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SYNTHESIS OF NEW TRICYCLIC SPIROBISPIDINES *VIA* RING CLOSING METATHESIS REACTION

Christian Hametner,*[a] Daniel Dangl,[a] Kurt Mereiter,[b] Martina Marchetti,[b] and Johannes Fröhlich[a]

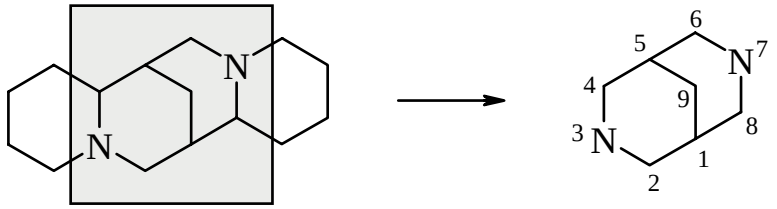
[a] Vienna University of Technology, Institute of Applied Synthetic Chemistry, Getreidemarkt 9/163, 1060 Vienna, Austria
E-mail: christian.hametner@tuwien.ac.at
[b] Vienna University of Technology, Institute of Chemical Technologies and Analytics, Getreidemarkt 9/164, 1060 Vienna, Austria

Abstract – New tricyclic spiro compounds based on 3,7-diazabicyclo[3.3.1]-nonane (bispidine) were synthesized by ruthenium-catalyzed ring closing metathesis reactions. The constitution of the newly formed double bond depending on the chain length and various conditions of the RCM reaction was analyzed.

INTRODUCTION

The development of new nitrogen-containing ligands for organic synthesis is of continuous interest. In particular for metal-catalyzed reactions, ligands derived from amino acids or alkaloids recently gained increasing importance.[1]

The tetracyclic alkaloid sparteine was introduced as an efficient ligand e.g. for Pd-catalyzed allylation reactions[2] or the addition of organolithium compounds to imines.[3] 3,7-Diazabicyclo[3.3.1]nonane (bispidine) constitutes the B and C rings of sparteine as well as many other lupanine alkaloids (Scheme 1). Some stable bispidine-metal complexes have been described in the literature, for instance with Ni^{II}, Cu^{II},[4] or Ni^{0},[5] and applications of bispidine ligands in transformations of organozinc compounds have been given.[6]



sparteine bispidine

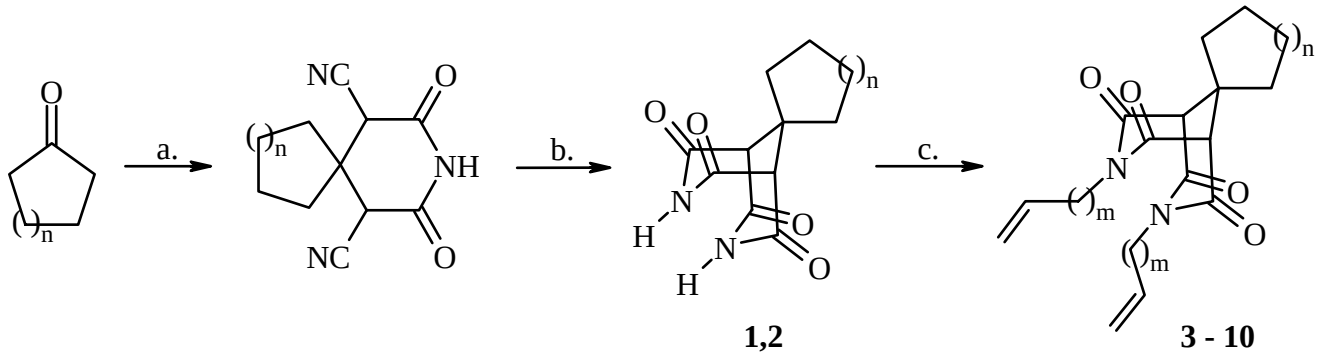
Scheme 1

Depending on the desired substitution pattern, several synthetic approaches towards bispidine derivatives are possible: a double Mannich reaction of piperidones with appropriate primary amines yields bispidinones,[7] a sequence starting from pyridine derivatives via hydrogenation leads to miscellaneous bispidine derivatives.[4] A third method describes the synthesis of 9,9-dialkyl-2,4,6,8-tetraoxobispidines by a Guareschi reaction[8,9] from a ketone, which may be cyclic to generate a spiro center at position 9.

We chose the latter as starting point for the construction of novel tricyclic spirobispidines of potential interest as precursors for new ligands. An additional bridge connecting the two nitrogen atoms should constitute the third ring and a ring closing metathesis (RCM) reaction[10] seemed a promising approach for its realization, leading to ring systems not previously described in the literature. Herein we present the synthesis of the metathesis precursors and results of RCM reactions under varying conditions, including the analysis of the configuration of the newly formed double bond.

RESULTS AND DISCUSSION

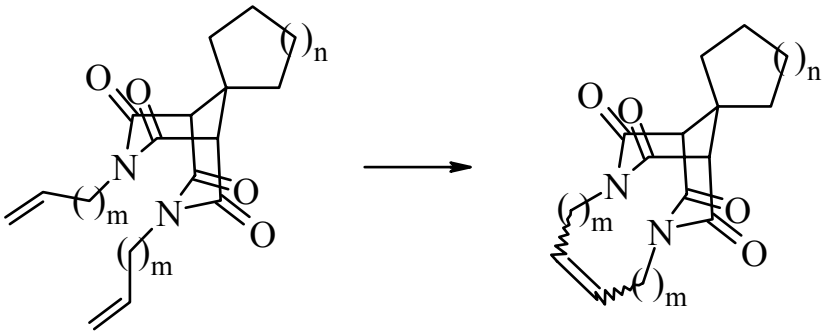
The *N*-unsubstituted spirotetraoxobispidines **1** and **2** were synthesized from cyclopentanone and cyclohexanone by a Guareschi reaction followed by acidic hydrolysis.[9] *N,N'*-Disubstitution was also performed in accordance to the literature,[9] introducing ω-alkenyl chains from propenyl to hexenyl (Scheme 2).



1,2 **3 - 10**

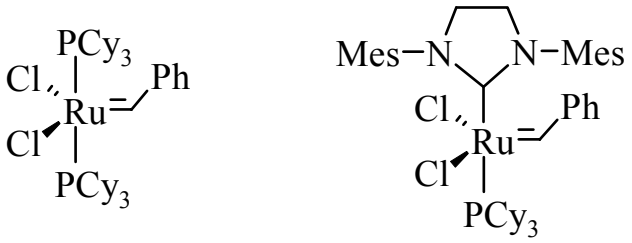
Scheme 2. Synthesis of dialkenyl spirobispidines (n=1-2, m=1-4): (a.) ethyl cyanoacetate, NH_3, dry EtOH, 49-65%; (b.) 60% H_2SO_4, 67-73%; (c.) K_2CO_3, bromoalkene, 29-71%

Three series of RCM reactions were carried out with these precursors (Scheme 3). Two of these were run under conventional heating, one using the more common 1st generation Grubbs catalyst, the other its 2nd generation analogue (Scheme 4), which tolerates a larger bandwidth of substrates, produces better yields, and shows more stability towards elevated temperatures, and the final one used microwave heating, where only the 2nd generation Grubbs is applicable.[11]



5 - 10 **11 - 16**

Scheme 3. General scheme of the ring closing metathesis reaction (n=1-2, m=2-4)



Scheme 4. RCM catalysts: Grubbs catalyst 1st (left) and 2nd (right) generation
(Cy = cyclohexyl, Mes = mesityl)

In the first series the precursors were subjected to metathesis reactions in dry degassed CH_2Cl_2 under reflux overnight using 10 mol% of 1st generation Grubbs catalyst (Table 1). No ring closure at all was observed starting from the dipropenyl compounds, neither here nor in any other of the following experiments. Apparently the distance between the nitrogen atoms of tetraoxobispidines is too short to be bridged via a 2-butenyl chain. All other experiments resulted in acceptable yields of ring-closed products, and the size of the spiro ring had no influence on the course of the reaction. Unexpected results were found for the configuration of the newly formed double bond: from the dibutenyl substrates **5** and **6** *E*-configured products **11** and **12** were formed exclusively, whereas dipentenyl precursors **7** and **8** selectively yielded **13a** and **14a** with opposite configuration. The configuration of the double bond was established by X-ray crystallography (as an example the structure of compound **13a** is shown in Figure 1). Only in the case of the dihexenyl starting compounds **9** and **10** mixtures of stereoisomers were obtained (the configuration and ratios given in the tables were determined by analysis of the olefinic signals in the ^{1}H-NMR spectra).

Substrate	m	n	Product	Yield	Double bond configuration
3	1	1	-	-	
4	1	2	-	-	
5	2	1	**11**	53%	*E*
6	2	2	**12**	48%	*E*
7	3	1	**13a**	60%	*Z*
8	3	2	**14a**	69%	*Z*
9	4	1	**15**	51%	*Z*/*E*= 2.6:1
10	4	2	**16**	60%	*Z*/*E*= 1.4:1

Table 1. Grubbs catalyst 1st generation, thermal heating (CH_2Cl_2, reflux, 15 h)

Analogous reactions were then carried out for all substrates with the use of 2nd generation Grubbs catalyst (Table 2), resulting in slightly better yields in most cases. While product composition was similar for the other chains, the opposite stereochemistry was observed in case of the dipentenyl compounds (Figure 2 shows the X-ray crystal structure of **13b**). Such a complete inversion of selectivity is unprecedented in the literature for these two catalysts.

Substrate	m	n	Product	Yield	Double bond configuration
3	1	1	-	-	
4	1	2	-	-	
5	2	1	**11**	80%	*E*
6	2	2	**12**	65%	*E*
7	3	1	**13b**	79%	*E*
8	3	2	**14b**	59%	*E*
9	4	1	**15**	36%	*Z*/*E*= 1.9:1
10	4	2	**16**	66%	*Z*/*E*= 1.5:1

Table 2. Grubbs catalyst 2nd generation, thermal heating (CH_2Cl_2, reflux, 15 h)

In the literature several applications of microwave heating in RCM chemistry are described with good yields and excellent substrate acceptance using 2nd generation Grubbs catalyst .[11,12] Thus another series of experiments was carried out (Table 3), where the reaction mixtures were heated by microwave irradiation (125 °C, 7 min) instead of refluxing overnight, mainly in order to investigate the influence of these differing conditions on the double bond configuration. Substantial difference to the conventional method was only

observed for the middle-sized substrates **7** and **8**, where the stereoselectivity was lost and isomeric mixtures were produced, as it was again the case for the large rings **15** and **16**. With the dibutenyl precursors however selectivity and good yields were preserved, so the syntheses of **11** and **12** can benefit from the typical short reaction times of this technique.

Substrate	m	n	Product	Yield	Double bond configuration
3	1	1	-	-	
4	1	2	-	-	
5	2	1	**11**	72%	*E*
6	2	2	**12**	66%	*E*
7	3	1	**13a/13b**	74%	*Z*/*E*= 1:1.5
8	3	2	**14a/14b**	65%	*Z*/*E*= 1:1.5
9	4	1	**15**	68%	*Z*/*E*= 2.4:1
10	4	2	**16**	63%	*Z*/*E*= 1.7:1

Table 3. Grubbs catalyst 2nd generation, microwave irradiation (CH_2Cl_2, 125 °C, 7 min)

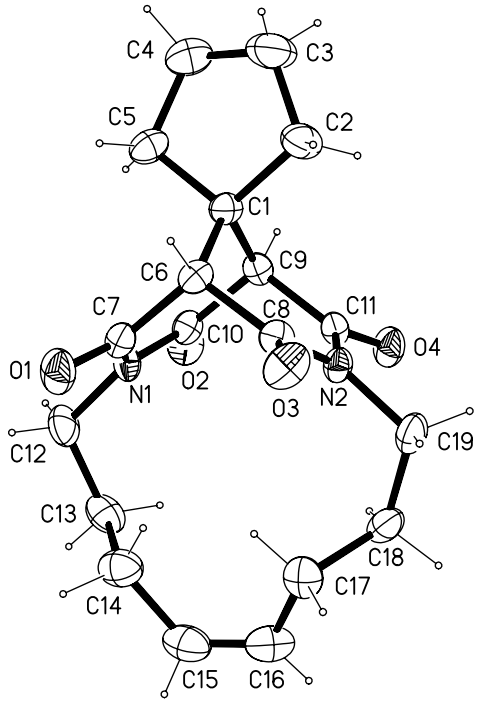


Figure 1. ORTEP view of the molecular structure of **13a** in crystalline state.

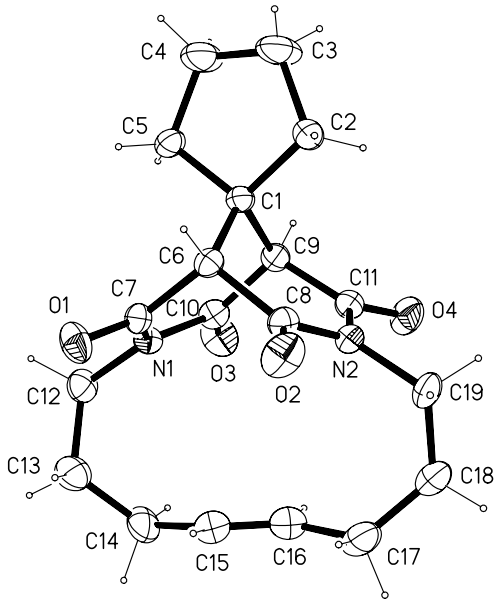
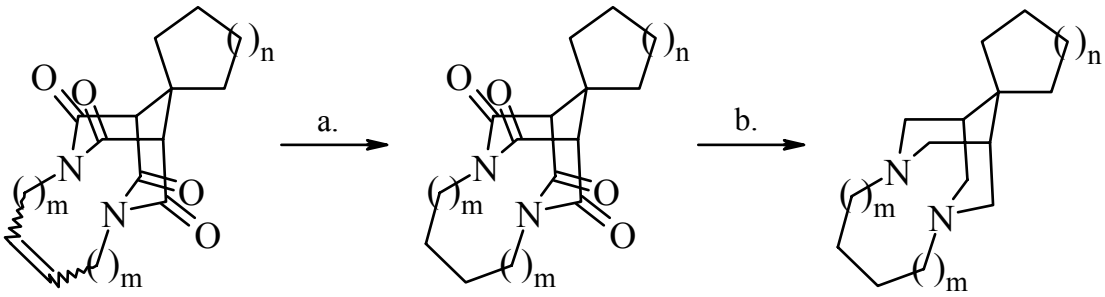


Figure 2. ORTEP view of the molecular structure of **13b** in crystalline state.

Finally the tricyclic parent systems should be approached by subjecting the metathesis products **11-16** to a two-step reduction sequence. The hydrogenation was performed in a Parr apparatus at 60 psi using 10% Pd/C as catalyst (Scheme 5) and worked well for the thirteen-membered (conversion of both isomers of **13** and **14** to **17** and **18**) as well as the fifteen-membered ring systems (syntheses of **19** and **20** from the isomeric mixtures **15** and **16**). However, the reaction failed for the smallest rings **11** and **12**, and an alternative attempt under homogeneous conditions using tris(triphenylphosphine)rhodium(I) chloride[13] (Wilkinson's catalyst) was unsuccessful as well.

The final reduction of the imido groups was carried out only with the hydrogenated products **17-20** by using sodium bis(2-methoxyethoxy)aluminium hydride solution (Red-Al®) in toluene to obtain amines **21-24**, which turned out to be quite unstable.



13 - 16 **17 - 20** **21 - 24**

Scheme 5. Hydrogenation and subsequent reduction of the metathesis products (n=1-2, m=3-4): (a.) 10% Pd/C, ethanol/dioxane, H_2, 60 psi, 93-98%; (b.) Red-Al®, toluene, 68-81%

In conclusion, we synthesized a series of new tricyclic ring systems based on 3,7-diazabicyclo[3.3.1]-nonane (bispidine) by ring closing metathesis reactions. The size of the new-formed rings ranges from 11 to 15, a nine-membered analogue could not be obtained. The configuration of the resulting double bond was found to be influenced not only by the size of the formed ring, but also by experimental parameters like the nature of the catalyst and the heating method. Some of the metathesis products were reduced to the tricyclic parent compounds. Various other applications of RCM chemistry on spirotetraoxobispidines are currently underway in our laboratory.

EXPERIMENTAL

General. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Dry dimethylformamide (DMF; from Acros) and dry ethanol (from Merck) were used as received, dry dichloromethane (CH_2Cl_2) was obtained by

refluxing over P_2O_5, dry toluene by refluxing over sodium. Flash column chromatography was performed on silica gel 60 from Merck (40 – 63 μm) by eluting with mixtures of light petroleum (boiling range 40 – 60°C) and ethyl acetate (EtOAc) of varying compositions. Microwave reactions were carried out on a CEM Explorer PLS^{TM} microwave unit. Melting points were determined using a Kofler-type Leica Galen III micro-hot-stage microscope and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, University of Vienna. NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker DPX-200 (200 MHz) spectrometer and chemical shifts are reported in ppm using Me_4Si as internal standard. MALDI-TOF spectra were obtained with a Shimadzu AXIMA LNR spectrometer using 5-chloro-2-mercaptobenzothiazole and 1,3-dihydroxynaphthaline as the matrices. Tetraoxo compounds **1** and **2** as starting materials were synthesized following a previously described method.

General Procedure for Dialkylated Tetraoxo Compounds 3-10. A solution of tetraoxo compound **1** or **2** (1.0 equiv.) in dry DMF (10% solution) was heated to a temperature of 60 °C to 70 °C. Then NaH (2.5 equiv.) was added, and the mixture was heated to reflux for about 1h. After cooling a solution of the freshly distilled bromoalkene (3.0 equiv) in dry DMF (50% solution) was added. The resulting mixture was refluxed for 90 min. Thereafter most of the solvent was distilled off under reduced pressure. CH_2Cl_2 was added to the residue and the mixture was washed with water. The aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with water for three times and dried over Na_2SO_4. After distilling off the solvent, the residue was either recrystallized or purified by flash column chromatography.

3',7'-Diprop-2-enylspiro[cyclopentane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (3). Tetraoxo compound **1** (3.0 g, 13 mmol) was reacted with allyl bromide (4.6 g, 38 mmol) to give **3** (1.9 g, 47%). Recrystallized from EtOAc, Mp 124-127 °C, TLC: R_f= 0.27 (light petroleum/EtOAc, 5:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.83 – 5.59 (m, 2 H), 5.25 – 5.07 (m, 4 H), 4.33 (d, J = 6.0 Hz, 4 H), 3.81 (s, 2 H), 1.87 – 1.49 (m, 10 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 164.8 (s, 4 C), 130.4 (d, 2 C), 119.2 (t, 2 C), 59.3 (d, 2 C), 43.0 (s, 1 C), 42.3 (t, 2 C), 35.2 (t, 2 C), 24.5 (t, 2 C) ppm. Anal. Calcd for $C_{17}H_{20}N_2O_4$ (316.36): C 64.54 H 6.37 N 8.85. Found: C 64.44 H 6.39 N 8.68.

3',7'-Diprop-2-enylspiro[cyclohexane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (4). Tetraoxo compound **2** (2.0 g, 8 mmol) was reacted with allyl bromide (2.9 g, 24 mmol) to give **4** (0.9 g, 34%). Purified by chromatography (light petroleum/EtOAc, 5:1), Mp 106-108 °C, TLC: R_f= 0.35 (light petroleum/EtOAc, 5:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.82 – 5.58 (m, 2 H), 5.27 – 5.07 (m, 4 H), 4.32 (d, J = 5.2 Hz, 4 H), 3.91 (s, 2 H), 1.63 – 1.39 (s, 10 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 164.6 (s, 4 C),

130.3 (d, 2 C), 119.6 (t, 2 C), 58.3 (d, 2 C), 42.2 (t, 2 C), 36.2 (s, 1 C), 32.4 (t, 2 C), 25.0 (t, 1 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{17}H_{20}N_2O_4$ (316.36): C 64.54 H 6.37 N 8.85. Found: C 64.44 H 6.39 N 8.68.

3',7'-Dibut-3-enylspiro[cyclopentane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (5). Tetraoxo compound **1** (3.0 g, 13 mmol) was reacted with 4-bromo-1-butene (5.1 g, 38 mmol) to give **5** (1.4 g, 29%). Purified by chromatography (light petroleum/EtOAc, 4:1), Mp 84-87 °C, TLC: R_f= 0.44 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.82 – 5.56 (m, 2 H), 5.04 – 4.86 (m, 4 H), 3.84 (t, J = 6.9 Hz, 4 H), 3.76 (s, 2 H), 2.37 – 2.22 (m, 4 H), 1.80 – 1.52 (m, 8 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.3 (s, 4 C), 134.4 (d, 2 C), 117.5 (t, 2 C), 59.5 (d, 2 C), 42.9 (s, 1 C), 39.3 (t, 2 C), 35.4 (t, 2 C), 32.1 (t, 2 C), 24.6 (t, 2 C) ppm. Anal. Calcd for $C_{19}H_{24}N_2O_4$ (344.41): C 66.26 H 7.02 N 8.13. Found: C 66.48 H 7.33 N 7.95.

3',7'-Dibut-3-enylspiro[cyclohexane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (6). Tetraoxo compound **2** (5.0 g, 20 mmol) was reacted with 4-bromo-1-butene (8.1 g, 60 mmol) to give **6** (5.1 g, 71%). Recrystallized from EtOAc, Mp 110-111 °C, TLC: R_f= 0.53 (light petroleum/EtOAc, 7:1), ^{1}H-NMR (200 MHZ, $CDCl_3$): δ = 5.79 – 5.52 (m, 2 H), 4.99 – 4.82 (m, 4 H), 3.86 (s, 2 H), 3.79 (t, J= 6.9 Hz, 4 H), 2.37 – 2.18 (m, 4 H), 1.60 – 1.39 (m, 10 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.0 (s, 4 C), 134.5 (d, 2 C), 117.4 (t, 2 C), 58.4 (d, 2 C), 39.3 (t, 2 C), 36.1 (s, 1 C), 32.5 (t, 2 C), 32.0 (t, 2 C), 25.1 (t, 1 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{20}H_{26}N_2O_4$ (358.44): C 67.02, H 7.31, N 7.82. Found: C 66.72 H 7.60 N 7.98.

3',7'-Dipent-4-enylspiro[cyclopentane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (7). Tetraoxo compound **1** (3.0 g, 13 mmol) was reacted with 5-bromo-1-pentene (5.7 g, 38 mmol) to give **7** (2.7 g, 57%). Purified by chromatography (light petroleum/EtOAc, 6:1), Mp 49-51 °C, TLC: R_f= 0.27 (light petroleum/EtOAc, 6:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.84 – 5.58 (m, 2 H), 5.06 – 4.83 (m, 4 H), 3.76 (s, 2 H) 3.71 (t, J = 7.6 Hz, 4 H), 2.08 – 1.86 (m, 4 H), 1.83 – 1.40 (m, 12 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.1 (s, 4 C), 136.9 (d, 2 C), 115.3 (t, 2 C), 59.4 (d, 2 C), 42.8 (s, 1 C), 39.9 (t, 2 C), 35.1 (t, 2 C), 30.7 (t, 2 C), 26.5 (t, 2 C), 24.5 (t, 2 C) ppm. Anal. Calcd for $C_{21}H_{28}N_2O_4$ (372.47): C 67.72 H 7.58 N 7.52. Found: C 67.68 H 7.81 N 7.40.

3',7'-Dipent-4-enylspiro[cyclohexane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (8). Tetraoxo compound **2** (4.2 g, 17 mmol) was reacted with 5-bromo-1-pentene (7.5 g, 50 mmol) to give **8** (4.5 g, 70%). Purified by chromatography (light petroleum/EtOAc, 7:1), Mp 41-43 °C, TLC: R_f= 0.24 (light petroleum/EtOAc, 7:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.83 – 5.57 (m, 2 H), 5.07 – 4.83 (m, 4 H), 3.88 (s,

2 H), 3.71 (t, J = 7.5 Hz, 4 H), 2.10 – 2.86 (m, 4 H), 1.63 – 1.39 (m, 14 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 164.9 (s, 4 C), 136.9 (d, 2 C), 115.3 (t, 2 C), 58.4 (d, 2 C), 39.9 (t, 2 C), 36.0 (s, 1 C), 32.4 (t, 2 C), 30.8 (t, 2 C), 26.4 (t, 2 C), 25.1 (t, 1 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{22}H_{30}N_2O_4$ (386.50): C 68.37 H 7.82 N 7.25. Found: C 68.64 H 7.96 N 7.30.

3',7'-Dihex-5-enylspiro[cyclopentane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (9). Tetraoxo compound **1** (2.4 g, 10 mmol) was reacted with 6-bromo-1-hexene (5.0 g, 30 mmol) to give **9** (1.6 g, 39%). Purified by chromatography (light petroleum/EtOAc, 6:1), Mp 32-34 °C, TLC: R_f= 0.55 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.86 – 5.58 (m, 2 H), 5.03 – 4.82 (m, 4 H), 3.80 – 3.63 (m, 6 H), 2.10 – 1.89 (m, 4 H), 1.79 – 1.21 (m, 16 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.2 (s, 4 C), 137.9 (d, 2 C), 114.9 (t, 2 C), 59.5 (d, 2 C), 42.8 (s, 1 C), 40.2 (t, 2 C), 35.2 (t, 2 C), 33.0 (t, 2 C), 26.8 (t, 2 C), 25.9 (t, 2 C), 24.5(t, 2 C) ppm. Anal. Calcd for $C_{23}H_{32}N_2O_4$ (400.52): C 68.97 H 8.05 N 6.99. Found: C 69.10 H 8.25 N 7.02.

3',7'-Dihex-5-enylspiro[cyclohexane-1,9'-[3,7]-diazabicyclo[3.3.1]nonane]-2',4',6',8'-tetraone (10). Tetraoxo compound **2** (1.8 g, 7.2 mmol) was reacted with 6-bromo-1-hexene (3.5 g, 21.6 mmol) to give **10** (1.9 g, 63%). Purified by chromatograph (light petroleum/EtOAc, 7:1), colourless oil, TLC: R_f= 0.45 (light petroleum/EtOAc, 7:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.84 – 5.58 (m, 2 H), 5.05 – 4.84 (m, 4 H), 3.87 (s, 2 H), 3.71 (t, J = 7.6 Hz, 4 H), 2.10 – 1.91 (m, 4 H), 1.63 – 1.17 (m, 18 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.0 (s, 4 C), 137.9 (d, 2 C), 114.8 (t, 2 C), 58.5 (d, 2 C), 40.1 (t, 2 C), 36.0 (s, 1 C), 33.0 (t, 2 C), 32.5 (t, 2 C), 26.8 (t, 2 C), 25.9 (t, 2 C), 25.1 (t, 1 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{24}H_{34}N_2O_4$ (414.55): C 69.54 H 8.27 N 6.76. Found: C 69.31 H 8.01 N 7.06.

General Procedure for Ring Closing Metathesis Products 11-16 under Thermal Heating. To a solution of the diolefine **5-10** (1.0 equiv.) in dry degassed CH_2Cl_2 (0.1% solution) were added either Grubbs catalyst 1st or 2nd generation (10 mol%) and the resulting mixture was refluxed for 15 h under an argon atmosphere. Thereafter the solvent was distilled off and the product purified by flash column chromatography (light petroleum/EtOAc, 4:1).

***E*-Spiro[cyclopentane-1,13'-[3,10]-diazatricyclo[8.3.1.1^{3,12}]-6-pentadecene]-2',11',14',15'-tetraone (11).** Diolefine **5** (500 mg, 1.54 mmol) was converted using Grubbs catalyst 2nd generation (120 mg, 10 mol%) to give **11** (370 mg, 80%) as colorless crystals. Mp 252-254 °C, TLC: R_f = 0.26 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.03 – 4.77 (m, 2 H), 4.32 – 4.07 (m, 2 H), 3.78 – 3.56 (m, 4 H), 2.50 – 2.00 (m, 4 H), 1.80 – 1.44 (m, 8 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 166.0 (s, 2

C), 165.1 (s, 2 C), 129.8 (d, 2 C), 60.2 (d, 2 C), 42.0 (s, 1 C), 38.1 (t, 2 C), 35.6 (t, 2 C), 29.5 (t, 2 C), 24.4 (t, 2 C) ppm. Anal. Calcd for $C_{17}H_{20}N_2O_4$ (316.36): C 64.54 H 6.37 N 8.85. Found: C 64.71 H 6.59 N 8.67.

***E*-Spiro[cyclohexane-1,13'-[3,10]-diazatricyclo[8.3.1.1^{3,12}]-6-pentadecene]-2',11',14',15'-tetraone (12).** Diolefine **6** (200 mg, 0.56 mmol) was converted using Grubbs catalyst 2nd generation (50 mg, 10 mol%) to give **12** (120 mg, 65%) as colorless crystals. Mp 243-244 °C, TLC: R_f = 0.36 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.04 – 4.81 (m, 2 H), 4.31 – 4.08 (m, 2 H), 3.84 (s, 2 H), 3.75 – 3.57 (m, 2 H), 2.50 – 2.05 (m, 4 H), 1.57 – 1.29 (m, 10 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.9 (s, 2 C), 164.9 (s, 2 C), 130.0 (d, 2 C), 59.6 (d, 2 C), 38.0 (t, 2 C), 35.4 (s, 1 C), 33.1 (t, 2 C), 29.7 (t, 2 C), 25.1 (t, 1 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{18}H_{22}N_2O_4$ (330.39): C 65.44 H 6.71 N 8.48. Found: C 65.15 H 6.99 N 8.37.

***Z*-Spiro[cyclopentane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]-7-heptadecene]-2',13',16',17'-tetraone (13a).** Diolefine **7** (500 mg, 1.34 mmol) was converted using Grubbs catalyst 1st generation (110 mg, 10 mol%) to give **13a** (270 mg, 60%) as colorless crystals. Mp 224-226 °C, TLC: R_f = 0.32 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.54 – 5.32 (m, 2 H), 3.99 – 3.85 (m, 4 H), 3.83 (s, 2 H), 1.87 – 1.42 (m, 16 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 166.0 (s, 4 C), 129.1 (d, 2 C), 60.2 (d, 2 C), 43.1 (s, 1 C), 39.3 (t, 2 C), 35.4 (t, 2 C), 28.2 (t, 2 C), 24.5 (t, 2 C), 23.3 (t, 2 C) ppm. Anal. Calcd for $C_{19}H_{24}N_2O_4$ (344.41): C 66.26 H 7.02 N 8.13. Found: C 66.29 H 7.21 N 8.08.

***E*-Spiro[cyclopentane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]-7-heptadecene]-2',13',16',17'-tetraone (13b).** Diolefine **7** (500 mg, 1.34 mmol) was converted using Grubbs catalyst 2nd generation (120 mg, 10 mol%) to give **13b** (370 mg, 80%) as colorless crystals. Mp 252-254 °C, TLC: R_f = 0.32 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = δ 5.24 – 4.97 (m, 2 H), 3.94 – 3.78 (m, 4 H), 3.65 (s, 2 H), 2.17 – 1.95 (m, 4 H), 1.86 – 1.38 (m, 12 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.2 (s, 4 C), 129.4 (d, 2 C), 59.6 (d, 2 C), 43.4 (s, 1 C), 42.0 (t, 2 C), 35.0 (t, 2 C), 29.6 (t, 2 C), 24.6 (t, 2 C), 24.4 (t, 2 C) ppm. Anal. Calcd for $C_{19}H_{24}N_2O_4$ (344.41): C 66.26 H 7.02 N 8.13. Found: C 66.21 H 7.30 N 8.09.

***Z*-Spiro[cyclohexane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]-7-heptadecene]-2',13',16',17'-tetraone (14a).** Diolefine **8** (500 mg, 1.29 mmol) was converted using Grubbs catalyst 1st generation (110mg, 10 mol%) to give **14a** (320 mg, 69%) as colorless crystals. Mp 202-205 °C, TLC: R_f = 0.52 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.48 – 5.29 (m, 2 H), 3.94 – 3.78 (m, 4 H), 3.90 (s, 2 H), 1.71 – 1.33 (m, 18 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.7 (s, 4 C), 129.1 (d, 2 C), 59.3 (d, 2

C), 39.1 (t, 2 C), 36.2 (s, 1 C), 32.7 (t, 2 C), 28.3 (t, 2 C), 25.0 (t, 1 C), 23.3 (t, 2 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{20}H_{26}N_2O_4$ (358.44): C 67.02 H 7.31 N 7.82. Found: C 66.75 H 7.26 N 7.64.

***E*-Spiro[cyclohexane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]-7-heptadecene]-2',13',16',17'-tetraone (14b).** Diolefine **8** (200 mg, 0.56 mmol) was converted using Grubbs catalyst 2nd generation (50 mg, 10 mol%) to give **14b** (117 mg, 59%) as colorless crystals. Mp 213-215 °C, TLC: R_f = 0.52 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.25 – 5.13 (m, 2 H), 4.00 – 3.86 (m, 4 H), 3.83 (s, 2 H), 2.24 – 2.01 (m, 4 H), 1.90 – 1.73 (m, 4 H), 1.61 – 1.34 (m, 10 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 164.9 (s, 4 C), 129.4 (d, 2 C), 58.5 (d, 2 C), 42.0 (t, 2 C), 36.5 (s, 1 C), 32.5 (t, 2 C), 29.8 (t, 2 C), 25.2 (t, 1 C), 24.8 (t, 2 C), 20.8 (t, 2 C) ppm. Anal. Calcd for $C_{20}H_{26}N_2O_4$ (358.44): C 67.02 H 7.31 N 7.82. Found: C 66.77 H 7.53 N 7.73.

Spiro[cyclopentane-1,17'-[3,14]-diazatricyclo[12.3.1.1^{3,16}]-8-nonadecene]-2',15',18',19'-tetraone (15). Diolefine **9** (500 mg, 1.25 mmol) was converted using Grubbs catalyst 1st generation (100mg, 10 mol%) to give **15** (240 mg, 51%) as colorless crystals. Mp 207-209 °C, TLC: R_f = 0.33 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.41 – 5.09 (m, 2 H), 3.87 – 3.59 (m, 6 H), 2.01 – 0.92 (m, 20 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.4 (s, 4 C), 131.2 (d, 2 C), 59.8 (d, 2 C), 43.0 (s, 1 C), 39.9 (t, 2 C), 35.4 (t, 2 C), 28.5 (t, 2 C), 27.0, (t, 2 C), 26.9, (t, 2 C), 24.4 (t, 2 C) ppm (Z-Isomer). δ = 165.3 (s, 4 C), 129.4 (d, 2 C), 59.7 (d, 2 C), 42.6 (s, 1 C), 35.2 (t, 2 C), 31.5 (t, 2 C), 28.0 (t, 2 C), 26.9 (t, 2 C), 26.8 (t, 2 C), 24.4 (t, 2 C) ppm (E-Isomer). Anal. Calcd for $C_{21}H_{28}N_2O_4$ (372.47): C 67.72 H 7.58 N 7.52. Found: C 67.81 H 7.73 N 7.47.

Spiro[cyclohexane-1,17'-[3,14]-diazatricyclo[12.3.1.1^{3,16}]-8-nonadecene]-2',15',18',19'-tetraone (16). Diolefine **10** (200 mg, 0.48 mmol) was converted using Grubbs catalyst 2nd generation (50 mg, 10 mol%) to give **16** (142 mg, 66%) as colorless crystals. Mp 176-177 °C, TLC: R_f= 0.53 (light petroleum/EtOAc, 4:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.41 – 5.08 (m, 2 H), 3.90 – 3.64 (m, 6 H), 1.98 – 1.72 (m, 4 H), 1.57 – 0.94 (m, 18 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.1 (s, 4 C), 129.4 (d, 2 C), 58.9 (d, 2 C), 39.8 (t, 2 C), 36.1 (s, 1 C), 32.6 (t, 2 C), 28.3 (t, 2 C), 27.0 (t, 2 C), 26.8 (t, 2 C), 25.1 (t, 1 C), 20.7 (t, 2 C) ppm (Z-Isomer). δ = 165.0 (s, 4 C), 131.2 (d, 2 C), 59.1 (d, 2 C), 39.7 (t, 2 C), 35.7 (s, 1 C), 32.7 (t, 2 C), 28.8 (t, 2 C), 27.0 (t, 2 C), 26.6 (t, 2 C), 25.1 (t, 1 C), 20.7 (t, 2 C) ppm (E-Isomer). Anal. Calcd for $C_{22}H_{30}N_2O_4$ (386.50): C 68.37 H 7.82 N 7.25. Found: C 68.21 H 7.91 N 7.06.

General Procedure for Ring Closing Metathesis Reactions under Microwave Irradiation: 0.3 mmol of diolefins **5-10** and Grubbs catalyst 2nd generation (25 mg, 10 mol%) were dissolved in dry CH_2Cl_2 (5

mL) and added to the reaction vessel under dry conditions. The reaction mixture was heated under microwave irradiation for 7 min at 125 °C. The solvent was evaporated and products **11-16** were purified by chromatography.

The results of these reactions are summarized in Table 3.

General Procedure for Hydrogenated Tricyclic Compounds 17-20. Metathesis products **13-16** (1.0 equiv.) were hydrogenated with Pd/C (10%) in dry ethanol/dioxane (10 mL) at 60 psi in a Parr apparatus for 5 h. The reaction mixture was filtered over hyflo, and the solvent was distilled off. The crude product was purified by chromatography (light petroleum/EtOAc, 3:1).

Spiro[cyclopentane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]heptadecane]-2',13',16',17'-tetraone (17). Compound **13b** (150 mg, 0.44 mmol) was hydrogenated using Pd/C (15 mg, 10%) to give **17** (150 mg, 98%) as colorless crystals. Mp 202-203 °C, TLC: R_f= 0.50 (light petroleum/EtOAc, 3:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.94 – 3.81 (m, 4 H), 3.76 (s, 2 H), 1.80 – 1.36 (m, 12 H), 1.25 – 0.89 (m, 8 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.9 (s, 4 C), 60.2 (d, 2 C), 43.1 (s, 1 C), 39.9 (t, 2 C), 35.3 (t, 2 C), 24.5 (t, 2 C), 24.4 (t, 2 C), 23.6 (t, 2 C), 22.1 (t, 2 C) ppm. Anal. Calcd for $C_{19}H_{26}N_2O_4$ (346.43): C 65.88 H 7.56 N 8.09. Found: C 65.81 H 7.38 N 8.06.

Spiro[cyclohexane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]heptadecane]-2',13',16',17'-tetraone (18). Compound **14a** (500mg, 1.39 mmol) was hydrogenated using Pd/C (50 mg, 10%) to give **18** (463 mg, 93%) as colorless crystals. Mp 217-218 °C, TLC: R_f= 0.53 (light petroleum/EtOAc, 3:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.93 – 3.77 (m, 6 H), 1.59 – 1.31 (m, 14 H), 1.26 – 0.87 (m, 8 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.6 (s, 4 C), 59.3 (d, 2 C), 39.7 (t, 2 C), 36.2 (s, 1 C), 32.7 (t, 2 C), 25.1 (t, 1 C), 24.6 (t, 2 C), 23.4 (t, 2 C), 22.1 (t, 2 C), 20.7 (t, 2 C) ppm. Anal. Calcd for $C_{20}H_{28}N_2O_4$ (360.46): C 66.64 H 7.83 N 7.77. Found: C 66.36 H 7.71 N 7.68.

Spiro[cyclopentane-1,17'-[3,14]-diazatricyclo[12.3.1.1^{3,16}]nonadecane]-2',15',18',19'-tetraone (19). Compound **15** (150 mg, 0.40 mmol) was hydrogenated using Pd/C (15 mg, 10%) to give **19** (140 mg, 94%) as colorless crystals. Mp 196-198 °C, TLC: R_f= 0.55 (light petroleum/EtOAc, 3:1), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.89 – 3.70 (m, 6 H), 1.80 – 1.27 (m, 12 H), 1.24 – 0.91 (m, 12 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.7 (s, 4 C), 59.7 (d, 2 C), 43.5 (s, 1 C), 40.5 (t, 2 C), 35.1 (t, 2 C), 27.7 (t, 2 C), 26.6 (t, 2 C), 25.5 (t, 2 C), 25.4 (t, 2 C), 24.4 (t, 2 C) ppm. Anal. Calcd for $C_{21}H_{30}N_2O_4$ (374.48): C 67.36 H 8.07 N 7.48. Found: C 67.30 H 8.08 N 7.40.

Spiro[cyclohexane-1,17'-[3,14]-diazatricyclo[12.3.1.1^{3,16}]nonadecane]-2',15',18',19'-tetraone (20). Compound **16** (90 mg, 0.23 mmol) was hydrogenated using Pd/C (10 mg, 10%) to give **20** (84 mg, 93%) as colorless crystals. Mp 181-183 °C, TLC: R_f= 0.79 (light petroleum/EtOAc, 3:2), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.87 – 3.70 (m, 6 H), 1.58 – 1.29 (m, 14 H), 1.25 – 0.90 (m, 12 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.0 (s, 4 C), 58.8 (d, 2 C), 40.4 (t, 2 C), 36.6 (s, 1 C), 32.5 (t, 2 C), 28.0 (t, 2 C), 26.7 (t, 2 C), 25.7 (t, 2 C), 25.4 (t, 2 C), 25.1 (t, 1 C), 20.8 (t, 2 C) ppm. Anal. Calcd for $C_{22}H_{32}N_2O_4$ (388.51): C 68.01 H 8.30 N 7.21. Found: C 67.74 H 8.36 N 7.09.

General Procedure for Diamines 21-24. To a solution of the appropriate hydrogenated tetraoxo compound (**17-20**, 1.0 equiv.) in dry toluene (10% solution) was added sodium bis(2-methoxyethoxy)aluminium hydride solution (Red-Al®, 65 wt% in toluene, 8.0 equiv.) and the resulting mixture was refluxed under an argon atmosphere for 15 h. The reaction mixture was hydrolyzed with NaOH (10% solution) and extracted with toluene for three times. The combined organic layers were dried over Na_2SO_4 and the solvent was distilled off. Products were purified by flash column chromatography (MeOH/NEt_3, 3:2).

Spiro[cyclopentane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]heptadecane] (21). Compound **17** (40 mg, 0.12 mmol) was reduced using Red-Al® solution (0.28 mL, 0.92 mmol) to give **21** (27 mg, 81%) as a yellow oil. TLC: R_f= 0.68 (MeOH/NEt_3, 3:2), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.83 – 2.34 (m, 8 H), 2.25 – 2.04 (m, 4 H), 1.75 – 0.90 (m, 22 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 60.0 (t, 2 C), 55.7 (t, 4 C), 39.4 (d, 2 C), 37.9 (s, 1 C), 35.1 (t, 2 C), 28.9 (t, 2 C), 27.5 (t, 2 C), 24.6 (t, 2 C), 23.9 (t, 2 C) ppm. MALDI-MS: *m/z*= 291.28 $[M + H]^+$ (calcd. for $C_{19}H_{35}N_2$: 291.28).

Spiro[cyclohexane-1,15'-[3,12]-diazatricyclo[10.3.1.1^{3,14}]heptadecane] (22). Compound **18** (67 mg, 0.19 mmol) was reduced using Red-Al® solution (0.45 mL, 1.45 mmol) to give **22** (41 mg, 72%) as a yellow oil. TLC: R_f= 0.64 (MeOH/NEt_3, 3:2), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.80 – 2.66 (m, 8 H), 2.34 – 2.21 (m, 4 H), 1.63 – 1.18 (m, 24 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 58.8 (t, 2 C), 53.8 (t, 4 C), 37.4 (d, 2 C), 33.1 (t, 2 C), 32.7 (s, 1 C), 28.9 (t, 2 C), 27.5 (t, 2 C), 26.6 (t, 1 C), 24.6 (t, 2 C), 20.6 (t, 2 C) ppm. MALDI-MS: *m/z*= 305.25 $[M + H]^+$ (calcd. for $C_{20}H_{37}N_2$: 305.29).

Spiro[cyclopentane-1,17'-[3,14]-diazatricyclo[12.3.1.1^{3,16}]nonadecane] (23). Compound **19** (30 mg, 0.08 mmol) was reduced using Red-Al® solution (0.19 mL, 0.64 mmol) to give **23** (19 mg, 74%) as a yellow oil. TLC: R_f= 0.70 (MeOH/NEt_3, 3:2), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.88 – 2.62 (m, 8 H), 2.30 – 2.07 (m, 4 H), 1.65 – 1.04 (m, 26 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 59.0 (t, 2 C), 56.1 (t, 4 C), 39.2 (d, 2

C), 38.5 (s, 1 C), 37.9 (t, 2 C), 35.2 (t, 2 C), 27.3 (t, 2 C), 27.2 (t, 2 C), 25. 9 (t, 2 C), 23.7 (t, 2 C) ppm. MALDI-MS: *m/z*= 319.32 $[M + H]^+$ (calcd. for $C_{21}H_{39}N_2$: 319.31).

Spiro[cyclohexane-1,17'-[3,14]-diazatricyclo[12.3.1.1^{3,16}]nonadecane] (24). Compound **20** (16 mg, 0.04 mmol) was reduced using Red-Al® solution (0.06 mL, 0.33 mmol) to give **24** (9 mg, 68%) as a yellow oil. TLC: R_f= 0.63 ($MeOH/NEt_3$, 3:2), ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.91 – 2.58 (m, 8 H), 2.32 – 2.08 (m, 4 H), 1.78 – 1.18 (m, 28 H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 58.7 (t, 2 C), 54.2 (t, 4 C), 37.3 (d, 2 C), 33.0 (t, 2 C), 32.8 (s, 1 C), 29.7 (t, 2 C), 26.3 (t, 1 C), 25.8 (t, 2 C), 25.5 (t, 2 C), 22.7 (t, 2 C), 20.6 (t, 2 C) ppm. MALDI-MS: *m/z*= 333.33 $[M + H]^+$ (calcd. for $C_{22}H_{41}N_2$: 333.33).

X-Ray Crystallographic Study:

General. X-ray data collection was carried out with a Bruker AXS Smart APEX CCD diffractometer and graphite monochromatized Mo Kα radiation, λ(Mo-Kα) = 0.71073 Å. For each crystal 3-4 sets of frames were measured to cover at least a hemisphere of the reciprocal space (ω-scans, Δω = 0.3°, 20-30 sec per frame). Corrections for absorption with program SADABS,[14] structure solution with direct methods and program SHELXS97, structure refinement on F^2 using the program SHELXL97.[15] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms had isotropic temperature factors and rided on the C-atoms to which they were bonded. Where necessary, disorder was taken into account by split atom models. Views of the molecular structures are shown in figs. 1 and 2. Bond lengths and angles show no unusual features.

Crystal data. 12: $C_{18}H_{24}N_2O_4$, M_r = 332.39; orthorhombic, space group *P*nma (no. 62), a = 6.829(1) Å, b = 12.369(2) Å, c = 18.996(2) Å, V = 1604.5(3) Å^3, Z = 4, D_c= 1.376 g cm^{-3}, μMo = 0.098 mm^{-1}, T = 297(2) K; Specimen: 0.80 × 0.10 × 0.04 mm; $T_{min/max}$ (multiscan absorption correction) = 0.92. θ_{max} = 25°; N_{total} = 15607, N_{unique} = 1479 (R_{int} = 0.044), N_{obs} ($F > 4\sigma(F)$) = 1192; R = 0.065, R_w = 0.178 (all data); $(\Delta\rho F)_{max}$ = 0.48 e Å^{-3}. The structure shows conformation disorder in the olefin part of the macrocycle.

13a: $C_{19}H_{24}N_2O_4$, M_r = 344.40; triclinic, space group *P*-1 (no. 2), a = 8.371(3) Å, b = 15.251(5) Å, c = 15.514(5) Å, α = 116.335(7)°, β = 94.816(7)°, γ = 90.124(7)°, V = 1767.0(10) Å^3, Z = 4, D_c= 1.295 g cm^{-3}, μMo = 0.091 mm^{-1}, T = 303(2) K; Specimen: 0.61 × 0.28 × 0.06 mm; $T_{min/max}$ (multiscan absorption correction) = 0.92. θ_{max} = 23°; N_{total} = 8152, N_{unique} = 4897 (R_{int} = 0.044), N_{obs} ($F > 4\sigma(F)$) = 4897; R = 0.092, R_w = 0.128 (all data); $(\Delta\rho F)_{max}$ = 0.21 e Å^{-3}. There are two independent molecules present in the structure, both being conformation disordered in the olefin part of the macrocycle.

13b: $C_{19}H_{24}N_2O_4$, M_r = 344.40; monoclinic, space group $P2_1$ (no. 4), a = 7.234(3) Å, b = 8.898(3) Å, c = 13.891(5) Å, β = 104.48(1)°, V = 865.7(5) Å^3, Z = 2, D_c= 1.321 g cm^{-3}, μMo = 0.093 mm^{-1}, T = 303(2) K; Specimen: 0.60 × 0.35 × 0.20 mm; $T_{min/max}$ (multiscan absorption correction) = 0.85. θ_{max} = 25°; N_{total} =

4742, N_{unique} = 2760 (R_{int} = 0.025), N_{obs} ($F > 4\sigma(F)$) = 2294; R = 0.078, R_w = 0.189 (all data); $(\Delta\rho F)_{max}$ = 0.30 e Å^{-3}. Structure ordered. Racemic substance forming a conglomerate, chirality indeterminate in the present experiment.

CCDC-240073 - 240075 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk].

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