Multi-gram synthesis of precursors of *bibrachial* diaza-paracyclophanes. Complexes with Zn^{2+}, Cu^{2+} and Co^{2+} ions

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This paper is dedicated to Professor Julio Alvarez-Builla on occasion of his 65th birthday

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Abstract

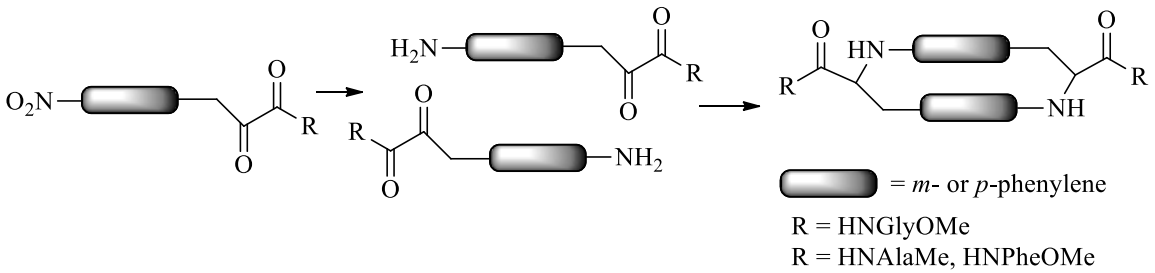
A multi-step synthetic strategy to obtain *N*-4-nitrophenyl-pyruvoyl-amino esters at a multi-gram scale has been developed. The subsequent domino reaction promoted by catalytic hydrogenation of the nitro group gave diaza-paracyclophane **3**, **13** and **14**. Complexation with Zn^{2+}, Cu^{2+} and Co^{2+} ions has been studied by UV-vis and ^{1}H NMR spectroscopic methods.

Keywords: Azaciclophanes, metal-complexes, π-systems, domino process, azamacrocycle

Introduction

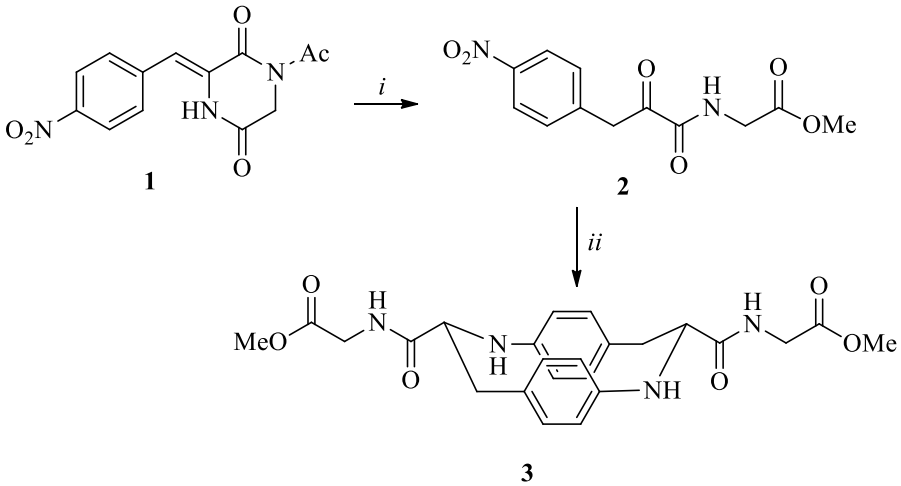
Cyclophanes are important in macrocyclic and supramolecular chemistry mainly because their large cavities primarily defined by the aromatic units are ready to accommodate charged or neutral guest molecules.[1-3] This property is mainly linked to "face-to-face" transannular interactions of the aromatic rings and to hydrogen bonding with functional groups of the aliphatic chains. Azacyclophanes, in which one or more methylene units are substituted by nitrogen atoms, have a particular behaviour since the nitrogen bridges play an important role in their excited states,[4] and they may offer additional lone pairs from nitrogen atoms for complexation with metal ions.[5] In particular Wurster's cyclophanes, which are composed of *p*-phenylenediamine units, contain redox-active moieties and their coordinating ability can be altered by physical or chemical means.[6] Different azacyclophanes containing *p*-phenylenedi(or tri)methylene subunits have been synthesized to study their coordination capabilities.[7] The most common synthetic strategies to get these ligands are the alkylation of terminal *N,N'*-ditosyldiamines with *p*-phenylenedimethylene dihalides,[8] the alkylation of terminal *p*-phenylene-

polymethylenediamine with a polymethylenedibromide,[9] or the condensation of polymethylenediamine or polyamine derivatives with an arenedialdehyde. In this respect we found that *m* and *p*-diazacyclophanes may be obtained through the catalytic hydrogenation of the nitro group in methyl *N*-[3-(3 or 4-nitrophenyl)-pyruvoyl]-amino esters because this reaction promotes a [1+1]-condensation to give a macrocycle and a final hydrogenation of the two imine functions (Scheme 1).



Scheme 1

The synthesis of *p*-diazacyclophane **3** (Scheme 2) started with the acid-promoted methanolysis of the 2,5-piperazinedione derivative **1** to give **2**, followed by catalytic reduction.[10] The final hydrogenation of the two imine functions, that could give mixtures of diastereomers with a syn or anti stereochemistry, was diastereoselective. The anti isomer was ruled out because the ^{1}H and ^{13}C-NMR spectra showed the symmetry of the molecule, which is only compatible with the syn isomer, that must be a mixture of (2*S*,6*S*)- and (2*R*,6*R*)-enantiomers although only the last one is shown. The syn configuration and the boat-like conformation of **3** were in accordance to *ab initio* calculations using the 3-21G(d) basis set at the Hartree-Fock (HF) density functional level in the gas phase.[13] This study also showed that benzene rings are parallel and nearly superposed and the two arms are equatorially disposed. The boat-like conformation has been proposed for other diazacyclophanes.[14]



1 **2** **3**

Scheme 2. Reported approach to paracyclophane **3**: i) HCl/MeOH (10%), microwave irradiation time 5 min, 130 ºC. *ii*) H_2, 10% Pd-C, EtOAc, 2 x 10^{-2}M.

These *bibrachial macrocycles*[11] contain two amino groups incorporated into the cyclophane ring[12] and could be ligands for different ions, but the synthetic approach depicted in Scheme 2 is not convenient to be extended to enantiomerically pure dipeptide anhydrides such as *cyclo*(Gly-L-Ala) or *cyclo*(Gly-L-Phe), because of the lability of stereocenters to the basic media required in the aldol-type condensation with *p*-nitrobenzaldehyde to obtain compounds of type **1**. Furthermore, the methanolysis of these compounds to obtain nitrophenylpyruvoyl amino esters requires to be improved for a multi-gram scale synthesis of diazacyclophane precursors because, by solubility reasons, it had to be performed at high dilutions (up to 0.003 M). Unfortunately, all attempts to find out other experimental conditions were unsuccessful, which moved us to study a multi-step approach to obtain these amino esters at a multi-gram scale. Here we describe this approach and the ability of diazacyclophanes for complexation with metal ions.

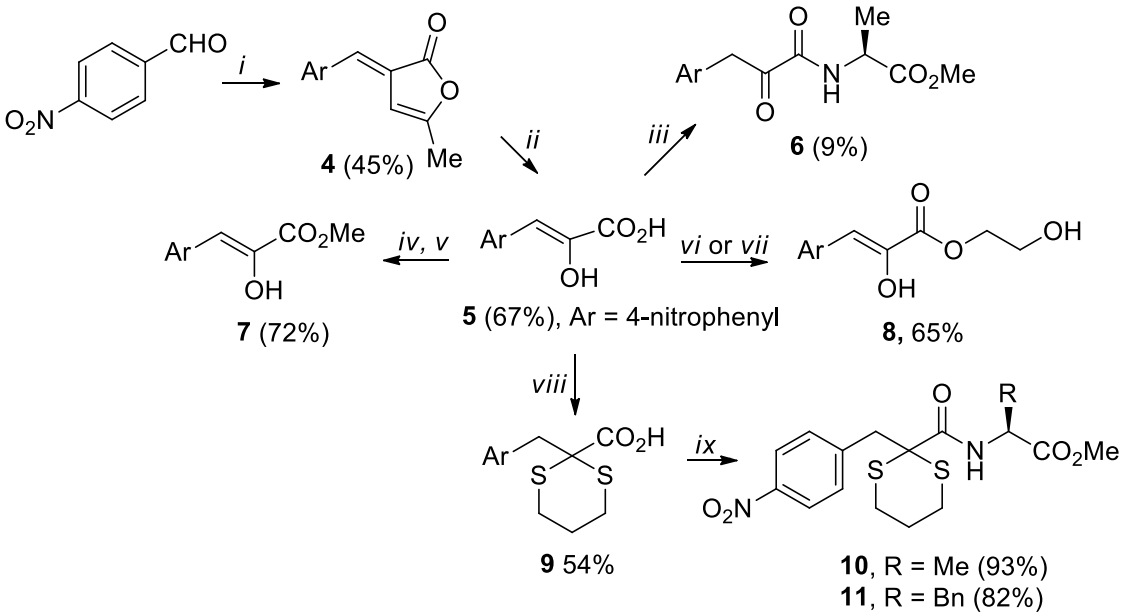
Results and Discussion

Synthesis of azacyclophanes (13) and (14)

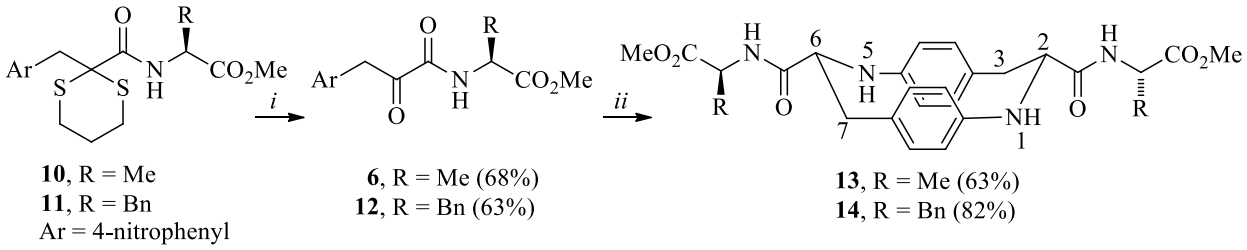
We first obtained compound **5** by acid hydrolysis of azalactone **4**[15] following well known procedures.[16] The subsequent coupling of **5** with methyl L-alaninate in the presence of EDC and Et_3N gave **6** in very low yield, indicating that protection of the ketone functional group was necessary, but the apparently simple transformation of compound **5**[15] or its methyl ester **7**[17] into the corresponding ketals was not a straight reaction. Treatment of **5** with ethylenediol, under $BF_3{\cdot}OEt_2$[18] or *p*TsOH[19] catalysis gave the 2-hydroxyethoxy ester **8,** and compound **7** was the only product obtained in the attempted synthesis of the dimethoxy ketal by treatment of **5** with trimethyl orthoformate.[20] Fortunately, we could obtain the 1,3-dithiane **9**, and this compound was condensed under standard conditions with methyl L-alaninate or L-phenylalaninate to afford compounds **10** or **11** with excellent yields (Scheme 3).

Deprotection of the α-ketoamide function in compounds **10** and **11** was performed by oxidation with HgO and $BF_3.OEt_2$[21] to give **6** and **12**, respectively (Scheme 4, Ar = 4-nitrophenyl). After a very careful purification to eliminate traces of any sulfur-containing derivative to avoid the poison of the catalyst, these compounds were submitted to catalyzed hydrogenation, that promoted a domino process[22] implying reduction of the nitro group, intermolecular condensation, and diastereoselective reduction of the two imine functions, to give **13** and **14**. In spite of the X-ray data absence, the symmetry showed in the NMR spectra of both compounds was only compatible with a 2,6 syn configuration. Intracyclic benzene protons in the ^{1}H NMR spectra of **3**, **13** and **14** were located in the normal aromatic region. ^{1}H and ^{13}C NMR spectra of compound **3** at room temperature were very simple, while ^{1}H NMR spectrum of **13**, and specially of **14**, showed less resolved signals. We think that the observed double signals are due to the presence of different rotamers, due to the expected higher energy barriers in the dynamic equilibrium between different conformations because of the presence of the Me or Bn

substituents in the side-chain. The possible contamination with the (*S*,2*S*,6*S*,*S*)-diastereomer seams less probable, since chemical shift differences in double signals are very small and attempts to isolate both possible diastereomers by column chromatography were unsucsessful. It appears that the chiral side-chains induce the diastereoselective hydrogenation of the imine functions, giving the (*S*,2*R*,6*R*,*S*)-diastereomer.



Scheme 3. Synthesis of protected *N*-[3-(4-nitrophenyl)-pyruvoyl]-amino esters **10** and **11**: *i*) *N*-Acetylglycine, NaOAc, Ac_2O, reflux, 2 h. *ii*) AcOH/HCl (1:2), reflux, 6 h. *iii*) Methyl alaninate hidrochloride, EDC, Et_3N, r.t. 16 h. *iv*) AcCl 0.3 eq., MeOH, reflux 16 h. *v*) $HC(OMe)_3$ 10 eq., MeOH, NH_4Cl 1.5 eq, reflux 2 h. *vi*) $BF_3.OEt_2$, ethylene glycol, dry THF, r.t. 16 h. *vii*) Ethylene glycol, dry toluene, PTSA, Dean–Stark distillation 120 ºC, 16 h. *viii*) $BF_3.OEt_2$, 1,3-propanedithiol, DCM, reflux, 16 h. *ix*) EDC, Et_3N, DCM, amino ester, r.t. 24 h.



Scheme 4. Synthesis of cyclophanes **13** and **14**: *i*) HgO and $BF_3.OEt_2$, THF/H_2O (85:15), 0 ºC. *ii*) Pd/C (20%), H_2, EtOAc, 16 h, r.t.

Complexation studies

Cyclophanes **3** and **14** were tested for their complexation behaviour with Cu(II), Zn(II) and Co(II) through UV-vis and ^{1}H NMR spectroscopic methods, since we have been unable up to now to get proper crystals for an X-ray study.

UV-vis spectra studies

Compounds **3** and **14** solved in MeOH showed UV-vis spectra with λ_{max} at 257, 247, 205, and 334 nm for **3** and 293, 240 and 209 nm for **14** (see Figure 1 and Supplementary Material). These data point out that the benzene rings in both ligands are rather unstrained, since the absorption maxima are similar to that of *p*-xylene (λ_{max} 268 nm).[23] Upon addition of $CuCl_2$, $CoCl_2$ or $ZnCl_2$, the intensity of the bands increased without no significant shifts in λ_{max} values. In the case of the complex of **14** with Co^{2+} the absorption band at 240 nm disappeared. The stoichiometry of the complexes with azacyclophane **3** was investigated by using the UV/Vis spectrum titration method and, according to Job plot experiments,[24] this compound forms a 1:1 complex with Zn^{2+} (Figure 1). The same stoichiometry was observed for the complex with Co^{2+}, while three complexes with 1:1, 1:2, and 1:3 stoichiometries appeared for Cu^{2+} (see Supplementary Material).

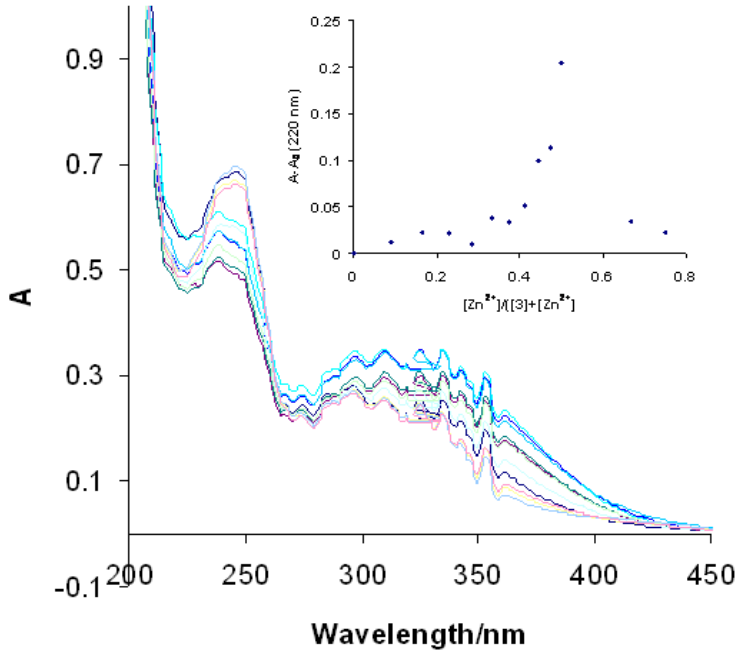


Figure 1. Job plot and UV-vis spectra of ligand **3** in methanol (33.3 μM) upon addition of methanol solutions of Zn^{2+} with μM concentrations 3.3, 6.6, 10.0, 13.3, 16.6, 20.0, 23.3, 26.6, 30.0, 33.3, 66.6, and 99.9.

NMR spectra studies

We chosed the Zn^{2+} ion to shed further light on the complexation modes in solution because it forms diamagnetic complexes. Upon addition of this ion to diazacyclophanes **3** and **14**, the main

differences were found in the chemical shifts of the intracyclic aromatic protons at the *ortho*-position respect to the amine group (*o*-NH-H(Ar)), which were higher in the complexes than in the free ligands. Lower field shifts were also observed in the CH-CH_2 intracyclic protons of the complexes while changes in the chemical shifts of the side-chain protons were not observed (Table 1).

Table 1. Chemical shifts comparison of significant protons in **3**, [Zn^{2+}. **3**], **14**, and [Zn^{2+}. **14**] in CD_3OD

Compounds	*o*-NH-H(Ar)	H-2 and H-6	H-3 and H-7
3	6.69 ppm	4.22 ppm	3.01 and 2.72 ppm
[Zn^{2+}. **3**],	6.83 ppm	4.33 ppm	3.07 and 2.81 ppm
14	6.67 ppm	4.15 ppm	2.65 and 2.86 ppm
[Zn^{2+}. **14**]	7.32 ppm	4.35 ppm	3.20 and 3.40 ppm

We show in Figure 2a the ^1H NMR spectrum of **3** in CD_3OD and in Figure 2b the spectrum of a 0.5 nM solution of Zn^{2+} in CD_3OD after addition to a 1 nM solution of **3** in the same solvent and 2 hours of reflux. The observed set of resonance signals of the same intensity in this solution, where the **3**/Zn^{2+} ratio is 1:0.5, indicates the presence of an equimolar amount of the free ligand and of the complex. Figure 2c shows the spectrum of a similarly treated solution where the ligand/metal ratio was 1:1. In this case, all proton signals corresponding to the free ligand has disappeared and only the proton signals of the complex are observed, indicating the formation of a stable 1:1 complex in solution.

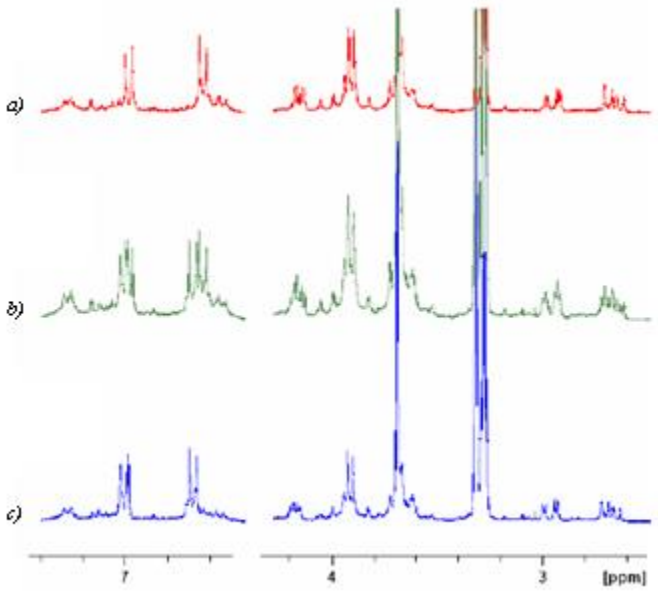


Figure 2. (a) ^{1}H NMR spectrum of **3** in CD_3OD. (b) ^{1}H NMR spectrum of a CD_3OD solution of **3**/Zn^{2+} in 1:0.5 ratio after 2 hours of reflux. (c) ^{1}H NMR spectrum of a similarly treated solution where the ligand/metal ratio was 1:1.

In conclusion, although to be sure of the true structure of the new complexes X-ray data should be necessary, it is rather clear that the trans-annular amine groups are involved in the complexation, because the main ^{1}H NMR differences between ligand and complexes have been found in the aromatic protons at the *ortho*-position respect to these amino groups and in the H-2 and H-6 protons These interactions would be compatible with 1:1 *endo*-complexes or with 2:2 *exo*-complexes, where the metal ions would be inside or outside of the pi-cavity, respectively.

Experimental Section

General. All reagents were of commercial quality and were used as received. Solvents were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator. Separations by flash chromatography were performed on silica gel with 40-63 μm particle size. Melting points were measured in a hot stage microscope, and are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds examined as films on NaCl disks. NMR spectra were obtained at 250 MHz for ^{1}H and 63 MHz for ^{13}C, with $CDCl_3$, DMSO-d_6 and CD_3OD as solvents (Servicio de Resonancia Magnetica Nuclear, Universidad Complutense). Elemental analysis were determined by the Servicio de Microanalisis Elemental, Universidad Complutense.

2-Methyl-4(4-nitrophenylmethylene)-2-oxazolin-5-one (4). A stirred mixture of *o*-nitrobenzaldehyde (30.0 g; 200 mmol), *N*-acetylglycine (13.4 g; 200 mmol), anhydrous sodium acetate (32.8 g; 400 mmol) and acetic anhydride (200 mL) was heated at 80-85 ºC. After 2 h., the dark brown mixture was poured into a mixture (200 mL) of equal volumes of water and ethanol, stirred for 30 min and cooled in ice. The crystals that formed were filtered off, washed with a water/ethanol mixture and dried in oven. Yield 45% (21 g) of **4**, yellow microcrystals (from acetone); m.p. 183-185 ºC; (lit[17] mp 182-183 ºC). IR (film) ν 1788, 1660, 1587cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.41 (d, *J* = 9.1 Hz, 2H), 8.32 (d, *J* = 9.1 Hz, 2H), 7.34 (s, 1H), 2.44 (3H, s); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 169.8, 167.7, 148.6, 140.1, 136.5, 133.5, 127.1, 124.7, 16.4. Anal. Calcd. For $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06. Found: C, 56.57; H, 3.12; N, 11.95.

2-Hydroxy-3-(4-nitrophenyl)-2-propenoic acid (5). The azalactone **4** (9 g, 39 mmol) was boiled under reflux with stirring in glacial acetic acid (27 mL) and concentrated hydrochloric acid (63 mL). After 6 h, the mixture was poured into water (150 mL), stirred and cooled on ice. The crystals, were filtered off, washed with water and dried in an oven at 80 ºC. Yield 67% (5.5 g) of **5**, brown microcrystals (from toluene); m.p.186 ºC (dec); (lit[15] mp 188 ºC (dec). IR (film) ν 3686, 1738 cm^{-1}. ^{1}H-NMR (250 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.23 (d, *J* = 8.9 Hz, 2H), 8.03

(d, *J* = 8.9 Hz, 2H), 6.55 (s, 1H); ^{13}C-NMR (63 MHz, DMSO-d_6) δ 166.0, 145.7, 145.6, 142.5, 130.1, 123.9, 107.2. Anal. Calcd. For $C_9H_7NO_5$: C, 51.68; H, 3.37; N, 6.70. Found: C, 51.39; H, 3.08; N, 6.44.

Methyl *N*-[3-(4-nitrophenyl)pyruvoyl]-L-alaninate (6). To a solution of **5** (1 g, 4.8 mmol) in CH_2Cl_2 (50 mL), methyl alaninate hydrochloride (0.66 g, 4.8 mmol), EDC (0.9 g, 4.8 mmol), and Et_3N (1.4 mL, 9.6 mmol) were added. The reaction mixture was stirred at room temperature for 16 h, diluted with CH_2Cl_2 (50 mL), washed with 1 M aq HCl (2 x 20 mL) and with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give **6** (120 mg, 9%) as a pale yellow oil. IR (film) ν 1738, 1604, 1518 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 4.57 (m, 1H), 4.36 (s, 2H), 3.79 (3H, s), 1.49 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 193.9, 172.1, 158.8, 147.2, 140.1, 130.8, 123.7, 52.7, 48.2, 42.8, 17.9. Anal. Calcd. For $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.87; H, 4.62; N, 9.37.

Methyl 2-hydroxy-3-(4-nitrophenyl)-2-propenoate (7). A stirred solution of compound **5** (5 g, 24 mmol) and AcCl (0.6 g, 7.2 mmol) in MeOH (100 mL) was refluxed for 16 h. The reaction mixture was concentrated under vacuum and the residue was crystallized. Yield 72%, white microcrystals (from EtOAc); m.p. 148-150 ºC; (lit[17] mp 150-151 ºC). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 6.86 (bs, 1H), 6.58 (s, 1H), 4.00 (s, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 165.9, 146.4, 141.7, 140.6, 130.2, 123.7, 108.3, 53.7.

2-Hydroxyethyl 2,2-dimethylenedioxa-3-(4-nitrophenyl)-propanoate (8)

Method A. $BF_3{\cdot}OEt_2$ (1.2 mL, 9.6 mmol) was added dropwise over a solution of **5** (1.0 g, 4.8 mmol) and ethylene glycol (0.3 mL, 4.8 mmol) in dry THF (50 mL). The reaction mixture was stirred at room temperature for 16 h. Aqueous $NaHCO_3$ (1 M, 30 mL) and AcOEt (100 mL) were added and the mixture was shaken. The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and the solvent was evaporated to give a crude product which was purified by flash column chromatography (silica gel), eluting with EtOAc, to get compound **8**, yield 54%.

Method B. A solution of **5** (1.0 g, 4.8 mmol) and ethylene glycol (0.3 mL, 4.8 mmol) in dry toluene (50 mL) was stirred in a round bottom flask equipped with a Dean–Stark distillation system. PTSA (20 mg) was added in one portion. The temperature was raised to 120 ºC and kept at this temperature, under stirring, for 16 h. The solution was allowed to cool to room temperature. After washing with aqueous $NaHCO_3$ (1 M, 30 mL), EtOAc (100 mL) was added and the mixture was shaken. The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and the solvent was evaporated to give a crude product, which was purified by flash column chromatography (silica gel) eluting with EtOAc to get compound **8** as a white oil, yield 65%. IR (film) ν 3468, 2961, 2905, 1738 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 4.28 (m, 2H), 4.03 (m, 2H), 3.80 (m, 4H), 3.32 (s, 2H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 169.3, 146.8, 141.9, 131.6, 122.9, 105.8, 67.0, 66.0, 60.4, 40.6. Anal. Calcd. For $C_{13}H_{15}NO_7$: C, 52.53; H, 5.09; N, 4.71. Found: C, 52.22; H, 4.88; N, 4.48.

3-(4-nitrophenyl)-2,2-trimethylenedithio-propionic acid (9). BF_3.OEt_2 (18 mL, 145 mmol) was added dropwise to a refluxing solution of **5** (20.2 g, 96 mmol) and 1,3-propanedithiol (10.6 mL, 100 mmol) in dry DCM (300 mL). The reaction mixture was stirred for 16 h, then the solution was allowed to cool to room temperature, quenched with water, and filtered. Yield 54% (15.5 g) of **9**, as brown microcrystals (from ethanol); m.p. 154–155 ºC. IR (film) ν 3408, 2312, 1691 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 3.48 (s, 2H), 3.15 (m, 2H), 2.74 (m, 2H), 2.12 (m, 1H), 1.83 (m, 1H); ^{13}C-NMR (63 MHz, DMSO-d_6) 171.5, 146.8, 143.7, 132.1, 122.9, 53.2, 43.2, 27.2, 24.1. Anal. Calcd. For $C_{12}H_{13}NO_4S_2$: C, 48.14; H, 4.38; N, 4.68. Found: C, 47.87; H, 4.02; N, 4.33.

General procedure to obtain (10) and (11)

To a solution of compound **9** (14.4 mmol), L-methyl alaninate or methyl L-phenylalaninate (14.4 mmol) and EDC (28.8 mmol) in dry DCM (200 mL), Et_3N (28.8 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, diluted with CH_2Cl_2 (50 mL), washed with 1 M aqueous HCl (2 x 20 mL) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography.

Methyl *N*-[3-(4-nitrophenyl)- 2,2-trimethylenedithio-propionyl]-L-alaninate (10). The crude product was purified by flash column chromatography (hexane/EtOAc 8:2) to obtain compound **10**, yield 87% as a yellow oil. IR (film) ν 3359, 2603, 1743, 1667 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.5 Hz, 2H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 6.5 Hz, 2H), 4.54 (sept, *J* = 8.6 Hz, 1H), 3.76 (s, 3H), 3.38 (d, *J* = 6.5 Hz, 1H), 3.33 (d, *J* = 6.5 Hz, 1H), 3.12 (ddd, *J* = 17.3, 12.2 and 2.9 Hz, 1H), 2.96 (m, 1H), 2.77 (m, 2H), 2.12 (m, 1H), 1.90 (m, 1H), 1.35 (d, *J* = 8.6Hz, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 173.0, 168.3, 147.4, 141.6, 131.5, 123.0, 59.5, 52.6, 49.0, 45.9, 42.8, 28.3, 24.1, 18.1. Anal. Calcd. For $C_{16}H_{20}N_2O_5S_2$: C, 49.98; H, 5.24; N, 7.29. Found: C, 49.79; H, 4.93; N, 7.02.

Methyl *N*-[3-(4-nitrophenyl)-2,2-trimethylenedithio-propionyl]-L-phenylalaninate (11). The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) to obtain compound **11** yield 82% as a yellow oil. IR (film) ν 3380, 1738, 1605 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.28 (m, 3H), 7.04 (d, *J* = 7.7 Hz, 2H), 4.82 (m, 1H,), 3.83 (d, *J* = 3.0 Hz, 2H), 3.78 (s, 3H), 3.13 (dd, *J* = 14.0 and 4.4 Hz, 1H), 2.97 (dd, *J* = 14.0 and 8.3 Hz, 1H), 2.83 (m, 1H), 2.61 (m, 3H), 1.98 (m, 1H), 1.87 (m, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 171.7, 168.8, 147.3, 141.4, 135.5, 131.4, 128.9, 128.8, 127.4, 123.0, 59.5, 54.0, 52.5, 45.8, 37.6, 30.9, 29.7, 28.1, 27.9, 24.0. Anal. Calcd. For $C_{22}H_{24}N_2O_5S_2$: C, 57.37; H, 5.25; N, 6.08. Found: C, 57.13; H, 4.96; N, 5.84.

General procedure for the deprotection reaction of (10) and (11)

A solution of **10** or **11** (5 mmol) in THF/H_2O (85:15, 100 mL) was added to a suspension of HgO (15.5 mmol) and BF_3.OEt_2 (15.5 mmol) in THF/H_2O (85:15) at 0 ºC. The reaction mixture was stirred for 20 h at 60 ºC, then CH_2Cl_2 (100 mL) was added and the precipitate filtered. The

organic layer was washed with brine, dried over Na_2SO_4 and the solvent evaporated in vacuo. The crude product was purified by flash column chromatography.

Methyl *N*-[3-(4-nitrophenyl)pyruvoyl]-L-alaninate (6). The crude product was purified by flash column chromatography (hexane/EtOAc 1:1) to obtain compound **6** yield 68% as a pale yellow oil.

Methyl *N*-[3-(4-nitrophenyl)-pyruvoyl]-L-phenylalaninate (12). The crude product was purified by flash column chromatography (hexane/EtOAc 6:4) to obtain compound **12** yield 63% as a yellow oil. IR (film) ν 3380, 1744, 1690, 1520 cm^{-1}.^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.28 (m, 3H), 7.09 (m, 2H), 4.85 (dd, *J* = 14.6 and 6.1 Hz, 1H), 4.36 (d, *J* = 16.5 Hz, 1H), 4.27 (d, *J* = 16.5 Hz, 1H) 3.77 (s, 3H), 3.21 (dd, *J* = 19.6 and 6.1 Hz, 1H), 3.13 (dd, *J* = 19.6 and 14.6 Hz, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 193.7, 170.7, 158.9, 147.3, 139.9, 135.0, 130.8, 129.0, 128.0, 127.4, 123.8, 53.3, 52.7, 42.9, 37.8. Anal. Calcd. For $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.45; H, 4.54; N, 7.37.

Synthesis of diazacyclophanes

A solution of compound **6 or 12** (2.4 mmol) in EtOAc (240 mL) with a 20% of Pd/C was hydrogenated at room temperature for 16 h. After filtration over Celite and evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography.

Methyl *N*-[4,8-(1,4)dibenzene-1,5-diazacyclooctaphan]-2,6-bisylenecarbonyl]-L-alaninate (13). The residue was purified by flash column chromatography (silica gel) eluting with hexane/EtOAc (6:4) to provide compound **13** as a yellow oil yield 63%. IR (film) ν 3369, 2953, 1738, 1651 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.2 Hz, 2H), 6.68 (d, *J* = 8.2 Hz, 2H), 4.63 (m, 1H), 4.27 (m, 1H), 3.78 (s, 3H), 3.14 (m, 1H), 2.84 (m, 1H), 1.41 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 173.1, 172.4, 145.4, 136.4, 126.1, 115.5, 72.9, 52.4, 47.6, 39.9, 18.3. Anal. Calcd. For $C_{26}H_{32}N_4O_6$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.54; H, 6.23; N, 11.03.

Methyl *N*-[4,8-(1,4)dibenzena-1,5-diazacyclooctaphan]-2,6-bisylenecarbonyl]-L-phenyl alaninate (14). The residue was purified by flash column chromatography (silica gel) eluting with EtOAc to get compound **14**, 82% yield as an orange oil. IR (film) ν 3374, 2349, 1738, 1660 cm^{-1}.^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.26 (3H, m), 7.10 (m, 1H), 7.05 (m, 4H), 6.65 (m, 2H), 4.90 (m, 1H), 4.19 (m, 1H), 3.73 (s, 3H), 3.13 (m, 2H), 3.10 (m, 1H), 2.60 (m, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 172.6, 172.5, 171.7, 171.6, 145.2, 135.8, 135.6, 130.5, 130.3, 129.2, 129.1, 128.6, 128.5, 127.1, 127.0, 126.3, 115.5, 115.4, 73.3, 73.2, 53.3, 53.0, 52.8, 39.8, 39.7, 38.0, 37.9. Anal. Calcd. For $C_{38}H_{40}N_4O_6$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.09; H, 5.93; N, 8.27.

Synthesis and characterization of the metal complexes

A solution of compound **3** or **14** (0.5 mmol) in MeOH (5 mL) was added 5 mL of a 0.1 M solution of corresponding metal salt [$ZnCl_2$, $CoCl_2$, and $CuCl_2$ (0.5 mmol)]. The reaction mixture

was stirred for 2 h at 60 ºC. After evaporation of the solvent under reduced pressure the solid residue was washed with petroleum ether.

[3·Zn^{2+}] complex. ^{1}H-NMR (250 MHz, MeOH) δ 7.17 (d, *J* = 16.5 Hz, 2H), 6.82 (d, *J* = 16.5 Hz, 2H), 4.33 (dd, *J* = 8.1 and 4.0 Hz, 1H), 4.00 (d, *J* = 5.3 Hz, 2H), 3.75 (s, 3H), 3.07 (dd, *J* = 13.9 and 4.0 Hz, 1H), 2.81 (dd, *J* = 13.9 and 8.1 Hz, 1H).

[14·Zn^{2+}] complex. UV-vis (λ_{max}): 218, 239, 288. ^{1}H-NMR (250 MHz, MeOH) δ 7.3 – 7.1 (m, 14H), 7.97 (m, 4H), 4.77 (dd, *J* = 8.1 and 5.9 Hz, 2H), 4.37 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.4 - 2.6 (m, 8H).

[14·Cu^{2+}] complex. UV-vis (λ_{max}): 204, 242. IR (film) ν: 2927, 1731, 1600. ^{1}H-NMR (250 MHz, MeOH) δ 7.4 – 7.0 (m, 9H), 4.66 (bs, 2H), 3.58 (s, 3H), 3.08 (bs, 4H).

UV/Vis titration of (14)·Cu^{2+} and 14·Co^{2+} complexes

The electronic absorption spectral titration was performed at room temperature on a UV-2401PC UV–vis spectrometer. The stoichiometry of the complexes was determined by means of the Job plot experiments.

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