (67%) of **11** as bright yellow crystals with melting range of 67–77°. UV (MeCN): 198 (4.40, sh), 218 (4.59), 252 (4.21), 303 (3.67). IR (KBr): 2974*m*, 2931*m*, 1675*w*, 1630*m*, 1596*m*, 1583*m*, 1482*m*, 1437*m*, 1374*m*, 1276*m*, 1226*m*, 1207*m*, 1129*s*, 1062*s*, 859*w*, 795*w*, 755*w*, 709*m*, 690*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*t*, J = 7.0, 4 *Me*CH_2O groups); 1.28–1.30 (*m*, $CH_2(8)$, $CH_2(9)$); 1.40–1.60 (*m*, $CH_2(7)$, $CH_2(10)$); 3.53–3.79 (*m*, 2 CH_2N, 4 MeC*H*$_2$O); 4.02–4.04 (*m*, 2 H of $CH_2(6)$ and $CH_2(11)$); 4.15–4.17 (*m*, 2 H of $CH_2(6)$ and $CH_2(11)$); 4.99 (*dd*, J = 6.0, 4.7, 2 O–CH–O); 6.92 (*ddd*, J = 8.2, 2.6, 1.0, H–C(1^4), H–C(4^4)); 7.14 (*dd*, J = 2.4, 1.6, H–C(1^2), H–C(4^2)); 7.22 ('*t*', J = 7.9, H–C(1^5), H–C(4^5)); 7.45 (*dt*, J = 7.7, 1.2, H–C(1^6), H–C(4^6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.3 (*q*, 2 Me); 15.4 (*q*, 2 Me); 24.2 (*t*, C(8), C(9)); 27.9 (*t*, C(7), C(10)); 57.9 (*t*); 62.6 (*t*); 62.7 (*t*); 67.5 (*t*, C(6), C(11)); 102.9 (*d*); 113.8 (*d*); 119.8 (*d*); 119.9 (*d*); 129.8 (*d*); 137.2 (*s*); 158.7 (*s*); 166.7 (*s*). EI-MS: 557 (2), 556 (6), 554 (2, M^+), 452 (10), 451 (32), 450 (22), 281 (12), 103 (100), 83 (7), 75 (49). Anal. calc. for $C_{32}H_{46}N_2O_6$ (554.73): C 69.29, H 8.36; found: C 69.34, H 8.27.

The related bisimine **11** with R = Me was directly used as crude product in one-pot procedures (see experimental protocol for **13** and **14** from **10**), and has, therefore, not been completely characterized.

N,N′*-Bis(2,2-dimethoxyethyl)-1,4(1,3)-dibenzena-5,12-dioxacyclododecaphane-2,3-diamine* (**12**). A suspension of diimine **11** (R = Et, 1.02 g, 2.04 mmol) and 10% Pd/C (430 mg, 20 mol-%) in dry MeOH (250 ml) was shaken under a H_2 atmosphere at 2 bar for 3 d. By evaporation of the solvent, **12** was obtained as a yellow oil in quant. yield, pure enough for further transformations. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.43–1.45 (*m*, $CH_2(8)$, $CH_2(9)$); 1.45 (br. *s*, 2 NH); 1.68–1.70 (*m*, $CH_2(7)$, $CH_2(10)$); 2.59 (*dd*, J = 12.3, 5.1, 2 H); 2.66 (*dd*, J = 12.3, 6.0, 2 H); 3.33 (*s*, 2 MeO); 3.34 (*s*, 2 MeO); 3.89 (*s*, H–C(2), H–C(3)); 3.90–3.93 (*m*, $CH_2(6)$, $CH_2(11)$); 4.47 (*dd*, J = 5.9, 5.2, 2 H); 5.89 (*dd*, J = 2.4, 1.7, H–C(1^2), H–C(4^2)); 6.73 (*ddd*, J = 8.2, 2.6, 0.8, 2 H); 6.92 (*dd*, J = 6.7, 1.4, 2 H); 7.23 ('*t*', 'J' = 7.9, H–C(1^5), H–C(4^5)). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.5 (*t*, C(8), C(9)); 27.0 (*t*, C(7), C(10)); 48.9 (*t*, C(6), C(11)); 53.7 (*q*, MeO); 53.9 (*q*, MeO); 65.5 (*t*, 2 CH_2N); 67.3 (*d*, C(2), C(3)); 104.1 (*d*); 111.8 (*d*); 116.7 (*s*); 120.2 (*d*); 128.8 (*d*); 157.9 (*s*).

Transformation to **14**. A soln. of diamine **12** (1.13 g, 2.24 mmol) and TsCl (0.95 g, 5 mmol) in dry pyridine (5 ml) and dry CH_2Cl_2 (10 ml) under N_2 was heated under reflux for 18 h. The solvent was removed at reduced pressure and the residue was dissolved in dry CH_2Cl_2 (10 ml) and MsOH (5 ml).

After refluxing for 3 d, the soln. was brought to pH 12 by addition of 10% aq. NaOH and the H_2O layer was extracted with CH_2Cl_2 (3×50 ml). The combined org. extracts were concentrated and the residue was fractionated by chromatography on basic Alox (petroleum ether (PE)/Et_2O 1:1). Only 20 mg (2%) of biisoquinoline **14** were isolated (for spectroscopic data, see next experiment).

1(1,7)-Isoquinolina-3(1,3)-benzena-4,11-dioxacycloundecaphan-2-one (**13**) *and 1,2(1,7)-Diisoquinolina-3,10-dioxacyclodecaphane* (**14**). A mixture of diketone **10** (0.97 g, 3.0 mmol), molecular sieves (4 Å, 1.0 g), and aminoacetaldehyde dimethyl acetal (0.82 ml, 0.79 g, 7.50 mmol) was heated for 3 h at 80° without solvent. CH_2Cl_2 (30 ml) was added, and the molecular sieves were filtered off. After evaporation of the solvent, the residue was dissolved in dry THF (80 ml), the soln. was cooled to $-0°$, and ethyl chloroformate (0.58 ml, 0.65 g, 6.0 mmol) was added. After stirring for 10 min, the mixture was allowed to warm to r.t., trimethyl phosphite (0.85 ml, 0.89 g, 7.2 mmol) was added, and stirring was continued for 18 h. Solvent and excess trimethyl phosphite were removed *in vacuo*, the residue was dissolved in dry CH_2Cl_2 (60 ml), and $TiCl_4$ (5.6 ml, 9.7 g, 51 mmol) was added. After stirring for 2 d at reflux temp., 100 ml of 10% aq. NaOH were added to the black suspension. The H_2O layer was extracted with CH_2Cl_2 (5×100 ml) and the combined org. layers were dried with Na_2SO_4 and concentrated to *ca.* 100 ml. Ethylene diamine (*ca.* 6 ml) were added, and the mixture was stirred at r.t. for 16 h and then filtered through a pad of basic Alox (AcOEt/EtOH 5:1 as eluent). After evaporation of the solvent, the residue was fractionated by chromatography over basic Alox (1. PE/AcOEt 1:1, 2. AcOEt, 3. AcOEt/EtOH 5:1).

1st Fraction: 70 mg (7%) of oily monoisoquinoline **13**. UV (MeCN): 230 nm (4.36), 332 (3.66), 340 (3.64, sh). IR (KBr): 2931*m*, 1675*s*, 1621*m*, 1581*m*, 1499*m*, 1480*m*, 1436*m*, 1383*m*, 1286*m*, 1254*m*, 1224*m*, 1209*m*, 1151*m*, 1032*w*, 854*w*, 802*w*, 751*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.31–1.33 (*m*, $CH_2(7)/CH_2(8)$); 1.51 (*t*, $J = 7.0$, 2 H); 1.63 (*t*, $J = 6.1$, 2 H); 3.89 (*t*, $J = 7.1$, 2 H); 4.27 (*t*, $J = 5.6$, 2 H); 6.78 (*d*, $J = 2.5$, H–C(1^8)); 7.18 (*ddd*, $J = 8.2$, 2.6, 1.1, H–C(3^4)); 7.30 (*dd*, $J = 9.1$, 2.5, H–C((1^6)); 7.35 (*t*, $J = 7.9$, H–C(3^5); 7.36 (*d*, $J = 1.6$, H–C(3^2)); 7.42 (*dt*, $J = 7.7$, 1.3, H–C(3^6)); 7.72 (*d*, $J = 5.4$, H–C(1^4)); 7.78 (*d*, $J = 9.0$, H–C(1^5)); 8.59 (*d*, $J = 5.5$, H–C(1^3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.4 (*t*, C(7), C(8)); 26.8 (*t*); 27.4 (*t*); 67.3 (*t*); 67.6 (*t*); 105.3 (*d*); 117.7 (*d*); 122.0 (*d*); 122.1 (*d*); 122.4 (*d*); 124.5 (*d*); 127.0 (*s*); 128.8 (*d*); 130.1 (*d*); 132.0 (*s*); 138.9 (*s*); 141.0 (*d*); 156.0 (*s*); 157.3 (*s*); 158.6 (*s*); 196.6 (*s*, C(2)). EI-MS: 348 (24), 347 (100, M^+), 346 (53), 330 (7), 319 (10), 264 (35), 263 (11), 248 (17), 237 (14), 236 (21), 235 (12), 220 (11), 219 (7), 121 (11). HR-EI-MS: 347.1540 ($C_{22}H_{21}NO_3^+$; calc. 347.1521).

2nd Fraction: Biisoquinoline **14** (201 mg, 18%) as colorless crystals. M.p. 221–225° (from AcOEt/PE 1:5). IR (KBr): 3045*w*, 2932*m*, 2859*w*, 1623*m*, 1579*m*, 1553*w*, 1499*s*, 1427*w*, 1300*w*, 1280*m*, 1198*s*, 1148*w*, 1030*w*, 849*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.29–1.45 (*m*, 6 H); 1.52–1.58 (*m*, 2 H); 3.90 (*ddd*, $J = 11.6$, 8.4, 3.4, 2 H); 4.02 (*ddd*, $J = 11.4$, 8.1, 4.2, 2 H); 6.84 (*d*, $J = 2.4$, H–C(1^8), H–C(2^8)); 7.38 (*dd*, $J = 9.0$, 2.5, H–C(1^6), H–C(2^6)); 7.74 (*d*, $J = 5.7$, H–C(1^4), H–C(2^4)); 7.86 (*d*, $J = 9.0$, H–C(1^5), H–C(2^5)); 8.70 (*d*, $J = 5.7$, H–C(1^3), H–C(2^3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 23.0 (*t*, C(6), C(7)); 27.5 (*t*, C(5), C(8)); 66.8 (*t*, C(4), C(9)); 108.7 (*d*); 120.9 (*d*); 123.4 (*d*); 128.1 (*s*); 129.0 (*d*); 132.1 (*s*); 141.8 (*d*); 156.4 (*s*); 156.6 (*s*). EI-MS: 372 (4), 371 (27), 370 (100, M^+), 353 (15), 288 (16), 287 (77), 271 (16), 270 (14), 259 (13), 242 (15), 229 (13). Anal. calc. for $C_{24}H_{22}N_2O_2$ (370.45): C 77.81, H 5.99, N 7.56; found: C 77.84, H 6.07, N 7.41.

X-Ray Structure Determination. **14**: $C_{24}H_{22}N_2O_2$, $M_r = 370.44$, monoclinic, space group $P2_1/n$, $a = 10.507(4)$, $b = 9.589(4)$, $c = 18.190(10)$ Å, $\beta = 92.69(4)°$, $V = 1830.7$ Å^3, $Z = 4$; $\rho_{calc.} = 1.344$ Mg/m^3, $F(000) = 784$; 4002 unique reflections (2788 with $I > 2\sigma(I)$); $T = 150$ K; *Siemens P4RA* four circle diffractometer, MoK_α radiation ($\mu = 0.086$ mm^{-1}), ω scans, absorption correction (ψ scan technique); structure solution with direct methods combined with conventional *Fourier* techniques, refinements based on F^2 with 4002 independent reflections, 264 parameters, R_1 ($I > 2\sigma(I)$) = 0.053, wR_2 (all data) = 0.134; min./max. difference electron density $-0.39/0.49$ eÅ^{-3}; non-H-atoms with anisotropic temp. factors, H-atoms from difference *Fourier* syntheses and recalculated at idealized positions (riding model, $U_{iso}(H) = 1.5U_{eq}(C)$). CCDC-673679 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

Computational Methods. For the DFT optimizations, we utilized *Becke*'s three-parameter hybrid exchange functional (B3) [24] in connection with the *Perdew–Wang* correlation functional (PW91) [25]

and a correlation-consistent valence polarized double-ζ (cc-pVDZ) basis set [26]. Our previous analyses on the performance of DFT methods to larger org. molecules shows that this combination gives excellent geometries and reasonable energies compared to high-level *ab initio* results [27]. The excellent agreement between the computed and X-ray geometries (*Fig. 1*) emphasizes this conclusion. The computed vibrational frequencies show that all structures are minima (no imaginary frequencies). All computations employed the Gaussian03 program suite [28].

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