A convenient one-step synthesis of mono-*N*-functionalized tetraazamacrocycles

Hélène Fensterbank,[a] Jiarong Zhu,[a] Didier Riou[b] and Chantal Larpent*[a]

[a] *LRC-CEA DSM 95-1, SIRCOB EP-CNRS 102 and* [b] *Institut Lavoisier, UMR-CNRS 173, Université de Versailles-St Quentin en Y., 45 avenue des Etats-Unis, F. 78035 Versailles Cedex*

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N-Monoalkylated azamacrocycles are selectively obtained by reacting cyclam (1,4,8,11-tetraazacyclotetradecane) with equimolar amounts of Michael acceptors in chloroform in the presence of one equivalent of acid (TsOH). This chemoselective addition provides a general route to new mono-substituted azamacrocycles with various pendant groups such as sulfonic acid, ester, amide, nitrile, sugar or crown ether. The selectivity for monoaddition results from protonation of the azamacrocycles in the presence of one equivalent of acid.

Introduction

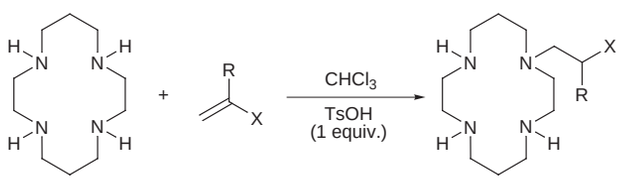
Interest in the synthesis and properties of chelating ligands based on polyazamacrocycles has expanded significantly over the last two decades since they find numerous applications in, for example, selective complexation and extraction of metallic cations or radiochemical and MRI contrast agents.[1,2] Owing to their remarkable complexation properties, the 14-membered tetraazamacrocycle **1** (cyclam) and its derivatives have received considerable attention and there is a great demand for economical and efficient syntheses of new bifunctional structures that may exhibit specific properties.

Different approaches have been devised for the synthesis of mono-*N*-substituted tetraazamacrocycles. One way follows a protection–alkylation–deprotection sequence.[3,4] Three tosyl or Boc groups have been introduced affording a varied functionalization of the remaining unprotected nitrogen.[3] Elegant routes to temporarily block three N atoms through phosphoryl, boron or metal carbonyl intermediates have also been developed.[4] A second way relies on the reaction of a great excess of tetraazamacrocycle toward the alkylating agent thereby minimizing polyalkylation.[5] Finally, Kruper *et al.* reported a selective alkylation of polyazamacrocycles involving α-haloesters and primary halides in non-polar aprotic solvents.[6]

In this context and in the course of our studies involving derivatization of cyclam, we are interested in developing methods of functionalization of tetraazamacrocycles avoiding the use of protecting groups. Here we wish to report a selective one-step access to mono-*N*-substituted cyclam derivatives through nucleophilic addition on commercially available or easily prepared Michael acceptors.

Results and discussion

N-Monoalkylated azamacrocycles are selectively obtained by reacting cyclam **1** with equimolar amounts of Michael acceptors **2** in chloroform in the presence of one equivalent of toluene-*p*-sulfonic acid TsOH (Scheme 1 and Table 1). When electrophiles like **2d** and **2j** bearing a sulfonic or a carboxylic acid group are used, the reactions are performed without TsOH. Monitoring of the reactions by TLC shows that they are achieved within 2 to 48 hours depending on the alkylating agent. The electrospray mass spectra of the reaction mixtures clearly demonstrate that the mono-adduct is the major product accompanied with slight amounts of di-alkylated products (*vide infra*). The *N*-monoalkylated cyclam derivatives **3**–**9** are purified by column chromatography on silica gel using a tertiary eluent



1 **2a-j** **3-9**

Scheme 1

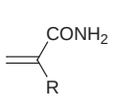
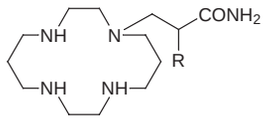
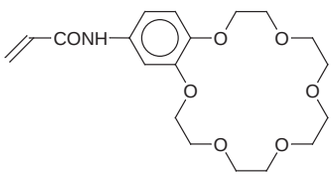
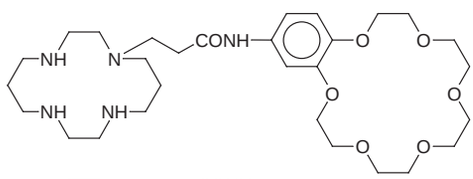
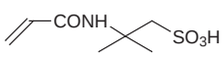
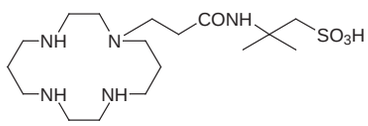
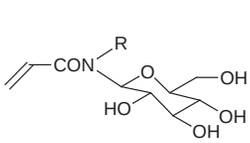
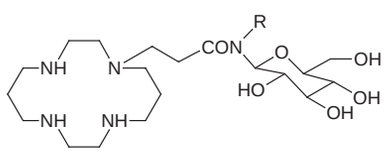
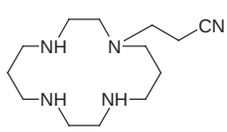
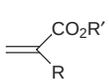
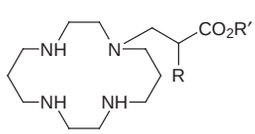
($CHCl_3$–MeOH–NH_4OH) and isolated with up to 80% yield. The yield of isolated product dramatically depends on the chromatographic separation: as a general trend, the lower the polarity of the product the higher the isolated yield.

Addition of cyclam **1** readily takes place at room temperature on electron-deficient acrylic double bonds with primary, secondary or tertiary amide, nitrile or ester substituents thus leading to a wide range of functionalized macrocycles. The reactions with acrylamides **2a**,**c**–**f** give rise to the highest reaction yields of mono-substituted macrocycle and allow the preparation of new functionalized cyclam derivatives like the bis-macrocycle **4** bearing two distinct sites of complexation, the amphiphilic macrocycles **6a**–**b** with a chiral sugar pendant group and the sulfonated water-soluble cage **5**. Addition of **1** to the highly electron-deficient double bond of acrylonitrile **2g** is less selective and leads to the formation of significant amounts of di-alkylated macrocycles. Macrocycles with an ester pendant group like **8a** obtained from acrylic esters are more efficiently isolated by chromatography using a non aqueous eluent involving $iPrNH_2$ rather than an eluent containing aqueous ammonia.

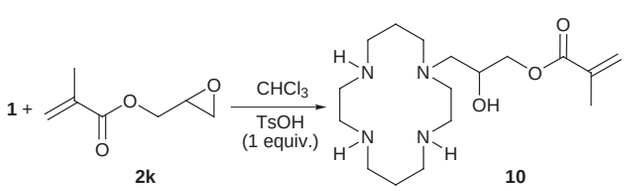
On the other hand, as already observed for other nucleophiles,[7] methacrylic derivatives **2b** and **2i** are much less reactive and give rise to lower reaction yields even after refluxing the reaction mixtures for a few days. However, the poor reactivity of methacrylates proved useful for the introduction of a polymerizable methacrylic moiety on cyclam by reacting, at room temperature, a methacrylic substrate bearing a second functionality able to undergo a nucleophilic reaction with cyclam. Thus, at room temperature in chloroform and in the presence of one equivalent of TsOH, cyclam specifically reacts with the epoxide moiety of glycidyl methacrylate **2k** leading to the isolation of the *N*-monoalkylated macrocycle **10** accompanied with small amounts of the other regioisomer resulting from the ring opening of the epoxide (Scheme 2).

The mono-*N*-substituted macrocycles **3**–**10** have been charac-

Table 1 Alkylation of cyclam **1** with Michael acceptors **2**

Michael acceptor			*N*-Functionalized tetraazamacrocycle[a]			
	R = H	**2a**		R = H	**3a**	r.t., 16h (81%)
	R = Me	**2b**		R = Me	**3b**	reflux, 4 days (45%)
		**2c**			**4**	r.t., 48h (69%)
		**2d**			**5**	r.t., 14 days (59%)[b]
	R = $C_{10}H_{21}$	**2e**[c]		R = $C_{10}H_{21}$	**6a**	r.t., 4h (42%)
	R = $C_{12}H_{25}$	**2f**[c]		R = $C_{12}H_{25}$	**6b**	r.t., 24h (66%)
		**2g**			**7**	r.t., 24h (57%)
	R = H; R′ = Et	**2h**		R = H; R′ = Et	**8a**	r.t., 18h (67%)
	R = Me; R′ = Et	**2i**		R = Me; R′ = Et	**8b**	reflux, 7 days (25%)
	R = H; R′ = H	**2j**		R = H; R′ = H	**9**	reflux, 4 days(63%)[b,c]

[a] Experimental conditions (isolated yield). [b] Without TsOH. [c] Prepared according to ref. 13. [d] Yield estimated by MS-electrospray; chromatographic purification only afforded a low yield of an impure product (29%).



Scheme 2

terized by IR, NMR and mass spectrometry. In every case the monoalkylation is confirmed by the spectroscopic data. The electrospray mass spectra show the $M + H^+$ ion (100%) and the NMR spectra show the expected non-equivalent ^{13}C and ^{1}H nuclei for the cyclam ring[5a] as well as additional signals due to the substituent. Moreover single crystals of **3a** suitable for X-ray diffraction analysis have been obtained by crystallization from chloroform–hexane. The resulting crystallographic structure demonstrates the monoalkylation (Fig. 1).

Addition of **1** or other azamacrocycles to Michael acceptors has been used to prepare tetra-*N*-substituted macrocycles[8] but, to the best of our knowledge, only one example of monoaddition using an excess of free base **1** has been described.[9] In our reactions, the presence of one equivalent of acid significantly increases the selectivity of the addition as demonstrated by monitoring the reaction of cyclam **1** (1 equiv.) and acrylamide **2a** (1 equiv.) in chloroform by mass spectrometry (electrospray): after 16 h at room temperature, without TsOH, the reaction mixture contained 40% of monoalkylated cyclam **3a**, 28% of disubstituted macrocycle and 32% unreacted **1** while, under the same conditions, in the presence of one equivalent TsOH, the percentage of monoalkylated cyclam **3a** reached 80% accompanied by disubstituted macrocycle (15%) and unreacted **1** (5%). The diminished nucleophilicity of the remaining secondary nitrogens resulting from monoprotonation of both starting and alkylated azamacrocycles in the presence of one equivalent of acid may account for the chemoselective addition that we observed. Indeed, according to the protonation constants ($pK_a = 11.6$, 10.6, 1.6 and 2.4),[10] the monoprotonated starting base **1** possesses only one nucleophilic nitrogen. Moreover, the monoalkylated macrocycle generated *in situ* is even more readily protonated. In the non-polar aprotic medium used in our reactions, a protonated structure,

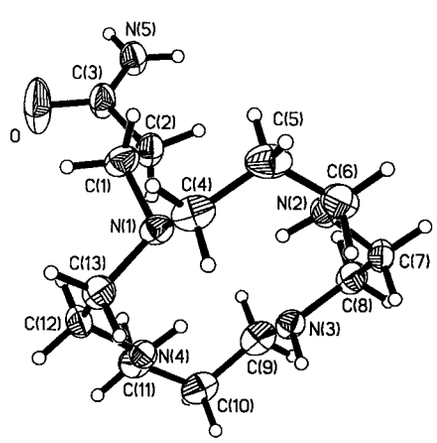


Fig. 1 ORTEP diagram of the molecular structure of **3a**.

where the proton is tightly associated with the tetraza framework through hydrogen bonding, may account for the poor nucleophilicity of the remaining secondary nitrogen atoms which prevents a second addition. Such diminished nucleophilicity resulting from protonation in non-polar solvents has already been invoked in the selective alkylation of other azamacrocycles with alkyl halides.[6] In addition, it is worth noting that Michael addition does not occur at room temperature in the presence of two equivalents of acid since the diprotonated cyclam is a poor nucleophile. Consequently, the preparation of *N*-alkylated macrocycles **5** and **9** from acidic Michael acceptors **2d** and **2j** is achieved without TsOH.

Conclusion

To conclude, this selective Michael addition is a versatile, one-step procedure which permits the synthesis of a wide range of functionalized cyclam derivatives with various pendant arms such as carboxylic or sulfonic acid, ester, amide, nitrile, sugar and even crown ether. Most of them are new compounds.[5a,b,11] These bifunctional macrocycles, especially the sugar-based amphiphilic cages **6a**,**b** and the unsymmetrical bis-macrocycle **4**, are promising molecules for selective complexation and extraction and they may exhibit antiviral properties. Moreover, it is hoped that the procedure reported here will be quite general[12] and the selectivity for monoaddition arising from protonation with one equivalent TsOH, depicted here in the case of cyclam **1**, is expected to be attainable with other azamacrocycles like cyclen which possess similar protonation constants.

Experimental

^{1}H and ^{13}C NMR spectra (300 and 75 MHz respectively) were acquired on a Bruker AM300 spectrometer. Infrared spectra were recorded on a FTIR spectrometer. Mass spectra were obtained on a MS-ENGINE (HP5989B) by direct introduction. Electrospray was used in the positive mode and the samples were diluted in H_2O–MeOH (20:80) + 1% HCOOH. TLC analysis was performed on silica plates (Merck $60F_{254}$) with the following indicators: 1) ninhydrin (0.2% in ethanol); 2) $Cu(NO_3)_2 \cdot 3H_2O$ (0.2% in ethanol). Column chromatography was carried out with silica gel GEDURAN SI60 from Merck. Ammonia in the eluent system $CHCl_3$–MeOH–NH_4OH was used as 32% in water. Cyclam (purity >98% from Fluka) was used without further purification. All Michael acceptors were commercially available with the exception of **2e** and **2f** which were prepared according to previously described procedures.[13]

3-(1,4,8,11-Tetraazacyclotetradecan-1-yl)propionamide 3a

A 10 mL round bottomed flask was charged with 200 mg (1 mmol) of cyclam **1**, 190 mg (1 mmol) of toluene-*p*-sulfonic acid monohydrate (TsOH) and 4 mL of chloroform. Acrylamide **2a** (71 mg, 1 mmol) and the tip of a spatula of 2,4-di-*tert*-butylphenol (radical inhibitor) were then added. The resulting reaction mixture was stirred for 16 hours at room temperature, concentrated and the product was chromatographed through silica gel ($CHCl_3$–MeOH–NH_4OH, 4:4:1) to yield a white solid (220 mg, 81%) which crystallized in acetonitrile. Crystals that were suitable for X-ray analysis were obtained by slow diffusion of 3 mL of hexane in a 0.5 mL chloroform solution of the product. Mp 121–122 °C; $R_f = 0.25$ ($CHCl_3$–MeOH–NH_4OH, 4:4:1); ν_{max} (neat)/cm^{-1} 1676 (CO), 1548; δ_H ($CDCl_3$) 1.70 (2H, m, $HNCH_2CH_2CH_2NH$), 1.77 (2H, m, $CH_2CH_2CH_2N(CH_2)_2$-CO), 2.42 (2H, t, $J = 6.6$ Hz, CH_2CO), 2.49–2.55 (4H, m, $CH_2NCH_2CH_2CO$), 2.61–2.75 (16 H, m), 5.44 (1H, br s, $CONH_2$), 7.37 (1H, br s, $CONH_2$); δ_C ($CDCl_3$) 25.97 and 28.40 ($CH_2CH_2CH_2$); 32.28 (CH_2CO); 47.13, 47.68, 48.33, 48.96, 49.16, 50.61, 52.83 and 54.28 (CH_2N); 175.20 (CO); *m*/*z* (electrospray) 272 (M + H$^+$, 100%) (Found: C, 57.6; H, 11.0; N, 25.7. $C_{13}H_{29}N_5O$ requires C, 57.5; H, 10.8; N, 25.8%).

2-Methyl-3-(1,4,8,11-tetraazacyclotetradecan-1-y l)propionamide 3b

Compound **3b** was synthesized from methacrylamide **2b** according to the procedure described above for **3a**. The reaction mixture was stirred at room temperature for 7 days, then brought to reflux for 4 days. It was chromatographed through silica gel using $CHCl_3$–MeOH–NH_4OH (elution gradient from 20:4:0.5 to 12:4:1). A colorless oil was obtained (80 mg of **3b**·0.4TsOH from 0.5 mmol of cyclam, 45%). $R_f = 0.50$ ($CHCl_3$–MeOH–NH_4OH, 3:2:1); δ_H ($CDCl_3$) 1.00 (3H, d, $J = 6.2$ Hz, CH_3CH), 1.57–1.70 (2H, m), 1.86 (3H, m), 2.12 (2H, m), 2.31 (3H, s, $CH_3C_6H_4$), 2.62–3.14 (16H, m), 7.13 (2H, d, TsOH), 7.70 (2H, d, TsOH).

N-(2,3,5,6,8,9,11,12,14,15-Decahydro-1,4,7,10,13,16-benzohexaoxacyclooctadecin-18-yl)-3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionamide 4

This was prepared from **2c** as described for **3a**. The reaction mixture was stirred at room temperature for 48 hours. Chromatography on silica gel ($CHCl_3$–MeOH–NH_4OH, 10:4:1) yielded a colorless oil (100 mg starting from 0.25 mmol of cyclam, 69%). $R_f = 0.51$ ($CHCl_3$–MeOH–NH_4OH, 2:2:1); ν_{max} (neat)/cm^{-1} 1651 (CO), 1555, 1517; δ_H ($CDCl_3$) 1.61 (2H, m, $CH_2CH_2CH_2$), 1.73 (2H, m, $CH_2CH_2CH_2$), 2.39–2.73 (20H, m, CH_2N and CH_2CO), 3.63–3.71 (12H, m, CH_2OCH_2), 3.83–3.86 (4H, m, CH_2OCH_2), 4.05–4.08 (2H, m, CH_2OAr), 4.10–4.13 (2H, m, CH_2OAr), 6.73 (1H, d, $J = 8.8$ Hz, H_{Ar}), 7.18 (1H, dd, $J = 8.6$, 2.2 Hz, H_{Ar}), 7.60 (1H, d, $J = 2.2$ Hz, H_{Ar}), 9.93 (1H, s, NHCO); δ_C ($CDCl_3$) 25.70 and 27.64 ($CH_2CH_2CH_2$); 35.78 (CH_2CO); 46.76, 47.05, 47.14, 47.76, 48.84, 49.89, 50.92, 52.62 and 53.58 (CH_2N); 68.54, 69.17, 69.31, 69.47, 70.44 and 70.49 (CH_2O); 105.64, 111.13 and 114.14 ($C_{Ar}H$); 133.64, 144.54 and 148.75 ($C_{Ar}O$ and $C_{Ar}N$); 170.76 (CO); *m*/*z* (electrospray) 303 (54%), 582 (M + H$^+$, 100), 605 (M + H$^+$ + Na$^+$, 19).

2-[3-(1,4,8,11-Tetraazacyclotetradecan-1-yl)propionylamino]-2-methylpropane-1-sulfonic acid 5

2-Acrylamido-2-methylpropane-1-sulfonic acid **2d** (207 mg, 1 mmol) was added to a solution of cyclam (200 mg, 1 mmol) in 4 mL of chloroform in the presence of the tip of a spatula of 2,4-di-*tert*-butylphenol. The reaction mixture was stirred at room temperature for 14 days and then chromatographed through silica gel using $CHCl_3$–MeOH–NH_4OH (elution gradient from 12:4:1 to 10:4:1) to yield a colorless oil (240 mg, 59%). $R_f = 0.54$ ($CHCl_3$–MeOH–i$PrNH_2$, 4:3:1); ν_{max} (neat)/cm^{-1} 1648 (CO), 1559 (NH), 1469, 1214, 1191, 1049; δ_H ($CDCl_3$) 1.51 (6H, s, CH_3), 1.80 (2H, m, $CH_2CH_2CH_2$), 1.93 (2H, m, CH_2-CH_2CH_2), 2.31 (2H, t, $J = 5.5$ Hz), 2.46 (2H, t, $J = 5.2$ Hz), 2.59–2.65 (4H, m), 2.79–2.89 (10H, m), 3.02 (2H, t, $J = 4.8$ Hz), 3.12 (2H, s, CH_2SO_3H); δ_C ($CDCl_3$) 24.98, 25.52 and 27.12 ($CH_2CH_2CH_2$ and CH_3); 34.97 (CH_2CO); 46.30, 46.78, 47.29, 48.63, 49.06, 50.53, 51.80, 51.94 and 52.20 (CH_2N); 58.88 (CH_2SO_3H); 172.13 (CO); *m*/*z* (electrospray) 408 (M + H$^+$, 34%), 815 (dimer + H$^+$, 100), 1223 (trimer + 2H$^+$, 50).

N-(β-D-Glucopyranosyl)-*N*-decyl-3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionamide 6a

This was prepared by reacting 0.25 mmol of cyclam with 0.25 mmol of **2e**[13] in 2 mL of chloroform in the presence of 0.25 mmol of TsOH. To the reaction mixture was added 2,4-di-*tert*-butylphenol (tip of a spatula) and stirred for 4 hours. The product was chromatographed through silica gel ($CHCl_3$–MeOH–NH_4OH, 12:4:1) to yield a colorless oil (60 mg, 42%). $R_f = 0.51$ ($CHCl_3$–MeOH–NH_4OH, 2:2:1). Product **6a** behaves as its precursor **2e** and exists in solution as a mixture of two rotamers due to hindered rotation around the amide N–C bond.[13] The *exo* and *endo* rotamers are designated A and B

respectively; ν_{max} (neat)/cm^{-1} 1648 (CO), 1573; δ_H (CD_3OD) 0.90 (3H, t, J = 6.6 Hz, CH_3), 1.30–1.35 (14H, m, CH_2 alkyl chain), 1.64–1.80 (6H, m, CH_2CH_2NCO and NCH_2CH_2-CH_2N), 2.57–2.93 (20H, m, CH_2NCH_2 and CH_2CO), 3.24–3.52 (6H, m, C*H*OH, C*H*CH_2OH, CH_2NCO), 3.62 (1H, dd, ^2J = 11.7, ^3J = 6.3 Hz, CH_2OH), 3.86 (1H, m, CH_2OH), 5.50 (1H, d, ^3J = 8.8 Hz, OC*H*N, A) (the *exo* A/*endo* B isomeric ratio 30 : 70 was calculated from the integration curves of the anomeric proton of rotamer A and of one proton CH_2OH of rotamers A and B; δ_C (CD_3OD) 14.46 (CH_3); 23.73, 26.02, 26.26, 27.51, 28.29, 28.40, 28.45, 28.79, 30.09, 30.47, 30.52, 30.73, 30.76, 31.23, 31.45, 31.87 and 33.06 (NCH_2CH_2CH_2N, CH_2 alkyl chain and CH_2CO); 43.05 (CH_2NCO, A or B); 44.72 (CH_2NCO, A or B); 47.55, 47.75, 47.84, 50.37, 50.57, 51.46, 51.66, 53.63, 54.47, 55.02 and 55.49 (CH_2N); 62.87 and 63.06 (CH_2OH); 71.31, 71.43, 71.55 and 72.08 (*C*HOH (C2 and C4)); 79.27, 79.38 and 80.53 (CHOH (C3 and C5)); 84.26 (O*C*HN, A); 88.03 (O*C*HN, B); 175.37 (CO, A); 175.83 (CO, B); *m*/*z* (electrospray) 201 (22%), 288 ([M + 2H$^+$]/2, 68), 574 (M + H$^+$, 100).

N-(β-D-Glucopyranosyl)-*N*-dodecyl-3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionamide 6b

This was prepared as described for **6a** starting from 0.5 mmol of cyclam and 0.5 mmol of **2f**.[13] The reaction mixture was stirred for 24 hours. Chromatography through silica gel ($CHCl_3$–MeOH–NH_4OH, 1 : 1 : 0 then 4 : 3 : 1) afforded 200 mg (66%) of a colorless oil. R_f = 0.27 ($CHCl_3$–MeOH–NH_4OH, 4 : 3 : 1). Product **6b** exists in solution as a mixture of two *exo* and *endo* rotamers designated A and B respectively (*vide supra*); ν_{max} (neat)/cm^{-1} 1651 (s), 1536 (w); δ_H (CD_3OD) 0.90 (3H, t, J = 6.6 Hz, CH_3), 1.29 (18H, m, CH_2 (3 to 11) alkyl chain), 1.65–1.80 (6H, m, CH_2CH_2NCO and NCH_2CH_2CH_2N), 2.56–2.88 (20H, m, CH_2NCH_2 and CH_2CO), 3.24–3.48 (6H, m, C*H*OH, C*H*CH_2OH, CH_2NCO), 3.62 (1H, dd, ^2J = 11.8, ^3J = 6.2 Hz, CH_2OH), 3.86 (1H, m, CH_2OH), 5.47 (1H, d, J = 8.8 Hz, OC*H*N, A) (the *exo* A/*endo* B isomeric ratio 28 : 72 was calculated from the integration curves of the anomeric proton of rotamer A and of one proton CH_2OH of rotamers A and B; δ_C (CD_3OD) 14.46 (CH_3); 23.73, 26.21, 26.43, 27.96, 28.31, 28.41, 28.73, 29.04, 30.07, 30.47, 30.52, 30.79, 31.29, 31.90 and 33.06 (NCH_2CH_2CH_2N, CH_2 alkyl chain and CH_2CO); 43.00 (CH_2NCO, A or B); 44.83 (CH_2NCO, A or B); 47.68, 47.97, 48.35, 49.13, 49.36, 50.42, 50.63, 51.51, 51.75, 54.12, 54.80, 54.96 and 55.15 (CH_2N); 62.88 and 63.08 (CH_2OH); 71.37, 71.45, 71.59 and 72.12 (CHOH (C2 and C4)); 79.25, 79.36 and 80.51 (CHOH (C3 and C5)); 84.33 (O*C*HN, A); 88.07 (O*C*HN, B); 175.34 (CO, A); 175.85 (CO, B); *m*/*z* (electrospray) 602 (M + H$^+$, 100%).

3-(1,4,8,11-Tetraazacyclotetradecan-1-yl)propionitrile 7

This was prepared from **2g** as described for **3a**. The resulting reaction mixture was stirred at room temperature for 24 hours. Chromatography through silica gel using $CHCl_3$–MeOH–$iPrNH_2$ (10 : 1 : 1) yielded a white powder (110 mg; 57%). R_f = 0.41 ($CHCl_3$–MeOH–$iPrNH_2$, 10 : 1 : 1); mp 68–70 °C; ν_{max} (neat)/cm^{-1} 2246 (CN), 1622, 1559; δ_H ($CDCl_3$) 1.67 (2H, m, CH_2CH_2CH_2), 1.75 (2H, m, CH_2CH_2CH_2), 2.49–2.55 (6H, m), 2.58–2.61 (4H, m), 2.65–2.75 (10H, m); δ_C ($CDCl_3$) 15.18 (*C*H$_2$CN); 25.99 and 28.47 (CH_2*C*H_2CH_2); 47.05, 47.62, 48.03, 48.13, 48.43, 49.43, 51.06, 52.69 and 54.39 (CH_2N); 118.90 (CN); *m*/*z* (electrospray) 254 (M + H$^+$, 100%) (Found: C, 54.3; H, 10.7; N, 24.5. $C_{13}H_{27}N_5.2H_2O$ requires C, 54.0; H, 10.8; N, 24.2%).

3-(1,4,8,11-Tetraazacyclotetradecan-1-yl)propionic acid ethyl ester 8a

This was prepared from **2h** as described for **3a**. The reaction mixture was stirred at room temperature for 18 hours and purified on silica gel ($CHCl_3$–MeOH–$iPrNH_2$, 20 : 1 : 1). The product was obtained as a colorless oil (200 mg, 67%). R_f = 0.48 ($CHCl_3$–MeOH–$iPrNH_2$, 10 : 1 : 1); ν_{max} (neat)/cm^{-1} 1740 (CO), 1649, 1571; δ_H ($CDCl_3$) 1.21 (3H, t, J = 7.2 Hz, CH_3), 1.64–1.75 (4H, m, CH_2CH_2CH_2), 2.42 (2H, t, J = 7.7 Hz), 2.47–2.72 (16H, m), 2.80 (2H, t, J = 7.7 Hz), 4.08 (2H, q, J = 7.2 Hz, CH_2O); δ_C ($CDCl_3$) 14.09 (CH_3); 26.03 and 28.49 (CH_2*C*H_2-CH_2); 30.59 (*C*H_2CO); 47.24, 47.58, 47.78, 48.62, 48.88, 49.10, 50.62, 52.71 and 54.24 (CH_2N); 60.24 (CH_2O); 172.71 (CO).

2-Methyl-3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionic acid ethyl ester 8b

This was prepared from **2i** as described for **3b** and performing the reaction at reflux for 7 days. Chromatography on silica gel using $CHCl_3$–MeOH–$iPrNH_2$ (20 : 1 : 1) yielded a colorless oil (80 mg, 25%). R_f = 0.44 ($CHCl_3$–MeOH–$iPrNH_2$, 10 : 1 : 1); ν_{max} (neat)/cm^{-1} 1734; δ_H ($CDCl_3$) 1.11 (3H, d, J = 6.6 Hz, CH_3CH), 1.21 (3H, t, J = 7.2 Hz, CH_3CH_2), 1.63–1.69 (4H, m, CH_2-CH_2CH_2), 2.32–2.77 (19H, m), 4.02 (1H, td, ^3J = 7.1, ^2J = 14.1 Hz, CH_2CH$_3$), 4.08 (1H, td, ^3J = 7.1, ^2J = 14.1 Hz, CH_2CH$_3$); δ_C ($CDCl_3$) 14.04 (CH_3); 15.83 (CH_3); 26.14 and 28.07 (CH_2-*C*H_2CH_2); 37.55 (*C*HCO); 47.24, 47.35, 47.66, 48.38, 48.60, 50.25, 52.80, 54.41 and 56.82 (CH_2N); 60.14 (CH_2O); 176.04 (CO); *m*/*z* (electrospray) 315 (M + H$^+$, 100%).

3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionic acid 9

Compound **9** was prepared from **2j** without TsOH according to the procedure described above for **5**. The reaction mixture was stirred at room temperature for 1 hour and heated at reflux for 4 days. The solvent was rotary evaporated and a MS analysis of the crude product was performed. Chromatography on silica gel with $CHCl_3$–MeOH–NH_4OH (4 : 3 : 1) gave 80 mg of a mixture of the desired product and of an impurity having a similar R_f. Upon standing in 1 mL of $CHCl_3$, white crystals formed and the pure product was isolated (9 mg, 3%) as shown by TLC analysis. R_f = 0.43 ($CHCl_3$–MeOH–NH_4OH, 2 : 2 : 1). δ_H (CD_3OD) 1.90 (m, 2H, CH_2CH_2CH_2), 1.99 (m, 2H, CH_2CH_2CH_2), 2.49 (t, J = 5.9 Hz, 2H, CH_2CO), 2.83–2.86 (m, 6H), 2.96–3.15 (m, 12H); δ_C (CD_3OD) 24.00 and 25.79 (CH_2*C*H_2CH_2); 34.73 (*C*H_2CO); 45.84, 45.97, 47.16, 47.58, 50.01, 50.52, 50.92, 51.73 and 55.12 (CH_2N); 179.72 (CO); *m*/*z* (electrospray of the crude product) 273 (M + H$^+$, 98); 545 (dimer + H$^+$, 100); 617 (35).

Reaction of 1 with glycidyl methacrylate 2k

The reaction was performed following the procedure described for the preparation of **3a**. The reaction mixture was stirred at room temperature for 2 days. The crude product was then chromatographed through silica gel using the following eluent system: $CHCl_3$–MeOH–$iPrNH_2$ (10 : 1 : 1) and afforded 100 mg of a colorless oil (29%). Polymerization readily takes place during the purification and concentration steps thus leading to poor isolated yield; the product must be stored at low temperature in the presence of a radical inhibitor like 2,4-di-*tert*-butylphenol. R_f = 0.40 ($CHCl_3$–MeOH–$iPrNH_2$, 10 : 1 : 1); ν_{max} (neat)/cm^{-1} 1723 (CO), 1638 (C=C); δ_H ($CDCl_3$) 1.53–1.72 (4H, m), 1.94 (3H, s, CH_3), 2.2–3.1 (19H, m), 3.65 (0.25H, dd, J = 13 Hz and 2.5 Hz, CH_2O, minor isomer), 3.81 (1H, m, C*H*OH), 3.89 (0.25H, dd, J = 13 and 3 Hz, CH_2O, minor isomer), 4.05 (1H, dd, J = 11Hz and 6 Hz, CH_2OCO), 4.17 (1H, dd, J = 11.0 Hz and 5.2 Hz, CH_2OCO), 5.03 (0.25H, m), 5.55 (1H, m, C=CH_2), 6.12 (1H, s, C=CH_2); *m*/*z* (electrospray) 343 (M + H$^+$, 100%), 685 (dimer + H$^+$, 73).

Single crystal X-ray diffraction of 3a

3a, $C_{13}H_{29}N_5O$, is monoclinic, space group $P2_1/c$ (nº 14) with lattice parameters a = 13.6057(4) Å, b = 8.9707(2) Å, c =

14.3365(3) Å, $\beta = 108.624(1)°$, $V = 1658.18(7)$ Å^3, $Z = 4$. The structure was refined with 4288 reflections ($I > 2\sigma(I)$) up to the reliability factors $R_1(F_o) = 0.0609$ and $wR_2(F_o^2) = 0.2023$.

The data were collected on a Siemens SMART three-circle diffractometer equipped with a CCD bidimensional detector; λ Mo-Kα = 0.71073 Å, graphite monochromated. A colorless fragment of crystal was affixed onto a glass fiber and centered in the X-ray beam. The exposure time was 30 s by frame. The data were reduced by the SAINT program and the absorption correction was performed with the SADABS program (G. Sheldrick, unpublished) specific to the CCD detector. The structure was solved with SHELX-TL, all the atoms were refined anisotropically except the H atoms for which geometrical constraints were applied. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www/rsc/org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/305.

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