NJC

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c5nj01927c

C-Functionalized chiral dioxocyclam and cyclam derivatives with 1,2,3-triazole units: synthesis, complexation properties and crystal structures of copper(II) complexes†

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Received (in Montpellier, France) 22nd July 2015,
Accepted 24th November 2015

DOI: 10.1039/c5nj01927c

www.rsc.org/njc

New *C*-functionalized *syn*- and *anti*-dioxocyclam and cyclam derivatives with 1,2,3-triazole units attached to carbon atoms within the skeleton were designed as valuable bifunctional chelating agents for applications in nuclear medicine. These macrocyclic chelators were prepared *via* a multi-step sequence involving α- and β-amino acids, and their copper(II) complexation properties were evaluated. A solution structure in which the triazoles are in axially coordinating positions was proposed for the [Cu(*anti*-**27**)]$^{2+}$ complex. Promising results have been obtained regarding the complexation kinetics (<10 s) and the pseudo-first order half-life for acid-assisted dissociation ($t_{1/2}$ = 3.21 d, 5 M HCl, 50 °C).

Introduction

Since the discovery of Cu-catalyzed azide–alkyne cycloaddition (AAC), allowing the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles, the latter have become a powerful tool in the chemical ligation of two molecules and have found multiple applications. Besides their use as stable linkers, the metal complexation capacity of 1,2,3-triazoles has also been explored by many research groups.[1–4] Indeed, both N2 and N3 nitrogen and C5 carbon atoms are capable of coordinating to metal ions. "Regular" triazoles, in which the N3 nitrogen atom is involved in coordination, are the most commonly investigated. Nevertheless, "inverse" ligands, in which the less-electron rich N2 nitrogen atom is involved in metal binding, have also been studied. 1,4-disubstituted 1,2,3-triazole moieties in the "regular" or "inverse" form can be simply obtained by permutation of the azide and alkyne building blocks.[2–4] We have previously reported various diaza-crown ethers (cyclic ligands) and alkyl diamines (acyclic ligands) armed with 1,2,3-triazole units which coordinate to transition metal ions (Cu^{2+}, Ni^{2+}, Zn^{2+}) *via* the N3 nitrogen atoms.[5]

Moreover, tetraazamacrocycles, such as cyclam, cyclen and their derivatives, display excellent coordination properties toward certain metal ions.[6] Due to their strong metal sequestration capacities, *N*-polysubstituted cyclen and cyclam derivatives (*e.g.* DOTA, TETA and CB-TE2A) are the most widely used molecular systems in various domains, notably waste water treatment,[7] catalysis,[8] and many medical applications such as molecular imaging (PET and SPECT).[9–14] The latter applications require systems which contain two different kinds of functional groups, allowing fixation of the radiometal and connection to a biomolecule *via* a coupling functional group, and thus these systems are commonly called bifunctional chelators (BFCs).[9–14] DOTA and NOTA are the most routinely used BFCs, despite the fact that they have not been optimized for biomedical applications. Indeed, BFCs should have excellent coordination properties, *i.e.* selectivity towards endogenous cations to avoid transmetallation and high thermodynamic, kinetic, and electrochemical stability to prevent transchelation in biological media.[9–14] The development of optimal BFCs is thus of considerable interest, and one emerging approach is the anchoring of the coupling functional group onto a carbon atom within the carbon skeleton. These *C*-monofunctionalized systems can be obtained by two principal routes, namely by the cyclization of linear tetraamines with various electrophiles[15] or by the bisaminal template approach.[16]

In connection with our research on systems containing 1,2,3-triazole units as metal-complexing agents,[5] we designed a new macrocyclic ligand family based on chiral *C*-functionalized cyclams engineered with two triazole heterocycles (Fig. 1). The triazole units on the carbon atoms within the skeleton could act as coordinating pendant arms and also as coupling functional groups. The four free $N_{secondary}$ macrocyclic amines in these systems could thus be more readily available for metal coordination. Indeed, the properties and structures of macrocyclic ligand

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† Electronic supplementary information (ESI) available: Crystallographic data for [Cu(*anti*-**23**)] and [Cu(*syn*-**25**)], UV-vis and CD spectra, and ESI-MS for copper(II) complexes. Characterization of enantiomers **1b–6b**. NMR spectra for all compounds. CCDC 1414285 and 1435292. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5nj01927c

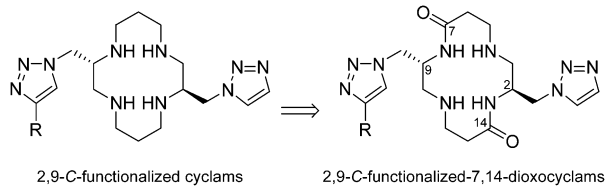


Fig. 1 Planned chiral macrocyclic structures.

complexes critically depend on, among other factors, the type and the intrinsic basicity of the donor atoms. The weakness of metal–$N_{tertiary}$ amine bonds relative to metal–$N_{secondary}$ amine bonds in *N*- or *C*-methylated cyclams has been reported and proven by the acid/base and metal complexation properties.[17] A few reports have already described tetraazamacrocycles, such as cyclen, cyclam and derivatives, in which the macrocyclic nitrogen atoms have been substituted with 1,2,3-triazole units. These *N*-functionalized ligands were developed for ion-sensing,[18–21] and molecular imaging, for example.[22,23]

The most appropriate pathway for our purposes appeared to be the use of chiral amino acids as building blocks. A few reports have described *C*-substituted cyclam derivatives which were synthesized starting from L-phenylalanine, L-valine, L-leucine[24] and L-proline,[25] and acted as catalysts for alkene oxidation. To the best of our knowledge, no reports have mentioned cyclams bearing *C*-appended triazoles.

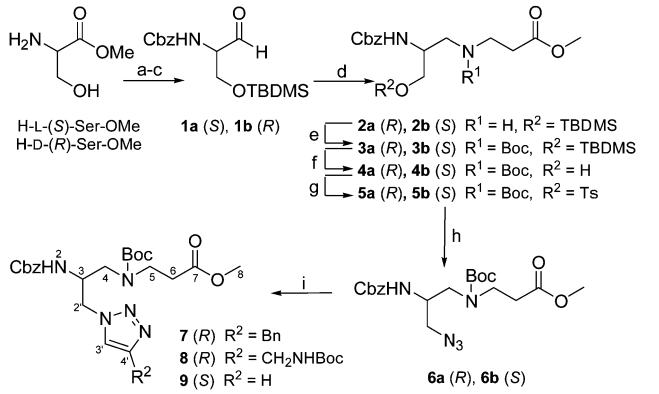
In this work, we developed the synthesis of 2,9-*C*-functionalized-7,14-dioxocyclams based in part upon the macrocyclization of linear precursors obtained from D- and L-serine and β-alanine building blocks. The carbonyl group reduction led to the 2,9-*C*-functionalized cyclams (Fig. 1). These macrocycles were engineered with two 1,2,3-triazole units linked in an ''inverse'' way. One of the triazole heterocycles was substituted on position 4 with a benzyl group, providing a model ligand useful for physico-chemical studies (Fig. 1, R = Bn). Furthermore, an aminomethyl group which could be used for linkage with a biomolecule was also introduced (Fig. 1, R = CH_2–NH_2). Metal ion complexation studies were performed in the presence of copper(II), which is one of the most promising radiometals for PET imaging.[9–14]

Results and discussion

Synthesis

The linear precursors required for macrocyclization were prepared by a multi-step synthesis involving reductive amination and peptidic coupling between D- and L-serine and β-alanine. Both D- and L-serine were used to ensure that the two pendant arms would be oriented in an *anti*-arrangement, which would improve the complexation properties.

Two parallel syntheses were performed using D- and L-serine, for which two protecting groups were required (Scheme 1). After the preliminary experiments, we found that a benzyloxycarbonyl protecting group for the α-*N* atom and a *tert*-butyldimethylsilyl protecting group for the hydroxymethyl side chain seemed appropriate for our purposes. The aldehydes **1a** (L-isomer) and **1b** (D-isomer), prepared by reduction of the corresponding ester



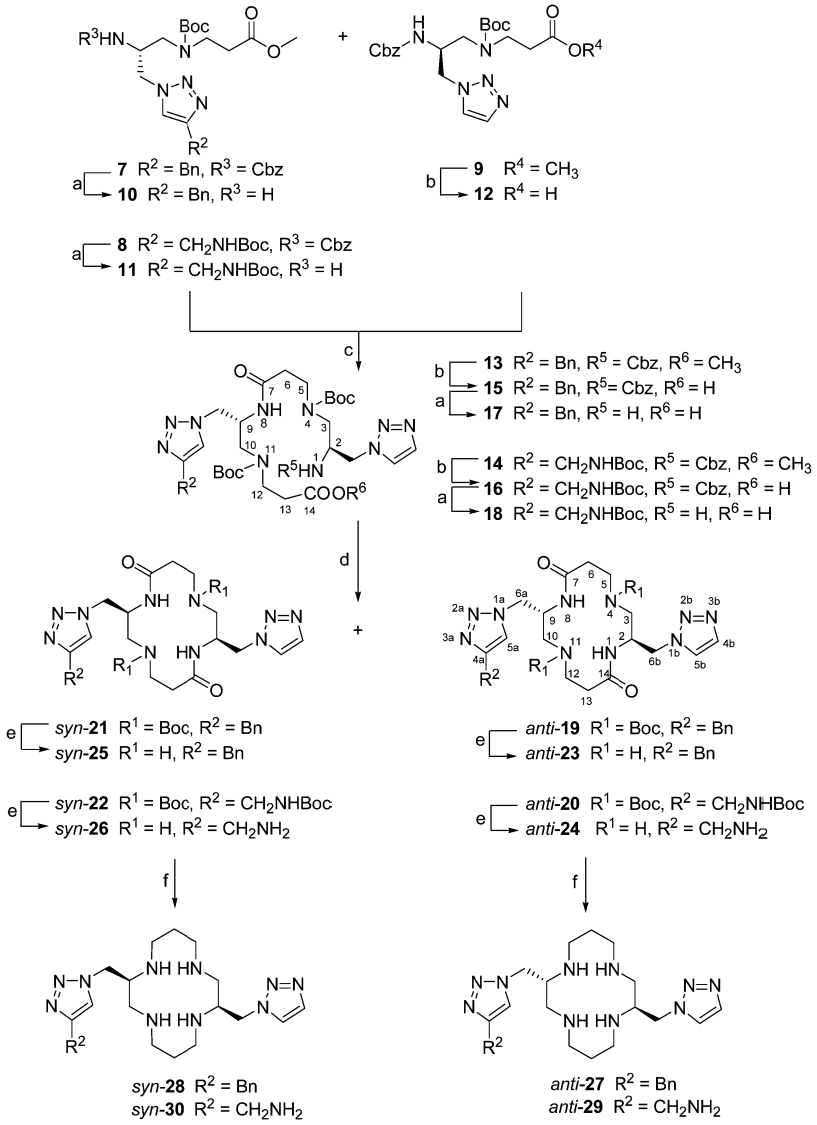
Scheme 1 Preparation of precursors for macrocyclization: *reagents and conditions*: (a) CbzCl, sat. aq. $NaHCO_3$; (b) TBDMSCl, pyridine, DMF; (c) DibalH (1.2 M in toluene), toluene, −78 °C, **1a**: 47%, **1b**: 51% (yields over 3 steps); (d) (1) HCl·H-βAla-OMe, DIEA, MeOH, 4 °C, (2) $NaBH_3CN$, AcOH, MeOH, **2a**: 67%, **2b**: 61%; (e) Boc_2O, TEA, CH_2Cl_2, **3a**: 91%, **3b**: 98%; (f) TBAF (1 M in THF), THF, **4a**: 85%, **4b**: 81%; (g) TsCl, TEA, DMAP (cat.), CH_2Cl_2, **5a**: 84%, **5b**: 91%; (h) NaN_3, DMF, 85 °C, **6a**: 96%, **6b**: 94%; (i) (1) trimethylsilylacetylene, $CuSO_4$, sodium ascorbate, H_2O/*t*BuOH (1/1.5), (2) TBAF (1 M in THF), THF, **9**: 72% (yield over 2 steps); (i) 3-phenylpropyne or *N*-*tert*-butyloxycarbonylpropargylamine, $CuSO_4$, sodium ascorbate, H_2O/*t*BuOH (1/1.5), **7**: 87%, **8**: 78%.

with DibalH in toluene at −78 °C, were obtained in 49 and 51% yields, respectively, over three steps. With the aldehydes **1a** and **1b** in hand, we turned our attention to the reductive amination step. The formation of the imine intermediate was carried out using a β-alanine methyl ester. Reduced dipeptides **2a** and **2b** were obtained in 67 and 61% yields, respectively, and were then treated with Boc_2O in CH_2Cl_2 in order to protect the secondary amine with a *tert*-butyloxycarbonyl group and facilitate further chemical manipulation. According to the Cahn–Ingold–Prelog priority rules, the C3 absolute configurations of the reduced dipeptides **2a** and **2b** were *R* and *S*, respectively. The *tert*-butyldimethylsilyl protecting group was removed by treatment with TBAF in THF. The reaction of alcohols **4a** and **4b** with tosyl chloride in dichloromethane gave the corresponding tosylates **5a** and **5b** in good yields. Substitution of the tosyl group with sodium azide was carried out in hot DMF and led to azido derivatives **6a** and **6b** in excellent yields. The synthesis of the 1,4-substituted-1,2,3-triazole moiety was next achieved by a standard click chemistry protocol involving the generation of Cu(I) from Cu(II) sulfate and sodium ascorbate in a 1/1.5 H_2O/*t*BuOH mixture.[2,26] Cycloaddition reactions were then performed with three alkyne partners, *i.e.* trimethylsilylacetylene, 3-phenylprop-1-yne and *N*-*tert*-butyloxycarbonylpropargylamine. Derivatives **7** and **8** were obtained in good yields by cycloaddition reactions between azide **6a** and 3-phenylprop-1-yne and *N*-*tert*-butyloxycarbonylpropargylamine, respectively. The 1,3-dipolar cycloaddition between trimethylsilylacetylene and **6b** led to a mixture of TMS-protected and non-protected products. Without purification, the crude mixture was treated with TBAF in THF to ensure complete removal of the trimethylsilyl group, which afforded compound **9** in 72% yield over two steps.

The next step consisted of a coupling reaction involving compound **9** and building blocks **7** and **8** bearing 4-substituted

triazoles (Scheme 2). Removal of the benzyloxycarbonyl group in **7** and **8** was achieved by catalytic hydrogenation with palladium on charcoal (Pd/C 10%) in EtOH and led to **10** and **11**, respectively, in quantitative yields. The acid **12** was obtained through saponification of the corresponding ester **9** by treatment with potassium carbonate in a 10/1 $MeOH/H_2O$ mixture. Coupling of amines **10** and **11** with the carboxylic acid **12** in the presence of HBTU in THF afforded the compounds **13** and **14** in excellent yields (80 and 85%, respectively). Another set of C- and N-terminus deprotections led to the free amino acids **17** and **18**, which could undergo macrocyclization through treatment with HATU in a 5/1 CH_2Cl_2/DMF mixture under high dilution conditions (5 mM). The corresponding cyclic structures *anti*-**19** and *anti*-**20** were obtained in 20 and 46% yields, respectively. No traces of dimerization product were detected, but two other compounds, *syn*-**21** and *syn*-**22** were formed in 27 and 23% yields, respectively. Careful analysis of the analytical data (NMR, MS and optical rotation) led us to the conclusion that *syn*-**21** and *syn*-**22** were stereoisomers resulting from C9-epimerization during the cyclization (see Scheme 2 for atom numbering). Epimerization was confirmed by the crystal structure of the [Cu(*syn*-**25**)] complex obtained by X-ray diffraction (see Fig. S1 and Table S1, ESI†). It was clearly established that this epimerization took place during the cyclization process. Indeed, compound **19** did not undergo C9-epimerization in the presence of cyclization reagents.

Amine and acid deprotections performed on **13** gave the corresponding amino acid **17** as a pure (2*S*,9*R*)-isomer, as shown by the LC/MS spectrum. Furthermore, the protected linear compound **13** did not form its C9-isomer when it was



Scheme 2 Route to targeted macrocycles: *reagents and conditions*: (a) H_2, Pd/C (10%), EtOH, quantitative yields; (b) K_2CO_3, $MeOH/H_2O$ (10/1), quantitative yields; (c) HBTU, TEA, THF, rt, 18 h, **13**: 80%, **14**: 85%; (d) HATU, DIEA, CH_2Cl_2/DMF (5/1), rt, 60 h, *anti*-**19**: 20%, *syn*-**21**: 27%, *anti*-**20**: 46%, *syn*-**22**: 23%; (e) TFA/DCM (1/9), quantitative yields; (f) (i) B_2H_6, THF, 0 °C to reflux, 18 h, (ii) 1 M HCl, reflux, 4 h, *anti*-**27**: 47%, *syn*-**28**: 67%, *anti*-**29**: 45%, *syn*-**30**: 48%.

placed under cyclization conditions (HATU, DIEA, DCM/DMF). Because the epimerizable centre is not contiguous to the activated carbonyl group, the observed epimerization cannot be rationalized by the classical oxazolone formation which could have occurred during acid activation. Thus the epimerization process is believed to occur through H9 abstraction by the triazole group itself, as observed for histidine derivatives with a methylene-imidazole side chain.[27] Two compounds, *anti*-**19** and *anti*-**20**, were thus obtained and had an *anti*-arrangement of the two triazole moieties. Two others, *syn*-**21** and *syn*-**22**, are C9-diastereoisomers of compounds *anti*-**19** and *anti*-**20**, respectively, and could be valuable intermediates in the synthesis of cross-bridged derivatives.

In an attempt to improve the yield of the cyclization step, other coupling conditions were tested for amino acid **18**. HCTU in CH_2Cl_2/DMF, PyBop in CH_2Cl_2 and DPPA in CH_3CN were used for this purpose. Compounds *anti*-**20** and *syn*-**22** were isolated with ratios ranging from 1/1 to 1/1.2 in every case, but without improvement of the macrocyclization yields (38, 39 and 30% global yields, respectively). The two diastereoisomers *anti*-**19**/*syn*-**21** and *anti*-**20**/*syn*-**22** were separated by column chromatography on silica gel. Removal of the *tert*-butyloxycarbonyl group was achieved by treatment with 1/9 TFA/DCM mixture to afford the water soluble salts *anti*-**23**, *anti*-**24**, *syn*-**25** and *syn*-**26** in quantitative yields and with high purity. Finally, diborane reduction of dioxocylams *anti*-**23**, *anti*-**24**, *syn*-**25** and *syn*-**26** was performed in refluxing THF and led to a borane–amine intermediate which was cleanly cleaved under acidic conditions by treatment with refluxing aqueous 1 M HCl.[28] The successful isolation of the pure amine ligands *anti*-**27** and *syn*-**28** was achieved by basification to pH 11–12 with KOH pellets and extraction with CH_2Cl_2. Isolation of compounds *anti*-**29** and *syn*-**30** required treatment of the acid aqueous phase with an anionic exchange resin, and pure amines were obtained between pH = 13 and pH = 9.

Coordination properties of *C*-functionalized dioxocyclam and cyclam derivatives

Physico-chemical studies were performed on *anti*-**23** and *anti*-**27**, in which one of the pendant arms is directed toward the upper face and the other pendant arm is directed toward the lower face of the macrocyclic structure. This arrangement of triazole units can assure a more favourable coordination arrangement, which is required for the development of BFCs for PET applications, for example. The coordination properties, complexation kinetics and kinetic inertness in acidic media of *anti*-**23** and *anti*-**27** were studied by UV-vis and CD spectroscopies, ESI-MS spectrometry and X-ray crystallography.

Structural characterization of complex [Cu(*anti*-23)]

Solid state structure. X-ray quality crystals were obtained after recrystallization from a MeOH/MeCN mixture at room temperature. The ORTEP diagram of [Cu(*anti*-**23**)] is shown in Fig. 2 with selected bond lengths and angles, and the corresponding crystallographic data are presented in Table 1.

[Cu(*anti*-**23**)] crystallized in the trigonal *R*3 space group. The copper(II) ion has a slightly distorted square pyramidal coordination, with two deprotonated amide nitrogen atoms and two amine nitrogen atoms in the equatorial plane. The axial position is occupied by the N3b′ nitrogen atom of the triazole unit of the neighbouring molecule, which links adjacent complexes (Fig. 3). The four donor atoms N1, N4, N8 and N11 are nearly coplanar with the copper(II) ion, which is 0.085 Å outside of the plane and is shifted towards the N3b′ atom.

The N–Cu–N angles for which the N atoms are separated by an ethylene chain are smaller by about 9° than those for which the N atoms are separated by a propylene chain (~85° *versus* ~94.7°).

The Cu–N_{amide} bonds (with N1 and N8) are slightly shorter than the Cu–N_{amine} bonds (with N4 and N11), ~1.96 Å *versus*

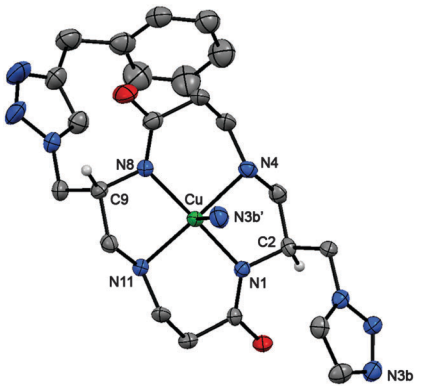


Fig. 2 ORTEP diagram of the [Cu(*anti*-**23**)] complex with thermal ellipsoids at 50% probability. H atoms have been omitted for clarity except on the C2 and C9 atoms. Averaged bond lengths and bond angles around the metal ion: N1–Cu 1.964 Å, N4–Cu 2.015 Å, N8–Cu 1.973 Å, N11–Cu 2.007 Å, N3b′–Cu 2.543 Å, N1–Cu–N11 94.55°, N11–Cu–N8 84.86°, N8–Cu–N4 94.80°, N4–Cu–N1 85.38°, N1–Cu–N3b′ 98.92°.

Table 1 Crystal data and X-ray experimental parameters for [Cu(*anti*-**23**)]

Compound reference	[Cu(*anti*-**23**)]
Chemical formula	$C_{23}H_{30}CuN_{10}O_2$[a]
Formula mass	542.11
Crystal system	Trigonal
a/Å	24.1919(6)
b/Å	24.1919(6)
c/Å	12.7495(2)
α/°	90
β/°	90
γ/°	120
Unit cell volume/Å^3	6461.9(3)
Temperature/K	100(2)
Space group	*R*3
No. of formula units per unit cell, *Z*	9
Radiation type	MoKα
Absorption coefficient, *μ*/mm^{-1}	0.797
No. of reflections measured	52 499
No. of independent reflections	6598
R_{int}	0.0414
Final R_1 value ($I > 2\sigma(I)$)	0.0295
Final w$R(F^2)$ value ($I > 2\sigma(I)$)	0.0742
Final R_1 value (all data)	0.0335
Final w$R(F^2)$ value (all data)	0.0768
Goodness of fit on F^2	1.024
Flack parameter	−0.006(5)
CCDC number	1414285

[a] Not including disordered solvent, presumably a mixture of MeOH and MeCN.

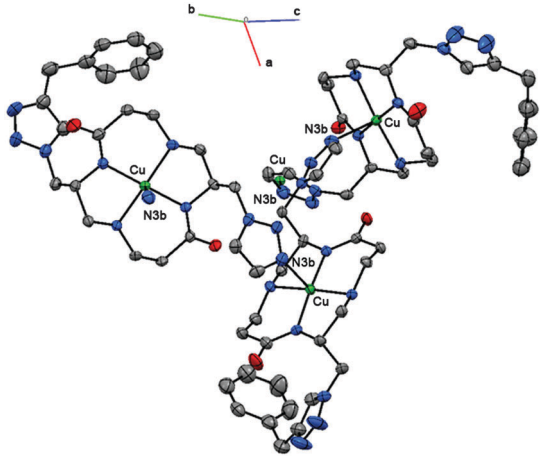


Fig. 3 Partial ORTEP representation of the crystal packing diagram of the [Cu(*anti*-**23**)] complex.

~2.01 Å, as might be expected due to the increased charge attraction between the deprotonated N_{amide} atoms and the metal cation. The second triazole arm with the benzyl substituent group remains non-coordinated to the metal ion. It is suggested that the *trans* amide groups (at the 7 and 14 positions, Scheme 2) significantly reduce the ability of the macrocyclic ring to adjust the coordination sphere around the copper(II) ion to give an octahedral geometry with two $N_{triazole}$ atoms in the axial positions.

Spectroscopic studies in aqueous solution. Circular dichroism and visible spectrophotometric titrations were performed in 5 mM solutions between pH 3 and 4.5 at room temperature (rt), and the spectra are presented in Fig. S2 and S3 (ESI†). Above pH 4.5, slow precipitation of [Cu(*anti*-**23**)] was observed because of the weak solubility of this neutral complex obtained by deprotonation of two amide groups. One band at 490 nm appeared in the visible absorption spectra upon increasing the pH, and an isosbestic point was observed, suggesting the formation of one species. This change observed in the d–d transition of the copper(II) ion can be attributed to the coordination of two deprotonated N_{amide} and two secondary N_{amine} atoms. The same change was observed in the CD spectra in the range of 300–800 nm, with a weak negative Cotton effect at 530 nm. Generally, the sign of a Cotton effect associated with a chromophore is dependent on the conformation of the asymmetric environment as well as the absolute configuration. The measured CD spectrum is the result of contributions from all conformations present in solution.[29] If the hexadecant rule holds in our case, the predominant Cotton effect in the d–d transition region must have the opposite sign for *anti*-**23** and *syn*-**25**, and for *anti*-**27** and *syn*-**28**. Accordingly, a stronger Cotton effect with the opposite sign was observed for the [Cu(*syn*-**25**)] complex. The [Cu(*anti*-**23**)] complex was also identified by high resolution ESI mass spectrometry in the positive ion mode. The mass spectrum showed one major peak with $z = 1$, corresponding to the $[M + H]^+$ molecular ion (Fig. S4, ESI† with isotopic pattern).

Dioxocyclam derivative *anti*-**23** was able to bind copper(II) with simultaneous dissociation of the two amide protons; thus, the metal binding was highly pH-sensitive, which is not compatible with radiopharmaceutical applications. Consequently, the complexation kinetics and proton-assisted dissociation of the [Cu(*anti*-**23**)] complex were not investigated in the following studies.

Structural characterization of complex [Cu(*anti*-27)]$^{2+}$

Spectroscopic studies in aqueous solution. After addition of 1 equivalent of Cu(II) to a 5 mM aqueous solution of *anti*-**27** ligand without adjustment of the pH (pH = 5.83), the colourless solution immediately turned into a pink mixture. The visible spectrum of the formed complex shows one band at $\lambda = 530$ nm ($\varepsilon = 75\ M^{-1}\ cm^{-1}$), corresponding to the d–d transition of the copper(II) ion (Fig. 4). The identity of this species was determined by high resolution ESI mass spectrometry in the positive ion mode. The mass spectra show four major peaks, all corresponding to the complex [Cu(*anti*-**27**)]$^{2+}$. Three peaks with $z = 1$ were observed, corresponding to the $[M + ClO_4^-]^+$, $[M + Cl^-]^+$ and $[M - H]^+$ molecular ions, as well as a peak with $z = 2$, corresponding to the $[M]^{2+}$ molecular ion (Fig. S5 and S6, ESI† with isotopic patterns and errors in mDa). The CD spectrum of the [Cu(*anti*-**27**)]$^{2+}$ complex shows a weak negative Cotton effect in the 400–650 nm region, while the ligand *syn*-**28** exhibits a stronger effect with the opposite sign in the same range in the presence of Cu^{2+} ion (Fig. S7, ESI†). After varying the pH of the aqueous solution of the [Cu(*anti*-**27**)]$^{2+}$ complex between pH = 2 and 11, neither the visible absorption spectrum nor the CD spectrum in the range of 300–800 nm showed any variation, suggesting that the Cu(II) complex remained unaltered in a wide pH range (Fig. S8 and S9, ESI†). To further characterize the [Cu(*anti*-**27**)]$^{2+}$ complex, the visible spectra of the copper(II) complexes of the non-substituted commercial cyclam, dioxocyclam and compound *anti*-**23** were obtained at 298 K, and are presented in Fig. 4 with the corresponding λ_{max} values. The spectrum of the [Cu(dioxocyclam)] complex was measured at a basic pH in order to fully deprotonate the two peptide functions required for metal coordination. A hypsochromic shift of λ_{max} for [Cu(*anti*-**27**)]$^{2+}$ → [Cu(*anti*-**23**)], and also for [Cu(cyclam)]$^{2+}$ → [Cu(dioxocyclam)], was observed. Billo proposed an empirical model, which was later improved by Prenesti, for the estimation of the visible spectrophotometric

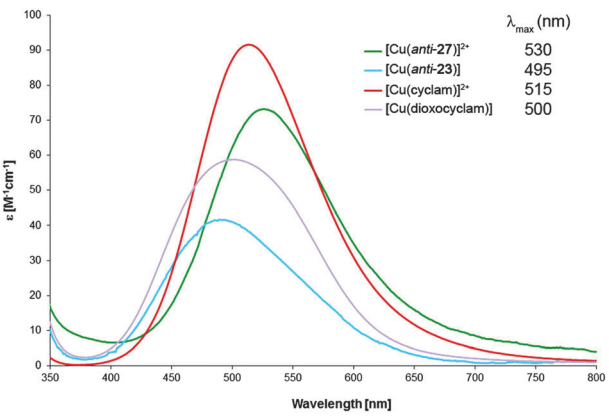


Fig. 4 Visible absorption spectra of [Cu(*anti*-**27**)]$^{2+}$ (pH = 6.5), [Cu(*anti*-**23**)] (pH = 4.5), [Cu(cyclam)]$^{2+}$ (pH = 6.9) and [Cu(dioxocyclam)] (pH = 10.5) in aqueous solution at 298 K.

Table 2 EPR parameters of [Cu(*anti*-**27**)]$^{2+}$ and [Cu(cyclam)]$^{2+}$ in frozen solution (water/ethylene glycol, 70/30) at 100 K

Compound	$g_\perp$	$g_\parallel$	$A_\perp$ [a]	$A_\parallel$ [a]
[Cu(*anti*-**27**)]$^{2+}$	2.052	2.190	37.5	195
[Cu(cyclam)]$^{2+}$	2.047	2.179	30	210

[a] In 10^{-4} cm^{-1}.

λ_{max} values of copper(II) complexes in aqueous solution.[30] According to this model, the individual ligand field contribution of metal–N_{amide} bonds is stronger than that of metal–N_{amine} bonds, leading to higher ligand field splitting Δo and lower λ_{max} values. A bathochromic shift of λ_{max} for [Cu(cyclam)]$^{2+}$ → [Cu(*anti*-**27**)]$^{2+}$ was detected, which can be explained by the coordination of the triazoles in axial positions in the [Cu(*anti*-**27**)]$^{2+}$ complex, since axial ligands decrease the d–d transition energy according to Billo's model. No bathochromic shift of λ_{max} for [Cu(dioxocyclam)] → [Cu(*anti*-**23**)] was observed, showing that in the [Cu(*anti*-**23**)] complex, the triazoles didn't coordinate to the metal ion in solution. This is consistent with the X-ray structures of the [Cu(*syn*-**25**)] and [Cu(*anti*-**23**)] complexes presented in Fig. S1 (ESI†) and Fig. 2, respectively. In both cases, the triazoles are unavailable for metal coordination because of the rigidity induced by the two deprotonated amide bonds in the macrocycle. Despite numerous crystallization efforts, we have been unable to obtain crystals of the [Cu(*anti*-**27**)]$^{2+}$ complex suitable for determination of the solid state structure by X-ray diffraction. Thus, on the basis of the above considerations, an axially coordinated structure can be proposed for the [Cu(*anti*-**27**)]$^{2+}$ complex in solution.

Electron paramagnetic resonance corroborates the axial coordination of the triazole group. The X-band EPR spectra of [Cu(*anti*-**27**)]$^{2+}$ and [Cu(cyclam)]$^{2+}$ in water/ethylene glycol (70/30 v/v%) were recorded at 100 K, and the simulated anisotropic parameters are reported in Table 2. The *g* values, $g_\parallel > g_\perp > 2$, are typical of axially elongated d^9 copper(II) complexes in the $d_{x^2-y^2}$ ground state.[31a] The *g* and *A* values of [Cu(*anti*-**27**)]$^{2+}$ are close to those of [Cu(cyclam)]$^{2+}$, suggesting a principally square-planar coordination geometry.[31b] Furthermore, the slight increase in the $g_\parallel$ value and the decrease in $A_\parallel$ on moving from [Cu(cyclam)]$^{2+}$ to [Cu(*anti*-**27**)]$^{2+}$ are associated with the red shift of λ_{max} (*vide supra*). Both observations are in agreement with the fact that the planar ligand field becomes weaker when the axial ligand field becomes stronger, according to ligand field theory.[31c–e]

Complexation kinetics of complex [Cu(*anti*-27)]$^{2+}$

During the evaluation of a new bifunctional chelator, some characteristics, such as the fast room temperature radiolabelling kinetics (on-rate) and the slow acid dissociation kinetics (off-rate), should be a priority. However, within the radiometallation protocol for ^{64}Cu, there are a large variety of labelling conditions for many different chelators.[9] Here are a few representative examples: DOTA conjugates are typically radiolabelled at pH 5–8 with temperatures in the range of 40–80 °C,[32,33] CB-TE2A conjugates typically require high temperatures and long reaction times (60 min at 90 °C),[33,34] and TETA and sarcophagine-like ligands (Diamsar) can be radiolabelled under mild conditions at ambient temperature in less than 60 min and are therefore more compatible with biological vectors.[35,36] The complexation kinetics of the *anti*-**27** macrocycle were studied in 0.4 M ammonium acetate buffer at pH 6.5 and at room temperature. After the addition of 1 equivalent of $CuCl_2$ in 0.05 M HCl, the visible spectrum of the mixture was measured over time (every 0.5 s). The variation in intensity of the band at 530 nm corresponds to the rapid formation of the [Cu(*anti*-**27**)]$^{2+}$ complex, which is complete (>99%) within 10 s (Fig. S10 and S11, ESI†). This instantaneous complex formation is very promising, since fast radiolabelling at room temperature is crucial for sensitive biomolecules, which are degraded at high temperature.

Pseudo-first order half-life for acid-assisted dissociation of the [Cu(*anti*-27)]$^{2+}$ complex

The kinetic stability of copper complexes for radiopharmaceutical applications is commonly evaluated by their proton-assisted dissociation under pseudo-first order conditions.[9,12] The half-life value obtained from this experiment is used, among other parameters, to predict the *in vivo* viability of a radiometallated chelator. The dissociation of [Cu(*anti*-**27**)]$^{2+}$ was monitored by following the changes in the visible absorption spectrum at 50 °C in 5 M HCl solution over 1 month (Fig. S12, ESI†). The experimental data were fitted with an exponential curve of pseudo-first order kinetics using the program Berkeley Madonna 8.3.18. This gave a half-life value of $t_{1/2}$ = 3.21 days (Fig. S13, ESI†). This result indicated the degree of kinetic stability of the complex relative to the most common cyclam-based systems in the literature ($t_{1/2}$ = 3.20 h for Cu–TETA at 50 °C in 5 M HCl, $t_{1/2}$ = 6.40 days for Cu–CB-TE2A at 90 °C in 5 M HCl).[37–39]

Conclusion

The stepwise synthesis of new *syn*- and *anti*-dioxocyclam and cyclam derivatives functionalized with two 1,2,3-triazole units on carbon atoms within the carbon skeleton was carried out starting from D- and L-serine and β-alanine. These new ligands provide four free $N_{secondary}$ macrocyclic amines, which are available for metal coordination. The triazole units could thus act as an integral part of the metal chelator, *via* the N2 nitrogen atoms. One of the 1,2,3-triazole moieties was functionalized with a benzyl or an aminomethyl group; the latter could be useful for conjugation with model peptides. During the cyclization step, a C9-epimerization phenomenon occurred, and *syn*-dioxocyclam and *syn*-cyclam derivatives were unexpectedly obtained *via* this stepwise route.

Regarding the physico-chemical properties, dioxocyclam derivative *anti*-**23** was able to bind to copper(II) with simultaneous dissociation of the two amide protons. Consequently, the metal binding was highly pH-sensitive, which is not compatible with radiopharmaceutical applications. Despite the fact that both triazole arms are not involved in the formation of the [Cu(*anti*-**23**)] complex, they play a key role in the stabilization of the [Cu(*anti*-**27**)]$^{2+}$ complex, as revealed by the different chemical

coordination behaviour. Fast complexation occurred under physiological/radiolabelling conditions (<10 s, rt), and the formed complex remained unaltered in a wide pH range (pH 2–11). Moreover, the complex was found to be inert towards acid assisted dissociation ($t_{1/2}$ = 3.21 d, 5 M HCl, 50 °C). From UV-vis and EPR spectroscopic studies, an axially coordinated structure was proposed for the [Cu(*anti*-**27**)]$^{2+}$ complex in solution.

We are continuing this work to investigate the bioconjugation reactions and radiolabelling of these chelators.

Experimental section

General

TLC analyses were performed on Kieselgel 60 F_{254} plates (Merck) using standard procedures. Compounds were visualized using UV light (254 nm) and/or 30% methanolic H_2SO_4/heat as the developing agent. Column chromatography was performed using silica gel SI 60 (63–200 μm) (Merck). High pressure column chromatography was performed using an axially compressed 20 mm id steel column (Separex-Novasep). FT-IR spectra were recorded on a Perkin-Elmer spectrum 1000 (NaCl window or KBr pellet, cm^{-1}). ATR-FT-IR spectra of Cu(II) complexes were obtained on an IRAffinity-1 Shimadzu spectrophotometer. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured on an Anton Paar MC300 polarimeter (deg mL g^{-1} dm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX250 spectrometer (250 MHz and 62.9 MHz, respectively) and a DRX400 spectrometer (400 MHz and 100.6 MHz, respectively). For complete assignment of ^{1}H and ^{13}C signals, two-dimensional ^{1}H,^{1}H COSY and ^{1}H,^{13}C correlation spectra were recorded. The chemical shifts are reported in ppm (δ) relative to residual solvent peaks. Elucidations of the chemical structures were based on ^{1}H, COSY, HSQC, ^{13}C and HMBC experiments (see Schemes 1 and 2 for atom numbering). UV-visible spectra were recorded on a Perkin-Elmer Lambda1050 UV-vis-NIR spectrophotometer using a 1 cm optical path length cell at T = 298 K. The circular dichroism (CD) spectra and also some visible absorption spectra were recorded on a MOS-450 spectrometer from Bio-Logic, coupled with a Metrohm 716 titrator combined with a Fisher Bioblock electrode for pH adjustments and controlled by a program written in Labview. ESI-HRMS spectra were obtained using a Bruker Daltonics MicrOTOF$_Q$ mass spectrometer. EPR spectra were recorded using a continuous-wave Bruker EMXplus 10/12 spectrometer (X-band frequency 9.412 GHz). Measurements were carried out in frozen (T = 100 K) water/ethylene glycol (70/30 v/v%) solution, and the concentration of the *anti*-**27** and cyclam ligands was 5 mM. CHN elemental analyses were performed using a Thermo Finnigan EA 1112 Series Flash Elemental Analyser. Reduced peptides **2–5** are named according to the literature.[40]

Crystal structure determination

CCDC 1414285 and 1435292. X-ray structures were determined using a SuperNova, Dual, Cu at zero, Atlas diffractometer equipped with a low temperature device using liquid N_2 to perform XRD intensity measurements at near 100 K. The X-ray source was a sealed tube emitting MoKα radiation (λ = 0.71073 Å, [Cu(*anti*-**23**)]) and also CuKα radiation (λ = 1.5418 Å, [Cu(*syn*-**25**)]). Diffraction pattern frames were processed with CrysAlis PRO, Agilent Technologies, Version 1.171.37.31 software. The structures were solved by direct methods using the SHELXT software package and refined on F^2 by full matrix least-squares using SHELXL software.[41] Crystal data, data collection parameters, and results of the analyses are listed in Table 1 and Table S1 (ESI†). Supplementary crystallographic data for the [Cu(*anti*-**23**)] structure (atomic coordinates, thermal parameters, and intramolecular bond distances and angles) are provided in the CIF.

Kinetic studies

The formation of the copper(II) complex of the *anti*-**27** ligand was studied under conditions used for radiolabelling: 0.4 M aq. ammonium acetate buffer at pH 6.5 and at 25 °C. The solution of *anti*-**27** (5 mM) was prepared in the buffer, and the kinetic measurements were started on the addition of 20 μL of a 0.25 M $CuCl_2$ solution prepared in 0.05 M HCl. Visible spectra between 300 and 900 nm were measured on a MOS-450 spectrophotometer from Bio-Logic equipped with a diode-array detector, allowing the spectrum to be recorded every 0.5 s.

The acid-assisted dissociation of the [Cu(*anti*-**27**)]$^{2+}$ complex was studied under pseudo-first order conditions in 5 M aq. HCl containing the complex at a concentration of 2.35 mM and at 50 °C. After addition of the concentrated acid to the sample solution, the mixture was maintained in a sealed tube at 50 °C and absorption spectra were measured over time at 0, 3.5, 20.5, 44, 96 and 720 hours. The experimental data were fitted with an exponential curve of pseudo-first order kinetics using the program Berkeley Madonna 8.3.18.

[Cu(*anti*-23)]

To a solution of 10.6 mg of *anti*-**23** ligand (0.015 mmol) in 1500 μL of water, a solution of 0.01 M $Cu(ClO_4)_2$ (1500 μL, 1 eq. of Cu^{2+}) was added. The solution was colourless and transparent. After addition of 1 M NaOH solution, the mixture turned pink in colour, and above pH 4.5 the slow formation of a pink precipitate was observed. The precipitate was dissolved on addition of 1 M HCl solution. Total precipitation of the complex was achieved by addition of 50 μL of 1 M NaOH. After filtration, the crude product was recrystallized from a MeOH/MeCN mixture by slow evaporation at rt to yield violet crystals. ESI-HRMS$^+$ (H_2O) m/z calculated for $[C_{23}H_{31}N_{10}O_2Cu]^+$, z = 1, $[M + H]^+$ 542.1922, found 542.1946 (−2.4 mDa). Anal. calcd for $CuC_{23}H_{30}N_{10}O_2{\cdot}2H_2O{\cdot}$ 3MeOH C, 46.31; H, 6.88; N, 20.77; found C, 46.51; H, 6.35; N, 20.35. IR (cm^{-1}) ν 3142, 2916, 2870, 1547, 1427, 1327, 1224, 1055, 976, 870, 791, 719, 700.

[Cu(*anti*-27)]$^{2+}$

To a solution of 6.8 mg of *anti*-**27** ligand (0.015 mmol) in 1500 μL of water, a solution of 0.01 M $Cu(ClO_4)_2$ (1500 μL, 1 eq. of Cu^{2+}) was added. The solution immediately turned pink in colour. The pH of the solution was approximately 6.

At this pH, very little precipitate could be formed due to the possible excess of copper(II), which precipitated as copper hydroxide. If present, this precipitate was filtered on cotton and the solvent was evaporated. The complex was obtained as a pink powder. UV-vis λ_{max} (H_2O)/nm 530 (ε/dm^3 mol^{-1} cm^{-1} 75). ESI-HRMS$^+$ (H_2O) m/z calculated for $[C_{23}H_{36}N_{10}CuCl]^+$, z = 1, $[M + Cl^-]^+$ 550.2103, found 550.2145 (−4.2 mDa); for $[C_{23}H_{35}N_{10}Cu]^+$, z = 1, $[M - H]^+$ 514.2337, found 514.2375 (−3.9 mDa); z = 2, $[M]^{2+}$ 257.6205, found 257.6238 (−3.3 mDa). IR (cm^{-1}) ν 3138, 2918, 1556, 1394, 1211, 1147, 1053, 1010.

Cbz-(L)-Ser(OTBDMS)-H 1a

A stirred solution of Cbz-(L)-Ser(OTBDMS)-OMe (12.8 g, 34.8 mmol) in anhydrous toluene (250 mL) was cooled to −78 °C under argon. DibalH (1.2 M solution in toluene, 40 mL, 48 mmol) was added dropwise *via* a syringe and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched by the addition of EtOAc and the temperature was allowed to warm up. A saturated aqueous solution of Rochelle's salt was poured portion-wise into the mixture under vigorous stirring until two clear layers were obtained and then separated. The aqueous layer was extracted with EtOAc (4 × 60 mL), and the organic phases were combined and washed with brine (40 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (silica, cyclohexane/EtOAc 90/10) to furnish the pure aldehyde (7.94 g, 23.5 mmol, 67%) as a colourless viscous liquid. $[\alpha]_D^{20}$ 7.6 (c 1.20, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 6H, H3′), 0.86 (s, 9H, H4′), 3.88 (dd, 1H, J_{gem} = 10.4 Hz, $J_{4,5}$ = 4.0 Hz, H2′), 4.21 (dd, 1H, J_{gem} = 10.4 Hz, $J_{4,5}$ = 2.5 Hz, H2′), 4.30–4.35 (m, 1H, H3), 5.14 (s, 2H, OCH_2Ph), 5.67 (d, 1H, $J_{3,4}$ = 6.1 Hz, H2), 7.36 (br s, 5H, H-Ar), 9.65 (s, 1H, H aldehyde); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = −5.7 (2 × C3′), 18.1 (OSi*C*(CH$_3$)$_3$), 25.6 (C4′), 61.2 (C3), 61.8 (C2′), 67.1 (OCH_2Ph), 128.1, 128.2, 128.5 (CH-Ar), 136.1 (C-Ar), 156.0 (C1), 198.7 (C4); IR: 3442, 3342, 2954, 2930, 2884, 1717, 1508.

Cbz-(L)-Ser(OTBDMS)Ψ[CH$_2$NH]βAla-OMe 2a

A stirred solution of **1a** (17.00 g, 50.40 mmol) in dry MeOH (600 mL) was cooled to 0 °C under an argon atmosphere. In a separate round bottom flask, β-alanine methyl ester hydrochloride (13.95 g, 100.80 mmol) was dissolved in MeOH (60 mL) and DIEA (17.14 mL, 100.80 mmol). The solutions were then mixed and stirred at 4 °C for 4 h, at which point acetic acid (8.68 mL, 156.24 mmol) was added, followed by $NaBH_3CN$ (4.48 g, 77.50 mmol). The resulting solution was stirred for another hour. Completion of the reaction was monitored by TLC (silica, hexane/EtOAc 80/20). MeOH was then removed under reduced pressure and the residue was dissolved in EtOAc (600 mL). The organic layer was washed successively with 10% aq. $NaHCO_3$ (200 mL) and brine (200 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica, cyclohexane/EtOAc from 70/30 to 20/80) to afford 16.4 g (67%) of **2a** as a viscous liquid. $[\alpha]_D^{20}$ 4.6 (c 0.56, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.00 (s, 6H, H3′), 0.84 (s, 9H, H4′), 1.48 (s, 1H, NH), 2.46 (t, 2H, $J_{6,5}$ = 6.4 Hz, H6), 2.66 (dd, 1H, J_{gem} = 12.2 Hz, $J_{3,4}$ = 5.7 Hz, H4), 2.80–2.91 (m, 3H, H4, H5), 3.72–3.80 (m, 4H, H2′, H8), 3.69–3.72 (m, 2H, H3, H2′), 5.06 (s, 2H, OCH_2Ph), 5.27 (d, 1H, $J_{2,3}$ = 5.7 Hz, H2), 7.23–7.34 (m, 5H, H-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = −5.6 (2 × C3′), 18.1 (OSi*C*(CH$_3$)$_3$), 25.8 (C4′), 34.6 (C6), 45.0 (C5), 50.4 (C4), 51.5 (C3, C8), 63.2 (C2′), 66.5 (OCH_2Ph), 128.0, 128.4 (CH-Ar), 136.5 (C-Ar), 156.1 (C1), 173.0 (C7); IR: 3338, 2953, 2929, 2896, 1726, 1500; MS (HR-ESI) m/z calcd for $C_{21}H_{37}N_2O_5$ $[M + H]^+$ 425.2466, found: 425.2476.

Cbz-(L)-Ser(OTBDMS)Ψ[CH$_2$NBoc]βAla-OMe 3a

A stirred solution of **2a** (12.4 g, 29 mmol) in anhydrous DCM (250 mL) was cooled to 0 °C under an argon atmosphere. Di-*tert*-butyl dicarbonate (14.0 g, 64 mmol) and Et_3N (8.90 mL, 64 mmol) were successively added. The resulting solution was allowed to warm to room temperature and stirred until completion (2 h, monitored by TLC), after which it was quenched by the addition of 1 N aqueous HCl. The two phases were separated and the organic layer was washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica, from cyclohexane to cyclohexane/EtOAc 80/20) to afford 13.90 g (91%) of compound **3a** as a viscous liquid. $[\alpha]_D^{20}$ 4.7 (c 1.16, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.03 (s, 6H, H3′), 0.88 (s, 9H, H4′), 1.42 (s, 9H, C(CH$_3$)$_3$), 2.55 (br s, 2H, H6), 3.15–3.20 (m, 1H, H4), 3.34–3.64 (m, 8H, H4, H5, H8, H2′), 3.87 (br s, 1H, H3), 5.07 (br s, 2.5H, H2, OCH_2Ph), 5.58 (br s, 0.5H, H2), 7.24–7.35 (m, 5H, H-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = −5.6 (2 × C3′), 18.1 (OSi*C*(CH$_3$)$_3$), 25.8 (C4′), 28.2 (C(*C*H$_3$)$_3$), 32.9, 33.5 (C6), 44.0 (C5), 48.4 (C4), 51.5 (C8), 52.4 (C3), 63.1 (C2′), 66.3 (OCH_2Ph), 80.2 (*C*(CH$_3$)$_3$), 127.8, 128.3 (CH-Ar), 136.5 (C-Ar), 155.1, 155.8, 156.2, 156.5 (C1, CO), 171.9, 172.3 (C7); IR: 3443, 3352, 2954, 2930, 2898, 2857, 1728, 1698, 1513; MS (HR-ESI) m/z calcd for $C_{26}H_{44}N_2NaO_7$ $[M + Na]^+$ 547.2816, found: 547.2810.

Cbz-(L)-Ser(OH)Ψ[CH$_2$NBoc]βAla-OMe 4a

A stirred solution of **3a** (13.87 g, 26.4 mmol) in dry THF (160 mL) was treated with *N*-tetrabutylammonium fluoride (1.0 M solution in THF, 55 mL, 55 mmol). The resulting solution was stirred overnight at room temperature and then diluted with H_2O (150 mL). THF was removed under vacuum and the product was extracted with EtOAc (3 × 80 mL). The extracts were combined and washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, cyclohexane/EtOAc 50/50) to afford 9.20 g (22.4 mmol, 85%) of compound **4a** as a viscous liquid. $[\alpha]_D^{20}$ 5.5 (c 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9H, C(CH$_3$)$_3$), 2.56 (t, 2H, $J_{5,6}$ = 6.9 Hz, H6), 3.15 (dd, 1H, J_{gem} = 13.9 Hz, $J_{3,4}$ = 5.1 Hz, H4), 3.36–3.84 (m, 10H, H3, H4, H5, H8, H2′, H3′), 5.07 (s, 2H, OCH_2Ph), 5.57 (d, 1H, $J_{2,3}$ = 7.3 Hz, H2), 7.24–7.34 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (C(*C*H$_3$)$_3$), 33.4 (C6), 44.0 (C5), 46.7 (C4), 51.1 (C3), 51.6 (C8), 61.2 (C2′), 66.6 (OCH_2Ph), 81.1 (*C*(CH$_3$)$_3$), 127.8, 127.9, 128.4 (CH-Ar), 136.3 (C-Ar), 156.1(C1), 156.9 (CO), 171.6 (C7);

IR: 3431, 3360, 2975, 2953, 1722, 1697, 1674, 1522; MS (HR-ESI) *m/z* calcd for $C_{20}H_{30}N_2NaO_7$ $[M + Na]^+$ 433.1945, found: 433.1949.

Cbz-(L)-ser(OTs)Ψ[CH_2NBoc]βAla-OMe 5a

A stirred solution of **4a** (9.20 g, 22.4 mmol) in dry CH_2Cl_2 (150 mL) was cooled to 0 °C under an argon atmosphere. Et_3N (9.40 mL, 67 mmol), tosyl chloride (6.48 g, 34 mmol) and DMAP (275 mg, 2.24 mmol) were successively added and the reaction mixture was stirred overnight at room temperature. The solution was diluted with CH_2Cl_2 (50 mL), and washed with sat. aq. $NaHCO_3$ (2 × 70 mL) and sat. aq. NaCl (50 mL). After drying over $MgSO_4$, filtration and evaporation of the solvent yielded the crude product, which was purified by column chromatography (silica, cyclohexane/EtOAc 75/25) to afford 10.65 g (18.8 mmol, 84%) of compound **5a** as a viscous colourless liquid. $[\alpha]_D^{20}$ 3.5 (*c* 0.65, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (s, 9H, C(CH_3)$_3$), 2.42 (s, 3H, H4′), 2.51–2.56 (m, 2H, H6), 3.19–3.65 (m, 7H, H4, H5, H8), 4.04 (br s, 3H, H2′, H3), 4.99–5.17 (m, 2.5H, OCH_2Ph, H2), 5.67 (s, 0.5H, H2), 7.26–7.33 (m, 7H, H-Ar, H3′), 7.77 (d, 2H, *J* = 8.2 Hz, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (C4′), 28.2 (C(CH_3)$_3$), 32.9, 33.5 (C6), 44.2 (C5), 48.0 (C4), 49.5, 50.1 (C3), 51.7 (C8), 66.6, 66.8 (OCH_2Ph), 69.2 (C2′), 80.8 (*C*(CH_3)$_3$), 127.8 (C3′), 127.9, 128.4 (CH-Ar), 129.9 (C3′), 132.3 (C-Ar), 136.3 (C-Ar), 145.0 (C-Ar), 154.8, 156.0 (C1), 156.0, 156.5 (CO), 171.9, 172.4 (C7); IR: 3338, 2975, 2954, 1726, 1698, 1527; MS (HR-ESI) *m/z* calcd for $C_{27}H_{36}N_2NaO_9S$ $[M + Na]^+$ 587.2034, found: 587.2044.

Compound 6a

To a solution of **5a** (10.65 g, 18.8 mmol) in DMF was added sodium azide (4.88 g, 75 mmol). The reaction mixture was heated to 85 °C overnight. The solvent was then removed by evaporation under high vacuum and the residue was partitioned between EtOAc (90 mL) and water (450 mL). The aqueous phase was extracted with EtOAc (4 × 90 mL). The combined organic extracts were washed with sat. aq. NaCl (2 × 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was obtained as a yellow oil and used without further purification (7.92 g, 18.2 mmol, 96%). $[\alpha]_D^{20}$ 3.5 (*c* 0.54, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 (s, 9H, C(CH_3)$_3$), 2.58 (br s, 2H, H6), 3.16–3.51 (m, 6H, H4, H5, H2′), 3.68 (s, 3H, H8), 3.98 (br s, 1H, H3), 5.10–5.26 (m, 2.4H, OCH_2Ph, H2), 5.76 (br s, 0.6H, H2), 7.29–7.35 (m, 5H, H-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.2 (C(CH_3)$_3$), 33.5 (C6), 44.1 (C5), 48.5 (C4), 50.8 (C3), 51.7 (C8), 52.4 (C2′), 66.6 (OCH_2Ph), 80.7 (*C*(CH_3)$_3$), 127.9, 128.0, 128.4 (CH-Ar), 136.3 (C-Ar), 156.1 (C1), 156.6 (CO), 172.0 (C7); IR: 3336, 2975, 2102, 1728, 1697, 1525; MS (HR-ESI) *m/z* calcd for $C_{20}H_{29}N_5O_6$ $[M + H]^+$ 458.2010, found 458.2023.

Compound 7

To a stirred solution of azide **6a** (2.55 g, 5.85 mmol) in *t*BuOH (20 mL) and H_2O (15 mL), 3-phenylpropyne (1.50 mL, 11.7 mmol, 2 eq.), anhydrous copper sulfate (187 mg, 1.17 mmol, 0.2 eq.) and sodium ascorbate (463 mg, 2.34 mmol, 0.4 eq.) were successively added. The reaction mixture was heated to 80 °C overnight. EtOAc and H_2O were added and the layers were separated. The organic layer was washed twice with sat. aq. NaCl, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (silica, cyclohexane/EtOAc 70/30 to 40/60) to afford 3.06 g (5.54 mmol, 87%) of **7** as a colourless oil. $[\alpha]_D^{20}$ −2.3 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9H, C(CH_3)$_3$), 2.52 (br s, 2H, H6), 3.18–3.56 (m, 4H, H4, H5), 3.64 (s, 3H, H8), 4.06 (s, 2H, H5′), 4.10 (br s, 1H, H3), 4.43 (m, 2H, H2′), 5.04 (m, 2H, OCH_2Ph), 5.42, 5.99 (2 br s, 1H, H2), 7.19–7.35 (m, 11H, H-Ar, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (C(*C*H_3)$_3$), 32.3 (C5′), 33.7 (C6), 44.4 (C5), 48.8 (C4), 51.2 (C2′), 51.9 (C8, C3), 66.9 (OCH_2Ph), 81.2 (*C*(CH_3)$_3$), 122.8 (C3′), 126.6 (CH-Ar), 128.0 (CH-Ar), 128.3, 128.6, 128.7 (CH-Ar), 128.8 (CH-Ar), 136.4 (C-Ar), 139.1 (C-Ar), 147.8 (C4′), 156.4 (C1), 156.9 (CO), 172.0 (C7); IR: 3319, 2922, 1719, 1690, 1522; MS (HR-ESI) *m/z* calcd for $C_{29}H_{38}N_5O_6$ $[M + H]^+$ 552.2817, found: 552.2818.

Compound 8

Prepared following the procedure described for compound **7** using *tert*-butyloxycarbonylpropargylamine.

Yield: 78%, colourless foam. $[\alpha]_D^{20}$ 1.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9H, C(CH_3)$_3$), 1.43 (s, 9H, C(CH_3)$_3$), 2.52 (br s, 2H, H6), 3.18–3.56 (m, 4H, H4, H5), 3.65 (s, 3H, H8), 4.14 (br s, 1H, H3), 4.37 (d, 2H, *J* = 3.7 Hz, H5′), 4.48 (m, 2H, H2′), 5.07 (m, 2H, OCH_2Ph), 5.13 (br s, 1H, NHBoc), 5.98 (br s, 1H, H2), 7.28–7.37 (m, 5H, H-Ar), 7.59 (br s, 1H, H3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (C(*C*H_3)$_3$, C8′), 33.6 (C6), 36.1 (C5′), 44.3 (C5), 48.7 (C4), 51.2 (C2′), 51.9 (C3, C8), 66.8 (OCH_2Ph), 79.7, 81.1 (2 × *C*(CH_3)$_3$), 123.2 (C3′), 128.0 (CH-Ar), 128.2 (CH-Ar), 128.5 (CH-Ar), 136.3 (C-Ar), 145.4 (C4′), 155.8 (CO), 156.3 (C1), 156.7 (CO), 172.0 (C7); IR: 3335, 2974, 2934, 1687, 1510, 1366, 1244; MS (HR-ESI) *m/z* calcd for $C_{28}H_{42}N_6NaO_8$ $[M + Na]^+$ 613.2956, found: 613.2964.

Compound 9

To a stirred solution of **6b** (4.15 g, 9.53 mmol) in *t*BuOH (45 mL) and H_2O (30 mL), trimethylsilylacetylene (5.40 mL, 38 mmol, 4 eq.), anhydrous copper sulfate (305 mg, 1.90 mmol, 0.2 eq.) and sodium ascorbate (755 mg, 3.80 mmol, 0.4 eq.) were successively added. The reaction mixture was heated to 80 °C for 60 h, after which EtOAc was added and the two phases were separated. The organic layer was washed twice with sat. aq. NaCl, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (silica, cyclohexane/EtOAc 100/0 to 25/75) to afford on the one hand 1.10 g (2.0 mmol) of silylated cycloadduct and on the other hand 2.97 g (6.4 mmol, 88%) of **9**. In a second step, the silylated triazole (1.10 g, 2.0 mmol) was treated with an excess of TBAF (1 M solution in THF, 10 mL, 10 mmol) in THF (20 mL) for 40 h. The reaction mixture was quenched with water and the solvent was removed under reduced pressure. The crude residue was taken up in EtOAc and was washed with brine, dried over $MgSO_4$ and evaporated. Purification by column chromatography (silica, cyclohexane/EtOAc 100/0 to 25/75) yielded 353 mg of **9** (0.76 mmol, 72% for 2 steps) as a colourless oil. $[\alpha]_D^{20}$ −2.4 (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H, C(CH_3)$_3$), 2.54 (br s, 2H, H6), 3.29–3.50 (m, 4H, H4, H5),

3.66 (s, 3H, H8), 4.18 (br s, 1H, H3), 4.55 (m, 2H, H2′), 5.08 (s, 2H, OCH_2Ph), 5.54 (br s, 0.5H, H2), 6.03 (br s, 0.5H, H2), 7.28–7.38 (m, 5H, H-Ar), 7.60–7.73 (m, 2H, H3′, H4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 ($C(CH_3)_3$), 33.5 (C6), 44.3 (C5), 48.6 (C4), 50.9 (C2′), 51.7 (C3), 51.8 (C8), 66.8 (OCH_2Ph), 81.0 ($C(CH_3)_3$), 124.7 (C4′), 127.9, 128.1, 128.4, 128.5 (CH-Ar), 133.9 (C3′), 136.3 (C-Ar), 156.2 (C1), 156.7 (CO), 172.0 (C7); IR: 3290, 2950, 1717, 1688, 1522; MS (HR-ESI) *m*/*z* calcd for $C_{22}H_{31}N_5O_6$ $[M + H]^+$ 462.2347, found: 462.2348.

Compound 13

Compound **7** (3.01 g, 5.45 mmol) and 10% Pd/C (500 mg, 16% w/w) were mixed in anhydrous EtOH (90 mL). The flask was flushed with H_2 and the mixture was stirred overnight at room temperature under a H_2 atmosphere. The catalyst was removed by filtration through a pad of celite, and washed with EtOH. The filtrate was concentrated under vacuum to afford the free amine **10** as a colourless wax which was used without further purification. To a solution of **9** (2.40 g, 5.19 mmol) in MeOH (25 mL) and H_2O (2.5 mL) was added K_2CO_3 (1.79 g, 13 mmol, 2.5 eq.). The mixture was stirred for 20 h at room temperature and then acidified to pH = 4 by addition of Amberlite resin IR120. After filtration, the resin was washed with EtOAc. The organic layer was washed twice with sat. aq. NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was dried under high vacuum to yield pure **12** as a white foam. A solution of the free amine **10** (2.15 g, 5.14 mmol, 1.03 eq.) in anhydrous THF (30 mL) was added under argon *via* a cannula to an ice-cold stirred solution of acid **12** (2.22 g, 5.0 mmol, 1 eq.) and HBTU (2.19 g, 5.50 mmol, 1.1 eq.) in anhydrous THF (80 mL). Et_3N (765 μL, 5.50 mmol, 1.1 eq.) was then added dropwise and the temperature was allowed to warm to room temperature. The reaction mixture was stirred overnight. The THF was evaporated under reduced pressure, and the residue was taken up in EtOAc and successively washed with 1 M aq. HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl. After drying over $MgSO_4$ and evaporation of the solvent under reduced pressure, the crude product was obtained and purified by column chromatography (silica, CH_2Cl_2/MeOH, 100/0 to 96/4). The desired compound **13** was obtained as a white foam (3.41 g, 4 mmol, 80%). $[\alpha]_D^{20}$ −4.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9H, $(CH_3)_3$), 1.44 (s, 9H, $(CH_3)_3$), 2.33 (m, 2H, H6), 2.54 (t, 2H, *J* = 6.0 Hz, H13), 3.16–3.59 (m, 8H, H3, H5, H10, H12), 3.65 (s, 3H, OCH_3), 4.07 (s, 2H, OCH_2Ph), 4.12–4.34, 4.35–4.45, 4.47–4.61 (3m, 6H, H2, H9, H6a, H6b), 5.06 (s, 2H, OCH_2Ph), 7.18–7.36 (m, 10H, H-Ar), 7.41 (s, 1H, H5b), 7.64 (br s, 2H, H5a, H4a); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (2 × $C(CH_3)_3$), 32.2 (CH_2Ph), 33.5 (C13), 35.8 (C6), 44.4, 44.6 (C5, C12), 48.6 (C3, C10), 50.6, 50.7 (C6a, C6b), 50.9, 51.1 (C2, C9), 51.9 (OCH_3), 66.8 (OCH_2Ph), 81.0, 81.1 (2 × $C(CH_3)_3$), 123.0 (C5a), 124.9 (C5b), 126.6, 128.0, 128.2, 128.6, 128.7, 128.8 (CH-Ar), 133.9 (C4b), 136.4 (C-Ar), 139.1 (C-Ar), 147.7 (C4a), 156.3 (CO), 156.9 (CO), 171.5, 172.0 (C7, C14); IR: 3283, 2972, 2930, 1675, 1530, 1414, 1366, 1244, 1157; MS (HR-ESI) *m*/*z* calcd for $C_{42}H_{59}N_{10}O_9$ $[M + H]^+$ 847.4461, found: 847.4453.

Compound 14

Prepared following the procedure described for compound **13** starting from **8** and **9**.

Yield: 85%, white foam. $[\alpha]_D^{20}$ −2.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9H, $(CH_3)_3$), 1.40 (s, 9H, $(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 2.33 (m, 2H, H6), 2.52 (t, 2H, *J* = 6.1 Hz, H13), 3.16–3.59 (m, 4H, H3, H10), 3.32–3.55 (m, 4H, H5, H12), 3.64 (s, 3H, OCH_3), 4.14–4.60 (m, 6H, H2, H9, H6b, H6a), 4.35 (d, 2H, *J* = 4.4 Hz, CH_2NH), 5.03 (s, 2H, OCH_2Ph), 5.39 (m, 1H, NHBoc), 6.10 (br s, 1H, NH), 7.04 (br s, 1H, NH), 7.25–7.33 (m, 5H, H-Ar), 7.64 (br s, 3H, H5a, H4a, H5b); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.3 (2 × $C(CH_3)_3$), 28.4 ($C(CH_3)_3$), 33.5 (C13), 35.7 (C6), 36.1 (CH_2NH), 44.3, 44.6 (C5, C12), 48.6, 48.8 (C3, C10), 50.2 (C2 or C9), 50.7, 51.0 (C6b, C6a), 51.4 (C2 or C9), 51.8 (OCH_3), 66.8 (OCH_2Ph), 79.6, 80.9, 81.0 (3 × $C(CH_3)_3$), 123.3 (C5a), 124.8 (C5b), 127.9, 128.1, 128.5 (CH-Ar), 133.8 (C4b), 136.3 (C-Ar), 145.6 (C4a), 155.9 (CO), 156.3 (CO), 156.8 (CO), 171.5, 172.0 (C7, C14); IR: 3327, 2974, 1675, 1505, 1477, 1416, 1365, 1244, 1157; MS (HR-ESI) *m*/*z* calcd for $C_{41}H_{64}N_{11}O_1$ $[M + H]^+$ 886.4781, found: 886.4776.

(2*S*,9*R*)-4,11-*N*-*tert*-Butyloxycarbonyl-9-[[4-(phenylmethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane *anti*-19

To a stirred solution of compound **13** (3.41 g, 4.0 mmol) in MeOH (50 mL) and H_2O (5 mL) was added K_2CO_3 (1.69 g, 12.2 mmol, 3 eq.). The mixture was stirred for 20 h at room temperature, acidified to pH = 1–2 by addition of 2 M aq. HCl and extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$ and evaporated under vacuum. The expected acid was obtained as a white foam and used without further purification. The obtained acid (3.33 g, 3.99 mmol) and 10% Pd/C (660 mg, 20% w/w) were mixed in anhydrous methanol (75 mL). The flask was flushed with H_2 and the mixture was stirred at room temperature under a H_2 atmosphere for 20 h. The catalyst was removed by filtration through a pad of celite and washed with MeOH. Evaporation of the solvent under vacuum afforded the linear precursor amino acid as a colourless wax in quantitative yield. To a solution of the linear deprotected precursor **17** (2.68 g, 3.83 mmol) in anhydrous CH_2Cl_2 (700 mL) at 0 °C was added DIEA dropwise (4.20 mL, 24 mmol, 10 eq.), followed by a solution of HATU (3.02 g, 7.94 mmol, 2 eq.) in DMF (80 mL). At the end of the addition, the temperature was allowed to warm to room temperature and the reaction mixture was stirred for 60 h. The solvents were evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2 (150 mL) and successively washed with 1 M aq. HCl solution (2 × 30 mL), sat. aq. $NaHCO_3$ solution (2 × 30 mL) and sat. aq. NaCl (40 mL). After drying over $MgSO_4$ and evaporation of the solvent under reduced pressure, the crude product was obtained and purified by column chromatography (silica, CH_2Cl_2/MeOH, 100/0 to 90/10). Two diastereoisomers were isolated (**19**, 528 mg, 0.78 mmol, 20% and **21**, 713 mg, 1.05 mmol, 27%).

Compound **19**: White foam; $[\alpha]_D^{32}$ = −2.2 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ = 1.41 (s, 18H, 2 × $C(CH_3)_3$),

2.17–2.53 (m, 4H, H6, H13), 2.84–3.90 (m, 8H, H3, H10, H5, H12), 4.02 (s, 2H, CH_2Ph), 4.19–4.78 (m, 6H, H6a, H6b, H2, H9), 7.18–7.30 (m, 5H, H-Ar), 7.65 (s, 1H, H5a), 7.71 (s, 1H, H4b), 7.97 (s, 1H, H5b); ^{13}C NMR (100 MHz, CD_3OD): δ = 28.7 (2 × C(CH_3)$_3$), 32.5 (CH_2Ph), 36.9, 37.8 (C6, C13), 47.5 (C5, C12), 51.8, 52.4 (C2, C9, C3, C10, C6a, C6b), 82.0 (2 × C(CH_3)$_3$), 124.7 (C5a), 126.7 (C5b), 127.5 (CH-Ar), 129.6 (CH-Ar), 134.4 (C4b), 140.5 (C-Ar), 148.5 (C4a), 157.9 (2 × CO), 174.5 (C7, C14); IR: 3337, 2980, 2930, 1697, 1655, 1524, 1466, 1412, 1367, 1286, 1250, 1219, 1157; MS (HR-ESI) m/z calcd for $C_{33}H_{49}N_{10}O_6$ $[M + H]^+$ 681.3831, found: 681.3845.

(2*S*,9*S*)-4,11-*N*-*tert*-Butyloxycarbonyl-9-[[4-(phenylmethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane *syn*-21

White foam; $[\alpha]_D^{32}$ −49.4 (*c* 1.00, $CHCl_3$). Two rotamers exist for **21**; only the major one is described. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30, 1.34 (2s, 18H, 2 × C(CH_3)$_3$), 1.91–2.63 (m, 4H, H6, H13), 2.76–3.04 (m, 2H, H3, H10), 3.20–3.39 (m, 2H, H5, H12), 3.63–3.90 (m, 4H, H5, H12, H3, H10), 4.05, 4.11 (s, 2H, CH_2Ph), 4.26–4.48 (m, 2H, H6a, H6b), 4.45–4.58 (m, 2H, H2, H9), 4.60–4.78 (m, 2H, H6a, H6b), 6.22, 6.30 (2d, 2H, NH), 7.06 (s, 1H, H5a), 7.19–7.33 (m, 5H, H-Ar), 7.52 (s, 1H, H5b), 7.70 (s, 1H, H4b); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (2 × C(CH_3)$_3$), 32.2 (CH_2Ph), 35.4, 35.5 (C6, C13), 47.5, 47.6 (C5, C12), 49.1, 49.3, 49.4, 49.6 (C2, C9, C6a, C6b), 51.0, 51.1 (C3, C10), 82.0, 82.1 (2 × C(CH_3)$_3$), 122.9 (C5a), 124.7 (C5b), 126.6 (CH-Ar), 128.6, 128.7 (CH-Ar), 133.7 (C4b), 138.9 (C-Ar), 147.7 (C4a), 154.9 (2 × CO), 172.1, 172.2 (C7, C14); IR: 3402, 2970, 2932, 1663, 1518, 1462, 1408, 1380, 1350, 1250, 1159; MS (HR-ESI) m/z calcd for $C_{33}H_{49}N_{10}O_6$ $[M + H]^+$ 681.3831, found: 681.3866.

(2*S*,9*R*)-4,11-*N*-*tert*-Butyloxycarbonyl-9-[4-[[(*N*-*tert*-butyloxycarbonyl)-aminomethyl]-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane *anti*-20

Prepared following the procedure described for compound **19** starting from **14**. Two diastereoisomers were isolated (**20**, 800 mg, 1.11 mmol, 46% and **22**, 400 mg, 0.55 mmol, 23%).

Compound **20**: Yield: 46%, white foam. $[\alpha]_D^{20}$ −0.3 (*c* 0.92, MeOH); ^1H NMR (250 MHz, CD_3OD): δ = 1.43 (s, 9H, C(CH_3)$_3$), 1.44 (s, 18H, 3 × C(CH_3)$_3$), 2.38–2.48 (m, 4H, H6, H13), 2.97–3.87 (m, 8H, H3, H10, H5, H12), 4.28 (s, 2H, CH_2NH), 4.25–4.72 (m, 6H, H6a, H6b, H2, H9), 7.71 (s, 1H, H4b), 7.80 (s, 1H, H5a), 7.97 (s, 1H, H5b); ^{13}C NMR (62.5 MHz, CD_3OD): δ = 28.7 (3 × C(CH_3)$_3$), 36.7 (C6, C13), 47.3 (C5, C12), 51.7, 52.3, 52.5 (C2, C9, C6a, C6b, C3, C10), 80.4, 82.0 (3 × C(CH_3)$_3$), 124.8 (C5a), 126.7 (C5b), 134.4 (C4b), 147.2 (C4a), 158.0 (3 × CO), 174.6 (C7, C14); IR: 2978, 2937, 1668, 1540, 1417; MS (HR-ESI) m/z calcd for $C_{32}H_{54}N_{11}O_8$ $[M + H]^+$ 720.4151, found: 720.4124.

(2*S*,9*S*)-4,11-*N*-*tert*-Butyloxycarbonyl-9-[(1*H*-1,2,3-triazol-1-yl)methyl]-2-[4-[[(*N*-*tert*-butyloxycarbonyl)aminomethyl]-1*H*-1,2,3-triazol-1-yl]methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane *syn*-22

Yield: 23%, white foam. $[\alpha]_D^{20}$ −19.8 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ = 1.41 (s, 18H, 2 × C(CH_3)$_3$), 1.44 (s, 9H, C(CH_3)$_3$), 2.32 (br d, 2H, H6, H13), 2.54 (br t, 2H, H6, H13), 3.13 (br s, 2H, H3, H10), 3.35 (m, 2H, H5, H12), 3.66 (m, 4H, H5, H12, H3, H10), 4.30 (s, 2H, CH_2NH), 4.40–4.54 (m, 4H, H6a, H6b, H2, H9), 4.61–4.74 (m, 2H, H6a, H6b), 7.74 (s, 1H, H4b), 7.77 (s, 1H, H5a), 7.96 (s, 1H, H5b); ^{13}C NMR (100 MHz, CD_3OD): δ = 28.8 (3 × C(CH_3)$_3$), 36.7 (CH_2NH_2), 37.0 (C6, C13), 46.7 (C5, C12), 50.8, 51.2 (C2, C9, C6a, C6b, C3, C10), 80.4, 82.5 (3 × C(CH_3)$_3$), 125.2 (C5a), 127.1 (C5b), 134.4 (C4b), 147.1 (C4a), 158.2 (3 × CO), 174.1 (C7, C14); IR: 2972, 2930, 1661, 1516, 1408; MS (HR-ESI) m/z calcd for $C_{32}H_{54}N_{11}O_8$ $[M + H]^+$ 720.4151, found: 720.4137.

(2*S*,9*R*)-9[[4-(Phenylmethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane, trifluoroacetate salt *anti*-23

TFA (2 mL, 26.5 mmol) was added dropwise to a stirred solution of **19** (340 mg, 0.50 mmol) in CH_2Cl_2 (25 mL) at 0 °C under an argon atmosphere. At the end of the addition, the temperature was allowed to warm to room temperature and the mixture was stirred for 3 h, at which point the reaction was complete (monitored by TLC). Water was added (20 mL) to quench the reaction and the two layers were separated. The organic phase was extracted once with distilled water (10 mL). The combined aqueous layers were then co-evaporated three times with Et_2O to remove residual TFA and freeze-dried to furnish the desired product as a TFA salt (350 mg, quantitative yield) as a white powder. $[\alpha]_D^{27}$ 3.9 (*c* 0.80, H_2O); ^1H NMR (400 MHz, D_2O): δ = 2.19–2.29 (m, 1H, H6 or H13), 2.42–2.52 (m, 2H, H6, H13), 2.54–2.62 (m, 1H, H6 or H13), 3.07–3.15 (m, 1H, H5 or H12), 3.15–3.23 (m, 1H, H5 or H12), 3.32–3.38 (m, 4H, H3, H10), 3.39–3.53 (m, 2H, H5, H12), 3.96 (s, 2H, CH_2Ph), 4.39–4.48 (m, 1H, H6a), 4.53–4.68 (m, 5H, H2, H9, H6a, H6b), 7.16–7.31 (m, 5H, H-Ar), 7.69 (s, 1H, H5a), 7.74 (s, 1H, H4b), 7.93 (s, 1H, H5b); ^{13}C NMR (100 MHz, D_2O): δ = 29.7, 29.8 (C6, C13), 30.7 (CH_2Ph), 42.4, 42.5 (C5, C12), 46.5, 46.7 (C2, C9), 46.9, 47.0 (C3, C10), 49.8 (C6b), 50.0 (C6a), 124.2 (C5a), 126.4 (C5b), 126.7 (CH-Ar), 128.5 (CH-Ar), 128.9 (CH-Ar), 134.0 (C4b), 139.1 (C-Ar), 147.9 (C4a), 174.0, 174.6 (C7, C14); IR: 2995, 1666, 1547, 1454; MS (HR-ESI) m/z calcd for $C_{23}H_{33}N_{10}O_2$ $[M + H]^+$ 481.2782, found: 481.2780.

(2*S*,9*S*)-9[[4-(Phenylmethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane, trifluoroacetate salt *syn*-25

Prepared following the procedure described for compound **23** starting from **21**. Quantitative yield, white foam. $[\alpha]_D^{27}$ −40.9 (*c* 0.83, H_2O); ^1H NMR (400 MHz, D_2O): δ = 2.19–2.28 (m, 1H, H6 or H13), 2.44–2.67 (m, 3H, H6, H13), 3.01–3.08 (dt, 1H, *J* = 3.8, 13.4 Hz, H5 or H12), 3.09–3.17 (dt, 1H, *J* = 3.8, 13.4 Hz, 1H, H5 or H12), 3.24–3.35 (m, 3H, H3, H10, H5 or H12), 3.37–3.61 (m, 3H, H3, H10, H5 or H12), 3.97 (s, 2H, CH_2Ph), 4.34–4.43 (m, 1H, H2 or H9), 4.44–4.52 (m, 2H, H2 or H9, H6a), 4.55–4.66 (m, 3H, H6a, H6b), 7.18–7.30 (m, 5H, H-Ar), 7.74 (s, 1H, H5a), 7.77 (s, 1H, H4b), 7.96 (s, 1H, H5b); ^{13}C NMR (100 MHz, D_2O): δ = 28.7, 29.0 (C6, C13), 30.6 (CH_2Ph), 42.3, 42.5 (C5, C12), 45.6 (C3, C10), 47.5, 48.2 (C2, C9), 49.7 (C6b), 50.1 (C6a), 124.4 (C5a), 126.5 (C5b), 126.8 (CH-Ar), 128.5 (CH-Ar), 128.9 (CH-Ar),

133.9 (C4b), 138.9 (C-Ar), 147.9 (C4a), 174.0, 174.8 (C7, C14); IR: 3028, 1665, 1547, 1452; MS (HR-ESI) *m*/*z* calcd for $C_{23}H_{33}N_{10}O_2$ $[M + H]^+$ 481.2782, found: 481.2798.

(2*S*,9*R*)-9[4-[(Aminomethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane, trifluoroacetate salt *anti*-24

Prepared following the procedure described for compound **23** starting from **20**. Quantitative yield, white foam. $[\alpha]_D^{20}$ −0.4 (*c* 0.66, H_2O); ^{1}H NMR (250 MHz, D_2O): δ = 2.47–2.56 (m, 2H, H6, H13), 2.57–2.68 (m, 2H, H6, H13), 3.14–3.28 (m, 2H, H5, H12), 3.31–3.46 (m, 4H, H3, H10), 3.49–3.59 (m, 2H, H5, H12), 4.25 (s, 2H, CH_2NH_2), 4.55–4.75 (m, 6H, H2, H9, H6a, H6b), 7.75 (s, 1H, H4b), 7.94 (s, 1H, H5b), 8.06 (s, 1H, H5a); ^{13}C NMR (62.5 MHz, D_2O): δ = 29.8, 29.9 (C6, C13), 33.8 (CH_2NH_2), 42.5 (C5, C12), 46.7 (C2, C9), 46.8 (C3, C10), 49.9, 50.2 (C6a, C6b), 125.8 (C5a), 126.3 (C5b), 134.1 (C4b), 140.0 (C4a), 174.5 (C7, C14); IR: 2978, 1668, 1543; MS (HR-ESI) *m*/*z* calcd for $C_{17}H_{30}N_{11}O_2$ $[M + H]^+$ 420.2578, found: 420.2568.

(2*S*,9*S*)-9-[4-[(Aminomethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-7,14-dioxo-1,4,8,11-tetraazacyclotetradecane, trifluoroacetate salt *syn*-26

Prepared following the procedure described for compound **23** starting from **22**. Quantitative yield, white foam. $[\alpha]_D^{20}$ −0.6 (*c* 0.90, H_2O); ^{1}H NMR (400 MHz, D_2O): δ = 2.49–2.57 (m, 2H, H6, H13), 2.62–2.73 (m, 2H, H6, H13), 3.14 (m, 1H, H5 or H12), 3.17 (m, 1H, H5 or H12), 3.32 (m, 1H, H3 or H10), 3.35 (m, 1H, H3 or H10), 3.44–3.52 (m, 2H, H5, H12), 3.52–3.62 (m, 2H, H3, H10), 4.24 (s, 2H, CH_2NH$_2$), 4.42–4.56 (m, 2H, H2, H9), 4.58–4.68 (m, 4H, H6a, H6b), 7.76 (s, 1H, H4b), 7.95 (s, 1H, H5b), 8.06 (s, 1H, H5a); ^{13}C NMR (100 MHz, D_2O): δ = 29.0 (C6, C13), 33.8 (CH_2NH_2), 42.5 (C5, C12), 45.8 (C3, C10), 47.6, 48.0 (C2, C9), 49.7, 50.0 (C6a, C6b), 125.8 (C5a), 126.4 (C5b), 134.0 (C4b), 140.0 (C4a), 174.5, 174.6 (C7, C14); IR: 3013, 1661, 1547; MS (HR-ESI) *m*/*z* calcd for $C_{17}H_{30}N_{11}O_2$ $[M + H]^+$ 420.2578, found: 420.2574.

(2*S*,9*R*)-9[[4-(Phenylmethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-1,4,8,11-tetraazacyclotetradecane *anti*-27

To a suspension of the TFA salt of *anti*-**23** (490 mg, 0.69 mmol) in dry THF (3 mL) under an argon atmosphere was slowly added a borane tetrahydrofuran complex solution (1 M in THF, 10 mL, 10 mmol, 15 eq.) at 0 °C. The mixture was stirred at room temperature for 3 h and then heated under reflux for 18 h. After cooling at 0 °C, the excess borane was hydrolyzed with a 1 : 1 mixture of water and THF (15 mL), after which the THF was evaporated under reduced pressure. A 6 N HCl solution (18 mL) was added and the mixture was heated to reflux for 4 h. After cooling at room temperature, KOH pellets were added until pH > 12. The solution was extracted with CH_2Cl_2 (6 × 15 mL), and the combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. After evaporation, compound **27** (138 mg, 47%) was obtained as a white foam. $[\alpha]_D^{20}$ −1.1 (*c* 0.8, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.55–1.68, 1.70–1.82 (2m, 4H, H6, H13), 2.21 (t, 2H, *J* = 11.5 Hz, H3, H10), 2.43–2.52 (m, 4H, H5, H12, H7, H14), 2.58 (dd, 1H, *J* = 11.5 Hz, 5.5 Hz, H3), 2.59 (dd, 1H, *J* = 11.5 Hz, 5.5 Hz, H10), 2.88 (m, 2H, H7, H14), 3.06 (m, 2H, H2, H9), 3.07–3.19 (m, 2H, H5, H12), 4.04 (s, 2H, CH_2Ph), 4.35 (dd, 1H, *J* = 14.0 Hz, 6.5 Hz, H6a), 4.44 (dd, 1H, *J* = 14.0 Hz, 6.5 Hz, H6b), 4.48 (dd, 1H, *J* = 14.0 Hz, 4.5 Hz, H6a), 4.55 (dd, 1H, *J* = 14.0 Hz, 4.5 Hz, H6b), 7.17–7.30 (m, 5H, H-Ar), 7.71 (s, 1H, H5a), 7.74 (d, 1H, *J* = 1.0 Hz, H4b), 8.00 (d, 1H, *J* = 1.0 Hz, H5b); ^{13}C NMR (100 MHz, CD_3OD): δ = 29.6 (C6, C13), 32.5 (CH_2Ph), 48.7, 48.8 (C5, C12), 51.4, 51.6 (C6a, C6b), 51.9 (C7, C14), 53.4, 53.5 (C3, C10), 59.1 (C2, C9), 124.8 (C5a), 126.8 (C5b), 127.5 (CH-Ar), 129.6 (CH-Ar), 134.4 (C4b), 140.5 (C-Ar), 148.6 (C4a); IR: 3246, 3182, 2916, 2806, 1639, 1547; MS (HR-ESI) *m*/*z* calcd for $C_{23}H_{37}N_{10}$ $[M + H]^+$ 453.3197, found: 453.3209.

(2*S*,9*S*)-9[[4-(Phenylmethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-1,4,8,11-tetraazacyclotetradecane *syn*-28

Prepared following the procedure described for compound **27** starting from **25**. Yield: 67%, white foam. $[\alpha]_D^{20}$ −15.5 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54–1.65, 1.66–1.79 (2m, 4H, H6, H13), 2.32–2.38 (m, 2H, H3, H10), 2.52–2.66 (m, 6H, H5, H12, H3, H10, H7, H14), 2.71–2.84 (m, 4H, H7, H14, H5, H12), 2.99–3.09 (m, 2H, H2, H9), 4.07 (s, 2H, CH_2Ph), 4.21 (dd, 1H, *J* = 14.0 Hz, 6.5 Hz, H6a), 4.30 (dd, 1H, *J* = 14.0 Hz, 5.0 Hz, H6a), 4.32 (dd, 1H, *J* = 14.0 Hz, 6.5 Hz, H6b), 4.44 (dd, 1H, *J* = 14.0 Hz, 5.0 Hz, H6b), 7.19–7.31 (m, 5H, H-Ar), 7.23 (s, 1H, H5a), 7.62 (s, 1H, H5b), 7.67 (s, 1H, H4b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2 (C6, C13), 32.4 (CH_2Ph), 48.5 (C5, C12), 50.4, 50.5 (C7, C14), 51.1 (C3, C10), 51.8 (C6b), 52.0 (C6a), 57.4 (C2, C9), 122.7 (C5a), 124.6 (C5b), 126.6 (CH-Ar), 128.7, 128.8 (CH-Ar), 133.8 (C4b), 139.3 (C-Ar), 147.6 (C4a); IR: 3278, 3238, 2918, 2816, 1655, 1547, 1452, 1431, 1219; MS (HR-ESI) *m*/*z* calcd for $C_{23}H_{37}N_{10}$ $[M + H]^+$ 453.3197, found: 453.3212.

(2*S*,9*R*)-9-[4-[(Aminomethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-1,4,8,11-tetraazacyclotetradecane *anti*-29

Prepared following the procedure described for compound **27** starting from **24**. After cooling at room temperature, the THF was removed under vacuum and the resulting aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and evaporated to dryness. The acidic aqueous phase was subjected to anionic exchange column chromatography and the resulting pure amine was collected from pH = 13 to pH = 9. Yield: 45%, white foam. $[\alpha]_D^{20}$ −0.1 (*c* 0.48, H_2O); ^{1}H NMR (400 MHz, D_2O): δ = 1.45–1.55, 1.61–1.68 (2m, 4H, H6, H13), 2.24–2.30 (m, 2H, H3, H10), 2.37–2.54 (m, 6H, H5, H12, H3, H10, H7, H14), 2.71–2.78, 2.82–2.88 (m, 4H, H7, H14, H5, H12), 3.05–3.13 (m, 2H, H2, H9), 3.79 (s, 2H, CH_2NH$_2$), 4.32–4.51 (m, 4H, H6a, H6b), 7.73 (s, 1H, H5a), 7.79 (s, 1H, H5b), 7.90 (s, 1H, H4b); ^{13}C NMR (100 MHz, D_2O): δ = 27.5 (C6, C13), 35.6 (CH_2NH_2), 45.2, 45.3 (C5, C12), 48.0 (C7, C14), 50.6, 50.7 (C6a, C6b), 50.9 (C3, C10), 56.2 (C2, C9), 123.8 (C5a), 126.4 (C5b), 133.9 (C4b), 148.8 (C4a); IR: 3417, 3251, 3189, 2952, 2905, 1578; MS (HR-ESI) *m*/*z* calcd for $C_{17}H_{34}N_{11}$ $[M + H]^+$ 392.2993, found: 392.2950.

(2*S*,9*S*)-9-[4-[(Aminomethyl)-1*H*-1,2,3-triazol-1-yl]methyl]-2-[(1*H*-1,2,3-triazol-1-yl)methyl]-1,4,8,11-tetraazacyclotetradecane *syn*-30

Prepared following the procedure described for compound **27** starting from **26**. After cooling at room temperature, the THF was removed under vacuum and the resulting aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and evaporated to dryness. The acidic aqueous phase was subjected to anionic exchange column chromatography and the resulting pure amine was collected from pH = 13 to pH = 9. Yield: 48%, white foam. $[\alpha]_D^{20}$ −34.7 (*c* 0.30, H_2O); ^{1}H NMR (400 MHz, D_2O): δ = 1.59–1.68 (m, 4H, H6, H13), 2.48–2.75 (m, 10H, H5, H12, H14, H3, H10), 3.17–3.25 (m, 2H, H2, H9), 3.60–3.62 (m, 2H, H7), 3.87 (s, 2H, CH_2NH$_2$), 4.38–4.59 (m, 4H, H6a, H6b), 7.73 (s, 1H, H5a), 7.80 (s, 1H, H5b), 7.92 (s, 1H, H4b). ^{13}C NMR (100 MHz, D_2O): δ = 27.1, 27.8 (C6, C13), 35.6 (CH_2NH_2), 44.9, 45.0, 47.7, 47.8, 49.4 (C14, C5, C12, C3, C10), 51.1, 51.3 (C6a, C6b), 55.8 (C9, C2), 61.5 (C7), 123.7 (C5a), 126.3 (C5b), 134.0 (C4b), 148.8 (C4a); IR: 3421, 3259, 3178, 2947, 2912, 1605; MS (HR-ESI) *m*/*z* calcd for $C_{17}H_{34}N_{11}$ $[M + H]^+$ 392.2993, found: 392.2991.

Acknowledgements

The authors thank the Région Lorraine for the post-doctoral funding of A.-S. Felten. The authors acknowledge S. Parant, B. Fernette, F. Lachaud and P. Lemière for technical assistance, NMR and ESI-MS, and E. Wenger for X-ray measurements at Université de Lorraine.

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