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Structure-driven design and synthesis of chiral dioxocyclam derivatives

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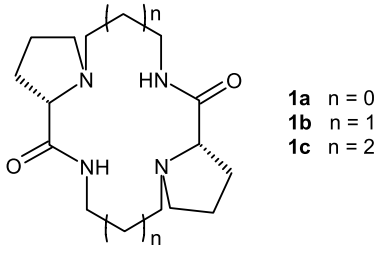
Abstract—Based on an analysis of previously reported structures and a potential geometry fit with substrates, a new family of chiral dioxocyclam derivatives have been designed. The synthesis of those ligands was accomplished starting from L-proline and α-D-amino acids (converted to β-amino acids) with a key step of macrocyclization reaction of amino esters. All ligands were converted into neutral copper(II) complexes (amide groups underwent deprotonation of upon treatment of ligands with copper(II) acetate). The complexes exhibit the desired shape of their active surfaces, as proved by X-ray analysis.

1. Introduction

Macrocyclic ligands, with nitrogen atoms as the electron pair donors, are known to exhibit an exceptionally high affinity for transition metal cations.[1] They are the subject of wide interest owing to their application in processes, such as ion sequestration,[2] catalysis[3] and for biomedical uses.[4,5] Cyclam derivatives, that belong to the mentioned group of compounds, not only form stable complexes with various transition cations,[6] but their complexes have been shown to catalyze organic reactions such as alkene epoxidation,[3,7,8] epoxide carboxylation,[9] electrochemical annulation,[10] and oxidation of hydrocarbons.[11] Despite the fact that in most of these reactions new stereogenic centres could be formed, the exploration of asymmetric catalysis has been so far limited.[12]

In this context, we were interested in the synthesis of a novel class of enantiomerically pure cyclam derivatives and its 12-membered and 16-membered analogues (Scheme 1).[13] Knowing that efficient asymmetric catalysis involves steric and electrostatic interaction between ligand, cation and substrates, and that this interaction depend on ligand structure, we decided to apply previously described methodology for the synthesis of a new class of chiral dioxocyclam derivatives and their complexes with Ni^{2+} and Cu^{2+} ions. Additionally, we would like to report herein on the design and structural study of the new compounds.



Scheme 1.

2. Results and discussion

2.1. Ligand design

In the preceding papers, we have presented an attractive and efficient synthetic route to optically pure dioxocyclam **1b**,[13] which upon deprotonation forms stable neutral complexes with Ni^{2+} and Cu^{2+}. X-ray analysis of **Ni·1b**[13] and **Cu·1b** (Fig. 1) shows that both complexes exhibit very similar tetrahedrally distorted square-planar geometry. Two pyrrolidine rings in **Ni·1b** and **Cu·1b** complexes are located at the same side of the macrocyclic ligand plane, which may result in inaccessibility of the metal cation from this side. Although the other side of the ligand, which is important for the possible interaction of the metal centre with a guest molecule, is approximately flat, it possesses a rectangular depression, which is parallel to the macrocycle plane and it

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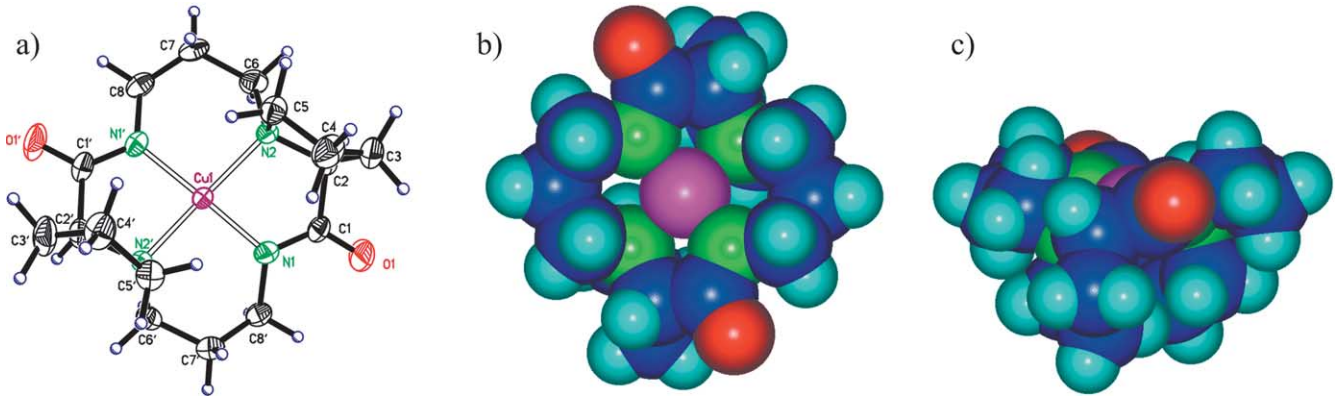


Figure 1. X-ray crystal structure of **Cu·1b**: (a) ORTEP presentation; (b) space filling view from the top; (c) space filling view from the side.

is surrounded by the hydrogens of the propylene bridges. The amide oxygens are located in the opposite vertices of this rectangular area. Both complexes have very similar structure, and in our opinion, this is a strong argument in favour of the thesis that the availability of the coordinated central atom should be similar for all complexes of the transition metals with a doubly-deprotonated tetradentate ligand of type **1b**. The geometry of such complexes can be symbolically illustrated as the model solid **C1** (Fig. 2).

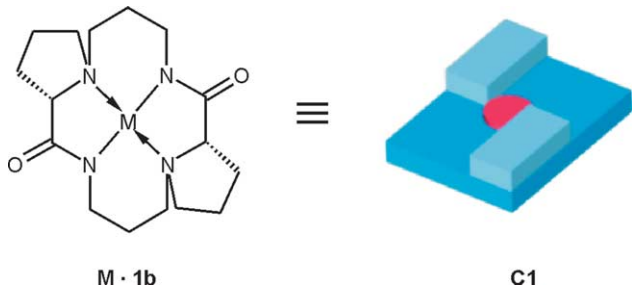


Figure 2. A schematic representation of **Cu·1b** geometry.

The features of the model complex **C1** can be summarised as follows: 1°—the geometry of the binding sites of the ligand is flat; 2°—the metal cation, which is coordinated inside the macrocycle gap, can be accessible for the substrate molecule only from one side, the other side of the macrocycle is completely inaccessible; 3°—the access to the metal cation being in the centre of the rectangle is limited by two groups located in the vertices of the rectangle. The above characterises the resulting molecule, with a C_2 axis as a symmetry element, which is perpendicular to the macrocycle plane and goes through the centre of the macrocycle gap or a cation therein.

The examples of previously prepared chiral catalytically active tetraazamacrocyclic derivatives are presented in Figure 3. Their geometry can be represented as the model **C2**. Analysis of those structures leads to the conclusion that their common feature is the presence of the C_2 axis positioned in the macrocycle plane.[14] Each of these systems have ternary stereogenic centres as the source of chirality. Thus, only one group, which modifies the close neighbourhood of the macrocycle gap, falls to each side of such a macrocycle.

Comparison of the models **C1** and **C2** reveals that complexes of **1b** provide a completely new topology. Moreover, it can be assumed that ligands of type **C2** offer too much flexibility to the interaction with a possible guest molecule (the substrate), and therefore, enantiotopic or enantiofacial discrimination will be less efficient (Fig. 4).

Thus, we found the geometry of type **C1** appealing and decided to extend our studies to more elaborate systems. We noticed that the depressions on **Ni·1b** and **Cu·1b** molecular surfaces are quite shallow, and thus we decided to prepare ligands that would have deeper cavities. The only reasonable site for modification of the model system **1b** is the less-crowded side of the macrocycle, which enables the access to the central metal cation, and therefore, is responsible for the chiral recognition of molecules. To achieve better similarity of the complex to the model solid **C1**, we resolved to insert an additional substituent into two opposite vertices of the above-mentioned rectangular

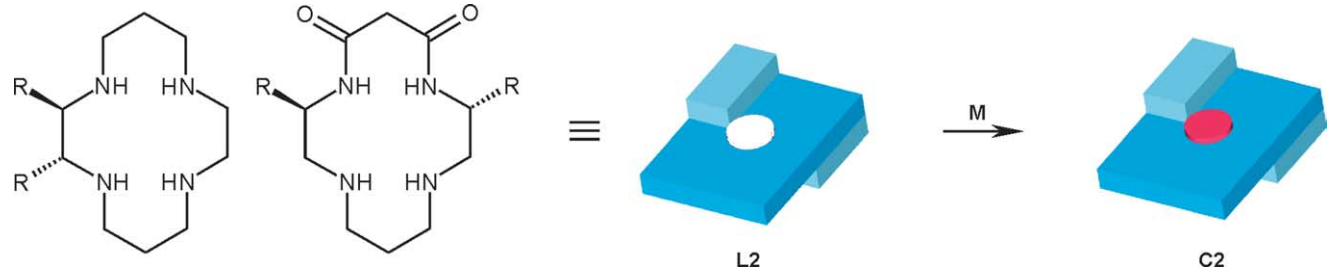


Figure 3. A schematic representation of the geometry of known chiral cyclam complexes.

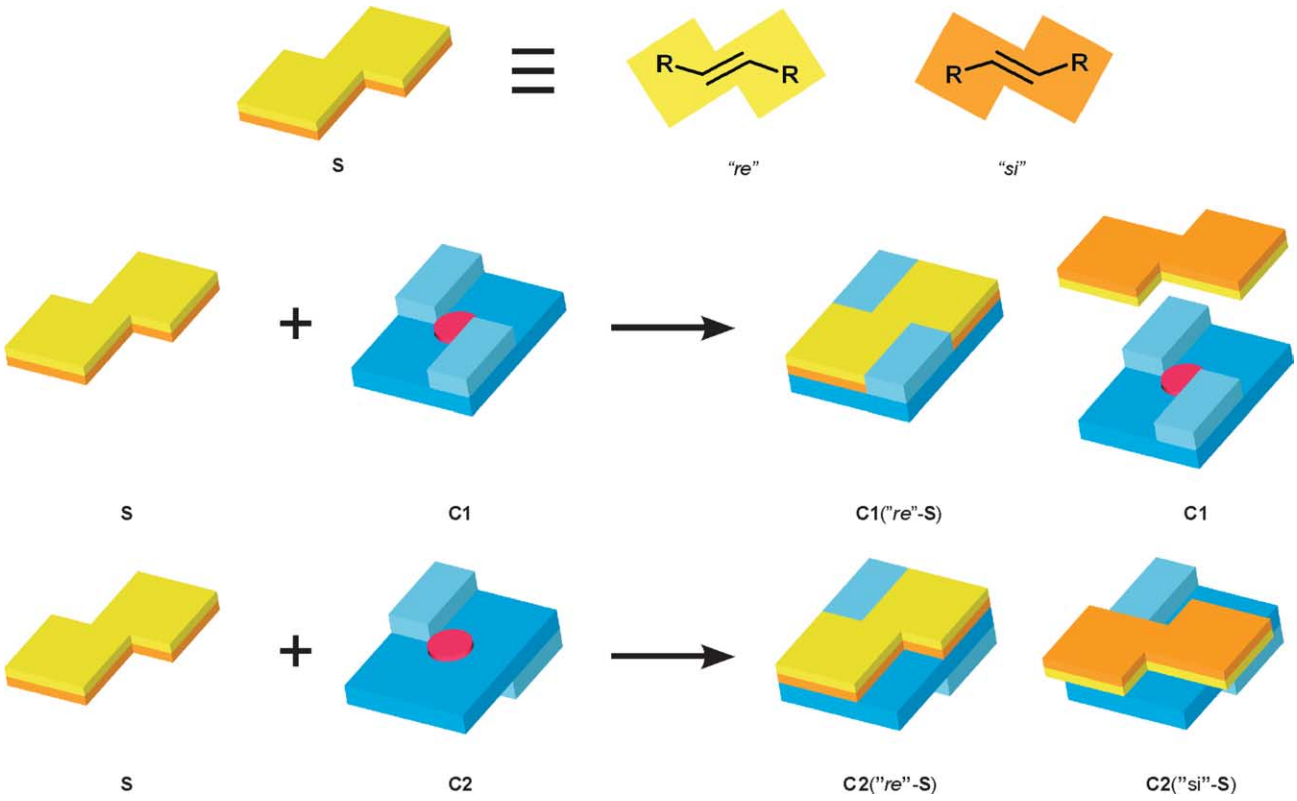


Figure 4. A schematic representation of the enantiofacial discrimination of the (*E*)-disubstituted olefins (S) by the molecules of shape **C1** and lack of such discrimination by the molecules of shape **C2**.

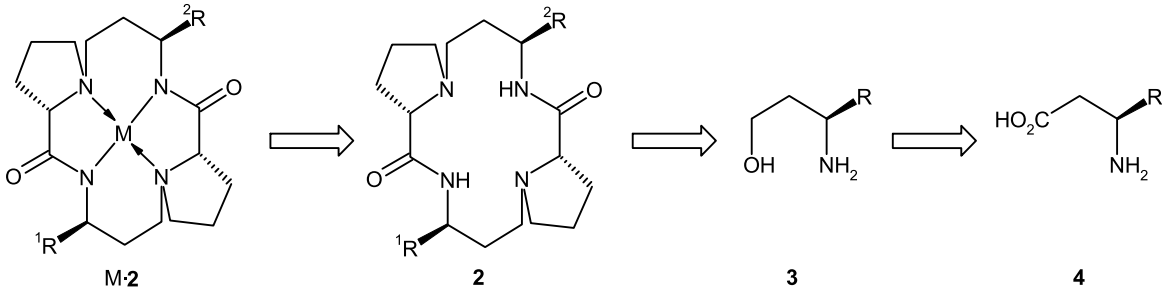
depression. The change from hydrogens to R groups leads to the ligands of type **2** (Scheme 2).

2.2. Preparation of ligands

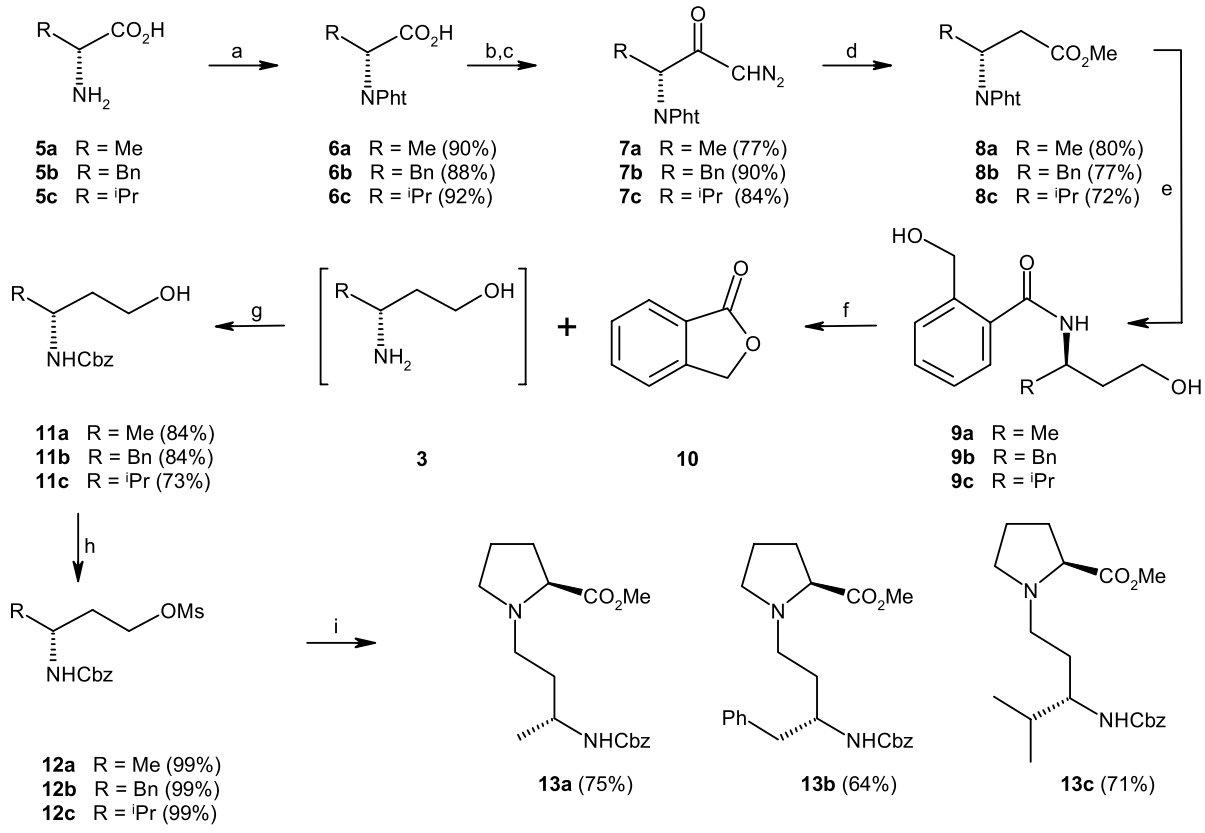
The retrosynthetic analysis indicates that precursors for modified ligands of type **2** are chiral 1,3-aminoalcohols **3**, which are closely related to D-β-amino acids (**4**) (Scheme 2). Therefore, it was necessary to synthesise the D-β-amino acids indicated by the retrosynthetic analysis, then to convert them into the intermediates **3** in order to prepare the ligands **2** using the already developed synthetic pathway.

Several methods for the preparation of the enantiomerically pure β-amino acids are known.[14c,15] Among them, the most practical one seemed to us the Arndt–Eistert synthesis (homologation of the easily available α-amino acids). We employed this method to prepare aminoalcohols **3**, and consequently ligands **2**, where R is methyl, benzyl and isopropyl, using three amino acids, viz, D-alanine (**5a**), D-phenylalanine (**5b**), and D-valine (**5c**), respectively. In the first step, the amino groups of the amino acids **5a–c** were protected by treating with the phthalic anhydride to afford the *N*-phthaloyl derivatives **6a–c** (Scheme 3). The *N*-protected acids **6a–c** were then converted into the corresponding acid chlorides, which reacted with an excess of diazomethane to give the respective diazoketones **7a–c** The key transformation, that is, the Wolff rearrangement was carried out by treating the methanolic solution of the diazoketone (**7a–c**) with a catalytic amount of silver benzoate, which resulted in formation of the rearranged methyl esters **8a–c** in good yields.

The *N*-phthaloyl protection was cleaved by the method of Ganem and co-workers.[16] The five-membered phthalimide ring was reductively opened by treatment with lithium borohydride to form the benzyl hydroxy function, and, simultaneously, the ester group was transformed to the hydroxymethyl group. The diols **9a–c**, under mild acidic



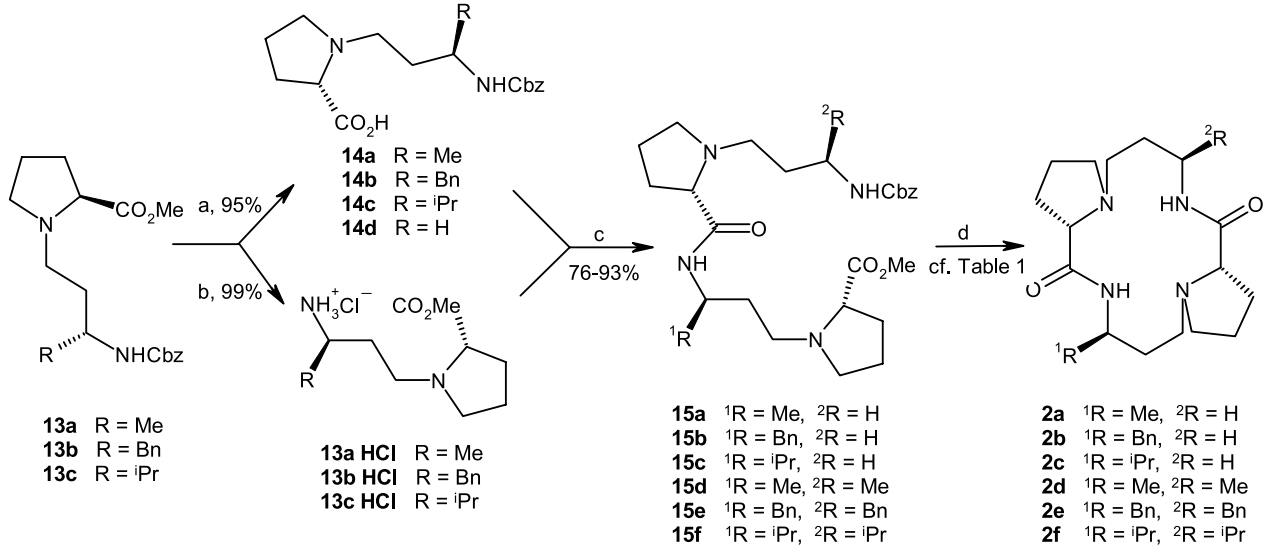
Scheme 2. The retrosynthetic analysis.



Scheme 3. Reaction conditions: (a) phthalic anhydride, Et_3N, toluene, reflux; (b) $SOCl_2$, cat. DMF; (c) CH_2N_2, Et_2O, toluene, 0 °C; (d) cat. $PhCO_2Ag$, Et_3N, MeOH, reflux; (e) $LiBH_4$, THF/H_2O; (f) AcOH, 80 °C; (g) CbzCl, CH_2Cl_2/aq NaOH; (h) Ms_2O, Et_3N, CH_2Cl_2; (i) L-Proline methyl ester, Et_3N, MeCN, reflux.

conditions, underwent lactonization, to give the lactone **10** and the elimination products, which were the desired amino alcohols of type **3**, the amino groups thereof were protected by treatment with benzyl chloroformate to yield the *N*-protected aminoalcohols **11a–c**. In each case, the overall yields for three last steps were high (~85%). The synthesis of *N*-Cbz-blocked aminoalcohols **11a–c** from the *N*-phthaloyl substrates (Scheme 3) only seemingly requires more effort than the synthesis starting from analogous *N*-Cbz-protected amino acids. The attempts to perform such a reaction sequence on the *N*-Cbz-protected substrates failed at the stage of formation of diazoketones. The esterification of alcohols **11a–c** with mesyl anhydride gave quantitatively *N*-blocked mesylates **12a–c**, which were then used for *N*-alkylation of L-proline methyl ester. This gave the chiral building blocks **13a–c**.

Hydrolysis of **13a–c** gives acids **14a–c**, that were subjected



Scheme 4. Reaction conditions: (a) aq NaOH/MeOH; (b) H_2/Pd-C, HCl/MeOH; (c) ^{t}BuOCOCl, Et_3N, CH_2Cl_2, −20 °C→0°; (d) H_2/Pd-C, MeOH; then MeOH, base, at rt or at 10 kbar, 50 °C, see Table 1.

Table 1. Effect of the reaction conditions on the yield of macrocyclisation of amino esters **15a–f**

Entry	Product	Conditions	Yield%
1	**2a**	NaOH, MeOH, rt, 1 day	75
2	**2b**	NaOH, MeOH, rt, 1 day	82
3	**2c**	NaOH, MeOH, rt, 1 day	77
4	**2d**	$NaOCH_3$, MeOH, rt, 30 days	15
5	**2d**	DBU, MeOH, 10 kbar, 50 °C, 3 days	24
6	**2d**	Et_3N, MeOH, 10 kbar, 50 °C, 3 days	36
7	**2d**	Et_3N, MeOH, 10 kbar, 50 °C, 7 days	40
8	**2e**	Et_3N, MeOH, 10 kbar, 50 °C, 7 days	5
9	**2f**	Et_3N, MeOH, 10 kbar, 50 °C, 7 days	2

to condensation with amino ester hydrochlorides **13a–c·HCl** to give corresponding pseudo-peptides **15d–e** (Scheme 4). In order to prepare monosubstituted compounds **15a–c**, the aminoester hydrochlorides **13a–c·HCl** were condensed with acid **14d** obtained from 3-aminopropanol in a similar way.[13b]

N-Cbz-protected amino esters **15a–c** are immediate precursors of the monosubstituted ligands **2** (R^1=H; R^2=Me, Bn or ^{i}Pr), while the compounds **15d–f** are the precursors of the disubstituted ligands **2** (R^1=R^2=Me, Bn or ^{i}Pr). The macrocyclisation of the α,ω-diester precursors to compounds of type **2** was attempted in the presence of sodium hydroxide in methanol, because these conditions proved to be most universal in the case of preparation of analogous compounds of type **2**. The singly-modified amino esters **15a–c**, underwent intramolecular amidation in the presence of methanolic NaOH, to afford the desired monosubstituted macrocycles **2a–c** (Scheme 4) in very good yields (75–82%, Table 1).

The disubstituted amino esters **15d–f** gave no macrocyclic products at all under the same conditions. The only products identified by ESI-MS were the salts of corresponding carboxylic acids. These results suggested that hydrolysis of the methyl ester group caused by hydroxyl anions is much faster than the desired intramolecular aminolysis. Therefore, the use of sodium methoxide appeared to be a possible way for overcoming this problem. This idea was tested using the disubstituted amino ester **15d** to give the macrocyclic diamide **2d** in 15% yield.

The more successful attempt to increase the reactivity of the amine/methyl ester system was the high-pressure reaction in the presence of a base (triethylamine or DBU). The yield for macrocyclic diamide **2d** improved (24–40%), but the other two diamides (**2e** and **2f**) formed in low yields (5 and 2%, respectively), which still allowed for their isolation and characterisation (Table 1).

The comparison of highly reactive monosubstituted amino esters **15a–c** with their disubstituted analogues **15d–f**, which react very reluctantly, leads to the conclusion that this is probably due to different character of the reacting amino groups. Although, in all cases, the ester carbonyl group is attacked by the primary amino group, this amino group is linked to a primary carbon atom in the case of highly reactive substrates (**15a–c**). In the case of amino esters **15d–f**, however, the primary amino group is linked to a secondary carbon atom.

2.3. Structural studies

Two compounds of type **2**, that is, the dimethyl derivative

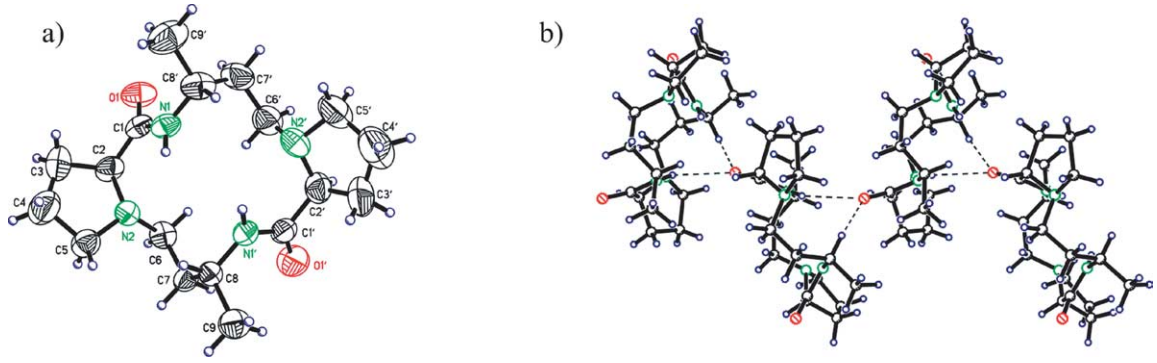


Figure 5. X-ray crystal structure of **2d**: (a) ORTEP presentation; (b) packing pattern.

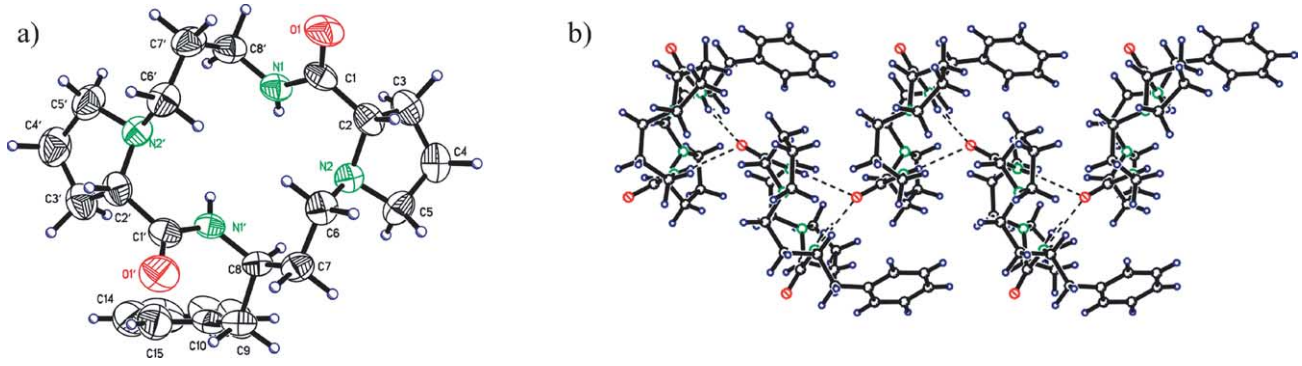


Figure 6. X-ray crystal structure of **2b**: (a) ORTEP presentation; (b) packing pattern.

2d and the monobenzyl derivative **2b**, gave monocrystals suitable for the X-ray diffraction analysis. The structures of these ligands along with their packing modes in the solid state are shown in Figures 5 and 6. The conformations of the macrocyclic rings in both structures are very similar. The proline rings are almost co-planar with the main planes of the macroring. Carbonyl oxygen atoms are positioned perpendicularly to the macroring plane and point to the same side of the macrocycle, slightly outside of the macrocycle centre. The amide hydrogen atoms are thus directed to the opposite side. It is worth mentioning that amide hydrogen atoms are in the close proximity of proline amine lone pairs (distances $H_{amide}\cdots N_{proline}$ in all cases are less than 2.4 Å) forming intramolecular five-membered hydrogen bonded rings. Additionally both amide hydrogen atoms form convergent hydrogen bonds with the carbonyl oxygen of the neighbouring molecule.

All ligands of type **2** form stable complexes with copper cations, in an analogous way to the parent ligand **1b**. The complexes of the mono- and dimethyl derivatives **Cu·2a** and **Cu·2d** gave monocrystals suitable for the X-ray structure determination. Their structures (Figs. 7 and 8) are similar to that of the parent complex **Cu·1b** (Fig. 1). Upon complexation, ligands underwent deprotonation losing amide hydrogen atoms and formed neutral complexes. The geometry of the metal centre is square-planar tetrahedrally distorted. Comparison of all structures reported thus far shows that the tetrahedral twist, defined as the rms deviation from the least-square plane passing through four nitrogen atoms, is slightly larger for all copper complexes (±0.35 Å for **Cu·1b**, ±0.33 Å for **Cu·2a**, ±0.39 Å for **Cu·2d**) than for the **Ni·1b** complex (±0.28 Å). The presence of one or two methyl groups, which are perpendicular to the macrocycle plane makes the crucial depressions on the surface much deeper, which is in agreement with our ligand design.

Preliminary experiments revealed that copper complexes with ligands of type **2** can act as catalysts in cyclopropanation of olefins. The reaction between methylstyrene and ethyldiazoacetete in the presence of **Cu·2b** led to the formation of *trans*-isomer of ethyl 2-methyl-3-phenylcyclopropanecarboxylate with 30% ee, however, no asymmetric induction was observed for the *cis*-isomer.

3. Conclusions

Most of the previously reproted chiral cyclams possesses C_2 symmetry axis that is parallel to the macrocyclic plane. In this paper, we have designed and synthesised a new class of chiral dioxocyclams having a C_2 symmetry axis that is perpendicular to the main plane of the macrocycle. The synthesis was accomplished using L-proline ester and amino alcohols as the starting materials. Such oxocyclams form neutral complexes with copper ions undergoing simultaneous deprotonation of amide groups. Since such complexes exhibit one potentially catalytically active surface that is approximately flat, we have also designed and synthesised the modified ligands in order to accomplish higher asymmetry of the complex surfaces. X-ray structure analyses confirmed the designed topology. Preparation of this family of compound proved the efficiency and

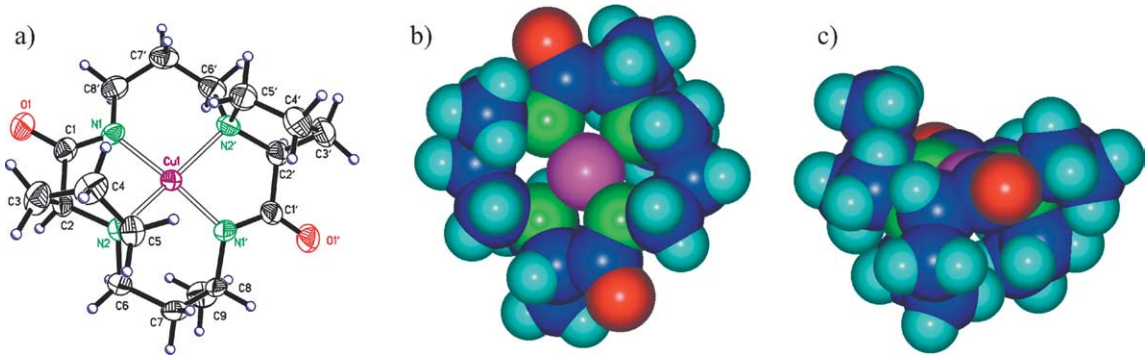


Figure 7. X-ray crystal structure of **Cu·2a**: (a) ORTEP presentation; (b) space filling view from the top; (c) space filling view from the side.

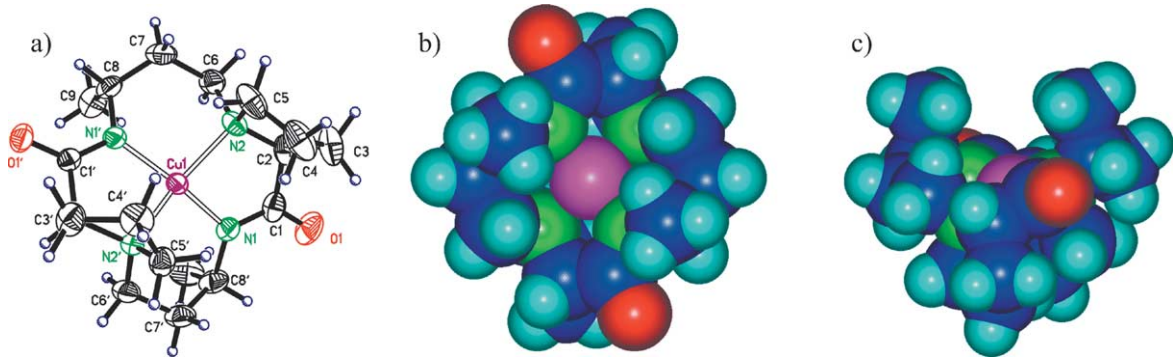


Figure 8. X-ray crystal structure of **Cu·2d**: (a) ORTEP presentation; (b) space filling view from the top; (c) space filling view from the side.

generality of our synthetic pathway that leads to the chiral analogues of cyclam.

4. Experimental

4.1. General remarks

Crystallographic data (excluding structure factors) for the structures discussed in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 273756-273760. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Summary of the crystallographic data and details concerning synthesis of *N*-protected amino alcohols **11a–c** are provided in the Supplementary material. If not stated otherwise, all reagents were obtained from commercial sources and used as received. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh), the thin-layer chromatography was carried out using Merck Kieselgel F_{254} plates.

4.2. General procedure for Cbz-protected aminoalcohol mesylation

Cbz-protected aminoalcohol (19.1 mmol) and triethylamine (1.1 equiv, 3.0 mL) was dissolved in dry dichloromethane (100 mL) and placed in cooling bath. Methanesulfonyl anhydride (1.1 equiv, 3.76 g) was added in a few portions with vigorous stirring to prevent local overheating. Reaction was completed right after the last portion of anhydride had been added (TLC). The mixture was transferred into a separator and washed with 0.5 M HCl aq (50 mL), satd $NaHCO_3$ aq (50 mL), and dried over anhydrous magnesium sulfate. Solvents were removed under reduced pressure and the solid residue was crystallized from CH_2Cl_2/hexane furnishing chromatographically pure mesylate (quant. yield) as colourless crystals.

4.2.1. (*R*)-1-Mesyloxy-*N*-(benzyloxycarbonyl)-3-aminobutane (12a). Prepared from alcohol **11a**. Colourless crystals; mp 67–70 °C; $[\alpha]_D^{20}$ −13.8 (*c* 0.54 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, TMS): δ=7.38–7.29 (m, 5H; arom.), 5.09 (br s, 2H; CH_2Ph), 4.64 (br s, 1H; N*H*), 4.37 (t, 2*H*, *J*=6.3 Hz; CH_2O), 3.96–3.84 (m, 1H; C*H*N), 2.97 (s, 3H; SO_2CH_3), 1.98–1.79 (m, 2H; CH_2), 1.22 (d, *J*=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C, TMS): δ=155.8, 136.4, 128.6, 128.2, 128.1, 67.0, 66.7, 44.3, 37.3, 36.4, 21.2; IR (KBr): ν=3338, 2971, 1680, 1539, 1457, 1349, 1259, 1161, 1091, 1034, 991, 965, 824, 758, 698, 527 cm^{-1}; MS (ESI HR, MeOH): calcd for $[C_{13}H_{19}NO_5SNa]^+$ 324.0876; found 324.0868; elemental analysis (%) calcd for $C_{13}H_{19}NO_5S$: C 51.8, H 6.31, N 4.65; found: C 51.6, H 6.56, N 4.52.

4.2.2. (*S*)-1-Mesyloxy-*N*-(benzyloxycarbonyl)-3-amino-4-phenylbutane (12b). Prepared from alcohol **11b**. Colourless crystals; mp 93–95 °C; $[\alpha]_D^{20}$ −8.2 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, TMS): δ=7.37–7.13 (m, 10H; arom.), 5.06 (d_{AB}, 2H, J_{AB}=12.2 Hz, δ_{AB}=16.8 Hz; OCH_2Ph), 4.68 (d, 1H, *J*=7.5 Hz; N*H*), 4.29–4.21 (m, 2H; CH_2O), 4.08–3.99 (m, 1H; C*H*N), 2.92 (s, 3H; SO_2CH_3), 2.87–2.78 (m, 2H; CH_2Ph), 2.07–1.98 (m, 1H; C*H*H), 1.84–1.75 (m, 1H; CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C, TMS): δ=155.9, 137.0, 136.4, 129.3, 128.6, 128.5, 128.2, 128.0, 126.8, 67.1, 66.7, 49.3, 41.2, 37.2, 33.7; IR (KBr): ν=3345, 3033, 2957, 1687, 1533, 1453, 1348, 1261, 1161, 1070, 1022, 988, 829, 750, 697, 527 cm^{-1}; MS (ESI HR, MeOH): calcd for $[C_{19}H_{23}NO_5SNa]^+$ 400.1189; found 400.1203; elemental analysis (%) calcd for $C_{19}H_{23}NO_5S$: C 60.48, H 6.10, N 3.71; found: C 60.54, H 6.34, N 3.57.

4.2.3. (*S*)-1-Mesyloxy-*N*-(benzyloxycarbonyl)-3-amino-4-methylpentane (12c). Prepared from alcohol **11c**. Colourless wax; mp 45–46 °C; $[\alpha]_D^{20}$ −20.6 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, TMS): δ=7.38–7.29 (m, 5H; arom.), 5.09 (d_{AB}, 2H, J_{AB}=12.2 Hz, δ_{AB}=22.1 Hz; CH_2Ph), 4.61 (br d, 1H, *J*=9.8 Hz; N*H*), 4.31–4.20 (m, 2H; CH_2OH), 3.70–3.63 (m, 1H; C*H*N), 2.94 (s, 3H; SO_2CH_3), 2.04–1.96 (m, 1H; C*H*), 1.82–1.66 (m, 2H; CH_2), 0.93 (d, *J*=6.8 Hz; CH_3), 0.90 (d, *J*=6.8 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C, TMS): δ=156.4, 136.5, 128.6, 128.2, 128.1, 67.5, 66.8, 53.1, 38.4, 37.1, 32.3, 19.0, 17.6; IR (KBr): ν=3356, 3035, 2957, 2876, 1694, 1529, 1468, 1354, 1245, 1169, 1055, 974, 911, 811, 738, 697, 645, 526, 457 cm^{-1}; MS (ESI HR, MeOH): calcd for $[C_{15}H_{23}NO_5SNa]^+$ 352.1189; found 352.1195; elemental analysis (%) calcd for $C_{15}H_{23}NO_5S$: C 54.71, H 6.99, N 4.26; found: C 54.48, H 7.25, N 4.09.

4.3. General procedure for L-proline methyl ester alkylation

A solution of L-proline methyl ester (19.3 mmol, 2.50 g), freshly prepared from its hydrochloride, mesylate (19.3 mmol) and triethylamine (1.0 equiv, 2.7 mL) in acetonitrile (10 mL) was kept at room temperature overnight and then stirred at 50 °C until all the mesylate was consumed (TLC). Solvents were evaporated under reduced pressure and the dry residue was partitioned between ethyl acetate (0.20 L) and water (25 mL). Organic layer was additionally washed with water (25 mL), brine and dried over anhydrous sodium sulfate. Chromatographic purification of the crude mixture on silica gel in ethyl acetate–hexane (7/3) afforded pure Cbz-protected aminoester as colourless oil.

4.3.1. (2*S*,9*R*)-2,6-Cyclo-6-aza-9-(benzyloxycarbonylamino)decanoic acid methyl ester (13a). Prepared from mesylate **12a** in 75% yield; $[\alpha]_D^{20}$ −42.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.37–7.26 (m, 5H; C_6H_5), 5.87 (br s, 1H; N*H*), 5.09 (d_{AB}, 2H, J_{AB}=12.3 Hz, δ_{AB}=22.2 Hz; CH_2Ph), 3.90–3.77 (m, 1H; C*H*CH$_3$), 3.70 (s, 3H; OCH_3), 3.19–3.11 (m, 2H; C*H*CO$_2$, NC*H*H), 2.91–2.83 (m, 1H; NCH*H*), 2.46–2.39 (m, 1H; NC*H*H), 2.29–2.23 (m, 1H; NCH*H*), 2.15–2.05 (m, 1H; C*H*H), 1.95–1.69 (m, 4H; 2×CH_2), 1.57–1.49 (m, 1H; CH*H*), 1.17 (d, 3H, *J*=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 156.0, 137.1, 128.5, 127.8, 66.2, 66.1, 53.1, 51.8, 51.2, 46.2, 34.1, 29.3, 23.3, 20.3; IR ($CHCl_3$): ν=3439, 3321, 2955, 2817, 1714, 1512, 1454, 1344 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{18}H_{27}N_2O_4$ [M+H$^+$]: 335.1965; found: 335.1955.

4.3.2. (2*S*,9*R*)-2,6-Cyclo-6-aza-9-(benzyloxycarbonylamino)-10-fenylodecanoic acid methyl ester (13b). Prepared from mesylate **12b** in 64% yield; $[\alpha]_D^{20}$ −29.1 (*c* 0.80 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.36–7.15 (m, 10H; 2×C_6H_5), 6.01 (d, 1H, *J*=7.8 Hz; N*H*), 5.08 (d_{AB}, 2H, J_{AB}=12.7 Hz, δ_{AB}=21.0 Hz; OCH_2Ph), 3.98 (br s, 1H; C*H*CH_2Ph), 3.70 (s, 3H; OCH_3), 3.16–3.09 (m, 2H; C*H*CO_2, NC*H*H), 2.99–2.88 (m, 2H; C*H*HPh, NC*H*H), 2.79–2.72 (dd, 1H, J_1=7.8 Hz, J_2=13.4 Hz; C*H*HPh), 2.44–2.39 (m, 1H; NCH*H*), 2.24–2.18 (m, 1H; NCH*H*), 2.13–2.05 (m, 1H; C*H*H), 1.95–1.70 (m, 4H; CH_2, 2× C*H*H), 1.51–1.43 (m, 1H; CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 156.0, 138.4, 137.1, 129.4, 128.4, 128.3, 127.8, 128.7, 126.2, 66.2, 66.1, 53.2, 51.8, 51.7, 51.4, 40.3, 30.8, 29.4, 23.3; IR ($CHCl_3$): ν=3445, 3318, 2954, 2814, 1714, 1511, 1454, 1338 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{24}H_{30}N_2O_4Na$ [M+Na^+]: 433.2098; found: 433.2121.

4.3.3. (2*S*,9*S*)-2,6-Cyclo-6-aza-9-(benzyloxycarbonylamino)-10-metyloundecanoic acid methyl ester (13c). Prepared from mesylate **12c** in 71% yield; $[\alpha]_D^{20}$ −37.1 (*c* 0.85 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ= 7.36–7.28 (m, 5H; C_6H_5), 5.38 (d, 1H, *J*=9.3 Hz; N*H*), 5.09 (d_{AB}, 2H, J_{AB}=12.3 Hz, δ_{AB}=30.6 Hz; CH_2Ph), 3.70 (s, 3H; OCH_3), 3.52–3.44 (m, 1H; NHC*H*), 3.18–3.11 (m, 2H; C*H*CO, NC*H*H), 2.79 (dt, 1H, J_1=8.0 Hz, J_2=12.0 Hz; NC*H*H), 2.49–2.41 (m, 1H; NCH*H*), 2.32–2.23 (m, 1H; NCH*H*), 2.15–2.04 (m, 1H; C*H*H), 1.95–1.69 (m, 5H; CH_2, C*H*H, CH*H*, C*H*), 1.58–1.48 (m, 1H; CH*H*), 0.90 (d, 3H, *J*=7.9 Hz; CH_3), 0.88 (d, 3H, *J*=7.1 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 156.5, 137.0, 128.4, 127.9, 127.8, 66.3, 66.1, 55.7, 53.4, 52.0, 51.8, 31.6, 30.4, 29.4, 23.3, 19.1, 18.4; IR ($CHCl_3$): ν=3441, 3331, 2963, 2816, 1719, 1513, 1456 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{20}H_{31}N_2O_4$ [M+H^+]: 363.2278; found 363.2297; elemental analysis calcd (%): C 66.30, H 8.29, N 7.73; found: C 66.09, H 8.36, N 7.62.

4.4. General procedure for amide bond formation

A mixture of *N*-benzyloxycarbonyl aminoester (3.69 mmol) and water (50 mL) was emulsified by vigorous stirring while heated in reflux, until saponification was complete (TLC) and the reaction mixture turned into a clear solution. Water was evaporated under reduced pressure. Residual traces of water were removed as water–dichloromethane azeotrope by dissolving crude product in dichloromethane followed by evaporation at atmospheric pressure, repeated three times. Crude *N*-benzyloxycarbonyl amino acid was used without further purification. Amino acid (3.69 mmol) and triethylamine (4 equiv, 2.0 mL) were dissolved in dry dichloromethane (37 mL). The solution was cooled to −20 °C under argon and *iso*-butylchloroformate (1 equiv, 0.49 mL) was added dropwise. The reaction mixture was stirred for 1 h at −20 °C, and then at 0 °C for additional 1 h. A solution of aminoester hydrochloride (3.32 mmol), prepared parallel by hydrogenolysis of *N*-benzyloxycarbonyl aminoester (3.32 mmol) in methanolic solution of hydrogen chloride (3.5 mmol) over 5% Pd-C; was added in dry CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to warm up and was kept at room temperature overnight. Solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate (0.17 L), washed with water (2× 50 mL), brine (30 mL) and dried over anhydrous magnesium sulfate. Purification by column chromatography afforded pure amide as a colourless oil.

4.4.1. (2*S*,9*R*,12*S*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-19-(benzyloxycarbonylamino)-9-metylo-11-oksononadecanoic acid methyl ester (15a). Prepared from acid **14d** and amine **13a** in yield 93%; $[\alpha]_D^{20}$ −67.6 (*c* 0.80 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.57 (d, 1H, *J*= 8.7 Hz; N*H*), 7.37–7.28 (m, 5H; C_6H_5), 5.08 (br s, 2H; CH_2Ph), 4.92 (br s, 1H; N*H*), 4.13–4.03 (m, 1H; C*H*CH_3), 3.68 (s, 3H; OCH_3), 3.32–3.12 (m, 4H), 3.11 (dd, 1H, J_1= 6.0 Hz, J_2=8.8 Hz; C*H*CO), 2.95 (dd, 1H, J_1=5.3 Hz, J_2= 9.8 Hz; C*H*CO_2), 2.84 (dt, 1H, J_1=8.0 Hz, J_2=12.1 Hz), 2.67–2.55 (m, 1H), 2.47–2.32 (m, 2H), 2.30–2.21 (m, 2H), 2.20–2.04 (m, 2H), 1.93–1.53 (m, 10H), 1.13 (d, 3H, *J*= 6.6 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ= 174.7, 173.9, 156.4, 136.6, 128.5, 128.4, 128.0, 68.1, 66.5, 66.2, 53.9, 53.4, 53.2, 51.8, 51.5, 43.2, 39.2, 34.6, 30.6, 29.3, 29.2, 24.0, 23.1, 20.3; IR ($CHCl_3$): ν=3680, 3452, 3326, 2974, 2815, 1720, 1655, 1517, 1455 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{26}H_{41}N_4O_5$ [M+H^+]: 489.3071; found 489.3120.

4.4.2. (2*S*,9*R*,12*S*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-9-benzylo-19-(benzyloxycarbonylamino)-11-oksononadecanoic acid methyl ester (15b, 76%). Prepared from acid **14d** and amine **13b** in 76% yield; $[\alpha]_D^{20}$ −58.6 (*c* 0.84 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): 7.61 (d, 1H, *J*=8.8 Hz; CON*H*), 7.38–7.17 (m, 10H; 2×C_6H_5), 5.11 (d_{AB}, 2H, J_{AB}=12.1 Hz, δ_{AB}=18.4 Hz; OCH_2Ph), 5.03 (br s, 1H; CO_2N*H*), 4.38–4.30 (m, 1H; C*H*CH_2Ph), 3.72 (s, 3H; OCH_3), 3.24–3.05 (m, 5H; CH_2NH, 2×NC*H*H, C*H*CO), 2.95–2.85 (m, 4H; CH_2Ph, NC*H*H, C*H*CO_2), 2.52–2.43 (m, 1H; NC*H*H), 2.42–2.36 (m, 1H; NCH*H*), 2.34–2.21 (m, 3H; 3×NCH*H*), 2.20–2.07 (m, 2H; C*H*H), 1.96–1.50 (m, 10H; 4×CH_2, 2×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 174.1, 156.4, 138.4, 136.6, 129.2, 128.5, 128.3, 128.2, 128.0, 126.2, 68.1, 66.6, 66.2, 53.9, 53.5, 53.2, 51.8, 51.7, 48.1, 40.2, 39.2, 32.1, 30.6, 29.3, 29.1, 24.0, 23.1; IR ($CHCl_3$): ν=3452, 3321, 2954, 2816, 1719, 1656, 1515, 1456 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{32}H_{45}N_4O_5$ [M+H^+]: 565.3384; found 565.3412; elemental analysis calcd (%): C 68.08, H 7.80, N 9.93; found: C 67.82, H 8.02, N 9.66.

4.4.3. (2*S*,9*S*,12*S*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-19-(benzyloxycarbonylamino)-11-okso-9-(2′-propylo) nonadecanoic acid methyl ester (15c). Prepared from acid **14d** and amine **13c** in 88% yield; $[\alpha]_D^{20}$ −67.7 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.37–7.29 (m, 5H; C_6H_5), 5.12–5.05 (m, 3H; N*H*, CH_2Ph), 4.99 (br s, 1H; N*H*), 3.79–3.72 (m, 1H; NHC*H*), 3.70 (s, 3H; OCH_3), 3.31–3.14 (m, 4H; NHCH_2, 2×NC*H*H), 3.10 (dd, 1H, J_1= 5.8 Hz, J_2=8.8 Hz; C*H*CO), 3.01 (dd, 1H, J_1=5.1 Hz, J_2= 9.7 Hz; C*H*CO), 2.76–2.65 (m, 2H; 2×NC*H*H), 2.43–2.33 (m, 2H; 2×NCH*H*), 2.31–2.23 (m, 2H; 2×NCH*H*), 2.21–2.05 (m, 2H; 2×C*H*H), 1.96–1.65 (m, 10H; 2×CH*H*, 3× CH_2, C*H*H, C*H*), 1.59–1.50 (m, 1H; CH*H*), 0.87 (s, 3H; CH_3), 0.86 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.8, 174.1, 156.4, 136.6, 128.5, 128.1, 128.0, 68.4, 66.6, 66.2, 53.9, 53.7, 53.5, 52.3, 52.2, 51.8, 39.3,

31.7, 31.1, 30.6, 29.6, 29.4, 24.1, 23.2, 19.2, 18.4; IR ($CHCl_3$): ν=3454, 3330, 2963, 2816, 1722, 1657, 1516, 1456 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{28}H_{45}N_4O_5$ [M+H$^+$] 517.3384; found: 517.3406.

4.4.4. (2*S*,9*R*,12*S*,19*R*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-19-(benzyloxycarbonylamino)-9-metylo-11-okso-icosanoic acid methyl ester (15d). Prepared from acid **14a** and amine **13a** in 87% yield; $[\alpha]_D^{20}$ −64.9 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.64 (d, 1H, *J*=8.1 Hz; N*H*), 7.37–7.29 (m, 5H; C_6H_5), 5.07 (br s, 2H; CH_2Ph), 4.92 (br s, 1H; N*H*), 4.11–4.04 (m, 1H; C*H*CH_3), 3.76–3.65 (m, 4H; C*H*CH_3, OCH_3), 3.21–3.16 (m, 1H), 3.13–3.07 (m, 2H), 2.99–2.92 (m, 1H), 2.89–2.81 (m, 1H), 2.64–2.54 (m, 1H), 2.53–2.46 (m, 1H), 2.38–2.22 (m, 3H), 2.20–2.06 (m, 2H), 1.92–1.54 (m, 10H), 1.16 (d, 3H, *J*=6.5 Hz; CH_3), 1.12 (d, 3H, *J*=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.6, 174.2, 155.8, 136.6, 128.5, 128.0, 67.7, 66.4, 66.3, 54.4, 53.4, 52.9, 51.8, 51.5, 45.7, 43.2, 36.2, 34.4, 30.8, 29.4, 24.1, 23.0, 21.5, 20.1; IR ($CHCl_3$): ν=3439, 3323, 2974, 2815, 1718, 1655, 1514, 1455 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{27}H_{43}N_4O_5$ [M+H$^+$] 503.3228; found: 503.3236; elemental analysis calcd (%): C 64.54, H 8.37, N 11.16; found: C 64.24, H 8.48, N 11.17.

4.4.5. (2*S*,9*R*,12*S*,19*R*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-9-benzylo-19-benzyloxycarbonyl-amino)-20-phenylo-11-oksoicosanoic acid methyl ester (15e). Prepared form acid **14b** and amine **13b** in 75% yield; $[\alpha]_D^{20}$ −49.1 (*c* 0.85 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): 7.64 (d, 1H, *J*=9.7 Hz; CON*H*), 7.35–7.11 (m, 15H; 3×C_6H_5), 5.04 (d_{AB}, 2H, J_{AB}=12.3 Hz, δ_{AB}=30.5 Hz; OCH_2Ph), 4.84 (d, 1H, *J*=8.4 Hz; CO_2N*H*), 4.28–4.21 (m, 1H; C*H*CH_2Ph), 3.88–3.81 (m, 1H; C*H*CH_2Ph), 3.66 (s, 3H; OCH_3), 3.17–3.11 (m, 1H; NC*H*H), 3.06 (dd, 1H, J_1=6.1 Hz, J_2=8.5 Hz; C*H*CO_2), 3.02–2.97 (m, 1H; NC*H*H), 2.92 (dd, 1H, J_1=4.2 Hz, J_2=9.7 Hz; C*H*CO), 2.86–2.70 (m, 5H; 2×CH_2Ph, NC*H*H), 2.57–2.48 (m, 1H; NC*H*H), 2.47–2.40 (m, 1H; NCH*H*), 2.37–2.31 (m, 1H; NCH*H*), 2.34–2.17 (m, 2H; 2×NCH*H*), 2.14–2.03 (m, 2H; 2×C*H*H), 1.91–1.47 (m, 10H; 4×CH_2, 2×C*H*H); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 174.3, 155.9, 138.5, 137.7, 136.6, 129.4, 129.2, 128.5, 128.4, 128.3, 128.1, 128.0, 126.5, 126.3, 67.6, 66.5, 66.3, 54.3, 53.5, 52.9, 51.8, 51.7, 50.9, 48.5, 41.6, 40.4, 33.2, 31.6, 30.8, 29.4, 24.2, 23.1; IR ($CHCl_3$): ν=3434, 3322, 2956, 2816, 1736, 1720, 1656, 1512, 1456, 1404, 1347 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{39}H_{51}N_4O_5$ [M+H$^+$] 655.3854; found: 655.3860.

4.4.6. (2*S*,9*S*,12*S*,19*S*)-2,6-Cyclo-12,16-cyclo–6,10,16-triaza-19-(benzyloxycarbonylamino)-20-metylo-11-okso-9-(2′-propylo)henicosanoic acid methyl ester (15f). Prepared from acid **14c** and amine **13c** in 93% yield; mp 64–66 °C; $[\alpha]_D^{20}$ −69.3 (*c* 0.70 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.41 (d, 1H, *J*=10.1 Hz; N*H*), 7.37–7.29 (m, 5H; C_6H_5), 5.08 (br s, 2H; CH_2Ph), 4.68 (d, 1H, *J*=9.7 Hz; N*H*), 3.77–3.71 (m, 1H; NHC*H*), 3.70 (s, 3H; OCH_3), 3.52–3.46 (m, 1H; NHC*H*), 3.20–3.15 (m, 1H; NC*H*H), 3.15–3.09 (m, 2H; NC*H*H, C*H*CO), 3.04 (dd, 1H, J_1=4.5 Hz, J_2=10.1 Hz; C*H*CO), 2.74–2.67 (m, 1H; NC*H*H), 2.65 (dt, 1H, J_1=5.6 Hz, J_2=11.5 Hz; NC*H*H), 2.52 (dt, 1H, J_1=4.4 Hz, J_2=11.5 Hz; NCH*H*), 2.41–2.33 (m, 1H; NCH*H*), 2.33–2.26 (m, 2H; 2×NCH*H*), 2.19–2.05 (m, 2H; 2×C*H*H), 1.94–1.51 (m, 12H; 2×CH*H*, 4×CH_2, 2×C*H*), 0.91–0.85 (m, 12H, 4×CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.8, 174.4, 156.3, 136.6, 128.5, 128.1, 128.0, 67.8, 66.6, 66.2, 54.9, 54.4, 53.9, 53.5, 52.4, 52.2, 51.8, 32.2, 32.1, 31.9, 31.2, 30.8, 29.5, 24.3, 23.2, 19.2, 18.9, 18.3, 17.6; IR (KBr): ν=3276, 2960, 2811, 1741, 1724, 1636, 1523, 1455 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{31}H_{51}N_4O_5$ [M+H$^+$] 559.3854; found: 559.3858; elemental analysis calcd (%): C 66.55, H 8.96, N 10.04; found: C 66.56, H 9.05, N 9.98.

4.5. Macrocyclization procedures

N-Cbz-protected aminoesters **15a–f** were subjected to catalytic hydrogenation (H_2 over Pd-C in methanol) prior to cyclization reactions. The aminoester (1.90 mmol), obtained from **15a–f**, was dissolved in 0.5 M NaOH solution in methanol (0.20 L), and allowed to stand at room temperature for 1 day. The reaction mixture was neutralized with aq HCl and evaporated to dryness. The solid residue was dissolved in water (20 mL) and extracted with $CHCl_3$ (4×20 mL). The combined chloroform extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatographic (CH_2Cl_2/methanol=19:1) followed by a recrystallization. Details of other macrocyclization procedures were described in our previous work.[13b]

4.5.1. (4*R*,7*S*,17*S*)-1,5,11,15-Tetraaza-4-methyltricyclo[15.3.0.0.^{7,11}]icosan-6,16-dion (2a) Recrystallization from CH_2Cl_2/hexane yielded **2a** as colourless crystals; mp 140–141 °C; $[\alpha]_D^{20}$ −53.4 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.45 (br s, 1H; N*H*), 8.36 (br s, 1H; N*H*), 4.09–4.01 (m, 1H; C*H*CH_3), 3.74–3.67 (m, 1H), 3.31–3.24 (m, 2H), 3.14–3.03 (m, 2H), 3.00 (dd, 1H, J_1=9.8 Hz, J_2=5.4 Hz; C*H*CO), 2.91 (dd, 1H, J_1=9.3 Hz, J_2=5.8 Hz; C*H*CO), 2.86–2.80 (m, 1H), 2.55 (dt, 1H, J_1=12.4 Hz, J_2=3.5 Hz), (ddd, 1H, J_1=12.8 Hz, J_2=5.0 Hz, J_3=2.3 Hz), 2.28–2.17 (m, 4H), 1.93–1.71 (m, 9H), 1.58 (ddt, 1H, J_1=15.2 Hz, J_2=5.0 Hz, J_3=1.6 Hz), 1.20 (d, 3H, *J*=6.6 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.8, 173.9, 70.5, 70.0, 56.3, 53.6, 53.4, 52.0, 44.9, 40.4, 31.2, 30.6, 30.5, 25.2, 24.2, 23.8, 19.2; IR ($CHCl_3$): ν=3678, 3325, 2822, 1654, 1530, 1471 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{17}H_{30}N_4O_2Na$ [M+Na$^+$] 345.2261; found: 345.2283.

4.5.2. (4*R*,7*S*,17*S*)-1,5,11,15-Tetraaza-4-benzylotricyclo[15.3.0.0.^{7,11}]icosan-6,16-dion (2b) Recrystallization from CH_2Cl_2/ether yielded **2b** as colourless crystals; mp 184–188 °C; $[\alpha]_D^{20}$ −71.5 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.13 (br s, 1H; N*H*), 8.08 (br s, 1H; N*H*), 7.30–7.18 (m, 5H; C_6H_5), 4.01–3.93 (m, 1H; NHC*H*), 3.55–3.47 (m, 1H; NHC*H*H), 3.26–3.16 (m, 4H; NHCH*H*, 2×NC*H*H, C*H*HPh), 3.07–2.97 (m, 2H; C*H*CO, NC*H*H), 2.91 (dd, 1H, J_1=6.3 Hz, J_2=9.6 Hz; C*H*CO), 2.82 (dt, 1H, J_1=2.5 Hz, J_2=12.3 Hz; NC*H*H), 2.67 (dd, 1H, J_1=8.6 Hz, J_2=13.3 Hz; CH*H*Ph), 2.46 (dt, 1H, J_1=3.2 Hz, J_2=12.5 Hz; NCH*H*), 2.40–2.34 (m, 1H; NCH*H*), 2.26–2.15 (m, 4H; 2×NCH*H*, 2×CHC*H*H), 1.89–1.63 (m, 10H; 2×CHCH*H*, 4×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$,

30 °C): δ=174.7, 174.1, 138.8, 129.3, 128.4, 126.3, 70.2, 69.6, 54.9, 53.4, 53.1, 52.2, 51.3, 39.2, 39.0, 30.5, 30.4, 28.0, 25.3, 24.1, 23.8; IR ($CHCl_3$): ν=3323, 2821, 1658, 1528, 1443 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{23}H_{35}N_4O_2$ [M+H$^+$] 399.2755; found: 399.2764; elemental analysis calcd (%) C 69.35, H 8.54, N: 14.07; found: C 69.33, H 8.51, N 13.87.

4.5.3. (4*R*,7*S*,17*S*)-1,5,11,15-Tetraaza-4-(2′-propylo)tricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2c) Recrystallization from CH_2Cl_2/hexane yielded **2c** as colourless crystals; mp 185–187 °C; $[\alpha]_D^{20}$ −76.4 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.13 (br s, 1H; N*H*), 8.94 (br s, 1H; N*H*), 3.59–3.48 (m, 2H; NHC*H*H, NHC*H*), 3.31–3.16 (m, 3H; NHCH*H*, 2×NC*H*H), 3.03 (dd, 1H, J_1=4.6 Hz, J_2=10.2 Hz; C*H*CO), 2.97–2.84 (m, 3H; 2×NC*H*H, C*H*CO), 2.53–2.42 (m, 2H; 2×NCH*H*), 2.29–2.15 (m, 4H; 2×NCH*H*, 2×CHC*H*H), 2.06–1.98 (m, 1H; $(CH_3)_2$C*H*), 1.91–1.69 (m, 10H; 2×CHCH*H*, 4×CH_2), 0.93 (d, 3H, J=6.8 Hz; CH_3), 0.88 (d, 3H, J=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=175.3, 173.4, 70.2, 69.3, 55.2, 55.0, 54.0, 53.2, 52.9, 39.5, 30.8, 30.7, 30.3, 27.1, 25.3, 24.5, 23.7, 20.1, 19.2; IR (KBr): ν=3364, 3304, 2961, 2813, 2772, 1673, 1648, 1539, 1513, 1435 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{19}H_{35}N_4O_2$ [M+H$^+$] 351.2755; found: 351.2781; elemental analysis calcd (%): C 65.14, H 9.71, N 16.00; found: C 64.90, H 9.87, N 15.83.

4.5.4. (4*R*,7*S*,14*R*,17*S*)-1,5,11,15-Tetraaza-4,14-dimethyltricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2d) Recrystallization from CH_2Cl_2/ether/hexane yielded **2d** as colourless crystals; mp decomposition at 222 °C; $[\alpha]_D^{20}$ −83.8 (*c* 0.25 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.72 (br s, 2H; 2×N*H*), 4.16–4.08 (m, 2H; 2×C*H*CH_3), 3.32–3.27 (m, 2H), 3.11 (dt, 2H, J_1=12.6 Hz, J_2=1.3 Hz), 2.96 (dd, 2H, J_1=5.8 Hz, J_2=9.6 Hz), 2.41 (ddd, 2H, J_1=12.8 Hz, J_2=5.2 Hz, J_3=1.9 Hz), 2.29–2.18 (m, 4H), 1.99–1.69 (m, 8H), 1.51–1.45 (m, 2H), 1.22 (d, 6H, J=6.6 Hz; 2×CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.0, 70.5, 53.6, 51.9, 44.9, 31.0, 30.8, 24.0, 19.3; IR (KBr): ν=3437, 3298, 2962, 2771, 1647, 1545, 1444 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{18}H_{33}N_4O_2$ [M+H$^+$] 337.2598; found: 337.2608.

4.5.5. (4*R*,7*S*,14*R*,17*S*)-1,5,11,15-Tetraaza-4,14-dibenzylotricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2e) $[\alpha]_D^{20}$ −35.3 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ= 8.52 (br s, 2H; 2×N*H*), 4.30–4.18 (m, 10H; 2×C_6H_5), 4.01 (br s, 2H; 2×NHC*H*), 3.35 (dd, 2H, J_1=5.5 Hz, J_2= 13.2 Hz; 2×C*H*HPh), 3.21 (t, 2H, J=7.7 Hz; 2×NC*H*H), 3.16–3.07 (m, 2H; 2×NC*H*H), 2.98 (dd, 2H, J_1=6.0 Hz, J_2=9.5 Hz, 2×C*H*CO), 2.68 (dd, 2H, J_1=9.7 Hz, J_2= 13.2 Hz; 2×CH*H*Ph), 2.37 (dt, 2H, J_1=3.3 Hz, J_2= 12.7 Hz; 2×NCH*H*), 2.29–2.21 (m, 2H; 2×CHC*H*H), 2.21–2.14 (m, 2H; 2×NCH*H*), 1.90–1.76 (m, 4H; 2× CHCH*H*, 2×C*H*H), 1.76–1.66 (m, 6H; 2×CH*H*, 2×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.3, 138.8, 129.3, 128.5, 126.3, 70.3, 53.2, 51.9, 51.4, 39.0, 30.6, 27.1, 23.9; IR ($CHCl_3$): ν=3288, 3066, 1674, 1541, 1455 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{30}H_{41}N_4O_2$ [M+H$^+$]: 489.3224; found: 489.3231.

4.5.6. (4*S*,7*S*,14*S*,17*S*)-1,5,11,15-Tetraaza-4,14-bis-(2′-propylo)tricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2f) ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.08 (br s, 2H; 2× N*H*), 3.44–3.29 (m, 2H; 2×C*H*CO), 3.23–3.18 (m, 2H; 2× NC*H*H), 3.05–2.93 (m, 4H; 2×NHC*H*, 2×NC*H*H), 2.45–2.36 (m, 2H; 2×NCH*H*), 2.26–2.16 (m, 4H; 2×NCH*H*, 2×CHC*H*H), 2.10–1.96 (m, 4H; 2×C*H*H, 2×$(CH_3)_2$C*H*), 1.90–1.61 (m, 8H; 2×CHCH*H*, 2×CH*H*, 2×CH_2), 0.96 (d, 6H, J=6.7 Hz; 2×CH_3), 0.91 (d, 6H, J=6.7 Hz; 2× CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=173.9, 69.8, 55.3, 53.3, 52.4, 31.0, 30.5, 27.6, 24.1, 20.6, 19.9; MS (HR ESI, MeOH): *m/z* calcd for $C_{22}H_{40}N_4O_2Na$ [M+Na$^+$]: 415.3043; found: 415.3050.

4.6. Preparation of complexes

Equimolar amount of diamide **2a–d** or **1b** and $Ni(OAc)_2$ or $Cu(OAc)_2$ were dissolved in methanol. The formed bright green solution is stirred at boiling temperature for about 5 min. During the heating colour of solution is changing from green to dark red or violet and acetic acid is evaporating. Solvents were evaporated and prepared complexes were crystallized from methanol/ether.

4.6.1. Complex Ni·1b. Mp 247 °C; $[\alpha]_D^{20}$ −294 (*c* 0.047 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=4.79–4.73 (m, 2H; 2×NC*H*H), 3.30–3.23 (m, 4H; 2×NCH*H*, 2× C*H*CO), 2.99 (dt, 2H, J_1=14.1 Hz, J_2=4.0 Hz; 2× NC*H*H), 2.78–2.70 (m, 2H; 2×NC*H*H), 2.28–2.21 (m, 2H; 2×NCH*H*), 2.19–2.21 (m, 2H; 2×NCH*H*), 2.07–1.95 (m, 4H; 2×CHCH_2), 1.93–1.82 (m, 4H; 2×CH_2), 1.64–1.57 (m, 2H; 2×C*H*H), 1.49–1.39 (m, 2H; 2×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=178.6, 74.4, 57.3, 55.7, 40.4, 26.5, 24.8, 21.2; IR (KBr): ν=3442, 3382, 2937, 2848, 1573, 1420 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$=570 (80), 480 (180), 210 (15,200), 240 nm (15,600 L cm^{-1} mol^{-1}); MS (HR LSIMS): *m/z* calcd for $C_{16}H_{27}N_4O_2Ni$ [M+H$^+$]: 364.1409; found: 364.1383.

4.6.2. Complex Cu·1b. Mp 215–217 °C; $[\alpha]_D^{20}$ +920 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3452, 2929, 2854, 1576, 1448, 1407 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$=493 (530), 269 (8400), 213 (32,000 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd for $C_{16}H_{26}N_4O_2CuNa$ [M+Na$^+$]: 392.1244; found 392.1236.

4.6.3. Complex Cu·2a. Mp 228–230 °C; $[\alpha]_D^{20}$ +308 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3432, 2962, 2887, 1576, 1444, 1405, 1333, 1300 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$= 497 (300), 270 (3600), 215 (15,000 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd for $C_{17}H_{28}N_4O_2NaCu$ [M+ Na$^+$]: 406.1400; found 406.1428.

4.6.4. Complex Cu·2b. Mp 90 °C; $[\alpha]_D^{20}$ +838 (*c* 0.14 in $CHCl_3$); IR ($CHCl_3$): ν=3667, 3363, 2979, 2858, 1582, 1453, 1404 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$=493 (300), 268 (3800), 212 (20,000 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd for $C_{23}H_{33}N_4O_2Cu$ [M+H$^+$]: 460.1894; found: 460.1894.

4.6.5. Complex Cu·2c. Mp 198–200 °C; $[\alpha]_D^{20}$ +480 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3482, 3393, 2953, 2860, 1586, 1571, 1450, 1397 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$= 504 (350), 301 (3800), 270 (4200), 214 nm (18,500 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd

for: $C_{19}H_{32}N_4O_2NaCu$ $[M+Na^+]$ 434.1713; found: 434.1735.

4.6.6. Complex Cu·2d. Mp decomposition at 260 °C; $[\alpha]_D^{20}$ +590 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3453, 2960, 2926, 2861, 1578, 1439, 1401 cm^{-1}; UV/vis (EtOH): λ_{max}=500, 272, 215 nm; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{18}H_{31}N_4O_2Cu$ $[M+H^+]$: 398.1738; found: 398.1756.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.049. Supplementary data available: synthesis of compounds **6** to **11**, and crystallographic details.

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