



HAL
open science

Macrocyclic 14-membered ring diketal diamines: Synthesis, conformational analysis and ^{99m}Tc radiolabeling evaluation

Radouane Affani, Philippe Auzeloux, Jean-Claude Madelmont, Denise Dugat

► **To cite this version:**

Radouane Affani, Philippe Auzeloux, Jean-Claude Madelmont, Denise Dugat. Macrocyclic 14-membered ring diketal diamines: Synthesis, conformational analysis and ^{99m}Tc radiolabeling evaluation. *European Journal of Organic Chemistry*, 2008, pp.2039-2048. hal-00270325

HAL Id: hal-00270325

<https://hal.science/hal-00270325v1>

Submitted on 4 Apr 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Macrocyclic 14-Membered Ring Diketal Diamines: Synthesis, Conformational Analysis and ^{99m}Tc Radiolabeling Evaluation

Radouane Affani,^[a] Philippe Auzeloux,^[b] Jean-Claude Madelmont,^[b] and Denise Dugat^{*,[a]}

Keywords: Amines / Macrocycles / Reduction / Conformation analysis / Chelates / Technetium

Chiral and achiral macrocyclic diketal diamines, analogs of cyclams, were synthesized from the previously obtained corresponding diketal dilactams by reduction with lithium aluminum hydride in the presence of a trace amount of triethylamine. In the $(15\text{--}30) \times 10^{-3} \text{ M}$ concentration range, the reaction led mainly to the expected doubly reduced compounds except in the *trans*-OMe substituted series ($R = \text{Ph}, \text{Me}$), in which it partially stopped at the single reduction stage. A conformational study conducted by liquid NMR spectroscopy

and molecular mechanics calculations showed that the most stable conformations were either set in a rectangular [3434]-type structure for *trans*-OMe compounds **7b** ($R = \text{Me}$) and **10b** ($R = \text{H}$) or stabilized by two intramolecular $\text{NH}\cdots\text{O}$ hydrogen bonds for all the other macrocyclic diamines. Tc-99m radiolabeling with the nitrido-technetium core $[\text{TcN}]^{2+}$ gave =10–20 % exchange yields.

Introduction

The design and synthesis of new macrocyclic ligands for specific purposes is the subject of much ongoing work. Among these compounds, 14-membered ring amines of the cyclam type have been shown to complex a wide variety of inorganic ions,^[1,2] and more particularly technetium, with which they form thermodynamically and kinetically stable chelates.^[3] These find important applications in diagnostic nuclear medicine as receptor- or tumor-imaging agents, often after coupling with peptides or antibodies.^[4,5a] In recent decades, the isotope ^{99m}Tc has become the most widely used γ -emitter for radioscintigraphy owing to its physical properties ($t_{1/2} = 6 \text{ h}$, $E_{\gamma} = 140 \text{ keV}$), availability from ^{99}Mo , and relatively low cost.^[5]

We have focused on the synthesis,^[6] conformation,^[7] and cationic recognition properties^[8] of new diversely substituted 14-membered ring diketal dilactam macrocycles (Figure 1) for several years. Selective reduction of the lactam link of these entities would yield diketal diamines, which are analogs of cyclams. Here we report on the synthesis, conformational analysis, and ^{99m}Tc labeling study of this new class of compounds.

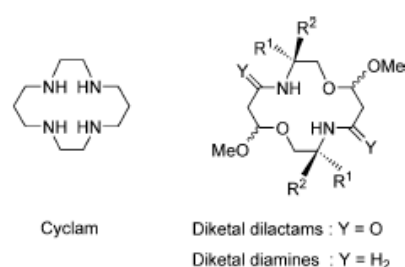


Figure 1. General structure of cyclam, diketal dilactams and diketal diamines.

Results and Discussion

Synthesis

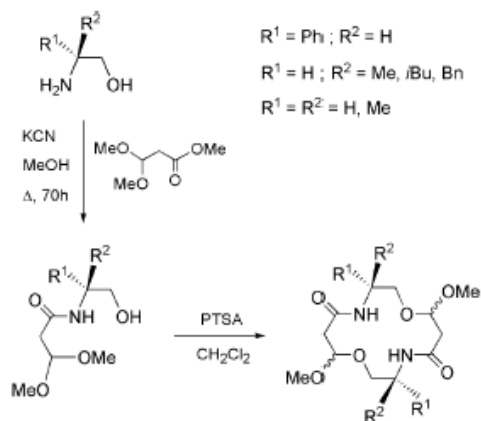
Chemistry

Macrocyclic diketal diamines were targeted by reduction of the corresponding diketal dilactams, which were prepared in two steps from β -amino alcohols (Scheme 1) and obtained in two or three diastereoisomeric forms depending on the achiral or chiral character of the starting compound, as previously reported.^[6]

Chiral series **1** and **2** provided three diastereoisomers (Figure 2): an unsymmetrical isomer **b**, in which the two OMe substituents are in a *trans* configuration and two isomers **a** and **c** of C_2 symmetry, in which the two OMe groups are in a *cis* arrangement; **a** (minor isomer) and **c** (major isomer) differ only by the *trans* or *cis* relationship of the OMe and R groups. Achiral series **3** led to two isomers **b** and **c** that both possessed some symmetry (center in **b**, C_2 axis in **c**).^[6a]

[a] Laboratoire SEESIB, UMR CNRS 6504, Université Blaise Pascal de Clermont-Ferrand, 63177 Aubière, France
E-mail: denise.dugat@univ-bpclermont.fr

[b] Laboratoire de Chimie Physique et Minérale, UFR Pharmacie, INSERM U484, Centre Jean Perrin, Université d'Auvergne, 63001 Clermont-Ferrand, France



Scheme 1.

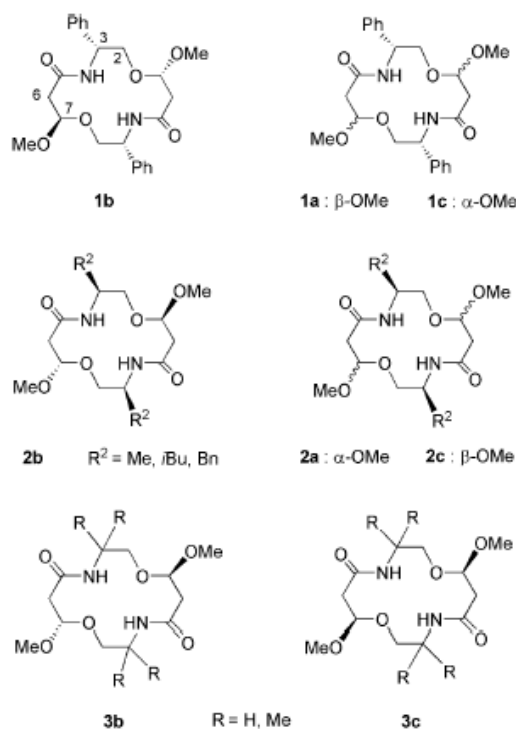


Figure 2. Structure and stereochemistry of diketal dilactams 1a,b,c, 2a,b,c and 3b,c.

The reduction study was conducted on the two major isomers **b** and **c** of three series (1; 2: $R^2 = \text{Me}$; 3: $R = \text{H}$). A first investigation of the selective reduction of the amide link of these compounds was made previously on macrocycle **1c** with several reagents ($\text{BH}_3\cdot\text{Me}_2\text{S}$, $i\text{BuAlH}_2$, Red-Al, LiAlH_4).^[9] The best results were obtained with lithium aluminium hydride (LAH, 10 equiv.) in the presence of small quantities of triethylamine, which reduced the effect of a side elimination reaction attributable to the presence of trace amounts of AlCl_3 in the LAH.^[9]

The same conditions were applied to the reduction of dilactams **1b**, **2b**, **2c**, **3b**, and **3c**, and in each case, the following were adjusted: (i) the concentration of the substrate,

Table 1. Reduction of diketal dilactams **1b,c**, **2b,c** and **3b,c** by LAH^[a] in THF.

Entry	Substrate [R]	$c_{\text{substrate}}$ [10^{-3} M]	NEt_3 [equiv.]	Time [h]	Conv. ^[b] [%]	Results ^[c] [%]
1	1c [Ph]	25	0.4	11	95	4c (30), 5c (8), 6 (8)
2 ^[d]	1b [Ph]	25	0.1	10	88	4b (4), 5b (34)
3 ^[d]	1b [Ph]	40	0.1	10	83	4b (3), 5b (31)
4	1b [Ph]	14	0.1	10	85	4b (4), 5b (48)
5	2b [Me]	12	0.1	18	93	7b (20), 8b (21), 9 (2)
6	2b [Me]	25	0.2	18	94	7b (41), 8b (20)
7	2b [Me]	30	0.2	20	93	7b (26), 8b (13)
8	2c [Me]	25	0.1	18	88	7c (22)
9	2c [Me]	30	0.1	20	94	7c (33)
10 ^[d]	3b [H]	15	0.2	8	79	10b (40)
11	3c [H]	30	0.2	7	93	10c (40), 11c (3)

[a] Molar ratio of LAH/substrate = 10:1. [b] Conversion rate based on the amount of recovered starting material. [c] Isolated yield by column chromatography; at the end of the process, unidentified polar compounds were invariably isolated in 13–22% yield, which increased with the reaction time. [d] Inverse addition order of the reactants imposed by the low solubility of the substrate in THF at high concentration. In these cases, the hydride used as a commercial THF solution was added to the substrate solution.

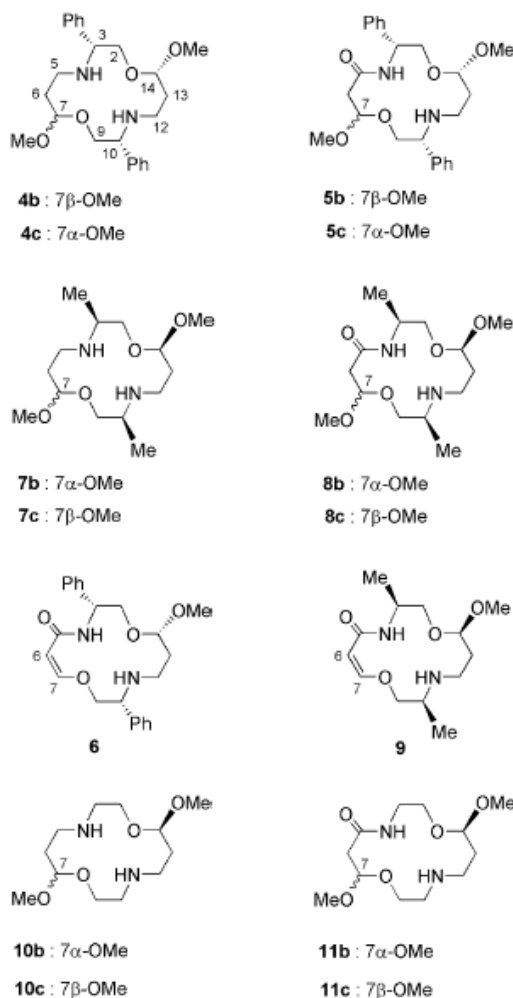


Figure 3. Structure and stereochemistry of compounds **4b,c**, **5b,c**, **6**, **7b,c**, **8b,c**, **9**, **10b,c** and **11b,c**.

Table 2. Comparison of some ^1H NMR spectroscopic data of aminolactams **5b**, **8b** and their dilactam precursors **1b**, **2b**, respectively.

Compd.	$\text{N}^4\text{-H}$ δ [ppm]	$\text{N}^{11}\text{-H}$ δ [ppm]	$\text{H}^7, \text{H}^{6\text{A}}, \text{H}^{6\text{B}}$ pattern	$\Delta\nu_{6\text{A},6\text{B}}$ [Hz]	$\text{H}^{14}, \text{H}^{13\text{A}}, \text{H}^{13\text{B}}$ pattern ^[a]	$\Delta\nu_{13\text{A},13\text{B}}$ [Hz]
1b	7.62	6.77	3dd	120.3	ABX	3.7
2b	7.04	6.00	3dd	108.0	ABX	11.6
5b	7.62	1.30	3dd	88.0	1dd, 2dddd	112.0
8b	7.03	1.98	3dd	68.0	1dd, 2dddd	76.0

[a] ABX system for $\Delta\nu_{13\text{A},13\text{B}} < 5 \times J_{13\text{A},13\text{B}}$ with $J_{13\text{A},13\text{B}} = 13.4\text{--}14.2$ Hz.

(ii) the amount of NEt_3 , and (iii) the reaction time (Table 1, Figure 3). Entry 1 (Table 1) recalls the optimal formation conditions of phenyl diketal diamine **4c**, which was invariably accompanied by two other compounds: diketal aminolactam **5c** and unsaturated ketal aminolactam **6**.^[9] These correspond, respectively, to the singly reduced macrocycle and to an elimination product, whose levels could be lowered either by using a higher substrate concentration for the first one or by adding a small amount of NEt_3 for the second one,^[9] as mentioned above. Reduction of phenyl diketal dilactam **1b** was then explored at three different concentrations (Table 1, Entries 2–4). In all cases, the reaction seemed to stop at the single reduction level to give rise almost exclusively to diketal aminolactam **5b**. In contrast, no trace of unsaturated macrocycle **6** was detected in the present case, as long as a certain amount of NEt_3 (0.1 equiv.) was engaged in the reaction. In the methyl series, the best formation conditions for diketal diamines **7b** and **7c** were found at concentrations of 25×10^{-3} M and 30×10^{-3} M, respectively (Table 1, Entries 6 and 9), and in the unsubstituted series at 15×10^{-3} M for **10b** (Table 1, Entry 10) and 30×10^{-3} M for **10c** (Table 1, Entry 11). In the last three cases, the reaction led almost exclusively and directly to the expected doubly reduced compounds.

Characterization

The structure and stereochemistry of derivatives **4–11** were established from IR, MS, 1D NMR [^1H , ^{13}C (J MOD)] and 2D NMR [COSY $^1\text{H}\text{--}^1\text{H}$, HSQC (heteronuclear single quantum correlation), and sometimes HMBC (heteronuclear multiple bond correlation)] spectroscopic data, which allowed identification of all hydrogen and carbon atoms.

In the ^1H and ^{13}C NMR spectra, diamines **4c**, **7c**, and **10b,c**, which all possess a symmetry element (C_2 for **4c**, **7c**, **10c**, center for **10b**) showed only one signal for each pair of identical groups of the macrocycle, whereas diamines **4b** and **7b** exhibited double signals due to the asymmetry of the two ring chains. Concerning *trans*-OMe aminolactams **5b** and **8b**, the reduced chain could be identified by comparison of their ^1H NMR characteristics with those of dilactams **1b** and **2b**: (i) The amide NH chemical shifts: in compounds **5b** and **8b**, the 4-NH doublet ($\delta = 7.62$ ppm) of **1b** and **2b** was still present, whereas the 11-NH signal was shifted upfield. (ii) The signal form of protons $\text{H}^{6\text{A}}$, $\text{H}^{6\text{B}}$ and $\text{H}^{13\text{A}}$, $\text{H}^{13\text{B}}$: in singly reduced compounds **5b** and **8b**, the 2dd of $\text{H}^{6\text{A}}$, $\text{H}^{6\text{B}}$ were still present, whereas the ABX

system characterizing $\text{H}^{13\text{A}}$, $\text{H}^{13\text{B}}$ in **1b** and **2b** was changed into a multiplet. These observations indicate that the reduced carbonyl group was the 12-CO of chain 2 (Table 2).

Discussion

Comparison of the results obtained in the three series ($\text{R} = \text{Ph}$, Me , H) shows that the reduction occurred more or less easily depending on the nature of the substituent and on the *cis* or *trans* stereochemistry of the OMe groups.

In the substituted series ($\text{R} = \text{Ph}$, Me), an identical accessibility of both carbonyl groups is observed on *cis* compounds **1c** and **2c**, which offer a completely unhindered face owing to the *cis* position of the four substituents. This led (i) in the phenyl series, to the obtention of doubly reduced compound **4c** at high concentration ($c = 25 \times 10^{-3}$ M), whereas a lower concentration increased the amount of singly reduced compound **5c**;^[9] (ii) in the methyl series, to the direct formation of macrocyclic diamine **7c**, irrespective of the concentration. Concerning *trans*-OMe derivatives **1b** and **2b**, the 5-CO carbonyl group of chain 1 in which the 3-R and 7-OMe groups are in a *trans* location was more difficult to reduce than the 12-CO group of chain 2 owing to the hindrance of the two faces of the molecules at the chain 1 level. This induced a degree of locking of the reaction at the single reduction step, which led almost exclusively to either aminolactam **5b** in the phenyl series or a mixture of diamine **7b** and aminolactam **8b** in the methyl series.

In the unsubstituted series ($\text{R} = \text{H}$), the absence of substituents at C^3 and C^{10} afforded the same accessibility to both carbonyl groups of *trans* dilactam **3b** and *cis* dilactam **3c** and allowed the formation of diamines **10b** and **10c** in similar yields.

In all series, the reduction occurred with moderate total yields (33–61%), which were difficult to improve.^[9] These results may be explained by the presence of polar compounds (Table 1) probably resulting from complexation between the generated diketal diamines and the Li^+ cation, which could therefore no longer catalyze the reaction,^[10] as previously reported for compound **4c**.^[9]

Conformational Analysis

^1H NMR Spectroscopic Data

The coupling constants of H^7/H^{14} and H^3/H^{10} with their vicinal hydrogen atoms give information on their position in the ring (Table 3).

Table 3. Coupling constants (J , in Hz) of the H^7 , H^{14} , H^3 , and H^{10} protons of the macrocyclic diketal diamines.

Compd. ^[a]	$J_{7,6A}$	$J_{7,6B}$	$J_{14,13A}$	$J_{14,13B}$	$J_{3,2A}$	$J_{3,2B}$	$J_{10,9A}$	$J_{10,9B}$
4b	7.8	1.8	9.1	2.0	7.0	3.0	2.8	10.0
4c	8.0	2.1	8.0	2.1	9.1	2.8	9.1	2.8
7b	8.1	2.6	9.2	1.6	2.6	9.7	1.9	5.4
7c	8.6	2.5	8.6	2.5	7.5	2.0	7.5	2.0
10b ^[b]	8.6	2.2	8.6	2.2	2.7	9.4	2.7	9.4
					4.1	2.3	4.1	2.3
10c ^[b]	7.2	2.7	7.2	2.7	2.8	7.7	2.8	7.7
					6.3	1.7	6.3	1.7

[a] For all compounds $|J_{6A,6B}| = |J_{13A,13B}| = 14.0$ – 14.7 Hz and $|J_{2A,2B}| = |J_{9A,9B}| = 9.5$ – 10.2 Hz. [b] First line: H^{3A} or H^{10A} , second line: H^{3B} or H^{10B} .

Thus, in all three diamines **4**, **7**, and **10**, the H^7 and H^{14} protons, which exhibit large and small coupling constants ($J = 7.2$ – 9.2 Hz and $J = 1.6$ – 2.7 Hz), very likely occupy an axial position, which implies an equatorial situation of the OMe groups. Also, in substituted amines **4** and **7**, the H^3 and H^{10} protons are characterized (i) in *cis* compounds **4c** and **7c**, by a large and a small J value ($J = 7.5$ – 9.1 Hz and $J = 2.0$ – 2.8 Hz), which are characteristic of axial hydrogen atoms, and so of equatorial 3-R and 10-R substituents; (ii) in *trans* derivatives **4b** and **7b**, by very different J values ($J = 9.7$ – 10.0 Hz and $J = 2.6$ – 2.8 Hz) for protons H^3 of **7b** and H^{10} of **4b**, to which an axial location can be assigned, and by two closer J values ($J = 5.4$ – 7.0 Hz and $J = 1.9$ – 3.0 Hz) corresponding to an equatorial position for protons H^3 of **4b** and H^{10} of **7b**. These considerations allow the identification of 3-Ph_{ax} and 10-Ph_{eq} groups in **4b** and 3-Me_{eq} and 10-Me_{ax} groups in **7b**.

Molecular Modeling

Monte-Carlo calculations indicate a high flexibility of macrocyclic diamines **4b,c**, **7b,c**, and **10b,c**, flexibility which is slightly increased relative to that of the precursory dilactams through the loss of rigidity due to the two amide link reductions. Fifteen conformations are thus observed within

9–13 kJ mol⁻¹ of the global minimum (Supporting information, Table S1) with energy differences ranging between 0.25 and 4.09 kJ mol⁻¹ for the two first conformers. Hence, conformers 2 will be taken into consideration exclusively for compounds **4b**, **4c**, **10b**, and **10c**, which present a weak $\Delta E_{\text{conf1} - \text{conf2}} \leq 2$ kJ mol⁻¹ (**4b**: 1.24, **4c**: 0.50, **10b**: 1.03, **10c**: 0.25 kJ mol⁻¹); this value is greater for **7b** (4.09) and **7c** (3.67).

The calculated H–H dihedral angles of all the diamines point to (Table 4): (i) an axial position of the H^7 and H^{14} protons ($\theta_{H^7, H^{6ax}}$ and $\theta_{H^{14}, H^{13ax}} = 174$ – 178°) corresponding to an energetically favorable equatorial location of the α and β -OMe groups; (ii) identical axial positions of the H^3 and H^{10} protons in *cis*-OMe chiral diamines **4c** and **7c**, again corresponding to an energetically favorable equatorial location of the 3,10-R substituents; (iii) different situations of the two hydrogens in the *trans*-OMe compounds with H^{3eq} and H^{10ax} , i.e., 3-Ph_{ax} and 10-Ph_{eq} in **4b**, and H^{3ax} , H^{10eq} , i.e., 3-Me_{eq} and 10-Me_{ax} in **7b**. These results agree with the above NMR spectroscopic data, but they underline a difference between the conformations of the diamines and dilactams: the invariable axial position of the 3,10-R substituents observed in dilactams **1b,c** and **2b,c**^[7] is transformed into a more favorable equatorial situation for both R groups in *cis* diamines **4c** and **7c** and for one of them in *trans* compounds **4b** and **7b**.

The torsion angles of the macrocyclic amines are given in Table 5. All exhibit invariable *transoid* conformations along the two bonds $C^{14}-O^1-C^2-C^3$, $C^7-O^8-C^9-C^{10}$ (± 172 – 178°) and *gauche* conformations along the bonds $O^1-C^2-C^3-N^4$, $O^8-C^9-C^{10}-N^{11}$ (± 43 – 60°) and $C^5-C^6-C^7-O^8$, $C^{12}-C^{13}-C^{14}-O^1$ (± 59 – 67°). In contrast, the values of the other angles correspond to *trans* (t) or *gauche* [g (positive value) or g' (negative value)] conformations depending on the macrocycle stereochemistry and the nature of the substituent.

In *trans*-OMe compounds, a [3434] or g₁g₂g₃t₄g₅'g₆'g₇'t₈ conformation^[7,11,12] corresponding to the ideal strain-free “rectangular” diamond lattice structure of the 14-mem-

Table 4. Calculated $H^7-C^7-C^6-H^6$, $H^{14}-C^{14}-C^{13}-H^{13}$ and $H^3-C^3-C^2-H^2$, $H^{10}-C^{10}-C^9-H^9$ dihedral angles of the conformers (cf) of diketal diamines **4b,c**, **7b,c**, and **10b,c**.

Compd.	θ [°]							
	$H^7-C^7-C^6-H^{6ax}$	$H^7-C^7-C^6-H^{6eq}$	$H^{14}-C^{14}-C^{13}-H^{13ax}$	$H^{14}-C^{14}-C^{13}-H^{13eq}$	$H^3-C^3-C^2-H^{2ax}$	$H^3-C^3-C^2-H^{2eq}$	$H^{10}-C^{10}-C^9-H^{9ax}$	$H^{10}-C^{10}-C^9-H^{9eq}$
4b cf 1	-174	+67	+178	-63	+56	-63	+180	-62
4b cf 2	-175	+67	+178	-63	+54	-64	+179	-62
4c cf 1	+178	-65	+178	-65	-178	-59	-177	-58
4c cf 2	+179	-64	+179	-63	-180	-61	-172	-54
7b cf 1	+176	-66	-177	+65	+168	+50	-44	+73
7c cf 1	-177	+66	-177	+66	+176	+57	+176	+57
10b cf 1 ^[a]	+177	-64	-177	+65	+164	+47	-164	-47
					+45	-73	-45	+73
10b cf 2 ^[a]	+177	-64	-177	+64	+180	-62	-180	+62
					-61	+58	+61	-58
10c cf 1 ^[a]	-175	+67	-175	+67	-174	-55	-174	-55
					-55	+64	-55	+64
10c cf 2 ^[a]	+179	+61	+179	+60	-180	-61	+167	+48
					-61	+57	+48	-72

[a] First line: H^{3ax} and H^{10ax} , second line: H^{3eq} and H^{10eq} .

Table 5. Torsional angles τ [°] for the conformers (cf) of macrocyclic diketal diamines **4b,c**, **7b,c**, and **10b,c** ($+40^\circ < g < +85^\circ$, $-40^\circ < g' < -85^\circ$, $\pm 156^\circ < t < \pm 180^\circ$).

Compd.	Chain	τ [°]								Nomenclature	Structure
		1	C14-O1-C2-C3	O1-C2-C3-N4	C2-C3-N4-C5	C3-N4-C5-C6	N4-C5-C6-C7	C5-C6-C7-O8	C6-C7-O8-C9		
	2	C7-O8-C9-C10	O8-C9-C10-N11	C9-C10-N11-C12	C10-N11-C12-C13	N11-C12-C13-C14	C12-C13-C14-O1	C13-C14-O1-C2			
4b cf 1	1	-176	+60	+178	+177	-70	+66	-177	tg'tg'/gt-tg'ttgg't	En IIIb ^[a]	
	2	-174	-57	+162	+176	+72	-61	-178			
4b cf 2	1	-180	+59	-180	-179	-70	+66	-178	tg'tg'/gt-tg'ttgg't	En IIIb ^[a]	
	2	-177	-58	+165	+177	+73	-61	-180			
7b cf 1	1	-174	+45	+69	-179	+171	-64	-78	tg'ttgg'g'-tg'g'ttgg'g'	Iib	
	2	+172	-44	-71	-175	-168	+63	-77			
10b cf 1	1	-172	+43	+72	+176	+168	-63	-77	tg'ttgg'g'-tg'g'ttgg'g'	Ib [3434]	
	2	+173	-43	-72	-176	-168	+63	+77			
10b cf 2	1	+179	-61	+169	-178	+73	-63	-179	tg'ttgg't-tg'ttgg'g'	IIIb	
	2	-179	+61	-169	+178	-73	+63	-179			
4c cf 1	1	-176	-55	+158	-174	+64	-64	-71	tg'ttgg'g'-tg'ttgg'g'	En IIc ^[a]	
	2	-176	-54	+157	-175	+64	-64	-71			
4c cf 2	1	-176	-57	+156	-174	+65	-64	-70	tg'ttgg'g'-tg'ttgg'g'	En IIc ^[a]	
	2	-78	-49	+156	-179	+64	-62	-71			
7c cf 1	1	+175	+55	-156	+170	-65	+65	+72	tg'ttgg'gg-tg'ttgg'gg	IIc	
	2	+175	+55	-156	+170	-65	+65	+72			
10c cf 1	1	-178	-54	+173	-84	-67	+67	-172	tg'tg'g'-gt-tg'g'gt	Ic	
	2	-178	-54	+173	-84	-67	+67	-172			
10c cf 2	1	+178	-62	+173	-83	-70	+60	-176	tg'tg'g'-gt-tg'ttgg'g'	IIIc	
	2	+173	+46	-169	+166	-78	+59	-176			

[a] En = Enantiomer of structure due to the (3*R*,10*R*,14*S*) configuration of phenyl macrocycles **4**. To make comparison with the (3*S*,10*S*,14*R*) methyl series and the (14*R**) unsubstituted series we have to consider the (3*S*,10*S*,14*R*) enantiomer of **4b** and **4c**, the designations of which would be tg'ttgg'ttgg'ttgg'g' and tg'ttgg'gg'ttgg'gg', respectively.

bered ring compounds is observed for the symmetry center macrocycle **10b** (conformer 1: structure Ib). Here, the *trans*-OMe groups are accommodated in the two opposite corners C⁷ and C¹⁴, defined by a gg or g'g' sequence, whereas the C³ and C¹⁰ carbon atoms form the other two corners (Figure 4). The oxygen O¹ and O⁸ atoms are located on the “three-bond” sides and the nitrogen N⁴ and N¹¹ atoms are located on the “four bond” sides. The O¹, N⁴ and O⁸, N¹¹ atoms are *endo* and point downwards and upwards, respectively; the N–H bonds form angles of $\approx 50^\circ$ with the macrocyclic plane. Methyl compound **7b** presents a very close conformation (structure Iib), which differs from Ib by the presence, at C¹⁴, of a “pseudocorner” characterized by a gg' sequence that induces a slight distortion of the rectangular shape. In compounds **4b** (conformers 1 and 2) and **10b** (conformer 2), the macrocycles adopt an anangular conformation (structure IIIb) derived from the above forms by rotation of the NH bonds that are now directed inside the cavity in a position parallel to the average cycle plane. This arrangement allows the formation of two intramolecular hydrogen bonds between the NH hydrogen atoms and the endocyclic ketal oxygen atoms of the other chain (Figure 4; Supporting Information, Table S2).

In *cis*-OMe compounds, identical N⁴–H \cdots O⁸ and N¹¹–H \cdots O¹ hydrogen bonds, which is consistent with C₂ symmetry, are observed for all the studied conformers that are generally characterized by the presence of two corners either in C⁵, C¹² [**10c** (conf. 1): structure Ic] or in C⁷, C¹⁴ [**4c** (conf. 1 and 2), **7c**: structure IIc]. An anomaly occurs for **10c** (conf. 2), in which the absence of a corner in C¹² induces a loss of symmetry, which is no longer in agreement with the NMR spectroscopic data.

For all these compounds, the average C–O, C–N, and C–C bond lengths are 1.430, 1.471, and 1.535 Å, respectively (Supporting Information, Table S3). In contrast, the heteroatom distances are variable and depend on the structure. Thus, the O¹–O⁸, N⁴–N¹¹, and O¹⁽⁸⁾–N¹¹⁽⁴⁾ distances increase in the order: *cis*-OMe compounds **4c**, **7c**, and **10c** (conf. 1, 2) (d_{average} : 3.549, 3.655, and 2.832 Å, respectively), *trans*-OMe compounds **4b** (conf. 1, 2) and **10b** (conf. 2) with hydrogen bonds (d_{average} : 3.969, 4.038, and 2.855 Å, respectively), *trans*-OMe compounds **7b** and **10b** (conf. 1) without hydrogen bond (d_{average} : 5.035, 5.040, and 4.261 Å, respectively) (Table 6).

Table 6. Interatomic distances [Å] of the O–O, N–N, and O–N bonds for the conformers (cf) of diketal diamines **4b,c**, **7b,c**, and **10b,c**.

Compound	d [Å]					
	O ¹ –O ⁸	N ⁴ –N ¹¹	O ¹ –N ¹¹	O ⁸ –N ⁴	O ¹ –N ⁴	O ⁸ –N ¹¹
4b cf 1	3.957	4.018	2.846	2.843	2.801	2.790
4b cf 2	3.967	4.024	2.866	2.848	2.791	2.798
4c cf 1	3.602	3.404	2.822	2.824	2.744	2.735
4c cf 2	3.635	3.379	2.809	2.836	2.767	2.689
7b cf 1	5.032	5.060	4.251	4.283	2.704	2.685
7c cf 1	3.517	3.468	2.828	2.828	2.750	2.750
10b cf 1	5.038	5.021	4.255	4.255	2.681	2.682
10b cf 2	3.984	4.072	2.863	2.863	2.833	2.833
10c cf 1	3.403	3.830	2.841	2.841	2.768	2.768
10c cf 2	3.589	4.196	2.899	2.795	2.871	2.667

Finally, we note that the centrosymmetric, endodontate, anangular structure IIIb of **10b** (conformer 2), corresponds to the most stable conformation of cyclam,^[13] whereas the structure Ib of **10b** (conformer 1) is close to the [3434]-B

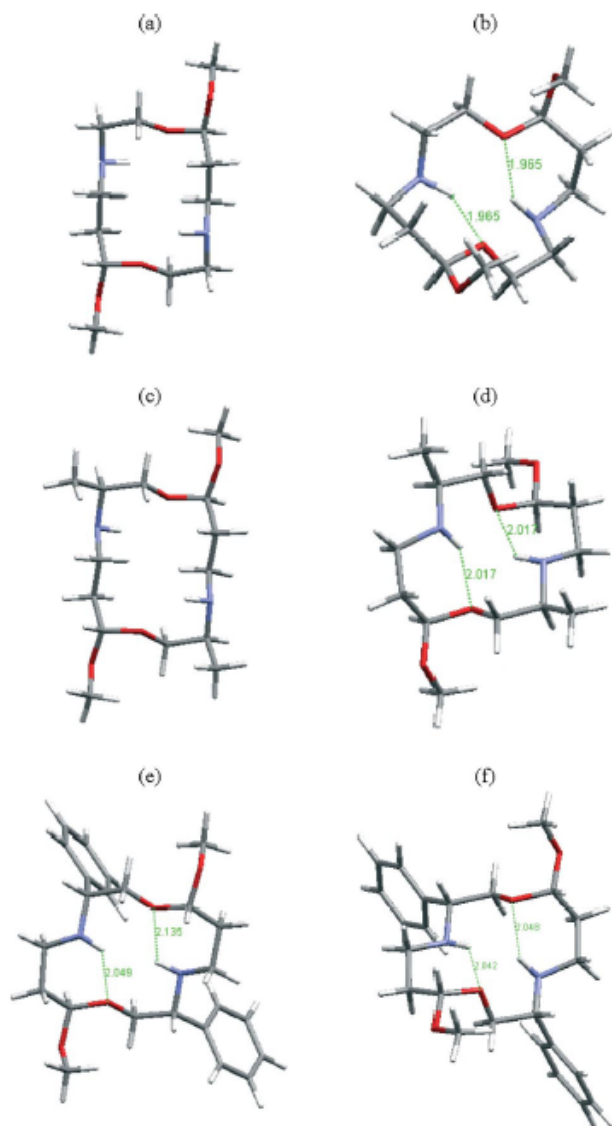


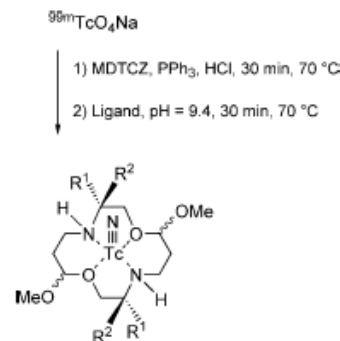
Figure 4. Top view representations of some diketal diamine macrocycles (conformer 1) by molecular modeling: (a) **10b**: structure Ib, (b) **10c**: structure Ic, (c) **7b**: structure IIb, (d) **7c**: structure IIc, (e) **4b**: enantiomer of structure IIIb, (f) **4c**: enantiomer of structure IIc. Intramolecular hydrogen bonds are indicated by green dashed lines with the corresponding interatomic distances.

conformation^[13b,14] of *4H*-cyclam⁴⁺ with, however, a difference in the position of the heteroatoms: *endo* in **10b** and *exo* in *4H*-cyclam⁴⁺.^[14b]

Tc-99m Radiolabeling

The study was performed on diketal amines **4c**, **7b,c**, and **10b,c**, and on the corresponding singly reduced compounds: amino lactams **5b,c**, **8b**, and **11c**. Of the two cores, [TcN]²⁺ and [TcO₂]⁺, generally used for ^{99m}Tc cyclam labeling,^[3,4] the first one was selected for the present study because its incorporation conditions in the ligands are compatible with the presence of ketal functionalities known to be sensitive to any acidic medium. Labeling of the diketal macrocycles

was thus performed in two steps by a published procedure: (i) the intermediate nitrido–technetium [Tc≡N]_{int}^V was prepared by acid reduction of a [^{99m}Tc]-pertechnetate(VII) solution by using triphenylphosphane as a reducing agent and *N*-methyl-*S*-methylthiocarbamate (MDTCZ) as a nitrogen (N³⁻) donor, (ii) the ligand exchange reaction was then carried out under basic conditions (pH 9.4) (Scheme 2).^[15,16]



Scheme 2.

The radiolabeling yields were measured by autoradiography of the spots obtained after thin-layer chromatography. No exchange was observed with diketal aminolactams **5**, **8**, and **11**. In contrast, for most of the diketal diamines except phenyl derivative **4c**, the yields ranged from 11 to 18% (**4c**: 0%, **7b**: 11%, **7c**: 17%, **10b**: 18%, **10c**: 14%); the best results were obtained with *cis*-OMe methyl compound **7c** and *trans*-OMe unsubstituted macrocycle **10b**. The exchange values do not seem sensitive to the dimensional variations of the macrocyclic cage of the studied chelates (Table 6), as *cis* and *trans* diamines gave nearly identical results.

Though low, these values are encouraging. They should be appreciably increased by introduction of C- or N-pivot pendant arms with electron-donor atoms liable to participate in the complex formation, as previously observed with differently C-substituted cyclams [substituent: 4-(aminomethyl)benzyl, labeling yield: 13%; substituent: 2-hydroxy-5-(aminomethyl)phenyl, labeling yield: 72%.^[4b]

Conclusions

Six macrocyclic diketal diamines were prepared by reduction of the corresponding diketal dilactams previously synthesized in two steps from chiral and achiral β-amino alcohols.^[6] The reaction was performed with lithium aluminium hydride in the presence of a trace amount of triethylamine, which prevented a side elimination reaction. In a 15–30 × 10⁻³ M concentration range, it led mainly to the doubly reduced compounds in the unsubstituted series (R = H) and in the *cis*-OMe substituted series (R = Ph, Me). In contrast, in the *trans*-OMe substituted series, the 5-CO carbonyl group of chain 1 was reduced with difficulty owing to the hindrance of the two macrocycle faces.

A conformational study of the obtained macrocyclic diamines was conducted by liquid NMR spectroscopy and molecular mechanics calculations. Both techniques showed

that the conformations depended closely on: (i) the nature of the 3,10-R substituents and (ii) the stereochemistry of the ketal OMe groups, which invariably occupied an energetically favorable equatorial position in all compounds. Thus, in *trans*-OMe macrocycles **10b** (R = H) and **7b** (R = Me), the most stable conformation corresponded exactly or closely to the rectangular [3434] structure, with the NH bonds directed away from each side of the ring. In contrast, in *trans*-OMe macrocycle **4b** (R = Ph) and in all *cis*-OMe derivatives **4c**, **7c**, and **10c**, the conformations were set by the presence of two NH \cdots O intramolecular hydrogen bonds that imposed to the N–H bond a position parallel to the cyclic plane.

Tc-99m radiolabeling by using the nitrido–technetium core [TcN]²⁺ gave approximately 10–20% exchange yields, which can probably be increased by introducing substituents with electron-donor atoms.

Experimental Section

General Remarks: Solvents were dried as follows: tetrahydrofuran (THF) was distilled from benzophenone ketyl, CH₂Cl₂ was refluxed and distilled from CaH₂, CH₃OH was distilled from magnesium. The organic layers were dried with Mg₂SO₄. Thin-layer chromatography (TLC) analysis was performed on aluminium plates precoated with silica gel (Merck 60 F₂₅₄). Visualization was accomplished by UV light or developed by spraying with a ceric sulfate and ammonium molybdate acid solution. Flash chromatography was carried out with silica gel (Merck 0.040–0.063 mm). Optical rotations were measured at the sodium D line (589 nm) by using a 1-dm quartz cell with a JASCO DIP-370 apparatus. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer. Mass spectra were performed with either a HP 5989B (CI), a micro Q-TOF Waters (ESI), or a ZabSpec TOF Micromass (ESI) apparatus. 1D (¹H and ¹³C-J MOD) and 2D (COSY ¹H–¹H, HSQC ¹H–¹³C) NMR spectra were recorded with a Bruker Avance 400 spectrometer (¹H: 400 MHz; ¹³C: 100 MHz), and 2D HMBC ¹H–¹³C were recorded with an Avance 500 apparatus long dist 7.7 Hz (¹H: 500 MHz; ¹³C: 125 MHz). The solvent (CDCl₃) was taken as an internal reference (δ = 7.27 ppm for ¹H and 77.1 ppm for ¹³C NMR). Protons and carbon atoms were assigned according to the numbering indicated in Figure 3. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Synthesis of Macrocyclic Diketal Dilactams 1b,c, 2b,c, and 3b,c: The preparation of these compounds was previously described.^[6]

General Procedure for the Reduction of Diketal Dilactams

Method A: To a suspension of LiAlH₄ (10 equiv.) in dry THF (0.5 mL for 1 mol of LAH) was added NEt₃ (0.01–0.04 equiv./LAH) and dropwise a solution of diketal dilactam (1 equiv.) in dry THF ($c_{\text{substrate}} = 14\text{--}30 \times 10^{-3}$ M). The reaction mixture was heated at reflux whilst stirring for 7–20 h. The excess amount of hydride was destroyed by the addition of H₂O (10 equiv./LAH). The precipitates were filtered and washed with THF and CH₂Cl₂. The organic layer was dried with MgSO₄ and evaporated in vacuo. Purification by flash chromatography (silica gel, Et₂O/MeOH) led to diketal diamines and diketal aminolactams.

Method B: To a solution of diketal dilactam (1 equiv.) in dry THF ($c_{\text{substrate}} = 15\text{--}40 \times 10^{-3}$ M), was added, dropwise whilst stirring, a solution of LiAlH₄ (1 M solution in THF, 10 equiv.) and NEt₃

(0.01–0.02 equiv./LAH). The reaction mixture was heated at reflux for 8–10 h. The excess amount of hydride was destroyed by the addition of H₂O (10 equiv./LAH). The precipitates were filtered and washed with THF and CH₂Cl₂. The organic layer was dried with MgSO₄ and evaporated in vacuo. Purification by flash chromatography (silica gel, AcOEt/MeOH or Et₂O/MeOH) led to diketal diamines and diketal aminolactams.

(3R,7S,10R,14S)-Diphenyl Diketal Diamine 4c, (3R,7S,10R,14S)-Diphenyl Diketal Aminolactam 5c, and (3R,7S,10R,14S)-Diphenyl Unsaturated Ketal Aminolactam 6: The preparation of these compounds was described previously.^[9]

(3R,7R,10R,14S)-Diphenyl Diketal Diamine 4b and (3R,7R,10R,14S)-Diphenyl Diketal Aminolactam 5b: These compounds were prepared from diketal dilactam **1b** (66.4 mg, 0.15 mmol), LiAlH₄ (57 mg, 1.5 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 15 μ L, 15 μ mol, 0.01 equiv./LAH), and THF (10.7 mL, $c_{\text{substrate}} = 14 \times 10^{-3}$ M) according to method A (reaction time 10 h). The excess amount of hydride was destroyed by the addition of H₂O (270 μ L, 15 mmol). Chromatography (AcOEt/MeOH, gradient 100:0–90:10) afforded diketal diamine **4b** (2.1 mg, 5.1 μ mol, 4%) and diketal aminolactam **5b** (26 mg, 61 μ mol, 48%) with 85% conversion rate. Data for **4b**: $R_f = 0.20$ (AcOEt/MeOH, 97:3, 2 elutions). $[\alpha]_D^{25} = -52.0$. ($c = 0.14$, CHCl₃). IR (CHCl₃): $\tilde{\nu} = 3430$ and 3360 (NH) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): $\delta = 1.67$ (dddd, ²J = 16.0 Hz, ³J = 6.1, 1.8, 1.5 Hz, 1 H, 6-H^B), 1.71 (dddd, ²J = 14.7 Hz, ³J = 6.2, 2.0, 1.5 Hz, 1 H, 13-H^B), 2.01 (m, 2 H, 6-H^A, 13-H^A), 2.27 (br. s, 2 H, 2 NH), 2.53 (ddd, ²J = 10.6 Hz, ³J = 10.2, 1.0 Hz, 1 H, 12-H^B), 2.64 (m, 2 H, 5-H^B, 12-H^A), 2.72 (ddd, ²J = 12.3 Hz, ³J = 6.8, 2.7 Hz, 1 H, 5-H^A), 3.14 (s, 3 H, OCH₃), 3.29 (s, 3 H, OCH₃), 3.42 (dd, ²J = 9.6 Hz, ³J = 10.0 Hz, 1 H, 9-H^B), 3.62 (dd, ²J = 9.7 Hz, ³J = 3.0 Hz, 1 H, 2-H^B), 3.78 (dd, ²J = 9.7 Hz, ³J = 7.0 Hz, 1 H, 2-H^A), 3.86 (dd, ²J = 9.6 Hz, ³J = 2.8 Hz, 1 H, 9-H^A), 3.95 (dd, ³J = 10.0, 2.8 Hz, 1 H, 10-H), 4.02 (dd, ³J = 7.0, 3.0 Hz, 1 H, 3-H), 4.56 (dd, ³J = 7.8, 1.8 Hz, 1 H, 7-H), 4.68 (dd, ³J = 9.1, 2.0 Hz, 1 H, 14-H), 7.25–7.42 (m, 10 H, 10 Ar-H) ppm. ¹³C NMR and HSQC (100 MHz, CDCl₃): $\delta = 31.7$ (C-6), 31.9 (C-13), 42.7 (C-5), 44.1 (C-12), 50.7 (OCH₃), 52.5 (OCH₃), 61.5 (C-3), 63.6 (C-10), 66.6 (C-2), 73.4 (C-9), 104.6 (C-14), 105.2 (C-7), 127.2–128.7 (10 Ar-CH), 140.4 (2 Ar-C) ppm. MS (CI): m/z (%) = 415 (93) [M + H]⁺, 383 (100) [M + H – CH₂OH]⁺. HRMS (ESI): calcd. for C₂₄H₂₅N₂O₄ [M + H]⁺ 415.2597; found 415.2584. Data for **5b**: $R_f = 0.40$ (AcOEt/MeOH, 97:3, 2 elutions). $[\alpha]_D^{25} = -46.9$ ($c = 0.51$, CHCl₃). IR (CHCl₃): $\tilde{\nu} = 3420$ (NH), 1682 (CO) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): $\delta = 1.30$ (br. s, NH amine), 1.68 (dddd, ²J = 14.2 Hz, ³J = 6.0, 1.8, 0.4 Hz, 1 H, 13-H^B), 1.96 (dddd, ²J = 14.2 Hz, ³J = 10.4, 9.4, 2.2 Hz, 1 H, 13-H^A), 2.53 (ddd, ²J = 11.1 Hz, ³J = 10.4, 0.4 Hz, 1 H, 12-H^B), 2.63 (dd, ²J = 15.8 Hz, ³J = 1.6 Hz, 1 H, 6-H^B), 2.65 (ddd, ²J = 11.1 Hz, ³J = 6.0, 2.2 Hz, 1 H, 12-H^A), 2.85 (dd, ²J = 15.8 Hz, ³J = 8.1 Hz, 1 H, 6-H^A), 2.95 (s, 3 H, OCH₃), 3.35 (s, 3 H, OCH₃), 3.51 (dd, ²J = 9.6 Hz, ³J = 10.1 Hz, 1 H, 9-H^B), 3.75 (dd, ²J = 9.7 Hz, ³J = 3.0 Hz, 1 H, 2-H^B), 3.89 (dd, ²J = 9.6 Hz, ³J = 2.6 Hz, 1 H, 9-H^A), 3.96 (dd, ³J = 10.1, 2.6 Hz, 1 H, 10-H), 4.05 (dd, ²J = 9.7 Hz, ³J = 3.2 Hz, 1 H, 2-H^A), 4.66 (dd, ³J = 9.4, 1.8 Hz, 1 H, 14-H), 4.80 (dd, ³J = 8.1, 1.6 Hz, 1 H, 7-H), 5.24 (ddd, ³J = 7.4, 3.2, 3.0 Hz, 1 H, 3-H), 7.25–7.42 (m, 10 H, 10 Ar-H), 7.62 (d, ³J = 7.4 Hz, 1 H, NH amide) ppm. ¹³C NMR and HSQC (100 MHz, CDCl₃): $\delta = 31.6$ (C-13), 41.0 (C-6), 44.4 (C-12), 50.3 (OCH₃), 52.7 (C-3), 53.4 (OCH₃), 63.5 (C-10), 68.8 (C-2), 73.3 (C-9), 101.0 (C-7), 104.4 (C-14), 126.8–128.6 (10 Ar-CH), 139.9 (Ar-C), 140.0 (Ar-C), 168.2 (CO) ppm. MS (CI): m/z (%) = 429 (100) [M + H]⁺, 397 (36) [M + H –

CH₃OH)⁺, 192 (16), 121 (15), 105 (54). HRMS (ESI): calcd. for C₂₄H₃₃N₂O₅ [M + H]⁺ 429.2390; found 429.2391.

(3S,7S,10S,14R)-Dimethyl Diketal Diamine 7b and **(3S,7S,10S,14R)-Dimethyl Diketal Aminolactam 8b**: These compounds were prepared from diketal dilactam **2b** (63.7 mg, 0.20 mmol), LiAlH₄ (76 mg, 2.0 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 40 μL, 40 μmol, 0.02 equiv./LAH), and THF (8.0 mL, c_{substrate} = 25 × 10⁻³ M) according to method A (reaction time 18 h). The excess amount of hydride was destroyed by the addition of H₂O (360 μL, 20 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal diamine **7b** (22.4 mg, 77.1 μmol, 41%) and diketal aminolactam **8b** (11.4 mg, 37.6 μmol, 20%) with 94% conversion rate. Data for **7b**: R_f = 0.20 (MeOH, 3 elutions). [α]_D²⁵ = +21.23 (c = 0.68, CHCl₃). IR (CHCl₃): ν̄ = 3337 (NH) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): δ = 1.00 (d, ³J = 6.4 Hz, 3 H, Me-10), 1.11 (d, ³J = 6.6 Hz, 3 H, Me-3), 1.82 (dddd, ²J = 14.0 Hz, ³J = 4.8, 1.6, 1.5 Hz, 1 H, 13-H^B), 1.83 (dddd, ²J = 14.6 Hz, ³J = 6.0, 3.1, 2.6 Hz, 1 H, 6-H^B), 1.94 (dddd, ²J = 14.6 Hz, ³J = 8.1, 7.3, 2.6 Hz, 1 H, 6-H^A), 2.05 (dddd, ²J = 14.0 Hz, ³J = 10.8, 9.2, 2.4 Hz, 1 H, 13-H^A), 2.30 (br. s, 2 H, 2 NH), 2.55 (ddd, ²J = 12.0 Hz, ³J = 10.8, 1.5 Hz, 1 H, 12-H^B), 2.68 (ddd, ²J = 11.0 Hz, ³J = 7.3, 3.1 Hz, 1 H, 5-H^B), 2.88 (m, 4 H, 3-H, 5-H^A, 10-H, 12-H^A), 3.14 (dd, ²J = 9.5 Hz, ³J = 9.7 Hz, 1 H, 2-H^B), 3.28 (s, 3 H, OCH₃), 3.33 (s, 3 H, OCH₃), 3.54 (ABX system, part AB, ²J = 9.7 Hz, ³J = 5.4, 1.9 Hz, Δν = 6.9 Hz, 2 H, 9-H^A, 9-H^B), 3.77 (dd, ²J = 9.5 Hz, ³J = 2.6 Hz, 1 H, 2-H^A), 4.56 (dd, ³J = 8.1, 2.6 Hz, 1 H, 7-H), 4.61 (dd, ³J = 9.2, 1.6 Hz, 1 H, 14-H) ppm. ¹³C NMR and HSQC (100 MHz, CDCl₃): δ = 16.1 (H₃C-10), 17.1 (H₃C-3), 32.2 (C-13), 32.3 (C-6), 42.2 (C-5), 43.5 (C-12), 50.6 (OCH₃), 52.1 (C-10), 52.6 (OCH₃), 52.9 (C-3), 69.2 (C-9), 72.8 (C-2), 104.1 (C-14), 104.3 (C-7) ppm. MS (ESI): m/z (%) = 313 (31) [M + Na]⁺, 291 (100) [M + H]⁺, 259 (18) [M + H – CH₃OH]⁺. HRMS (ESI): calcd. for C₁₄H₃₁N₂O₄ [M + H]⁺ 291.2284; found 291.2296. Data for **8b**: R_f = 0.40 (MeOH, 3 elutions). [α]_D²⁵ = +8.89 (c = 0.74, CHCl₃). IR (CHCl₃): ν̄ = 3407 and 3340 (NH), 1660 (CO) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): δ = 1.04 (d, ³J = 6.4 Hz, 3 H, Me-10), 1.25 (d, ³J = 6.7 Hz, 3 H, Me-3), 1.87 (ddt, ²J = 14.2 Hz, ³J = 6.4, 1.5 Hz, 1 H, 13-H^B), 1.98 (br. s, 1 H, NH amine), 2.06 (dddd, ²J = 14.2 Hz, ³J = 10.5, 9.3, 2.0 Hz, 1 H, 13-H^A), 2.55 (dd, ²J = 15.8 Hz, ³J = 1.5 Hz, 1 H, 6-H^B), 2.59 (ddd, ²J = 12.6 Hz, ³J = 10.5, 1.5 Hz, 1 H, 12-H^B), 2.72 (dd, ²J = 15.8 Hz, ³J = 8.2 Hz, 1 H, 6-H^A), 2.93 (dq, ³J = 9.3, 6.4, 2.0 Hz, 1 H, 10-H), 2.94 (ddd, ²J = 12.6 Hz, ³J = 6.4, 2.0 Hz, 1 H, 12-H^A), 3.23 (dd, ²J = 9.7 Hz, ³J = 9.3 Hz, 1 H, 9-H^B), 3.30 (s, 3 H, OCH₃), 3.35 (s, 3 H, OCH₃), 3.45 (dd, ²J = 9.6 Hz, ³J = 2.2 Hz, 1 H, 2-H^B), 3.72 (dd, ²J = 9.6 Hz, ³J = 2.1 Hz, 1 H, 2-H^A), 3.78 (dd, ²J = 9.7 Hz, ³J = 2.0 Hz, 1 H, 9-H^A), 4.21 (dq, ³J = 7.5, 6.7, 2.2, 2.1 Hz, 1 H, 3-H), 4.60 (dd, ³J = 9.3, 1.5 Hz, 1 H, 14-H), 4.69 (dd, ³J = 8.2, 1.5 Hz, 1 H, 7-H), 7.03 (d, ³J = 7.5 Hz, 1 H, NH lactam) ppm. ¹³C NMR and HSQC (100 MHz, CDCl₃): δ = 16.1 (H₃C-10), 17.7 (H₃C-3), 31.9 (C-13), 40.8 (C-6), 43.8 (C-12), 44.9 (C-3), 50.9 (OCH₃), 53.1 (C-10), 53.2 (OCH₃), 69.6 (C-2), 71.5 (C-9), 100.7 (C-7), 104.4 (C-14), 168.1 (CO) ppm. MS (ESI): m/z (%) = 305 (100) [M + H]⁺, 273 (42) [M + H – CH₃OH]⁺, 247 (11), 215 (7). HRMS (ESI): calcd. for C₁₄H₂₉N₂O₅ [M + H]⁺ 305.2076; found 305.2063.

(3S,10S,14R)-Dimethyl Unsaturated Ketal Aminolactam 9: This compound was obtained from diketal dilactam **2b** (63.7 mg, 0.20 mmol), LiAlH₄ (76 mg, 2.0 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 20 μL, 20 μmol, 0.01 equiv./LAH), and THF (16.5 mL, c_{substrate} = 12 × 10⁻³ M) according to method A (reaction time 18 h). The excess amount of hydride was destroyed by the addition of H₂O (360 μL, 20 mmol). Chromatography (Et₂O/

MeOH, gradient: 100:0–0:100) afforded diketal diamine **7b** (10.8 mg, 37.2 μmol, 20%), diketal aminolactam **8b** (11.9 mg, 39.1 μmol, 21%), and unsaturated ketal aminolactam **9** (1.0 mg, 3.7 μmol, 2%) with 93% conversion rate. Data for **9**: R_f = 0.60 (MeOH, 3 elutions). IR (CHCl₃): ν̄ = 3426 (NH), 1662 (CO), 1604 (C=C) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): δ = 1.04 (d, ³J = 6.4 Hz, 3 H, Me-10), 1.29 (d, ³J = 6.9 Hz, 3 H, Me-3), 1.78 (br. s, 1 H, NH amine), 1.90 (dddd, ²J = 14.6 Hz, ³J = 6.5, 1.8, 1.0 Hz, 1 H, 13-H^B), 2.06 (dddd, ²J = 14.6 Hz, ³J = 10.5, 9.5, 1.5 Hz, 1 H, 13-H^A), 2.51 (ddd, ²J = 10.6 Hz, ³J = 10.5, 1.0 Hz, 1 H, 12-H^B), 2.97 (m, 2 H, 12-H^A, 10-H), 3.30 (s, 3 H, OCH₃), 3.51 (dd, ²J = 9.2 Hz, ³J = 2.8 Hz, 1 H, 2-H^B), 3.77 (dd, ²J = 9.2 Hz, ³J = 1.6 Hz, 1 H, 2-H^A), 3.90 (ABX system, part AB, ²J = 10.0 Hz, ³J = 13.0, 1.0 Hz, Δν = 6.2 Hz, 2 H, 9-H^A, 9-H^B), 4.29 (dq, ³J = 7.0, 6.9, 2.8, 1.6 Hz, 1 H, 3-H), 4.57 (dd, ³J = 9.5, 1.8 Hz, 1 H, 14-H), 4.96 (d, ³J = 6.9 Hz, 1 H, 6-H), 6.45 (d, ³J = 6.9 Hz, 1 H, 7-H), 7.48 (d, ³J = 7.0 Hz, 1 H, NH lactam) ppm. MS (ESI): m/z (%) = 295 (100) [M + Na]⁺, 273 (24) [M + H]⁺, 241 (44) [M + H – CH₃OH]⁺. HRMS (ESI): calcd. for C₁₃H₂₅N₂O₄ [M + H]⁺ 273.1814; found 273.1829.

(3S,7R,10S,14R)-Dimethyl Diketal Diamine 7c: This compound was prepared from diketal dilactam **2c** (63.7 mg, 0.20 mmol), LiAlH₄ (76 mg, 2.0 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 20 μL, 20 μmol, 0.01 equiv./LAH), and THF (6.7 mL, c_{substrate} = 30 × 10⁻³ M) according to method A (reaction time 20 h). The excess amount of hydride was destroyed by the addition of H₂O (360 μL, 20 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal diamine **7c** (18.0 mg, 62 μmol, 33%) with 94% conversion rate. R_f = 0.30 (MeOH, 3 elutions). [α]_D²⁵ = +53.4 (c = 0.97, CHCl₃). IR (CHCl₃): ν̄ = 3332 (NH amine) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): δ = 1.06 (d, ³J = 6.6 Hz, 6 H, 2 Me), 1.87 (dddd, ²J = 14.4 Hz, ³J = 7.4, 2.5, 1.2 Hz, 2 H, 6-H^B, 13-H^B), 2.00 (dddd, ²J = 14.4 Hz, ³J = 9.7, 8.6, 2.2 Hz, 2 H, 6-H^A, 13-H^A), 2.58 (ddd, ²J = 11.1 Hz, ³J = 9.7, 1.2 Hz, 2 H, 5-H^B, 12-H^B), 2.75 (br. s, 2 H, 2 NH), 2.86 (m, 4 H, 3-H, 10-H, 5-H^A, 12-H^A), 3.30 (s, 6 H, 2 OCH₃), 3.53 (ABX system, part AB, ²J = 10.2 Hz, ³J = 7.5, 2.0 Hz, Δν = 25.3 Hz, 4 H, 2-H^A, 2-H^B, 9-H^A, 9-H^B), 4.62 (dd, ³J = 8.6, 2.5 Hz, 2 H, 7-H, 14-H) ppm. ¹³C NMR and HSQC (100 MHz, CDCl₃): δ = 16.7 (H₃C-3, H₃C-10), 31.8 (C-6, C-13), 43.0 (C-5, C-12), 51.5 (2 OCH₃), 52.5 (C-3, C-10), 69.4 (C-2, C-9), 103.8 (C-7, C-14) ppm. MS (ESI): m/z (%) = 313 (81) [M + Na]⁺, 291 (100) [M + H]⁺, 259 (22) [M + H – CH₃OH]⁺. HRMS (ESI): calcd. for C₁₄H₃₁N₂O₄ [M + H]⁺ 291.2284; found 291.2295.

(7S*,14R*)-Diketal Diamine 10b: This compound was prepared from diketal dilactam **3b** (58.0 mg, 0.20 mmol), LiAlH₄ (1 M THF solution, 2 mL, 2.0 mmol, 10 equiv.), NEt₃ (1 M solution in THF, 40 μL, 40 μmol, 0.02 equiv./LAH), and THF (11.3 mL, c_{substrate} = 15 × 10⁻³ M) according to method B (reaction time 8 h). The excess amount of hydride was destroyed by the addition of H₂O (360 μL, 20 mmol). Chromatography (Et₂O/MeOH, gradient 100:0–0:100) afforded diketal diamine **10b** (16.6 mg, 63.2 μmol, 40%) with 79% conversion rate. R_f = 0.30 (MeOH/NH₄OH, 99.5:0.5, 2 elutions). IR (CHCl₃): ν̄ = 3300 (NH) cm⁻¹. ¹H NMR and COSY ¹H–¹H (400 MHz, CDCl₃): δ = 1.27 (br. s, 2 H, 2 NH), 1.87 (dddd, ²J = 14.5 Hz, ³J = 7.0, 2.2, 2.0 Hz, 2 H, 6-H^B, 13-H^B), 2.02 (dddd, ²J = 14.5 Hz, ³J = 9.9, 8.6, 2.5 Hz, 2 H, 6-H^A, 13-H^A), 2.70 (ddd, ²J = 11.9 Hz, ³J = 9.9, 2.0 Hz, 2 H, 5-H^B, 12-H^B), 2.77 (ddd, ²J = 12.3 Hz, ³J = 4.1, 2.3 Hz, 2 H, 3-H^B, 10-H^B), 2.87 (ddd, ²J = 12.3 Hz, ³J = 9.4, 2.7 Hz, 2 H, 3-H^A, 10-H^A), 2.88 (ddd, ²J = 12.0 Hz, ³J = 7.1, 2.5 Hz, 2 H, 5-H^A, 12-H^A), 3.32 (s, 6 H, 2 OCH₃), 3.54 (ddd, ²J = 10.0 Hz, ³J = 9.4, 2.3 Hz, 2 H, 2-H^B, 9-H^B), 3.90 (ddd, ²J = 10.0 Hz, ³J = 4.1, 2.7 Hz, 2 H, 2-H^A, 9-H^A),

4.60 (dd, $^3J = 8.6, 2.2$ Hz, 2 H, 7-H, 14-H) ppm. ^{13}C NMR and HSQC (100 MHz, CDCl_3): $\delta = 32.0$ (C-6, C-13), 46.0 (C-5, C-12), 49.5 (C-3, C-10), 51.9 (2 OCH_3), 66.0 (C-2, C-9), 104.5 (C-7, C-14) ppm. MS (ESI): m/z (%) = 263 (100) $[\text{M} + \text{H}]^+$, 231 (37) $[\text{M} + \text{H} - \text{CH}_3\text{OH}]^+$. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 263.1971; found 263.1973.

(7*R,14*R**)-Diketetal Diamine 10c and (7*R**,14*R**)-Diketetal Aminolactam 11c:** These compounds were prepared from diketetal dilactam 3c (58 mg, 0.20 mmol), LiAlH_4 (76 mg, 2.0 mmol, 10 equiv.), NEt_3 (1 M solution in THF, 20 μL , 20 μmol , 0.01 equiv./LAH), and THF (6.7 mL, $c_{\text{substrate}} = 14 \times 10^{-3}$ M) according to method A (reaction time 7 h). The excess amount of hydride was destroyed by the addition of H_2O (360 μL , 20 mmol). Chromatography ($\text{Et}_2\text{O}/\text{MeOH}$, gradient 100:0–0:100) afforded diketetal diamine 10c (19.5 mg, 74.4 μmol , 40%) and diketetal aminolactam 11c (1.5 mg, 5.6 μmol , 3%) with 93% conversion rate. Data for 10c: $R_f = 0.25$ ($\text{MeOH}/\text{NH}_4\text{OH}$, 99.5:0.5, 2 elutions). IR (CHCl_3): $\tilde{\nu} = 3350$ (NH) cm^{-1} . ^1H NMR and COSY $^1\text{H}-^1\text{H}$ (400 MHz, CDCl_3): $\delta = 1.89$ (dddd, $^2J = 14.7$ Hz, $^3J = 7.9, 2.7, 2.5$ Hz, 2 H, 6- H^{B} , 13- H^{B}), 1.98 (dddd, $^2J = 14.7$ Hz, $^3J = 7.8, 7.2, 2.2$ Hz, 2 H, 6- H^{A} , 13- H^{A}), 2.72 (br. s, 2 H, 2 NH), 2.77 (m, 4 H, 3- H^{B} , 10- H^{B} , 5- H^{B} , 12- H^{B}), 2.89 (m, 4 H, 3- H^{A} , 10- H^{A} , 5- H^{A} , 12- H^{A}), 3.35 (s, 6 H, 2 OCH_3), 3.61 (ddd, $^2J = 9.8$ Hz, $^3J = 7.7, 1.7$ Hz, 2 H, 2- H^{B} , 9- H^{B}), 3.89 (ddd, $^2J = 9.8$ Hz, $^3J = 6.3, 2.8$ Hz, 2 H, 2- H^{A} , 9- H^{A}), 4.62 (dd, $^3J = 7.2, 2.7$ Hz, 2 H, 7-H, 14-H) ppm. ^{13}C NMR and HSQC (100 MHz, CDCl_3), HMBC (125 MHz, CDCl_3): $\delta = 31.1$ (C-6, C-13), 44.9 (C-5, C-12), 48.9 (C-3, C-10), 53.4 (2 OCH_3), 65.7 (C-2, C-9), 104.5 (C-7, C-14) ppm. MS (ESI): m/z (%) = 275 (31) $[\text{M} + \text{Na}]^+$, 263 (100) $[\text{M} + \text{H}]^+$, 231 (14) $[\text{M} + \text{H} - \text{CH}_3\text{OH}]^+$. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 263.1971; found 263.1982. Data for 11c: $R_f = 0.45$ ($\text{MeOH}/\text{NH}_4\text{OH}$, 99.5:0.5, 2 elutions). IR (CHCl_3): $\tilde{\nu} = 3400, 3360, 3280$ (NH), 1655 (CO) cm^{-1} . ^1H NMR and COSY $^1\text{H}-^1\text{H}$ (400 MHz, CDCl_3): $\delta = 1.83$ (dddd, $^2J = 14.4$ Hz, $^3J = 7.2, 2.5, 2.2$ Hz, 1 H, 13- H^{B}), 1.95 (dddd, $^2J = 14.4$ Hz, $^3J = 8.7, 7.9, 2.5$ Hz, 1 H, 13- H^{A}), 2.20 (br. s, 1 H, NH amine), 2.52 (dd, $^2J = 14.8$ Hz, $^3J = 2.0$ Hz, 1 H, 6- H^{B}), 2.67 (ddd, $^2J = 11.4$ Hz, $^3J = 8.7, 2.5$ Hz, 1 H, 12- H^{B}), 2.69 (dd, $^2J = 14.8$ Hz, $^3J = 7.7$ Hz, 1 H, 6- H^{A}), 2.77 (ddd, $^2J = 12.7$ Hz, $^3J = 6.8, 2.6$ Hz, 1 H, 10- H^{B}), 2.82 (m, 2 H, 10- H^{A} , 12- H^{A}), 3.18 (ddd, $^2J = 14.0$ Hz, $^3J = 9.0, 4.0, 2.5$ Hz, 1 H, 3- H^{B}), 3.32 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 3.55 (ddd, $^2J = 9.5$ Hz, $^3J = 9.0, 1.5$ Hz, 1 H, 2- H^{B}), 3.58 (ddd, $^2J = 9.7$ Hz, $^3J = 6.8, 2.6$ Hz, 1 H, 9- H^{B}), 3.76 (dddd, $^2J = 14.0$ Hz, $^3J = 7.0, 5.8, 1.5$ Hz, 1 H, 3- H^{A}), 3.80 (ddd, $^2J = 9.5$ Hz, $^3J = 5.8, 2.5$ Hz, 1 H, 2- H^{A}), 3.85 (ddd, $^2J = 9.7$ Hz, $^3J = 6.8, 2.6$ Hz, 1 H, 9- H^{A}), 4.56 (dd, $^3J = 7.9, 2.2$ Hz, 1 H, 14-H), 4.75 (dd, $^3J = 7.7, 2.0$ Hz, 1 H, 7-H), 6.95 (br. s, 1 H, NH lactam) ppm. ^{13}C NMR and HSQC (400 MHz, CDCl_3): $\delta = 31.6$ (C-13), 39.3 (C-3), 40.8 (C-6), 45.3 (C-12), 48.8 (C-10), 53.0 (OCH_3), 53.8 (OCH_3), 64.4 (C-9), 65.8 (C-2), 100.6 (C-7), 104.2 (C-14), 169.2 (CO) ppm. MS (ESI): m/z (%) = 315 (53) $[\text{M} + \text{K}]^+$, 299 (80) $[\text{M} + \text{Na}]^+$, 277 (100) $[\text{M} + \text{H}]^+$, 263 (11), 245 (14) $[\text{M} + \text{H} - \text{CH}_3\text{OH}]^+$, 219 (12). HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{25}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 277.1763; found 277.1776.

Molecular Modeling: The MACROMODEL molecular modeling program (version 7.0)^[17] with AMBER force field^[18] was used to determine the global minimum conformations of the macrocyclic diketetal diamines. The method known as Monte-Carlo multiple minimum search (MCM) was applied. The structures were written from the minimum conformation of the corresponding diketetal dilactams.^[7] A minimum of 5000 conformations were minimized for every compound. Detection conditions for hydrogen bonds: interatomic distances $d < 2.5$ Å, angles: $\text{N}-\text{H}\cdots\text{O} < 90^\circ$, and $\text{H}\cdots\text{O}-\text{R} < 60^\circ$.

Tc-99m Radiolabeling

General: [$^{99\text{m}}\text{Tc}$] Sodium pertechnetate was purchased from Centre Jean Perrin (Clermont-Ferrand). All solvents were degassed under an atmosphere of argon before used. TLC radioactive spots were scanned and recorded by using an AMBIS 101 detector equipped with a computer-controlled multiwire proportional counter.

Macrocycle Labeling: Four solutions were successively introduced in a reaction vial placed under an argon atmosphere: (1) a solution of *N*-methyl-*S*-methylthiocarbamate (MDTCZ, 1 mg, 7.4 μmol) in ethanol (0.4 mL, $c = 18.4 \times 10^{-3}$ M), (2) a solution of PPh_3 (1 mg, 3.8 μmol) in ethanol (0.2 mL, $c = 19.0 \times 10^{-3}$ M), (3) a solution of HCl in water (0.1 mL, 1 M), and (4) a solution of $^{99\text{m}}\text{TcO}_4\text{Na}$ (28.8 MBq, 0.78 mCi, total technetium: 1.0 ng, 5.4 pmol) in normal saline (2.7 mL). The mixture was heated to 70 °C for 30 min and then cooled to room temperature. The pH was adjusted by adding NaOH (0.1 mL, 1 M) and a buffer solution of $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$ (9:1, pH 9.4). A part (0.7 mL) of this mixture was introduced, under an atmosphere of argon, in a second reaction vial containing a solution of the ligand (2.4–4.2 μmol) in ethanol (0.7 mL). The resulting mixture was heated to 70 °C for another 30 min. A thin-layer chromatography (aluminium oxide, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 94:6) gave radioactive spots corresponding to the following radiochemical yields: 4c-TcN (0%), 7b-TcN (11%), 7c-TcN (17%), 10b-TcN (18%), and 10c-TcN (14%).

Supporting Information (see footnote on the first page of this article): Molecular modeling data for all calculated diketetal diamine structures; relative energy of the 15 first conformers of compounds 4, 7, and 10; interatomic distances between the NH hydrogen atoms and the endocyclic acetalic oxygen atoms of diketetal diamines 4, 7, and 10; bond lengths C–O, C–N, and C–C of diketetal diamines 4, 7, and 10.

Acknowledgments

The authors wish to thank F. Pelissier for technical assistance, B. Légeret for mass spectrometry, J. Guyot for molecular modeling, and the PAC (Plan Auvergne Cancer) for financial support.

- [1] a) E. Kimura, *Tetrahedron* 1992, 48, 6175–6217 and references cited therein; b) F. Bellouard, F. Chuburu, J. J. Yaouanc, H. Handel, Y. Le Mest, *Eur. J. Org. Chem.* 1999, 3257–3261; c) G. Dubois, C. Reyé, R. J. P. Corriu, S. Brandès, F. Denat, R. Guillard, *Angew. Chem. Int. Ed.* 2001, 40, 1087–1090; d) F. Barbet, F. Rascalou, H. Chollet, J. L. Babouhot, F. Denat, R. Guillard, *Anal. Chim. Acta* 2004, 502, 179–187.
- [2] a) D. E. Reichert, J. S. Lewis, C. J. Anderson, *Coord. Chem. Rev.* 1999, 184, 3–66; b) C. J. Anderson, M. J. Welch, *Chem. Rev.* 1999, 99, 2219–2234; c) W. A. Volkert, T. J. Hoffmann, *Chem. Soc. Rev.* 2004, 33, 246–266 and references cited therein; e) R. Delgado, V. Félix, L. M. P. Lima, D. W. Price, *Dalton Trans.* 2007, 2734–2745.
- [3] a) D. E. Troutner, J. Simon, A. R. Ketring, W. Volkert, R. A. Holmes, *J. Nucl. Med.* 1980, 21, 443–448; b) J. Simon, D. E. Troutner, W. A. Volkert, R. A. Holmes, *Radiochem. Radioanal. Lett.* 1981, 47, 111–123; c) W. A. Volkert, D. E. Troutner, R. A. Holmes, *Int. J. Appl. Radiat. Isot.* 1982, 33, 891–896; d) A. Marchi, R. Rossi, L. Magon, A. Duatti, U. Casellato, R. Grazianni, M. Vidal, F. Riché, *J. Chem. Soc., Dalton Trans.* 1990, 1935–1940.
- [4] a) J. Franz, W. A. Volkert, E. K. Barefield, R. A. Holmes, *Nucl. Med. Biol.* 1987, 14, 569–572; b) J. R. Morphy, D. Parker, R. Alexander, A. Bains, A. F. Carne, M. A. W. Eaton, A. Harrison, A. Millican, A. Phipps, S. K. Rhind, R. Titmas, D. Wea-

- therby, *J. Chem. Soc., Chem. Commun.* **1988**, 156–158; c) W. Stahl, G. Breipohl, L. Kuhlmann, A. Steinsträsser, H. J. Gerhards, B. A. Schölkens, *J. Med. Chem.* **1995**, *38*, 2799–2801; d) M. L. Thakur, H. Kolan, J. Li, R. Wiaderkiewicz, V. R. Pallela, R. Duggaraju, A. V. Schally, *Nucl. Med. Biol.* **1997**, *24*, 105–113; e) A. Boshi, L. Ucelli, C. Bolzati, M. Marastoni, R. Tomatis, S. Spisani, S. Traniello, A. Piffanelli, *Nucl. Med. Biol.* **2000**, *27*, 791–795; f) S. Murugesan, S. J. Shetty, O. P. D. Noronha, A. M. Samuel, T. S. Srivastava, C. K. K. Nair, L. Kothari, *Appl. Radiat. Isot.* **2001**, *54*, 81–88; g) F. Turpin, F. Masri, F. Riché, E. Berthommier, P. Emond, M. Vidal, P. Auzeloux, C. Loc'h, N. Neuquelman, L. Mauclair, *J. Label Compd. Radiopharm.* **2002**, *45*, 379–393.
- [5] a) S. Liu, D. S. Edwards, *Chem. Rev.* **1999**, *99*, 2235–2268 and references cited therein; b) S. S. Jurisson, J. D. Lydon, *Chem. Rev.* **1999**, *99*, 2205–2218 and references cited therein.
- [6] a) A.-G. Valade, D. Dugat, G. Jeminet, J. Royer, H.-P. Husson, *Eur. J. Org. Chem.* **2001**, *11*, 2041–2053; b) D. Dugat, A. Chiaroni, C. Riche, J. Royer, H.-P. Husson, *Tetrahedron Lett.* **1997**, *38*, 5801–5804.
- [7] D. Dugat, A.-G. Valade, B. Combourieu, J. Guyot, *Tetrahedron* **2005**, *61*, 5641–5653.
- [8] Y. Pointud, A.-G. Valade, C. Pointon, D. Dugat, G. Jeminet, J.-L. Beltran, *Supramol. Chem.* **2003**, *15*, 261–269.
- [9] R. Affani, D. Dugat, *Synth. Commun.* **2007**, *37*, 3729–3740.
- [10] a) J.-L. Pierre, H. Handel, R. Perraud, *Tetrahedron* **1975**, *31*, 2795–2798 and references cited therein; b) E. C. Ashby, J. R. Boone, *J. Am. Chem. Soc.* **1976**, *98*, 5524–5531; c) K. E. Wieggers, S. G. Smith, *J. Org. Chem.* **1978**, *43*, 1126–1131.
- [11] a) J. Dale, *Acta Chem. Scand.* **1973**, *27*, 1115–1129; J. Dale, *Acta Chem. Scand.* **1973**, *27*, 1130–1148; b) In Dale's convention, the numbers in brackets indicate the number of C–C bonds between corner carbon atoms corresponding to gg or g'g' sequences; thus, the [3434] conformer has two “three-bond” sides and two “four-bond” sides.
- [12] a) V. L. Shannon, H. L. Strauss, R. G. Snyder, C. A. Elliger, W. L. Mattice, *J. Am. Chem. Soc.* **1989**, *111*, 1948–1958; b) In Snyder's designation, the letters g, g', and t, corresponding to *gauche* and *trans* bonds, refer to dihedral angles varying significantly from +60°, –60°, and 180°.
- [13] a) G. H. Robinson, S. A. Sangokoya, T. Pennington, M. F. Self, *J. Coord. Chem.* **1989**, *19*, 287–294; b) M. Meyer, V. Dahaoui-Gindrey, C. Lecomte, R. Guillard, *Coord. Rev.* **1998**, *178–180*, 1313–1405 and references cited therein.
- [14] a) M. Studer, A. Riesen, T. A. Kaden, *Helv. Chim. Acta* **1989**, *72*, 1253–1258; b) R. D. Hancock, R. J. Motekaitis, J. Mashishi, I. Cukrowski, J. H. Reibenspies, A. E. Martell, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1925–1929.
- [15] a) A. Duatti, A. Marchi, R. Pasqualini, *J. Chem. Soc., Dalton Trans.* **1990**, *12*, 3729–3733; b) R. Pasqualini, V. Comazzi, E. Bellande, A. Duatti, A. Marchi, *Appl. Radiat. Isot.* **1992**, *43*, 1329–1333; c) R. Pasqualini, A. Duatti, E. Bellande, V. Comazzi, V. Brucato, D. Hoffschir, D. Fagret, M. Comet, *J. Nucl. Med.* **1994**, *35*, 334–341.
- [16] a) P. Auzeloux, J. Papon, E. M. Azim, M. Borel, R. Pasqualini, A. Veyre, J.-C. Madelmont, *J. Label Compd. Radiopharm.* **1999**, *42*, 325–335; b) P. Auzeloux, M.-F. Moreau, J. Papon, M. Bayle, M. Borel, R. Pasqualini, J.-C. Madelmont, *J. Label Compd. Radiopharm.* **1999**, *42*, 567–579; c) P. Auzeloux, J. Papon, E. M. Azim, M. Borel, R. Pasqualini, A. Veyre, J.-C. Madelmont, *J. Med. Chem.* **2000**, *43*, 190–198.
- [17] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440–467.
- [18] S. J. Weiner, P. A. Kollman, D. T. Nguyen, D. A. Case, *J. Comput. Chem.* **1986**, *7*, 230–252.