Factors Influencing the Course of the Macrocyclization of α,ω-Diamines with Esters of α,ω-Dicarboxylic Acids

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The efficient synthesis of eight new macrocyclic amides (lactams) *via* reaction of diesters with diamines under normal dilution conditions is described. The role of intermolecular H-bond formation and steric hindrance is discussed based on ^{1}H- and ^{15}N-NMR studies of appropriate model compounds. Principles for the optimal choice of esters that can be efficiently transformed into diamides have been developed.

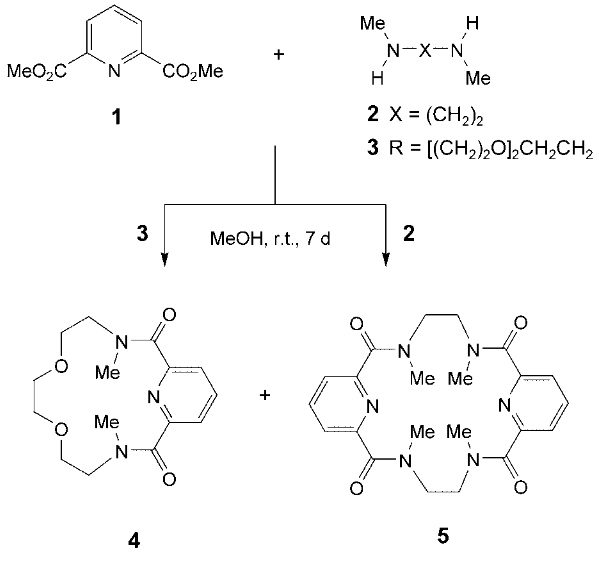
Introduction. – The architecture of naturally occurring macrocycles has long provided the stimulus for the development of new methods for the synthesis of cyclic polyaza and polyoxa compounds [1]. The synthesis of macrocycles possessing both N- and O-atoms to produce receptors with distinct properties has been pursued by many research groups due to the potential application of these compounds in medicine, catalysis, and sensor technology, *etc.* Such macrocycles have been made by a variety of methods, including high-dilution techniques [2] and routes based on template effects [3]. The groups of *Kimura* [4] and *Morphy* [5] reported that, consistent with earlier findings of *Tabushi et al.* [6], neither high-dilution nor templates are required for the condensation of diesters with α,ω-diamines to form macrocyclic diamides. Later, we found that this reaction can even be carried out at room temperature [7] and that various diesters, as long as they possess a heteroatom in α-position to the C=O group, are efficient substrates [8–11]. Structural elements such as OCH_2CO_2Me [8, 10a,b], NCH_2CO_2Me [10c][11], or SCH_2CO_2Me [11], as well as derivatives of pyridine [9][10d] and pyrazine [9], were successfully used, whereas esters of simple aliphatic diacids (*e.g.*, adipinate) were found to be unreactive unless high pressure was applied [7b]. Recently, we have optimized the reaction conditions for macrocyclizations [11], using MeONa as a catalyst, which speeds up the reaction, improves the yields, and broadens the scope of the reaction by including less-reactive esters like dimethyl phthalate. Our results showed that there is no template effect operating in these reactions. Others have also made use of these (or similar) conditions for the synthesis of a wide scope of macrocyclic amides [12][13].

Our interest in the reaction of diesters and diamines has been motivated not only by its broad scope, but also by the amazing observation that standard dilution of reagents is enough to obtain high yields of macrocyclization. For this reason and keeping with our long-standing interest in diazacoronands, we undertook detailed studies to gain insight into the driving forces that govern such reactions. We chose 2,6-bis(carbamoyl)pyridine or analogous model compounds in this study due to their function in cation receptors [14], anion receptors [15], neutral-molecule receptors [16], knots [17], dendrimers [18], and helical structures [19]. Additionally, dimethyl pyridine-2,6-dicarboxylate (**1**) has already been used for the preparation of macrocyclic amides in combination with α,ω-diaminoalkanes [9b], α,ω-diamino ethers [9a], and aliphatic polyamines [12][20].

Results and Discussion. – There is a fundamental difference in the course of the reaction of diacid dichlorides with diamines in toluene, CH_2Cl_2, or THF and that of diesters with diamines in MeOH. What kind of forces lead to excellent yields of macrocyclic products in the latter reaction? And why do acid chlorides at the same concentration give rise to polycondensation products only? One has to note that diacid dichlorides are usually far too reactive to give macrocyclic products under normal conditions. Both reaction pathways involve the formation of the amide bond *via* the reaction of the ester (or acid chloride) and the amino group to afford an intermediate (referred to as 'amino-amido-ester' and 'amino-amido-acid chloride', resp.) that can cyclize to generate the respective diamide. Our initial notion was that MeOH selectively mediates some form of preorganization of the 'amino-amido-ester' intermediate, which would increase the chance for ring closure *vs.* oligocondensation.

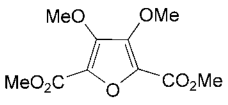
To verify our hypothesis, we designed a few experiments with selected diamines and diesters to clarify some crucial issues. To check whether the presence of the amide H-atom is crucial for effective macrocyclization, we carried out the reactions of **1** with two secondary α,ω-diamines of different lengths (*Scheme 1*). We expected that the reactivity of the amines **2** and **3** [21] would be reduced by the *N*-Me groups as

Scheme 1



compared to analogous primary diamines. In both cases, the yields of the macrocyclic products **4** and **5** were significantly lower than the yields obtained with the nonmethylated analogs (10 *vs.* 54% [15b], and 2.7 *vs.* 83% [9a], respectively). Even in the presence of MeONa [11], the yield of **5** was still very low (4%), although the conversion of **1** increased from 27 to 53%. These results may indicate that the low yields of **4** and **5** result not only from effects of the *N*-methyl groups, but are also attributable to the lack of some form of preorganization.

We already reported that dimethyl diesters lacking a heteroatom between the two ester groups (like those originating from isophthalic acid and pyridine-3,5-dicarboxylic acid) do not react with $H_2N[(CH_2)_2O]_2(CH_2)_2NH_2$ in the absence of MeONa, whereas very small amounts of di- and/or tetramides were formed in its presence [11]. Hence, we came up with the hypothesis that the reactivity of the ester groups is at least as crucial (or even more important than) the heteroatom between these groups. To verify this hypothesis, we synthesized compounds **6**–**9** and tested their reactivities toward diamines. The furane-2,5-dicarboxylate **6**, which has an exceptionally high average electron density and an O-atom between the ester groups, did not react with diamine **10**, not even after 18 months (*Scheme 2*, *Table 1*). However, when MeONa was present, diamide **11** could be obtained in 30% yield (*Table 2*). The results obtained for isophthalates relative to **6** indicate that, when the reactivity of ester groups is increased by addition of catalyst, the course of the reaction starts to depend on the presence (or absence) of a heteroatom placed between the two ester groups.



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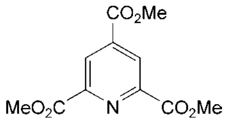

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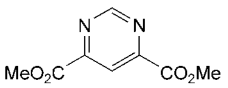

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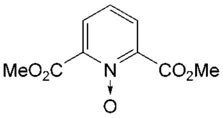

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Table 1. *Degree of Conversion and Yields of Products in the Reactions of Diesters* **1** *and* **6**–**9** *with Diamine* **10** (in MeOH)

Ester	Reaction time	Conversion [%]	Dimerization		Tetramerization	
			Product	Yield [%]	Product	Yield [%]
1	7 d	97	**12**	83	**14**	6
6	365 d	0	**11**	0		0
7	7 d	99	**13**	83		0
8	7 d	100	**15**	2	**16**	6
9	7 d	100	**20**	4	**21**	32

Scheme 2

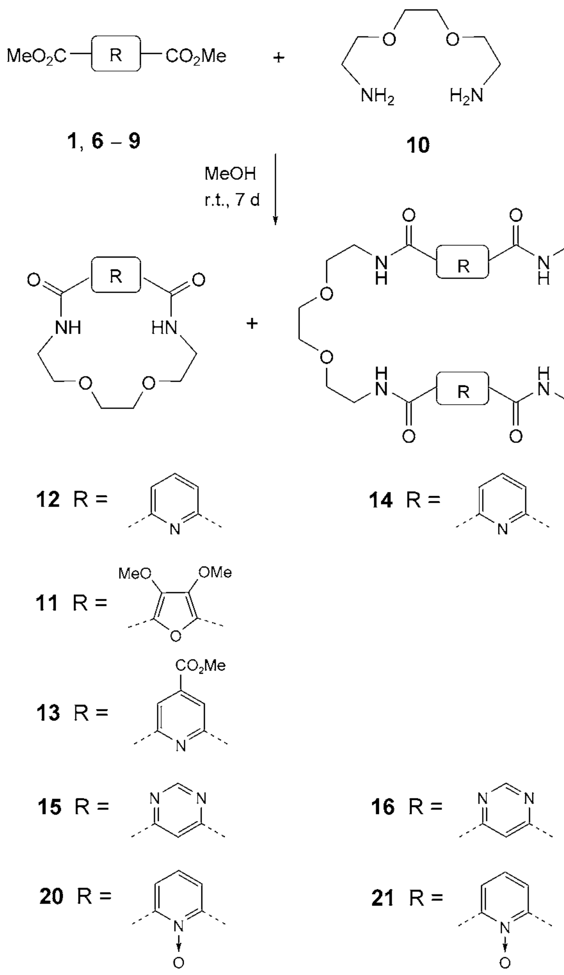


Table 2. *Degree of Conversion and Yields of Products in the Reactions of Diesters* **1** *and* **6**–**9** *with Diamine* **10** (in MeOH containing 10 equiv. of NaOMe)

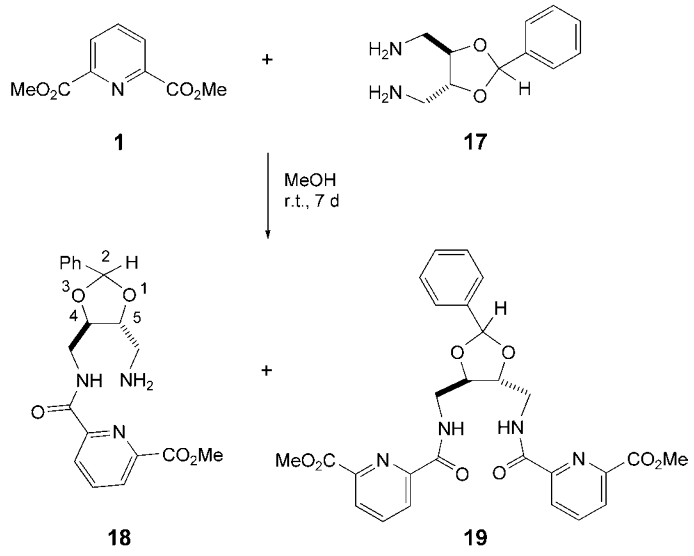
Ester	Reaction time	Conversion [%]	Dimerization		Tetramerization	
			Product	Yield [%]	Product	Yield [%]
1	12 h	100	**12**	84	**14**	4
6	7 d	100	**11**	36		0
7	–	–	–	–	–	–
8	12 h	100	**15**	2	**16**	6
9	12 h	100	**20**	67	**21**	26

Compound **7**, an analog of **1** with an additional ester group in 4-position, could theoretically undergo two different modes of macrocyclization (*Scheme 2*). However, we found that **7** reacts with **10** exclusively in the 2- and 6-positions (*Table 1*). The yields of the diamides **12** and **13** were identical1)), although in **7**, the electron densities at *all* ester groups is similar. These results further confirmed the role played by heteroatoms in the macrocyclization process.

At this point, we decided to test a compound possessing the two CO_2Me groups in α-position to N-atoms, but lacking a heteroatom between the ester groups, compound **8** being such a representative. Here, the ester groups were very reactive, and **8** was completely consumed in the reaction with **10** within 12 h in the absence of catalyst. Nevertheless, only very small amounts of diamide **15** (2%) and tetramide **16** (6%) were formed in this reaction (*Scheme 2*, *Tables 1* and *2*), along with a number of very polar compounds. Neither prolongation of the reaction nor addition of MeONa changed the results.

Another important issue was the effect of substrate conformation (rigidity) on the yield of macrocyclic products. As reported [7][9], the rigidity of an ester might influence the yields of diamides, depending on the length of the α,ω-diamine used, but no such studies have been made with rigid diamines. Therefore, we designed the optically active diamine **17** [8] as a rigid analog of 1,4-diaminobutane, restricted by a dioxolane ring. Consequently, in the reaction with **1**, the intermediate **18** was sterically hindered, preventing ring closure. Indeed, this reaction led to the formation of the open-chain compounds **18** (54%) and **19** (4%) instead of the corresponding cyclic tetramide formed with butane-1,4-diamine [9b] (*Scheme 3*). Also, under high-pressure conditions, which increase the rate of the reaction [7b][22], no cyclic products were isolated.

Scheme 3



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1) Small amounts of tetramer (**14**) were found only in the reaction with **1**, but not with **7**.

To investigate solvent effects, we studied the product distribution of the model reaction between **1** and **10** in various solvents *Table 3*.

Table 3. *Solvent Effects in the Cyclization of Diester* **1** *with Diamine* **10**. Conditions: 7 d, r.t.

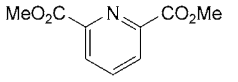
Solvent	Conversion of **1** [%]	Yield of **12** [%]	Yield of **14** [%]
Toluene	0.1	–	–
THF	0.3	–	–
$CHCl_3$	8	–	–
MeCN	70	–	–
$MeNO_2$	49	8	2
DMF	58	27	5
EtOH	64	57	5
MeOH	97	83	6
H_2O	100	–	–
neat	100	21	traces

The model reaction, when performed in nonpolar solvents such as toluene, THF, or $CHCl_3$, resulted in almost quantitative recovery of the ester **1**. This means that the reactivity of the ester group towards amino groups in nonpolar solvents is very low. More-polar solvents like MeCN and $MeNO_2$ gave rise to totally different results. While the conversion of the ester was very high in MeCN, no cyclic products were obtained. Under similar conditions, the conversion was *ca.* 50% in $MeNO_2$, and diamide **12** was obtained in 8% yield. The conversion was also *ca.* 50% in DMF, but the yield of **12** increased to 27%. In EtOH, the conversion of **1** was 64%, and the yield of **12** was 57%, *i.e.*, the ratio conversion yield was roughly the same as for MeOH (*Table 3*). Apparently, the reaction in EtOH is slower than in MeOH, but the ring closure seems to be similar mechanistically. The reaction in H_2O led to total ester hydrolysis, but, surprisingly, the reaction of a neat mixture of **1** and **10** led to as much as 21% of the diamide. Hence, even in such a 'concentrated solution', the reaction still leads to macrocyclic products.

The presence of a strong intramolecular H-bond in the solid-state structure of both macrocyclic and nonmacrocyclic pyridine-2,6-dicarboxamides is well-known [9] [23]. In light of the above results, it would, nevertheless, be unreasonable to propose that an intramolecular H-bond is responsible for the preorganization of the 'amino-amido-ester'. Such a bond would be much stronger in $CDCl_3$ or toluene than in MeOH, which is a strong competitor, but MeOH is a solvent in which macrocylization is most effective. However, intermolecular H-bonds between MeOH molecules and the intermediary 'amino-amido-ester' might be responsible for the observed high yields of the macrocyclization. Such a H-bond array would, undoubtedly, also comprise the heteroatom placed between the two ester groups. Yet, there might be an alternative explanation for some of the above results, namely that the H-atom placed between the CO_2Me groups of **7** and **8** might pose a steric hindrance for the amide H-atom, which would prevent the remaining free amine arm from turning towards the second ester group. To distinguish steric from H-bond effects, we synthesized ester **9**, which possesses an *N*-oxide moiety. Clearly, an O-atom causes much more significant steric hindrance than a H-atom, but may still form a H-bond with an amide NH or other groups. The reaction of ester **9** with amine **10** was carried out under standard conditions, and also in the presence of MeONa (*Tables 1* and *2*). Under uncatalyzed conditions, the yield of diamide **20** was only 4%, and that of tetramide **21** was 32% (*Table 1*). In contrast, in the presence of MeONa, the yield of **19** increased to 67%, while that of **21** remained essentially the same (*Table 2*). These results strongly suggest that steric hindrance can significantly change the mode of complexes of macrocyclization, without necessarily hampering the success of the reaction.

With all of these results in hand, we conducted comparative NMR studies in MeOH and two solvents that hamper macrocyclization ($CDCl_3$ and CD_3CN). Ester **1**, the macrocyclic diamide **12**, and *N*^{2},*N*^{6}-dimethylpyridine-2,6-dicarboxamide (**22**) were chosen as model compounds. We recorded ^1H-, and ^{13}C-, and ^{15}N-NMR spectra. Recently, ^{15}N-NMR spectroscopy has been successfully used to determine the coordination mode of macrocylic amides [14d]. Given that N-atoms indeed participate in H-bond interactions, ^{15}N-NMR spectra could provide excellent insight into these processes. Our assumption was that there was a strong intramolecular H-bond in **12**, at least in nonpolar solvents. If so, the chemical shifts of N_{Py} (pyridyl N-atom) and NHCO should be susceptible to changes in the strength of intramolecular H-bonds. As expected, there was an upfield shift of *ca.* 8 ppm for N_{Py} of **1** *vs.* **12** in CD_3OD (*Table 4*). However, N_{Py} of **22** showed the same chemical shift as in **12**, which suggests that there is a H-bond in both cases (no differentiation). The same conclusion can be draw for the chemical shifts of the amide NH groups: basically, there is no difference for **22** in all three solvents. These results, unfortunately, do not confirm the role of a putative intramolecular H-bond in the reaction. Also, the comparisons of the chemical shifts of NH for **12** and **22** are not conclusive. The observation that only in MeOH there is no difference between the NH resonances of **12** and **22**, however, may be important. Analyses of COSY and other correlation spectra did not reveal any differences.

Table 4. *^{15}N- and ^1H-NMR Chemical Shifts of N-Atoms and Amide NH Groups of Compounds* **1**, **12**, *and* **22**



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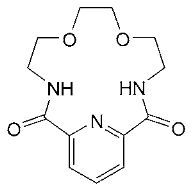

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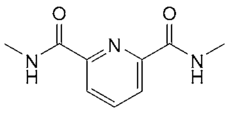

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Solvent	Atom(s)	^{15}N-NMR			Atom(s)	^1H-NMR	
		1	**12**	**22**		**12**	**22**
CD_3OD	NHCO	–	161.3	159.2	NHCO	8.95	8.95
	N_{Py}	244.4	236.3	237.2			
$CDCl_3$	NHCO	–	160.7	158.0	NHCO	8.1	8.75
	N_{Py}	246.3	235.7	235.4			
CD_3CN	NHCO	–	160.4	158.4	NHCO	8.34	8.66
	N_{Py}	246.5	235.7	236.2			

Conclusions. – The reactions of diesters with diamines depend on both the structures of both substrates and the type of solvent used. Our detailed study has led to the following conclusions. *1*) There is a need to strictly distinguish the reactivity of the ester groups [11] from the molecule's ability to efficiently organize an intermolecular H-bond array between the intermediary 'amino-amido-ester' and MeOH molecules. While the reactivity allows for significant conversion of an ester, the heteroatom placed between CO_2Me groups leads to higher yields of macrocyclic diamides. *2*) Esters that are both reactive and possess a suitably placed heteroatom (*e.g.*, esters of aliphatic acids bearing OCH_2CO_2Me [8][10a,b], NCH_2CO_2Me [10c][11], or SCH_2CO_2Me [11] moieties, as well as esters of pyridine-2,6-dicarboxylic and analogous acids) are perfect substrates that give macrocyclic diamides in at least 40% yield. *3*) Esters that are not reactive (*e.g.*, esters of simple aliphatic diacids [7b], except for oxalates [24] and malonates [6a][13b], as well as esters possessing $OCH_2CH_2CO_2Me$ [11], furan, pyrrole, an tiophene derivatives, *etc.*, can be forced to react with diamines in the presence of basic catalyst (or under high-pressure) to give macrocylic products in moderate to good yields. *4*) Potentially reactive diesters with an unsuitably placed hetaroatom (*e.g.*, **8** or tartrates) do not afford macrocyclic products in acceptable yields, not even in the presence of a basic catalyst. *5*) All primary α,ω-diamines are good substrates for the macrocyclization reaction, except for sterically congested ones. Reactions with secondary α,ω-diamines lead to only traces of macrocyclic diamides. *6*) MeOH is the best solvent for this kind of macrocyclization reaction. The reactivity of **1** in all nonpolar solvents is very low and increases gradually as the polarity of the solvent increases (*Table 3*). These observations clarify to some extent the phenomenon of efficient macrocylization and should help to direct the wise choice of the optimal substrates and conditions for this type of reaction.

Experimental Part

General. Column chromatography (CC) was carried out on silica gel (*Kieselgel 60*, 200–400 mesh). Compounds **3** [21] and **17** [8], as well as diesters **1** [12], **6** [25], **8** [26], and **9** [27], were prepared according to literature procedures. All other diamines were distilled prior to use. Melting points (m.p.) were measured on a *Köfler* type hot-stage apparatus (*Boetius*), uncorrected. ^1H- and ^{13}C-NMR Spectra were recorded on *Varian Gemini* (200 and 50 MHz, resp.) and/or *Bruker AM-500* (500 and 125 MHz, resp.) spectrometers, in $CDCl_3$ or CD_3OD; chemical shifts δ in ppm relative to $SiMe_4$ (=0.00 ppm), coupling constants J in Hz. High-resolution mass spectrometry (HR-MS): *AMD-604 Intectra* instrument, in the electron-impact (EI), liquid secondary-ion (LSI), or electrospray-ionization (ESI) mode.

Pulsed-Field NMR Experiments. All experiments were performed on a *Bruker AVANCE-500* Spectrometer at 500 MHz, equipped with an *Oxford* narrow-bore magnet, an *SGI INDY* host workstation, and XWINMR software (Vers. 2.5). The instrument was equipped with three frequency channels with a wave-form memory and an amplitude-shaping unit, a three-channel gradient control unit (GRASP III), a variable-temperature, a precooling, and a temperature-stabilization unit. For all measurements, a 1 H/BB (^{109}Ag-^{31}P) triple-axis gradient probe (*ID500-5EB*; *Nalorac Gryogenic Corp*), with 5 mm i.d. was used. The NMR probe was tuned to the ^{13}C (125.75 MHz) or the ^{15}N frequency (50.67 MHz). All spectra were acquired at a temp. of 298 K, with $SiMe_4$ as an internal standard. A combination of 2D homonuclear ^1H- and heteronuclear ^1H-, ^{15}N-, and ^{13}C-correlated experiments were applied to study the structures of the compounds under investigation. The standard instrumental parameters for acquisition of the gradient 2D COSY, 2D HMQC, and 2D HMBC were applied. Data were processed with the *Bruker* software XWINMR 2.5 using standard-processing parameters.

Trimethyl Pyridine-2,4,6-tricarboxylate (**7**). The synthesis was performed based on the procedure of *Hünig* and *Wehner* [28] for a similar compound. 2,4,6-Trimethylpyridine (5.26 g, 43 mmol) was dissolved in conc. H_2SO_4 (150 ml). After cooling to 0°, CrO_3 (39 g, 0.39 mol) was added in small portions over 3 h. The mixture was heated to 75° for 24 h, poured into a mixture of ice/H_2O (0.5 l), and kept at 4°. After 3 d, pyridine-2,4,6-tricarboxylic acid precipitated (7.0 g, 33 mmol; 76.3%) as light violet crystals, which were suspended in MeOH

(40 ml) containing conc. H_2SO_4 (0.7 ml). The mixture was refluxed overnight. After cooling in a refrigerator, crystals separated and were collected to afford **7** (4.5 g, 41% over two steps). M.p. 149–151° (lit. 154.5° [29]). IR (KBr): 3080, 1747, 1442, 1365, 1280, 1242, 1163, 999, 757, 719, 690. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.81 (*s*, 2 H); 4.07 (*s*, 6 H); 4.05 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 164.2; 163.7; 149.2; 140.1; 126.3; 53.2; 53.1. Anal. calc. for $C_{11}H_{11}NO_6$ (253.21): C 52.18, H 4.38, N 5.33; found: C 51.94, H 4.38, N 5.09.

General Procedures for the Synthesis of Macrocyclic Amides. Method A: An equimolar 0.1M soln. of *α*,*ω*-diamine and dimethyl dicarboxylate in anh. MeOH was left at ambient temp. over a period of at least 7 d. The solvent was evaporated, and the residue was purified by CC (SiO_2; CH_2Cl_2 with 0.5–10% MeOH).

Method B: Na Metal (2.30 g, 100 mmol) was added to anh. MeOH (100 ml). Then, the mixture was cooled to 5°, and the *α*,*ω*-diamine (10 mmol) and dimethyl dicarboxylate (10 mmol) were added. This mixture was left at ambient temp. over a period of at least 12 h. The solvent was evaporated, and the residue was purified by CC (SiO_2; CH_2Cl_2 with 0.5–10% MeOH).

3,12-Dimethyl-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(17),14(18),15-triene-2,13-dione (**4**). *Method A:* 2.7%. *Method B:* 4.0%. M.p. 186–189°. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.18 (*d*, *J* = 7.3, 2 H); 8.09–7.87 (*m*, 1 H); 3.90–3.38 (*m*, 12 H); 3.19 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 162.3; 148.0; 139.4; 124.0; 70.6; 69.10; 47.2; 38.8. HR-MS: 307.1528 (M^+, $C_{15}H_2N_3O_4^+$; calc.: 307.1532).

3,6,14,17-Tetramethyl-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene-2,7,13,18-tetraone (**5**). *Method A:* 10.1%. Colorless crystals. M.p. 245–249°. IR (KBr): 3436, 3010, 2924, 1636, 1501, 1418, 1353, 1315, 1076, 840, 759, 645. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.9–8.1 (*m*, 2 H); 7.8–7.9 (*m*, 4 H); 4.2–4.4 (*m*, 4 H); 3.6–3.8 (*m*, 4 H); 3.22 (*s*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 168.2; 152.4; 138.5; 125.4; 47.7; 41.7. EI-MS: 438 (50.5, M^+), 410 (20.3), 367 (23.0), 354 (44.8), 190 (22.5), 176 (20.0), 163 (32.6), 162 (38.9), 161 (65.7), 149 (45.4), 148 (100), 106 (30.5), 105 (31.4), 78 (30.9), 77 (33.8). Anal. calc. for $C_{22}H_{26}N_6O_4$ (438.48): C 60.26, H 5.98, N 19.17; found: C 59.98, H 6.10, N 18.97.

15,16-Dimethoxy-6,9,17-trioxa-3,12-diazabicyclo[12.2.1]heptadeca-1(16),14-diene-2,13-dione (**11**). *Method B:* 36%. Colorless crystals. M.p. 182–183°. IR (KBr): 3436, 2905, 1667, 1570, 1525, 1341, 1206, 1101, 841, 609, 565. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23 (br. *s*, 2 H); 4.19 (*s*, 6 H); 3.71 (*s*, 2 H); 3.6–3.7 (*m*, 2 H); 3.56 (*q*, *J* = 5.0, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 157.2; 144.3; 128.9; 70.8; 68.6; 62.4; 38.4; 29.7. EI-MS: 328 (100, M^+), 196 (38), 182 (32), 168 (40), 154 (34), 83 (29.0). HR-LSI-MS: 328.1293 (M^+, $C_{14}H_{20}N_2O_7^+$; calc.: 328.1271). Anal. calc. for $C_{14}H_{20}N_2O_7$ (328.32): C 51.22, H 6.14, N 8.53; found: C 51.31, H 6.38, N 8.70.

Methyl 2,13-Dioxo-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-16-carboxylate (**13**). *Method A:* 83%. Colorless crystals. M.p. 241–243°. IR (KBr): 3401, 3386, 2909, 2882, 1735, 1691, 1530, 1451, 1264, 1241, 1117, 1097, 653. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.8–8.9 (*m*, 4 H); 4.02 (*s*, 3 H); 3.6–3.8 (*m*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 164.4; 161.8; 149.4; 141.3; 123.3; 70.6; 68.4; 53.0; 38.9. HR-MS: 337.1264 (M^+, $C_{15}H_{19}N_3O_6^+$; calc.: 337.1274). Anal. calc. for $C_{15}H_{19}N_3O_6$ (337.33): C 53.41, H 5.68, N 12.46; found: C 53.51, H 5.58, N 12.50.

6,9-Dioxa-3,12,15,17-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (**15**). *Method A:* 2%. *Method B:* 2%. Colorless crystals. M.p. 183–184°. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.22 (*d*, *J* = 1.3, 1 H); 8.68 (*d*, *J* = 1.3, 1 H); 8.30 (br. *t*, *J* = 5.5, 2 H); 3.6–3.8 (*m*, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 162.0; 156.9; 115.7; 70.3; 69.4; 39.5. HR-LSI-MS: 281.1243 ($[M+H]^+$, $C_{12}H_{17}N_4O_4^+$; calc.: 281.1250).

6,9-Dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione 18-Oxide (**20**). *Method A:* 4%. *Method B:* 67%. Colorless crystals. M.p. 241–243°. IR (KBr): 3173, 2913, 2879, 1696, 1683, 1560, 1386, 1097. ^{1}H-NMR (400 MHz, $CDCl_3$): 11.60 (br. *s*, 2 H); 8.32 (*d*, *J* = 7.9, 2 H); 7.57 (*t*, *J* = 7.9, 1 H); 3.5–3.7 (*m*, 12 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 158.7; 143.2; 128.7; 127.5; 71.1; 68.6; 39.4. HR-ESI-MS: 318.1076 ($[M+Na]^+$, $C_{13}H_{17}N_3O_5Na^+$; calc.: 318.1060). Anal. calc. for $C_{13}H_{17}N_3O_5$ (295.29): C 52.88, H 5.80, N 14.23; found: C 52.64, H 5.79, N 14.12.

6,9,23,26-Tetraoxa-3,12,15,17,20,29,32,34-octaazatricyclo[29.3.1.1^{14,18}]hexatriaconta-1(35),14,16,18(36),31,33-hexaene-2,13,19,30-tetraone (**16**). *Method A:* 6%. *Method B:* 6%. Colorless crystals. M.p. 216–218°. IR (KBr): 3333, 2939, 1694, 1518, 1423, 1269, 1141, 1102, 1077, 665. ^{1}H-NMR (200 MHz, CF_3COOD): 9.30 (*s*, 2 H); 8.93 (*s*, 2 H); 3.6–4.2 (*m*, 24 H). ^{13}C-NMR (50 MHz, CF_3COOD): 160.5; 158.7; 119.0; 98.1; 72.1; 71.4; 42.1. HR-LSI-MS: 561.2417 ($[M+H]^+$, $C_{24}H_{33}O_8N_8^+$; calc.: 561.2421). Anal. calc. for $C_{24}H_{32}N_8O_8 \cdot 2\,H_2O$ (596.59): C 48.32, H 6.08, N 18.78; found: C 48.00, H 6.25, N 18.87.

6,9,23,26-Tetraoxa-3,12,20,29,35,36-hexaazatricyclo[29.3.1.1^{14,18}]hexatriaconta-1(35),14,16,18(36),31,33-hexaene-2,13,19,30-tetraone 35,36-Dioxide (**21**). *Method A:* 32%. *Method B:* 26%. Colorless crystals. M.p. 234–244°. IR (KBr): 3436, 3221, 2925, 2875, 1681, 1535, 1518, 1390, 1116. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.88 (br. *s*, 2 H); 8.53 (*d*, *J* = 8.0, 2 H); 7.58 (*t*, *J* = 8.0, 1 H); 3.6–3.8 (*m*, 12 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 159.4; 141.4;

130.9; 127.5; 69.9; 69.2; 39.7. HR-ESI-MS: 613.2212 ($[M + Na]^+$, $C_{26}H_{34}N_6O_{10}Na^+$; 613.2229). Anal. calc. for $C_{26}H_{34}N_6O_{10}$ (590.58): C 52.88, H 5.80, N 14.23; found: C 52.63, H 5.94, N 14.02.

*Methyl 6-({[(4*R*,5*R*)-5-(aminoethyl)-2-phenyl-1,3-dioxolan-4-yl]methylamino}carbonyl)pyridine-2-carboxylate* (**18**; diastereoisomer mixture). *Method A:* 54%. $[\alpha]_D^{23} = -9.8$ ($c = 1.0$, DMSO). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.90 (br. *t*, 1 H); 8.4–8.3 (*m*, 1 H); 8.20 (*m*, 1 H); 8.00 (*m*, 1 H); 7.6–7.2 (*m*, 5 H); 6.00 (*s*, 0.5 H); 5.93 (*s*, 0.5 H); 4.3–3.5 (*m*, 4 H); 3.99 (*s*, 1.5 H); 3.98 (*s*, 1.5 H); 3.2–2.9 (*m*, 2 H); 2.28 (br. *s*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 164.8; 164.1; 163.9; 149.9; 149.8; 146.6; 146.5; 138.5; 138.5; 137.2; 137.2; 129.5; 129.4; 128.4; 128.3; 127.3; 127.3; 126.7; 126.6; 126.6; 126.4; 125.4; 125.4; 125.0; 103.5; 103.4; 81.7; 80.4; 79.3; 78.2; 52.8; 43.5; 43.4; 41.1; 41.0. HR-LSI-MS: 372.1558 ($[M + H]^+$, $C_{19}H_{22}N_3O_5^+$; calc.: 372.1559).

*Methyl 6-({[(4*R*,5*R*)-5-({[6-(Methoxycarbonyl)pyridin-2-yl]carbonylamino}methyl)-2-phenyl-1,3-dioxolan-4-yl]methylamino}carbonyl)pyridine-2-carboxylate* (**19**). *Method A:* 4%. $[\alpha]_D^{23} = -24.8$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.62 (*t*, $J = 5.4$, 2 H); 8.42–8.34 (*m*, 2 H); 8.22 (*m*, 2 H); 8.00 (*m*, $J = 7.8$, 2 H); 7.6–7.3 (*m*, 5 H); 6.03 (*s*, 1 H); 4.4–4.2 (*m*, 2 H); 4.00 (*s*, 3 H); 3.98 (*s*, 3 H); 4.0–3.8 (*m*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 164.9; 164.0; 149.8; 149.8; 146.6; 146.6; 138.5; 129.6; 128.4; 127.3; 126.8; 125.5; 103.8; 78.9; 52.9; 40.8; 40.7. HR-MS: 534.1746 (M^+, $C_{27}H_{26}N_4O_8^+$; calc.: 534.1751).

REFERENCES

[1] G. W. Gokel, S. H. Korzeniowski, 'Macrocyclic Polyether Synthesis'; Springer, Berlin, 1982; M. Pietraszkiewicz, *J. Coord. Chem.* **1992**, *27*, 151; J. S. Bradshaw, K. E. Krakowiak, R. M. Izatt, 'Aza Crown Macrocycles', Vol. 51, John Wiley & Sons, New York, 1993.

[2] B. Dietrich, J.-M. Lehn, J.-P. Sauvage, *Tetrahedron Lett.* **1969**, *10*, 2885.

[3] S. Kulstad, L. A. Malmsten, *Acta Chem. Scand., Ser. B* **1979**, *33*, 469; A. M. Arif, C. J. Gray, F. A. Hart, M. B. Hursthouse, B. C. Shoop, *Inorg. Chim. Acta* **1985**, *109*, 179; G. A. Lawrance, M. Rossignoli, B. W. Skelton, A. H. White, *Austr. J. Chem.* **1987**, *40*, 1441.

[4] E. Kimura, Y. Kuramoto, T. Koike, H. Fujiioka, M. Kodama, *J. Org. Chem.* **1990**, *55*, 42.

[5] R. J. Morphy, D. Parker, R. Alexander, A. Bains, A. F. Carne, M. A. Eaton, A. Harrison, A. Hillican, A. Phipps, S. K. Rhind, R. Tetmas, D. Weatherby, *J. Chem. Soc., Chem. Commun.* **1998**, 156.

[6] a) I. Tabushi, H. Okino, Y. Kuroda, *Tetrahedron Lett.* **1976**, *17*, 4339; b) I. Tabushi, Y. Taniguchi, H. Kato, *Tetrahedron Lett.* **1977**, *18*, 1049.

[7] a) J. Jurczak, S. Kasprzyk, P. Sałański, T. Stankiewicz, *J. Chem. Soc., Chem. Commun.* **1991**, 956; b) J. Jurczak, S. Kasprzyk, P. Sałański, T. Stankiewicz, *High Pressure Res.* **1992**, *11*, 139; c) J. Jurczak, T. Stankiewicz, P. Sałański, S. Kasprzyk, P. Lipkowski, *Tetrahedron* **1993**, *49*, 1478.

[8] D. T. Gryko, P. Piątek, P. Sałański, J. Jurczak, *Tetrahedron: Asymmetry* **1998**, *9*, 1771.

[9] a) D. T. Gryko, P. Piątek, A. Pęcak, M. Pałys, J. Jurczak, *Tetrahedron* **1998**, *54*, 7505; b) A. Szumna, D. T. Gryko, J. Jurczak, *Heterocycles* **2002**, *56*, 361.

[10] a) D. T. Gryko, P. Piątek, J. Jurczak, *Synthesis* **1999**, 336; b) P. Tarnowski, P. Piątek, R. R. Siciński, *Supramol. Chem.* **2000**, *12*, 217; c) M. Achmatowicz, J. Jurczak, *Tetrahedron: Asymmetry* **2001**, *12*, 111; d) P. Piątek, M. M. Gruza, J. Jurczak, *Tetrahedron: Asymmetry* **2001**, *12*, 1763.

[11] D. T. Gryko, D. Gryko, J. Jurczak, *Synlett* **1999**, 1310; D. T. Gryko, D. Gryko, J. Jurczak, *Supramol. Chem.* **2000**, *12*, 101.

[12] I. Dierck, G. G. Herman, A. M. Goemine, G. P. Van der Kelen, *Bull. Chem. Soc. Belg.* **1993**, *102*(1), 63.

[13] a) A. Mason, I. O. J. Sutherland, *J. Chem. Soc., Chem. Commun.* **1994**, 1131; b) N. Fukada, T. Ohtsu, M. Miwa, M. Mashino, Y. Takeda, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1397; c) V. P. Solovev, N. N. Strakhova, V. P. Kazachenko, A. F. Solotnov, V. E. Baulin, O. A. Raevsky, V. Rudiger, F. Eblinger, H. J. Schneider, *Eur. J. Org. Chem.* **1998**, *7*, 1379; d) Y. Gok, Y. Atalay, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1997**, *28*, 287; e) A. A. Chekhlov, V. E. Baulin, I. V. Martynov, *Dokl. Acad. Nauk.* **1998**, *358*, 74; f) I. Bitter, A. Grün, B. Balázs, G. Tóth, G. Horváth, L. Töke, *Synth. Commun.* **1999**, *29*, 3905; g) R. Ostaszewski, L. Prodi, M. Montalti, *Tetrahedron* **1999**, *55*, 11553; h) B. Balázs, G. Tóth, G. Horváth, A. Grün, V. Csokai, L. Töke, I. Bitter, *Eur. J. Org. Chem.* **2001**, 61; i) Q. Yuan, E. Fu, X. Wu, M. Fang, P. Xue, C. Wu, J. Chen, *Tetrahedron Lett.* **2002**, *43*, 3935.

[14] a) E. Weber, F. Vögtle, *Ann. Chem.* **1976**, 891; b) S. Kumar, M. S. Hundal, N. Kaur, R. Singh, H. Singh, G. H. Nee Sood, M. M. Ripoll, J. S. Aparicio, *J. Org. Chem.* **1996**, *61*, 7819; c) E. Weber, F. Vögtle, *Ann. Chem.* **1976**, 891; d) D. T. Gryko, A. Pęcak, W. Koźmiński, P. Piątek, J. Jurczak, *Supramol. Chem.* **2000**, *12*, 229; e) A. Szumna, D. T. Gryko, J. Jurczak, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1553.

[15] a) S.-S. Sun, A. J. Lees, *Chem. Commun.* **2000**, 1687; b) A. Szumna, J. Jurczak, *Eur. J. Org. Chem.* **2001**, 4031; c) A. Szumna, J. Jurczak, *Helv. Chim. Acta* **2001**, *84*, 3760; d) J.-H. Liao, C.-T. Chen, J.-M. Fang, *Org. Lett.* **2002**, *4*, 561.
[16] M. Herm, O. Molt, T. Schrader, *Chem.–Eur. J.* **2002**, *8*, 1485.
[17] O. Safarovsky, M. Nieger, R. Fröhlich, F. Vögtle, *Angew. Chem., Int. Ed.* **2000**, *39*, 1616.
[18] B. Huang, J. R. Parquette, *Org. Lett.* **2000**, *2*, 239.
[19] Q. Yu, T. E. Baroni, L. Liable-Sands, G. P. A. Yap, A. L. Rheingold, A. S. Borovik, *Chem. Commun.* **1999**, 1467; V. Berl, I. Huc, R. G. Khoury, J.-M. Lehn, *Chem.–Eur. J.* **2001**, *7*, 2798; V. Berl, I. Huc, R. G. Khoury, J.-M. Lehn, *Chem.–Eur. J.* **2001**, *7*, 2810; d) T. Yano, R. Tanaka, T. Nishioka, I. Kinoshita, K. Isobe, L. J. Wright, T. J. Collins, *Chem. Commun.* **2002**, 1396.
[20] M. Kodama, T. Koike, E. Kimura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1627.
[21] J. Schnekenburger, *Arzneim. Forsch.* **1975**, *25*, 1853.
[22] K. Matsumoto, S. Hashimoto, T. Uchida, T. Okamoto, S. Otani, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3138.
[23] D. S. Marlin, M. M. Olmstead, P. K. Mascharak, *J. Mol. Struct.* **2000**, *554*, 211.
[24] R. Tripier, O. Siri, F. Rabiet, F. Denat, R. Guilard, *Tetrahedron Lett.* **1999**, *40*, 79.
[25] P. X. Iten, A. A. Hofmann, H. C. Eugster, *Helv. Chim. Acta* **1978**, *61*, 430.
[26] R. R. Hunt, J. F. W. McOmie, E. R. Sayer, *J. Chem. Soc.* **1959**, 525.
[27] S. Caron, N. M. Do, J. E. Sieser, *Tetrahedron Lett.* **2000**, *41*, 2299.
[28] S. Hünig, I. Wehner, *Synthesis* **1989**, 552.
[29] M. Eckert, H. Loria, *Monatsh. Chem.* **1917**, *38*, 246.

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