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Synthesis of Isoxazolopyridobicyclooxacalix[4]arenes: A New Family of Heteracalixarene Systems

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A new family of isoxazolopyridobicyclooxacalix[4]arenes was obtained by reaction of dichloroisoxazolopyridines with phloroglucinol. X-ray crystallography and density functional calculations were used for their structural determination and evaluation of their chemical properties. Their role as metal chelators was studied by mass spectrometry. This new family of heteracalixarenes is of potential interest for host–guest interactions.

Introduction

Calixarenes[1] are a particularly interesting class of macrocyclic compounds that continue to receive a large degree of attention as a result of their wide ranging and practically useful features. Host–guest properties of these compounds towards cations, anions and neutral species are useful for analytical purposes,[2] as well as for the preparation of new catalytic systems.[3] In addition, a biological role of calixarene-containing structures was recently evidenced due to their ability to simulate supramolecular cavities of active sites.[4] Among this class of compounds, calixarenes containing heterocyclic systems, that is, heteracalixarenes, are of great interest as a consequence of both their increased functionality and wide molecular diversity. Such a variety derives from the nature and the position of the heteroatoms, the dimensions of the ring systems and the nature of the substituents that afford inner cavities that are easily tuneable in both their structural and electronic properties. In this way, modulation of the physicochemical properties of the macromolecule can be achieved.[5] Conformational aspects are also important: cone, partial cone and alternate structures have been described previously.[6] Recently, during an investigation of oxacalixarenes[7] the synthesis and structure of some heterobicyclooxacalix[4]arenes were described, and these compounds were found to be conformationally restricted analogues of oxacalixarenes with a cage-like structure of high symmetry.[8] This prompted us to design calixarene structures based on aromatic isoxazolopyridines, a class of molecules that we previously considered from a synthetic, structural and chemical behaviour (namely, photochemical) point of view. Condensation of a pyridine system with an isoxazole moiety increases the mobility of chlorine atoms, which allows easy substitution by suitable nucleophiles. In addition, it is possible to increase the structural diversity of the final products by well-known thermal and/or photochemical modifications of the five-membered nucleus.[9]

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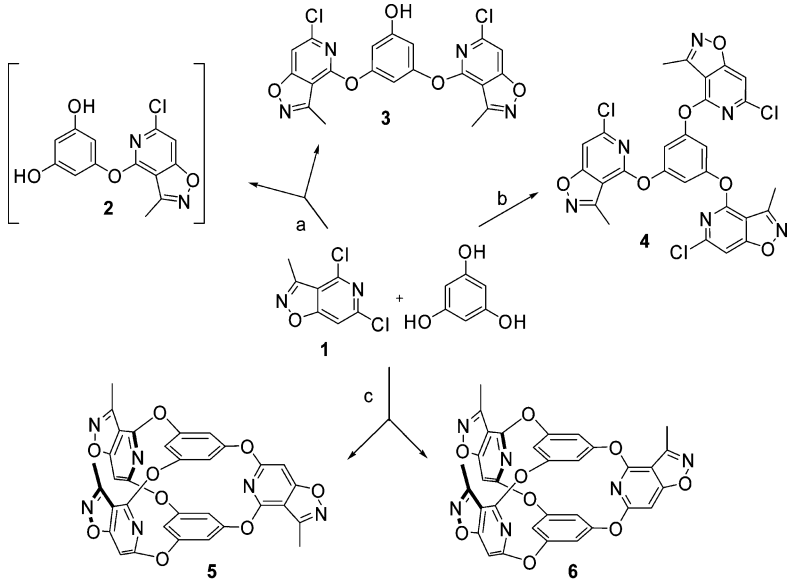
Results and Discussion

Reaction of 4,6-dichloro-3-methylisoxazolo[4,5-*c*]pyridine (**1**)[10] with phloroglucinol in the presence of DBU allowed the preparation of the compounds reported in Scheme 1. Careful selection of both reagent ratio and reaction temperature (Entry a, b or c) allowed isolation of each compound.

When the reaction was carried out according to the conditions described in Entry a (Scheme 1), diether **3** was obtained in 70% yield. A 1:1:1 molar ratio of reagents was insufficient, and this compound was only formed in 40% yield with the corresponding amount of starting material **1** recovered. Only a trace amount of monosubstituted compound **2** was evidenced in the crude reaction mixture by electrospray ionization mass spectrometry (ESI-MS), which shows the corresponding very-low intensity protonated molecule. Probably, the increased acidity of compound **2** owing to the heteroaryl substituent causes this compound to be more reactive than phloroglucinol towards dichloro derivative **1**.

When operating under the conditions described in Entry b (Scheme 1), trisubstituted phloroglucinol **4** was obtained as the sole product. Finally, when the reaction temperature was raised to 120 °C and the reaction time to 18 h (Entry c, Scheme 1), bicyclooxacalix[4]arene isomers **5** and **6** (in a 2.75:1 molar ratio) were obtained and separated by column chromatography. Proton NMR spectra allowed structure assignments of these compounds. In fact, for com-



Entry	*T* [°C]	Time [h]	Molar ratio[a]
a	20	14	1:2:2
b	60	3	1:3:3
c	120	18	1:3:1.5

[a] phloroglucinol/DBU/dichloroisoxazolopyridine

Scheme 1. Experimental conditions for the synthesis of compounds **3**–**6**.

pound **6** the protons of the phenolic moieties resonate as a singlet due to equivalent chemical shifts, whereas series of multiplets is observed for compound **5**. Owing to their scarce polarity, both compounds **5** and **6** do not give any ESI-MS signal, either as positive or negative ions. In contrast, they can be ionized as protonated molecules by atmospheric pressure chemical ionization, which produces intense ions suitable for MS–MS experiments for structural characterization. The atmospheric pressure chemical ionization (APCI) MS–MS spectrum obtained by selecting [**5** + H]$^+$ as the precursor ion is reported in Figure 1. As it is shown, the main gas-phase decomposition pathways involve successive loss of HCN and CO, mainly due to the dismantling of the isoxazole moieties. It is noteworthy that after one electron removal neither radical cations of isoxazolopyridines[11,12] nor those of benzisoxazoles[13] show elimination of HCN. In the present case, both the effect of protonation and the linkage of the isoxazolopyridine moiety in the calix assembly play crucial roles in driving gas-phase decompositions.

The structure of compound **6**, crystallized as its chloroform solvate, was confirmed by X-ray analysis (Figure 2). It crystallizes in a highly symmetric space group (i.e., $\bar{R}$), and it shows C_{3i} symmetry with a 1,3-alternate conformation, which is also observed in other analogous compounds.[7a,7b] One third of the atoms constitute the asymmetric unit, whereas the remaining atoms are generated by symmetry. This causes the two phenyl rings to be parallel and eclipsed with a distance of 4.437(1) Å between their centroids. This arrangement results in an intramolecular π–π interaction between the two rings that stabilizes the molecule. The three nitrogen atoms of the pyridine moieties point into the cavity in a trigonal planar array and the N···N distances are 4.81(1) Å. They act as possible nucleophilic sites for interactions with included ligands. The nitrogen and oxygen atoms of the isoxazole moiety point out from the molecule, and they should play an important role in interactions with species surrounding the calixarene into the formed cavity. Conjugation between the bridging oxygen atoms and the pyridine rings is supported by the significantly shorter C–O bond length [1.364(5) Å average bond length] versus the O–C phenyl ring carbon atoms [1.403(3) Å average bond length]. The three methyl groups are *cis* oriented.

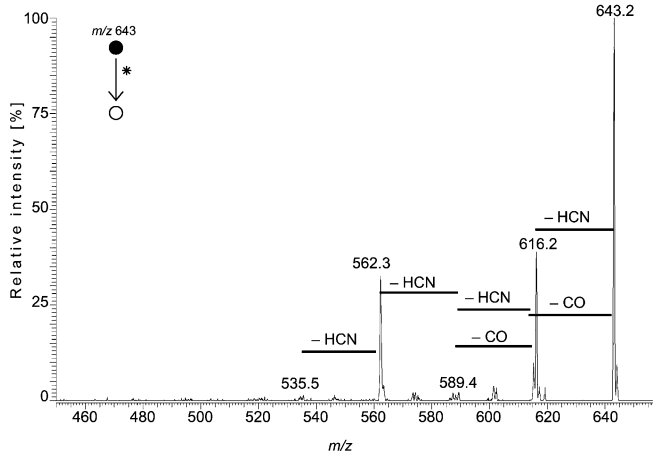


Figure 1. APCI MS–MS spectrum of [**5** + H]+ (*m*/*z* = 643) selected as the precursor ion.

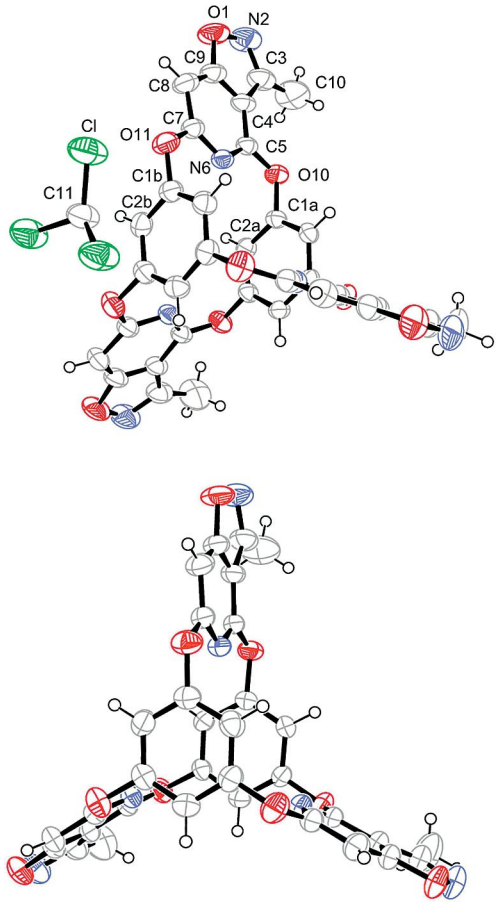


Figure 2. Two views of the ORTEP drawing of compound **6**·$CHCl_3$ (50% probability thermal ellipsoids). The site-occupation factor for the reported chloroform molecule is 0.55(4). In the bottom view, the chloroform molecule is omitted for clarity.

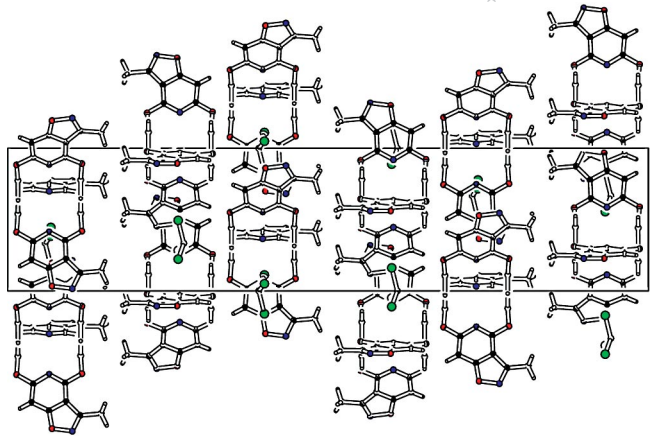
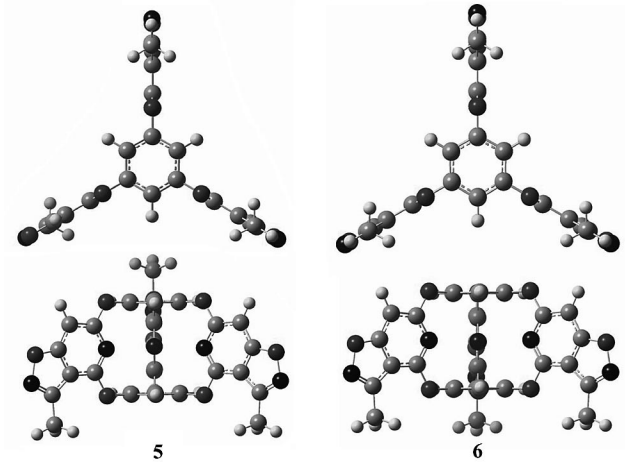


Figure 3. Crystal packing views along the *x* axis of **6**·$CHCl_3$.



	d [Å] N···N	
	5	**6**
calculated	4.839	4.839
X-ray	–	4.811(5)

Figure 4. Two different views of the energy-minimized structures [B3LYP/6-31G(d,p)] of compounds **5** and **6**.

The chloroform molecule shows statistical disorder and three different positions were refined for it with site occupation factors of 0.56(4), 0.29(4) and 0.16(1), respectively. The chlorine atoms show intermolecular interactions with O1, N2 N6 and O10. The crystal packing of **6**·$CHCl_3$ is shown in Figure 3. The different layers of molecules along the *bc* plane are formed by chloroform and heteracalixarene molecules. The heteracalixarene moieties are arranged in a head-to-head fashion with the methyl groups of the two adjacent layers oriented on the same side.

Aimed at evaluating the relative stability of both compounds **5** and **6**, density functional theory calculations were carried out (Figure 4). Concerning compound **6**, the calculations optimized a structure quite close to that obtained from the crystal data.

The intramolecular distance between the nitrogen atoms of the cavity was calculated to be 4.839 Å for both **5** and **6**, which is close to that determined in the X-ray structure of **6**·$CHCl_3$. All the nitrogen and oxygen atoms in both **5** and **6** have negative atomic charges; the nitrogen atoms are oriented in towards the cavity and the oxygen atoms bridging the phenyl and the pyridine moieties have the most negative charges. It was determined by calculations that both **5** and **6** have almost the same energy (Table 1), which suggests that the alternate orientation of the methylisoxazolo moiety does not influence the stability of the entire molecule.

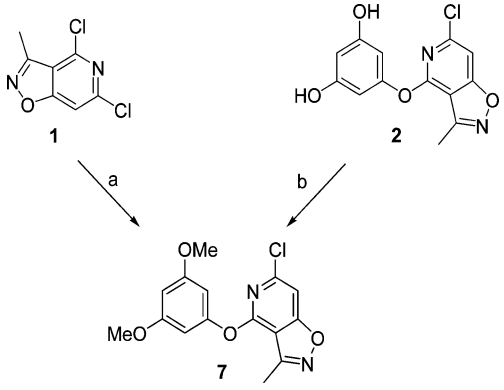
Similarly, when compound **4**, which represents a possible intermediate for the formation of the calix systems, was treated according to the Entry c (Scheme 1), compounds **5** and **6** were obtained. In any case, careful analysis of the crude reaction mixture also allowed monosubstituted ether **2** to be isolated from the fractions with low R_f values. Treatment of this fraction with an excess amount of ethereal diazomethane (Scheme 2) gave corresponding dimethyl ether **7**, which was also easily obtained from dichloro derivative **1** and 3,5-dimethoxyphenol.

Results obtained from syntheses carried out at 20 or 60 °C (Entries a or b, Scheme 1) strongly suggest that the formation of compound **2** arises from cleavage of **3** and/or **4**. After elution of compounds **5** and **6**, further chromato-

Table 1. Energy values for the minimized structures of compounds **5** and **6**.

Compound	B3LYP/6-31G(d,p)[a]	ZPVE[b]	SCF + ZPVE[a]	ΔE (SCF+ZPVE)[c]
5	–2273.784290	0.449097	–2273.335193	+0.19
6	–2273.784624	0.449129	–2273.335495	0

[a] Units of Hartree. [b] Zero-point vibrational energies corrected by 0.9613,[16] units of Hartree particle^{-1}. [c] Units of kcal mol^{-1}.



Scheme 2. Synthesis of dimethoxy derivative **7**. Reagents and conditions: (a) 3,5-dimethoxyphenol, DBU, DMSO, r.t.; (b) excess diazomethane, methanol.

graphic elution showed, when submitted to electrospray negative-ion analysis, the presence of ions with m/z = 511, which corresponds to both oxacalixarenes **8** and **9** (Figure 5).

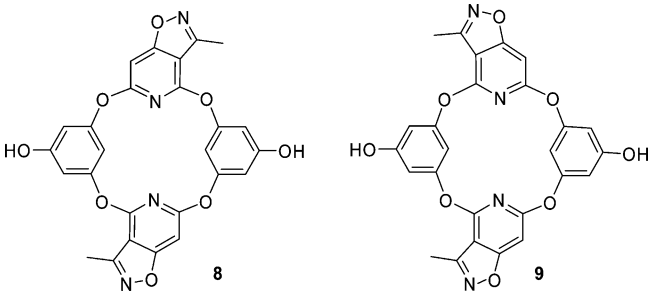


Figure 5. Structures of calixarenes **8** and **9**.

Attempts to separate these compounds were unsuccessful due to their very similar chromatographic behaviour and limited quantities. However, the NMR spectrum of the mixture confirmed the postulated structures.

The versatility of compounds **5** and **6** as metal-ion chelators was initially tested by ESI-MS analysis, a very useful "ion-fishing" technique. Owing to their affinity for metal ions such as silver and nickel, compounds **5** and **6** form stable complexes that yield intense positive ions when submitted to electrospray ionization (Figure 6). By mixing **5** with $NiCl_2$, the ESI(+) spectrum reported in Figure 6a was obtained. The most abundant ions are due to $[M + Ni^{II} + Cl]^+$ (m/z = 735), in which one coordination site of the metal is constituted by chlorine, so the overall complex has a charge of +1. In addition, ions at m/z = 755 are attributable to $[M + Ni^{II}_2 – 3H]^+$. When **5** is mixed with $AgNO_3$, abundant ions at m/z = 751 due to $[M + Ag]^+$, in agreement with their isotopic cluster, are formed (Figure 6b). Other ions at m/z = 771 are due to the mixed-metal complex $[M + Ag + Na – H]^+$, whose overall monopositive charge requires deprotonation of the calixarene moiety. Alkaline metal ions and Cu^{II} did not produce detectable complexes. These results are very useful to verify the progress of the synthetic procedure and suggest potential use of these heteracalixarenes as selective metal chelators.

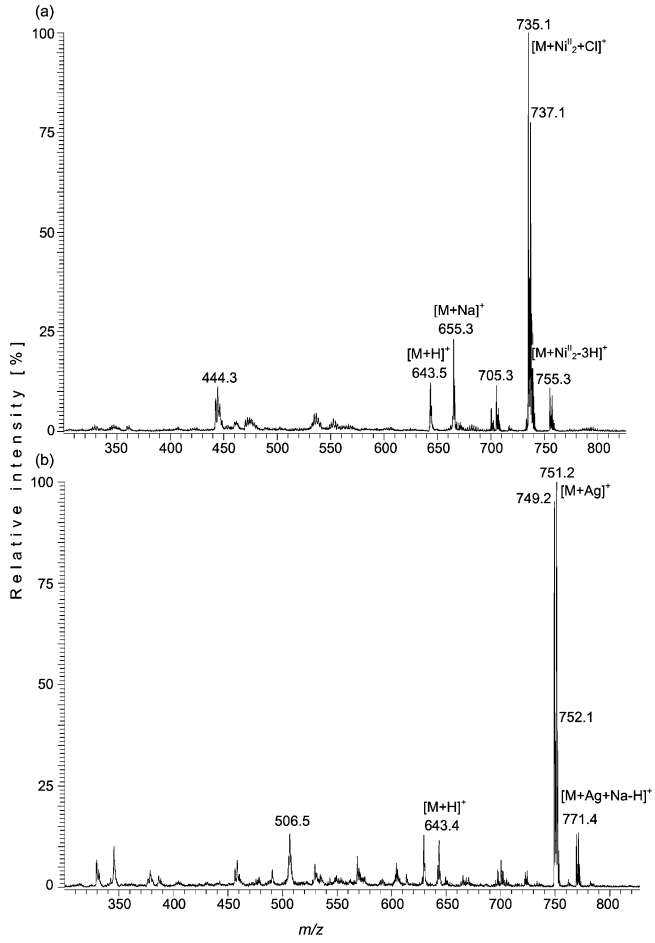
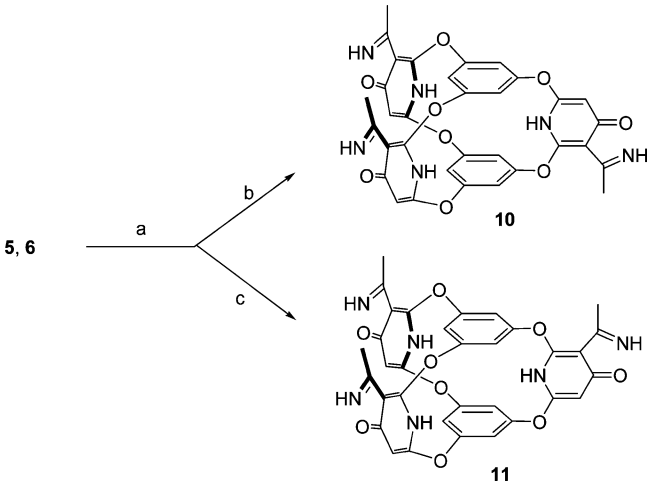


Figure 6. Electrospray spectra (positive mode) obtained by mixing **5** with $NiCl_2$ (a) or $AgNO_3$ (b).

Catalytic hydrogenation of both compounds **5** and **6** allowed the preparation in quantitative yield of the corresponding modified bicyclooxacalix[4]arenes **10** and **11** (Scheme 3), which show a major degree of functionalization on the outside rim. In this way it is expected that these compounds will exhibit greater solubility in polar solvents and in acidic or basic systems. In addition, further chemical modifications could be achieved on the enamino and pyridone moieties.



Scheme 3. Catalytic hydrogenation of bicyclooxacalix[4]arenes. Reagents and conditions: (a) H_2, 10% Pd on carbon, ethyl acetate, 60 psi, r.t.; (b) from **5**; (c) from **6**.

Conclusions

The synthetic strategy described herein offers efficient access to bicyclooxacalix[4]arenes of potential interest for host–guest interactions. By operating under different conditions, some reaction intermediates were isolated and fully characterized. X-ray crystallography was successfully used for the determination of the structural and conformational parameters of one major compound. Density functional calculations showed that the orientation of the isoxazolopyridine moiety has only a minor effect on the stability of the molecule. Chelating properties towards metal ions, in particular Ag^{I} and Ni^{II}, were studied by mass spectrometry. Catalytic hydrogenation gives access to differently functionalized heteracalixarene systems.

Experimental Section

General Information: ^1H and ^{13}C NMR spectra were recorded at 27 °C ($CDCl_3$), unless otherwise stated, with a Bruker AC200 instrument operating at 200.13 and 50.33 MHz, respectively, or with a Bruker Avance 400 instrument operating at 400.13 and 100.62 MHz, respectively. The chemical shifts are reported in ppm on the δ scale by using the solvent peak as a reference value. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet, br. = broad. Mass spectra were recorded as positive ions or negative ions with a LCQ-DECA Thermo instrument by using electrospray or APCI. GC–MS experiments were carried out with a Saturn 2000 ion trap (EI, 70 eV) coupled with a Varian 3800 gas chromatograph (Varian, Walnut Creek, CA, USA) equipped with a J&W DB5-MS column (30 m × 0.25 mm ID, 0.25 μm film thickness). All solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel (0.040–0.063 mm).

General Procedure for the Reactions of Phloroglucinol with 4,6-Dichloro-3-methylisoxazolo[4,5-*c*]pyridine: A solution of phloroglucinol (1 mM, 126 mg) in DMSO (5 mL) and different amounts of DBU (2 mmol, 0.3 mL or 3 mmol, 0.45 mL; Scheme 1) was stirred at room temperature for 0.5 h. 4,6-Dichloro-3-methylisoxazolo[4,5-*c*]-pyridine (**1**) in different molar ratios (2 mmol, 406 mg or 3 mmol, 609 mg or 1.5 mmol, 305 mg; Scheme 1) was dissolved in DMSO (5 mL) and added to the solution. The final solution was heated at different temperatures (20, 60, 120 °C) for different times (14, 3, 18 h) according to Scheme 1. The reaction mixture was poured into an ice–water mixture and repeatedly extracted with ethyl acetate (3 × 20 mL), washed with water and dried with Na_2SO_4; the solvents were then evaporated under vacuum. The residue was purified by flash chromatography to give compounds **2**–**6** and **8** and **9**.

5-(6-Chloro-3-methylisoxazolo[4,5-c]pyridine-4-yloxy)benzene-1,3-diol (2): Obtained according to Entry c (Scheme 1) after purification by column chromatography (petroleum ether/EtOAc, 2:1) and recrystallization from cyclohexane. Yield: 25 mg (9%). White solid. M.p. 179–180 °C. R_f = 0.10 (petroleum ether/EtOAc, 2:1). ^1H NMR (400 MHz, CD_3OD): δ = 2.51 (s, 3 H), 6.16 (s, 2 H), 6.19 (s, 1 H), 7.34 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 11.29, 95.98, 101.23, 102.24, 108.81, 150.29, 155.45, 155.68, 158.30, 160.37, 172.93 ppm. ESI-MS: m/z = 291/293 $[M - H]^-$. $C_{13}H_9ClN_2O_4$ (292.67): calcd. C 53.35, H 3.10, N 9.57; found C 53.12, H 3.07, N 9.74.

3,5-Bis(6-chloro-3-methylisoxazolo[4,5-*c*]pyridin-4-oxy)phenol (3): Obtained according to Entry a (Scheme 1) after purification by column chromatography (petroleum ether/EtOAc, 4:1). Yield: 320 mg (70%). White solid. M.p. 220–222 °C. R_f = 0.28 (petroleum ether/EtOAc, 4:1). ^1H NMR (200 MHz): δ = 2.65 (s, 6 H), 6.51–6.61 (m, 3 H), 7.15 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3/CD_3OD$): δ = 11.16, 101.56, 105.77, 106.36, 107.65, 148.90, 153.39, 154.16, 156.36, 158.72, 171.34 ppm. ESI-MS: m/z = 457/459 $[M - H]^-$. $C_{20}H_{12}Cl_2N_4O_5$ (459.24): calcd. C 52.31, H 2.63, N 12.20; found C 52.09, H 2.74, N 12.39.

1,3,5-Tris(6-chloro-3-methylisoxazolo[4,5-*c*]pyridin-4-yloxy)benzene (4): Obtained according to Entry b (Scheme 1) after purification by column chromatography (petroleum ether/EtOAc, 4:1). Yield: 345 mg (55%). Very electrostatic white solid. M.p. > 270 °C. R_f = 0.28 (petroleum ether/EtOAc, 4:1). ^1H NMR (400 MHz): δ = 2.72 (s, 9 H), 7.16 (s, 3 H), 7.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 11.45, 29.69, 102.15, 112.53, 148.94, 153.29, 154.04, 155.89, 171.60 ppm. ESI-MS: m/z = 625/627/629 $[M + H]^+$. $C_{27}H_{15}Cl_3N_6O_6$ (625.80): calcd. C 51.82, H 2.42, N 13.43; found C 51.63, H 2.31, N 13.57.

7,22,34-Trimethyl-4,9,13,19,24,28,31,36,40-nonaoxa-8,23,35,41,43,45-hexa-azadecacyclo[14.14.10.1^{3,29}.1^{5,12}.1^{14,18}.1^{20,27}.1^{32,39}.0^{6,10}.0^{21,25}.0^{33,37}]pentatetraconta-1,3(42),5,7,10,12(45),14,15,17,20,22,25,27(43),29,32,34,37,39(41)octadecaene (5): Obtained according to Entry c (Scheme 1) after separation from compound **6** by column chromatography (petroleum ether/EtOAc, 9:1) and recrystallization from cyclohexane. Yield: 141 mg (22%). White solid. M.p. > 270 °C. R_f = 0.68 (petroleum ether/EtOAc, 9:1). ^1H NMR (400 MHz): δ = 2.62 (s, 9 H), 6.53–6.55 (m, 3 H), 6.59–6.62 (m, 3 H), 6.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 11.32, 84.94, 85.02, 103.37, 115.32, 115.40, 115.78, 115.88, 153.53, 153.64, 153.79, 153.87, 154.96, 155.09, 156.62, 163.51, 173.02 ppm. APCI-MS: m/z = 643 $[M + H]^+$. $C_{33}H_{18}N_6O_9$ (642.53): calcd. C 61.69, H 2.82, N 13.08; found C 61.81, H 2.74, N 13.36.

7,25,34-Trimethyl-4,9,13,19,23,28,31,36,40-nonaoxa-8,24,35,41,43,45-hexaaza-decacyclo[14.14.10.1^{3,29}.1^{5,12}.1^{14,18}.1^{20,27}.1^{32,39}.0^{6,10}.0^{22,26}.0^{33,37}]pentatetraconta-1,3 (42),5,7,10,12(45),14,15,17,20,22(26),24,27(43),29,32,34,37,39(41)octadecaene (6): Obtained according to Entry c (Scheme 1) after separation from compound **5** by column chromatography (petroleum ether/EtOAc, 9:1) and recrystallization from cyclohexane. Yield: 51 mg (8%). White solid.

M.p. > 270 °C. R_f = 0.72 (petroleum ether/EtOAc, 9:1). ^{1}H NMR (400 MHz): δ = 2.62 (s, 9 H), 6.47 (s, 3 H), 6.66 (s, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 11.33, 85.11, 103.29, 115.25, 115.99, 153.75, 154.81, 156.55, 163.54, 173.03 ppm. APCI-MS: *m*/*z* = 643 [M + H]$^+$. $C_{33}H_{18}N_6O_9$ (642.53): calcd. C 61.69, H 2.82, N 13.08; found C 61.59, H 2.97, N 12.83.

6-Chloro-4-(3,5-dimethoxyphenoxy)-3-methylisoxazolo[4,5-*c*]pyridine (7): A solution of 3,5-dimethoxyphenol (0.154 g, 1 mM) in DMSO (3 mL) and DBU (1 mM) was stirred at room temperature for 0.5 h. 4,6-Dichloro-3-methylisoxazolo[4,5-*c*]pyridine (**1**; 0.203 g, 1 mM) dissolved in DMSO (3 mL) was added, and the solution was kept at room temperature for 3 h. The reaction mixture was poured into an ice–water mixture and repeatedly extracted with ethyl acetate, washed with water and dried with Na_2SO_4; the solvents were then evaporated under vacuum to give compound **7** (288 mg, 90%) as a white solid that was purified by recrystallization from cyclohexane. M.p. 109–111 °C. ^{1}H NMR (200 MHz): δ = 2.68 (s, 3 H), 3.78 (s, 6 H), 6.37, 6.39 (m, 3 H), 7.18 (s, 1 H) ppm. ^{13}C NMR (50 MHz): δ = 11.28, 55.49, 97.99, 99.96, 101.40, 107.89, 149.00, 153.64, 154.13, 161.30, 171.43 ppm. GC–MS: *m*/*z* = 320/322 [M]$^{+\cdot}$. $C_{15}H_{13}ClN_2O_4$ (320.73): calcd. C 56.17, H 4.09, N 8.73; found C 56.46, H 4.23, N 8.46.

The same compound (identical m.p. and spectroscopic data) was obtained in quantitative yield by reaction of 5-(6-chloro-3-methylisoxazolo[4,5-c]pyridine-4-yloxy)benzene-1,3-diol (**2**) with an excess amount of diazomethane in ether.

11,26-Dimethyl-2,8,13,17,23,28-hexaoxa-12,27,31,33-tetraazaheptacyclo[22.6.1.1^{3,7}.1^{9,16}.1^{18,22}.0^{10,14}.0^{25,29}]tetratriaconta-1(31),3(34),4,6,9,11,14,16(33),18(32),19,21,24,26,29-tetradecaene-5,20-diol 8 and 11,29-Dimethyl-2,8,13,17,23,27-hexaoxa-12,28,31,33-tetraazaheptacyclo[22.6.1.1^{3,7}.1^{9,16}.1^{18,22}.0^{10,14}.0^{26,30}]tetratria-conta-1(30),3(34),4,6,9,11,14,16(33),18(32),19,21,24(31),25,28-tetradecaene-5,20-diol (9): Obtained according to Entry c (Scheme 1) after separation from compound **2** by column chromatography (petroleum ether/EtOAc, 2:1) as a single chromatographic fraction. Yield: 50 mg (10%). White solid. R_f = 0.08 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ = 2.58 (s, 6 H, 2 CH_3), 6.03 (t, 2 H, CHPh), 6.12 (t, 2 H, CHPh), 6.21 (d, 4 H, CHPh), 6.25 (t, 2 H, CHPh), 6.30 (t, 2 H, CHPh), 6.36 (d, 4 H, CHPh), 6.69 (s, 2 H, CHPyr), 6.71 (s, 2 H, CHPyr) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 11.27, 86.36, 86.82, 96.73, 104.78, 106.94, 107.14, 107.63, 107.93, 108.20, 108.57, 155.14, 155.37, 156.82, 157.85, 160.19, 160.49, 164.83, 165.42, 174.26 ppm. ESI-MS: *m*/*z* = 511 [M – H]$^-$. $C_{26}H_{16}N_4O_8$ (512.43): calcd. C 60.94, H 3.15, N 10.93; found C 61.09, H 3.10, N 10.64.

Catalytic Hydrogenation of Compounds 5 and 6: A mixture of compound **5** or **6** (50 mg) and 10% Pd/C (10 mg) in ethyl acetate (50 mL) was shaken in a Parr apparatus under hydrogen pressure (60 psi) for 1 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated in vacuo to give compounds **10** and **11**, respectively, in quantitative yield.

6,18,27-Triethanimidoyl-4,10,16,22,25,31-hexaoxa-32,34,36-triazaheptacyclo[11.11.7.1^{3,23}.1^{5,9}.1^{11,15}.1^{17,21}.1^{26,30}]hexatriaconta-1,3(33),5,8,11(35),12,14,17,20,23,26,29-dodecaene-7,19,28-trione (10): R_f = 0.45 (ethyl acetate/petroleum ether, 4:1). M.p. 122–123 °C. ^{1}H NMR (200 MHz, [D$_6$]DSMO): δ = 2.49 (s, 9 H), 5.52 (m, 3 H), 6.38 (m, 3 H), 6.41 (m, 3 H), 5.92, 6.27, 6.51 (exch. br., 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 25.38, 92.26, 94.30, 98.42, 115.52, 115.60, 153.70, 154.21, 156.77, 163.45, 164.89, 174.60, 177.40, 182.94 ppm. ESI-MS: *m*/*z* = 753/755 [M – 2H + Ag]$^-$. $C_{33}H_{24}N_6O_9$ (648.58): calcd. C 61.11, H 3.73, N 12.96; found C 60.95, H 3.68, N 13.06.

6,20,27-Triethanimidoyl-4,10,16,22,25,31-hexaoxa-32,34,36-triazaheptacyclo[11.11.7.1^{3,23}.1^{5,9}.1^{11,15}.1^{17,21}.1^{26,30}]hexatriaconta-1,3(33),5,8,11(35),12,14,17,20,23,26,29-dodecaene-7,19,28-trione (11): R_f = 0.25 (ethyl acetate/petroleum ether, 4:1). M.p. 124–126 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.47 (s, 9 H), 5.52 (m, 3 H), 5.95 (exch. br., 3 H), 6.23 (s, 3 H), 6.55 (s, 3 H), 6.64 (exch. br., 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 25.32, 92.16, 94.29, 98.43, 115.38, 115.68, 153.73, 154.20, 164.83,165.77, 177.28, 182.93 ppm. ESI-MS: *m*/*z* = 753/755 [M – 2H + Ag]$^-$. $C_{33}H_{24}N_6O_9$ (648.58): calcd. C 61.11, H 3.73, N 12.96; found C 61.32, H 3.59, N 13.12.

X-ray Crystallography: Single crystals of **6**·$CHCl_3$ were obtained by dissolving a few milligrams of powder in chloroform and allowing the solution to concentrate at room temperature. A Siemens P4 four-circle diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and the ω scan technique were used for data collection. The structure was solved by direct methods implemented in the SHELXS-97 program.[14] The refinement was carried out by full-matrix anisotropic least-squares methods on F^2 for all reflections for non-hydrogen atoms by using the SHELXL-97 program.[15] The cocrystallized chloroform molecule shows statistical disorder with three different positions, whose site occupancy factors were refined to 0.55(4), 0.29(4), and 0.16(1), respectively.

CCDC-668972 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Theoretical Calculations: Density functional theory calculations were carried out for compounds **5** and **6** by using Gaussian 03[16] implemented on a IBM SP RS/6000 Power 5 supercomputer at Cineca in Bologna (Italy). All geometries were fully optimized without any constraints at the Becke 3LYP (B3LYP)[17] method with the 6-31G(d,p) level of theory. The final lowest-energy geometries were confirmed as a minimum on the potential energy surface by normal-mode vibrational frequency calculations that produced all real frequencies. Zero-point energies and statistical thermodynamic properties at 298.15 K and 1 atm were calculated at the B3LYP/6-31G(d,p) level of theory. A scaling factor of 0.9613 was used for zero-point energies.[18]

Supporting Information (see footnote on the first page of this article): Spectroscopic characterization of compounds **2**–**11**.

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