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Molecular Recognition of Neutral Molecules by Metalloclefts: Synthesis, X-ray Structure, ^{1}H NMR Spectroscopy, Electrochemistry, and Molecular Modeling

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*Metallo*clefts **2** and **10a–b** and *metallo*macrocycles **7a–c** possessing a Lewis acidic uranyl cation were synthesized from the corresponding aldehydes. The complexation of these compounds with neutral molecules was assessed by ^{1}H NMR spectroscopy, X-ray structure determination, polarography, and molecular modeling. ^{1}H NMR titration experiments and the crystal structure of **10b**·4-*tert*-butylpyridine indicate that the neutral guests coordinate with their Lewis basic site at the uranyl, and that π-π stacking of the aromatic rings of host and guest stabilizes the complexes. Free energies of complexation, for a series of hosts and guests, obtained from polarographic titration data, vary from 1.5 to $\geq$6.3 kcal mol^{-1}. Compared to the reference salophene–uranyl **11** the stabilities of the complexes are enhanced up to 1.7 kcal mol^{-1} for **2** and up to 1.6 kcal mol^{-1} for **10a–b**; for the more rigid metallomacrocycles **7** increases up to 2.2 kcal mol^{-1} were found. The calculated and experimentally determined relative energies of complexation of 4-methylpyridine vs pyridine with **2**, **10a–b**, and **11** correspond quantitatively.

Introduction

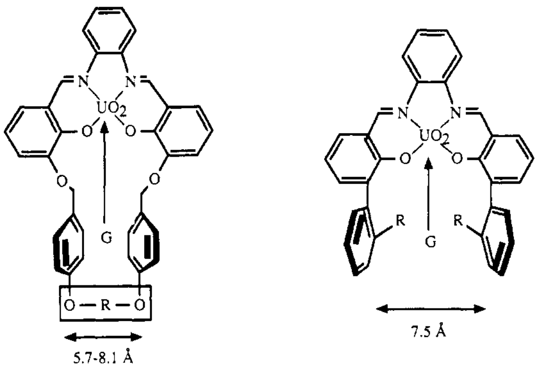
The complexation of *neutral molecules* has become a rapidly growing field since the pioneering work of Pedersen on synthetic host molecules.[1] Most work has concentrated on (macro)cyclic hosts,[2] e.g. calixarenes,[2a] carcerands,[2b,c] cavitands,[2c,d] cryptophanes,[2e] and (aza)cyclophanes[2f–j] of which complexes in solution and in the solid state have been reported.

Investigations in our and other laboratories showed that (metallo)macrocycles containing an intraannular Brønsted or Lewis acid can enhance the stability of complexes with neutral molecules.[3,4] From Bandoli's[5] and our work[3a,b,6] it is known that a Lewis acidic uranyl cation complexed in a salophene unit [*N*,*N*′-phenylenebis(salicylideneaminato)] prefers a pentagonal bipyramidal coordination, with the two oxygens at the apical positions and with both the four coordinating sites of the salophene moiety and a neutral molecule at the equatorial positions.

Recently, organic clefts were recognized as a new class of host molecules with very promising complexing properties.[7] Bell et al.,[7a] Kelly et al.,[7b,c] Rebek et al.,[7d–g] and Zimmerman et al.[7h,i] showed that complexes with diamines, aryl amines, dicarboxylic acids, amino acids, nucleic acids, uric acid, urea, and 2,4,7-trinitrofluorene are formed via (multiple) hydrogen bonding.

We wish to report that introduction of a Lewis acid in a molecular cleft gives a new class of host molecules, *metalloclefts*. By attaching aromatic rings to salophene–uranyl complexes (Chart I) two types of interactions may stabilize the complex formed, viz. coordination to the uranyl moiety and π-π stacking of the aromatic systems of host and guest. The distance between the nearly parallel, aromatic cleft walls of ~5.7–8.1 Å (vide infra) is approximately the same as regarded optimal (6.8 Å) for π-π stacking.[8]

Chart I



In this paper the synthesis of different types of metalloclefts is described. Their complexation properties have been studied by ^{1}H NMR spectroscopy, X-ray crystallography, polarography, cyclic voltammetry, coulometry, and molecular modeling.

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(1) (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967,** *89,* 2495. (b) Pedersen, C. J. *J. Org. Chem.* **1971,** *36,* 1690.

(2) (a) Gutsche, C. D. *Calixarenes,* Monographs in Supramolecular Chemistry, Vol. 1; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989; pp 149–185. (b) Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989,** *111,* 4527. (c) Cram, D. J. *Angew. Chem.* **1988,** *100,* 1041. (d) Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J. *J. Am. Chem. Soc.* **1989,** *111,* 3688. (e) Collet, A. *Tetrahedron* **1987,** *43,* 5725. (f) Diederich, F. *Angew. Chem.* **1988,** *100,* 372. (g) Koga, K.; Odashima, K. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989,** *7,* 53. (h) Murakami, Y.; Kikuchi, J. *Pure Appl. Chem.* **1988,** *60,* 549. (i) Brown, A. B.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1989,** *111,* 3640. (j) Hamilton, A. D.; Muehldorf, A.; Chang, S.-K.; Pant, N.; Goswami, S.; van Engen, D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989,** *7,* 27.

(3) (a) van Staveren, C. J.; Fenton, D. E.; Reinhoudt, D. N.; van Eerden, J.; Harkema, S. *J. Am. Chem. Soc.* **1987,** *109,* 3456. (b) van Staveren, C. J.; van Eerden, J.; van Veggel, F. C. J. M.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1988,** *110,* 4994. (c) van Staveren, C. J.; Aarts, V. M. L. J.; Grootenhuis, P. D. J.; Droppers, W. J. H.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1988,** *110,* 8134. (d) Skowronska-Ptasinska, M.; Aarts, V. M. L. J.; Egberink, R. J. M.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1988,** *53,* 5484. (e) van Eerden, J.; Skowronska-Ptasinska, M.; Grootenhuis, P. D. J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1989,** *111,* 700.

(4) McDaniel, C. W.; Bradshaw, J. S.; Izatt, R. M. *Heterocycles* **1990,** *30,* 665.

(5) Bandoli, G.; Clemente, D. A.; Croatto, U.; Vidali, M.; Vigato, P. A. *J. Chem. Soc., Chem. Commun.* **1971,** 1330.

(6) To be published: the corresponding free host crystal structure of the salophene–uranyl–crown ether·urea complex reported in refs 3a and 3b and the structure of a salophene–uranyl–crown ether with a pyridine moiety modified crown ether part.

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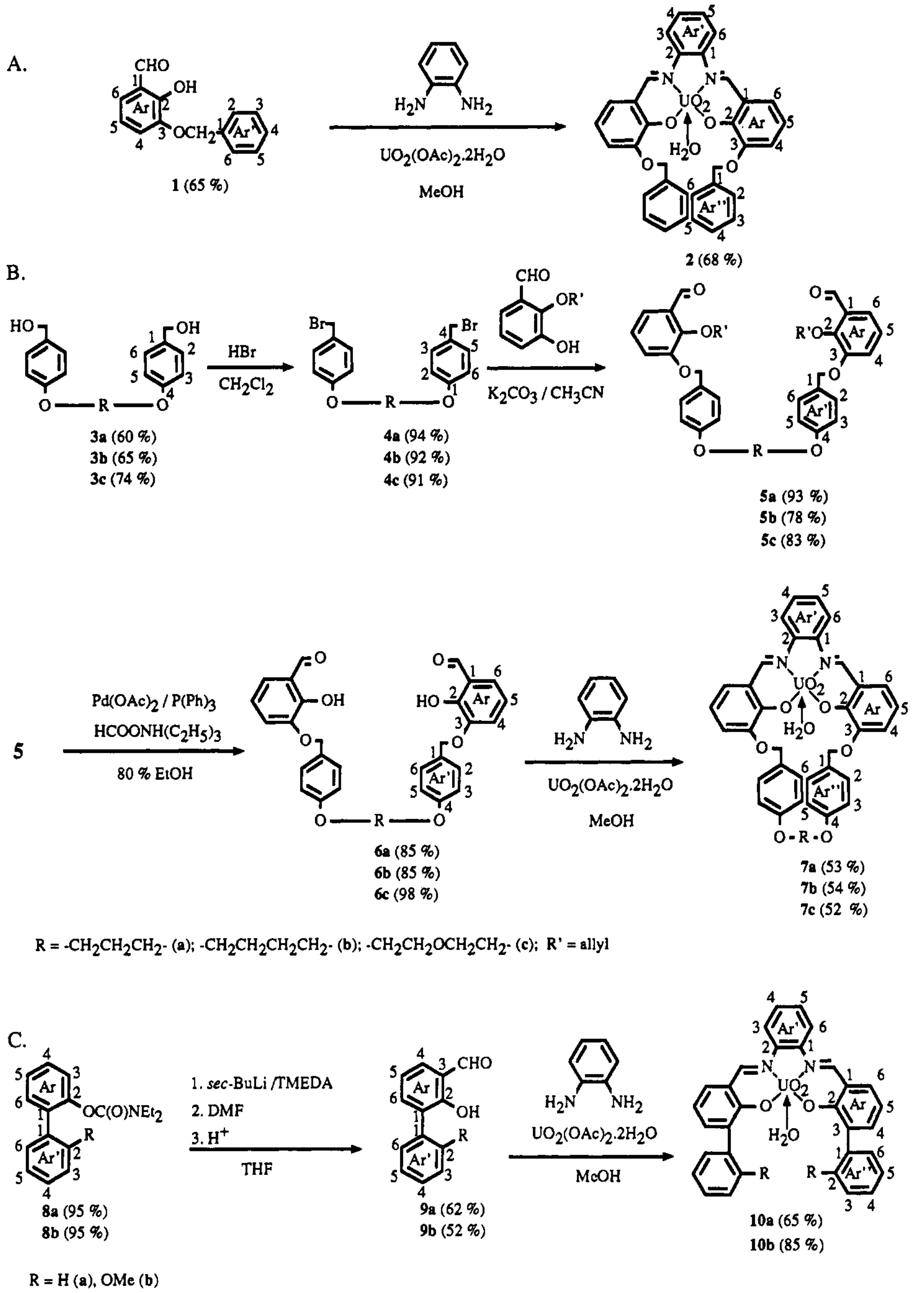
Scheme I



R = -CH$_2$CH$_2$CH$_2$- (a); -CH$_2$CH$_2$CH$_2$CH$_2$- (b); -CH$_2$CH$_2$OCH$_2$CH$_2$- (c); R' = allyl

R = H (a), OMe (b)

Results and Discussion

Synthesis. Aldehyde 1[9] was prepared from 2,3-dihydroxybenzaldehyde and benzyl bromide in DMSO with 2 equiv of NaH to achieve selective introduction of the benzyl group in the 3-position in 65% yield. Condensation of 1 and 1,2-benzenediamine in MeOH gave, after the addition of uranyl acetate, the metallocleft 2 in 68% yield. The ^{1}H NMR spectrum of 2 shows a singlet at 9.37 ppm due to the imine bond with the lone pair of the imine nitrogen coordinating to the uranyl moiety.[3a,b] In the IR spectrum the imine and the uranyl–oxygen bond reveal absorptions at 1603 and 905 cm^{-1}, respectively.[5] According to the elemental analysis and the Karl–Fischer titration one water molecule is present, probably at the fifth equatorial position (Scheme I).[10] In order to study the effect of rigidification on the complexation properties of these clefts, metallomacrocycles 7 were prepared. Contrary to the metallomacrocycles that we have reported previously,[3a,b] the bridge in compounds 7 only serves to fix the aromatic walls of the metallocleft. Starting from 4-hydroxybenzyl alcohol and 1,3-dibromopropane, 1,4-dibromobutane, and diethylene glycol ditosylate, respec-

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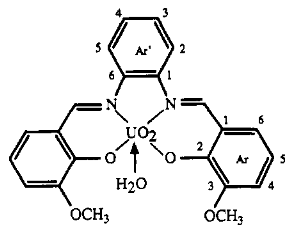
(7) (a) Bell, T. W.; Lui, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. (b) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (c) Kelly, T. R.; Bilodeau, M. T.; Bridger, G. J.; Zhao, C. *Tetrahedron Lett.* **1989**, *30*, 2485. (d) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (e) Rebek, J., Jr.; Askew, B.; Ballester, P.; Costero, A. *J. Am. Chem. Soc.* **1988**, *110*, 923. (f) Tadayoni, B. M.; Parris, K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 4503. (g) Tjivikua, T.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 1249. (h) Zimmerman, S. C.; VanZyl, C. M.; Hamilton, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1373. (i) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054.

(8) Saenger, W. *Principles of Nucleic Acid Structures*; Springer-Verlag: New York, 1984.

(9) No experimental procedure and analytical data were reported by Kessar, S. V.; Gupta, Y. P.; Mohammad, T.; Goyal, M.; Sawal, K. K. *J. Chem. Soc., Chem. Commun.* **1983**, 400.

(10) Assignments for comparability reasons are not always consistent with Chemical Abstract nomenclature.

Chart II



11 (81 %)

tively, the diols **3a**, **3b**, and **3c**, were synthesized in 60–74% yield. The diols **3** were converted to dibromides **4** with HBr in dichloromethane in 91–94% yield. The unstable dibromides **4** were used immediately or could be stored at −40 °C. Reaction of dibromides **4** with 2-(2-allyl)-3-hydroxybenzaldehyde[3b] in CH_3CN and using potassium carbonate as a base gave the diallyl compounds **5** in 78–93% yield. Deallylation of the compounds **5** could be achieved with $Pd(OAc)_2$, PPh_3, and an equimolar mixture of formic acid and triethylamine in 80% aqueous ethanol[11] to give aldehydes **6** in 85–98% yield. The ^{1}H NMR spectra of compounds **6** exhibit aldehyde peaks at 9.90–9.92 ppm and hydroxyl peaks at 10.97–11.00 ppm. Macrocyclization of dialdehydes **6** with 1,2-benzenediamine was carried out by slow addition of both a solution of the diamine and a solution of aldehyde **6** to a refluxing solution of $UO_2(OAc)_2{\cdot}2H_2O$ in methanol to afford macrocycles **7** in 52–54% yield. The ^{1}H NMR spectra of **7** exhibit signals at 9.37–9.38 ppm, and in the IR spectra absorptions are present at 1600–1602 cm^{-1}, which indicate imine bond formation. The absorptions at 900–899 cm^{-1} in the IR spectra correspond to the uranium–oxygen vibrations. The fast atom bombardment spectra show very distinct M$^+$ peaks, which proved that the uranyl cation is tightly complexed. The elemental analyses and Karl-Fischer titrations are in agreement with the macrocyle **7** having one water molecule complexed at the fifth equatorial position.[6]

Another type of metallocleft is based on biphenyls. The carbamates **8**[12] could be obtained in excellent yields by reaction of 1,1′-biphenyl-2-ol or the monomethyl ether of 1,1′-biphenyl-2,2′-diol[13,14] with diethylcarbamoyl chloride and potassium carbonate as a base in CH_3CN. Treatment of the carbamates **8** with 1.1 equiv of *sec*-BuLi, and TMEDA in THF[15–17] followed by quenching with DMF, and acidic workup to remove the carbamate moiety, afforded the aldehydes **9** in 52–62% yield. The ^{1}H NMR spectra show peaks at 9.87–9.95 ppm and the IR spectra absorptions at 1651–1655 cm^{-1} indicating that the aldehyde groups were introduced. Addition of uranyl acetate to a refluxing solution of the aldehydes **9** and 1,2-benzenediamine gave the metalloclefts **10a** and **10b** in 65% and 85% yield, respectively. The absorptions in the ^{1}H NMR spectra at 9.46 and 9.40 ppm and in the IR spectra at 1603 and 1605 cm^{-1} for **10a** and **10b**, respectively, proved imine bond formation. The presence of the uranyl moiety is in agreement with the uranium–oxygen vibrations in the IR spectra at 900 and 899 cm^{-1} for metallocleft **10a** and **10b**, respectively. The presence of water in **10a** and **10b** was confirmed by elemental analyses and Karl–Fischer titrations.

In order to study the contribution of the aromatic walls of the metalloclefts to the complexation properties we have also synthesized compound **11** (Chart II). Starting from 2-hydroxy-3-methoxybenzaldehyde and 1,2-benzenediamine, **11** was prepared in 81% yield according to the procedure described for metallocleft **10a**. The (M + H)$^+$ peak in the FAB mass spectrum at *m*/*z* 645 (calcd 645 for $C_{22}H_{18}N_2O_6U$ + H) confirms the formation of the uranyl containing compound **11**.

Complexation. According to CPK models and molecular modeling studies[18] the aromatic rings of the metallocleft **2** are parallel at distances from 6 Å to more than 10 Å. In the metallomacrocycles **7** rotations around the $O{-}CH_2$ and $CH_2{-}C_6H_5$ bonds are restricted by connecting the two aromatic rings of the original cleft **2** by a spacer. The hosts **7** are more preorganized than **2** and need only small conformational adaptations to accommodate a guest. The distances between the aromatic rings are 5.7–8.1 Å.

In the biphenyl-based metalloclefts **10a** and **10b** the only conformational freedom is the rotation of the phenyl groups of the biphenyl unit. The distances between the parallel aromatic rings are 7.5 Å.

The complexation with neutral guests was studied by ^{1}H NMR spectroscopy. The stability constant of 367 ± 10 M^{-1} for the **10b**·benzylamine complex in CD_3CN was calculated[19] both from the chemical shifts of the benzylic signal of the guest and the methoxy signal of the host in the 500-MHz ^{1}H NMR spectrum. Due to very small chemical shift differences upon complexation, overlap of host and guest signals, or very broad peaks over a wide range of host–guest ratios, association constants of the other complexes (see Table III) could not be determined. From titration experiments in $CDCl_3$ we could only obtain *qualitative* information about the complexation. Details are given in the Experimental Section.

In the **2**·4-*tert*-butylpyridine, **10b**·pyridine, and **10b**·4-*tert*-butylpyridine complexes the H-2(6) protons of pyridine and 4-*tert*-butylpyridine show *downfield* shifts due to coordination at the uranyl.[20] For the complexes of the benzylic type (**2** and **7a**) shifts are more downfield than for biphenyl cleft **10b**. Models of the benzylic type cleft complexes show that the H-2(6) protons of pyridine and 4-*tert*-butylpyridine are located at the uranyl site of the cleft, contrary to cleft **10b** where the H-2(6) protons of pyridine and 4-*tert*-butylpyridine are between the aromatic rings. In the first case the relative large downfield shift of the H-2(6) proton is due to coordination at the uranyl. In the latter case the relative small downfield shift of the H-2(6) proton is the result of two opposite effects: a downfield shift due to coordination on the uranyl and an

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(11) Yamada, T.; Goto, K.; Mitsuda, Y.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 4557.

(12) No analytical data were reported by: (a) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997. (b) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093.

(13) Musso, H.; Matthies, H.-G. *Chem. Ber.* **1961**, *94*, 356.

(14) Our procedure differs from the procedure described in ref 13 in alkylating agent and solvent. We used iodomethane and acetonitrile instead of dimethyl sulfate and acetone.

(15) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.

(16) A O→C 1,3-carbamoyl migrated product was obtained at −70 °C: ^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1 H, OH), 7.6–7.2 (m, 7 H, Ar H), 6.90 (dd, $J_{5,4} = J_{5,6} = 6.9$ Hz, 1 H, H-5), 3.55 (q, $J = 7.0$ Hz, 4 H, CH_2), 1.28 (t, $J = 7.0$ Hz, 4 H, CH_3); IR (KBr) 1718 (C=O) cm^{-1}; mass spectrum (EI), *m*/*z* 269.142 (M$^+$, calcd for $C_{17}H_{19}NO_2$ 269.146).

(17) Only the elemental analysis results and mp were reported by: (a) Ferguson, L. N.; Calvin, M. *J. Am. Chem. Soc.* **1950**, *72*, 4324. (b) Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1862.

(18) The X-ray structures in refs 3a, 3b, and 6 showed nearly identical coordinates for the uranyl–salophene moiety. We decided to take for the salophene–uranyl moiety the average coordinates, and for the rest of the molecule standard bond lengths.

(19) de Boer, J. A. A.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J.; de Jong, F. *J. Am. Chem. Soc.* **1982**, *104*, 4073.

(20) (a) Subramanian, M. S.; Pai, S. A.; Manchanda, V. K. *Austr. J. Chem.* **1973**, *26*, 85. (b) Forchioni, A.; Librando, V.; Pappalardo, G. C. *J. Chem. Soc., Dalton Trans.* **1977**, 638.

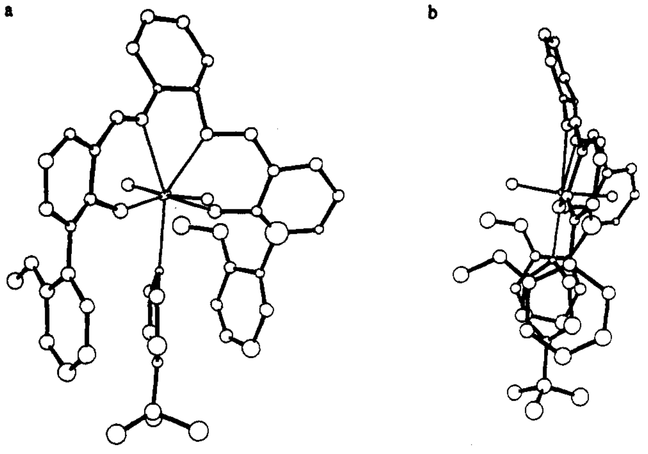

Figure 1. (a) Front and (b) side view of the **10b**·4-*tert*-butylpyridine complex.

upfield shift due to shielding of the aromatic rings of the host. The result of these two opposite effects for the **10b**·benzylamine complex is an upfield shift of the benzylic protons.

The upfield shift, due to shielding of the methoxy protons in the **10b**·benzylamine complex is in agreement with inclusion in the cleft. In the **2**·4-*tert*-butylpyridine complex the *tert*-butyl signal shifts upfield because the *tert*-butyl group is between the aromatic rings of the cleft. In the **10b**·4-*tert*-butylpyridine complex the *tert*-butyl signal shifts downfield because the *tert*-butyl group is, contrary to the **2**·4-*tert*-butylpyridine complex, outside the cleft (vide infra).

From the observed shifts in the ^{1}H NMR spectra we conclude that these neutral molecules coordinate with the Lewis base recognition site to the uranyl and are situated in the cleft.

In addition a solid host–guest complex was isolated. The 1:1:0.75 complex of **7a**·pyridine·CH_3CN precipitated from a solution of **7a** and pyridine in CH_3CN. The presence of **7a**, C_5H_5N, and CH_3CN is evident from the peaks in the FAB and EI mass spectra at *m/z* 867.7, 79.0, and 41.0, respectively. From a titration experiment with both C_5H_5N and CH_3CN in $CDCl_3$ we concluded that C_5H_5N is incorporated in the cavity, because upon addition of excess of C_5H_5N the H-2(6) pyridine signal shifts from 9.12 ppm to the value of free C_5H_5N while the CH_3CN signal did not shift at all. Unfortunately no suitable crystals for X-ray analysis could be obtained of this complex.

Definite proof for coordination to the uranyl and encapsulation in the cleft was obtained from the X-ray structure of the **10b**·4-*tert*-butylpyridine complex. Details of the structure determination are given in the Experimental Section. The ORTEP[21] view of the complex is shown in Figure 1 (metal coordinations are depicted by bonds).

Orange red single crystals were grown by slow diffusion of diisopropyl ether into a solution of cleft **10b** and an excess of 4-*tert*-butylpyridine in CH_3CN.

The uranyl oxygens at the apical positions are found at 1.82–1.84 Å. At the equatorial positions uranyl is coordinated by two phenolate oxygens ($UO_2^{2+}\cdots O$ 1.91 and 2.30 Å), two salophene nitrogens ($UO_2^{2+}\cdots N$ 2.45 and 2.64 Å), and a pyridine nitrogen ($UO_2^{2+}\cdots N$ 2.43 Å). These five coordinating atoms and uranium are found within 0.11 Å of their mean plane, resulting in a pentagonal bipyramidal coordination.

Table I. Polarographic Data for the Reduction at a Dropping Mercury Electrode at 20 °C in 0.1 M TEAP in CH_3CN vs Ag/AgCl

compd	$E_{1/2}$ (V)	I_d (nA)	slope (mV)	conc (mM)
2	−0.940	94.443	57	1.003
7a	−1.008	99.606	78	0.946
7b	−1.015	101.245	84	1.071
7c	−1.021	20.781	88	0.2
10a	−0.940	63.971	60	0.853
10b	−1.085	189.277	62	0.967
11	−0.928	77.137	56	1.035

The Schiff base moiety deviates distinctly from planarity with angles between the adjacent aromatic rings of 38° and 53°, respectively. The deformation of the salophene unit is necessary to accommodate the large uranyl cation.[3a,b] The mean planes of the nearly parallel (angle 6°) aromatic rings of the cleft with biphenyl angles both of 61° are at 8.25 Å. The mean plane of 4-*tert*-butylpyridine and the mean planes of the cleft aromatic rings have angles of 25° and 30°, respectively. The semiparallel rings are likely the result of the fact that the distance between the aromatic rings of the cleft is somewhat too large for an optimal contact. The *tert*-butyl group is outside of the cavity, the same is true for the complex in solution as was concluded from the ^{1}H NMR spectrum (vide supra).

Electrochemistry. Polarography is one of the generally accepted standard techniques in inorganic[22] and supramolecular chemistry[23] to measure the stability constants of complexes between metal cations and neutral (macrocyclic) ligands. Using the same principles, we have used polarography to determine the stability constants of complexes of *metallo*clefts/*metallo*macrocycles and *neutral* guests.

For the uranyl cation one- and two-electron reductions have been reported.[22] We found with coulometry at a potential of −1.2 V in CH_3CN with TEAP ($Et_4N^+ClO_4^-$) as supporting electrolyte that the first reduction step of **2**, **7a**, **10b**, and **11** (a set of representative examples for the different types of hosts) is a one-electron transfer.

The reduction properties of **2**, **7**, **10**, and **11** were further studied with DC polarography in CH_3CN with TEAP as the supporting electrolyte.[24] The polarograms were recorded in the range −0.7 to −1.2 V and they were evaluated by a computerized method described by Zollinger et al.[25] (Table I).

Remarkably, there is a large difference between the reduction potentials of the biphenyl-based clefts **10a** and **10b**. Different substituents attached to the salophene moiety, e.g. a benzyloxy (**2**),[26] a phenyl (**10a**), or a methoxy (**11**)[27] group, hardly affect the reduction potential. Therefore it was unexpected that the introduction of a

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[21] Johnson, C. K. ORTEP, Report ORNL-3794; Oak Ridge National Laboratory, Oak Ridge, TN, 1965.

[22] Heyrovski, J.; Kuta, J. *Grundlagen der Polarografie*; Schwabe, K., Ed.; Akademie-Verlag: Berlin, 1965.

[23] Izatt, R. M.; Bradshaw, J. S.; Nielsen, N. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.

[24] The compounds **2** and **11** were studied in more detail because the polarograms show for both complexes not only one major wave but also a wave at a less negative potential of −800 and −600 mV, respectively. This small wave may be due to adsorption at the mercury drop.[22] Evidence for this phenomena was obtained from the cyclic voltammograms recorded between −0.3 and −1.1 V at scan rates of 1.0–6.0 V/s, starting at different points in the cathodic (reductive) or anodic (oxidative) sweep. Finally, the prewaves in the polarograms and the cyclic voltammograms of **2** and **11** disappear after the addition of a complex giving guest.

[25] Zollinger, D. P.; Bos, M.; van Veen-Blaauw, A. M. W.; van der Linden, W. E. *Anal. Chim. Acta* **1985**, *167*, 89.

[26] Formally it is not correct to take into account the compounds **7** because of their difference in slope compared to **2**, **10**, and **11**.

[27] The removal of the methoxy groups from compound **11** results in a compound were the first reduction step is found at −0.6 V in the polarogram.

Table II. Typical Input for 10b • Benzylamine

$E_{1/2}$ (mV)	$G \times 10^{-3}$ (M)	$H \times 10^{-3}$ (M)	I_d (nA)
−1075.81	-	2.9363	550.557
−1098.10	1.2526	2.9291	564.509
−1106.53	2.4990	2.9218	575.512
−1112.34	3.7392	2.9145	586.176
−1115.84	4.9733	2.9073	593.532
−1118.72	6.2012	2.9001	604.538

methoxy moiety in the phenyl groups (**10b**) would result in a cathodic shift of 145 mV. An explanation was offered by molecular modeling using QUANTA/CHARMm[28] which shows that a coordinating water molecule can form at least one H-bond with the oxygens of the methoxy groups. The result is that this water molecule is more tightly complexed to the uranyl, and the water molecule donates more electrons to the uranyl moiety. This will result in a more negative reduction potential.

To the best of our knowledge, nothing is known about the stability of complexes in solution of uncharged uranyl containing hosts and neutral organic guests.

Because the host is the electrochemical active species, the guest was added in the titration experiments; the polarographic data were evaluated with the computer program POLAG.[29] The program takes into account half-wave potentials ($E_{1/2}$), limiting currents (I_d), host, and guest concentrations after each addition of guest. A typical example of data input for POLAG is given in Table II for measurements on the **10b**·benzylamine complex. Each entry gives for $E_{1/2}$ and I_d the average value of three experiments. The association constant of 360 M^{-1} calculated from the data given in Table II is in good agreement with the value of 367 M^{-1} obtained from a ^{1}H NMR titration experiment (vide supra). We agree with Schneider et al.[30] that the presence or absence of an ion-buffer does not effect the stability of a complex consisting of a *neutral* guest and a *neutral* host.

In Table III the calculated free energies of the host–guest complexes are given. Several conclusions can be drawn from the data presented in Table III:

(i) A wide variety of guests can be complexed, e.g. pyridines, pyridine *N*-oxide, isoquinoline, benzylamine, and benzamide, giving stable complexes with free energies of complexation up to more than 6.3 kcal mol^{-1}. Aniline and 2,6-dimethylpyridine give in general complexes of low stability.

(ii) In some cases an anodic shift instead of the usual cathodic shift was observed upon addition of guest.[31] From this observation it was concluded that in these cases the coordination of the neutral guests to the uranyl is less favorable than for the water molecule present. However the π-π stacking contribution to the stability of the complex is large enough to compensate for this.

(iii) The free energies of complexation increase with the basicity of the pyridines. This is nicely demonstrated in the series pyridine, 4-methylpyridine, and 4-aminopyridine with pK_a's of respectively 5.2, 6.1, and 9.1.[32a]

(iv) The complexes of isoquinoline (pK_a = 5.4)[32b] with **2**, **7a**, and **7b** are stabilized more than the corresponding pyridine complexes, compared to compound **11**. Rebek[7d] has also shown that extended π-systems give complexes of higher stability.

(v) Steric effects can lower the stabilities of the complexes as was found for some of the 4-*tert*-butylpyridine complexes and for all 2,6-dimethylpyridine complexes. The steric hindrance between the two methyl groups and the uranyl oxygens at the apical positions prevents efficient coordination of the pyridine nitrogen to the uranyl.

(vi) Comparison between complexes with host **11** and the complexes with the hosts **2**, **7a**, **7b**, **7c**, and **10a** showed that the introduction of an extended cleft results in more stable complexes. For the flexible metallocleft **2**, increases of stability of the complexes up to 1.7 kcal mol^{-1} were found compared to **11**. For the metallomacrocycles **7** an even larger increase of the complex stabilities was observed. The maximal stability increase is 2.2 kcal mol^{-1} for the **7b**·benzylamine complex. In the case of **7b**·4-aminopyridine, **7b**·pyridine *N*-oxide, and **7c**·pyridine *N*-oxide the complex stabilities were too high to be measured. The required concentration to measure the stability of those complexes is approximately 10^{-5} M but the lower limit of the polarographic instrumentation for this type of compounds is 2×10^{-4} M. In nearly all cases **7b** forms the most stable complexes. Molecular modeling using QUANTA/CHARMm shows a distance of 6.8–6.9 Å for the benzyl groups of cleft **7b**, which is regarded as the optimal distance of aromatic rings for π-π stacking.[8] For **7a** and **7c** those distances are 5.6 and 7.8 Å, respectively. The biphenyl based hosts show increases up to 1.6 kcal mol^{-1} compared to **11**. The distance between the aromatic rings of the biphenyl clefts of 8.25 Å (vide supra) could be the reason that the stability increase is less as for the hosts **7** with distances closer to 6.8 Å. The more stable water complex of **10b** might explain for the lower stabilities of the complexes of **10b** compared to **10a**.

Calculations. In an attempt to rationalize the relative stabilities of the complexes we have performed molecular mechanics calculations.[33] In the relative simple molecular mechanics approach the energy of complexation is defined as the difference in steric energies between the complex and the free host and guest, respectively (eq 1). If the

$$\Delta E_{\mathrm{compl}} = E_{\mathrm{host\text{-}guest}} - E_{\mathrm{host}} - E_{\mathrm{guest}} \tag{1}$$

complexes of two different guest molecules with a particular host are compared, a relative energy of complexation can be calculated, with omission of E_{host} (eq 2).

$$\Delta\Delta E_{\mathrm{compl\cdot 1\text{-}2}} = (E_{\mathrm{host\cdot guest1}} - E_{\mathrm{host\cdot guest2}}) - (E_{\mathrm{guest1}} - E_{\mathrm{guest2}}) \tag{2}$$

For the Schiff base moiety and the uranyl cation not all parameters were available. Comparison of one published[3b] and two unpublished[6] crystal structures containing this unit showed its invariance, therefore this unit was kept fixed. For the uranyl cation the nonbonded parameters were determined to reproduce hydration geometry and enthalpy.[34] Atomic charges were derived from ab initio calculations at the 6-31G** level by Mulliken population analysis on (fragments of) the molecules involved. The energies of complexation were calculated for the hosts **2**, **10a**, **10b**, and **11** with 4-methylpyridine and 4-*tert*-butylpyridine relative to pyridine. Data are given in Table

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(28) CHARMm and QUANTA, version 2.1A, Polygen Corp.: Waltham, 1989.

(29) Leggett, D. J. *Talanta* **1980**, *27*, 787.

(30) Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442.

(31) Anodic shifts are rare but not unprecedented: Crow, D. R. *Polarografie of Metal Complexes*; Academic Press: London and New York, 1969; pp 56–58.

(32) (a) Tenenbaum, L. E. *Pyridine and its Derivatives*; The Chemistry of Heterocyclic Compounds, Part 2; Klingsberg, E., Ed.; Interscience Publishers, Inc.: New York, 1961; pp 175–178. (b) *Beilstein Handbuch der Organischen Chemie*; Boit, H. G., Ed.; Springer-Verlag: Berlin, 1978; Vol 20, E IV 3410.

(33) Damewood, J. R., Jr.; Urban, J. J.; Williamson, T. C.; Rheingold, A. L. *J. Org. Chem.* **1988**, *53*, 167.

(34) Marcus, Y. *Ion Solvation*; Wiley: Chichester, 1985.

Table III. Free Energy of Complexation ΔG (kcal mol^{-1}) in CH_3CN^{a,b}

guest/host	11	2	7a	7b	7c	10a	10b
pyridine	2.55	3.50	3.66	3.89	<2.5	2.63	1.88
4-methylpyridine	2.89	3.87	4.33	4.01	3.75	3.53	2.29
4-*tert*-butylpyridine	2.80	3.19	4.18	3.44	<2.5	3.51	2.35
2,6-dimethylpyridine	<1.5	<2.0	<2.5	2.85^c	<2.5	<2.5^c	<1.5^c
4-aminopyridine	>4.0^d	>4.0^d	5.21	>5.6	5.55	4.59	4.60
pyridine *N*-oxide^e	>4.0^d	>4.0^d	6.30	>6.3	>6.3	4.69	4.79
aniline	<1.5	<2.0	<2.5	<2.5	<2.5	<2.5^c	<1.5^c
isoquinoline	<1.5	3.17	3.62	3.61	<2.5	<2.5	2.69^c
benzylamine	2.52	3.07	4.60	4.76	4.66	4.13	3.43
benzonitrile	<1.5	3.00^c	2.89^c	3.52^c	<2.5	<2.5	<1.5
benzamide	4.27	3.27	3.76	4.51	<2.5	<2.5	<1.5
N-phenylurea	3.79	<2.5	<2.5	3.42	<2.5	3.87^c	2.89^c
methyl phenyl sulfoxide	3.11	2.84	3.69	3.37	<2.5	<2.5	3.02

^{a} Estimated error from repeated titration experiments is 0.10 kcal mol^{-1}. ^{b} Maximal values are given when very small shifts (<10 mV) are observed and due to limited solubility of the host no higher concentration could be achieved. The values are estimated from the observed reduction potential shift of the host upon addition of known amounts of guest compared with the maximal observed shift. Minimal values are given when due to limited sensibility of the instrumentation no lower concentration of the host could be achieved. In both estimations the concentration of the host is taken into account. ^{c} Upon addition of guest less negative potentials are determined. ^{d} Cannot be measured due to the prewave. ^{e} In water a reduction potential of −1.278 V was found: Ochiaci, E. *J. Org. Chem.* **1953**, *18*, 534. Although the reduction potentials of the host are close to this value upon addition of guest (−1.10 to −1.15 V) no reduction is observed in CH_3CN.

Table IV. Relative Energies of Complexation ($\Delta\Delta E_{compl}$) from Molecular Mechanics Calculations and Experimental Relative Free Energies of Complexation ($\Delta\Delta G_{exp}$) (kcal mol^{-1}) Relative to the Pyridine Complexes

	4-methylpyridine		4-*tert*-butylpyridine	
guest/host	$\Delta\Delta E_{compl}$	$\Delta\Delta G_{exp}$	$\Delta\Delta E_{compl}$	$\Delta\Delta G_{exp}$
2	−0.7	−0.4	−2.7	0.3
10a	−0.6	−0.7	−1.4	−0.9
10b	−0.2	−0.4	−1.4	−0.5
11	−0.6	−0.3	−2.0	−0.3

IV. The experimental and calculated relative free energies of complexation of 4-methylpyridine vs pyridine show a nearly quantitative agreement, although the solvent CH_3CN was not taken into account. For 4-*tert*-butylpyridine no agreement could be observed between calculated and experimental determined values. This disagreement can be due to the omission of solvation effects. In order to account for the role of the solvent, CH_3CN must be included in the calculations. Molecular dynamics calculations based on the solvent model of Jorgensen et al.[35] for CH_3CN are under investigation.

Conclusions

Convenient routes are developed for the synthesis of the metallohosts **2**, **7**, **10**, and **11**. ^1H NMR spectroscopy and X-ray analysis demonstrated inclusion of a neutral molecule in the cleft or cavity, via coordination at the uranyl and π-π stacking between the aromatic rings of the hosts and the guest.

Coulometry reveals that the first reduction step of **2**, **7a**, **10b**, and **11** (representative examples) is a one-electron reduction. From the polarographic data free energies of complexation up to more than 6.3 kcal mol^{-1} in CH_3CN were calculated. Upon introduction of a cleft the complexes with pyridine *N*-oxide, pyridine (derivatives), isoquinoline, benzylamine, and benzonitrile are stabilized, up to 1.7 kcal mol^{-1}, compared to compound **11**. Rigidifying the cleft **2** gives even more stable complexes ($\Delta\Delta G \leq 2.2$ kcal mol^{-1}) with a maximum stability for complexes of **7b** in most cases. The biphenyl clefts show stability-increases of the complexes up to 1.6 kcal mol^{-1} compared to **11**.

Molecular mechanics calculations showed a good agreement between the experimentally determined and calculated relative energies of complexation of 4-methylpyridine vs pyridine for the clefts **2**, **10a–b**, and **11**. Because of the disagreement in other cases, which might be due to the neglect of solvation, current efforts are concentrated on calculations which take solvation into account.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$, CD_3CN, CD_3COCD_3, or DMSO-d_6 with TMS as internal standard. Assignments of the NMR spectra are according to Scheme I (Chart II for compound **11**). Positive ion fast atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as a matrix. Melting points were uncorrected. CH_3CN and DMSO (dimethyl sulfoxide) were dried over molecular sieves (4 Å) prior to use. Petroleum ether refers to the fraction with bp 40–60 °C. Other chemicals were of reagent grade and were used without purification. Column chromatography was performed with silica gel (Merck; 0.015–0.040 mm). All reactions were carried out in a nitrogen atmosphere except lithiations which were carried out under argon. Dropwise additions over a period of several hours were always carried out with a perfusor. If not stated otherwise the organic layers were dried, after extraction from the water layer, over $MgSO_4$ and concentrated in vacuo.

Care should be taken when handling uranyl containing compounds because of their toxicity and radioactivity.

2-Hydroxy-3-(phenylmethoxy)benzaldehyde (1).[36] To a suspension of NaH (6.82 g, 0.24 mol, 80% in oil), prewashed with petroleum ether, in DMSO (100 mL) was added a solution of 2,3-dihydroxybenzaldehyde (14.4 g, 0.10 mol) in DMSO (50 mL) at 20–25 °C. After 1 h of stirring, a solution of benzyl bromide (17.1 g, 0.10 mol) in DMSO (25 mL) was added at 20–25 °C, and stirring was continued for 24 h, whereupon the mixture was poured into water (500 mL) and extracted with $CHCl_3$ (2 × 125 mL). The aqueous layer was acidified with 6 M HCl to adjust the pH to 2–4 and was again extracted with $CHCl_3$ (3 × 150 mL). The latter combined $CHCl_3$ layers were washed with 1 M HCl (2 × 150 mL) and filtered over silica gel to give pure aldehyde **1**: yield 65%; mp 86–87 °C (diethyl ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 11.04 (s, 1 H, OH), 9.90 (s, 1 H, CHO), 7.4–6.9 (m, 8 H, Ar H), 5.18 (s, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 196.4 (d, CHO), 152.3 (s, C-2), 147.2 (s, C-3), 136.5 (s, C′-1), 128.6, 128.0, 127.3 (d, C′-2, C′-3, C′-4), 125.3, 121.0, 119.4 (d, C-4, C-5, C-6), 121.1 (s, C-1), 71.4 (t, OCH_2); IR (KBr) 1658 (C=O) cm^{-1}; mass spectrum (EI), *m/z* 228.077 (M^+, calcd for $C_{14}H_{12}O_3$ 228.079).

Dioxo[[2,2′-[1,2-phenylenebis(nitrilomethylidyne)]bis-[6-(phenylmethoxy)phenolato]](2−)-*N*,*N*′,*O*,*O*′]uranium·H_2O (2·H_2O). To a refluxing solution of aldehyde **1** (1.0 g, 4.4 mmol) in methanol (75 mL) was added dropwise a solution of 1,2-

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[35] Jorgensen, W. L.; Briggs, J. M. *Mol. Phys.* **1988**, *63*, 547.

[36] No satisfactory elemental analysis could be obtained.

benzenediamine (0.24 g, 2.2 mmol) in MeOH (25 mL). After 1.5 h UO$_2$(OAc)$_2$·2H$_2$O (0.93 g, 2.2 mmol) was added and reflux was maintained for 15 min whereupon the mixture was allowed to cool to room temperature. The solvent was evaporated in vacuo. The reaction mixture was solved in CHCl$_3$ (50 mL) and washed with water (50 mL) to yield an orange solid: yield 68%; mp 194–196 °C (CH$_2$Cl$_2$/petroleum ether); ^{1}H NMR (CDCl$_3$) δ 9.37 (s, 2 H, CH=N), 7.4–7.2 (m, 18 H, Ar H), 6.56 (dd, $J_{5,4} = J_{5,6}$ = 7.7 Hz, 2 H, Ar H-5), 5.14 (s, 4 H, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 165.4 (d, CH=N), 161.3 (s, C-2), 150.1 (s, C-3), 146.8 (s, C′-1), 137.7 (s, C″-1), 128.9, 128.4, 128.2, 127.6, 127.4 (d, C-6, C′-4, C″-2, C″-3, C″-4), 124.8 (s, C-1), 119.3, 117.6 (d, C-4, C-5, C′-3), 72.3 (t, CH$_2$); IR (KBr) 1603 (C=N), 905 (OUO) cm^{-1}; mass spectrum (FAB), *m/z* 798 ((M + 2H)$^+$, calcd 798). Anal. Calcd for C$_{34}$H$_{26}$N$_2$O$_6$U·H$_2$O (M_r 814.634): C, 50.13; H, 3.46; N, 3.44. Found: C, 50.43; H, 3.29; N, 3.34. Karl–Fischer calcd for 1 H$_2$O 2.21, found 1.96.

General Procedure for the Synthesis of Compounds 3. A mixture of 4-hydroxybenzyl alcohol (6.2 g, 0.05 mol), 1,3-dibromopropane (**3a**), 1,4-dibromobutane (**3b**), or diethylene glycol ditosylate (**3c**) (0.025 mol) and K$_2$CO$_3$ (13.8 g, 0.10 mol) was refluxed in CH$_3$CN (200 mL) for 8 h. After cooling to room temperature the solvent was evaporated, water (200 mL) was added and the mixture was extracted several times with CH$_2$Cl$_2$ until the aqueous layer became clear pink. After concentration in vacuo pure white solids **3** were obtained.

4,4′-[1,3-Propanediylbis(oxy)]bis(benzenemethanol) (3a): yield 60%; mp 138–141 °C (acetone); ^{1}H NMR (CDCl$_3$) δ 7.28 (d, J = 8.6 Hz, 4 H, Ar H-2), 6.89 (d, J = 8.6 Hz, 4 H, Ar H-3), 4.60 (s, 4 H, CH_2OH), 4.16 (t, J = 6.2 Hz, 4 H, OCH_2CH$_2$), 2.4–2.1 (m, 2 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 158.5 (s, C-4), 133.2 (s, C-1), 128.6 (d, C-2), 114.6 (d, C-3), 65.1 (t, CH$_2$OH), 64.5 (t, OCH$_2$CH$_2$), 29.3 (t, OCH$_2$$CH_2$); mass spectrum (EI), *m/z* 288.141 (M$^+$, calcd 288.136). Anal. Calcd for C$_{17}$H$_{20}$O$_4$ (M_r 288.343): C, 70.81; H, 6.99. Found: C, 70.55; H, 7.31.

4,4′-[1,4-Butanediylbis(oxy)]bis(benzenemethanol) (3b): yield 65%; mp 126–130 °C (acetone); ^{1}H NMR (CDCl$_3$) δ 7.29 (d, J = 8.8 Hz, 4 H, Ar H-2), 6.89 (d, J = 8.8 Hz, 4 H, Ar H-3), 4.61 (s, 4 H, CH_2OH), 4.1–3.9 (m, OCH_2CH$_2$), 2.2–2.0 (m, 4 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 158.6 (s, C-4), 133.1 (s, C-1), 128.6 (d, C-2), 114.6 (d, C-3), 67.5 (t, OCH$_2$CH$_2$), 65.1 (t, CH$_2$OH), 26.0 (t, OCH$_2$$CH_2$); mass spectrum (EI), *m/z* 302.153 (M$^+$, calcd 302.152). Anal. Calcd for C$_{18}$H$_{22}$O$_4$ (M_r 302.369): C, 71.50; H, 7.33. Found: C, 71.18; H, 6.99.

4,4′-[Oxybis(2,1-ethanediyloxy)]bis(benzenemethanol) (3c): yield 74%; mp 95–97 °C (acetone); ^{1}H NMR (CDCl$_3$) δ 7.27 (d, J = 8.7 Hz, 4 H, Ar H-2), 6.89 (d, J = 8.7 Hz, 4 H, Ar H-3), 4.61 (s, 4 H, CH_2OH), 4.1–3.9 (m, 4 H, Ar OCH_2CH$_2$O), 4.0–3.9 (m, 4 H, Ar OCH$_2$CH_2O); ^{13}C NMR (CDCl$_3$) δ 158.4 (s, C-4), 133.4 (s, C-1), 128.6 (d, C-2), 114.7 (d, C-3), 70.0, 67.6 (t, Ar OCH$_2$CH$_2$O), 64.8 (t, CH$_2$OH); mass spectrum (EI), *m/z* 300.155 ((M − H$_2$O)$^+$, calcd 300.146). Anal. Calcd for C$_{18}$H$_{22}$O$_5$ (M_r 318.369): C, 67.91; H, 6.96. Found: C, 67.81; H, 7.26.

General Procedure for the Synthesis of Compounds 4. Compound **3** (12.5 mmol) was added to a mixture of HBr (47%, 50 mL) and CH$_2$Cl$_2$ (150 mL) and stirred for 1 h until conversion was completed (TLC; SiO$_2$, CHCl$_3$–MeOH, 10:1). The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 150 mL). The combined organic layers were washed with a saturated solution of NaHCO$_3$. The unstable compounds **4**, which could not be recrystallized, must be used immediately or be stored at −40 °C.

1,1′-[1,3-Propanediylbis(oxy)]bis[4-(bromomethyl)benzene] (4a): yield 94%; mp 139–143 °C; ^{1}H NMR (CDCl$_3$) δ 7.29 (d, J = 8.6 Hz, 4 H, Ar H-3), 6.85 (d, J = 8.6 Hz, 4 H, Ar H-2), 4.48 (s, 4 H, CH$_2$Br), 4.14 (t, J = 6.0 Hz, 4 H, OCH_2CH$_2$), 2.4–2.1 (m, 2 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 158.9 (s, C-1), 130.4 (d, C-3), 130.0 (s, C-4), 114.7 (d, C-2), 64.4 (t, OCH$_2$CH$_2$), 33.8 (t, CH$_2$Br), 29.2 (t, OCH$_2$$CH_2$); mass spectrum (EI), *m/z* 411.967 (M$^+$, calcd 411.968). Anal. Calcd for C$_{17}$H$_{18}$Br$_2$O$_2$ (M_r 414.136): C, 49.30; H, 4.38. Found: C, 49.15; H, 4.38.

1,1′-[1,4-Butanediylbis(oxy)]bis[4-(bromomethyl)benzene] (4b): yield 92%; mp 122–125 °C; ^{1}H NMR (CDCl$_3$) δ 7.27 (d, J = 8.8 Hz, 4 H, Ar H-3), 6.81 (d, J = 8.8 Hz, 4 H, Ar H-2), 4.45 (s, 4 H, CH$_2$Br), 4.1–3.9 (m, 4 H, OCH_2CH$_2$), 2.0–1.9 (m, 4 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 159.0 (s, C-1), 130.4 (d, C-3), 129.9 (s, C-4), 114.7 (d, C-2), 67.5 (t, OCH$_2$CH$_2$), 33.9 (t, CH$_2$Br), 25.9 (t, OCH$_2$$CH_2$); mass spectrum (EI), *m/z* 425.984 (M$^+$, calcd 425.983). Anal. Calcd for C$_{18}$H$_{20}$Br$_2$O$_2$ (M_r 428.163): C, 50.49; H, 4.71. Found: C, 50.41; H, 4.64.

1,1′-[Oxybis(2,1-ethanediyloxy)]bis[4-(bromomethyl)benzene] (4c): yield 91%; mp 131–132 °C; ^{1}H NMR (CDCl$_3$) δ 7.30 (d, J = 8.7 Hz, 4 H, Ar H-3), 6.86 (d, J = 8.7 Hz, 4 H, Ar H-2), 4.48 (s, 4 H, CH$_2$Br), 4.2–4.1 (m, 4 H, Ar OCH_2CH$_2$O), 4.0–3.8 (m, 4 H, Ar OCH$_2$CH_2O); ^{13}C NMR (CDCl$_3$) δ 158.8 (s, C-1), 130.4 (d, C-3), 130.2 (s, C-4), 114.9 (d, C-2), 69.9, 67.7 (t, Ar OCH$_2$CH$_2$O), 33.8 (t, CH$_2$Br); mass spectrum (EI), *m/z* 441.973 (M$^+$, calcd 441.978). Anal. Calcd for C$_{18}$H$_{20}$Br$_2$O$_3$ (M_r 444.162): C, 48.68; H, 4.54. Found: C, 48.40; H, 4.50.

General Procedure for the Synthesis of Compounds 5. A mixture of dibromide **4** (2.5 mmol), 3-hydroxy-2-(2-propenoxy)benzaldehyde[3b] (0.90 g, 5.0 mmol), and K$_2$CO$_3$ (1.38 g, 10.0 mmol) in CH$_3$CN (100 mL) was refluxed for 6 h. The solvent was evaporated in vacuo. To the resulting mixture was added 1 M HCl (100 mL), and the mixture was extracted with CH$_2$Cl$_2$ (3 × 100 mL) to yield after flash chromatography (CHCl$_3$) the yellow solids **5**.

3,3′-[1,3-Propanediylbis(oxy-4,1-phenylenemethyleneoxy)]bis[2-(2-propenyloxy)benzaldehyde] (5a): yield 93%; mp 89–92 °C (CH$_2$Cl$_2$/petroleum ether); ^{1}H NMR (CDCl$_3$) δ 10.43 (s, 2 H, CHO), 7.5–6.9 (m, 14 H, Ar H), 6.3–5.8 (m, 2 H, CH=), 5.5–5.1 (m, 4 H, OCH_2CHCH$_2$), 5.05 (s, 4 H, Ar OCH$_2$ Ar), 4.66 (d, J = 5.9 Hz, 4 H, =CH$_2$), 4.17 (t, J = 6.0 Hz, 4 H, OCH_2CH$_2$), 2.4–2.1 (m, 2 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 190.3 (d, CHO), 158.8 (s, C′-4), 152.1, 151.7 (s, C-2, C-3), 133.1 (d, CH=), 130.3 (s, C-1), 129.1 (d, C′-2), 128.5 (s, C′-1), 124.0, 120.2, 119.5 (d, C-4, C-5, C-6), 118.9 (t, =CH$_2$), 114.6 (d, C′-3), 75.1 (t, OCH$_2$CHCH$_2$), 71.0 (t, Ar OCH$_2$ Ar), 64.4 (t, OCH$_2$CH$_2$), 29.3 (t, OCH$_2$$CH_2$); IR (KBr) 1687 (C=O) cm^{-1}; mass spectrum (EI and FAB), *m/z* 431 ((M − C$_{10}$H$_9$O$_3$)$^+$, calcd 431). Anal. Calcd for C$_{37}$H$_{36}$O$_8$ (M_r 608.687): C, 73.03; H, 5.96. Found: C, 73.36; H, 6.11.

3,3′-[1,4-Butanediylbis(oxy-4,1-phenylenemethyleneoxy)]bis[2-(2-propenyloxy)benzaldehyde] (5b): yield 78%; mp 97–100 °C (CH$_2$Cl$_2$/petroleum ether); ^{1}H NMR (CDCl$_3$) δ 10.45 (s, 2 H, CHO), 7.5–6.9 (m, 14 H, Ar H), 6.3–5.8 (m, 2 H, CH=), 5.5–5.1 (m, 4 H, OCH_2CHCH$_2$), 5.07 (s, 4 H, Ar OCH$_2$ Ar), 4.66 (d, J = 5.9 Hz, 4 H, =CH$_2$), 4.2–3.9 (m, 4 H, OCH_2CH$_2$), 2.1–1.9 (m, 4 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 190.3 (d, CHO), 114.6 (d, C′-3), 71,1 (t, Ar OCH$_2$ Ar), 67.5 (t, OCH$_2$CH$_2$), 26.0 (t, OCH$_2$$CH_2$); IR (KBr) 1683 (C=O) cm^{-1}; mass spectrum (EI), *m/z* 604.246 ((M − H$_2$O)$^+$, calcd 604.246). Anal. Calcd for C$_{38}$H$_{38}$O$_8$ (M_r 622.713): C, 73.30; H, 6.15. Found: C, 73.04; H, 6.13.

3,3′-[Oxybis(2,1-ethanediyloxy-4,1-phenylenemethyleneoxy)]bis[2-(2-propenyloxy)benzaldehyde] (5c): yield 83%; mp 79–84 °C (CH$_2$Cl$_2$/petroleum ether); ^{1}H NMR (CDCl$_3$) δ 10.44 (s, 2 H, CHO), 7.5–6.9 (m, 14 H, Ar H), 6.2–5.8 (m, 2 H, CH=), 5.5–5.1 (m, 4 H, OCH_2CHCH$_2$), 5.06 (s, 4 H, Ar OCH$_2$ Ar), 4.67 (d, J = 5.9 Hz, 4 H, =CH$_2$), 4.2–3.9 (m, 8 H, Ar OCH$_2$CH$_2$O); ^{13}C NMR δ 190.3 (d, CHO), 114.8 (d, C′-3), 71.1 (t, Ar OCH$_2$ Ar), 70.0, 67.6 (t, Ar OCH$_2$CH$_2$O); IR (KBr) 1683 (C=O) cm^{-1}; mass spectrum (FAB), *m/z* 461 ((M − C$_{10}$H$_9$O$_3$)$^+$, calcd 461). Anal. Calcd for C$_{38}$H$_{38}$O$_9$ (M_r 638.713): C, 71.46; H, 6.00. Found: C, 71.15; H, 6.21.

General Procedure for the Synthesis of Compounds 6. A mixture of diallyl compound **5** (1.21 mmol), Pd(OAc)$_2$ (5 mg, 0.024 mmol), PPh$_3$ (25 mg, 0.097 mmol), and HCOONHEt$_3$ (1.10 g, 7.28 mmol) in 80% EtOH (100 mL) was refluxed for 3 h.[11] The solvent was evaporated and the product was purified by flash chromatography (CHCl$_3$–MeOH, 50:1).

3,3′-[1,3-Propanediylbis(oxy-4,1-phenylenemethyleneoxy)]bis[2-hydroxybenzaldehyde] (6a):[36] yield 85%; mp 132–136 °C (CH$_2$Cl$_2$/petroleum ether); ^{1}H NMR (CDCl$_3$) δ 10.97 (s, 2 H, OH), 9.90 (s, 2 H, CHO), 7.4–6.8 (m, 14 H, Ar H), 5.09 (s, 4 H, Ar OCH$_2$ Ar), 4.14 (t, J = 6.2 Hz, 4 H, OCH_2CH$_2$), 2.4–2.0 (m, 2 H, OCH$_2$CH_2); ^{13}C NMR (CDCl$_3$) δ 196.3 (d, CHO), 158.8 (s, C′-4), 152.3 (s, C-2), 147.2 (s, C-3), 129.1 (d, C′-2), 128.6 (s, C′-1), 125.2, 121.2, 119.4 (d, C-4, C-5, C-6), 121.1 (s, C-1), 114.6 (d, C′-3), 71.3 (t, Ar OCH$_2$ Ar), 64.4 (t, OCH$_2$CH$_2$), 29.3 (t, OCH$_2$$CH_2$); IR (KBr) 1657 (C=O) cm^{-1}; mass spectrum (EI), *m/z* 391.155 ((M − C$_7$H$_5$O$_3$)$^+$, calcd for C$_{24}$H$_{23}$O$_5$ 391.155).

3,3′-[1,4-Butanediylbis(oxy-4,1-phenylenemethyleneoxy)]bis[2-hydroxybenzaldehyde] (6b):[36] yield 85%; mp 141–145 °C (CH$_2$Cl$_2$/petroleum ether); ^{1}H NMR (CDCl$_3$) δ 11.00 (s, 2 H, OH), 9.92 (s, 2 H, CHO), 7.4–6.8 (m, 14 H, Ar H), 5.11

(s, 4 H, Ar $\mathrm{OCH_2}$ Ar), 4.1–3.9 (m, 4 H, $\mathrm{OC}H_2\mathrm{CH_2}$), 2.1–1.9 (m, 4 H, $\mathrm{OCH_2C}H_2$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 196.3 (d, CHO), 67.5 (t, $\mathrm{OCH_2CH_2}$), 26.0 (t, $\mathrm{OCH_2C}H_2$); IR (KBr) 1656 ($\mathrm{C{=}O}$) cm^{-1}; mass spectrum (EI), *m/z* 542.195 (M$^+$, calcd for $\mathrm{C_{32}H_{30}O_8}$ 542.194).

3,3′-[Oxybis(2,1-ethanediyloxy-4,1-phenylenemethyleneoxy)]bis[2-hydroxybenzaldehyde] (6c):[36] yield 98%; mp 112–116 °C ($\mathrm{CH_2Cl_2}$/petroleum ether); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 10.97 (s, 2 H, OH), 9.90 (s, 2 H, CHO), 7.4–6.8 (m, 14 H, Ar H), 5.09 (s, 4 H, Ar $\mathrm{OCH_2}$ Ar), 4.2–4.1 (m, 4 H, Ar $\mathrm{OC}H_2\mathrm{CH_2O}$), 3.9–3.8 (m, 4 H, Ar $\mathrm{OCH_2C}H_2\mathrm{O}$); ^{13}C NMR δ 196.4 (d, CHO), 69.9, 67.5 (t, Ar $\mathrm{OCH_2CH_2O}$); mass spectrum (EI), *m/z* 420.150 ((M − $\mathrm{C_7H_6O_3}$)$^+$, calcd for $\mathrm{C_{25}H_{25}O_6}$ 420.150); IR (KBr) 1659 ($\mathrm{C{=}O}$) cm^{-1}.

General Procedure for the Synthesis of Compounds 7. To a refluxing solution of $\mathrm{UO_2(OAc)_2{\cdot}2H_2O}$ (0.37 g, 0.87 mmol) in MeOH (300 mL) were added both a solution of compound **6** (0.87 mmol) in $\mathrm{CH_2Cl_2}$ (25 mL) and a solution of 1,2-benzenediamine (0.09 g, 0.87 mmol) in MeOH (25 mL) in 3 h. After another hour of reflux the hot mixture was decanted to separate off the precipitated side products. Upon partial evaporation of the solvent (till 100 mL) the crude product precipitated. After filtration the mother liquor was concentrated further (till 50 mL), and the precipitated product was again filtered off. The combined and in vacuo dried precipitates were dissolved in $\mathrm{CH_2Cl_2}$ (100 mL), and washed with water (2 × 25 mL) to give pure orange solids **7**.

[16,17-Dihydro-10,13:19,22-dietheno-3,7:25,29-dimetheno-9*H*,15*H*,23*H*-8,14,18,24,1,31-benzotetraoxadiazacyclotritriacontine-36,41-diolato(2−)-*N*^{1},*N*^{31},*O*^{36},*O*^{41}]dioxouranium·$\mathrm{H_2O}$ (7a·$\mathrm{H_2O}$): yield 53%; mp >230 °C dec; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 9.38 (s, 2 H, $\mathrm{CH{=}N}$), 7.6–7.0 (m, 16 H, Ar H), 6.68 (dd, $J_{5,4} = J_{5,6} = 7.9$ Hz, 2 H, Ar H-5), 5.06 (s, 4 H, Ar $\mathrm{OCH_2}$ Ar), 4.32 (t, $J = 5.5$ Hz, 4 H, $\mathrm{OC}H_2\mathrm{CH_2}$), 2.4–2.2 (m, 2 H, $\mathrm{OCH_2C}H_2$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 165.3 (d, $\mathrm{CH{=}N}$), 159.4 (s, C″-4), 150.2 (s, C-3), 146.5 (s, C′-1), 130.2 (d, C″-2), 129.6 (s, C″-1), 129.0, 127.5 (d, C-6, C′-4), 123.9 (s, C-1), 119.6, 117.1 (d, C-4, C-5, C′-3), 114.9 (s, C″-3), 71.6 (t, Ar $\mathrm{OCH_2}$ Ar), 64.0 (t, $\mathrm{OCH_2CH_2}$), 29.8 (t, $\mathrm{OCH_2C}H_2$); IR (KBr) 1600 ($\mathrm{C{=}N}$), 900 (OUO) cm^{-1}; mass spectrum (FAB), *m/z* 869 ((M + H)$^+$, calcd 869). Anal. Calcd for $\mathrm{C_{37}H_{30}N_2O_8U{\cdot}H_2O}$: C, 50.12; H, 3.64; N, 3.16. Found: C, 50.34; H, 3.59; N, 3.00. Karl-Fischer calcd for 1 $\mathrm{H_2O}$ 2.03, found 2.17.

[16,17-Dihydro-10,13:19,22-dietheno-3,7:25,29-dimetheno-9*H*,15*H*,23*H*-8,14,18,24,1,31-benzotetraoxadiazacyclotritriacontine-36,41-diolato(2−)-*N*^{1},*N*^{31},*O*^{36},*O*^{41}]dioxouranium·$\mathrm{C_5H_5N{\cdot}0.75CH_3CN}$ (7a·$\mathrm{C_5H_5N{\cdot}0.75CH_3CN}$). To a solution of macrocycle **7a**·$\mathrm{H_2O}$ (50 mg) in $\mathrm{CH_3CN}$ (60 mL) was added pyridine (0.5 mL). The complex crystallized slowly and was filtered off and dried in vacuo: mp >230 °C dec; ^{1}H NMR ($\mathrm{CDCl_3}$) δ calcd (s, 2 H, $\mathrm{CH{=}N}$), 9.12 (d, $J = 4.4$ Hz, 2 H, Py H), 7.6–6.6 (m, 19 H, Ar H, Py H), 6.68 (dd, $J_{5,4} = J_{5,6} = 7.7$ Hz, 2 H, Ar H-5), 5.05 (s, 4 H, Ar $\mathrm{OCH_2}$ Ar), 4.30 (t, $J = 5.9$ Hz, 4 H, $\mathrm{OC}H_2\mathrm{CH_2}$), 2.3–2.2 (m, 2 H, $\mathrm{OCH_2C}H_2$), 1.99 (s, 0.75 $\mathrm{CH_3CN}$); due to low solubility no ^{13}C NMR spectrum could be recorded; IR (KBr) 1603 ($\mathrm{C{=}N}$), 899 (OUO) cm^{-1}; mass spectrum (EI), *m/z* 41.0 (M$^+$, calcd $\mathrm{CH_3CN}$ 41.0), 79.0 (M$^+$, calcd $\mathrm{C_5H_5N}$ 79.0); mass spectrum (FAB), *m/z* 869.7 ((M + H)$^+$, calcd 869.7). Anal. Calcd for $\mathrm{C_{37}H_{30}N_2O_8U{\cdot}C_5H_5N{\cdot}0.75CH_3CN}$ (M_r 947.734): C, 53.39; H, 3.84; N, 5.37. Found: C, 53.57; H, 3.72; N, 4.98.

Dioxo[15,16,17,18-tetrahydro-10,13:20,23-dietheno-3,7:26,30-dimetheno-9*H*,24*H*-8,14,19,25,1,32-benzotetraoxadiazacyclotritriacontine-37,42-diolato(2−)-*N*^{1},*N*^{32},*O*^{37},*O*^{42}]uranium·$\mathrm{H_2O}$ (7b·$\mathrm{H_2O}$): yield 54%; mp >230 °C dec; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 9.38 (s, 2 H, $\mathrm{CH{=}N}$), 7.7–6.9 (m, 16 H, Ar H), 6.69 (dd, $J_{5,4} = J_{5,6} = 7.3$ Hz, 2 H, Ar H-5), 5.06 (s, 4 H, Ar $\mathrm{OCH_2}$ Ar), 4.3–4.1 (m, 4 H, $\mathrm{OC}H_2\mathrm{CH_2}$), 2.1–1.9 (m, 4 H, $\mathrm{OCH_2C}H_2$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 165.3 (d, $\mathrm{CH{=}N}$), 67.5 (t, $\mathrm{OCH_2CH_2}$), 25.6 (t, $\mathrm{OCH_2}C\mathrm{H_2}$); IR (KBr) 1602 ($\mathrm{C{=}N}$), 899 (OUO) cm^{-1}; mass spectrum (FAB), *m/z* 882 (M$^+$, calcd 882). Anal. Calcd for $\mathrm{C_{38}H_{32}N_2O_8U{\cdot}H_2O}$ (M_r 900.725): C, 50.67; H, 3.80; N, 3.11. Found: C, 50.89; H, 3.96; N, 2.84. Karl-Fischer calcd for 1 $\mathrm{H_2O}$ 2.00, found 2.13.

Dioxo[15,16,18,19-tetrahydro-10,13:21,24-dietheno-3,7:27,31-dimetheno-9*H*,25*H*-8,14,17,20,26,1,33-benzopentaoxadiazacyclopentatriacontine-38,43-diolato(2−)-*N*^{1},*N*^{33},*O*^{38},*O*^{43}]uranium·$\mathrm{H_2O}$ (7c·$\mathrm{H_2O}$): yield 52%; mp >200 °C dec; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 9.37 (s, 2 H, $\mathrm{CH{=}N}$), 7.6–6.9 (m, 16 H, Ar H), 6.69 (dd, $J_{5,4} = J_{5,6} = 7.3$ Hz, 2 H, Ar H-5), 5.06 (s, 4 H, Ar $\mathrm{OCH_2}$ Ar), 4.3–4.0 (m, 8 H, Ar $\mathrm{OCH_2CH_2O}$); ^{13}C NMR (acetone-d_6/acetonitrile-d_3) δ 167.2 (d, $\mathrm{CH{=}N}$), 70.7, 69.1 (t, Ar $\mathrm{OCH_2CH_2O}$); IR (KBr) 1601 ($\mathrm{C{=}N}$), 899 (OUO) cm^{-1}; mass spectrum (FAB), *m/z* 899 ((M + H)$^+$, calcd 899). Anal. Calcd for $\mathrm{C_{38}H_{32}N_2O_9U{\cdot}H_2O}$ (M_r 916.724): C, 49.79; H, 3.74; N, 3.06. Found: C, 49.56; H, 3.97; N, 2.92. Karl-Fischer calcd for 1 $\mathrm{H_2O}$ 1.97, found 1.95.

General Procedure for the Synthesis of Compounds 8. A mixture of 1,1′-biphenyl-2-ol (**8a**) or the monomethyl ether of 1,1′-biphenyl-2,2′-diol (**8b**)[13] (0.050 mol), diethylcarbamoyl chloride (7.45 g, 0.055 mol), and $\mathrm{K_2CO_3}$ (13.8 g, 0.100 mol) was refluxed in $\mathrm{CH_3CN}$ (200 mL) for 7 h (conversion complete on TLC; $\mathrm{SiO_2}$, $\mathrm{CHCl_3}$). Cooling to room temperature, filtration of $\mathrm{K_2CO_3}$ and evaporation of the solvent and residual diethylcarbamoyl chloride yielded pure colorless oils **8**.

Diethylcarbamic acid, [1,1′-biphenyl]-2-yl ester (8a):[12] yield 95%; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.5–7.1 (m, 9 H, Ar H), 3.23 (q, $J = 7.1$ Hz, 4 H, $\mathrm{C}H_2\mathrm{CH_3}$), 1.01 (t, $J = 7.1$ Hz, 6 H, $\mathrm{CH_2C}H_3$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 154.0 (s, $\mathrm{C{=}O}$), 148.5 (s, C-2), 138.1 (s, C′-1), 135.1 (s, C-1), 130.6, 129.0, 128.2, 128.0, 127.1, 125.4, 123.2 (d, C-3, C-4, C-5, C-6, C′-2, C′-3, C′-4), 41.9, 41.6 (t, $\mathrm{CH_2}$), 13.4, 13.2 (q, $\mathrm{CH_3}$); IR (KBr) 1718 ($\mathrm{C{=}O}$) cm^{-1}; mass spectrum (EI), *m/z* 269.141 (M$^+$, calcd for $\mathrm{C_{17}H_{19}NO_2}$ 269.142).

Diethylcarbamic acid, 2′-methoxy-[1,1′-biphenyl]-2-yl ester (8b):[12b] yield 95%; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.4–6.8 (m, 8 H, Ar H), 3.71 (s, 3 H, $\mathrm{OCH_3}$), 3.4–2.9 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_3}$), 1.2–0.7 (m, 6 H, $\mathrm{CH_2C}H_3$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 156.7 (s, C′-2), 153.8 (s, $\mathrm{C{=}O}$), 149.1 (s, C-2), 131.5, 127.1 (s, C-1, C′-1), 131.2, 131.1, 128.8, 128.1, 124.8, 122.8, 120.2 (d, C-3, C-4, C-5, C-6, C′-4, C′-5, C′-6), 111.1 (d, C′-3), 55.3 (q, $\mathrm{OCH_3}$), 41.9, 41.4 (t, $\mathrm{CH_2}$), 13.7, 13.2 (q, $\mathrm{CH_3}$); IR (KBr) 1719 ($\mathrm{C{=}O}$) cm^{-1}; mass spectrum (EI), *m/z* 299.154 (M$^+$, calcd for $\mathrm{C_{18}H_{21}NO_3}$ 299.152).

General Procedure for the Synthesis of Compounds 9. To a solution of carbamate **8** (2.0 mmol) and TMEDA (0.26 g, 2.2 mmol) in THF (20 mL) was added *sec*-BuLi (1.1 equiv) at −110 or −70 °C for **8a** and **8b**, respectively. After the mixture was stirred for 1 h, dry DMF (1.0 equiv) was added, and the resulting mixture was allowed to come to room temperature overnight. The reaction mixture was acidified with 1 M HCl to adjust the pH to 4 and stirred for another 30 min. After evaporation of most of the THF the aqueous solution was extracted with $\mathrm{CH_2Cl_2}$ (3 × 150 mL). The crude products were purified by flash chromatography to yield pure yellow solids **9**.

2-Hydroxy-[1,1′-biphenyl]-3-carboxaldehyde (9a):[17] eluent $\mathrm{CHCl_3}$/MeOH, 100:1; yield 62%; mp 38–40 °C ($\mathrm{CH_2Cl_2}$/petroleum ether) (lit. mp 50 °C[17a] and 47–48 °C[17b]); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 11.72 (s, 1 H, OH), 9.95 (s, 1 H, CHO), 7.7–7.5 (m, 7 H, Ar H), 7.13 (dd, $J_{5,4} = J_{5,6} = 7.5$ Hz, 1 H, Ar H-5); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 196.8 (d, CHO), 158.8 (s, C-2), 137.7 (d, C-6), 136.3 (s, C′-1), 133.1 (d, C-4), 130.4 (s, C-1), 129.2, 128.2, 127.6 (d, C′-2, C′-3, C′-4), 120.8 (s, C-3), 119.9 (d, C-5); IR (KBr) 1655 ($\mathrm{C{=}O}$) cm^{-1}; mass spectrum (EI), *m/z* 198.066 (M$^+$, calcd 198.068). Anal. Calcd for $\mathrm{C_{13}H_{10}O_2}$ (M_r 198.221): C, 78.77; H, 5.08. Found: C, 78.80; H, 4.96.

2-Hydroxy-2′-methoxy-[1,1′-biphenyl]-3-carboxaldehyde (9b):[36] eluent $\mathrm{CHCl_3}$; yield 52%; mp 117–119 °C ($\mathrm{CH_2Cl_2}$/petroleum ether); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 11.28 (s, 1 H, OH), 9.87 (s, 1 H, CHO), 7.6–6.9 (m, 7 H, Ar H), 3.74 (s, 3 H, $\mathrm{OCH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 196.5 (d, CHO), 159.2 (s, C-2), 156.9 (s, C′-2), 138.8, 133.0, 131.3 (d, C′-4, C′-5, C′-6), 129.3, 120.5, 119.3 (d, C-4, C-5, C-6), 127.8, 125.3 (s, C-1, C′-1), 120.6 (s, C-3), 111.3 (d, C′-3), 55.7 (q, $\mathrm{OCH_3}$); IR (KBr) 1651 ($\mathrm{C{=}O}$) cm^{-1}; mass spectrum (EI), *m/z* 228.078 (M$^+$, calcd for $\mathrm{C_{14}H_{12}O_3}$ 228.079).

Dioxo[[3,3′-[1,2-phenylenebis(nitrilomethylidyne)]bis[[1,1′-biphenyl]-2-olato]](2−)-*N*,*N*′,*O*,*O*′]uranium·1.75$\mathrm{H_2O}$ (10a·1.75$\mathrm{H_2O}$).[37] A mixture of aldehyde **9a** (0.51 g, 2.58 mmol) and 1,2-benzenediamine (0.14 g, 1.29 mmol) was refluxed in $\mathrm{CH_2Cl_2}$ (50 mL) for 0.5 h whereupon $\mathrm{UO_2(OAc)_2{\cdot}2H_2O}$ (0.55 g, 1.29 mmol) was added. After addition, reflux was maintained for 0.5 h before cooling to room temperature. Water (50 mL) was added, and the resulting mixture was stirred for 2 h. The organic layer was separated off and concentrated in vacuo. The crude

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(37) Hygroscopy is demonstrated in successive runs with a Karl–Fischer titration. Due to hygroscopy elemental analyses and Karl–Fischer titrations did not fit (always) with each other and did not give (always) one water molecule for one host molecule.

product was dissolved in a minimal amount of CH_2Cl_2 and upon addition of petroleum ether pure cleft **10a** precipitated: yield 65%; mp >200 °C dec; ^1H NMR ($CDCl_3$) δ 9.46 (s, 2 H, CH=N), 7.9–7.4 (m, 18 H, Ar H), 6.81 (dd, 2 H, $J_{5,4} = J_{5,6} = 7.5$ Hz, Ar H-5); ^{13}C NMR (DMSO-d_6) δ 166.0, 165.8 (C-2, CH=N), 145.7 (C'-1), 138.2, 135.2, 134.6, 130.7, 128.7, 126.9, 125.5, 123.8, 119.2, 115.8 (Ar C) (due to low solubility further assignment is not attempted); IR (KBr) 1603 (C=N), 900 (OUO) cm^{-1}; mass spectrum (EI), *m/z* 736.209 (M^+, calcd 736.200). Anal. Calcd for $C_{32}H_{22}N_2O_4U \cdot 1.75H_2O$ (M_r 768.090): C, 50.04; H, 3.35; N, 3.65. Found: C, 50.41; H, 3.29; N, 3.65. Karl-Fischer calcd for 1.75 H_2O 4.10, found 4.11.

Dioxo[[3,3'-[1,2-phenylenebis(nitrilomethylidyne)]bis-[2'-methoxy-[1,1'-biphenyl]-2-olato]](2−)-*N*,*N'*,*O*,*O'*]uranium·H_2O (10b·H_2O).[37] To a refluxing solution of aldehyde **9b** (1.96 g, 8.6 mmol) in MeOH (200 mL) was added a solution of 1,2-benzenediamine (0.46 g, 4.3 mmol) in MeOH (25 mL). After 0.5 h $UO_2(OAc)_2 \cdot 2H_2O$ (1.82 g, 4.3 mmol) was added. Reflux was maintained for 0.5 h whereupon the reaction mixture was allowed to cool to room temperature. The solvent was partially evaporated to precipitate the crude product, which was filtered off. The precipitate was solved in CH_2Cl_2 (200 mL) and washed with water (200 mL). The organic layer was concentrated in vacuo to yield **10b**: yield 85%; mp >180 °C dec; ^1H NMR ($CDCl_3$) δ 9.40 (s, 2 H, CH=N), 7.7–7.0 (m, 16 H, Ar H), 6.78 (dd, $J_{5,4} = J_{5,6} = 7.0$ Hz, 2 H, Ar H-5), 3.67 (s, 6 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 167.8 (s, C-2), 165.8 (d, CH=N), 157.6 (s, C''-2), 146.8 (s, C'-1), 137.6, 135.3, 132.4 (d, C''-4, C''-5, C''-6), 130.4, 129.6 (s, C-3, C''-1), 128.8, 128.6 (d, C-6, C'-4), 124.1 (s, C-1), 121.0, 119.6, 117.2 (d, C-4, C-5, C'-3), 113.1 (d, C''-3), 56.8 (q, OCH_3); IR (KBr) 1605 (C=N), 899 (OUO) cm^{-1}; mass spectrum (EI), *m/z* 796.232 (M^+, calcd 796.230). Anal. Calcd for $C_{34}H_{26}N_2O_6U \cdot 2H_2O$ (M_r 832.650): C, 49.05; H, 3.63; N, 3.36. Found: C, 49.07; H, 3.47; N, 3.25. Karl-Fischer calcd for 1 H_2O 2.21, found 2.02.

Dioxo[[2,2'-[1,2-phenylenebis(nitrilomethylidyne)]bis[6-methoxyphenolato]](2−)-*N*,*N'*,*O*,*O'*]uranium·1.5H_2O (11·1.5H_2O).[37] A mixture of 2-hydroxy-3-methoxybenzaldehyde (1.52 g, 10 mmol) and 1,2-benzenediamine (0.54 g, 5 mmol) in CH_2Cl_2 (100 mL) was refluxed for 0.5 h. After addition of $UO_2(OAc)_2 \cdot 2H_2O$ (2.12 g, 5 mmol) reflux was maintained for 1 h. Partial evaporation of the solvent was followed by dropwise addition of petroleum ether to precipitate the product yielding after filtration and drying in vacuo pure **11** as an orange solid: yield 81%; mp >230 °C dec; ^1H NMR (CD_3CN) δ 9.57 (s, 2 H, CH=N), 7.8–7.3 (m, 8 H, Ar H), 6.77 (dd, $J_{5,4} = J_{5,6} = 7.9$ Hz, 2 H, Ar H-5), 3.91 (br s, 6 H, OCH_3); ^{13}C NMR (DMSO-d_6) δ 166.6 (d, CH=N), 161.1 (s, C-2), 151.2 (s, C-3), 146.9 (s, C'-1), 128.8, 127.4 (d, C-6, C'-4), 124.4 (s, C-1), 120.4, 117.5, 116.0 (d, C-4, C-5, C'-3), 56.2 (q, OCH_3); IR (KBr) 1602 (C=N), 902 (OUO) cm^{-1}; mass spectrum (FAB), *m/z* 645 ($(M + H)^+$, calcd 645). Anal. Calcd for $C_{22}H_{18}N_2O_6U \cdot {}^3/_2H_2O$ (M_r 671.449): C, 39.35; H, 3.15; N, 4.17. Found: C, 39.68; H, 2.88; N, 3.88. Karl-Fischer calcd for $^3/_2$ H_2O 4.02, found 3.80.

^{1}H NMR Measurements. Quantitative data were obtained with a 500-MHz NMR spectrometer operating at a digital resolution of 0.0004 ppm. Measurements were carried out at 298 K in CD_3CN, with the CD_3 peak set arbitrarily on 1.9400 ppm. Concentrations of host **10b** and 4-*tert*-butylpyridine were 5.5184 × 10^{-3} and (2.5882–49.5000) × 10^{-3} M, respectively. Association constants were evaluated by nonlinear regression as described by de Boer et al.[19]

Qualitative data were obtained with a 80-MHz spectrometer operating at a digital resolution of 0.0025 ppm. Measurements were carried out at 298 K in $CDCl_3$ with TMS as an internal standard. Host starting concentrations of **2** and **10b** were about 0.01 M and the concentrations of pyridine, 4-*tert*-butylpyridine, and benzylamine were 0.005–0.0020 M. The concentration of **7** was 0.0025 M and for pyridine 0.0025–0.0250 M.

Only shifts were considered with $\Delta\delta \geq 0.020$ ppm. The reported values are the maximum observed shifts. Between parentheses the chemical shift value of the free host or guest and the assignment is given. The chemical shift of the guest is concentration independent in the reported concentration range.

2·4-*tert*-butylpyridine: ^1H NMR δ 10.360 (8.52, d, 2 H, H-2(6)), 1.126 (1.317, s, 9 H, $C(CH_3)_3$).

2·benzylamine: ^1H NMR δ 4.483 (3.783, s, 2 H, CH_2).

7a·pyridine: ^1H NMR δ 9.122 (8.629, dd, 2 H, H-2(6)).

11·pyridine: ^1H NMR δ 8.676 (8.629, dd, 2 H, H-2(6)), 3.532 (3.674, s, 6 H, OCH_3).

11·4-*tert*-butylpyridine: ^1H NMR δ 3.496 (3.674, s, 6 H, OCH_3), 1.376 (1.317, s, 9 H, $C(CH_3)_3$).

11·benzylamine: ^1H NMR δ 3.656 (3.674, s, 6 H, OCH_3), 3.630 (3.783, s, 2 H, CH_2).

Crystal Structure Determination. The crystal structure of **10b**·4-*tert*-butylpyridine was determined with X-ray diffraction methods. Crystal data: $C_{43}H_{39}N_3O_6U$; FW = 931.8; lattice type, triclinic; space group, $P\bar{1}$; $T = 293$ K; $a = 9.970$ (3) Å; $b = 15.175$ (3) Å; $c = 12.623$ (5) Å; $\alpha = 92.13$ (1) (deg); $\beta = 100.46$ (1) (deg); $\gamma = 92.60$ (1) (deg); $V = 1874$ Å^3; $Z = 2$; $D_c = 1.65$ (g/cm^3); $F(000) = 916$; $\mu = 41.6$ cm^{-1}; θ range, 3–20 (deg); measured unique refln = 3488; obsd refln [$F^2 > 3\sigma(F)^2$] = 2278; no. of variables = 218; $R(\%) = 13.4$; $R_w(\%) = 15.0$ and $p = 0.04$.

Reflections were measured in the $\omega/2\theta$ scan mode using graphite monochromated Mo Kα radiation. Lattice parameters were determined by least-squares methods from 25 centered reflections. Intensities were corrected for decay during data collection using three control reflections, measured every hour. Only small crystals could be obtained, so the accuracy of the structure determination is low.

The uranium cation was located by the Patterson method and the rest of the non-hydrogen atoms by successive difference Fourier syntheses. Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered observed and were included in the refinement (on F) by full-matrix least-squares. Weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, $\sigma(I)$ based on counting statistics and p an instability factor obtained from plots of F_o vs weighted error. An empirical absorption correction, using DIFABS,[38] was performed. Parameters refined were scale factor, positional and thermal parameters (anisotropic for U-atom and isotropic for other atoms). No hydrogen atoms were included. The final difference Fourier map showed no significant features. All calculations were done using SDP.[39]

Electrochemistry. The polarographic measurements were carried out with a Metrohm Polarecord E506 polarograph in conjunction with a E505 polarographic stand. This polarograph was operated in the three-electrode mode with a dropping mercury electrode (DME) as cathode, a platinum wire as auxiliary electrode, and an Ag/AgCl electrode (Metrohm 6.0724.140) as reference. The reference electrode was filled with 0.1 M $Et_4N^+Cl^-$ (Merck, synthetic quality, recrystallized from EtOH) in MeOH (Merck, pa quality). The measurements were performed at 20 ± 1 °C in a 0.1 M solution of $Et_4N^+ClO_4^-$ (Fluka, purum) in CH_3CN (Merck, DNA synthesis quality). According to a Karl-Fischer titration 0.0255% (0.1 M) H_2O was present in the CH_3CN. The reference electrode was brought into contact with the sample via a double salt bridge of the following configuration:

$$Ag/AgCl{:}Et_4N^+Cl^- - MeOH{:}Et_4N^+ClO_4^- - CH_3CN{:}sample$$

The characteristics of the DME electrode glass capillary were $m = 1.065$ mg/s, natural drop time = 5.30 s, and height of the mercury column 64 cm. A mechanical drop time of 1.000 s was maintained during all experiments. Oxygen was expelled by bubbling with CH_3CN-saturated, deoxygenated (copper scraps, 600 °C) nitrogen (Hoekloos, very pure) for at least 20 min. The sample starting concentrations were 0.2–6.0 mM of host. After manual addition (Hamilton syringe; 50 or 250 μL) of guest (50–500 mM in 0.1 M solutions of $Et_4N^+ClO_4^-$ in CH_3CN) polarograms were recorded in triplo in the DC-tast mode with scan speed 5 mV/s. Number of additions were 5–8. The values of half-wave potential, limiting current and slope of the log plot were calculated by a computerized curve-fitting method described by Zollinger et al.[25] Stability constants were obtained from polarographic data (half-wave potential and limiting current) with POLAG[29] using least-squares fitting procedures. The error between experimental and calculated values for the half wave potentials were <1 mV, to achieve this accuracy deviations in the slope must be <3 mV. Compound **11** was used as a reference and measured several times to detect $E_{1/2}$ fluctuations. Cyclic voltammetry was carried out with an AUTOLAB computerized system for electrochemistry

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(38) Walker, N.; Stuart, D. *Acta Crystallogr., Sect. A* **1983**, *39*, 158.

(39) *Structure Determination Package*; B. A. Frenz and Associates, Inc.: College Station, TX, and Enraf-Nonius: Delft, 1983.

(ECO CHEMIE, Utrecht, The Netherlands). The measurements were performed at a stationary hanging mercury drop electrode (Metrohm, 663 VA). The electrode types and fillings were the same as used in polarography. The solvent and the supporting electrolyte were also the same as used in polarography. Oxygen was expelled by bubbling CH_3CN-saturated nitrogen (Hoekloos, very pure) through for at least 5 min.

Coulometry was carried out with a Metrohm coulostat E524 and a Metrohm integrator E525. The coulostat was operated with a constant potential (potentiostatic coulometry). The electrode types and fillings were the same as used in polarography. The solvent and the supporting electrolyte were also the same as used in polarography and cyclic voltammetry. A mercury pool was used as cathode, and it was separated from the platinum counterelectrode by a salt bridge. Oxygen was expelled by bubbling CH_3CN-saturated nitrogen (Hoekloos, very pure) through for at least 10 min.

Calculations. Molecular mechanics calculations were performed with CHARMm and the graphical QUANTA interface.[28] Force-field parameters were taken from CHARMm. With molecular mechanics the steric energy minima of the complexes and of isolated guest molecules were determined by variation of all the relevant degrees of freedom: position and orientation of the guest and rotatable bonds in the substituent to the Schiff base moiety of the host.

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Supplementary Material Available: Tables of positional and thermal parameters of all non-hydrogen atoms, bond distances and angles, and dihydral angles of the **10b**·4-*tert*-butylpyridine complex, ^{1}H NMR spectra of the compounds **1**, **6a**, **6b**, **6c**, and **9b**, and drawings of the calculated structures of the pyridine, 4-methylpyridine, and 4-*tert*-butylpyridine complexes of **2**, **10a**, **10b**, and **11** (23 pages). Ordering information is given on any current masthead page.

Hexacyclic Indole Alkaloids. A Highly Convergent Total Synthesis of Cuanzine

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A novel route to the hexacyclic indole alkaloid cuanzine 1 has been developed. Key synthetic steps include the cyclocondensation of the imine 8 with the dihydrofuran 10 followed by homogeneous-catalyzed hydrogenation, wherein the COOMe group at C(20) serves as a diastereocontrol element in establishing the C(15) stereogenicity. In order to define local energy minima, the conformational space of some intermediates has been explored by empirical force field calculations (MM2).

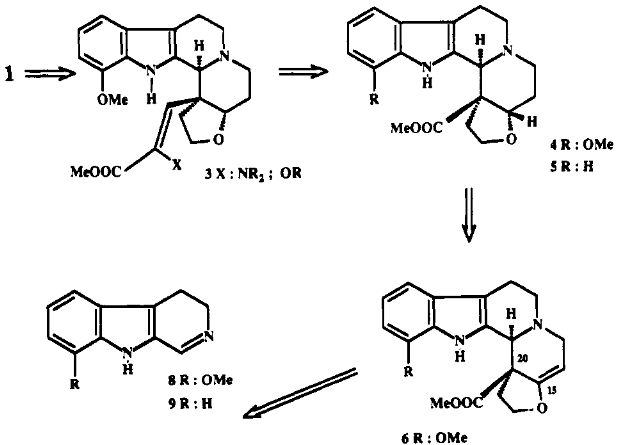
Cuanzine **1**, a representative hexacyclic indole alkaloid, was first isolated from the roots of *Voacanga chalotiana* (Apocynaceae) in the 1970s and intensively studied for its vasodilating, antihypertensive, and antiarrhythmic activities.[1] This compound belongs to a subgroup of eburnanes having an oxygen atom bridging C(15) to C(18) in a cis-fused D/F ring junction.[2]

Although the oxygenation at C(15) and/or C(18) in the conjectural biogenetic precursors does not occur in any of the eburnanes previously isolated, the occurrence of a tetrahydrofuran ring is very common amongst biogenetically related Aspidosperma alkaloids, viz. benenine, modestanine, hazuntine, vandrikine.[3]

Cuanzine was originally assigned the *R* configuration for C(16) of **2** on the basis of spectroscopic evidence. This assignment was later reversed to that of **1** by using MM2 empirical force field calculations, and this structure has been proven conclusively by single-crystal X-ray analysis of cuanzine hydrochloride.[4]

We recently reported a synthetic approach to the ABCDF pentacyclic framework of **1** that featured an intermolecular imino Diels–Alder reaction as pivotal step,[5] and in the meantime Langlois and co-workers have completed a conceptually similar entry to 12-demethoxycuanzine.[6] In this paper we describe an alternative approach which allows the stereoselective synthesis of **1** in a highly convergent manner and the essential elements of

Scheme I



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(1) (a) Bombardelli, E.; Bonati, A.; Gabetta, B.; Martinelli, E. M.; Mustich, G.; Danieli, B. *Tetrahedron* 1974, *30*, 4141. (b) Bombardelli, E.; Bonati, A.; Danieli, B.; Gabetta, B.; Martinelli, E. M.; Mustich, B. *Experientia* 1974, 979. (c) Inverni della Beffa S.p.A., Fr. Demande 2,303,544; *Chem. Abstr.* 1977, *87*, 28999c.

0022-3263/91/1956-2380$02.50/0